

JAK INHIBITOR CLINICAL RESPONSE IN POLYARTHRITIS: CASE REPORT

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SUMMARY – The heterogeneity of rheumatoid arthritis (RA) presentation and molecular signature of RA subclasses in patients with early changes of small peripheral joints still remains a challenging problem. In clinical setting, classification of the disease subtypes is not possible and treatment adjustment is based on the continuous Disease Activity Score for disease severity recognition. A new approach in the treatment appears with the novel non biologic targeted synthetic disease-modifying antirheumatic drugs from the group of Janus kinase 1 and 3 (JAK1 and JAK3), blocking interleukin (IL)-2, IL-4, IL-7, IL-9, IL-15 and IL-21. We report a case of a 48-year-old patient who had suffered from polyarthritis from his age 40. Initial laboratory tests showed low inflammatory parameters and magnetic resonance imaging of both hands indicated an early stage of RA. Methylprednisolone and methotrexate therapy was initiated. The patient underwent additional tests, but there was not sufficient evidence for a precise diagnosis. According to the European League Against Rheumatism/American College of Rheumatology score-based algorithm, the patient was classified as seronegative RA based on joint involvement, duration of the disease, and synovitis not better explained by another disease. A partial clinical effect of the administered therapy (steroids as monotherapy and in combination, methotrexate and leflunomide) was noticed with the use of systemic steroids, but dramatic improvement was only achieved with a JAK inhibitor targeted therapy. Although the use of anti TNF- α blocker is a proposed procedure and the drug has not yet been registered in Europe, we took the opportunity to apply this new medication option. The patient, a construction worker, was treated for 20 months, which led to complete remission of the disease, without the need of basic or corticosteroid therapy. Full functional capacity necessary in his demanding job was also achieved. This result raised a question of timely introduction of immunomodulators in the polyarthritis treatment steps.

Key words: *Arthritis, rheumatoid – therapy; Janus kinases – antagonists and inhibitors; Adjuvants, immunologic*

Introduction

Early changes of small peripheral joints can be a great diagnostic puzzle even for an experienced rheu-

matologist. Clinical findings of painful, swollen and functionally damaged small joints are commonly seen in inflammatory conditions with different etiopathogenesis, such as rheumatic arthritis (RA), reactive arthritis and psoriatic arthritis. Differential diagnosis also includes gout¹⁻⁵, the most common type of inflammatory arthritis⁶. Precise diagnosis is particularly difficult to make in the initial phase of disease, posing difficulties on making treatment decision.

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A network of intercellular signaling cytokines is the central control mechanism in the pathogenesis of RA. Cytokine patterns vary over time: early RA involves interleukin (IL)-4, IL-13 and IL-15, while in chronic disease the central role of tumor necrosis factor (TNF)- α and IL-6 has been confirmed by successful therapeutic blockade in clinical setting⁷. Besides intercellular, there are many intracellular signaling molecules (particularly kinases) that regulate the cytokine-receptor-mediated functions. Janus kinase 1 (JAK1) mediates the function of several cytokines, interferons and growth factors, which has been confirmed by positive clinical outcomes of JAK1 blockade^{8,9}.

The heterogeneity of RA patient presentation and molecular signature of RA subclasses still remains a challenging problem. By genome-wide expression profiling technologies of disease-relevant gene clusters and correlation analysis with clinical parameters, researchers are trying to provide evidence for the molecular signature of the disease^{10,11}.

Predictive power to identify seronegative (anti-citrullinated peptide antibody) patients with early arthritis at risk of developing RA belongs to the CD4 T cell gene signature, which implicates IL-6-mediated STAT3 signaling¹². Upregulation of SPP1-like cluster genes can serve to distinguish rheumatoid arthritis and other entities (i.e. osteoarthritis). A higher level of SPP1 protein can be detected in synovial fluids from RA patients. SPP1 is a secreted phosphoglycoprotein functioning as a cytokine, DC activator and co-stimulator of T cell proliferation.

In clinical setting, classification of the disease subtypes is not possible. Treatment adjustment is based on continuous Disease Activity Score (DAS) measurements for disease severity recognition ('treat-to-target' concept)¹³⁻¹⁷.

A new approach in the treatment of RA patients has appeared with the development of new non biologic targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) from the group of JAK inhibitors. JAK exhibits the function of some cytokines, interferon and growth hormone¹⁸. The inhibition of Janus kinase 1 and 3 (JAK1 and JAK3) blocks IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 and modulates the immune response.

