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ABSTRACTS

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ABSTRACTS

KEYNOTE LECTURES

BUILDING BRIDGES IN RHEUMATOLOGY: A VIEW FROM THE EULAR PRESIDENT

Daniel Aletaha

FIFTY SHADES OF ONCORHEUMATOLOGY

Zoltán Szekanecz

RARE AND ORPHAN (AT)

AUTOINFLAMMATION

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Background: The concept of autoinflammation is a relatively recent addition to the field of immunology, with autoimmunity being a more established area in rheumatology. Additionally, autoinflammation is a rare phenomenon in adults. The recent description of a new disease, VEXAS syndrome, caused by a somatic rather than a germline mutation, has shed light to a new diseases concept.
Aim: This talk will provide an overview of the historical development of the concept of autoinflammation and discuss recent advances in the field. It will then proceed to examine more common clinical diseases, such as familial Mediterranean fever and Morbus Still, before turning to the new description of VEXAS syndrome.
Methods and results: This presentation will provide an overview of the various autoinflammatory diseases, with a particular focus on VEXAS.
Discussions and Conclusions: We will discuss the latest data on the clinical manifestations and treatment options for VEXAS syndrome.

RARE AND ORPHAN OSTEOLOGIC CASES

Roland Kocijan
Hanusch Krankenhaus, Vienna, Austria

The Vienna Bone and Growth Center (VBGC) is a medical facility focusing on the diagnosis, treatment, and research of rare bone disorders (RBDs). As an integral part of the European Reference Network for Rare Bone Disorders (ERN BOND), the VBGC plays a critical role in advancing the understanding and management of these complex conditions.
In adulthood, main focus lays on three RBDs: X-linked hypophosphatemia (XLH), hypophosphatasia (HPP), and osteogenesis imperfecta (OI). Besides the differences in pathophysiology and clinical appearance, quality of life is reduced in all RBD patients.

X-linked hypophosphatemia (XLH) is a genetic disorder characterized by low phosphate levels in the blood, leading to rickets, bone pain, and dental issues. The VBGC utilizes advanced diagnostic tools, including genetic testing and biochemical assays, to identify and manage XLH, ensuring personalized treatment plans that often include phosphate supplementation and active vitamin D analogs or FGF-23-inhibition using burosumab. Current research topics of the VBGC include enthesiopathies, a common problem in adult XLH.
Hypophosphatasia (HPP) is another focus of the VBGC, a rare inherited disorder affecting bone mineralization due to defective alkaline phosphatase activity. Patients with HPP present with a spectrum of symptoms, from severe skeletal abnormalities in infancy to milder forms in adults, often mimicking rheumatologic disorders. Circulating miRNAs could act as new biomarkers for diagnosis of HPP and follow-up under enzyme replacement therapy.
Osteogenesis imperfecta (OI), commonly known as brittle bone disease, is a genetically heterogeneous disorder characterized by bone fragility and frequent fractures. Bisphosphonate therapy, surgical interventions, and comprehensive rehabilitation services are state-of-the-art. However, new treatment options such as sclerostin inhibition or targeting TGF-β are currently under investigation.
The transition from pediatric to adult care is a critical phase in the management RBD. Effective transition helps prevent gaps in care that could lead to complications, ensures that patients are equipped to manage their condition independently, and facilitates the adaptation of treatment plans to the evolving needs of adult patients.

VASCULITIC ENTITIES

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Background: About 36 million people living in the European Union suffer from a rare disease, making rare diseases in sum relatively common. Among the known primary vasculitides is a substantial proportion of rare diseases and diseases manifesting primarily with immunodysregulation or primary immunodeficiency may manifest with inflammatory vessel involvement.
Aim: To give insights into diagnosis and treatment of the rare and orphan diseases among primary vasculitides and rare diseases manifesting with inflammatory vessel changes.
Overview: Among primary vasculitides with predominately large vessel involvement Takayasu's artertitis, a granulomatous arteritis predominantly affecting the aorta and/or its major branches is very rare, progressive diseases with increased mortality and an estimated prevalence of 8–40/million. Among small vessel vasculitides especially eosinophilic granulomatosis with polyangiitis (EGPA) has to be mentioned as a very rare disease. In the field of EGPA major advances in therapy have been made recently with the introduction of rituximab und IL-5-targeted therapies. Of note, among patients with primary vasculitides rare vasculitis-causing diseases can be found. Among the more frequent ones is VEXAs-syndrome, caused by mutations in UBA1 and found in patients presenting with features of polyarteritis nodosa. Also, monogenic autoinflammatory diseases can predominantly manifest with inflammatory vessel changes. Among these diseases are DADA2, HA20, interferonopathies and Sting-associated vasculopathy with onset in infancy (SAVI).
Conclusion: Many vasculitis belong to the orphan disease, but it is currently increasingly recognized, that among other diseases entities such as monogenic autoinflammatory diseases, patients may present primarily with inflammatory vessel involvement.

VEXAS SYNDROME — A CALL FOR INTERNATIONAL COLLABORATION TO FACILITATE ACCURATE DIAGNOSIS AND FOSTER FUTURE RESEARCH

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Background: VEXAS (ORPHA:596753) syndrome is a rare, potentially fatal, adult-onset disease caused by somatic mutations in the UBA1 gene in hematopoietic progenitor cells. It presents with inflammatory and hematological symptoms in middle and older age, predominantly in males [1]. Multisystem inflammation most commonly affects the skin, eyes, joints, blood vessels, cartilage,

and lungs. Patients may meet classification criteria for several rheumatic diseases and/or hematological disorders [2]. The disease is currently underdiagnosed [3], partly due to a lack of awareness and access to reliable diagnostic methods.
Aim: To initiate international collaboration between Central European countries to raise awareness of VEXAS syndrome, facilitate accurate diagnosis, and harmonize data and sample collection.
Methods: A country delegates from participating countries will be selected. An information leaflet summarizing clinical features of VEXAS syndrome will be distributed to clinicians. Patients with adult-onset, undiagnosed inflammatory conditions and classifiable inflammatory rheumatic diseases, which are a) resistant to standard therapy, b) associated with hematologic disorders or c) associated with atypical inflammatory manifestations, will be considered for UBA1 testing. A simple core set datasheet will be completed for every patient with a clinically suspicious phenotype. Data and biologic sample collection from patients with proven UBA1 mutations will be performed uniformly at participating sites. Biological material will be stored in the Institute of Rheumatology bio-bank, based on a uniform protocol of collection and processing.
Discussion: International collaboration is indispensable to promote research of rare diseases, such as VEXAS syndrome. Increased awareness will improve diagnosis and facilitate treatment of individual patients. Analysis of laboratory and clinical features of patients with suspicious phenotype with and without UBA1 mutations will identify disease-specific manifestations. Data collected will be used for formulation and validation of classification criteria in the future. Harmonized collection of data and biologic samples from patients with UBA1 mutations will simplify future research collaboration.
Conclusion: The newly recognized VEXAS syndrome provides a unique opportunity for international collaboration between Central European countries, potentially leading to improved diagnosis, treatment, and prognosis of patients, as well as a better understanding of the disease.
Acknowledgements: Supported by Ministry of Health of the Czech Republic, grant nr. NU23-10-00160, and BBMRICZ LM2023033.

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TRANSITION

DECREASING FRICTION IN "RHEUM-ADULTING". IS THERE A MAGLEV OPTION?

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Background: Changing from pediatric to adult rheumatologic care is a critical point in the life of the patients. Research has shown that achieving readiness and successful transfer is a prolonged process involving multiple stakeholders: the patients, the parents, and the providers. Numerous reports from larger centers have focused on recommendations for an optimal transfer. Those include suggestions for transition policies, measuring readiness, transition coordinator availability, "handing-over" visits, or having a specific adolescent and young adult clinic bridging this critical period of the patient's life.
Aim: Identification of a core set of easily applicable steps even with limited resources.
Methods: We have reviewed the available literature on PubMed regarding adolescent transitioning to adult medical care preferentially in rheumatology and identified high-yield items.
Results and Discussion: The pediatric rheumatology service carries a lot of weight to achieve successful transfer. Nevertheless, the cornerstone of this goal is self-advocacy closely linked to adulting, the act or practice of attending to the ordinary tasks required of a responsible adult. A written transition policy has been reported to be beneficial but the process itself needs to be personalized. Detailed expectations based on age and maturity can help to "grow up" to this challenge over time. Office visit recommendations could be templated based on underlying diagnosis groups and logged by the patient for easier adherence and continuity. The same document might

even serve as a summary when changing providers. The division or hospital webpage could offer available adult rheumatology providers based on various areas in the country and could point to appropriate resources of health care insurance applicable based on country policies. Video conferencing platforms could serve during new patient visits by the adult provider as needed in the case of complicated patients or if requested by the patient. Following up with first-visit attendance with the adult provider could help avoid lapses in care.
Conclusion: Changing medical caretakers is a potentially perilous time in the lives of adolescents and young adults with chronic conditions. By implementing center-specific but proven policies it might be possible to avoid disease flares and lapse in care.

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TRANSITION CARE PROGRAMME FOR CHRONIC RHEUMATIC DISEASES IS STILL A CHALLENGE: EVIDENCE FROM THE 2023 ERN-RECONNET TRANSITION OF CARE TASK FORCE SURVEY

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Background: European Reference Networks (ERNs) address the complexities of rare diseases by connecting healthcare providers (HCPs) across Europe. ERNs aim to facilitate discussions, review diagnoses, conduct research, and establish treatment guidelines. ERN ReCONNET focuses on rare connective tissue and musculoskeletal diseases. Despite these initiatives, challenges persist in transitioning care, especially for paediatric-onset rare diseases.
Aim: To obtain a snapshot of the transitional care programme for rheumatic diseases across Europe
Methods: To assess transitional care standards within ERN ReCONNET, in September 2023, a Transition of Care Task Force comprising of expert clinicians, patient advocates, and coordination team members was formed in 2023. The task force developed a 45-item survey on the EUSURVEY platform to assess transitional care practices and opinions. Ethical approval was not required. In November 2023, an offcial collaboration between ERN ReCONNET and ERN RITA facilitated distribution of the survey to relevant centers. The survey was available to be filled online from 27 December 2023 till 15 March 2024.
Results: Sixty-seven responses were collected from 59 centers across 20 European countries. Respondents included adult and paediatric rheumatologists, internal medicine specialists, and geneticists. Transition policies varied among centers, but 29 (43%) respondents claimed to have a formal process. Designated staff members mainly comprised doctors overseeing transition coordination. Thirty (44%) respondents claim to follow clinical guidelines, 18 (27%) reported lacking awareness or formal procedures. Paediatric rheumatologists were often identified as key figures in initiating transition processes. Joint clinics involving both adult and paediatric HCPs were available in 21 centers. The age of patients for starting the transition of care was identified to be 15-18 years old for most of the respondents (n = 37, 63%). Patient opinion was a key factor for transition for only two respondents.
Conclusion: The survey revealed heterogeneity in transition practices and resources across ERN ReCONNET centers. Challenges in patient identification, readiness evaluation, and coordination were made evident. Lack of guidelines and engagement from adult centers posed significant obstacles. Despite these challenges, respondents generally perceived the efficacy of ongoing tran-

sition processes positively. The point of view of patients to confirm the efficacy of the program remains an unmet need.

GOOD CLINICAL PRACTICE IN TRANSITION OF CHILDHOOD-ONSET SYSTEMIC LUPUS ERYTHEMATOSUS (CSLE) PATIENTS FROM PEDIATRIC TO ADULT RHEUMATOLOGY CARE

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Background: The importance of transition of cSLE patients from pediatric to adult rheumatology care is twofold. First, transition is a pivotal process that may affect different aspects of patients' disease coping. Second, it represents a unique opportunity to collect data relevant to the impact of the disease during childhood that can serve as predictors of future disease outcomes.
Aim: To analyze a group of cSLE patients transitioned to adult care in our tertiary lupus center.
Methods: In our center, patients with cSLE are transitioned to adult care after they have reached 18 years of age. At that time, the patient is seen by their pediatric rheumatologist, immediately followed by the adult rheumatologist. The pediatric rheumatologist prepares an overview of the disease course which serves as a basis for a consultation between the pediatric and adult rheumatologist. The following data are retrospectively retrieved at diagnosis (or first visit) and transition: sociodemographics and classification criteria according to ACR-1997, SLICC-2012 and ACR/EULAR-2019. Parameters necessary to calculate the SLEDAI-2000 index and the SLICC/ACR damage index are retrieved at an annual basis, as well as the use of immunosupressants.
Results: We have identified a total of 88 patients (12 males, 76 females), born between 1970 and 2003 with cSLE that transitioned from pediatric to adult care. Data loss was associated with continuation of follow-up at another hospital or even loss of administrative tracking (change in surname in females or follow-up prior to the introduction of the computer-based system in our institution).
Discussion: Patients with cSLE represent a unique population that deserves special care due to the multifaceted nature of the disease, higher expected damage accrual compared to patients with adult-onset SLE, as well as a high psychosocial burden. Loss to follow-up should be minimized due to its potential impact on adverse disease outcomes.
Conclusions: Efforts in transitioning cSLE patients should be focused on identifying obstacles toward continuous and regular follow-up of SLE patients in the post-transition period.

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TRANSITION-RELATED OUTCOMES AMONG A COHORT OF PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS

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Introduction: A major goal in juvenile idiopathic arthritis (JIA) long-term management is to ensure a successful transition to adult age. This study aims to assess transition outcomes in a group of JIA patients during their passage from pediatric to adult healthcare assistances at a single center. Method: This is a cross-sectional study. All patients with JIA undergoing transition from the Pediatric Rheumatology Service of the IRCCS "Burlo Garofolo" Hospital, Trieste, to the adult Rheumatology Service of "Santa Maria della Misericordia" Hospital, Udine, between 2017 and 2022, were enrolled. Clinical and laboratory data were collected. A semi-structured survey exploring patients' satisfaction was distributed through email. Numerical variables were compared using the Student's t-test or Mann-Whitney test. Categorical variables were compared with the Fisher's exact test.

Results: We recruited 36 patients (26 female, 72.2%): 9 with polyarticular course JIA, 13 oligoarticular, 8 psoriatic arthritis, 3 systemic JIA, and 3 enthesitis-related arthritis. Mean age at transition was 18.6 (Q1–Q3, 18.3–19.1). JADAS-27 score significantly decreased after the transition, with a mean difference of 2.6 ($p = 0.014$). No patients were lost to follow-up and in 8 out of 36 (22.2%) a step-up therapy was needed within the first 12 months. Among these, no correlation was found with JIA subtype, age at onset, type of involved joints and other variables explored. Finally, the 15 patients who answered the survey (response rate 50%) were satisfied about the transition process.
Conclusions: This study described a real life transition experience from pediatric to adult rheumatology care, showing good transition outcome measures, with no patients lost to follow-up and reduction of JADAS-27 score after completing the process.

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PREGNANCY AND REPRODUCTIVE HEALTH IN INFLAMMATORY RHEUMATIC DISEASES (HR)

ANTIPHOSPHOLIPID SYNDROME AND PREGNANCY

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Obstetric antiphospholipid syndrome (OAPS) represents a form of antiphospholipid syndrome characterized by recurrent pregnancy miscarriages, fetal death, and manifestations of placental insufficiency, which is accompanied by the presence of antiphospholipid autoantibodies (aPL): anticardiolipin antibodies (aCL), antiβ2 glycoprotein 1 antibody, and circulating lupus anticoagulant (LA)
In obstetric antiphospholipid syndrome, the main pathological findings include impaired remodeling of spiral arteries, inflammation of the decidua with neutrophil infiltration, local production of tumor necrosis factor alpha (TNF-α), deposition of complement split products, and placental infarction. Antiphospholipid antibodies have both a direct harmful effect on the embryo and an impact on the placenta, causing a pro-inflammatory state.
The clinical features of the disease include, most often, recurrent miscarriages, preeclampsia, stillbirth, and fetal growth restriction.
Risk factors for adverse outcomes in OAPS include previous thrombosis, double and triple aPL positivity, and lupus anticoagulant positivity.
Standard treatment for OAPS therapy includes low-molecular-weight heparin and low-dose aspirin. However, approximately 20% of OAPS patients are considered refractory and require additional therapy. This may consist of steroids, hydroxychloroquine, immunoglobulins, TNF-α inhibitors, statins, eculizumab, and plasmapheresis.

Keywords: obstetric antiphospholipid syndrome; antiphospholipid antibodies; pregnancy morbidity

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REPRODUCTIVE HEALTH IN MEN WITH INFLAMMATORY RHEUMATIC DISEASES

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Reproductive health and family planning may pose challenges for patients with inflammatory rheumatic diseases. Compared to studies in women, available data in men is scarce. The nature of inflammatory rheumatic disease and treatment can affect male sexual function and intimate relationships, fertility and gonadal function, contraception and family planning.

Erectile dysfunction may be associated with endothelial dysfunction, elevated pro-inflammatory cytokines such as TNF-α and certain medications and comorbidities. The frequency and severity of fertility disorders depend on the underlying disease as well as the treatment. Hypogonadism, antibodies to sperm and sperm disorders occur frequently in patients with systemic lupus erythematosus. Also, cyclophosphamide therapy has a clear impact on gonadal function.
Gonadal dysfunction in patients with rheumatoid arthritis may be associated with the disease activity or immune-mediated. Sulfasalazine, and less likely methotrexate may cause transient infertility, whereas alkylating agents such as cyclophosphamide may lead to permanent changes. Men with inflammatory arthritis who are affected before or during the peak of their reproductive age are more likely to experience fertility disorders and have fewer children compared to men who develop the disease later.
In family planning, preconception treatment choices are focused on preserving fertility and excluding teratogenicity. Among biological therapies TNF-α inhibitors and rituximab are recommended, while endorsement for other biological drugs and Janus kinase inhibitors is limited due to a lack of research. According to available data, treatment of the underlying disease in men with inflammatory rheumatic diseases does not cause congenital malformations in offspring, except for the preconception use of cyclophosphamide. Sperm cryopreservation should be considered as an effective options for preserving fertility in men undergoing cytotoxic therapy.
Men with inflammatory rheumatic diseases have specific needs, therefore a targeted healthcare strategy is recommended.

Conflict of interest statement:
No conflicts of interest.

SSA-ANTIBODIES IN SYSTEMIC AUTOIMMUNE DISEASES AND PREGNANCY

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Background: Anti-Ro/SS-A antibodies are among the most frequently detected antibodies in the sera of patients with systemic autoimmune diseases. Traditionally, together with anti-La/SS-B antibodies, they are mostly associated with Sjögren's syndrome (SjS) (in 60% of cases). Furthermore, these antibodies are often (30% of cases) present in patients with systemic lupus erythematosus (SLE). They are also found in other systemic connective tissue diseases, as well as neoplasia and infections.
Aim: To make an insight into the so far published data on SSA-antibodies and their clinical implications.
Discussion: According to data from various studies, the prevalence of SS-A antibodies in the population is 0.5–2.7%. Anti-SS-A antibodies react with one of two antigens, Ro52 and Ro60, named after their molecular weight. Ro52 (also called TRIM21) is found in the cell's cytoplasm and is believed to participate in the regulation of inflammatory processes. Ro60 (also called TROVE2) is found in the nucleus and plays a role in the regulation of transcription and stability of messenger ribonucleic acid (mRNA). It is also associated with cell survival after ultraviolet radiation.
Recently published studies examined differences in the clinical manifestations of autoimmune diseases depending on the presence of anti-Ro52 and/or anti-Ro60 antibodies, and described different phenotypes of SjS, SLE and neonatal lupus, as well as systemic sclerosis (SScl) and inflammatory myositis. Antibodies directed at Ro52 (TRIM21) are associated with a more severe clinical presentation in patients with SjS, development of interstitial lung disease in patients with SScl and renal damage in SLE, and a weaker response to immunosuppressive therapy in patients with myositis.
The association with the development of congenital heart block (CHB) is well known. After the 12th week of pregnancy, anti-SSA antibodies can cross the placenta and damage the developing fetal tissue, leading to CHB and transient neonatal lupus. Routine weekly echocardiography is frequently recommended, but the surveillance of these pregnancies is still controversial.
Conclusion: Data from the literature indicate the importance of determining both types of anti-Ro/SSA antibodies; anti-Ro52 and anti-Ro60, considering their role in predicting the course and prognosis of the disease and response to treatment.

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REPRODUCTIVE HEALTH OF WOMEN WITH SYSTEMIC AUTOIMMUNE DISEASES

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A female organism shows an intense immune response when exposed to foreign pathogens, but can also tolerate fetal development in utero. However, this strong immunological arrangement can become unbalanced and lead to the development of an autoimmune disease.
In addition to their role in sex differentiation, sex hormones are one of the key stimulators in the development of the immune system. Both the cells of innate and acquired immunity make their extracellular and intracellular receptors available for sex hormone antigens. This stimulation leads to cell proliferation and potentiates the formation or activation of various inflammatory molecules.
While oestrogens tend to stimulate inflammatory reactions, androgens and progesterone have predominantly immunosuppressive and anti-inflammatory effects. In patients with autoimmune diseases, the androgen level is usually reduced, with increased androgens being converted into oestrogens in the inflamed tissue (intracrinology).
Natural changes in the female body that are associated with significant hormonal fluctuations, hormone replacement therapies and other treatments that involve high hormone levels, such as artificial insemination, contraception or sex reassignment, carry the risk of developing or exacerbating an existing autoimmune disease.
Future clinical trials should focus on the therapeutic use of androgens and progesterone or tissue-specific estrogen complexes in modulating the pathologic autoimmune response.

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PREGNANCY OUTCOMES IN PATIENTS WITH INFLAMMATORY RHEUMATIC DISEASES TREATED WITH BIOLOGICS: A TERTIARY CENTRE EXPERIENCE

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Background: Biologics are often used for treatment of inflammatory rheumatic diseases in women in their childbearing age. According to current knowledge, the use of TNF inhibitors is considered safe in the first and second trimester of pregnancy.
Aim: The goal of our research was to analyse data on the course and outcome of pregnancies in women treated with biologics.
Methods: The data was obtained by searching the database of the Department for Rheumatology and Clinical Immunology. The medical documentation of 10 pregnant women treated with biologics due to rheumatoid arthritis (n = 5), spondyloarthritis (n = 3), psoriatic arthritis (n = 1) and juvenile idiopathic arthritis (n = 1) during the period from 2013 to 2023 was analysed. Observed parameters included the time of drug exposure, concomitant therapy, outcome and duration of pregnancy, mode of delivery, birth weight and the presence of fetal malformations.
Results: A total of 18 pregnancies was investigated: with certolizumab 13, adalimumab 2, tocilizumab 2, etanercept 1. Concomitant therapy included low-dose prednisolone, hydroxychloroquine, sulfasalazine, methotrexate. The average age of women at the time of conception was 32 (range from 24 to 41). Due to the high activity of the disease, certolizumab was introduced to two patients in the second trimester, while the rest of the patients became pregnant on certolizumab therapy, which was continued during pregnancy. The average duration of certolizumab administration during pregnancy was 24 weeks. Three spontaneous abortions were recorded in the first trimester in patients treated with tocilizumab, etanercept and certolizumab. The rest of the

pregnancies were normal, with no recorded complications, completed on time. Ten pregnancies were terminated by caesarean section, and five by spontaneous delivery. All newborns, except for one child from a twin pregnancy, were of normal birth weight (> 2500 g). There were no congenital malformations. The child of a mother treated with tocilizumab in the first trimester developed pneumonia in the second month of life.

Conclusions: Our data do not differ from data from the available literature. The use of certolizumab during pregnancy had no effect on the pregnancy outcome, birth weight or the occurrence of malformations.

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TOPICS IN PEDIATRIC RHEUMATOLOGY

BIOLOGICAL DIFFERENTIATION OF JIA AND MOVING TOWARDS A NEW NOMENCLATURE

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Chronic inflammatory arthritis in chidlhood (i.e., juvenile idiopathic arthritis, JIA) is one of the most common chronic diseases in pediatric population with heterogeneous clinical presentation, therapeutic response and course. Current classification system of JIA is pragmatic and mainly based on clinical phenotype and basic biologic factors such as common genetic origins (presence or absence of HLA-B27) and presence or absence of autoantibodies (rheumatoid factor). Most patients in the early-onset age group have an oligoarticular phenotype, are commonly antinuclear antibody positive and have the highest risk for extraarticular manifestations such as chronic anterior uveitis. This group seems to be unique to childhood with no corresponding clinical correlates in adults. Other forms of JIA exhibit high clinical and genetic similarity to chronic arthritis of adult onset, but this has not been reflected in the terminological overlap between childhood- and adult-onset arthritis.

Accumulating clinical, genetic and biologic data recognize distinct forms of chronic inflammatory arthritis across all ages necessitating a new approach to defining biological categories within chronic arthritis. Moreover, an ongoing research and clinical trials on the effectiveness of disease-modifying anti-rheumatic drugs and biologic therapies in distinct forms of chronic arthritis are providing insight into a more personalized approach to treatment. Redefining the classification across ages could further allow extrapolation of knowledge from studies in adults and improve access of novel therapies for children with chronic arthritis. An additional insight on biologic mechanism of chronic arthritis in children is increasingly provided also by a growing number of inborn errors of immunity that can mimic JIA and can be misdiagnosed as JIA.

AUTOINFLAMMATORY DISEASES — RECOMMENDATIONS AND REAL WORLD DATA FROM CECR

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Background: Autoinflammatory diseases mediated by Interleukin-1 (IL-1 AID) constitute the largest category within this group. Notably, significant disparities exist between the recommendations for diagnosis, treatment, and patient follow-up and the actual clinical practices.
Aim: Our aim was to examine the day-to-day clinical practices regarding the diagnosis, treatment, and follow-up of IL-1 AID patients in Central and Eastern Europe and compare them with the 2021 recommendations of the European Alliance of Associations for Rheumatology (EULAR)/ American College of Rheumatology (ACR).
Methods: In 2023, a collaborative meeting convened representatives from 10 Central and Eastern European countries to deliberate on the current clinical practices related to IL-1 AID: Croatia, Czech Republic, Hungary, Latvia, Lithuania, Poland, Romania, Serbia, Slovakia, and Slovenia.
Results: Except for Latvia and Lithuania, specialized centers for diagnosing and treating IL-1 AID with multidisciplinary teams exist in all surveyed countries. Various countries offer massive parallel sequencing panels for autoinflammatory diseases, with turnaround times for results typically ranging from 3 to 6 months. In Slovenia, Hungary, Romania, and Latvia, the waiting period is relatively brief, typically ranging from 1 to 3 months for results from the panel. Public health insurance covers the costs of genetic analyses in most countries. Access to disease-specific laboratory assessments, such as S100 proteins, is limited. None of the countries surveyed offer the ability to determine mevalonate kinase enzyme activity or measure IL-1 in serum. Both anakinra and canakinumab are accessible in all countries except Latvia, where canakinumab is unavailable. Notably, the Czech Republic, Croatia, and Slovenia utilize fewer patient-reported outcomes and disease assessment tools in their routine practices compared to other countries. Structured transition programs for IL-1 AID patients are lacking in most countries, although Czech Republic, Slovenia, and Hungary offer pediatricians the option to continue monitoring patients as they transition into adulthood. The starting age of the transition process varies, but in most countries, it generally commences later, usually around 18 years of age or later.
Conclusions: Central and Eastern European countries demonstrate potential for adhering to the 2021 EULAR/ACR recommendations for IL-1 AID. However, determining the prevalence and incidence of these diseases in this region remains a persistent challenge for future research.

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DEFICIENCY OF ADENOSINE DEAMINASE 2 (DADA2) — FIRST CASES IN SLOVAKIA

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Background: DADA2 is a monogenic autoinflammatory disease first identified as the cause of systemic vasculitis resembling polyarteritis nodosa with fever, livedo racemosa, peripheral necrosis and early-onset stroke. With 378 published cases, DADA2 is a rare disease, known cases represent only a fraction of the estimated 35,000 affected individuals worldwide.
Aim: To present the first 3 Slovak patients with genetically and biochemically confirmed DADA2.
Case characteristics: Patient 1 presented with acute haemolytic anaemia at 8 months (M) of age, multiform exanthema (11 M) and arthralgia, fever, splenomegaly and livedo racemosa (21 M). First treated for systemic juvenile idiopathic arthritis, clinical condition and inflammatory parameters (CRP 50–110 mg/L) improved with high-dose corticosteroids (CS), add-on therapy with methotrexate and later cyclosporine A did not enable CS dose reduction. At age 2.5 years, 2 heterozygous variants (pathogenic c.140G>C and new c.881+1G>C) in the ADA2 gene and absence of ADA2 activity (–1 U/L) were confirmed. Treatment with etanercept lead to clinical inactivity and enabled weaning of CS.
Patient 2 presented at 4.4 years with suspected acute mesencephalic ischaemia, intermittent fevers, livedo racemosa, splenomegaly and lymphadenopathy. Permanently elevated CRP (50–

60 mg/L) and B-lymphopenia with hypogamaglobulinaemia were noted, regular IVIG substitutions were indicated for suspected CVID. At 5.3 years, the pathogenic variant c.506G>A and a VUS c.505C>T in the ADA2 gene and low ADA2 activity (3.1 U/L) were confirmed. Treatment with etanercept resulted in decreased inflammatory activity.
Patient 3 was first hospitalized at 2 M for loss of consciousness due to suspected Blackfan-Diamond anaemia (Hb 51 g/L) and required multiple blood transfusions. At 7 M, the homozygous pathogenic variant c.1196G>A in the ADA2 gene and absent ADA2 activity (–11.2 U/L) were confirmed. Etanercept did not improve severe anaemia and the patient underwent peripheral haematopoietic stem cell transplantation (2.2 years) and due to graft failure re-transplantation (2.9 years) that normalized his ADA2 activity.
Conclusion: The first Slovak DADA2 patients illustrate 3 very distinct phenotypes of DADA2 that required different diagnostic and therapeutic approaches. Undiagnosed patients can be expected in our populations. Our experience demonstrates the need for a low threshold of clinical suspicion and interdisciplinary care.