The aim of this case report is to remind that classification of the disease subtype and effective RA treatment are impeded by the paucity of accurate diagnostic tests. Also, excellent clinical response to JAK inhibitor was demonstrated in a clinical trial, in a patient who, due to technical reasons, could not have previously received TNF- α blockers.

Case Report

A 48-year-old patient had suffered from polyarthritis for eight years. The patient noticed the symptoms two years before seeking medical care. No similar symptoms were reported in the family medical history. Swelling, redness, pain and functional disturbances appeared in the frontal part of his feet, knees, carpometacarpal and metacarpophalangeal joints, bilaterally. The initial blood test results were within the reference ranges (complete blood count, erythrocyte sedimentation rate, transaminases, creatinine and urea), with the only exception of slightly increased uric acid, measuring 404 $\mu\text{mol/L}$ (reference range: 182-403 $\mu\text{mol/L}$). Oral therapy with methylprednisolone (daily dose of 20 mg) along with nonsteroidal anti-inflammatory drugs was introduced. Considering the normal values of rheumatoid factor (RF) and C-reactive protein (CRP), as well as the wrist x-ray showing no pathological changes, the early stage of RA was diagnosed and methotrexate was added in therapy in a weekly dose of 7.5 mg. However, diagnostic procedures failed to indicate a definitive diagnosis and therapy did not result in disease remission. The prescribed therapy was continued and the patient was treated for the next two years.

Over the two-year period, *Ureaplasma urealyticum* was isolated from the urethral smear and antibiotics were administered without any effect on the disease progression. HLA typing determined the A 2.11, B 13.35, DR 1.7.53, DQ 1.2 loci.

On additional diagnostic workup, magnetic resonance imaging (MRI) of both hands (Figs. 1-3) showed signs of tenosynovitis of flexor tendons, bone marrow edema, tethering of tissue with erosion of the joint surface, which was interpreted as RA. A daily dose of 20 mg of leflunomide and a weekly dose of 12.5 mg of methotrexate was introduced in therapy. After a liver lesion developed, as indicated

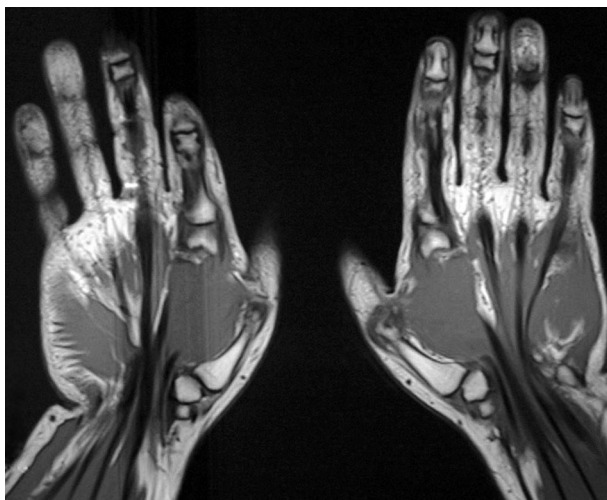


Fig. 1. Magnetic resonance imaging: T1 weighted coronal image of both hands.

by the high liver enzymes alanine transaminase 120 U/L (reference range: 12-48 U/L), aspartate aminotransferase 59 U/L (reference range: 1-38 U/L) and γ -glutamyltransferase 74 U/L (reference range: 1-55 U/L), methotrexate therapy was substituted by meth-



Fig. 2. Magnetic resonance imaging: T1 weighted transverse image of the left hand.

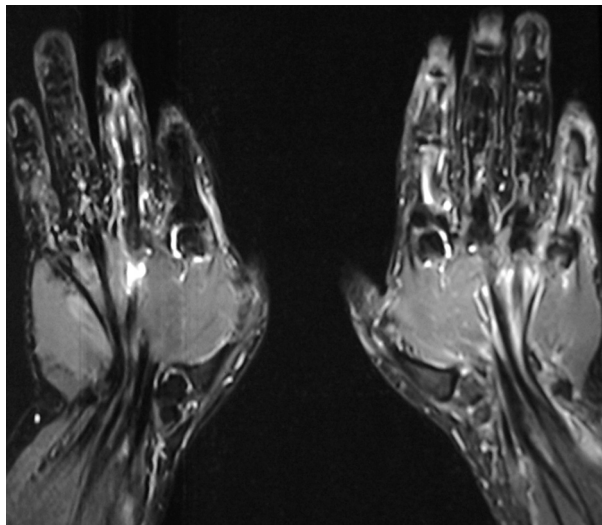


Fig. 3. Magnetic resonance imaging: coronal Short TI Inversion Recovery (STIR) sequence of both hands.