VACCINATION RECOMMENDATIONS FOR PATIENTS WITH RHEUMATIC DISEASES

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Vaccinations are the most effective preventive measure against infection. Patients with rheumatic diseases are often immunocompromised because of the disease itself and/or because of the therapy they are receiving. Infections present a major threat to their health. The degree of immunosuppression depends mainly on the treatment they are receiving. The new update recommendations for vaccinations in children with autoimmune inflammatory rheumatic diseases were published recently [1]. The last update on recommendations for adult patients with rheumatic diseases was published in 2019 [2]. In general, there are no major safety concerns for vaccination with non-live vaccines, including vaccines for SARS-CoV-2, regardless of the therapy, but live attenuated vaccines should be withheld in patients treated with immunosuppressive therapies. Uncertainty about safety, immunogenicity, and long-term efficacy, risk of disease flare and risk of disseminated infection following vaccinations with live attenuated vaccines should be taken into account in planning the vaccinations in these patients. However in children, in a case of a high risk of infection, vaccination can be considered on a case-to-case basis. MMR booster is recommended for children treated with methotrexate and should be considered also in patients treated with biologics. A recent multicentre retrospective study conducted by PRES Vaccination working party provided some evidence about the safety of booster MMR. A multicentre prospective study on MMR booster is ongoing.
Vaccine coverage in children with rheumatic diseases treated with immunomodulatory therapy is suboptimal for vaccines included in National Immunisation Programs (NIP) and even worse for influenza and other vaccines not included in NIP. Treating physicians have a major role in improving vaccination coverage for their patients especially for influenza every winter season. The vaccination status and indications for vaccinations in patients with rheumatic diseases should be assessed yearly by the treating physician or rheumatology team [1, 2].

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FUTURE OF RHEUMATOLOGY (CZ)

LOOKING FORWARD: WHAT'S NEXT IN RHEUMATOLOGY?

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The field of rheumatology is evolving rapidly, driven by advancements in scientific research, a growing understanding of disease pathogenesis, and improved diagnostic and therapeutic strategies. The integration of novel biomarkers, artificial intelligence, precision medicine, and advanced imaging techniques is enhancing diagnostic accuracy and personalized treatment approaches. This presentation aims to provide an overview of future directions in rheumatology, focusing on the increasing prevalence of rheumatic diseases due to rising life expectancy, innovative treatments, and the challenges posed by the shortage of rheumatologists. Digital health, including telemedicine, mobile health apps, and wearable technology, is becoming integral to patient care, enhancing monitoring, adherence, and overall management of chronic rheumatic diseases. These digital tools promise to streamline patient management. To conclude, I strongly believe that the future of rheumatology is bright with numerous advancements on the horizon that promise to improve the attractiveness of the specialty, but also standard of care and patient outcomes.

ARTIFICIAL INTELLIGENCE IN RHEUMATOLOGY — REALITY AND FUTURE PROSPECTS

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Artificial Intelligence (AI) and machine learning will be involved in various areas of medicine. In rheumatology, AI could be used to study the pathogenesis of diseases. A great amount of data is derived from -omics studies, which would be analyzed with the help of AI. In addition, Big Data studies have been ongoing related to various rheumatic and musculoskeletal diseases (RMDs). AI might help imaging and laboratory diagnostics, drug development aiming at personalized therapy, the development of biomarkers, prediction of disease outcome and various other areas. The realistic future and other future prospects will be discussed in this presentation.

THE ROLE OF PRECISION MEDICINE IN RHEUMATOLOGY

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The term „precision medicine", formerly also „personalised medicine", refers to a personal approach to the treatment and prevention based on an assessment of variability in genetic predisposition, immune processes, external environment and lifestyle. This is particularly important in rheumatology, where many diseases are heterogeneous. By identifying a disease specific subgroup, we can select the treatment that has the greatest chance of effect while also not administering drugs that we know are most likely ineffective and potentially harmful. To do this, we need to know the most detailed characteristics of the pathobiological processes taking place in the patient and an applicable knowledge of the mechanism of action of the drug that will enable us to select it. Some subgroups of rheumatic diseases will be used in the presentation as examples, such as RA or various subtypes of idiopathic inflammatory myopathies (IIM). Current approaches to therapy and prognosis already differ in part between the variants. A number of ongoing clinical trials are taking into account the mechanisms of the disease subtype, which significantly increases the chance of demonstrating the effectiveness of much-needed treatments in diseases where there is a high unmet need. Detailed investigation of autoimmune mechanisms will also allow us to comment on comorbidities and prognosis. We now know that certain autoantibodies define a high probability of cancer-associated disease such as in scleroderma or IIM. It appears that analysis of the detailed spectrum of autoantibodies may refine this association in a significant way. Detection of the presence of other autoantibodies may negate this association. It is clear that with the rapid recognition of ever more detailed aspects of disease pathogenesis, the role of various biomarkers and precision medicine will expand rapidly to the benefit of patients.

GENETIC ASSOCIATION BETWEEN TNF-α POLYMORPHISMS (RS361525, RS1800629, AND RS1799724) AND CLINICAL COURSE OF IDIOPATHIC INFLAMMATORY MYOPATHIES AND OVERLAP SYNDROME

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Background: Dermatomyositis (DM) and polymyositis (PM) are idiopathic inflammatory myopathies (IIMs) characterized by muscle weakness and immune-mediated muscle damage. Although the exact pathogenesis of IIMs is unclear, cytokines like TNF-α are believed to play a significant role.

Aim: This study explores the association between TNF-α gene polymorphisms and the clinical progression of DM, PM, and overlap syndrome (OS).

Methods: We performed a case-control study on TNFA gene polymorphisms in patients with DM, PM, and OS, recruited from the University Hospital in Kraków, Poland, from 2014 to 2020. Genotyping for TNFA polymorphisms (rs361525, rs1800629, and rs1799724) was conducted using PCR and TaqMan assays. Clinical data were collected to assess the relationship between genotypes and disease manifestations. A healthy control group (n = 38), matched for sex was included for comparison. Statistical analyses were employed to determine the significance of these associations.

Results: Among the 56 patients with DM, PM, or OS, notable associations were observed between TNFA polymorphisms and clinical manifestations. The rs1800629 polymorphism was significantly linked to increased disease susceptibility ($p = 0.010$), with a higher frequency of the AG genotype in patients compared to controls. Conversely, rs361525 and rs1799724 polymorphisms showed no significant differences. The rs1800629 AG genotype was associated with interstitial lung disease ($p = 0.024$), while the rs1799724 CT genotype was linked to skin manifestations such as Gottron's sign ($p = 0.030$) and shawl sign ($p = 0.021$). No significant differences were observed for the rs361525 variant.

Discussions: Polymorphisms in the promoter region of the TNF-α gene can influence the level of TNF-α potentially affecting the inflammatory response [1]. The rs1800629 TNF-α promotor polymorphism has been associated several times with the development of autoimmune diseases [2]. Furthermore, a correlation was identified between the rs1800629 TNFA genotype and myositis in adults with an increased disease susceptibility [1]. TNF-α can lead to fever, fatigue, weight loss, anorexia, malaise, however, the reports of the influence of TNF-α polymorphism rs361525 on the transcriptional regulation of TNF have been conflicting [3]

Conclusions: Our results suggest that specific TNFA polymorphisms may affect the clinical course of IIMs. Further studies with larger sample sizes are needed to validate these associations and investigate additional genetic factors.

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2. doi: 10.1186/s40064-016-3197-y.
3. doi: 10.5114/ceji.2018.74873.

MUSCULOSKELETAL MANIFESTATIONS OF METABOLIC DISEASES (SK)

NITISINONE IN THE TREATMENT OF ALKAPTONURIA-RESULTS FROM SONIA STUDY

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Background: Alkaptonuria (AKU) is a rare, genetic, mutisystem, chronic, slowly progressive and disabling disease. AKU is caused by a deficiency in the tyrosine metabolic pathway, causing excessive production and accumulation of homogentisic acid (HGA). No HGA lowering therapy was approved for the treatment of AKU before.

Aim: SONIA 1 study was a pilot, multicentre, randomised dose-response study to investigate the effect of once daily nitisinone on urinary HGA excretion in patients with AKU. Based on the positive results, SONIA 2 study followed, aimed on the safety and efficacy of nitisinone in patients with AKU.

Methods: SONIA 2 study was conducted as a multicentre, open-label, randomised trial. The primary endpoint was to demonstrate superiority of nitisinone (10 mg/day) in patients with AKU compared to control in reducing urinary HGA. The secondary objective was to demonstrate the effect on clinical parameters and to assess the safety of nitisinone treatment. Patients aged 25 years or older with confirmed AKU (total n = 138) were randomly assigned (1:1) to receive oral nitisinone or no treatment.The study demonstrated that nitisinone provides longh-term reduction in serum an urine HGA. There was also a significant decrease of disease progression, as measured by various clinical parameters. Incidence of adverse effects was similar in nitisinone-treated and untreated group.

Conclusion: SONIA 2 study proved the efficacy and safety of nitisinone in the treatment AKU patients. The results from this study played an important role in the process of approval nitisinone for the treatment of AKU by the European Medicine Agency (EMA). EMA finally approved nitisinone 10mg tablets (Orfadin) in 2020. Orfadin became fully reimbursed in Slovakia for the patients with AKU in 2022.

THE EFFECT OF NITISINONE ON BONE MINERAL DENSITY IN PATIENT WITH ALKAPTONURIA

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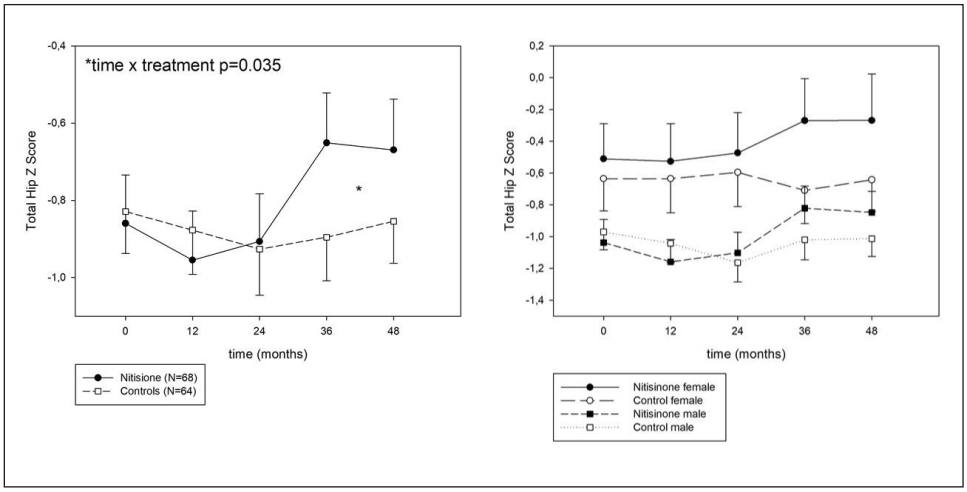
Alkaptonuria (AKU) is an autosomal recessive inherited condition (OMIM#203500) characterized by a lack of homogentisate 1,2 dioxygenase (HGD) activity (EC:1.13.11.5), due to mutations at the HGD gene loci, leading to accumulation of homogentisic acid (HGA). HGA undergoes oxidation via a benzoquinone acetate intermediary, resulting in deposition of melanin-like HGA pigment in joint and spine cartilage, tendons, and ligaments, in a process known as ochronosis. The ochronotic spine becomes rigid and liable to further changes resulting in severe disability. Osteopenia and fractures are common findings in patients with AKU. There is now a potent HGA-lowering therapy in AKU. Nitisinone, an inhibitor of hydroxy-phenylpyruvate dioxygenase (HPPD; EC 1.13.11.27), potently and rapidly decreases HGA [1]. However, prospective data and description of the effect of nitisinone treatment on bone mineral density (BMD) are lacking [2]. The aim of the study was to determine effects of nitisinone on BMD in patients with AKU aged 25 years or older who were randomly assigned to receive either oral nitisinone 10mg daily (n = 68) or no treatment (n = 64). The total hip BMD Z scores were recorded yearly at baseline, 12, 24, 36 and 48 months. At baseline, the treatment and non-treatment groups did not differ in total hip BMD Z scores (–0.86 (0.13) in nitisinone *vs*. –0.83 (0.11) in non-treatment group). There was a significant (F = 2.62, p = 0.035) interaction between the effects of time and treatment on the total hip Z scores (Fig. 1). The difference in the total hip BMD Z score at month 48 compared to baseline tended to be higher in patients on nitisinone compared to untreated patients (0.07 (0.06) in nitisinone *vs*. –0.06 (0.06) in non-treatment group, p = 0.056). Our results demonstrate a modest beneficial effect of 10 mg/day of nitisinone on the BMD in AKU during the relatively limited follow-up time.



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OBESITY, METABOLIC SYNDROME AND MUSCULOSKELETAL MANIFESTATIONS

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Obesity and metabolic syndrome increase the risk for the most prominent musculoskeletal diseases, such as sarcopenic obesity, osteoporosis, tendinopathy, and osteoarthritis, conditions which contribute significantly to patients' disability. The consequent damage and pain associated with these conditions likely develop through low-level systemic inflammation in addition to loading due to obesity, and reduced mobility due to sarcopenia. Muscle mass is a key predictor of longevity in older adults. Since muscle is highly plastic, undergoes regular remodelling and is responsible for the majority of total body glucose utilization, it is a vulnerable tissue in a chronic low-level inflammatory environment, as seen in metabolic dysfunction. Impaired muscle integrity, defined as persistent muscle loss, intramuscular lipid accumulation, or connective tissue deposits increased with obesity are positively correlated with insulin resistance. Impaired muscle integrity is the risk factor for tendinopathy, osteoporosis, and osteoarthritis. Musculoskeletal disorders are common in individuals with type 1 and type 2 diabetes mellitus. Prolonged uncontrolled hyperglycaemia may result in the accumulation of less soluble glycosylated collagen in connective tissues. This in turn alters the structure of extra cellular matrix and collagenase activity. Hyperglycaemia-induced aberrant levels of insulin or insulin growth factors may lead to neuropathic complications, which enhances pain through central sensitization. In obese individuals with type 2 diabetes mellitus increased levels of insulin-like growth factor-1 (IGF-1) may contribute to development of calcification and ossification of ligaments, as seen in diffuse idiopathic skeletal hyperostosis (DISH). Diabetes is associated with numerous musculoskeletal disorders and inefficient control of diabetes may cause persistent musculoskeletal pain over time. Neuropathic joints are commonly observed in the foot and ankle of patients. Diabetic polyneuropathy, limited joint mobility syndrome, adhesive capsulitis, carpal tunnel syndrome, flexor tenosynovitis, and gouty arthritis are among the most other common musculoskeletal manifestations of metabolic and endocrine disorders.

SKELETAL MANIFESTATIONS OF ACROMEGALY

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Acromegaly is rare endocrine disorder affecting many organs in the body, including musculoskeletal system. This presentation is focused on endocrine-mediated osteoporosis caused by acromegaly. RH and insulin-like growth factor-1 (IGF-1) stimulate linear bone growth through complex hormonal interactions and activate epiphyseal prechondrocytes. Through receptor activator of nuclear factor kappaB (RANK), its ligand (RANK-L) and the osteoprotegerin system, GH stimu-

lates the production of osteoprotegerin and its accumulation in the bone matrix. Disruption of this mechanism can lead to specific bone damage. However, the primary concern of bone disease in disorders of GH secretion is the prevention of osteoporotic fractures, so it is important to establish bone quality that better reflects the patient's true predisposition to fracture. Bone structure can be determined by several methods such as bone biopsy, quantitative CT, trabecular bone score (TBS) or 3D-DXA. A clinically usable method that estimates bone quality based on DXA images of the lumbar spine is TBS. TBS in addition to bone mineral density (BMD) is a promising predictor of osteoporotic fracture risk in women with postmenopausal osteopenia. In acromegaly, TBS better defines fracture risk because BMD is normal or even elevated. TBS helps monitor the effect of growth hormone treatment. Despite these findings, TBS should not be used alone, but all fracture risk factors, BMD and bone turnover indicators should be comprehensively considered.

Key words: rowth hormone; acromegaly; bone quality

YOUNG RHEUMATOLOGIST

GLUCOCORTICOIDS IN ANCA-ASSOCIATED VASCULITIS

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Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) represents a group of autoimmune diseases characterized by inflammation and necrosis of small to medium vessels. Among the heterogeneous group of vasculitides, AAVs have traditionally stood out as a primary focus of interest since, despite significant advances in diagnostic and therapeutic approaches, they continue to pose a serious threat to patients due to severe multi-organ involvement, leading to substantial morbidity and mortality.

Glucocorticoids remain a cornerstone in both the induction and maintenance therapy, as their potent anti-inflammatory and immunosuppressive effects are crucial in achieving remission. It is well understood, however, that prolonged glucocorticoid therapy itself carries a risk of substantial long-term morbidity, including increased infection rates, metabolic disturbances, osteoporosis, as well more chronic, albeit less severe adverse effects such as weight gain and skin atrophy, which are often among the chief complaints of patients. Moreover, high dose GC therapy, particularly in the form of i.v. pulses, is also associated with more severe adverse events such as osteonecrosis or thromboembolism and can also induce a range of psychiatric conditions.

The dosage, duration, and cumulative exposure to glucocorticoids have become key focal points in studies evaluating various and emerging treatments. Consequently, the glucocorticoid-sparing effect has become a critical objective of therapeutic advancement, which is particularly evident with the introduction of the complement 5a receptor antagonist, avacopan, where glucocorticoid-sparing is a key feature of its therapeutic profile.

Guidelines on glucocorticoid therapy specifics have evolved over recent years. The results of the PEXIVAS trial have been pivotal in the approach to therapy tapering, leading to current international recommendations that favor faster tapering regimens to improve outcomes. However, even in the 2022 EULAR recommendations, the specifics of dosage, including the utilization of intravenous pulses at the start of therapy, are addressed with uncertainty, and are ultimately left to the attending physician's discretion. In conclusion, analyses of the nuances of glucocorticoid treatment continue, and as more data accumulates into large international registries, clinicians will be better equipped to optimize glucocorticoid use in AAV therapy.

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DIFFERENT PHENOTYPES OF ANTI-MDA-5 MYOSITIS

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Background: Idiopathic inflammatory myopathies are rare connective tissue diseases with different clinical presentations and outcomes. With the discovery of muscle-specific and muscle-associated antibodies serologically based phenotypes were distinguished [1]. Myositis with anti-MDA5 antibodies is often misdiagnosed due to its unique clinical presentation and frequent amyopathic course.

Aim: The study aimed to present the spectrum of symptoms and different courses of anti-MDA-5 myopathy, based on the cases of patients hospitalized in one Polish center. Based on the presented cases, the complex landscape of MDA5 syndrome and available therapeutic options were explored.

Methods: Digital database of USK-WAM Hospital in Lodz, Poland was screened to identify patients with anti-MDA5-positve myositis. Medical records of 3 identified patients were analyzed. Data on the initial and following symptoms, administered treatment and outcomes was gathered. PUBMED database was thoroughly searched to provide a review of current knowledge on anti-MDA5 myositis.

Results: Each of our patients with anti-MDA5-positive dermatomyositis presented characteristic yet slightly different scope of symptoms. All of the patients presented with typical skin lesions. In patient 1 at the onset of the disease arthritis, muscle weakness and xerostomia occurred, followed by interstitial lung disease with pneumomediastinum. In this patient remission was particularly difficult to achieve. In the patient 2 the disease started from organizing pneumonia and fever. For the patient 3 cutaneous ulcerations were the most bothersome symptom, along with polyarthritis. Despite muscle weakness, muscles enzymes were within the normal ranges or only slightly elevated. In all of the patients posing the proper diagnosis was challenging and delayed.

Discussion: Dermatomyositis with anti-MDA5 antibodies in usually amyopathic, with a high risk of severe rapidly progressive interstitial lung disease (RP-ILD), frequent polyarthritis, general symptoms and prominent cutaneous lesions such as skin ulcerations and palmar papules [2]. According to the literature, 3 clusters can be identified — RP-ILD cluster with the worst prognosis, rheumatoid cluster with the most favorable outcome and vasculopathic cluster with intermediate prognosis [3].

Conclusions: Anti-MDA5 myositis differs from other myopathies due to its unique clinical presentation. Raising awareness about this rare subtype can lead to earlier diagnosis and more effective treatment.

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2. doi: 10.3389/fimmu.2021.773352.
3. doi: 10.1212/WNL.0000000000009727.

IGG4-RD OR ANCA-VASCULITIS?

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We present a case of a 65-year-old female patient referred to the rheumatology clinic due to elevated ANA levels. At presentation, she reported mild burning in the left eye, night sweats, unintentional weight loss of 4 kg, and increased inflammatory markers. Initial treatment with glucocorticoids (prednisolone 25 mg/d) initiated by the general doctor resulted in a temporary reduction of inflammation. The patient had a history of chronic rhinitis for 8 years, characterized by dark red nasal secretions and progressive hearing loss, necessitating hearing aids. Notably, she had previously experienced episcleritis and had a history of COPD I. Family history revealed one sister with large vessel vasculitis and another with Morbus Ormond.

Physical examination showed no synovial swelling, but the patient reported arthralgias in multiple joints. Laboratory tests indicated elevated CRP (82 mg/L) and abnormal immunological parameters, including MPO-ANCA, p-ANCA, ANA, and IgG4 levels. A nasal mucosa biopsy revealed

fibrotic areas and vasculitic changes in small vessels. Imaging studies demonstrated ground-glass opacities in the lungs, enlarged hilar lymph nodes, and hypodense renal changes. A targeted renal biopsy confirmed granulomatous vasculitis and lymphoplasma cell-rich tubulointerstitial nephritis, with increased IgG4-positive plasma cells and an IgG4/IgG ratio of > 40%.
These findings indicated a rare overlap of two pathologies: IgG4-related disease (IgG4-RD) with renal involvement and ANCA-associated vasculitis, characterized by epithelioid granulomas. Induction therapy with rituximab and glucocorticoids resulted in rapid clinical and laboratory remission, which was sustained during glucocorticoid tapering.
This case exemplifies the coexistence of IgG4-RD and ANCA-associated vasculitis. While granulomatous lesions in renal biopsies are typically associated with PR3 vasculitis, they can also occur in MPO vasculitis. The relationship between these conditions remains unclear, and further research is needed to determine the implications of ANCA positivity in IgG4-RD. This case highlights the importance of considering concurrent ANCA vasculitis in patients presenting with IgG4-RD.

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FREQUENCY OF SPONTANEOUS REPORTS OF MAJOR ADVERSE CARDIOVASCULAR EVENTS AND VENOUS THROMBOEMBOLISM IN PATIENTS ON JAK INHIBITORS COMPARED TO ADALIMUMAB

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Background: An increased risk of major adverse cardiovascular events (MACE) and venous thromboembolism (VTE) in patients receiving JAK inhibitors for the treatment of rheumatic diseases has been demonstrated in previous studies.
AIM To analyse the frequency of suspected adverse reactions (ADRs) to JAK inhibitors (MACE and VTE) in comparison with adalimumab, in the EudraVigilance database.
Methods: Analysis of reported suspected ADRs related to three JAK inhibitors tofacitinib, baricitinib and upadacitinib, as well as a TNF-α inhibitor adalimumab has been conducted. Data have been collected using the online EudraVigilance database for the time interval from 2013 to 2023, and an overall number of 26067 ADRs for adalimumab and 8742 for JAK inhibitors group has been reported. Frequency of specific ADRs (acute myocardial infarction (AIM), stroke, pulmonary embolism, deep vein thrombosis (DVT)) has been evaluated throughout all medication groups, as well as proportions of the specific ADRs compared to the total annual number of ADRs for each drug. Proportions were compared between JAK inhibitors and adalimumab.
Results: The proportion of stroke in the JAK inhibitor group was not statistically different compared to the adalimumab group, whereas the proportion of reported AIM (66/8742), pulmonary embolism (343/8742) and deep vein thrombosis (174/8742) in the JAK inhibitor group was higher compared to adalimumab (220, 155 and 68/28067 respectively).
Discussion: The results of this analysis are in accordance with the recommendations issued by the European Medicines Agency (EMA), regarding an increased risk of PE in patients treated with tofacitinib and baricitinib. A potentially increased risk of VTE in patients with rheumatic diseases treated with JAK inhibitors has been described in a recent meta-analysis, implying a necessity for caution in patients with higher risk for VTE. The frequency of AIM and stroke as a MACE was not different between the two groups, but in the light of recent research and registry data, a subgroup analysis of different JAK inhibitors seems to be necessary.
Conclusions: These findings underscore the need for careful evaluation of patients with rheumatic diseases treated with JAK inhibitors, as well as close follow-up for potential development of additional VTE and cardiovascular risk factors.

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ASSOCIATIONS BETWEEN GENOTYPE AND LOWER DHEAS LEVELS IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Although decreased production of adrenal androgens has been found in female patients with rheumatoid arthritis (RA), the underlying mechanisms abnormality are not yet completely understood.
Aim: Our study aimed to assess the role of genetic factors in decreased dehydroepiandrosterone sulfate (DHEAS) levels in female RA patients.
Methods: Single-nucleotide polymorphisms (SNPs) in ZKSCAN5 (rs11761528), SULT2A1 (rs2637125), HHEX (rs2497306), and ARPC1A (rs740160) genes were examined in 448 female RA patients and 648 healthy female controls. In subjects with available serum samples (112 RA patients and 91 controls), serum DHEAS concentrations were measured. Statistical analysis of the obtained data was performed using IBM SPSS Statistics 19 software.
Results: No statistically significant differences have been found in the allele frequencies in DHEAS-related loci in RA patients and controls. RA patients had significantly lower serum DHEAS concentrations compared to controls. After adjustments for age and glucocorticoid dose, lower serum DHEAS concentrations were detected in RA patients compared to controls ($p = 0.006$). The cumulative number of alleles associated with lower DHEAS within studied genes present in each individual negatively correlated with DHEAS levels in RA patients, but not in controls. Linear regression analysis showed an association of the ZKSCAN5 gene T allele with lower and the ARPC1A gene T allele with higher DHEAS levels in RA patients but not in the control group.
Discussion: In line with other studies, we confirmed lower DHEAS levels in female RA subjects compared with controls, indicating association of RA with decreased adrenal androgen production [1, 2]. We observed a significant effect of ZKSCAN5 and ARPC1A polymorphisms on serum DHEAS levels in RA patients which is in agreement with meta-analysis of Zhai et al. [3].
Conclusion: Our findings suggest that complex interactions exist between genotype and adrenal androgen hypofunction in RA.

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EFFECTS OF JAK INHIBITION ON ARTERIAL INFLAMMATION AND BONE IN RHEUMATOID ARTHRITIS

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Background: Rheumatoid arthritis (RA) has been associated with increased cardiovascular (CV) risk and osteoporosis. JAK inhibitors might have beneficial effects on the vasculature and bone.
Aim: We wished to assess the effects of JAK inhibition on vascular and bone status in RA.
Methods: Thirty RA patients were treated with tofacitinib (5 or 10 mg BID) for 12-months. We assessed DAS28, ESR, CRP, RF, anti-CCP, lipid levels and bone biomarkers at baseline, months 6 and 12. DXA and QCT scans were performed to determine areal and volumetric BMD, respectively. ^{18}FDG-PET/CT was used to determine vascular and synovial inflammation. Vascular pathophysiology was assessed by ultrasound (cIMT, PWV, FMD).
Results: Tofacitinib significantly reduced vascular and synovial inflammation as determined by ^{18}FDG-PET/CT. Articular SUVmeansyn ($p = 0.010$), SUVmeansyn/liv ($p = 0.001$) and aortic TBRmaxvasc ($p < 0.001$) significantly decreased over time. Synovial inflammation as determined by PET/CT variably and positively associated with aCCP, RF, CRP, ApoB, lipoprotein A (LpA), IMT and PWV. Articular SUV values were independently associated with CRP, ApoB, LpA,

IMT and PWV, while aortic TBRmaxvasc was determined by HAQ and PWV. No significant changes were observed in the areal BMD of femoral neck and vertebrae. According to bone biomarkers CTX levels significantly decreased from baseline to 6 months ($p = 0.009$) and 12 months ($p = 0.003$). OPG levels also increased after 6 months ($p = 0.006$) and 12 months of treatment ($p = 0.004$).

Discussions: Tofacitinib enhanced bone formation, while decreased bone resorption, leading to a positive balance of bone turnover. The combination of tofacitinib treatment with lower levels of DKK1 or anti-CCP antibody predicted changes in DXA vertebral BMD. The combination of therapy with lower age or levels of CRP predicted changes in QCT cortical BMD. Treatment with tofacitinib effectively reduced both synovial and vascular inflammation simultaneously as determined by ^{18}F-FDG-PET/CT and attenuated the further development of bone loss in RA.

Conclusions: Disease activity and systemic inflammation may play a role in influencing both vascular pathophysiology and synovial inflammation. Our findings suggest that autoimmunity, age, bone and inflammatory markers, may all play a role in modulating the effects of tofacitinib on BMD changes. Furthermore, ^{18}F-FDG-PET/CT may be suitable method for simultaneous assessment of vascular and synovial inflammation.

MINOR SALIVARY GLAND PROTEOME REVEALS DIFFERENT SUBGROUPS OF PATIENTS WITH SJÖGREN'S DISEASE ASSOCIATED WITH DISTINCT CLINICAL PHENOTYPES

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Background: Sjoegren's disease (SjD) is known to be clinically heterogeneous. Several approaches have been proposed to stratify SjD patients, but none of them investigated the salivary gland proteome.

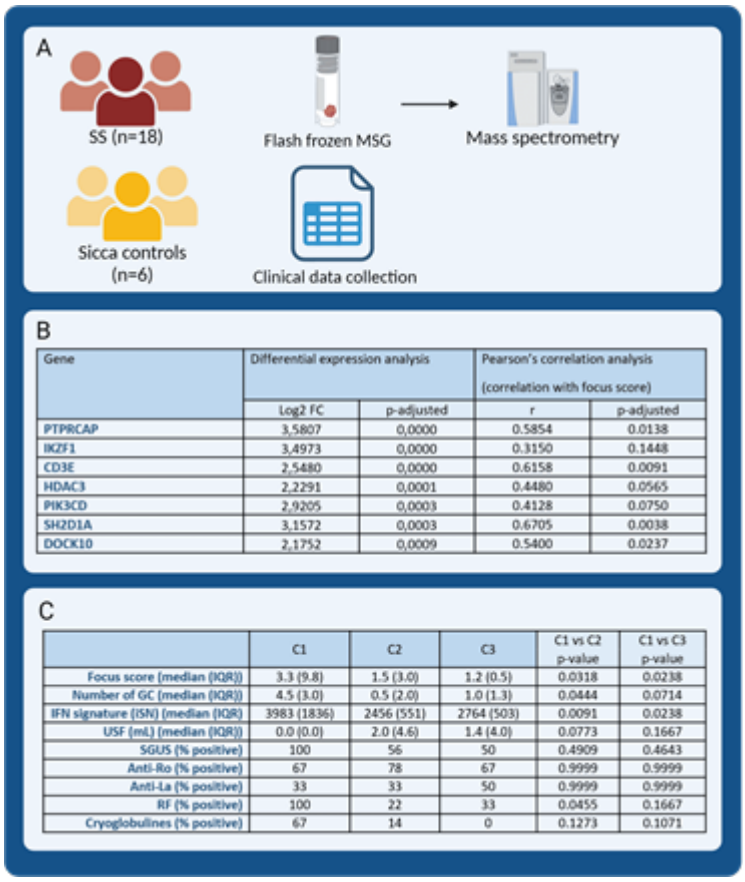
Aim: The aim of our study was to investigate the proteomic profiles of minor salivary glands (MSG) and identify subgroups of SjD patients.

Methods: The study included 18 patients with SjD who met the 2016 ACR/EULAR classification criteria and 6 controls with sicca symptoms who did not meet the criteria. Clinical data were collected (Fig. 1A). Flash frozen MSG tissues were analyzed by mass spectrometry and proteins were identified and quantified using Spectronaut software. Correlations were evaluated using Pearson correlation analysis. Unsupervised hierarchical clustering was used to group SjD patients based on their protein expression profiles. Interferon signatures were calculated based on protein expression according to the Gottenberg et al. [1]. Differences in clinical parameters between these clusters were statistically analyzed using the Mann-Whitney U test or Fisher's exact test.

Results: We identified 5577 proteins, 7 of which — PTPRCAP, IKZF1, CD3E, HDAC3, PIK3CD, SH2D1A, and DOCK10 — were found to be upregulated in patients with SjD compared to the sicca controls. Among these, PTPRCAP, CD3E, HDAC3, PIK3CD, SH2D1A and DOCK10 showed a positive correlation with the focus score in MSG tissues (Fig. 1B).

Unsupervised hierarchical clustering identified three distinct clusters of patients with SjD. Patients from cluster 1 ($n = 3$) had significantly higher focus scores, higher number of germinal centers (GC), significantly higher IFN signatures and lower unstimulated salivary flow compared to patients from cluster 2 ($n = 9$) and cluster 3 ($n = 6$). In addition, cluster 1 had higher percentage of patients testing positive in salivary gland ultrasound (SGUS), rheumatoid factor (RF) and cryoglobulines (Fig. 1C).

Discussion and Conclusion: The total number of proteins identified in our analysis exceeds that of previous studies. Subclusters of patients with SjD based on protein profiles of MSG tissues correlate with SjD-relevant measures. Patients from cluster 1 show more prominent glandular damage and presence of risk factors for lymphoma development, such as presence of GC, cryoglobulinemia and RF positivity.



B

Gene	Differential expression analysis		Pearson's correlation analysis (correlation with focus score)	
	Log2 FC	p-adjusted	r	p-adjusted
PTPRCAP	3,5807	0,0000	0.5854	0.0138
IKZF1	3,4973	0,0000	0.3150	0.1448
CD3E	2,5480	0,0000	0.6158	0.0091
HDAC3	2,2291	0,0001	0.4480	0.0565
PIK3CD	2,9205	0,0003	0.4128	0.0750
SH2D1A	3,1572	0,0003	0.6705	0.0038
DOCK10	2,1752	0,0009	0.5400	0.0237

C

	C1	C2	C3	C1 vs C2 p-value	C1 vs C3 p-value
Focus score (median (IQR))	3.3 (9.8)	1.5 (3.0)	1.2 (0.5)	0.0318	0.0238
Number of GC (median (IQR))	4.5 (3.0)	0.5 (2.0)	1.0 (1.3)	0.0444	0.0714
IFN signature (ISN) (median (IQR)	3983 (1836)	2456 (551)	2764 (503)	0.0091	0.0238
USF (mL) (median (IQR))	0.0 (0.0)	2.0 (4.6)	1.4 (4.0)	0.0773	0.1667
SGUS (% positive)	100	56	50	0.4909	0.4643
Anti-Ro (% positive)	67	78	67	0.9999	0.9999
Anti-La (% positive)	33	33	50	0.9999	0.9999
RF (% positive)	100	22	33	0.0455	0.1667
Cryoglobulines (% positive)	67	14	0	0.1273	0.1071

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SPONDYLARTHRITIS (PL)

EPIDEMIOLOGY OF PSA IN POLAND — RESULTS OF A NATIONWIDE STUDY

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Aim: To estimate the actual incidence and prevalence of SD in Poland for the period 2013-2021, overall and by gender, age and region.

Methods: We used electronic administrative health claims collected from 2009 to 2022 by the National Health Fund (Narodowy Fundusz Zdrowia, NFZ), a single public health care payer in Poland. The NFZ database comprises individually reported data claimed to the payer. The data include detailed service descriptions and demographic variables describing the patient. The data collected in databases are anonymous, but individual patients can be distinguished and matched by their IDs, which are pseudonymized national identification numbers. PsA patients were defined as persons who had at least one visit with ICD-10 codes M07.0, M07.1, M07.2, M07.3 or L40. 5, in any type of treatment and simultaneously had at least one reimbursable prescription for a drug whose active ingredient is methotrexate (ATC L01BA01, ATC L04AX03) or sulfasalazine (ATC A07EC01) or cyclosporine (ATC L04AD01, ATC S01XA18), or leflunomide (ATC L04AA13) or non-steroidal anti-inflammatory drugs (NSAIDs) or biologics and targeted synthetic disease-modifying antirheumatic drugs.

Results: The standardised incidence in Poland in 2021 was 2,957, or approximately 1.1 per 100,000 inhabitants, and the total number of alive patients with PsA in Poland was 36,357, of whom 61% were women. Between 2013 and 2021, the majority of new diagnoses of SD were made in patients aged 35–55 years, regardless of gender. In 2021, the peak incidence of SD was

around 45 years of age. The prevalence of PsA in Poland in 2021 was approximately 0.1%. The largest proportion of patients with PsA was observed among individuals aged 55-64 years (27% of all patients with PsA), while the smallest proportion was observed among patients younger than 18 years (0.2% of the total number of patients).

CARDIOVASCULAR RISK FACTORS AND COMORBIDITIES IN PSORIATIC ARTHRITIS

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As early as in 2006 cardiovascular diseases and their risk factors were found to be more common in patients with inflammatory rheumatic diseases (RA, PsA, and AS) than in matched controls [1]. Cardiovascular diseases are currently still more prevalent in patients with inflammatory rheumatic diseases, including PsA compared with healthy controls and, more importantly, this elevated risk is highly influenced by an increased prevalence of traditional cardiovascular risk factors. There is still a need for an identification and treatment of these traditional risk factors [2].

In particular, PsA is associated with an increased risk of developing severe cardiovascular events such as myocardial infarction and stroke, some of them being fatal. While certain risk factors like age, sex, and family history are non-modifiable, the others are potentially modifiable and these include hypertension, smoking, dyslipidemia, diabetes, and obesity.

A systematic review and meta-analysis in 2021 showed that pooled prevalence of cardiovascular diseases and their risk factors are substantial elevated in PsA — for instance: any CVD (19.4%), angina (3.6%), myocardial infarction (3.2%), stroke (2.8%), hypertension (34.2%), metabolic syndrome (28.2%), obesity (27.4%), hyperlipidemia (24.2%) [3].

Cardiovascular comorbidities are also associated with different PsA disease features, and there is still research needed on their impact on longitudinal outcomes such as disease activity, treatment response, health status, health quality, work productivity and mortality.

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DEPRESSION AND COMORBIDITIES IN AXIAL SPONDYLOARTHRITIS

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Background: It is well known that comorbidities are more prevalent in patients with axial spondyloarthritis (axSpA) than in general populations. The most prevalent comorbidities are cardiovascular diseases. Less is known about other comorbidities, such as depression or thyroid disease.
Aim: The aim of our study was to assess the frequency of depression and thyroid dysfunction in patients with axSpA, their relationship with disease activity, inflammatory markers and assess the impact of treatment with tumor necrosis factor alfa (TNFα) inhibitors on that disorders.
Methods: Forty patients (28 male, 12 female; mean age 40 ± 11 years) with axSpA, qualified to receive anti-TNF-α treatment, were prospectively assessed. Patients underwent full clinical and biochemical assessment before and after 6 months of therapy. Disease activity was assessed by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Inflammatory markers were assessed routinely by the hospital central laboratory. The presence of depressive disorders was assessed with Beck's Depression Inventory (BDI) scale. Additionally, serum levels of tryptophan, serotonin and kynurenine were marked. Serum concentrations of thyroid stymulating hormone (TSH) was measured as a screening test for thyroid function. As a control group, 20 healthy volunteers (7 male and 13 female, mean age 38 ± 5 years) were recruited.
Results: Considering cut-off scores of ≥ 11 for BDI, 14 of 40 the participants (35%) had depression. Additionally, the predominance of the kynurenine pathway in axSpA patients compared to the control group was demonstrated ($p < 0.001$). Statistically significant improvement in the BDI score was observed after anti-TNFα treatment (10±6 *vs*. 5 ± 4; $p < 0.001$) and only 5 patients

(12%) achieved the BDI ≥ 11 after treatment. Surprisingly, the groups of patients with and without depression did not differ significantly in terms of disease activity, inflammatory parameters, or tryptophan metabolites. Moreover, no significant changes in serum levels of tryptophan and its metabolites in axSpA patients after treatment was found, despite clinical improvement. Subclinical hyperthyroidism was discovered in one patient, and subclinical hypothyroidism in three. While in the control group, no above-mentioned disorders were observed.
Conclusions: Depression and thyroid disorders are common in patients with axSpA, even without clinical symptoms. Patients should be regularly screened for these symptoms.

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DIFFICULT TO TREAT (HU)

DIFFICULT TO TREAT RHEUMATOID ARTHRITIS

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Albeit the management options of rheumatoid arthritis (RA) improved significantly with new targeted therapies, there are still many patients (10–30%) not reaching treatment goals. Difficult-to-treat rheumatoid arthritis (DTR RA) refers to cases of RA, that do not respond adequately to standard therapies. D2T RA is a complex condition involving several factors, including persistent inflammation, comorbidities, psycho-social factors, pain syndromes, patient non-adherence, or misdiagnosis. The appropriate management of D2T RA requires a comprehensive, multidisciplinary approach that addresses the unique characteristics of the disease and individual patient factors. Therefore, in most D2T RA cases, the treatment strategy should integrate both pharmacological and non-pharmacological treatment options. D2T RA represents a significant healthcare challenge, and much research focuses on understanding factors contributing to the D2T state. This presentation aims to provide a state-of-the-art overview of D2T RA, including ongoing research and future perspectives.

DIFFICULT-TO-TREAT PSA

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Background: The better understanding of the pathomechanisms of autoimmune disorders and the development of pharmaceutical techniques have led to the spread of targeted therapies, which have resulted to a breakthrough in the treatment of rheumatic musculoskeletal diseases (RMDs) in the last two decades. Despite this, however, a significant proportion of patients remain symptomatic, the recognition of which has inspired the concept of difficult to treat (D2T) diseases.
Objectives: Our aim was to collect and summarize the most important new informations and attempts of definition of difficult-to-treat disease within spondyloarthritis, especially with regard to psoriatic arthritis.
Methods: I searched the pubmed database for the latest articles about D2T-SpA and D2T-PsA.
Results: Spondyloarthritis is a heterogeneous family of diseases that can affect many domains, many organ systems of our body. Although the pathomechanism of the disease is similar in different domains, the differences that can be detected have an impact on the efficacy of different types of drugs: the same drug has a different expected therapeutic effect in another domains. However, there is a great variability within the disease as to which organs are affected and to what extent.

For these reasons, there is currently no consensus on what can be considered a difficult-to-treat disease in SpA and PsA. The number of publications dealing with persistent disease activity and treatment resistance is over 500, but the wide variation in definitions also makes them difficult to analyse. Their assessment is further complicated by the fact that the disease is associated with a high rate of comorbidities, which may also cause persistence of patients' complaints. Both the EULAR and GRAPPA are working to build the right consensus.

Conclusions: Until the international organisations can develop appropriate recommendations, as clinicians it is advisable to use analogies, i.e. to reconsider the full clinical picture of patients with persistent complaints, what may be the underlying cause of the complaints and to modify the patient's treatment as appropriate, in accordance with the guidelines set out in rheumatoid arthritis.

1. Difficult-to-treat psoriatic arthritis: a scoping literature review informing a GRAPPA research project. RMD Open. 2024 Jan 8;10(1):e003809.
2. Characteristics Of Difficult-To-Treat Psoriatic Arthritis: A Comparative Analysis. Semin Arthritis Rheum. 2023;63:152275.
3. Characteristics of difficult-to-treat axial spondyloarthritis: Results of a real-world multicentric study. Joint Bone Spine. 2024;91(2):105670.

DIFFICULT-TO-TREAT SYSTEMIC LUPUS ERYTHEMATOSUS

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Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with very diverse organ manifestations, severity and prognosis. Although treatment options have grown slowly but substantially, and the determinants of the disease course and prognosis are much better explored, there are several challenges in the treatment of SLE.

Life expectancy is still significantly lower than in the general population, and damage accrual puts a high burden on the patient and the health systems. The presentation will address the recent new information and possible therapeutic options regarding the following issues:

Complete renal response is achieved in less than half of the patients with lupus nephritis. What are the predictors of a poor response and what are the novel treatment options that could increase the success rate?

In up to 30% of patients, the disease follows a frequently relapsing course. Each relapse carries the risk of increasing irreversible damage and the prolonged use of corticosteroids.What are the potential solutions to reduce relapse rate?

Fatigue, chronic pain, depression and cognitive dysfunction are poorly characterised manifestations, however, these are regarded as the major problem by many of the patients. What are the recent trends in addressing these issues?

Personalized treatment approach could theoretically aid in the identification of the best treatment target and could increase the likelihood of a good treatment response. What are the data on personalized medicine in SLE?

CAN WE DEFINE DIFFICULT-TO-TREAT SYSTEMIC SCLEROSIS?

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Systemic sclerosis (SSc) is a chronic autoimmune rheumatic disease characterized by microvascular alterations, immunopathology and widespread fibrosis involving various organs. It is considered difficult to treat due to several reasons: complex pathogenesis, heterogeneity, late diagnosis, limited treatment options for certain organ manifestations, lack of personalized medicine. Despite recent advances in the management of SSc over the last decades the disease presents significant morbidity and mortality. Although available treatment protocols brought significant advancements in terms of survival in SSc-associated interstitial lung disease and pulmonary arterial hypertension, less success has been achieved in the treatment of Raynaud's phenomenon and digital ulcers and the results are modest in case of heart, gastrointestinal, and renal manifestations. Treatment primarily focuses on managing symptoms, preventing complications or irreversible organ damage, and slowing disease progression. Medications such as immunosuppressants, vasodilators, and antifibrotic agents may be used to target specific aspects of the disease, but their effectiveness varies among individuals and different organ manifestations respond differently to

the combination of the three treatment targets. There are patients who do not respond to even to optimized treatment and deteriorate even with adequate therapy. They can be considered difficult-to treat (D2T) cases. We have created a possible score system based on the individual organ manifestations and highlighted treatment options for the D2T SSc category.

DIFFICULT TO TREAT GIANT CELL ARTERITIS

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Giant cell arteritis (GCA) represents the most frequent large vessel vasculitis in individuals aged 50 years or more in Europe and North America. Affecting large and medium sized arteries, particularly aorta, aortic arch branches and branches of external carotid arteries, GCA may lead to a significant morbidity (e.g. risk of irreversible visual impairment, ischemic stroke, vascular stenoses), and damage (e.g. aortic aneurysm/dissection) if it is not recognized and/or treated timely and appropriately.
Systemic glucocorticoids are still the mainstay of treatment, however nowadays commonly combined with a steroid sparing agent such as tocilizumab or methotrexate. Nonetheless, GCA remains a challenging disease due to its chronic, relapsing, and sometimes highly refractory course. In the presentation, we will discuss cases of treatment resistant GCA, and highlight the need to verify the accuracy of the diagnosis, the adherence to treatment and impact of comorbidities in each individual case.

SJÖGREN DISEASE (SI)

SALIVARY GLAND ULTRASOUND — A USEFUL TOOL IN SJÖGREN'S DISEASE

Alojzija Hocevar

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Sjögren's disease (SjD) is a complex, slowly progressive connective tissue disease with variable of clinical manifestations. The disease is mainly characterized by damage and dysfunction of the exocrine glands, particularly the salivary and lacrimal glands, and the B-cell hyperreactivity. With an estimated prevalence of about 60 cases per 105 people and an incidence of about 7 cases per 105 people, SjD is one of the more prevalent systemic autoimmune diseases. The diagnosis of this highly heterogeneous disease is based on a combination of several assessments. Over the last two decades, ultrasound of the major salivary glands has proven to be an extremely useful diagnostic tool in suspected SjD. In fact, ultrasound is nowadays almost indispensable in the management of the SjD patients. Compared to other imaging modalities it is widely available, non-invasive, inexpensive and provides high spatial resolution. Morphological change typical for SjD is glandular inhomogeneity due to focal or diffuse hypoechoic areas. Persistent glandular inflammation ultimately leads to glandular atrophy, fatty infiltration and fibrosis, manifested by diffuse hyperechogenic bands.
In addition to its diagnostic role, studies have shown that the addition of ultrasound to the classification criteria could further improve their performance. Next, ultrasound can be used as a tool to stratify SjD patients. Patients with sonographically normal salivary glands have namely a milder disease phenotype with more preserved glandular function, less pronounced immunological profile, lower systemic disease activity and less damage accrual over time. By using Doppler ultrasound to evaluate glandular vascularization, one might further determine inflammatory activity in the salivary glands. Finally, first reports on the improvement of salivary gland ultrasound morphology with study medications are optimistic, and point to another potential role of ultrasound, being a tool to evaluate the effectiveness of treatment.

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SJÖGREN'S DISEASE FOLLOW-UP; THE ROLE OF ULTRASOUND

Katja Perdan Pirkmajer[1], Katja Lakota, Sonja Praprotnik, Žiga Rotar, Alojzija Hočevar

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Background: Salivary gland (SG) ultrasound (US) helps to diagnose and stratify patients with Sjögren's disease (SjD). However, US studies evaluating morphological changes over time are scarce.

Objectives: To evaluate the potential progression of US morphological changes of SG in a well-defined SjD cohort.

Methods: One hundred and fifty-one SjD patients diagnosed between January 2016 and December 2018, and fulfilling the ACR/EULAR 2016 classification criteria1 were invited to participate in a follow-up (FU) US study that was carried out between May and September 2023. In 82/151 patients who responded to the invitation, the follow-up time [median (IQR) was 73.1 (63.6, 81.3) months]. A detailed clinical and laboratory evaluation, Schirmer's test, SGUS using Hočevar scoring system2, and ESSDAI were repeated, and ESSPRI calculated. For the purpose of the study, a cut-off for significant US progression was set at US score change > 12 points (from baseline).

Results: Patients' baseline characteristics are presented in Table 1. At FU visit 43 (52.4%) and 42 (51.2%) patients reported worsening of ocular and oral sicca symptoms. Median ESSPRI at FU was 6.0 (4.0; 6.9) and was at least 5 in 53 (64.6%) patients. None of the included patients developed a new lymphoma during FU. At FU visit 41 (50.0%) patients had US changes consistent with SjD [at baseline 33 (40.2%)]. Significant increase of US score was found in 18 (21.9%) patients compared to baseline. We found no significant differences in patient age (p=0.516), symptom duration, time (p = 0.222), oral dryness (p = 1.0), glandular swelling (p = 0.722), ESR (p = 0.423), gamma globulins (p = 0.617), baseline ESSDAI (p = 0.352), follow-up ESSPRI (p = 0.384) or immunomodulatory treatment (p = 1.0) in patients with and without SGUS progression. There was a trend toward higher minor salivary gland focus score in those who US progressed (p = 0.091).

Discussion: Most of the SjD patients in our cohort showed stable glandular disease based on US evaluation. Nevertheless, 20% of SjD patients had significant US morphological glandular progression-without firm association between patients baseline characteristics or disease activity and US glandular progression.

Conclusion: Ultrasound is useful in glandular FU of SjD.

Characteristics	Baseline	Follow-up
Female gender	78 (95.1%)	-
Age (years)*	60 (48; 69)	-
Symptom duration (months)*	7 (10; 48)	-
Smoking - no	102 (68.4%)	
active	26 (17.4%)	
past	21 (14.0%)	
History of lymphoma	4 (2.7%)	-
Positive minor SG histology	65/79 (82.3%)	-
Anti-SSA	56/82 (68.2%)	-
Positive US (SGUS)	33 (40.2%)	41 (50.0%)
US score*	13 (6; 24)	17 (8; 41)
ESSDAI*	2 (0; 4)	0.5 (0; 2)
ESSPRI*	-	6.0 (4.0; 6.9)
ESR (mm/h)*	22 (11; 32)	22 (13; 37)
Gammaglobulins (g/L)*	14 (11; 17)	12 (10; 16)
Immunomodulatory treatment	-	19(23.2%)

*Median (IQR)

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LUNG INVOLVEMENT IN SJÖGREN'S SYNDROME

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Primary Sjögren's Syndrome (pSS) is an increasingly recognized autoimmune disease, primarily affecting secretory gland tissue. The estimated prevalence in Slovenia is 0,60% and incidence 4 in

100.000 adults. The typical clinical signs are xerophthalmia and xerostomia. In approx. 30–50% of patients extra-glandular manifestations can develop.
Lung involvement is relatively common. It affects 9–22% of patients with pSS. It has impact on both life quality and mortality. They found a 4-fold increase in 10 years mortality. ILD in pSS was described as a late manifestation, but more recently a variable time of onset of pSS-ILD has been observed. In 10–51% of patients ILD can develop years before the onset of pSS.
Exertional dyspnea and presenting dry cough are the most frequent symptoms of lung involvement. Carbon monoxide lung diffusion capacity and loss of forced vital capacity are mostly observed. For proper diagnosis high resolution computer tomography (HRCT) scan is the standard procedure. Typical pSS pattern on HCRT is lymphocytic interstitial pneumonia, which is followed by nonspecific interstitial pneumonia, usual interstitial pneumonia and organizing pneumonia.
Multidisciplinary teams consisted of pulmonologists, rheumatologists, radiologists and pathologists are required for treatment decisions.
At the time being glucocorticoids with immunosuppressants (cyclophosphamide and mycophenolate mofetil) are used for treatment of pSS-ILD. Recently antifibrotic agent nintedanib was added as a treatment option for slowing the fibrotic progression.
The aims of this presentation are to describe clinical features, imaging, pathology, together with diagnostic criteria, prognosis and management of pSS-ILD patients and to present the recommendations for diagnostics and treatment of ILD in patients with connected tissue diseases including pSS in Slovenia.

Key words: primary Sjögren's syndrome; lung; interstitial lung disease

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THE DIAGNOSTIC POTENTIAL OF INDUCIBLE T-CELL COSTIMULATOR (ICOS) EXPRESSION ON T LYMPHOCYTES IN THE PERIPHERAL BLOOD OF PATIENTS WITH SJÖGREN DISEASE

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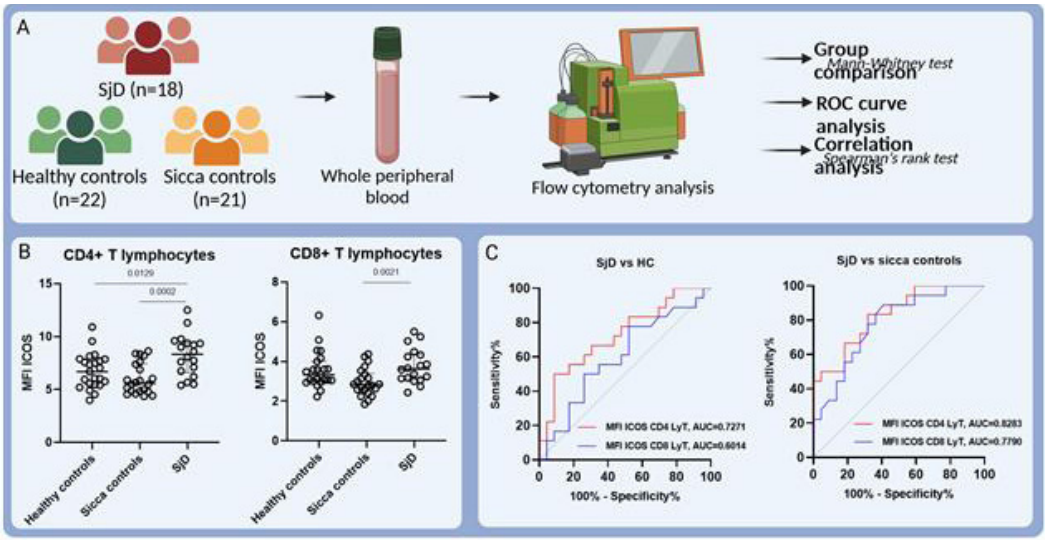
Background: Inducible T-cell costimulator (ICOS) is a costimulatory receptor expressed on activated T cells. Transcriptomic studies indicate its upregulation in both salivary glands and peripheral blood of Sjogren's disease patients. However, studies evaluating ICOS expression on the surface of T lymphocytes by flow cytometry for its diagnostic potential are lacking.
Objective: We aimed to evaluate the surface expression of ICOS in peripheral blood T lymphocytes in SjD patients, its associations with clinical characteristics, and its diagnostic utility.
Methods: Surface expression of ICOS was measured in CD4+ and CD8+ T lymphocytes from whole blood samples of 18 newly diagnosed SjD patients, 21 sicca controls, and 22 healthy controls by flow cytometry. Group comparisons were made using the Mann-Whitney U test and diagnostic utility was evaluated via ROC curve analysis. Correlations with clinical characteristics were analyzed using Spearman's rank correlation test (Fig. 1A).
Results: The surface expression of ICOS on CD4+ T lymphocytes was elevated in SjD patients compared to both sicca and healthy controls. In contrast, the expression of ICOS on CD8+ T lymphocytes was higher in SjD patients when compared to sicca, but not when compared to healthy controls (Fig. 1B). In addition, surface expression of ICOS on CD4+ T lymphocytes was positively associated with levels of gammaglobulin, the presence of anti-Ro, anti-La autoantibodies, and rheumatoid factor.
The ICOS expression in CD4+ T lymphocytes showed good ability to discriminate between SjD and healthy controls (AUC = 0.7271, p = 0.0135) and between SjD and sicca controls (AUC = 0.8283, p = 0.0004). In contrast, the expression of ICOS in CD8+ T lymphocytes had lower diagnostic accuracy as it only differentiated between SjD and sicca controls (AUC = 0.7790, p = 0.0027), but not between SjD and healthy controls (AUC = 0.6014, p = 0.2699) (Fig. 1C).

Discussion and Conclusion ICOS expression on the surface of T lymphocytes is elevated in SjD patients. However, this elevation is more prominent in CD4+ T lymphocytes. ICOS expression in CD4+ T lymphocytes has significant diagnostic utility and is superior to the diagnostic utility of ICOS expression in CD8+ T lymphocytes.



POSTERS

HLA DRB1*04 ALLELE IS UNCOMMON IN THE SPONDYLOARTHRITIS AND PSORIATIC ARTHRITIS GROUP COMPARED TO THE HLA B*44 GROUP AVERAGE AND THE RHEUMATOID ARTHRITIS GROUP

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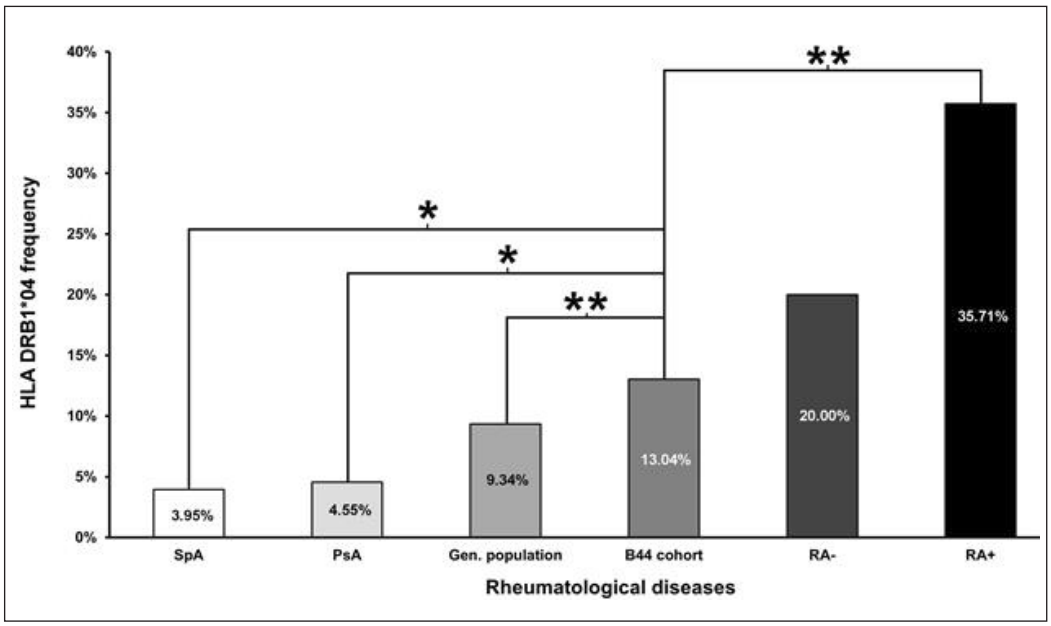
Background: HLA B*44 is not associated with any inflammatory rheumatic disease (IRDs). However, twenty-five years ago, gastroenterologists reported that type 2 arthropathy is more common in patients with inflammatory bowel disease (IBD) and B*44 allele [1]. Type 2 arthropathy affects peripheral joints and is not connected to IBD activity.
Aim: To find the most significant HLA A, B, or DR allele connection to the most common IRDs in the HLA B*44 positive patients.
Methods: This study was designed as a retrospective cross-sectional analysis of data from HLA B*44 positive patients found in the medical electronic archives of the Department of Rheumatology and Clinical Immunology and the Department of Physical and Rehabilitation Medicine with Rheumatology, Clinical Hospital Center Split in Croatia. Data was available from May 1, 2018, to May 30, 2024.
Results: The frequency of the second allele beside HLA B*44 in 303 patients did not differ from the general population [2]. 120 patients have been diagnosed with a definitive IRD. The most common diagnoses were: spondyloarthritis-SpA (n = 42), rheumatoid arthritis-RA (n = 42, seropositive = 22, seronegative = 20), and psoriatic arthritis-PsA (n = 33). A positive trend was shown for HLA B*27 in SpA and HLA B*38 in PsA but the numbers were too small for statistical significance. Only the frequency of HLA DRB1*04 was significant: low frequency in SpA (3.9%) and PsA (4.5%) group, and high frequency in seropositive RA (35%) (Fig. 1).
Discussion: The HLA-DRB1*04 allele was more frequent in patients with RA, as previously described in the Croatian population [3]. The presence of the HLA DRB1*04 allele in patients with polyarthralgia or still not fully developed IRD should direct us to intensive follow-up and earlier

ultrasound examination of small joints of hands and feet. However, a frequency of this allele below the group average has not been described for SpA and PsA.
Conclusions: HLA DRB1*04 is rare in HLA B*44 positive patients with SpA and PsA. Pain in the spine and joints as well as the lack of HLA DRB1*04 were present in 96% of SpA patients.