ylprednisolone (daily dose of 10 mg). Due to the side effects of methylprednisolone, the patient reduced the dosage on his own. With dosage reduction below 5 mg a day, relapse of the disease occurred. Screening for other autoimmune diseases was negative.

More than 5 years of the presence of clinical symptoms despite DMARD and corticosteroid therapy, oral therapy with JAK inhibitor was introduced in a daily dose of 2x10 mg, together with the existing dose of methylprednisolone of 10 mg daily. The outcome of this therapy was reduction of all symptoms and regression of swelling, which occurred after one month, and total remission of the disease without the need of further symptomatic therapy, which was achieved after 20 months of therapy with JAK inhibitor in the same dosage. To the present, the patient has been taking JAK inhibitor monotherapy, without any subjective problems.

Discussion

There is wide variation in the responsiveness to virtually any treatment in RA consistent with the heterogeneous nature of the disease. For better detection of diverse cellular responses in general, and for classification of the disease subtypes which could enable more specific medication choices, a molecular portrait in the diagnostic procedure is necessary¹⁹. In daily clinical practice, DAS represents actual disease

activity well in the majority of patients. Clinical trials as well as clinical practice have demonstrated this concept to be effective in achieving remission in early RA^{20,21}. However, precise defining of the entity and the right choice of therapy can pose a problem, especially in initial stages of the disease.

In the patient presented, the initial test results were not informative enough to differentiate rheumatologic entities and to make a precise diagnosis. There was no complete evidence for diagnosing RA (negative RF and anti cyclic citrullinated peptide (aCCP), low parameters of system inflammation)²².

According to the European League Against Rheumatism/American College of Rheumatology (EULAR-ACR) score-based algorithm, the patient was classified as seronegative RA based on joint involvement, duration of the disease and synovitis not better explained by another disease. Current classification simplifies categorization of patients with early RA; however, the diagnosis requires a highly trained specialist able to differentiate early symptoms of RA from other pathology. In some patients, it requires at least five years or more from the onset of symptoms to the diagnosis to meet the minimum diagnosis system requirements.

In the presented patient, elements of psoriatic arthritis, in differential diagnostic procedures, were not established either by physical examination or by positive medical history or typical HLA genotype^{23,24}. Moreover, the role of higher values of uric acid as the etiology of arthritis did not appear to be meaningful. The omission of HLA-B 27, despite positive testing for *Ureaplasma urealyticum*, brings the diagnosis of seronegative spondyloarthropathies into question^{25,26}.

According to literature data²⁷⁻²⁹, the greatest diagnostic help in such cases is MRI, which shows joint structure and soft tissue in detail³⁰. Typical MRI shows thickening of synovial membrane, pannus formation, tendinitis, bone marrow edema, and bone erosion. In the present case report, bone marrow edema pointed to RA, but as similar test results can also be found in the group of patients with psoriatic arthritis (symmetrical inflammation of joints inside the synovial cavity), it is not always possible to differentiate it from RA³¹.

In our patient, the disease relapse was not always accompanied with the signs of systemic inflammation,

which did not fit in the typical RA patient profile and did not help judge the level of arthritis suppression. A partial clinical effect of the administered therapy (steroids as monotherapy and in combination, methotrexate and leflunomide) was noticed with the use of systemic steroids, but dramatic improvement was only achieved with the JAK inhibitor targeted therapy. Significantly, JAK inhibitor plays its role in blocking cytokine receptors with common gamma chain, further signal transduction and gene transcription³²⁻³⁴. It is blocking IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21, the cytokines secreted in various immune conditions, as demonstrated not only in rheumatic diseases but also in psoriasis, keratoconjunctivitis, inflammatory intestinal diseases, prevention of transplant rejection, and cancer³⁵⁻⁴⁴.