Figure 1. HLA DRB1*04 frequency in IRD in HLA B*44.
General population (n = 10000 alleles); HLA B*44 group (n = 606), SpA (n = 84), PsA (n = 66), seronegative RA (n = 40), seropositive RA (n = 44). *p < 0.05; **p < 0.005.



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HAPTOGLOBIN GENOTYPING IN ADULT IGAV PATIENTS

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Background: IgA vasculitis (IgAV) is a small-vessel vasculitis characterized by heterogenous clinical presentation, involving skin, joints, bowel and kidneys. Acute phase protein haptoglobin (Hp) plays a crucial role in oxidative stress reduction by binding and removing free haemoglobin (Hb) from the circulation. The Hp gene has two codominant alleles (Hp1, Hp2) resulting in three Hp genotypes (Hp1-1, Hp2-1, Hp2-2). Phenotypically the polymorphs differ in molecular size, structure, antioxidant activity and plasma concentration. Hp1-1 genotype has been previously linked to the pathophysiology of IgA nephropathy.
Aim: Recently, we investigated haptoglobin as a novel marker of visceral involvement in adult IgAV. In order to assess the role of specific Hp genotypes in this disease, we genotyped our cohort of adult IgAV patients.
Methods: 91 adults with IgAV were genotyped for the presence of two Hp alleles (Hp1, Hp2) using the Taqmann genotyping assay on patient blood samples (sequence of primers and probes used are 5'-CGTTATTAGGAGGAGCTGTTGCT-3' (forward primer), 5'-CACACCAGTA-

AGAGCAGAAGAG-3' (reverse primer), VIC-ATTCTCAGAACAAGAGGCA-3' (binding to equally to intron 4 of Hp1 and intron 6 of the Hp2 allele), and FAM-CTCAGAACCAGAG-GCA-3' (binding to a site in intron 4 of Hp2). Clinical characteristics and laboratory parameters were collected at diagnosis (no treatment). Statistical analysis was performed using SPSS for the assessments of among different Hp genotype groups.

Results: Genotype frequencies in our adult IgAV population were 16.5%, 48.4%, and 35.2% for Hp1-1, Hp2-1 and Hp2-2. In all three genotypes extensive skin involvement was present in 47-59%, joint involvement in 6-13%; bowel involvement in 20-26% and kidney involvement in 47-53%. Also other clinical and laboratory parameters were not significantly different between different Hp genotypes. The level of serum haptoglobin did not differ with genotype [median (IQR) Hp1-1 2.5 (1.75–3.05), Hp2-1 2 2 (1.9 –3.1) and Hp2-2 2 (1.4–2.575) p = 0.17].

Discussions: The frequency of Hp genotype groups corresponded to the Hp genotype distribution in the Slovenian population (Hp1-1 8%, Hp2-1 52%, Hp2-2 39%) . Moreover, the study found no statistically significant clinical and laboratory differences among patients' Hp genotype groups.

Conclusions: Our study suggests that different Hp genotypes do not influence the clinical presentation of IgAV.

CLINICAL INDICATORS OF DIFFICULT-TO-TREAT RHEUMATOID ARTHRITIS REVEALED BY MACHINE LEARNING

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Despite advances in biologic (b-) and targeted synthetic (ts-) DMARDs, a significant subset of rheumatoid arthritis (RA) patients remain symptomatic, meeting the definition of „difficult-to-treat" (D2T) RA1.

This study aimed to identify crucial clinical indicators that can differentiate patients at risk of developing D2T RA at enrollment into the registry (baseline) or one to two years prior to meeting the definition of D2T RA.

We retrospectively analysed 8,543 RA patients from the Czech Republic biologics registry ATTRA2 (2002–2023) who commenced treatment with b/tsDMARDs. D2T RA was defined according to EULAR criteria 1. For comparison, we identified patients in sustained clinical remission as those with a Simple Disease Activity Index (SDAI) < 3.3 and Swollen Joint Counts (SJC) ≤ 1 over two consecutive follow-ups 12 weeks apart. All patients initiated b/tsDMARDs treatment.

At each time point, we selected all patients meeting the D2T RA definition and matched them with an equal number of RA patients in sustained remission, ensuring they were comparable in terms of age, gender, duration of disease, and duration of biological treatment. We employed machine learning techniques such as lasso, ridge, support vector machine, random forest, and XGBoost with Shapley additive explanation (SHAP) values to interpret model results and assess the impact of various features.

Altogether, 641 patients with D2T RA (mean age 50.6 years at baseline; 84% female) were compared with 641 RA patients in sustained remission, matched by age, gender, disease duration, and b/tsDMARD treatment at each time point.

The machine learning model demonstrated accuracy and area under the receiver operating characteristics curve (AUC) ranges of 0.606–0.747 and 0.656–0.832, respectively, for predicting D2T RA. The SHAP analysis identified key predictors of D2T RA, such as clinical disease activity measures, CRP, and duration of b/tsDMARD treatment (Fig. 1). The best performance of these predictors was one year before the patients met the D2T RA.

These findings provide valuable insights enhancing the early identification and management of patients at risk for D2T RA, potentially improving treatment strategies and outcomes. Future research should focus on optimising and validating these predictive models.

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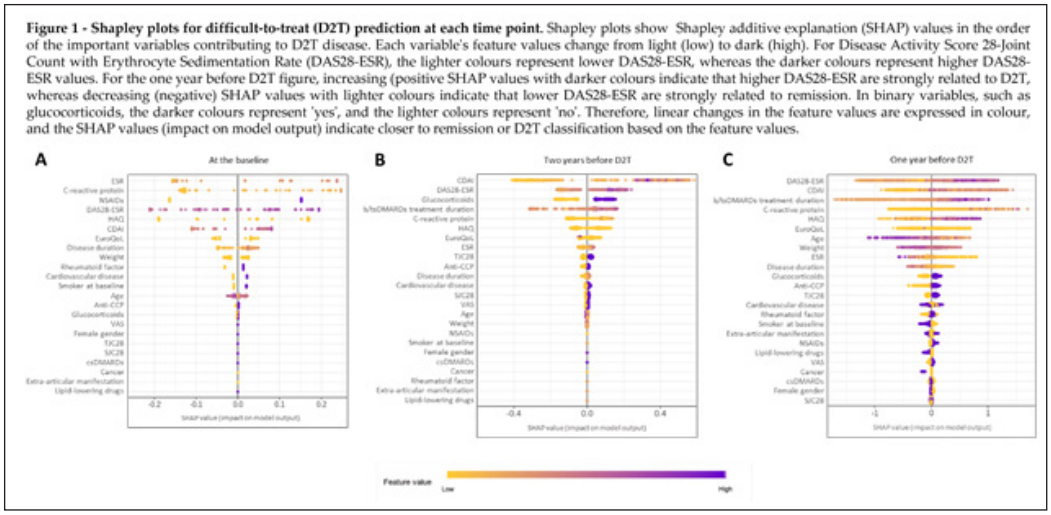

Figure 1 - Shapley plots for difficult-to-treat (D2T) prediction at each time point. Shapley plots show Shapley additive explanation (SHAP) values in the order of the important variables contributing to D2T disease. Each variable's feature values change from light (low) to dark (high). For Disease Activity Score 28-Joint Count with Erythrocyte Sedimentation Rate (DAS28-ESR), the lighter colours represent lower DAS28-ESR, whereas the darker colours represent higher DAS28-ESR values. For the one year before D2T figure, increasing (positive SHAP values with darker colours indicate that higher DAS28-ESR are strongly related to D2T, whereas decreasing (negative) SHAP values with lighter colours indicate that lower DAS28-ESR are strongly related to remission. In binary variables, such as glucocorticoids, the darker colours represent 'yes', and the lighter colours represent 'no'. Therefore, linear changes in the feature values are expressed in colour, and the SHAP values (impact on model output) indicate closer to remission or D2T classification based on the feature values.

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NUTRITIONAL COUNSELLING IN PATIENTS WITH RHEUMATOLOGIC DISEASES

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Background: Patients with rheumatologic diseases have a high risk of malnutrition and sarcopenia due to chronic mild to moderate inflammation and low physical activity.
Aim: Nutritional counselling should improve the nutritional and functional status of patients.
Methods: Thirty-five patients were admitted to the Department of rheumatology outpatient service of the University Medical Centre Ljubljana for nutritional counselling between October 2023 and November 2024. In fifteen patients, nutritional counselling was performed at baseline and after 3 months using the NRS 2002 screening tool, evaluation of a 3-day food diary, body composition, grip strength, and the 30-second chair stand test. The GLIM diagnostic criteria were used to diagnose malnutrition. Patients were prescribed an individualised nutritional intervention in which they were asked to follow a Mediterranean diet. In case of malnutrition, they were given 2 servings/day of an high protein oral nutritional supplement (HP-HMB) containing beta-hydroxy-beta-methylbutyrate. In addition, they were advised to perform resistance band exercises 2 times a week.
Results: At the beginning of the study, 28 patients were examined and after 3 months, 15 patients were re-examined, including 12 women and 3 men. The average age of the men was 81 years and that of the women 68 years. Indications for referral were: possible sarcopenia (87%), weight loss (74%), insufficient protein intake (27%), cachexia (7%) and sarcopenia (7%). According to the GLIM criteria, 14 (93%) of the included patients were malnourished, of whom 1 (7%) was severely malnourished. Six (40%) patients met the criteria for sarcopenia and one patient (7%) met the criteria for sarcopenic obesity. At the re-examination after three months, handgrip strength had improved by an average of 2 kg and the 30-second chair stand test had improved by an average of 3 repetitions.
Discussion: The results of the nutritional counselling provided insight into the high risk of malnutrition and sarcopenia in patients with rheumatologic diseases. Despite the heterogeneous patient population, nutritional intervention with the Mediterranean diet and HP-HMB oral supplementation in combination with resistance training showed positive results.
Conclusion: Nutritional counselling for patients with rheumatologic diseases showed an improvement in muscle function and general physical performance, which can have a long-term effect on their quality of life.

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SAFETY, EFFECTIVENESS AND IMMUNOGENICITY OF VARICELLA VACCINATION IN CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS TREATED WITH ANTICYTOKINE THERAPY

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Background: Children with juvenile idiopathic arthritis (JIA) on immunosuppressive therapy are at risk for severe varicella. According to the EULAR/PReS recommendations VZV vaccination can be considered also in patients on specified anticytokine therapy, but level of evidence for this approach is low [1].
Aim: To prospectively evaluate safety, effectiveness and long-term immunogenicity of varicella vaccination in children with JIA, treated with anticytokine therapy.
Methods: This is a prospective case-control study. Varicella zoster virus (VZV)-naive patients with stable JIA on anticytokine therapy and normal values of lymphocyte populations, who were at risk for contracting varicella, were vaccinated against VZV. After vaccination, we monitored adverse events (AE), disease activity and vaccine effectiveness and measured VZV-specific humoral and cellular immunity by Liaison and intracellular cytokine staining, respectively. Healthy children after varicella vaccination were included as controls (HC).
Results: Sixteen patients were vaccinated against VZV on anticytokine therapy (12 on TNFα -inhibitors, 3 on IL6-inhibitors, 1 on IL1-inhibitor; 14 were concomitantly on methotrexate or tacrolimus). Fifty-two HC after VZV vaccination were included.
There were no serious AE or vaccine-strain infections after vaccination. Two patients had an increase in disease activity within 3 months after the 2nd dose. Five patients (31%) and 11 HC (21%) reported mild AE, including injection site reactions, fever, rash and arthralgia ($p = 0.5$).
Four patients had mild breakthrough varicella 4 months to 4.5 years after vaccination (mean follow-up time 8.9 ± 3.3 years), and no HC (mean follow-up time 2.6 ± 1.5 years).
After 2nd vaccination 13/16 patients developed VZV-specific humoral immunity and 10/12 patients VZV-specific cellular immunity. VZV IgG levels were initially higher in vaccinated HC compared to patients but comparable at 2–3 yrs after vaccination.
Discussion: In our cohort vaccination against varicella was safe, but not always effective or immunogenic. However all cases of breakthrough varicella were mild.
Conclusions: Varicella vaccination was safe and effective in preventing severe disease in all vaccinated patiens. Our results strengthen the current EULAR/PreS recommendations for vaccination against VZV in JIA patients on anticytokine therapy.

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RELAPSING POLYCHONDRITIS ASSOCIATED WITH BILATERAL SCLERITIS AND HEART BLOCK — CASE REPORT AND LITERATURE REVIEW

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Background: Relapsing polychondritis (RPC) is a rare systemic inflammatory disease that primarily affects cartilaginous structures of the nose, ears, respiratory tract and joints, and occasionally non-cartilaginous tissues such as the eyes, heart and blood vessels. Cardiac involvement is estimated to be present in 24% of patients with RPC and is usually subclinical, but can lead to fatal cardiac complications [1]. Scleritis and episcleritis are the most common ocular symptoms associated with RPC, occurring in 20–61% of patients [2].
Aim: We present a case of a patient with RPC presenting for the first time with heart block and bilateral scleritis who was successfully treated with pulse methylprednisolone therapy and parenteral cyclophosphamide. We also review the existing literature on heart block associated with RPC.

Results: A 58-year-old man with arterial hypertension presented with systemic symptoms, syncope, nasal pain, bilateral red eyes, hoarseness and anterior neck pain. Nasal chondritis and symptoms suggestive of laryngeal cartilage involvement lead to the diagnosis of RPC. Bilateral anterior and posterior scleritis was observed and type II atrioventricular (AV) block was noted. Following treatment with methylprednisolone pulse and cyclophosphamide infusions, complete remission of the heart block and scleritis was achieved.
Discussion: Conduction abnormalities associated with RPC are rare (4–6%) — usually grade I to III AV block. From 1966 to 2024, 11 cases of AV block associated with RPC have been described in the literature and we added one case. As in our case, the majority of patients (10/12) had active RPC at the onset of AV block. Most patients (7/12) were treated with high-dose corticosteroids and 2/12 with methylprednisolone pulses. Conduction abnormalities resolved after therapy in 5/12 patients, pacemaker implantation was required in 6/12 patients, and 2 patients died [3].
Conclusion: The present case is, to our knowledge, the second published case of a patient with RPC and concomitant heart block successfully treated with methylprednisolone pulses. Pulse therapy with methylprednisolone in patients with active RPC and conduction abnormalities may lead to regression of AV block without the need for pacemaker implantation.

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THE USEFULNESS OF THE CHA2DS2-VASC SCORE TO PREDICT ISCHEMIC STROKE IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS WITHOUT ATRIAL FIBRILLATION — A SINGLE-CENTRE RETROSPECTIVE STUDY

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Background: Systemic lupus erythematosus (SLE) is a complex autoimmune disease characterized by immune dysregulations with an increased risk of cardiac and cerebrovascular complications, leading to elevated morbidity and mortality. Despite advancements in SLE management, there is a lack of tools to quantify the contribution of traditional cardiovascular risk factors to inflammation.
Aim: This study evaluates the utility of the CHA2DS2-VASc (congestive heart failure/hypertension/age/diabetes/stroke/vascular disease/age/sex category) score, originally developed for non-valvular atrial fibrillation (AF), in predicting ischemic stroke among SLE patients without AF, given its parameters related to cardiovascular risks.
Methods: We conducted a retrospective analysis of medical records for SLE patients treated at the University Hospital in Kraków, Poland from January 2012 to June 2022, collecting comprehensive clinical and laboratory data. The CHA2DS2-VASc score was calculated for each patient, excluding those with AF, and statistical analyses were performed to assess its predictive ability for ischemic stroke using Cox models and ROC curves.
Results: The study included 787 SLE patients without atrial fibrillation, with a median age of 49 years and a predominance of women (89.58%). The most common comorbidities were arterial hypertension (47.78%) and hypercholesterolemia (43.84%). Ischemic stroke occurred in 47 patients during a median follow-up of 44.5 years, with the incidence rising from 0.00% at a CHA2DS2-VASc score of 0 to 29.41% at scores ≥ 6. Patients with a CHA2DS2-VASc score > 3 had a 2.72-fold higher risk of ischemic stroke compared to those with scores ≤ 3. Moreover, patients with > 3 points in the CHA2DS2-VASc score presented longer disease duration, were older at last visit and, as expected, had more often events of ischemic stroke.
Discussion: The findings shed light on several key risk factors of cardiovascular events, with potential implications for developing diagnostic and therapeutic strategies. Furthermore, a CHA2DS2-VASc score of > 3 points in SLE patients without AF is found to be associated with a significantly higher rate of ischemic stroke.

Conclusion: Our study underscores the importance of the CHA2DS2-VASc score in predicting ischemic stroke risk among SLE patients without AF. Prospective studies are required to assess the primary triggers of ischemic stroke in SLE.

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PSYCHOLOGICAL SKILLS OF PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS: A CROSS-SECTIONAL STUDY AT A HUNGARIAN PAEDIATRIC RHEUMATOLOGY CENTER

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Background: During the treatment of chronic diseases, the focus of medical care includes maintaining the physical health, the emotional well-being and mental health of children as well. Studies have shown that children with JIA are at a higher risk for psychological problems compared to their healthy peers [1, 2].
Aim: to estimate the neuropsychological and behavioural functions in different treatment groups and to specify possible factors that influence these skills.
Methods: We conducted a retrospective analysis of 112 patients treated at the Pediatric Rheumatology Unit of Semmelweis University in Budapest between 2015 and 2016. Patients were categorized into three treatment groups: combined therapy with TNF inhibitors and methotrexate (MTX) and/or salazopyrin (60 patients), MTX monotherapy (34 patients), and TNF inhibitor monotherapy (18 patients). Psychological assessments and the Child Behaviour Checklist (CBCL) were used to evaluate behavioural skills. Neuropsychological functions in patients over 6 years old were assessed using the Woodcock Johnson III Tests. We collected and stratified demographic and disease-specific data. Treatment group comparisons were adjusted for age, age at diagnosis, sex, therapy duration, and disease activity.
Results: No significant differences in neuropsychological variables were found between treatment groups, neuropsychological state was not influenced by age, sex, therapy duration, or disease activity. Behavioural problems were significantly more common ($p < 0.05$) in younger patients. Additionally female patients showed a higher susceptibility ($p < 0.05$) to have borderline values in the assessment of anxiety and depression.
Discussion: Neuropsychological characteristics were generally normal, and behavioural problems were rare among our patients. However, younger female patients were more prone to mood disorders.
Conclusion: We suggest that psychological assessment and care are crucial for patients with JIA to ensure improved long-term quality of life.

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SUSAC SYNDROME — DIFFERENT TREATMENT APPROACHES FOR ONE DISEASE (ANALYSIS OF CASE SERIES)

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Background: Susac syndrome is a rare, autoimmune, occlusive endotheliopathy affecting blood vessels in the central nervous system (CNS), retina, and inner ear. During the first medical evaluation, a classical triad of symptoms is present for less than 20% of patients, making diagnosis establishment challenging. Due to the lack of randomized trials and prospective studies, recommendations regarding treatment are obtained from case series.
Aim: Analysis of the course, disease activity, flares, and treatment options in patients with Sysac syndrome.
Methods: We present a case series of 4 patients treated in the rheumatology department.

Results: The first patient is a 45-year-old man with CNS symptoms' predominance, treated with prednisone, methotrexate, and sulfasalazine (IVIG and GCS i.v. were used during the flare-ups). The second is a 37-year-old woman with laryngological symptoms' predominance, treated with methylprednisolone orally and mycophenolate mofetil during the stable stage and methylprednisolone and IVIG during flares up. The third patient is a 38-year-old woman with no clear predominance from any symptoms with a good response to azathioprine. The last one is a 43-year-old man with ophthalmological symptoms initially treated with cyclophosphamide (6200 mg total dose) and IVIG, later with azathioprine and mycophenolate.
Discussions: The course of Susac syndrome varies between patients. The onset can start with neurological, ophthalmological, or laryngological symptoms excessively, making the diagnosis difficult initially. As the manifestations differ between patients, the treatment is a difficult challenge and depends on the severity of clinical symptoms.
Conclusion: According to the recent recommendation, GCS, immunomodulatory drugs, and IVIG are the cornerstone of the Susac syndrome treatment. The described cases highlight the differences in the course of the disease and the response to immunosuppressive therapy.

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DEPRESSION AND ANXIETY ARE SUBSTANTIALLY UNDERRECOGNIZED IN RA, AXSPA AND PSA — DATA FROM REAL-WORLD RHEUMATOLOGICAL PRACTICE

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Background: Depression and anxiety are common in inflammatory arthritis (IA) and have a great impact on disease activity and quality of life [1]. However, they might be underrecognized in rheumatological practice, partly due to lack of easily accessible diagnostic tools.
Aim: Assessing the prevalence of depressive and anxiety disorders among patients with rheumatoid arthritis (RA), axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA) in real-world out-patient clinic by different screening modalities.
Methods: This cross-sectional study used data from the PolNorRHEUMA registry [2]. Demographic and clinical data were collected during routine visits to a rheumatology outpatient clinic between October 1, 2023, and August 5, 2024. Depression and anxiety were assessed using the following: 1) medical history of comorbidities documented by the physician, 2) specific questions in the MDHAQ form, 3) diagnostic tools for depression (PHQ-9) and anxiety (GAD-7). Results are presented as medians or counts. Group characteristics were compared using the Chi-Square test or Kruskal-Wallis ANOVA with Bonferroni post-hoc analysis. Spearman's correlation analysis was performed between scores on PHQ-9/GAD-7 and MDHAQ form components. A correlation coefficient greater than 0.5 indicated a strong correlation.
Results: The study included 56 RA, 39 axSpA and 33 PsA patients, with mean ages of 60.5, 41 and 45 years, respectively. Strikingly, only one PsA patient had a confirmed diagnosis of depression, with no officially diagnosed anxiety disorders. However, depressive symptoms were present in 67.9% of RA, 51.3% of axSpA and 48.5% of PsA patients according to the PHQ-9 scale. Additionally, 57.1%, 47.4% and 30.3% of patients respectively showed signs of anxiety as per the GAD-7 scale (Fig. 1). We found a strong correlation between specific questions in MDHAQ and both PHQI-9 and GAD-7 scales (ranging 0.46–0.66).
Discussion: Both depression and anxiety are leading factors in "difficult to treat" patients, not only falsely increasing subjective compounds of disease activity assessment but also directly aggravating immunologic responses. Detecting and proper management of psychological aspects is essential in holistic approach to rheumatic patients.
Conclusion: Depression and anxiety seem to be greatly underestimated in everyday rheumatological practice. MDHAQ may be a simple tool detecting patients for further evaluation of these disorders.

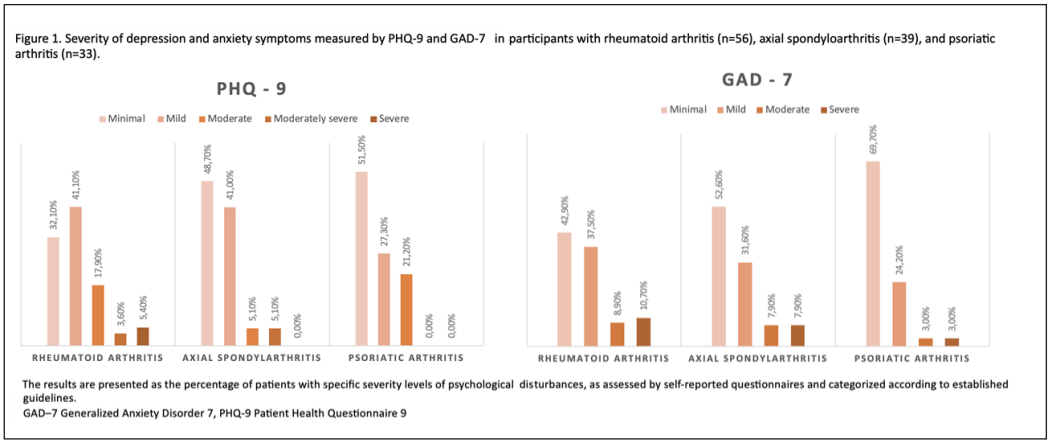

Figure 1. Severity of depression and anxiety symptoms measured by PHQ-9 and GAD-7 in participants with rheumatoid arthritis (n=56), axial spondyloarthritis (n=39), and psoriatic arthritis (n=33).

The results are presented as the percentage of patients with specific severity levels of psychological disturbances, as assessed by self-reported questionnaires and categorized according to established guidelines.
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THE ROLE OF COMPLETE BLOOD COUNT DERIVED BIOMARKERS IN RHEUMATOID ARTHRITIS PATIENTS UNDERGOING TREATMENT WITH TOCILIZUMAB

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Background: Rheumatoid arthritis (RA) is a challenging disorder that requires advanced treatment strategies. Tocilizumab, an Interleukin-6 receptor inhibitor, has shown promise as a therapeutic option. However, limited data exists on whether cost-effective and easily obtainable biomarkers derived from complete blood count (CBC), such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and systemic immune response index (SIRI), can be used to predict treatment outcomes for RA patients undergoing tocilizumab treatment. This area requires further investigation.
Aim: The study aimed to determine if CBC biomarkers can predict tocilizumab treatment outcomes in RA patients and to explore the correlation between NLR, PLR, SII, SIRI, and DAS28.
Methods: 30 RA patients receiving tocilizumab and 28 age and sex-matched controls were enrolled in the study. The values of hematological biomarkers were collected from CBC. A disease activity score based on DAS28-ESR was calculated. Correlation analysis was conducted by calculating Pearson's correlation coefficient. The change in disease activity between the groups according to the baseline level of hematological biomarkers was compared by t-test. A receiver operating characteristic (ROC) curve analysis was performed on each biomarker to determine predictive capabilities.
Results: The ROC curve analysis demonstrated that the area under the curve (AUC) for each biomarker did not surpass the threshold indicative of predictive capability. The AUC values for NLR, PLR, SII, and SIRI were as follows: 0.358, 0.407, 0.377, 0.448. Also, no significant positive correlation has been identified between NLR, PLR, SII, SIRI, and Das-28.
Discussion: The findings showed that NLR, PLR, SII, and SIRI do not predict the outcomes of tocilizumab treatment in RA patients. Also, they cannot replace DAS28 for evaluating disease activity and severity in these patients. These results highlight that while NLR, PLR, SII, and SIRI reflect systemic inflammation in various conditions, they do not specifically capture the inflammatory processes targeted by tocilizumab in RA.
Conclusion: Our findings highlight the need for ongoing exploration beyond traditional hematological markers to improve RA treatment strategies. Larger studies and longer follow-up periods may help uncover subtle trends not detected in this study.

THE INCIDENCE OF WHIPPLE'S DISEASE IN LJUBLJANA AND GORENJSKA REGION

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Background: Whipple's disease is very rare systemic infection caused by Tropheryma whipplei, which if unrecognized, is associated with high morbidity and poor outcome.
The aim of our study was to retrospectively estimate the incidence rate of Whipple's disease in two regions of our country.
Methods: Potential cases of Whipple's disease were ascertained by searching the electronic medical records at our rheumatological department for the 10th Revision of the International Statistical Classification of Diseases code K92, for the period between January 2014 and May 2024. The list was compared with the list of patients treated and followed under the diagnosis of Whipple's disease at the Department of infectious disease of our university medical centre.
Results: During the 10-year observation period we diagnosed Whipple's disease in 10 patients, 5 males and 5 females, with a median (IQR) age at diagnosis of 72.9 (52.7; 78.1) years. Eight patients were residents of Ljubljana or Gorenjska region. Based on the adult population (aged 18 years or more) of the two regions, the incidence of Whipple's disease can be estimated at 1.1 cases per million adults (95% CI: 0.5; 2.2). In clinical picture articular symptoms were the most frequent manifestation (8/10), followed by weight loss (7/10), gastrointestinal symptoms (5/10), myalgias (4/10), fever (3/10), cardiac (3/10) and CNS (3/10) involvement. Six out of 10 patients were unsuccessfully treated as a presumed rheumatic disease with an immunomodulatory therapy before the final diagnosis was made. Three female patients had a history of known autoimmune disease (one case of each SLE, multiple sclerosis and axial spondylarthritis).
Conclusion: Although a retrospective and single center study, our study shows compared to historical data an increasing incidence of Whipple's disease, which might be related to a better disease diagnostics, but also to the increased susceptibility to infection due to more intensive immunomodulatory therapies used in the last decade.

OUR EXPERIENCES WITH IGG4 RELATED DISEASE

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Background: IgG4 related disease (IgG4RD) is rare and peculiar, though increasingly recognized chronic fibrotic-inflammatory autoimmune disease. The aim of our study was to explore the characteristics of patients diagnosed with IgG4 RD at our rheumatological department.
Methods: The medical database of patients treated at our department in the period from 2010 to 2023 was checked for the diagnosis of IgG4RD, using the search term "IgG4". The records of the patients retrieved were then carefully reviewed.
Results: During 14-year period we diagnosed IgG4RD in 26 patients (22 males; 84.6%), with a median (IQR) age at diagnosis of 62 (54; 68) years. Median (IQR) symptom duration time before diagnosis was 7 (3; 15) months. In 18 patients (69.2%) histology was taken and was consistent with IgG4RD in all cases. Serum IgG4 level was elevated in 19/22 patients (84.4%). Overall, 21/26 patients (80.8%) fulfilled ACR-EULAR 2019 classification criteria1 for IgG4 RD. The most common clinical disease subtype2 was retroperitoneal/aortitis subtype (46%), followed by Mikulicz/systemic (31%), and head and neck limited subtype (19%). With 4% pancreatic/biliary subtype was the least common.
Conclusion: The analysis of our IgG4RD patients showed that, as rheumatologists, we mainly recognize the retroperitoneal/aortic and Mikulic/systemic subtypes, and that there is room for improvement, especially with earlier recognition of the disease.

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CELLULAR MIRNA-31 AND MIRNA-125B AS PREDICTORS OF REMISSION IN PATIENTS WITH EARLY RHEUMATOID ARTHRITIS

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Background: Rheumatoid arthritis (RA) is an autoimmune disease significantly affecting the quality of life. Despite diagnostic and treatment advances, new biomarkers are essential in order to effectively manage disease activity and predict treatment response. MicroRNAs (miRNAs) show potential as these biomarkers.
Aim: The study aimed to investigate a broad spectrum of miRNAs in early RA (ERA) patients to identify those that can predict remission after six months of therapy.
Methods: A total of 768 miRNAs were measured in peripheral blood mononuclear cells using TaqMan Array Human MicroRNA Cards in two cohorts of 4 ERA (< 6 months disease duration) patients: those who achieved SDAI/CDAI remission and those who did not respond to therapy after twelve months. Thirteen miRNAs with at least 1.5-fold change were selected and validated in 59 ERA patients (43 females/16 males; mean age 55 ± 17 years) and 54 healthy controls (42 females/13 males; mean age 50 ± 15 years) at baseline and one month therapy. Quantitative PCR determined miRNA expression. Prediction of remission was analyzed using ROC curves.
Results: Baseline miRNA-31 expression predicted remission [SDAI index: AUC = 0.671 (95% CI: 0.527–0.815]; p = 0.029], as did miRNA-125b expression (SDAI: AUC = 0.696 [95% CI: 0.553 — 0.839];p= 0.012, CDAI: AUC= 0.673 [95% CI: 0.523 — 0.823]; p = 0.028] after six months of therapy. Changes in miRNA-31 and miRNA-125b expressions after one month predicted remission achievement by Boolean2.0 score [miRNA-31: AUC = 0.710 (95% CI: 0.563–0.857) p = 0.011; miRNA-125b: AUC = 0.665 (95% CI: 0.508–0.823); p = 0.045] at six months. These changes also predicted major disease improvement (≥ 85% reduction) according to SDAI [miRNA-31: AUC = 0.684 (95% CI: 0.539–0.829); p = 0.022; miRNA-125b: AUC = 0.728 (95% CI: 0.581–0.875); p = 0.004], and for miRNA-125b, also according to CDAI [AUC = 0.664 (95% CI: 0.501–0.826); p = 0.046] at six months.
Discussion: We identified that cellular miRNA-31 and miRNA-125b can predict remission achievement and disease improvement in ERA patients, potentially serving as early biomarkers for therapy response. Further studies are needed to confirm their role.
Conclusion: Cellular expressions of miRNA-31 and miRNA-125b effectively predicted remission after six months, suggesting their potential as prognostic biomarkers in ERA patients.

Acknowledgement
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RACAND SYNDROME IN A 80-YEAR-OLD WOMAN — A CASE REPORT

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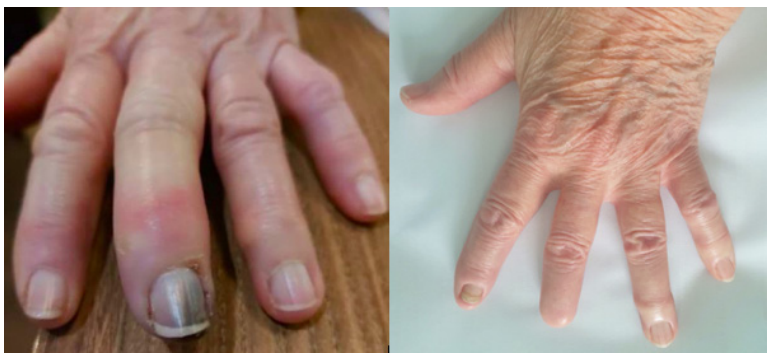
Background: RACAND syndrome is a rare entity which is distinct from established subsets of systemic sclerosis (SSc) and is characterized by a triad of Raynaud's phenomenon (RP), anticentromere antibodies (ACA) and digital necrosis in absence of other SSc-related findings or diagnostic criteria [1]. It has been described only a few times throughout medical literature [1–3].
Case report: We report a case of a 80-year-old woman who presented with fingertip gangrene of the 3rd finger of both hands. She had a medical history of hypertension and palpitations and was otherwise healthy. RP, sclerodactyly and skin thickening were absent. Initially she was treated with amlodipine, rosuvastatin, and dabigatran (due to newly diagnosed paroxysmal atrial fibrillation) and hyperbaric oxygen therapy. CT angiography showed no stenoses in the aorta, aortic branches and upper limb arteries. One month following initial presentation, both gangrenous fingertips autoamputated, while cyanosis of the 2nd fingertip bilaterally appeared. Further investigations

showed positive ANA with highly positive ACA, negative ANCA (MPO and Pr3), anti -dsDNA, cryoglobulins and antiphospholipid antibodies, as well as normal complement levels. Therapy with intravenous prostacyclin analog — iloprost (20 μg daily in monthly 5-day cycles) and 15 mg of oral prednisone was started. After initiating iloprost therapy, cyanosis of 2nd fingertips regressed, and no new signs of digital ischaemia appeared. Due to good response, iloprost dose was soon lowered to 3-day cycles of 20 μg every 6 weeks, and prednisone tapered to 5mg daily. During one year follow-up the patient is well, with no signs of new digital ischaemia. Additional diagnostic workup showed no other signs of systemic or cutaneous manifestations of SSc, with the exception of oesophagitis, insufficiency of the cardia and gastritis, which is managed well with proton pump inhibitors and might also be an incidental finding due to its high prevalence.

Conclusion: The described patient presented with signs and findings characteristic of RACAND syndrome, except the absence of typical Raynaud's phenomenon. Initial gangrene resulted in autoamputation; however further ischaemia was abrogated with treatment. This case report highlights the importance of considering this rare entity in the differential diagnosis of finger ischaemia.



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COMPARATIVE ANALYSIS OF ANTI-DOUBLE STRANDED DNA ANTIBODIES DETECTION ASSAYS

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Background: Anti-double-stranded DNA antibodies (anti-dsDNA) are a specific biomarker for the diagnosis and treatment of systemic lupus erythematosus (SLE). However, the different commercial kits have different performance, so that at least two different assays must be used for more accurate results.

Aim: This study aimed to compare two semi-quantitative indirect immunofluorescence methods using Crithidia luciliae (CLIFT) kits from different manufacturers and to evaluate the QUANTA Flash dsDNA chemiluminescent immunoassay (CLIA) against the routine in-house Farr-FIA method. Additionally, we assessed two diagnostic algorithms combining these methods.

Methods: We analyzed 192 serum samples from patients from the Department of Rheumatology, UMC Ljubljana, using CLIFT kits from Immuno Concepts and Inova Diagnostics, followed by Farr-FIA and CLIA on the BIO-FLASH analyzer. Cohen's kappa was used to evaluate the agreement between the CLIFT assays and between CLIA and Farr-FIA. Spearman's correlation coefficient evaluated the correlation between CLIA and Farr-FIA results. The diagnostic algorithms are shown in Figure 1.

Results: The Cohen's kappa value for agreement between the CLIFT assays was 0.83, indicating near perfect agreement. The correlation between Farr-FIA and CLIA was strong, with a Spearman correlation coefficient of 0.71 ($p < 0.001$). When comparing results as positive or negative, the kappa value between Farr-FIA and CLIA was 0.76. The diagnostic algorithms identified

62 positive and 109 negative samples, with an agreement of 89.1% (171/192). Discrepancies were found in 10.9% (21/192) of cases. Algorithm 2, which detected both medium- and high-avidity anti-dsDNA, identified 15 additional positive samples that were not detected by Algorithm 1, while Algorithm 1 found 6 positive samples that were not detected by Algorithm 2.
DiscussionS: The different methods detect anti-dsDNA antibodies with different avidities, and the use of algorithms enable the detection of clinically significant anti-dsDNA. The algorithms showed an agreement of 89.1%, indicating their utility in enhancing diagnostic accuracy.
Conclusions: Our results show strong agreement between the automated CLIA method and the in-house Farr-FIA method, as well as between two CLIFT assays. The diagnostic performance of testing algorithms should be further assesed.

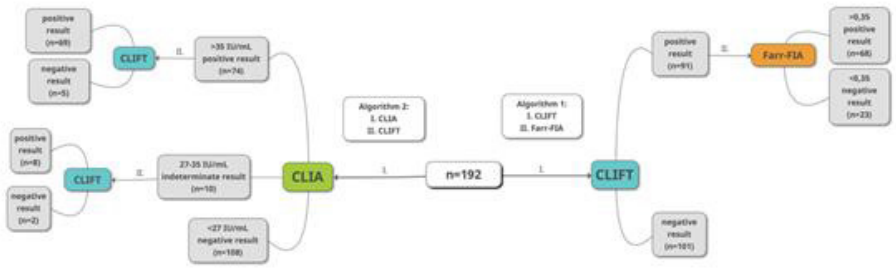

Figure 1 Comparison of two algorithms: Algorithm 1 uses the IIF CLIFT (Immuno Concepts) as a screening method to detect medium-to-high avidity anti-dsDNA and in-house Farr-FIA method to confirm positive results by detecting high avidity anti-dsDNA. Algorithm 2 combines CLIA that detects low-medium-high avidity anti-dsDNA, as initial method, followed by the CLIFT (Inova Diagnostics) to verify positive medium-to-high avidity results.

COMPARISON OF THE USE OF CLINICAL AND LABORATORY INDICATORS OF DISEASE ACTIVITY IN SYSTEMIC LUPUS ERYTHEMATOSUS AND PRIMARY SJÖGREN'S SYNDROME WITH POLYARTHRITIS

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Background: Involvement of musculoskeletal system is common manifestation of systemic connective tissue diseases,so it is important to use appropriate tools to assess the activity of arthritis.
Aim: The aim of the study was to compare the use of selected disease activity indices and to assess relationship between those indices and inflammatory parameters in systemic lupus erythematosus (SLE) and primary Sjögren's syndrome (pSS) with polyarthritis.
Methods: 17 patients with SLE and 16 with pSS were analyzed.In all patients joint tenderness and swelling, intensity of pain and disease activity were assessed.Laboratory markers of inflammation were determined and disease activity was calculated using DAS,SDAI,CDAI,PAS and STR scales in all patients,SLEDAI and BILAG in SLE and ESSDAI in pSS.The indices of arthritis activity were compared between the diseases and correlation and conformity of indices were determind in both diseases.
Results: All the indices analysed,except for STR were found comparably useful in both diseases. In pSS ESSDAI did not correlate with other scales.The indices with CRP,especially DAS28 (CRP) and PAS underestimated the activity of arthritis in patients with SLE as compared to DAS28 (ESR).Most of the disease activity scales,apart from STR and ESSDAI correlated with inflammation markers in both diseases.
Discussions: In this study indices typical for SLE-BILAG and SLEDAI showed correlations with scales traditionally used in RA (except for STR).Also Ceccarelli showed correlation between the DAS28 (ESR) and SLEDAI-2K ($r = 0.4$; $p = 0.0006$) [1]. However, 56.3% patients without joint involvement according to SLEDAI-2K had moderate or high disease activity according to the

DAS28 (ESR) [1].Therefore,it can be assumed that SLEDAI-2K has low sensitivity in detecting arthritis and using the DAS28 (ESR) as a second tool should be useful.
This work and other studies have shown that the use of the DAS 28 (ESR) and DAS 28 (CRP) scales has adequate sensitivity in pSS.However,these indicators showed good correlation with the joint domain of ESSDAI,in contrast to the presented work [2].
Conclusions: DAS, SDAI, CDAI and PAS scales are useful for assessing musculoskeletal involvement in SLE and pSS and additionally SLEDAI and BILAG in SLE.The usefulness of the STR scale in these diseases and the ESSDAI in pSS was not confirmed. Inflammatory markers in SLE and pSS play secondary role in assessment of disease activity. The strong correlations between CDAI and other disease activity scales allow to assess properly arthritis whitout inflammatory parameters.

Correlations between disease activity indicators in pSS (n=16)

		DAS 28 OB.	DAS 28 CRP	DAS original OB	DAS original CRP	CDAI	SDAI	STR 28	STR 68	PAS	ESSDAI
DAS 28 OB	r	1,000	0,923	0,969	0,868	0,905	0,927	-0,699	-0,599	0,597	0,353
	p	X	<0,001	<0,001	<0,001	<0,001	<0,001	0,003	0,014	0,015	0,180
DAS 28 CRP	r	0,923	1,000	0,943	0,963	0,907	0,954	-0,646	-0,525	0,664	0,353
	p	<0,001	X	<0,001	<0,001	<0,001	<0,001	0,007	0,037	0,005	0,181
DAS original OB	r	0,969	0,943	1,000	0,951	0,867	0,922	-0,724	-0,615	0,697	0,346
	p	<0,001	<0,001	x	<0,001	<0,001	<0,001	0,002	0,011	0,003	0,189
DAS original CRP	r	0,868	0,963	0,951	1,000	0,822	0,902	-0,665	-0,544	0,742	0,330
	p	<0,001	<0,001	<0,001	x	<0,001	<0,001	0,005	0,030	0,001	0,212
CDAI	r	0,905	0,907	0,867	0,822	1,000	0,917	-0,656	-0,558	0,490	0,436
	p	<0,001	<0,001	<0,001	<0,001	x	<0,001	0,006	0,025	0,054	0,091
SDAI	r	0,927	0,954	0,922	0,902	0,917	1,000	-0,623	-0,520	0,495	0,352
	p	<0,001	<0,001	<0,001	<0,001	<0,001	x	0,010	0,039	0,051	0,181
STR 28	r	-0,699	-0,646	-0,724	-0,665	-0,656	-0,623	1,000	0,953	-0,667	-0,214
	p	0,003	0,007	0,002	0,005	0,006	0,010	x	<0,001	0,005	0,425
STR 68	r	-0,5988	-0,525	-0,615	-0,544	-0,558	-0,520	0,953	1,000	-0,617	-0,192
	p	0,014	0,037	0,011	0,030	0,025	0,039	<0,001	x	0,011	0,477
PAS	r	0,597	0,664	0,697	0,742	0,490	0,495	-0,667	-0,617	1,000	0,180
	p	0,015	0,005	0,003	0,001	0,054	0,051	0,005	0,011	x	0,504
ESSDAI	r	0,353	0,353	0,346	0,330	0,436	0,352	-0,214	-0,192	0,180	1,000
	p	0,180	0,181	0,189	0,212	0,091	0,181	0,425	0,477	0,504	x

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EARLY INSIGHTS FROM THE JUVENILE INFLAMMATORY RHEUMATISM (JIR)-CLIPS IGAV NETWORK — STRATEGIES FOR MANAGING ATYPICAL SKIN MANIFESTATIONS IN IGAV

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Background: The severity and duration of skin manifestations of IgA vasculitis (IgAV) have been associated with disease prognosis and different treatment strategies.
Aim: The JIR-CliPS network aims to gather real-life clinical practice strategies (CliPS) used by physicians worldwide to present variations in the diagnosis and management of IgAV.
Methods: An online questionnaire in English was distributed to analyze diagnostic and therapy pathways of IgAV with the atypical skin manifestation across various clinical scenarios. The project is funded by COST (European Cooperation for Science and Technology) action CA21168.
Results: Between September 2022 and February 2024, 238 questionnaires were distributed, and 80 responses from physicians from 34 countries were received. Sixty-six percent of respondents had over 10 years of experience with IgAV, predominantly pediatric rheumatologists (88%). Most respondents (79%) often encountered patients with a typical IgAV rash lasting less than four weeks and rarely atypical rashes (45%). Lesions resembling erythema multiforme/target-like lesions (68%), ulcerations (66%), necrotic lesions (61%), and subcutaneous nodules (59%) were identified as atypical for IgAV. Skin biopsies were most frequently considered for recurrent atypi-

cal rashes (77%) and atypical rashes lasting over four weeks (65%). Dermatologists performed biopsies in 86% of cases. In scenarios where a typical rash persisted for less than four weeks without other clinical features of IgAV, a majority of respondents (88%) wouldn't initiate treatment. However, oral prednisolone (< 2 mg/kg body weight/day) was recomended if the rash was atypical, or typical and persisted for more than four weeks (36% and 58%, respectively). For recurrent rashes, 48% favored low to moderate doses of oral prednisolone. Colchicine emerged as the second choice treatment for recurrent rashes and typical rashes lasting over four weeks (24% and 11%, respectively).

Discusions and conclusions: Our findings highlight that decisions regarding diagnostic approach and therapy for IgAV vary based on the duration and characteristics of the rash. Low-dose glucocorticoids are frequently chosen for persistent or atypical skin presentations. Skin biopsies are infrequently required but are often considered for atypical and recurrent rashes. These survey findings highlight the complexity of managing IgAV skin manifestations, emphasizing the need for individualized approach.

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PREVALENCE OF FAMILIAL AUTOIMMUNE DISEASES IN JUVENILE IDIOPATHIC ARTHRITIS

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Background: Autoimmune diseases are relatively common, estimated to affect 5 to 10% of the population. There is evidence for clustering of autoimmunity in individuals and families.

Aim: To evaluate the prevalence of familial autoimmune diseases in children with juvenile idiopathic arthritis (JIA).

Methods: A retrospective, single small center study was performed. Patients diagnosed with JIA who were examined at our pediatric clinic in the last 10 years were enrolled. JIA was classified according to International League Against Rheumatism (ILAR) criteria. Data was collected from patients' medical records.

Results: A total of 115 patients were included. The mean age of children with JIA was 8.1 years. 74 patients (64.3%) were female. 31 patients with JIA (26.9%) had at least one family member with autoimmune disease. The most common familial autoimmune disease was psoriasis (8 patients), then rheumatoid arthritis (7 patients), psoriatic arthritis (7 patients), juvenile idiopathic arthritis (5 patients), autoimmune thyroid disease (3 patients) and ankylosing spondylitis (1 patient).

Discussions: According to our study family members of children with JIA have a higher prevalence of autoimmune diseases. The most common familial autoimmune diseases were psoriasis, rheumatoid arthritis and psoriatic arthritis.

Conclusion: Familial autoimmune diseases prove to be a risk factor for JIA development. There is evidence that autoimmune diseases may share common genetic susceptibility factors.

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MONOCLONAL GAMMOPATHY IN SYSTEMIC LUPUS ERYTHEMATOSUS: CLINICAL COURSE, MALIGNANCY RISK, AND MORTALITY RATE — A SINGLE-CENTER RETROSPECTIVE COHORT STUDY

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Background: Rheumatic diseases were previously associated with increased incidence of monoclonal gammopathy (MG) and its malignant transformation. The present study aimed to investi-

gate the prevalence, malignant transformation risk, clinical correlates and prognostic impact of monoclonal gammopathy (MG) in systemic lupus erythematosus (SLE).

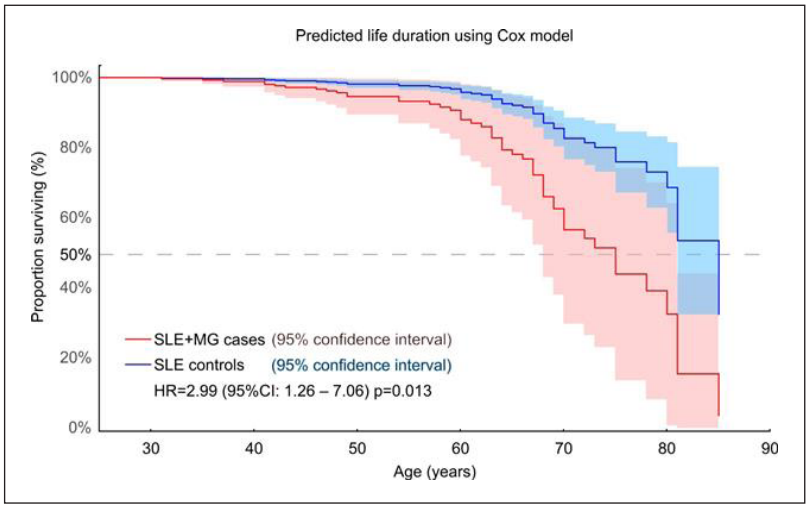
Aim: The aim of our study was to explore [1] the prevalence of and [2] risk of malignant transformation of MG in a cohort of SLE patients, [3] determine the clinical differences in SLE cases with and without MG and [4] assess the significance of MG as a risk factor of unfavorable outcomes in SLE.

Methods: A retrospective cohort study of 1039 SLE patients fulfilling 1997 ACR, 2019 EULAR/ACR and/or 2012 SLICC criteria managed at two tertiary care departments of University Hospital (Krakow, Poland) from January 2012 until November 2019.

Results: SLE + MG cases were older at SLE diagnosis compared to non-MG SLE controls (53 ± 15 years *vs.* 37 ± 15 years, respectively, $p < 0.01$), had higher rates of lymphopenia, anemia, hemolysis, serous effusions, and interstitial lung disease (all $p < 0.05$), and were more frequently treated with cyclophosphamide (57% *vs.* 28%, $p < 0.01$) or rituximab (13% *vs.* 3%, $p < 0.01$). Most MG cases were detected within a year following SLE diagnosis (Q25,Q75: 0, 12 years). Over a median 11-year follow-up (Q25,Q75: 6, 19 years), 34.8% of the SLE + MG cohort were diagnosed with malignancy, compared to 8.1% among SLE controls ($p < 0.001$). MG was associated with the relative hazard of death of HR 2.99 (95% CI 1.26–7.06, $p < 0.05$) and a median survival of 5 years (Q25,Q75: 1, 14; range 0–41) for SLE+MG cases, as compared to 12 years (Q25,Q75: 6, 19; range 0–62) for the controls.

Discussions: SLE+MG patients showed higher rates of complications, malignancy risk, and mortality. Findings suggest MG as a marker of immunodeficiency in SLE, impacting disease course and outcomes.

Conclusions: Our study emphasizes heightened malignancy and mortality rates in SLE + MG cases. The link between immunosuppression, MG incidence and progression warrants further research.



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ASSESSMENT OF COGNITIVE FUNCTIONS IN PSORIATIC ARTHRITIS PATIENTS

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Background: Rheumatic diseases and psoriasis (PsO) are associated with an increased risk of cognitive dysfunction. However, data about cognitive status in psoriatic arthritis (PsA) is limited.

Aim: To assess cognitive functions in patients with PsA in comparison to a control group.

Methods: Sixty-seven adult patients with PsA and 69 healthy controls, with minimum 8 years of formal education, were consecutively enrolled in a single-centre cross-sectional study. Persons with fibromyalgia, vitamin B12 and folic acid deficiency, serious neurological or psychiatric disorders, and chronic inflammatory disease other than PsA and PsO were not included. PsO patients were not included in the control group. Cognitive functions were assessed using the Montreal Cognitive Assessment (MoCA) and the Trail Making Test (TMT) A and B. Depression and anxiety symptoms were measured using Beck Depression Inventory-II (BDI-II) and State-Trait Anxiety Inventory (STAI). Visual Analog Scale pain and FACIT-Fatigue were recorded. Standard clinical assessments for PsA and PsO were conducted.
Results: Patients with PsA performed significantly worse on the TMT-A test ($p = 0.005$). No significant differences between the groups in TMT-B, as well as in MoCA total and individual domain scores were observed. The proportion of individuals with mild cognitive impairment (MoCA < 26) did not significantly differ between PsA (n = 25, 37.3%) and control groups (n = 17, 24.6%, $\chi^2 = 2.00$, $p = 0.157$). MoCA and TMT showed no correlation with clinical parameters of PsA and PsO severity. PsA patients exhibited higher levels of depression, anxiety, and fatigue (Tab. 1). No significant differences in sociodemographic parameters were noticed.
Discussion: PsA patients underperformed on the TMT-A test. The results of the MoCA test were similar between the groups, which is in contrast to observations of DiCarlo and Garcia et al. who reported cognitive impairment in PsA patients [1, 2]. Only minor differences in cognitive status between the PsA and control groups in this study are in concordance with data form Booth et al. suggesting no increased risk of dementia among people with immune-mediated inflammatory diseases [3]. Increased levels of depression and anxiety were consistent with earlier observations.
Conclusions: PsA patients might be at slightly increased risk of cognitive decline, but further research is needed to precisely determine the risk.

Table 1. Cognitive functions, depression, anxiety, and fatigue assessment results (Mann-Whitney U test)

	PsA (N=67)	Controls (N=69)	*p- value*
MoCA	27.0 [17.0, 30.0]	27.0 [19.0, 30.0]	0.650
TMT-A	36.0 [15.0, 182]	28.0 [13.0, 89.0]	**0.005**
TMT-B	80.0 [33.0, 300]	65.0 [31.0, 270]	0.162
BDI-II	8.0 [0, 37.0]	6.0 [0, 34.0]	**0.020**
STAI-S	34.0 [21.0, 70.0]	31.0 [20.0, 77.0]	0.228
STAI-T	39.0 [23.0, 73.0]	35.0 [22.0, 71.0]	**0.015**
FACIT-Fatigue	38.0 [8.0, 52.0]	42.0 [20, 52.0]	**0.004**

Legend: values are expressed as median [min, max]; **MoCA** – Montreal Cognitive Assessment; **TMT-A** – Trail Making Test A; **TMT-B** – Trail Making Test B; **BDI-II** – Beck Depression Inventory-II; **STAI-S** – State-Trait Anxiety Inventory, State scale; **STAI-T** – State-Trait Anxiety Inventory, Trait scale; **FACIT-Fatigue** – Functional Assessment Chronic Illness Therapy-Fatigue questionnaire

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IMPLEMENTATION OF GOTREATIT® SOFTWARE ENHANCES TREAT-TO-TARGET STRATEGY IN AXIAL SPONDYLARTHRITIS PATIENTS CARE: RESULTS FROM POLNOR-RHEUMA COHORT STUDY

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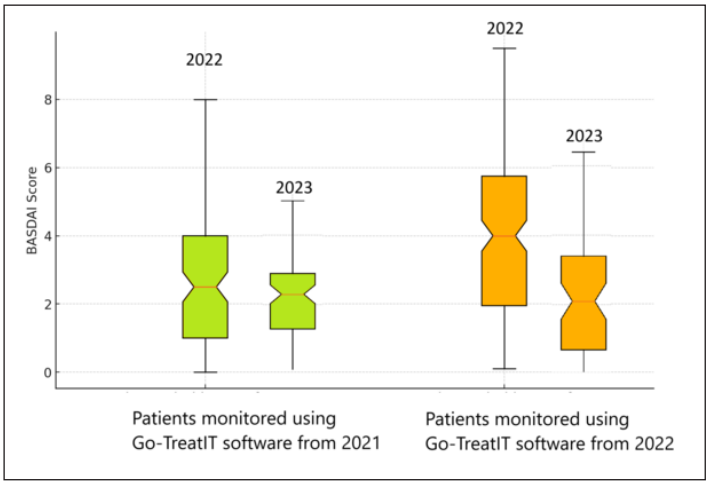
Background: The treat-to-target (T2T) strategy has become crucial in managing axial spondyloarthritis (axSpA). However, its implementation in routine clinical practice remains challenging. Dedicated software solutions may facilitate this process, but their impact on patient outcomes is not well-documented.
Aim: To evaluate the impact of implementing Go-TreatIT software on achieving therapeutic goals in SpA patients.
Methods: This prospective cohort study, part of the POLNOR-Rheuma project, was conducted at the Rheumatology Clinic of the University Hospital in Krakow. SpA patients were randomly recruited and monitored using Go-TreatIT software from 2021. We compared BASDAI scores of

patients enrolled in 2021 (GTI group) with a random group of clinic patients newly included in the observation in 2022 (control group). Both groups were followed for one year.

Results: The study included 52 patients in the GTI group and 58 in the control group. At baseline, the mean BASDAI score for the GTI group (measured in 2022) was 2.82 ± 1.86, significantly lower than the control group's baseline score of 3.49 ± 2.26 ($p = 0.053$). After one year of observation, both groups achieved similar BASDAI scores (GTI: 2.84 ± 1.68, Control: 2.72 ± 1.84, $p = 0.78$), indicating good disease control. The GTI group showed a 5–10% average decrease in disease activity over the observation period.

Discussion: The implementation of Go-TreatIT software was associated with better initial BASDAI scores in the GTI group, suggesting earlier achievement of therapeutic goals. The Comparison of scores after one year indicates that the software facilitates quicker attainment of disease control. The study's limitations include its single-center design and potential confounding factors not accounted for in this analysis.

Conclusion: The implementation of Go-TreatIT software enhances the effectiveness of the T2T strategy in SpA care, as evidenced by improved initial BASDAI scores and maintained disease control. This approach shows promise in optimizing SpA management in routine clinical practice.



STREAMLINED GENETIC DIAGNOSIS AND MANAGEMENT OF AUTOINFLAMMATORY DISEASES: A COLLABORATIVE INITIATIVE IN HUNGARY

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Background: Autoinflammatory diseases are disorders marked by recurrent inflammation without high-titer autoantibodies or antigen-specific T cells, manifesting as periodic fever, rashes, and systemic symptoms. Early and accurate diagnosis is crucial but often hindered by the complexity and inaccessibility of necessary diagnostic tests, leaving many patients undiagnosed.

Unmet need: Underdiagnosis of autoinflammatory diseases is prevalent due to the need for specialized labs and expert interpretation, which are not widely accessible. Genetic tests require sophisticated equipment and specialized personnel, while administrative processes are labor-intensive, hindering timely and accurate diagnosis and treatment.

Aim: A collaboration between Semmelweis University, national academic partners, and industry collaborators, aims to streamline and standardize the processes for identifying, referring, genetically testing, and treating patients with suspected autoinflammatory diseases in Hungary.

The Genetic Testing Laboratory at Semmelweis University provides free genetic tests, including next-generation sequencing (NGS). We accept samples from the Periodic Fever Outpatient Clinic and referrals from partner rheumatology experts. Additionally, we have launched a dedicated website (http://immungenetika.hu/en/homepage/) to enhance information accessibility for parents and healthcare professionals.

Results: In our study, we included 46 affected children (22 girls and 24 boys) with an average age of 9.7 years for girls and 6.5 years for boys. We identified four cases with likely pathogenic variants in dominantly inherited genes and nine cases with likely pathogenic variants in recessively inherited genes. Preliminary results show improved referral and testing rates. Our first interim analysis is scheduled for October, with more detailed findings to be presented at the upcoming meeting, providing insights into the effectiveness of our standardized procedures, their impact on patient care and diagnosis accuracy.
Conclusion: Our project underscores the importance of a coordinated approach to diagnosing and managing autoinflammatory diseases. By providing free genetic testing, streamlining referrals and sample collection, we are addressing significant barriers to care. Initial findings show improved referral and testing rates, likely leading to better patient outcomes. The upcoming interim analysis will provide further insights into the project's impact. Continued collaboration and process refinement are essential to sustain and expand the benefits, ultimately improving the quality of life for patients with autoinflammatory diseases in Hungary.