Exclusive cytokine expression patterns are characteristic of a distinct autoimmune disease. For example, in a subgroup of patients with RA, IFN type I molecular signature is upregulated, but it could mean that this cytokine profile is patient-specific rather than a disease-specific phenomenon. A further characteristic of this subgroup of patients is increased activity of complement and coagulation cascades. IFN/STAT-1 activation in RA synovium could be an attempt to limit inflammation⁴⁵. However, there is evidence for cytokine hierarchy in RA with TNF- α at its peak⁴⁶. But, blockade of TNF and IL-6 have a similar inhibitory effect on joint damage progression in patients with either early or late disease⁴⁷. Compared with cytokine inhibition, B-cell depletion and inhibition of T cell co-stimulation have a somewhat delayed effect on joint damage, suggesting their effect on upstream pathogenetic events.

Our patient, a construction worker, was treated with JAK inhibitor for 20 months, which led to complete remission of the disease, without the need of basic or corticosteroid therapy, as well as to full functional capacity in his demanding job.

Conclusion

This case report of a patient with chronic small peripheral joint arthritis and without evidence of tolerance against citrullinated antigens breaking demonstrates that distinct disease mechanisms are at play in RA pathology. We aimed to emphasize that effective

RA treatment is currently impeded by the paucity of accurate diagnostic and prognostic tests in the early disease. The main question in our patient treatment was how the then-available medication could best be used. Although the use of anti TNF- α blocker is the proposed procedure and the drug has not yet been registered in Europe, we used the opportunity to apply the JAK inhibitor. The result showed total suppression of rheumatoid activity and raised a question of timely use of immunomodulators in polyarthritis treatment steps.

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Sažetak

KLINIČKI ODGOVOR NA JAK INHIBITORE U BOLESNIKA S POLIARTRITISOM: PRIKAZ SLUČAJA

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Raznolikost kliničke slike reumatoidnog artritisa (RA) i molekularna specifičnost podvrsta RA kod bolesnika s ranim promjenama na perifernim zglobovima još uvijek predstavljaju velik izazov. U kliničkim uvjetima klasifikacija podtipova bolesti nije moguća, a prilagodba terapije temelji se na kontinuiranoj ljestvici DAS za procjenu težine bolesti. Novi pristup u liječenju pojavljuje se s novim ne-biološkim ciljnim sintetskim antireumaticima koji modificiraju bolest (*targeted synthetic disease-modifying antirheumatic drugs*, tsDMARDs) iz skupine Janus kinaza 1 i 3 (JAK1 i JAK3) koji blokiraju interleukin (IL)-2, IL-4, IL-7, IL-9, IL-15 i IL-21. Prikazuje se slučaj 48-godišnjeg bolesnika koji je u dobi od 40 godina obolio od poliartritisa. Početni laboratorijski nalazi pokazali su mirne upalne parametre, a nalaz magnetske rezonancije obiju šaka ukazivao je na rani stadij RA. U terapiju su uvedeni metilprednizolon i metotreksat. Bolesnik je prošao dodatnu obradu, ali nije bilo dovoljno elemenata za postavljanje točne dijagnoze. Prema algoritmu EULAR-ACR bolest je klasificirana kao seronegativni RA s obzirom na zahvaćenost zglobova, trajanje bolesti i sinovitis koji se nisu mogli bolje opisati kao neki drugi entitet. Djelomičan klinički odgovor na danu terapiju (steroidi u monoterapiji te metotreksat i leflunomid u kombinaciji) zabilježen je pri upotrebi sistemskih steroida, no dramatično poboljšanje postignuto je tek upotrebom ciljane terapije JAK inhibitorima. Iako je po preporukama indicirana upotreba anti TNF- α blokatora, iskoristili smo priliku primijeniti novi lijek iako isti još nije registriran u Europi. Nakon dvadeset mjeseci liječenja JAK inhibitorom kod ovog bolesnika, građevinskog radnika, došlo je do potpune remisije bolesti bez potrebe za bazičnom ili kortikosteroidnom terapijom. Također je postignut i potpuni funkcionalni kapacitet u njegovom zahtjevnom zanimanju. Dobiveni rezultati dovode u pitanje pravodobnost davanja imunomodulatora u algoritmu liječenja poliartritisa.

Ključne riječi: Reumatoidni artritis – terapija; Janusove kinaze – antagonisti i inhibitori; Adjuvansi, imunološki