THE CLINICAL PHENOTYPES OF PATIENTS WITH IGG4-RELATED DISEASE DEPENDING ON SEX — OBSERVATIONS FROM ONE CLINICAL CENTRE

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Background: The diagnosis of IgG4-related disease (IgG4-RD) requires take into account clinical symptoms, results of imaging tests, assessment of serum level of immunoglobulin G4, and histopathological examination of biopsy of lesions/infiltrates characteristics sites for IgG4-RD. At the beginning other causes that may be responsible for clinical symptoms and tests results should be excluded.
Aim: Assessment of the clinical features of patients hospitalized during next 2 years in whom IgG4-RD was confirmed. The incidence of specific disease locations was also compared by patient's sex.
Material and methods: Laboratory tests were performed during hospitalization among others: CRP, C3,C4 components of complement, IgG4 serum level and histopathological assesement of infiltrates suspected of IgG4-RD.
Results: Thirteen patients were included (mean age 54 ± 11 y.o.). All patients were referred due to suspicion of IgG4-RD. The other reasons for such clinical changes were excluded. In all patients glucocorticosteroids(GCs) were administered in different doses before the establishment of IgG-RD diagnosis. In table 1 the main clinical features of analysed patients.
The periorbital site and lacrimal glands sites were the main IgG4-RD localisation for female patients (F/M 6:1), it was confirmed by MRI) or CT, one female patients presented Riedel's thyroiditis and for one mediastinum were the active place for infiltration. Among males retroperitoneal fibrosis, pancreas infiltrations and one case of pleura and parapleural area of the lungs and one mesenteritis were found, in this subgroup one patient presented periorbital involvement. The time from first symptoms to diagnosis was difficult to estimate. Even in one case it was approximately 15 ys. with GCs treatment and temporary improvement.
Discussion and Conclusions: Observations show diversity of sites/organ involvement in IgG4-RD. According to observations on larger groups, IgG4-RD patients presented the different clinical phenotypes of disease. Our small group confirmed that in female group the head and neck involvement dominate. In presented group majority female patients had periorbital involvement. It is difficult to refer to general statistics with such a small group (which is limitation of this analysis), but it was dominated by women in contrast to many other studies. The serum concentration of IgG4 was not such increased as suspected, probably due GCs treatment.

No	sex	First symptoms (years) to diagnosis of IgG4-RD	Localisation			CRP mg/L	Serum IgG4 level (relation to the normal limit)	Histopathology IgG4/HPF and/or IgG4/IgG (%)	Response to GCs
			One	Two	More than 2				
1	F	15	1			1	2.5x	>100 IgG4+/HPF). IgG4/IgG>40%.	Yes
2	F	< 1 year (9 months)	1			1	N	50-80 IgG4+/HPF, IgG4+/IgG < 40%	Yes
3	M	15		1		2	< N	IgG4+/IgG 50%	Yes
4	M	5			1	19	N	19 IgG4/HPF IgG4+/IgG 40%	Yes
5	M	½ year (6 months)			1	62	N	24 IgG4/HPF IgG4+/IgG >40%	Yes
6	F	1.5	1			1	N	30 IgG4/HPF	yes
7	F	4		1		1	1.5x	70-80IgG4/HPF IgG4/IgG>40%	yes
8	F	4			1	1	1.5x	IgG4/IgG >70%	yes
9*	M	3	1			2	1,5x	Under evaluation	yes
10	F	15			1	1	4	>40IgG4/HPF IgG4:IgG>40%	yes
11	M	2			1	3	>5x	20 IgG4/HPF IgG4:IgG<40%	yes
12	F	1	1			23	1,5x	26 IgG4/HPF IgG4:IgG>40%	yes
13	F	9	1			5	>5x	lymphocytic infiltration of salivary glands – under further evaluation	yes

Table 1 The main clinical features of analysed patients

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PULMONARY MANIFESTATIONS IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that typically affects small and medium-sized joints symmetrically. It may also be characterized by systemic involvement — respiratory, cardiovascular, and hematopoietic. Recently, there has been an increased awareness of RA-associated lung disease and subsequently, the importance of its management and treatment.

Aim: To examine the association of demographic characteristics, habits, clinical features, and the presence of rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (ACPA) with the occurrence of pulmonary manifestations in patients with RA.

Methods: Our study included patients diagnosed with RA who were monitored over 5 years (January 1, 2019 — December 31, 2023) at the Department of Rheumatology, Clinical Immunology and Allergology, Clinical Hospital Center Osijek, Croatia.

Results: A total of 97 RA patients were involved in our study, including 18 males and 79 females. The patients were divided into two groups depending on the presence of clinical manifestations, radiographic changes on X-ray, and high-resolution CT scan (HRCT). The presence of pulmonary manifestations was found in 25.8% of patients. There were no significant differences in age and gender between patients with pulmonary manifestations and those without. There were also no significant differences in smoking history, RF, and ACPA values based on the presence or absence of pulmonary manifestations.

Discussions: The difference in results between our and other similar studies, mainly regarding the correlation of pulmonary manifestations with RF and ACPA values, can be attributed to poor heterogeneity, and a smaller number of patients. In the future, considering specific diagnostic methods, such as chest HRCT, would give a better insight into possible pulmonary manifestations in RA patients.
Conclusions: This study's results revealed lung involvement in 25% of RA patients but did not confirm a statistically significant difference between RA patients with pulmonary manifestations and those without based on demographic characteristics, habits, clinical features, and the presence of RF and ACPA. Further investigations involving specific diagnostic procedures and higher numbers of patients are needed to evaluate potential risk factors for lung involvement in RA patients.

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COMBINATION OF RITUXIMAB AND TOFACITINIB IN TREATMENT OF ANTI-MDA5 ANTIBODY POSITIVE DERMATOMYOSITIS — TWO CASE REPORTS

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Background: Anti-melanoma differentiation-associated gene 5 (MDA5) antibody (Ab) positive dermatomyositis (DM) is a rare systemic autoimmune disease characterized by amyopathy or hypomyopathy with typical skin symptoms and rapidly progressive interstitial lung disease (RP-ILD). It is often refractory to immunosuppressive therapy and has poor prognosis [1]. In recent literature it has been shown possible relationship between MDA5-DM and COVID-19 vaccination and infection [2].
Case presentation: A 55-year-old and 52-year-old woman were admitted to the hospital due to fever, cough and skin symptoms. Patohistological finding of the skin biopsy supported diagnosis of dermatomyositis, while chest computed tomography (CT) and lung biopsy revealed ILD. A high titer of anti-MDA5-Ab was present in the myositis antibody panel. Firstly, patients received a 3 day course of pulse methylprednisolone at 500 mg/day, but in the both cases the condition was complicated by the development of glucocorticoid psychosis so therapy was discontinued. Considering ILD progressed rapidly and first patient started oxygen therapy, we initiated plasma exchange (performed 4 times) and tofacitinib 5 mg twice a day, followed by rituximab within 6 months. In the second case we started tofacitinib, followed by rituximab within 4 weeks. Furthermore, patients showed progressive clinical improvement; their skin symptoms were relieved, the titer of anti-MDA5-Ab decreased and follow up chest CT showed amelioration.
Conclusion: Anti-MDA5-Ab positive DM is frequently associated with RP-ILD and high mortality rates in which early detection and treatment are of extreme importance. In this case we reported the potential utility of combination of rituximab and tofacitinib in treatment of anti-MDA5-Ab positive DM.

Key words: anti-MDA5 antibody; dermatomyositis; interstitial lung disease; rituximab; tofacitinib

Table 1. Characteristics of patients with anti-MDA5 Ab-positive DM with RP-ILD

	Case 1	Case 2
Age/Sex	55/F	52/F
Clinical manifestations	Fever, cough, Gottron's and inverse Gottron's papules, heliotrope rash, ulcerated skin lesions	Fever, cough, Gottron's and inverse Gottron's papules, heliotrope rash
Laboratory parameters (at onset)	Ferritin (1600 ug/L), LDH (433 U/L), CK (320 U/L), anti MDA5+++	Ferritin (820 ug/L), LDH (310 U/L), CK (146 U/L), anti MDA5+++
Previous SARS-CoV-2 infection/vaccination	Yes/yes	No/yes
HRCT Chest findings	Diffuse infiltrative OP pattern	OP pattern
Treatment	Steroid pulses* - 500 mg, Plasmapheresis (4x), TOF, RTX	Steroid pulses* - 500 mg, TOF, RTX
Complications	Severe glucocorticoid-induced psychosis	Mild glucocorticoid-induced psychosis
Outcome	Alive (24 months), anti MDA5 neg., Improved	Alive (18 months), anti MDA5+, Improved
LDH = lactate dehydrogenase, OP = organizing pneumonia, TOF = tofacitinib, RTX = rituximab, *Administered for three consecutive days		

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IL-40 IS UP-REGULATED IN THE SYNOVIAL FLUID AND CARTILAGE OF OSTEOARTHRITIS PATIENTS AND CONTRIBUTES TO THE ALTERATION OF CHONDROCYTES PHENOTYPE IN VITRO

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Background: IL-40 is a novel cytokine associated with autoimmune connective tissue disorders. We have previously shown an accumulation of IL-40 in the joint and its expression by immune cells and fibroblasts.

Aims: We aimed to assess the role of IL-40 in association with hyaline cartilage and chondrocyte activity.

Methods: Immunohistochemistry was employed to detect IL-40 in paired samples of loaded and unloaded regions of osteoarthritis (OA) cartilage. Synovial fluid IL-40 was analysed by ELISA in OA (n = 31) and control individuals after knee injury (n=34). The impact of IL-40 on chondrocytes was tested in vitro.

Results: IL-40 was found in chondrocytes of the superficial zone of the OA cartilage, both in loaded and unloaded explants. Additionally, only biopsies from loaded explants showed IL-40 positivity in transitional zone chondrocytes. Levels of IL-40 were significantly elevated in the synovial fluid from OA patients compared to controls ($p < 0.001$) and correlated with synovial fluid leukocyte counts in OA ($r = 0.444$, $p = 0.014$). Chondrocytes exposed to IL-40 increased in the secretion of pro-inflammatory cytokines IL-6 ($p < 0.0001$) and IL-8 ($p < 0.01$). Moreover, a dose dependent up-regulation of matrix degrading metalloproteinases MMP-1 ($p < 0.01$), MMP-3 ($p < 0.05$) and MMP-13 ($p < 0.001$) upon IL-40 treatment was observed in contrast to untreated chondrocytes.

Discussions: IL-40 is accumulated in the cartilage and synovial fluid of OA patients. Based on our in vitro study, extracellular IL-40 appears to play a role in promoting inflammation and cartilage destruction by driving chondrocyte behaviour towards a more aggressive phenotype.

Conclusions: Our study is the first to demonstrate the local over production of IL-40 in the OA joint and its implication in the regulation of inflammation and cartilage destruction.

CAN WE PREDICT THE NEED FOR TREATMENT WITH BIOLOGIC AND TARGETED SYNTHETIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS AT THE TIME OF DIAGNOSIS OF RHEUMATOID ARTHRITIS?

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Background: RA is very heterogeneous in terms of clinical presentation and severity. Many cytokines and chemokines are involved in the pathogenesis. A significant proportion of patients are potentially "difficult to treat" and respond inadequately to conventional synthetic and b/tsDMARDs. Earlier targeted treatment could improve outcomes for this subgroup of patients.
Aim: To identify serum biomarkers at the time of diagnosis that predict the need for treatment with more than one bDMARD and tsDMARD during the first 3 years after diagnosis and thus identify potentially difficult-to-treat (D2T) RA patients.
Methods: Patients who were diagnosed with RA at the Department of Rheumatology, UMC Ljubljana, between 2018 and 2020 and whose blood was drawn at the time of diagnosis were included. Clinical data (date of diagnosis and treatments 3 years) and laboratory results (CRP, SR, SAA, RF and ACPA) were obtained from the medical records. In addition, samples were analyzed for the levels of 40 cytokines/chemokines and 5 acute phase proteins (LEGENDplexes, BioLegend, using the MACSQuant flow cytometer, Miltenyi Biotec). Patients were divided into two groups: Group 1: patients who were successfully treated with MTX and/or a first bDMARD, Group 2: patients who started a second bDMARD or tsDMARD. The Mann-Whitney test was used to test the research hypothesis.
Results: In our cohort of 74 RA patients, 12 (16.2%) patients started a second bDMARD/tsDMARD treatment within the first 3 years (Group 2). Age ($p = 0.0003$) and levels of CCL13 ($p = 0.011$), α2-macroglobulin ($p = 0.016$), CCL8 ($p = 0.034$), SAA ($p = 0.037$) and CRP ($p = 0.045$) were found to differ significantly between groups. Another 5 biomarkers (CCL22, CXCL9, TNFRII, α-1-AGP and IL-6) also differed between the groups, but not significantly (Tab. 1).
Discussions: Potentially D2T-RA patients were younger at the time of diagnosis and had lower levels of CCL13, α2-macroglobulin, CCL8, CXCL9, CCL22, TNFRII and higher levels of SAA, CRP, α-1-AGP and IL-6.
Conclusion: We found significantly different levels of several biomarkers at the time of diagnosis between RA patients with a favorable response to treatment and potentially D2T-RA after 3 years of follow-up. These biomarkers may thus identify potentially D2T-RA patients at the time of diagnosis.

Table 1: Characteristics of the RA patient groups (number, age and sex) and 10 selected analytes out of 50 tested that differ between the groups

	Group 1	Group 2	Increased or decreased in Group 2	Mann Whitney U, p value
Number (% of all, N=74)	62 (83.8)	12 (16.2)		
Sex (male:female ratio)	20:42	2:10		0.28*
Age (years, median (IQR))	62.5 (55.8-69.0)	39.0 (28.1-56.5)	↓	0.0003
MCP-4, CCL13 (pg/mL, median (IQR))	204.73 (142.93-312.56)	135.96 (89.91-176.34)	↓	0.011
α2-macroglobulin (μg/mL, median (IQR))	3193.40 (2633.62-3667.97)	2771.43 (1944.07-3052.21)	↓	0.016
MCP-2, CCL8 (pg/mL, median (IQR))	46.76 (39.11-56.11)	34.27 (24.92-46.61)	↓	0.034
MDC, CCL22 (pg/mL, median (IQR))	1574.70 (1234.94-2029.51)	1479.09 (1102.03-1509.30)	↓	0.051
MIG, CXCL9 (pg/mL, median (IQR))	337.70 (203.48-506.54)	236.23 (89.91-176.34)	↓	0.063
TNFRII (pg/mL, median (IQR))	413.87 (260.70-664.20)	312.68 (205.18-397.81)	↓	0.100
SAA (mg/L), median (IQR))	25.55 (9.13-99.40)	69.65 (27.35-418.00)	↑	0.037
CRP (mg/L, median (IQR))	14.00 (5.00-40.00)	39.50 (13.25-99.25)	↑	0.045
α-1-AGP (μg/mL, median (IQR))	2302.89 (1751.55-3066.41)	2852.22 (2351.33-4344.02)	↑	0.076
IL-6 (pg/mL, median (IQR))	58.97 (30.30-121.36)	100.71 (71.66-126.94)	↑	0.132

*Chi-square test

RITUXIMAB IN CSDMARD-REFRACTORY SYSTEMIC SCLEROSIS — PRELIMINARY DATA FROM A PROSPECTIVE, OBSERVATIONAL, MONOCENTER STUDY

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Background: Currently, there are only a few bDMARDs with limited evidence of efficacy for the treatment of systemic sclerosis (SSc) with progressive disease non-responsive to csDMARDs.
Aims: To assess the efficacy of rituximab in SSc patients with progressive skin involvement/ polyarthritis/ interstitial lung disease (ILD) non-responsive to methotrexate (MTX)/ cyclophosphamide (CYC)/ mycophenolate (MMF) in a monocentric, prospective, observational study.
Methods: In total, 24 SSc patients (21 females, 5 lcSSc/19 dcSSc, mean age 48, disease duration 5.7 years, modified Rodnan skin score (mRSS) 17, disease activity (ESSG, European Scleroderma Study Group) 4.1) with progressive skin thickening/ arthritis/ILD non-responsive to MTX/CYC/MMF were treated with 2 (n = 8) or 3 (n = 16) series of rituximab (1g *i.v.* at day 0 and 14, every 6 months). Before each series of rituximab, mRSS, finger-to-palm (FTP) distance, inter-labial/incisal distance, disease activity [Visual Analog Scale (VASph); ESSG] were assessed, patient-reported outcomes assessing global function (Scleroderma Health Assessment Questionnaire, SHAQ), quality of life (Medical outcomes study Short Form 36, SF-36), fatigue (Fatigue Impact Scale, FIS), depression (Beck's Depression Inventory-II, BDI-II), physical activity (Human Activity Profile, HAP), gastrointestinal (UCLA_SCTC_GIT_2.0) and pulmonary (St. George's Respiratory Questionnaire, SGRQ) symptoms were filled out. Peripheral blood was analyzed for routine laboratory parameters, and stored for biobanking.
Results: We observed a statistically significant improvement in mRSS and disease activity (VASph, ESSG) at months (M) 6 and 12, and a significant increase in C3 (M6, M12) and C4 (M6) levels

and a borderline decrease in ESR (M12), a trend toward an increase in Forced Vital Capacity (FVC) at M12, and a significant improvement of respiratory symptoms (SGRQ-Activity Scale). In addition, left hand function improved significantly (deltaFTP-left-hand, M6), the overall function (HAQ, M12) had a trend to improve. We observed a significant reduction of depression (BDI-II, M6), and a trend toward an improvement in mental aspects of the quality of life (SF-36-Mental Component Summary, M6) (Tab. 1).

Discussions: Our result are consistent with the current evidence [1].

Conclusions: Treatment with rituximab in SSc patients with progressive skin-/articular-/ILD- involvement non-responsive to csDMARDs significantly improved the skin score, disease activity, hand function, breathlessness, depression, and increased complement levels.

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Table 1.

Parameter	Month 0 (n=24)	Month 6 (n=24)	Month 12 (n=16)	p-value (p_m0-m6; p_m0-m12)
mRSS	18.6 ± 10.0	14.6 ± 8.9	13.4 ± 9.8	**p<0.0001; p=0.0009**
ESSG	4.08 ± 1.98	1.32 ± 0.76	1.06 ± 0.81	**p<0.0001; p<0.0001**
VASph (mm)	60.3 ± 17.0	30.5 ± 8.1	27.6 ± 7.9	**p<0.0001; p<0.0001**
ESR (mm/h)	22.3 ± 19.2	24.6 ± 19.4	15.9 ± 7.7	p=0.5025; p=0.0782
C3 (g/L)	1.27 ± 0.20	1.36 ± 0.16	1.33 ± 0.19	**p=0.0258; p=0.0217**
C4 (g/L)	0.23 ± 0.10	0.26 ± 0.11	0.22 ± 0.10	**p=0.0191**; p=0.1665
FVC (%)	77.3 ± 21.0	78.0 ± 19.8	79.9 ± 21.8	p=0.4049; p=0.1324
SGRQ-AS	91.1 ± 68.3	80.7 ± 66.1	39.3 ± 30.5	p=0.1444; **p=0.0022**
dFTP-R (cm)	5.88 ± 3.27	6.18 ± 2.75	6.72 ± 2.93	p=0.0726; p=0.8683
dFTP-L (cm)	5.87 ± 3.13	6.50 ± 2.56	7.09 ± 2.60	**p=0.0266**; p=0.4015
HAQ	1.22 ± 0.72	1.13 ± 0.80	0.98 ± 0.80	p=0.3077; p=0.0961
SF36-MCS	39.9 ± 12.8	44.0 ± 13.9	45.7 ± 10.5	p=0.1371; p=0.4897
BDI-II	17.2 ± 14.4	15.5 ± 14.4	12.0 ± 9.9	**p=0.0340**; p=0.8991

Acronyms: Data are presented as mean ± SD. Significant results are highlighted in bold (p<0.05).Month 0, before the first series of rituximab; month 6, before the second series of rituximab; before the third series of rituximab; mRSS, modified Rodnan skin score; ESSG, European Scleroderma Study Group activity score; ESR, erythrocyte sedimentation rate; C3, complement 3; C4, complement 4; FVC, forced vital capacity; dFTP-R/L, delta (i.e., extension – flexion) finger to palm right/left hand; VASph, disease activity assessed by a physician using the visual analog scale 0-100 mm; HAQ, Health Assessment Questionnaire; SF36-MCS, Medical outcomes study Short Form 36-Mental Component Summary; BDI-II, Beck's Depression Inventory-II, SGRQ-AS, St. George´s Respiratory Questionnaire-Activity Scale.

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ASSESSMENT OF CARDIOVASCULAR RISK IN PATIENTS WITH SYSTEMIC SCLEROSIS — TESTING THE TOOLS BASED ON SCORE AND ITS MODIFICATIONS COMPARED TO ULTRASOUND EXAMINATION OF SUBCLINICAL ATHEROSCLEROSIS

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Introduction: Cardiovascular (CV) risk is increased in systemic sclerosis (SSc). Nevertheless, to date, there is no specific tool recommended for evaluation of CV risk in SSc.

Aim: to evaluate the CV risk in SSc compared to healthy controls (HC) and to explore the accuracy of SCORE, SCORE2 and its modifications.

Methods: 92 SSc patients (81 females; mean age 52; mean disease duration 6.8 years; dcSSc 28/lcSSc 64) and 197 HC (147 females, mean age 56.7) with no history of CV disease were included. Subclinical ATS (carotid artery disease (CARD), carotid intima-media thickness (CIMT), pulse wave velocity (PWV), ankle-brachial index (ABI)), and body composition (densitometry, bioelectrical impedance analysis) were examinated. The risk of fatal CV events was evaluated by SCORE and SCORE2, in SSc also by the modified (mSCORE) (coefficient 1.5 recommended by EULAR for infammatory arthritis), and 3.59 (SCOREx3.5; SCORE2x3.5) based on the estimated CV risk in SSc [1].

Results: SSc patients had a trend to more prevalent dyslipidemia ($p = 0.063$) and significantly more often prediabetes ($p < 0.001$) compared to HC. Prevalence of diabetes mellitus, arterial hypertension were comparable, but SSc used more often antihypertensives ($p < 0.001$) including calcium channel blockers

SSc had significantly increased prevalence of CARD, unfavorable CIMT and ABI ($p < 0.05$ for all) compared to HC, but a trend to lower SCORE and comparable SCORE2.

In SSc, the CV risk and markers of subclinical ATS were associated especially with age, HbA_{1c}, disease duration, and mean arterial pressure ($p < 0.05$ for all).

The SCORE, mSCORE and SCORE2 were inaccurate in CV risk estimation when compared with US examination. Multiplying the SCORE and SCORE2 by coefficient 3.59 showed significantly higher accuracy (Fig. 1).

Discusion: Coeficient 3.59 may be appropriate for estimating the CV risk in SSc. Results should be verified in more studies.

Conclusions: This cross-sectional case-control study demonstrated a significantly increased risk of subclinical ATS in SSc compared to HC, despite the opposite trend in CV risk calculated by SCORE/SCORE2. The CV risk in SSc was associated especially with age, disease duration, and HbA_{1c} levels. SCORE and SCORE2 underestimated the CV risk, but using the coefficient 3.59 [1] sigificantly increases their accuracy.

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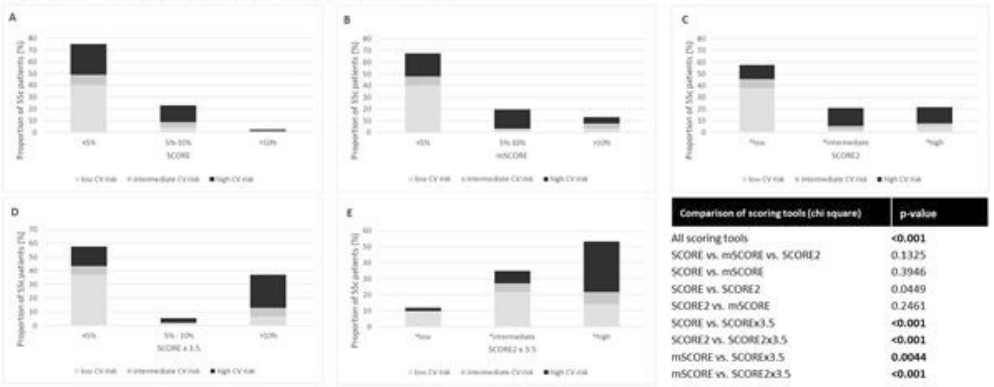
Figure 1: Comparison of CV risk calculated by SCORE, mSCORE and SCORE2 and modified SCOREx3.5 and SCORE2x3.5 and findings of subclinical atherosclerosis on ultrasound examination of carotides

Cardiovascular risk category based on the cardiovascular risk scoring systems showed in vertical columns (calculated by SCORE, mSCORE, SCORE2; SCOREx3.5, and SCORE2x3.5):
*low, <2.5% (for <50 years of age), <5% (for 50-69 years of age), <7.5% (for ≥70 years of age);
*intermediate, 2.5-7.5% (for <50 years of age), 5-10% (for 50-69 years of age), 7.5-15% (for ≥70 years of age);
*high, ≥7.5% (for <50 years of age), ≥10% (for 50-69 years of age), ≥15% (for ≥70 years of age).

Cardiovascular risk based on US examination findings marked by grayscale:
Black, highest risk (CIMT >1.0mm, > 1 paque or 1 plaque >1,9mm)
Dark grey, medium risk (CIMT 0.9-1.0mm, maximum 1 plaque < 1,9mm)
Light grey, low risk (CIMT <0.9mm, no plaques)



Comparison of scoring tools (chi square)	p-value
All scoring tools	**<0.001**
SCORE vs. mSCORE vs. SCORE2	0.1325
SCORE vs. mSCORE	0.3946
SCORE vs. SCORE2	0.0449
SCORE2 vs. mSCORE	0.2461
SCORE vs. SCOREx3.5	**<0.001**
SCORE2 vs. SCORE2x3.5	**<0.001**
mSCORE vs. SCOREx3.5	**0.0044**
mSCORE vs. SCORE2x3.5	**<0.001**

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EFFICIENCY AND SAFETY PROFILE OF BIOLOGIC AGENTS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: RETROSPECTIVE ANALYSIS FROM SINGLE TERTIARY CENTRE

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Objective: In recent years, biologic drugs, rituximab (RTX), belimumab and anifrolumab, have been increasingly used in the treatment of moderate to severe forms of systemic lupus erythematosus (SLE). Although these drugs appear to be promising, data on their effectiveness in „real life" are still lacking. Therefore, our aim was to analyze the indications, effectiveness and safety of biologic drugs in SLE.

Methods: We conducted a retrospective review of SLE patients treated with biologic agents in our center from May 2021 to October 2023. The data were obtained from medical records.

Results: A total of 14 SLE patients treated with biologics were included in this study, with a female to male ratio of 11:3. 6 patients received RTX due to arthritis (n = 2) and nephritis (n = 4). A good

therapeutic response was achieved in 5 patients. In 1 patient with lupus nephritis, there was no response. Side effects developed in 2 patients with nephritis (hypogammaglobulinemia and cytomegalovirus pneumonia). Belimumab was prescribed to 5 patients. Indications were: skin changes refractory to the standard treatment in 3 patients, arthritis in 1 patient and combination of the skin lesions and arthritis in 1 patient. Clinical improvement was achieved in 4 patients. There was no efficacy in the patient with arthritis. Unfortunately, 1 patient developed progressive multifocal leukoencephalopathy during treatment with belimumab, while no significant adverse effects were noted in the other treated patients. 2 male patients were treated with anifrolumab because of skin affection and arthritis, while the female patient had only skin changes. Anifrolumab was effective in 2 patients, while it was discontinued in 1 patient due to worsening of SLE and pneumonia.
Conclusions: Target biologics have contributed to great progress in the treatment of SLE, which is in concordance with the results of our study, despite the small number of patients. Of course, the use of these drugs is burdened with side effects which require more intensive follow-up of the patients.

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SCLEREDEMA DIABETICORUM

Bence Pokoly, László Fónyad, Eszter Mercédesz Müller, Péter Vince Bálint

Scleredema diabeticorum is a peculiar complication of diabetes mellitus, which is considered rare or perhaps more precisely rarely recognized in everyday clinical practice. It belongs to the group of primary cutaneous mucinoses. It has an unknown underlying pathomechanism and can primarily affect the skin and subcutaneous connective tissue. This causes diffuse induration and non-pitting swelling, which begins on the posterior neck and upper back and can therefore lead to limited cervical mobility. Occasionally even internal organs can be affected, giving rise to potentially life-threatening complications. First a brief historical overview and concerns regarding classification issues based on etiology and underlying conditions will be shared. Following this we will describe its usual clinical appearance and summarize specific histological changes which are a characteristic of this progressive disease. We will showcase various prevalence data, diagnostic and differential diagnostic considerations, and the potential regiment of treatment options. Finally we will present an in-depth case report, richly illustrated with microscopic and ultrasound pictures.

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PRO-INFLAMMATORY MONOCYTES AND CD11C EXPRESSION IN ACPA POSITIVE INDIVIDUALS WITH ARTHRALGIA AND THEIR ASSOCIATIONS WITH SUBCLINICAL SYNOVITIS PRECEDING THE ONSET OF ARTHRITIS

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Background: Autoantibodies against citrullinated proteins (ACPA) increase the risk of clinical arthritis and can be detected years before rheumatoid arthritis (RA) onset. EULAR's definition of clinically suspect arthralgia (CSA) helps to differentiate patients at risk of RA from those with other types of arthralgia. We previously identified a shift towards pro-inflammatory monocyte subsets in individuals at risk for RA. CD11c, involved in pro-inflammatory cytokine production, is highly expressed in the mononuclear cells of RA patients.
Aim: To study monocyte subsets and CD11c expression in at-risk individuals with arthralgia.
Methods: Individuals from the At Risk of RA (ARRA) prospective observational cohort were defined as having arthralgia without clinical arthritis at baseline and being either ACPA+ and/or meeting the EULAR definition of CSA. Baseline peripheral blood samples were analyzed us-

ing flow cytometry. Monocytes were classified into classical, intermediate, and nonclassical subsets. CD11c membrane expression was assessed in each subset. Ultrasound (US) synovitis was evaluated using GLOESS and US7 scores.

Results: Out of 207 at-risk individuals, 46 developed clinical arthritis (progressors) within a median of 8 months of follow-up. Individuals who had not yet progressed to arthritis with symptom duration >12 months at the latest assessment were defined as non-progressors (n = 151). There were no significant differences in the % of monocyte subsets between ACPA+/ACPA– or CSA+/CSA- individuals. However, ACPA+ individuals had higher CD11c expression in both classical (p = 0.024) and nonclassical (p = 0.040) monocyte subsets than ACPA- individuals. No differences in monocyte subsets were observed between progressors and non-progressors, but ACPA+ progressors meeting CSA criteria had higher CD11c expression in classical (p = 0.030) and nonclassical (p = 0.015) monocytes and a trend towards higher expression in intermediate monocytes when compared to all non-progressors. In progressors; baseline % of intermediate and nonclassical monocytes positively correlated with baseline tender joint count, DAS-CRP, and US-detected subclinical synovitis, while classical monocytes correlated with these parameters negatively (Tab. 1).

Conclusions: We show increased CD11c expression in monocytes of ACPA+ individuals at risk for RA, particularly in progressors meeting CSA criteria. The positive correlation of pro-inflammatory monocyte subsets with subclinical activity, assessed before the development of clinical arthritis, suggests their potential role in RA pathogenesis.

Acknowledgement
Projects NU22-05-00226, MHCR-023728, SVV-260638

Variable	Monocyte subpopulation	p-value	Spearman's correlation coeficient r_s
Tender joint count	% classical	0,0025	-0,4452
	% intermediate	0,0225	0,3434
	% nonclassical	0,0111	0,3794
DAS-CRP score	% classical	0,0051	-0,4149
	% intermediate	0,0006	0,4987
	% nonclassical	0,0260	0,3355
GLOESS score	% classical	0,0365	-0,3548
	% intermediate	0,0600	0,3211
	% nonclassical	0,0088	0,4362
US7 score	% classical	0,0549	-0,3810
	% intermediate	0,0141	0,4755
	% nonclassical	0,0547	0,3811

CRTAC1: A NOVEL INDICATOR OF LUNG INVOLVEMENT IN SYSTEMIC SCLEROSIS

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Background: Interstitial lung disease (ILD) represents the leading cause of mortality in patients with Systemic Sclerosis (SSc). Cartilage acidic protein-1 (CRTAC1), secreted by alveolar type-2 epithelial (AT2) cells, is implicated in ILD and a potential biomarker for assessing AT2 cell health in lavage fluid and plasma [1]. Despite its significance, there is an absence of data on CRTAC1 in the context of SSc.

Aim: This study aims to investigate the role of CRTAC1 in SSc patients, particularly in relation to pulmonary involvement.

Methods: We collected plasma samples from 76 SSc patients (65 females, mean age 43.6, mean disease duration 6.7 years, lcSSc:45, dcSSc:31, ILD:43, all fulfilled the 2013 ACR/EULAR criteria) and 89 healthy individuals (HC, 37 females, mean age 41.1). Patients were examined by experienced rheumatologists and assessed for the European Scleroderma Study Group activity score (ESSG), modified Rodnan skin score (mRSS), forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), diffusing capacity for carbon monoxide (DLCO) and Medsger Disease Severity Scale (DSS). CRTAC1 levels were measured using the CRTAC1 ELISA (Ray Biotech).
Results: CRTAC1 levels in plasma were significantly lower in SSc patients compared to HCs ($p < 0.001$). CRTAC1 was decreased in SSc patients with ILD compared to SSc patients without ILD ($p = 0.048$). Regression analysis adjusted for body mass index, C-reactive protein and age showed a negative association with DSS pulmonary involvement ($p = 0.016, \beta = -2.46$) and ESSG ($p = 0.1, \beta = -1.66$) and a positive association with DLCO ($p = 0.081, \beta = 1.77$), FEV1 ($p = 0.099$, $\beta = 1.68$) and FVC ($p = 0.098, \beta = 1.68$). CRTAC1 levels were also decreased in SSc patients with gastrointestinal tract ($p = 0.014$) and joint ($p = 0.005$) involvement and pulmonary arterial hypertension ($p = 0.018$). No other significant associations were detected between the systemic levels of CRTAC1 and the examined clinical or laboratory parameters of interest. Gender was not found to be a confounding factor.
Conclusion: Systemic levels of CRTAC1 are decreased in SSc patients, especially among those with ILD, reduced lung function, and elevated disease activity.

Acknowledgement
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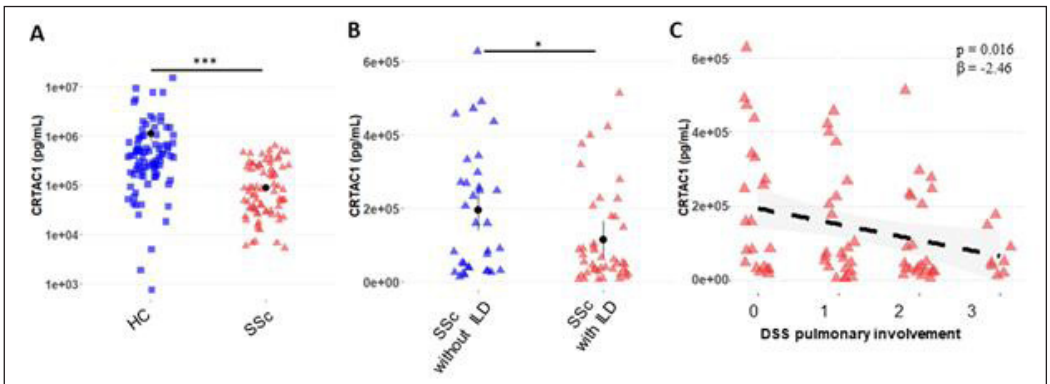

Figure 1. Systemic levels of CRTAC1 in (A) patients with systemic sclerosis (SSc) vs. healthy controls (HC), and (B) the presence of interstitial lung disease (ILD) or (C) stratified according to the degree of severity of pulmonary involvement (Medsger Disease Severity Scale (DSS)). The error bars represent 95% confidence intervals with the estimated mean. * p<0.05; ** p<0.01; *** p<0.001

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NON-VITAMIN K ORAL ANTICOAGULANTS VERSUS WARFARIN IN PATIENTS WITH TRIPLE POSITIVE ANTIPHOSPHOLIPID SYNDROME — A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Long-term anticoagulation is recommended in patients with antiphospholipid syndrome (APS). However, the safety and effectiveness of direct oral anticoagulants (DOACs) in the latter is still an open question.

Methods: This review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A systematic search was performed on PubMed, the Cochrane Library, Web of Science and Scopus between 11th October 2023 and 20th October 2023. The risk of bias assessment was performed using the Revised Cochrane risk-of-bias tool for cluster-randomized trials. Clinical trials and randomized controlled trials including effectiveness (rate of tromboemobilic events — TEs) and safety data on DOACs versus warfarin in patients with triple APS, were considered for inclusion. For meta-analysis, mean difference with a 95% confidence interval was obtained and all results were depicted as forest plots.
Results: Of 741 studies, three were included with a total of 124 participants treated with rivaroxaban or apixaban, versus 125 on warfarin. In analyzing all TE, there was a higher incidence of TE in DOAC group compared to warfarin group, however with none or borderline statistical significance using random- effects meta-analysis model (OR = 3.73, 95% CI: 1.01; 13.77, p = 0.05) with no significant heterogeneity between studies (I^2 = 0%; p = 0.37). The results of the analysis is depicted in Figure 1. When considering only arterial thromboembolic events (ATE), there was a statistically significant higher incidence of ATE in the DOAC group compared to warfarin group (OR = 11.54, 95% CI: 1.34; 99.28, p = 0.03) with no significant heterogeneity between studies (I^2 = 0%, p = 0.67).
Conclusions: Current data indicates that rivaroxaban administration in triple positive APS carries a higher risk of developing TEs. However, apixaban and dabigatran have only been evaluated in two studies while edoxaban was not evaluated. Subsequently, the exact role of DOACs is to be explored and their safety remains debatable. Thus, warfarin for now remains the gold standard for thromboprophylaxis in the APS setting.

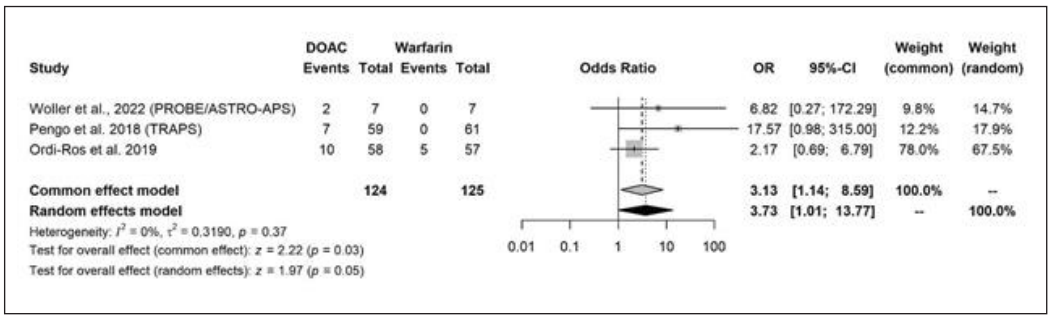

Figure 1. Meta-analysis of all TE in DOAC group compared to warfarin group

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METHOTREXATE INDUCED PARADOXICAL PSORIASIS

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Methotrexate (MTX) is one of the first-line drug in the treatment of psoriatic arthritis (PsA) according to the recommendations of the European League of Associations for Rheumatology. MTX in low dose can cause a range of adverse effects, from mild to severe or life threatening. The occurrence of paradoxical psoriasis (PP) during treatment with MTX has not been published in the literature so far.
We present a 60-year-old patient with psoriatic arthritis sine psoriase who developed PP during treatment with MTX. A month after the introduction of the MTX, psoriasis guttate evolved. It was proven by dermatologist and pathohistological findings. Serologic evidence of recent streptococcal infection was not present. The MTX therapy was discontinued, and the clinical status of the skin and joints worsened. Treatment with ixekizumab was started, which led to remission of the disease.

Unlike MTX, tumor necrosis factor-alpha inhibitors are known to induce PP and other paradoxical cutaneous reactions. The aim of this case report is to highlight the possibility of developing paradoxical psoriasis during treatment with MTX.

Key words: methotrexate, paradoxical psoriasis, psoriatic arthritis

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A CASE REPORT: INTERFERONOPATHY OR NF-KB DISORDER?

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Background: Interferonopathies and NF-kappaB-pathies represent a newly identified subset of autoinflammatory conditions. They are characterized by dysregulation in either the type I interferon or NF-kappaB signaling pathways.
Aim: We present a case of monogenic autoinflammatory disease exhibiting features of both interferonopathy and NF-kappaB-pathy.
Methods: Information about the patient was collected from the medical records.
Results: The disease onset occurred immediately after birth, characterized by painful erythematous subcutaneous infiltrates, initially on the face and later spreading to the trunk and extremities. The patient experienced intermittent fevers and exhibited elevated inflammatory markers including hyperferritinemia, hypercomplementemia, hyperfibrinogenemia, increased sedimentation rate, elevated C-reactive protein, leukocytosis with neutrophilia, and thrombocytosis. Transaminase levels and dyslipidemia were also elevated. Notably, cerebrospinal fluid analysis revealed pleocytosis with monocyte predominance and significant hypoglycorachia, although extensive microbiological investigations failed to identify an underlying infection explaining the prolonged inflammatory state. Skin biopsy demonstrated histological features consistent with lobular panniculitis. Considering the clinical presentation, exclusion of infectious and malignant etiologies, and a highly positive interferon signature, an autoinflammatory disorder was suspected. CANDLE syndrome emerged as the leading candidate in the differential diagnosis. Subsequently, the patient developed cyclical episodes of abdominal pain accompanied by hematochezia and diarrhea. Esophagogastroduodenoscopy and colonoscopy revealed acute colitis with increased eosinophils on histological examination. Following the diagnosed condition, treatment commenced with systemic glucocorticoids, initiated at gradually decreasing doses alongside the Janus kinase inhibitor, baricitinib. This regimen led to partial improvement, though full disease control was not achieved. Subsequently, whole exome sequencing identified a pathogenic variant in exon 5 (c.671+1G>C) of the IKBKG gene, confirming the diagnosis of NEMO-NDAS (NEMO deleted exon 5-autoinflammatory syndrome). Therapy with a tumor necrosis factor alpha inhibitor (adalimumab) was initiated. Despite treatment, the patient continues to experience febrile episodes with elevated inflammatory markers and recurrent skin manifestations. Additionally, there has been significant growth delay, with the patient weighing only 6000 grams at 18 months of age.
Conclusions: Interferonopathies and NF-kappaB-pathies denote a recently identified category of autoinflammatory conditions. It's crucial for clinicians to recognize the clinical indicators of disruptions in the type I interferon and NFkappaB pathways to suspect these conditions accurately and guide appropriate diagnostic investigations.

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EXTENDED MONITORING OF IGA VASCULITIS NEPHRITIS PATIENTS: THE CROATIAN NATIONAL CENTER'S FINDINGS

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Background: The discussion surrounding the duration of follow-up for IgA vasculitis (IgAV) patients at risk of developing nephritis (IgAVN) remains unresolved.
Aim: Hence, our research sought to delineate the clinical and laboratory traits of individuals with IgAVN, alongside probing factors linked to both short and long-term prognoses in these patients.
Methods: We extracted patients diagnosed with IgAVN from the national cohort of individuals with IgAV diagnosed between 2010 and 2024, followed-up for a minimum of six months.
Results: During the specified timeframe, 739 patients received an IgAV diagnosis, with 155 subsequently developing IgAVN. Among these, 93 were monitored for more than six months. Of these, 38 patients were biopsied. In the others, the diagnosis was made based on the pathological findings of the urine. The median age at IgAVN diagnosis was 7.62 (5.62, 11.64) years, with nephritis typically appearing 4 (0, 20) days after initial symptoms, though onset could occur as late as 559 days afterward. Nephritic syndrome manifested in 14 patients (15%), nephrotic syndrome in 6 (6.5%), and the remainder exhibited abnormal urine findings. Median follow-up was 15 (9.5, 43.5) months. Treatment predominantly consisted of systemic glucocorticoids (50.5%), followed by immunosuppressants (17.2%). 33% of patients received NSAIDs for joint manifestations. At the six-month mark post-diagnosis, abnormalities in urine persisted in 34 patients (36.6%), decreasing to 14 patients (15%) after 12 months, signifying a noteworthy enhancement in laboratory results ($p < 0.01$). However, after 6 and 12 months, patient outcomes did not significantly differ ($p = 1.0$), with 78 patients (83.9%) experiencing a good outcome. There was no significant outcome difference between patients with isolated erythrocyturia and those with proteinuria ($p = 0.74$).
Conclusions: Our findings indicate that IgAVN typically arises within the initial 4 days of IgAV onset, with most patients experiencing a positive outcome. However, there's no notable contrast in outcomes between individuals with isolated erythrocyturia and those with proteinuria. Our study highlights that 4% of patients developed IgAVN after surpassing six months but less than twelve months of monitoring. This underscores the importance of extending follow-up to at least twelve months for individuals with IgAV.

Support
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THE EFFECT OF CYTOKINE BLOCKING AGENTS ON THE LONG-TERM IMMUNOGENICITY OF TETANUS TOXOID VACCINE IN CHILDREN WITH RHEUMATIC DISEASES

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Background: The optimal time for tetanus booster vaccination in adolescents with rheumatic diseases (RD) treated with anti-cytokine therapy (ACT) is not known.
Aim: To determine long-term immunogenicity after the fifth dose of tetanus vaccine, given according to the National Immunization Program (NIP), in adolescents with RD, and to determine if the timing of the sixth booster dose in the NIP is appropriate also for patients treated with ACT.
Methods: We conducted a retrospective study and collected data from adolescents with RD at regular visits at the rheumatology outpatient clinic, UCH, Ljubljana, Slovenia. Patients received the fifth dose of tetanus vaccine according to the NIP at least two years before inclusion in the study. The anti-tetanus toxoid IgG levels were measured using ELISA, levels above 0.1 IE/mL were considered protective. We compared levels between those treated with ACT and those never

treated with systemic medications. For statistical analysis, we used a student's t-test for two independent samples.

Results: We collected data for 44 adolescents with RD (75% female). Most prevalent diagnosis was juvenile idiopathic arthritis (93%). Among the enrolled patients, 22 (50%) were treated with ACT (mostly (91%) with anti-TNFα). Twelve (27%) were treated with immunomodulatory therapy, and ten (23%) never received any systemic medications. We measured the IgG levels 5.6 ± 1.9 years after the fifth dose. On average, the IgG levels were lower in patients treated with ACT compared to untreated patients, with IgG 0.64 ± 0.51 IE/mL and 0.71 ± 0.46 IE/mL, respectively. Difference was, however, not statistically significant (p-value = 0.75).

Three (9%) patients (two treated with anti-TNFα, one with anti-IL-1) had IgG levels below the threshold and were considered unprotected. We measured their IgG levels 5.3 to 6.2 years after the fifth dose. After, all three were vaccinated with the sixth dose of the vaccine ahead of the vaccination planned in the NIP. They developed adequate responses, with IgG levels of 2.22, 0.62, and 1.52 IE/mL, respectively.

Discussions and Conclusion: Our preliminary results suggest that patients with RD treated with ACT tend to have lower anti-tetanus toxoid IgG levels compared to the untreated patients and could benefit from an earlier booster tetanus vaccination than indicated in the NIP.

SERUM LEVELS OF ANTI-IL-6 AUTOANTIBODIES IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHY

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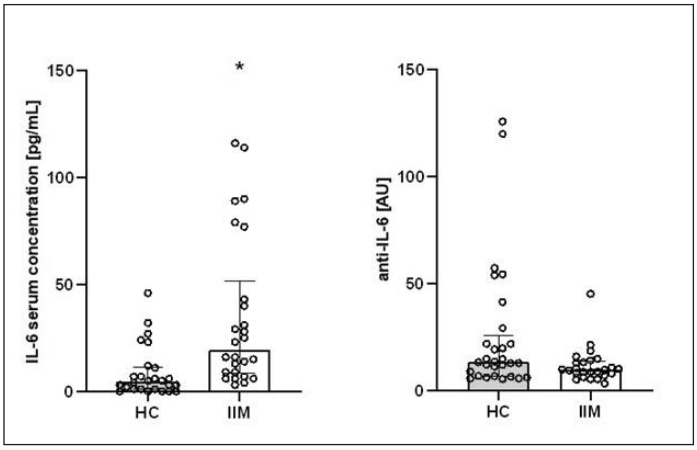
Background: Antibodies against interleukin-6 (anti-IL-6) are a class of anti-cytokine autoantibodies that bind interleukin-6 (IL-6). Although their exact function is not yet known, they can neutralize the function of IL-6 or prolong its circulation time. They are present in the serum of some healthy individuals, and their serum levels are elevated in some pathological conditions, such as systemic sclerosis. In severe infections, neutralising anti-IL-6 antibodies can limit the immune response. In contrast, they may have a protective function in an overreactive immune system.

Aim: We aimed to measure serum levels of IL-6 and anti-IL-6 antibodies in a cohort of patients with idiopathic inflammatory myopathy (IIM).

Methods: We collected serum samples from 26 IIM consecutive IIM patients and 26 age- and sex-matched controls without rheumatic diseases to measure IL-6 and anti-IL-6 IgG levels by ELISA. In 7 randomly selected samples with detectable anti-IL-6 levels, acid dissociation was performed to release all anti-IL-6 antibodies complexed with IL-6. In this way, we ensured that the lower levels of anti-IL-6 antibodies detected in the IIM cohort were not due to their unavailability for anti-IL-6 ELISA. We also confirmed that the autoantibodies detected in both cohorts were of high avidity by performing ELISA in the presence of increasing concentrations of a chaotropic agent (NaCl).

Results: Our IIM cohort included 12 patients with dermatomyositis, 8 with antisynthetase syndrome, 3 with polymyositis, 2 with immune-mediated necrotising myopathy and 1 with overlap syndrome. The median serum IL-6 concentration in IIM patients was 20 pg/ml, thus significantly higher than in healthy controls with a median value of 5 pg/ml ($p < 0.0001$). Conversely, the level of anti-IL-6 antibodies was lower in IIM patients (median 10 AU) than in healthy controls (median 13 AU), but this difference did not reach statistical significance ($p = 0.09$). A decreasing trend was observed in older individuals of both cohorts.

Discussion and conclusion: Our results demonstrated higher IL-6 serum concentration and slightly, but insignificantly lower serum levels of anti-IL-6 antibodies in IIM patients compared to healthy controls. Further functional tests are required to determine if these autoantibodies can neutralize or change the kinetics of IL-6.



SERIOUS MULTI-SYSTEMIC IMMUNE-RELATED ADVERSE EVENTS IN A PATIENT WITH PLEURAL MESOTHELIOMA TREATED WITH CHECKPOINT INHIBITORS (IPILIMUMAB — NIVOLUMAB)

Katja Stopar

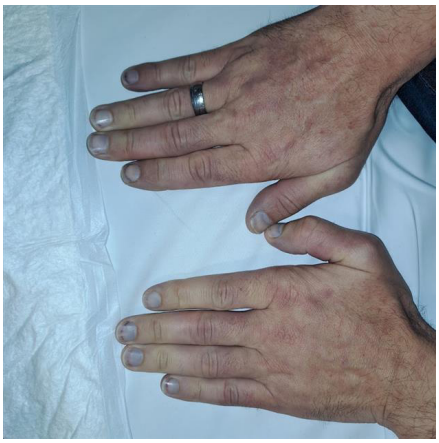
Checkpoint inhibitors (CPI) are effective in treating malignancies with poor prognosis by enhancing the immune system function and promoting antitumor response. Based on the data, rheumatic and musculoskeletal immune-related adverse events (irAEs) are observed in 10-15% patients receiving CPI, the commonest being arthralgias (arthritis), myalgias, sicca symptoms, rarely all vessel-sized vasculitis and myositis.

We present a case of a 44 years old man diagnosed with pleural mesothelioma with pericardial infiltration in 2022. After neoadjuvant chemotherapy (carboplatin/pemetrexed) decortication of left lungs and diaphragm reconstruction was done. In October 2023 due to disease progression CPI (ipilimumab/nivolumab) was started.

In February 2024, after receiving three infusions of CPI, patient reported new onset rashes on the skin of lower limbs, joint pain and whitening of fingers when exposed to cold. At clinical examination nonnecrotic palpable purpura on the lower limbs, arthritis of ankle joints, severe cyanosis of several fingers in addition to splinter hemorrhages of nails were seen. Detailed immunoserological tests, including ANA, ANCA, antiphospholipid antibodies were negative, as were inflammatory parameters and CBC. Skin biopsy was performed and revealed small vessel immune-complex vasculitis. Treatment with i.v. iloprost, nifedipin, Aspirin and medium dosed methylprednisolone was started, that lead to the resolution of episodes of Raynaud phenomena and skin purpura.

Two weeks after discharge the patient reported paresthesia and muscle weakness in stock distribution on the lower limbs with foot drop. Neurological examination was suspicious for polyneuropathy and electromyography was consistent with mononeuritis multiplex (bilateral involvement of sural and peroneal nerves). In addition, while being asymptomatic, ECG revealed a new development of diffuse ST segment depression. Values of troponin were normal, however based on raising values of proBNP, a CPI induced myocarditis was suspected. Immunomodulatory therapy was intensified with methylprednisolone pulses, intravenous immunoglobulins and cyclosporine with good and prompt short-term clinical response — an improvement in neurological status and lowering of proBNP. CPI was discontinued.

In conclusion, the patient with pleural mesothelioma on CPI therapy developed broad spectrum of irAE, which were well-controlled with immunomodulatory therapy (targeting both T and B cells).



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EFFECTIVITY AND TOLERABILITY OF ANTIFIBROTIC THERAPY IN CONNECTIVE TISSUE DISEASE ASSOCIATED INTERSTITIAL LUNG DISEASES — REAL WORLD DATA

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Background: Connective tissue diseases associated interstitial lung diseases (CTD-ILD) comprises a wide disease spectrum from asymptomatic ILD to progressive pulmonary fibrosis (PPF). This latter group particularly contribute to patients' mortality. Management of CTD-ILD is usually overseen by rheumatologists at the same time it should be an ILD team work involving pulmonologists, radiologists and other specialists. The pattern and extension of structural changes evaluated by high resolution chest computed tomography will influence our treatment decision whether immunosuppressive (ISU) or antifibrotic or the combination of the two is used.
Aim: Authors aimed to evaluate the effectiveness and tolerability of antifibrotic therapy in their CTD-ILD patient cohort in real world setting.
Methods: A retrospective evaluation of CTD-ILD patients treated with antifibrotics (nintedanib/pirfenidone) was performed from December 2019 to June 2024 in the ILD Center at the University of Debrecen, Hungary. Lung function and DLCO tests (before and 6, 12, 24 months after therapy initiation) were performed as well as HRCT pattern and fibrotic involvement in percentage of total lung volume has been analysed by three independent radiologists to measure the effectivity of the applied treatment.
Results: Antifibrotics has been initiated in 63 CTD-ILD patients (46 female, 17 male, age: 61.6 ± 11.3 years av.). The distribution of patients according to diagnosis was the following: systemic sclerosis (SSc) (n = 20), rheumatoid arthritis (RA) (n = 20), idiopathic inflammatory myopathies (IIM) (n = 6), primary Sjögren's syndrome (n = 3), mixed connective tissue disease (MCTD) (n = 2), ANCA associated vasculitides (n = 2), interstitial pneumonia with autoimmune features (n = 2) and RA+IIM and SSc+IIM overlap syndromes (n = 5), and 95% of total patients were treated with ISU therapy besides antifibrotics. Usual interstitial pneumonia (UIP) was detected in 50.2% and non-specific interstitial pneumonia (NSIP) in 49.8% of patients, and the average fibrotic involvement was 22% before starting antifibrotics. The average therapeutic timeframe was 13.4 months during which numerical improvement has been documented in FVC and DLCO in 61% of patients. Antifibrotic treatments needed to be stopped in 15% in total treated patients, 4 patients died of PPF.
Conclusion: Using antifibrotic treatment is an effective way to hault progression and preserve lung capacity in CTD-ILD patients together with ISU therapy.

THE IMPORTANCE OF PAIN REDUCTION AND IMPROVING FUNCTIONAL OUTCOMES IN RHEUMATIC DISEASE TREATMENT — ETORICOXIB IN REAL-WORLD CLINICAL SETTING: ITS TREATMENT OUTCOME IN PATIENTS WITH RHEUMATIC DISEASES

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Background: Rheumatic diseases cause pain and functional impairment. Nonsteroidal anti-inflammatory drugs (NSAIDs) are vital in managing rheumatologic diseases, reducing pain and inflammation. Selective NSAIDs, such as etoricoxib, effectively control pain and inflammation and therefore improve patients' functional outcomes, that are crucial for their overall well-being and improved life quality.

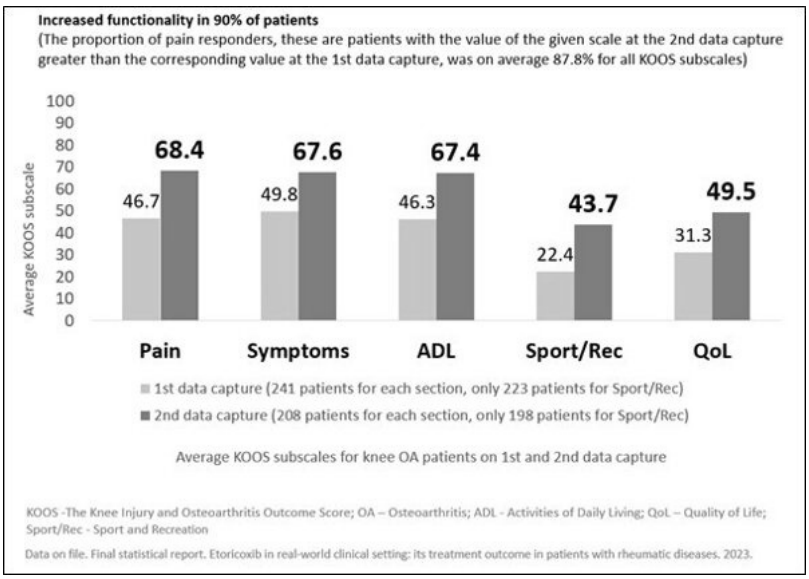
Aim: The RED study aimed to evaluate Krka's etoricoxib real-world effectiveness in reducing pain intensity in patients with various rheumatic diseases, and evaluate influence on functional outcomes in patients with knee osteoarthritis with Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire.

Methods: This international, non-interventional, observational, prospective, multicenter study evaluated etoricoxib's effectiveness in treating rheumatic diseases (OA, RA, AS, acute gouty arthritis) according to the investigator's consideration and in compliance with SmPC. The study enrolled 1,188 patients, with two data captures over 8 (± 4) weeks.

Results: Etoricoxib treatment resulted in a clinically meaningful pain reduction for 70.9% (n = 829) of patients (pain ≤ 30 mm on VAS/baseline reduction ≥ 50%). All KOOS subscales showed statistically significant improvements ($p < 0.001$). The lowest average subscale score was for Sport/Recreation (i.e., 22.4 ± 18.7). Occurrence of gastro-intestinal (GI) symptoms decreased from 12.4% at baseline visit (for naive as well as previously treated patients) to less than 1.7%, with no serious cardio-vascular (CV) events recorded, even in patients with hypertension.

Discussion: The study supported both hypotheses: etoricoxib significantly reduced pain intensity and improved KOOS parameters. Major improvement in pain scores was expected as etoricoxib is deemed one of the most effective NSAIDs. Due to reduction of disease's impact on the functionality of patients with knee osteoarthritis, there was the increase in all KOOS subscales between data captures. The lowest KOOS score was for Sport/Recreation showing the biggest negative influence of disease on patients' sporting and recreational activities however, patients' ability to recreate almost doubled after the treatment. Low incidence of GI symptoms and no serious CV or other AE related to etoricoxib treatment indicates a good safety profile.

Conclusion: The RED study indicates that Krka's etoricoxib is effective and well-tolerated in treating rheumatic diseases, reducing pain intensity and improving functional outcomes with minimal GI and CV side effects.



MEVALONATE KINASE DEFICIENCY: AN UPDATED CLINICAL OVERVIEW CONSIDERING THE REVISED SHARE RECOMMENDATIONS

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Background: Mevalonate kinase deficiency (MKD) is a rare autoinflammatory disease, and the guideline that assists in its diagnosis and management, the 2015 SHARE Guideline, will soon reach its ten-year mark.
Aim: Our goal was to review the literature that has been published since SHARE guidelines were last updated, and to assist in the care of MKD patients by providing up-to-date recommendations in our summary.
Methods: A comprehensive PubMed search identified articles published post-last SHARE review. From 407 initial publications, 279 were excluded by title/abstract screening and 214 more by full-text analysis. Using a standardized data extraction form, we acknowledged the need for a scoping review due to challenges in orphan disease research and limited high-level evidence. Adopting Burns et al's Levels of Evidence and grading recommendations, a working group formulated proposed recommendations. Consensus was reached with an agreement level above 7/9 points, negating further consultation.
Results: We propose 3 overarching principles, accompanied by 15 recommendations pertaining to the diagnosis of MKD, 14 recommendations concerning the treatment of MKD patients, and 4 recommendations addressing the vaccination of MKD patients.
Discussions: These statements emphasize the importance of managing MKD patients within a multidisciplinary team led by experts in hereditary autoinflammatory disorders, integrating genetic counseling, and educating patients and caregivers on targeted therapies, lifestyle changes, and regular follow-ups. Encouraging patient participation in clinical studies or registries is crucial for advancing understanding and treatment. Diagnosis relies on genetic tests for MVK gene mutations, and treatment recommendations evolve with new research and clinical experience. Maintaining vaccination schedules, with adjustments guided by immunomodulatory treatments and expert consultation, is essential.
Conclusions: Through this systematic literature review, we aim to provide a valuable resource for clinicians and researchers, fostering a deeper understanding of MKD and guiding optimal patient care.

THE RELATIONSHIP BETWEEN CENTRAL OBESITY AND DISEASE ACTIVITY IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Rheumatoid arthritis (RA) is a chronic autoimmune disease associated with increased incidence of metabolic syndrome (MetS). Central obesity is one of the most important

risk factor for MetS, included in the classification criteria of MetS. Obestity is considered a risk factor for RA and associated with the disease activity.

Aim: To assess the incidence of central obesity and associations between central obesity and parameters of RA activity.

Methods: This study included 65 patients with RA (57 female, 8 male), treated with conventional synthetic disease-modifying anti-rheumatic drugs. The central obesity was diagnosed according to the International Diabetes Federation (IDF) criteria, when the waist circumference was ≥ 94 cm in men and ≥ 80 cm in women. The activity of RA was assessed with clinical, laboratory, and ultrasound (US) parameters.

Results: The central obesity was found in 46 RA patients (70.8%) [40 female (70.2%), 6 male (75%)]. Patients with RA and central obesity in comparison without central obesity, were characterized by significantly higher disease activity and inflammatory parameters. In patients with *vs.* without central obesity we found: higher Disease Activity Score in 28 joints (DAS28): 5.2 (± 1.2) *vs.* 4.3 (± 1.6) (p = 0.01); erythrocyte sedimentation rate (ESR) 41.1 (± 26.6) *vs.* 22.3 (± 18.23) mm/h (p = 0.007); C-reactive protein (CRP) 17.5 (7.1–33.6) *vs.* 5.6 (1.5–14.9) mg/L (p = 0.02); the degree of synovial vascularisation in power Doppler US (PDUS) 5.2 (± 4.1) *vs.* 3.1 (± 2.7) (p = 0.04); Health Assessment Questionnaire (HAQ) value 1.4 (± 0.6) *vs.* 0.9 (± 0.6) (p=0.01). Significantly positive correlations were found between the waist circumference value and HAQ (p = 0.003, r = 0.36), DAS28 (p = 0.004, r = 0.36), ESR (p < 0.001, r = 0.45), CRP (p = 0.005, rs = 0.34).

Discussions: The results of this study demonstrate that central obesity is common in patients with RA (in about 70% of patients in our group). The relationship has been found between central obesity and RA activity, evaluated with several clinical, laboratory, and US parameters.

Conclusions: The occurrence of central obesity is associated with higher disease activity in patients with RA.

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INCREASED SYSTEMIC S100A4 LEVELS IN SCLERODERMA-RELATED INTERSTITIAL LUNG DISEASE DECREASE WITH CYCLOPHOSPHAMIDE/RITUXIMAB TREATMENT AND SERVE AS PREDICTORS FOR TREATMENT RESPONSE AND EARLY DISEASE PROGRESSION

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Background: Our previous studies demonstrated that S100A4 is overexpressed in scleroderma (SSc) skin, fibroblasts, and preclinical models of SSc. Inhibition of S100A4 by murine mAbs (6B12) prevented the progression and induced regression of established dermal fibrosis induced by bleomycin.

Aim: This study assessed the potential role of systemic S100A4 as a biomarker of SSc-related features and a predictor of treatment response and disease progression.

Methods: Systemic levels of S100A4 were measured by ELISA (CUSABIO, Houston, USA) in 104 age-/sex-matched healthy controls (HC) and four different cohorts:

1) cross-sectional SSc patients (n = 117; mean age 55.8, disease duration 5.0 years);

2) SSc patients with active interstitial lung disease (ILD) treated with 6 (n = 24) or 12 (n = 16) months of iv cyclophosphamide;

3) SSc patients with progressive skin involvement and/or arthritis and/or ILD treated with 2 (n = 8) or 3 (n = 16) 6-month cycles of rituximab; and

4) VEDOSS (Very Early Diagnosis of SSc) patients with Raynaud´s phenomenon who did not progress (n = 15) or progressed (n = 11) to SSc. Data are presented as median (IQR).

Results: 1) S100A4 was significantly increased in SSc [67.2 (43.1–88.7) *vs.* 51.1 (35.9–60.8) ng/mL in HC; $p < 0.0001$], especially in SSc with ILD [72.7 (49.1–95.2) *vs.* 54.7 (37.5–77.1) ng/mL without ILD; $p = 0.0124$] and borderline with GI [69.3 (50.3–96.7) *vs.* 63.1 (38.9–84.4) ng/mL without GI; $p = 0.0854$]. S100A4 was associated with lung function tests and borderline with disease duration (Tab. 1).
2) Treatment of active SSc-ILD with CPA significantly decreased S100A4 over 6 months [76.3 (52.9–98.6) *vs.* 73.2 (44.4–98.6) ng/mL; $p = 0.013$], whereas baseline S100A4 predicted the decrease in systemic inflammation (Tab. 1).
3) Treatment of progressive SSc with rituximab significantly decreased S100A4 over 6 months [83.7 (70.4–109.6) *vs.* 81.5 (60.2–100.4) ng/mL; $p = 0.0455$]. Baseline S100A4 predicted an improvement in hand function, fatigue, depression, whereas a change in S100A4 was associated with function, quality of life, fatigue, and physical activity (Tab. 1).
4) Over an average of 3.5 years of follow-up in VEDOSS patients, S100A4 significantly decreased ($p = 0.0073$) in non-progressors (13/15), whereas increased in 8/11 progressors (inter-group $p = 0.0429$). S100A4 was associated with CRP and age in non-progressors and the titer of ANA in progressors (Tab. 1).
Conclusions: Systemic S100A4 levels are elevated in SSc (especially in ILD), decrease with cs/bDMARD treatment, and predict the treatment response and progression to early disease.

Acknowledgment
Supported by MHCR023728.

Table 1.

Correlated parameters			p-value	Spearman/Pearson r
I. Cross-sectional cohort of SSc patients (n=117)				
S100A4		FVC	**0.0296**	-0.2012
		FEV1	**0.0376**	-0.1925
		Disease duration	0.0677	0.1702
II. Patients with active SSc-ILD treated with cyclophosphamide (500 mg/m² i.v.) for 6 months (n=24) or 12 months (n=16)				
S100A4_m0		ESR_m0-m6	**0.0032**	0.5283
		CRP_m0-m6	**0.0042**	0.4722
III. SSc patients with active/progressive skin-/ interstitial lung-/ articular involvement non-responsive to csDMARDs treated with two cycles (m0, m6; n=8) or three cycles (m0, m6, m12; n=16) of rituximab (1 g i.v. at day 0 and 14)				
S100A4_m0		CHFS_m0	0.0502	0.4040
		UCLA-reflux_m0	0.0742	0.3712
		UCLA-distention_m0	0.0881	0.3557
		UCLA-soilage_m0	0.0836	0.3604
		UCLA-social functioning_m0	0.0711	0.3749
		UCLA-emotional wellbeing_m0	**0.0225**	0.4637
		UCLA-total score_m0	**0.0273**	0.4502
		CHFS_m0-m6	**0.0348**	0.4325
		FIS-cognitive dimension_m0-m6	0.0894	-0.3623
		FIS-social dimension_m0-m6	**0.0245**	-0.4674
		BDI-II_m0-m6	**0.0219**	-0.4654
		UCLA-soilage_m0-m12	0.0696	0.4809
S100A4_m0-m6		HAQ_m0	**0.0067**	-0.5380
		SHAQ global_m0	**0.0394**	-0.4231
		SF36-PCS_m0	0.0913	0.3603
		FIS-social dimension_m0	**0.0319**	0.4483
		FIS-total score_m0	0.0695	-0.3852
		HAP-AAS_m0	**0.0173**	0.4811
		HAP-AAS_m6-m0	**0.0441**	-0.4144
IV. VEDOSS patients who progressed to SSc (n=11) or did not develop SSc (n=15)				
Non-progressors	S100A4_baseline	CRP_baseline	**0.0175**	0.6442
		Age_baseline	0.0790	-0.4674
	S100A4_FU-baseline	CRP_baseline	**0.0360**	-0.5844
Progressors	S100A4_FU-baseline	ANA_FU	0.0815	-0.5472

Acronyms: Significant results are highlighted in bold ($p<0.05$). FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; CHFS, Cochin Hand Function Scale; UCLA, UCLA SCTC GIT 2.0 questionnaire assessing the gastrointestinal problems; FIS, Fatigue Impact Scale; BDI-II, Beck's Depression Inventory-II; HAQ, Health Assessment Questionnaire; SHAQ global, aggregated score of HAQ and Scleroderma HAQ visual analog scales II-VI; SF36-PCS, Medical outcomes study Short Form 36-Physical Component Summary; HAP-AAS, Human Activity Profile-Adjusted Activity Score assessing the level of physical activity the patient is capable of performing; FU, last follow-up; ANA, titer of antinuclear antibodies.

UPDATED SAFETY ANALYSIS OF FILGOTINIB IN MODERATE TO SEVERE ACTIVE RHEUMATOID ARTHRITIS PATIENTS OVER A MEDIAN OF 4.3 YEARS

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Background: Filgotinib (FIL) is an oral JAK1-preferential inhibitor approved at doses of 100 mg (FIL100) and 200 mg (FIL200) for treating moderate to severe active rheumatoid arthritis (RA). Previous safety analyses indicated similar tolerability between the doses, with a lower incidence of herpes zoster in FIL100 compared to FIL200 [1].

Aim: To update on selected treatment-emergent adverse events (TEAEs) for FIL over a median (maximum) exposure of 4.3 (8.3) years.

Methods: Data were integrated from seven clinical trials, including DARWIN Phase II studies (NCT01888874, NCT01894516), FINCH Phase III studies (NCT02889796, NCT02873936, NCT02886728), and long-term extension studies DARWIN 3 (NCT02065700) and FINCH 4 (NCT03025308). Exposure-adjusted incidence rates (EAIRs)/100 patient-years of exposure (PYE) were calculated for major adverse cardiovascular events (MACE), venous thromboembolism (VTE), arterial systemic thromboembolism (ASTE), nonmelanoma skin cancer (NMSC), other malignancies, herpes zoster, serious infections and deaths. Data were analyzed up to May 8, 2023.

Results: In total, 3,691 patients received FIL, totaling 14,127 PYE. Median exposure was 4.3 years for pooled FIL, 3.6 years for FIL100 and 4.4 years for FIL200. Baseline demographics and disease characteristics were similar across doses.[2] Incidences of MACE, VTE, ASTE, NMSC, malignancies (excluding NMSC), serious infections, herpes zoster and all-cause mortality were low and consistent with previous data (Tab. 1). The EAIR/100 PYE for serious infections was 2.2 (95% CI: 1.8, 2.6) for FIL100 and 1.7 (95% CI: 1.5, 2.0) for FIL200. For herpes zoster, the EAIR was 1.1 (95% CI: 0.8, 1.4) for FIL100 and 1.4 (95% CI: 1.2, 1.7) for FIL200 (Tab. 1). Due to the shorter exposure duration in FIL100 (5,202.2 PYE) compared to FIL200 (8,924.5 PYE), comparisons should be interpreted with caution.

Discussion and Conclusions: The safety profile of FIL remains consistent over time, with no new safety concerns identified. Both doses showed stable safety results, maintaining the previously observed similar tolerability and adverse event rates.

Table 1. Frequencies and EAIRs of Selected Adverse Events in Original and Ongoing Long-Term Extension Rheumatoid Arthritis Clinical Trials, Including Current and Previous Data Cut

	Data cut (completed studies* and May 2, 2022 [DARWIN 3]/May 6, 2022 [FINCH 4])		Current data (completed studies† and May 8, 2023 [FINCH 4])	
	FIL100 (PYE=5,202.2) n=1,647	FIL200 (PYE=8,924.5) n=2,267	FIL100 (PYE=5,202.2) n=1,647	FIL200 (PYE=8,924.5) n=2,267
	n (%), EAIR per 100 PYE (95% CI)		n (%), EAIR per 100 PYE (95% CI)	
MACE‡	22 (1.3), 0.5 (0.3, 0.7)	27 (1.2), 0.3 (0.2, 0.5)	29 (1.8), 0.6 (0.4, 0.8)	34 (1.5), 0.4 (0.3, 0.5)
VTE‡	9 (0.5), 0.2 (0.1, 0.4)	15 (0.7), 0.2 (0.1, 0.3)	12 (0.7), 0.2 (0.1, 0.4)	16 (0.7), 0.2 (0.1, 0.3)
ASTE	1 (<0.1), <0.1 (0.0, 0.1)	1 (<0.1), <0.1 (0.0, 0.1)	1 (<0.1), <0.1 (0.0, 0.1)	1 (<0.1), <0.1 (0.0, 0.1)
NMSC	9 (0.5), 0.2 (0.1, 0.4)	27 (1.2), 0.3 (0.2, 0.5)	11 (0.7), 0.2 (0.1, 0.4)	30 (1.3), 0.3 (0.2, 0.5)
Malignancies (excluding NMSC)	30 (1.8), 0.7 (0.4, 0.9)	57 (2.5), 0.7 (0.5, 0.9)	35 (2.1), 0.7 (0.5, 0.9)	62 (2.7), 0.7 (0.5, 0.9)
Herpes zoster	49 (3.0), 1.1 (0.8, 1.5)	114 (5.0), 1.5 (1.2, 1.8)	55 (3.3), 1.1 (0.8, 1.4)	120 (5.3), 1.4 (1.2, 1.7)
Serious infections	97 (5.9), 2.2 (1.8, 2.2)	149 (6.6), 1.9 (1.6, 2.2)	110 (6.7), 2.2 (1.8, 2.6)	154 (6.8), 1.7 (1.5, 2.0)
All-cause mortality	26 (1.6), 0.6 (0.4, 0.8)	57 (2.5), 0.7 (0.5, 0.9)	36 (2.2), 0.7 (0.5, 0.9)	66 (2.9), 0.7 (0.6, 0.9)

*Completed studies: FINCH 1, 2 and 3; DARWIN 1 and 2; †Completed studies: FINCH 1, 2 and 3; DARWIN 1, 2 and 3; ‡Positively adjudicated MACE/VTE.

ASTE, arterial systemic thromboembolism; CI, confidence interval; EAIR, exposure-adjusted incidence rate; FIL100/200, filgotinib 100/200 mg; MACE, major adverse cardiovascular events; NMSC, nonmelanoma skin cancer; PYE, patient-years of exposure; VTE, venous thromboembolism

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LONG-TERM EFFICACY OF FILGOTINIB MONOTHERAPY AND COMBINATION THERAPY: INTERIM RESULTS FROM A POST HOC ANALYSIS OF THE FINCH 4 STUDY

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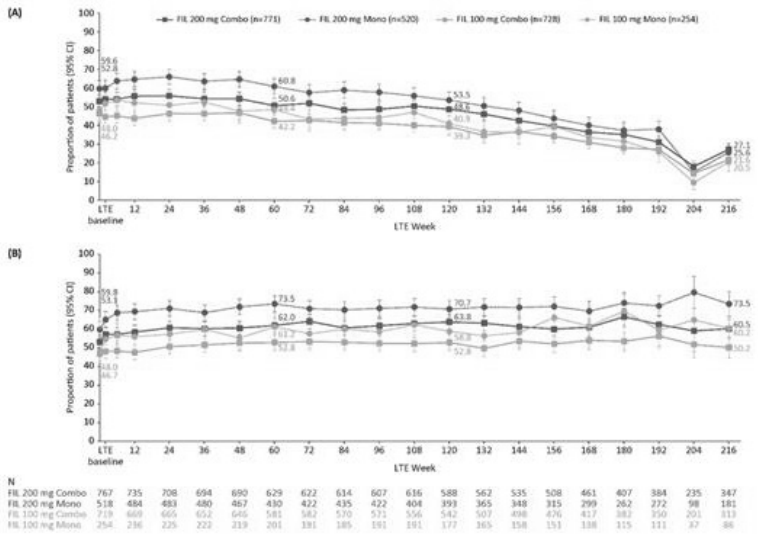
Background: FINCH 4 (NCT03025308) is an ongoing, open-label, long-term extension study assessing the safety and efficacy of filgotinib (FIL) in patients with rheumatoid arthritis (RA) who have completed one of the Phase III parent studies (FINCH 1, 2 or 3) [1–3].
Aim: This post hoc interim analysis of FINCH 4 characterizes the long-term efficacy of FIL administered as monotherapy or in combination therapy.
Methods: Patients from FINCH 1, 2 and 3 enrolled in FINCH 4 were pooled and assessed according to treatment groups: FIL 200 mg (FIL200) and FIL 100 mg (FIL100) as monotherapy or combination therapy. Combination therapy included FIL with methotrexate or other conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), while monotherapy was FIL without these concurrent treatments from baseline of FINCH 4 for the study's duration. Least-squares (LS) mean change from the parent study baseline in Disease Activity Score in 28 joints using C-reactive protein (DAS28-CRP) was analyzed using a mixed-effects model for repeated measures. DAS28-CRP < 2.6 response rates were analyzed using observed cases (OC) and nonresponder imputation (NRI).

Results: As of May 8, 2023, 2,273 patients were included in the analysis. At Week 216, the LS mean change (95% CI) from the parent study baseline in DAS28-CRP was –3.0 (–3.1, –2.9) in the FIL200 combination therapy arm, –3.3 (–3.4, –3.2) in the FIL200 monotherapy arm, –2.8 (–2.9, –2.7) in the FIL100 combination therapy arm and –2.9 (–3.1, –2.7) in the FIL100 monotherapy arm. NRI analysis showed that DAS28-CRP < 2.6 was achieved by 27.1% in the FIL200 combination therapy arm, 25.6% in the FIL200 monotherapy arm, 21.6% in the FIL100 combination therapy arm and 20.5% in the FIL100 monotherapy arm. (Fig. 1A). In the OC analysis, the corresponding proportions were 60.2%, 73.5%, 50.2% and 60.5% (Fig. 1B).

Discussion and Conclusion: Interim results from FINCH 4 indicate that, based on the NRI analysis, 20.5–27.1% of patients achieved DAS28-CRP < 2.6 at Week 216, and based on the OC analysis, 50.2–73.5% achieved this target. These findings indicate sustained DAS28-CRP improvements over time, regardless of FIL being used as monotherapy or combination therapy.

Figure 1. Proportion of responders to achieve DAS28-CRP <2.6 as per the **(A)** NRI and **(B)** OC analyses



In part A, the decrease in the proportion of patients achieving DAS28-CRP <2.6 at Week 204 was attributed to a study protocol amendment, which resulted in some patients missing the Week 204 visit due to an increase in the data collection interval – patients with missing data were considered nonresponders.

CI, confidence interval; Combo, combination therapy; DAS28-CRP, Disease Activity Score in 28 joints using C-reactive protein; FIL, filgotinib; LTE, long-term extension; Mono, monotherapy; NRI, nonresponder imputation; OC, observed cases

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INTERIM FINDINGS ON PATIENT-REPORTED OUTCOMES, DISEASE ACTIVITY AND SAFETY IN RHEUMATOID ARTHRITIS PATIENTS TREATED WITH FILGOTINIB FOR UP TO 18 MONTHS FROM FILOSOPHY AND PARROTFISH

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Background: FILOSOPHY (NCT04871919) and PARROTFISH (NCT05323591) are ongoing prospective, observational Phase IV studies conducted in Europe and France, focusing on the use of filgotinib in patients with rheumatoid arthritis (RA).

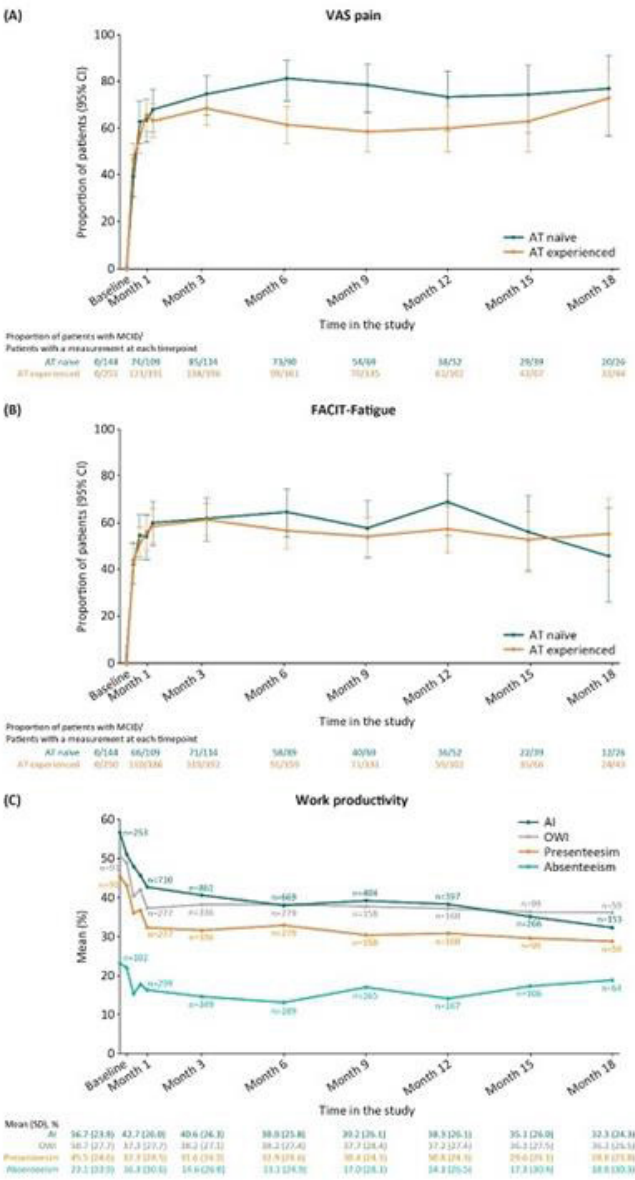
Aim: To report baseline characteristics, patient-reported outcomes (PROs), effectiveness and safety of filgotinib treatment over 18 months.

Methods: The studies enrolled RA patients starting filgotinib for the first time in daily practice. Assessments included VAS pain, FACIT-Fatigue, Work Productivity and Activity Impairment questionnaire, RAID, DAS28-CRP, CDAI, and HAQ-DI. Clinically meaningful changes were defined as a reduction of ≥10 mm in VAS pain and an increase of ≥ 4 in FACIT-Fatigue scores, evaluated in both advanced therapy (AT)-naive and AT-experienced patients. Treatment-emergent adverse events (TEAEs) were also recorded.

Results: As of July 2023, 1,177 patients had been treated, with a median follow-up of 322 days. Clinically meaningful improvements in pain and fatigue were observed from Week 1 in both AT-naive and AT-experienced patients, continuing up to Month 18 (Fig. 1A and 1B). Work productivity and daily activity impairment showed improvements from Week 1, sustained up to Month 18 (Fig. 1C). Disease activity improvements were noted as early as Month 1. By Month 18, 60.3% of patients achieved a DAS28-CRP ≤ 2.6, and 15.4% had DAS28-CRP > 2.6 and ≤ 3.2. CDAI scores ≤ 2.8 were reported by 36.8% of patients, while 34.2% had CDAI scores > 2.8 and ≤ 10. Median HAQ-DI improved from 1.4 at baseline to 0.8 at Month 1 and Month 6. Median RAID scores reduced from 6.6 at baseline to 5.8 at Week 1 and 3.9 at Month 6. TEAEs were reported in 52.5% of the patients, leading to treatment discontinuation in 7.7% of cases. There were six deaths, one of which was considered related to the study treatment.

Discussion and Conclusion: Filgotinib treatment led to significant improvements in pain, fatigue, work productivity and RAID scores as early as Week 1. DAS28-CRP, CDAI and HAQ-DI showed improvements from Month 1 onwards. These benefits were maintained up to Month 18 (and up to Month 6 for RAID and HAQ-DI).

Figure 1. Proportion of patients with a clinically meaningful improvement from baseline in **(A)** VAS pain score, **(B)** FACIT-Fatigue score and **(C)** mean work productivity over time



Absenteeism (percent work time missed due to health) is calculated for those who are currently employed. Presenteeism (percent impairment while working due to health) is calculated for those who are currently employed and actually worked in the past 7 days. Percent OWI is calculated for those who are currently employed. Percent AI is calculated for all respondents. For all domains, a lower score is an improvement.

AI, activity impairment; AT, advanced therapy; CI, confidence interval; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy–Fatigue; MCID, minimal clinically important difference; OWI, overall work impairment; SD, standard deviation; VAS, visual analog scale

IDENTIFICATION OF RISK FACTORS FOR EXACERBATION OF ANCA-ASSOCIATED VASCULITIS TO BUILD MODEL OF PERSONALIZED MAINTENANCE TREATMENT REGIMEN

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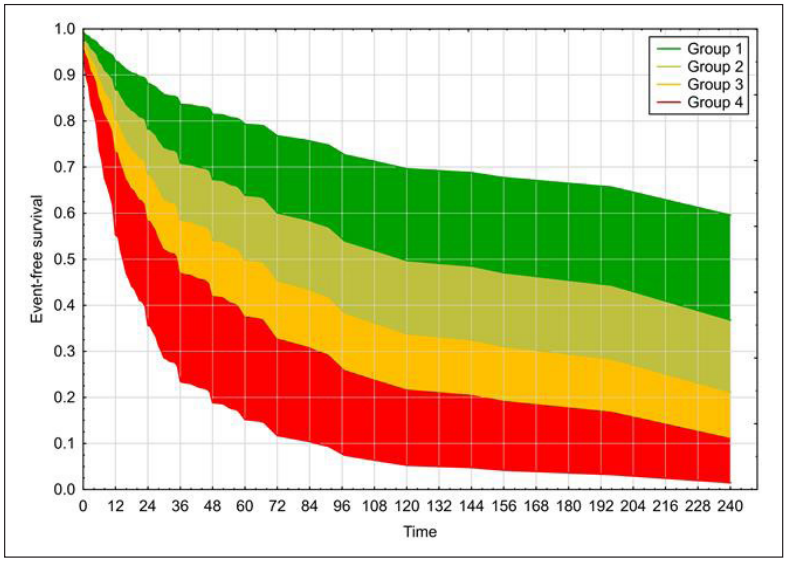
Background/Objectives: ANCA associated vasculitides (AAV) are a heterogeneous group of rare diseases with unknown etiology and the clinical spectrum ranging from life-threatening systemic disease, through single organ involvement to minor isolated skin changes. Individual disease course prognosis and maintenance treatment regimen selection are difficult due to heterogeneity of the AAV clinical picture, and varied response to therapy. The ability to predict the risk of relapse in AAV course is the key point for maintenance therapy duration and this is unmet need of actual guidelines.

Methods: We conducted a multicenter study of all adult patients diagnosed with AAV (648–GPA, 170–MPA cases). Their clinical and laboratory data were collected in the POLVAS registry by 12 referral centers. Cox proportional hazard analyses were applied to calculate hazard ratios (HR) and 95% confidence intervals for the first remission as an endpoint. First one-dimensional models were used to identify potentially relevant variables. Then, using stepwise regression with different orders of inclusion and exclusion of variables, a multidimensional model was obtained

Results: Analysis of 818 AAV cases identified seven significant risk factors of AAV relapse: gender, skin, ENT or eye involvement, maximal ever creatinine < 475 umol, and CRP at baseline > 10 ng/mL. The next step was to divide the AAV patient into 4 groups with a different risk of relapse over time (Fig. 1).

Comparison of different groups shows that in group 1 the first 24 months are crucial, whereas in groups 2 and 3 the highest number of relapses occur in the first 36 months. In group 4 patients have the highest risk of relapse and what is more almost all of them will experience the AAV relapse in long-term perspective. These differences between the groups may help guide personalized decisions about the duration of maintenance therapy.

Conclusions: Analysis of data from POLVAS registry allowed for identifying risk factors of AAV relapse and building a model able to define AAV patients' subsets characterized by different probability of disease relapse.



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PERIPHERAL NERVE AND GASTROINTESTINAL INVOLVEMENT IN ANCA-NEGATIVE EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS — A CASE REPORT

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Background: Anti-neutrophil cytoplasm antibodies (ANCA) appear in eosinophilic granulomatosis with polyangiitis (EGPA) in 30–40% of cases and are associated with different phenothype of disease [1]. We present a case of ANCA-negative EGPA patient with peripheral nerve and gastrointestinal involvement.

Case presentation: 71-year-old male was admitted to hospital one year ago because of weight loss, rectal bleeding and unsteady gait. He had bronchial asthma for 6 years. Laboratory testing revealed severe eosinophilia 12,18 × 10^9/L. With endoscopy we detected gastritis and multiple large intestine ulcera. Biopsy of duodenal and colon mucosa revealed dense eosinophilic infiltration. Due to rapidly progressive left-sided peroneal paresis, weakened right dorsiflexion and loss of sensations in both feet, he could no longer walk. EMG study was typical for severe axonal sensorimotor neuropathy. Histopathology findings of a sural nerve biopsy proved chronic vasculitis with arterial thrombosis and eosinophilic infiltration. The ANCA panel test was negative.

We started therapy with cyclophosphamide 1g/month and methylprednisolon 1 mg/kg/day with rapid dose tapering. Meanwhile he suffered a proxymal deep vein thrombosis of left leg and was treated with apixaban. After 6 pulses of cyclophosphamide he continued maintenance therapy with mepolizumab 300 mg/month and methylprednisolone 2 mg/day. After 12 months he is still in remission and is able to walk independently.

Discussion: Peripheral neuropathy in EGPA occurs in 50–98%, especially in ANCA positive patients.1 Gastrointestinal involvement can be observed in 30–78% of cases regardless of ANCA positivity.1 Our patient had eosinophilic colitis and neuropathy despite absence of ANCA.

A principal eosinophil-activating cytokine in EGPA eosinophilic inflammation is interleukin IL-5. 1 Mepolizumab, a humanized monoclonal antibody against interleukin IL-5 has been shown effective in maintaining remission also in our case.

In EGPA, deep vein thromboses can occur as consequence of prothrombogenic effect of eosinophillia mainly during active-disease phase and regardless of ANCA positivity [2, 3]. No specific guidelines are available for anticoagulant treatment duration of thromboses in vasculitis.3 In our case, due to patient's age and mobility impairment during active disease phase we decided that the benefit of long-term anticoagulation therapy outweighs potential risks and he continues apixaban treatment.

Conclusion: Systemic EGPA manifestations may have different clinical courses and requires carefull multidisciplinary team treatment.