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Psoriatic arthritis - Tofacitinib as a new treatment

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Abstract

Introduction:
JAK inhibitors are used in the treatment of psoriatic arthritis when there is a lack of effective response or intolerance to first-line drugs or their use must be discontinued due to the presence of side effects. JAK inhibitors inhibit the JAK-STAT signaling pathway which plays a significant role in the pathogenesis of many inflammatory and autoimmune diseases. This mechanism leads to a reduction in the level of pro-inflammatory cytokines which causes rapid improvement in the patient's clinical condition. Tofacitinib is the best-known drug in this group; its use carries an increased risk of cardiovascular events and reactivation of the varicella-zoster virus. Regular monitoring of patients results in faster detection of the first signs of undesirable effects and the cessation of their progression. The drug's safety profile is acceptable and the benefits outweigh possible complications.
Aim of the study:
The aim of the study is to summarize the available knowledge about tofacitinib treatment in psoriatic arthritis. The way of work, effectiveness of treatment and potential side effects were summarized and described.
Materials and methods:
The literature available in PubMed database was reviewed using the following keywords: "Psoriatic arthritis", "Tofacitinib", "JAK inhibitors", "JAK-STAT"
Conclusion:
Tofacitinib treatment in rheumatology is used in psoriatic arthritis. The rapid improvement in the clinical condition of patients treated with JAK inhibitors is due to their direct impact on the modulation of the pathogenesis of the disease. The predictable benefits of therapy outweigh the side effects which can be detected at an early stage with regular monitoring of the patient.

Key words: Psoriatic arthritis; Tofacitinib; JAK inhibitors; JAK-STAT

Introduction:

Psoriatic arthritis is a heterogeneous disease that is difficult to control. Thanks to the emergence of a new generation of biological drugs, there is a chance for disease remission in people who have not previously achieved an effective response or have developed intolerance to first-line drugs, or had to discontinue them due to side effects. A new group of drugs are Janus kinase inhibitors, represented by Tofacitinib. This is the best-known representative of

the group. Janus kinases - JAK are a family of cytosolic tyrosine kinases that regulate the transduction of cytokine signals, including those involved in the pathogenesis of psoriatic arthritis. The mechanism of action of this group of drugs involves the inhibition of the JAK-STAT signaling pathway, which plays a huge role in the pathogenesis of PsA by taking part in the formation of many pro-inflammatory cytokines [1]. Tofacitinib therapy is currently approved by both the FDA and EMA for the treatment of PsA [17]. Currently, the number of studies regarding the effectiveness of tofacitinib is limited, yet this drug is on the list of drugs approved for the treatment of psoriatic arthritis. The conducted research clearly proves its effectiveness. The improvement in the clinical condition of patients treated with tofacitinib is very rapid. However, you should pay special attention to the side effects of the drug and regularly monitor people taking it. The advantages of therapy outweigh the disadvantages, and the safety profile is acceptable [33].

Psoriatic arthritis:

Psoriatic arthritis (PsA) was distinguished as a separate disease in 1946 by the American Rheumatism Association, which today is called the American College of Rheumatology. PsA is classified as a chronic, progressive, inflammatory, immunological disease of the musculoskeletal system of a debilitating nature. The inflammatory process affects the skin, joints, tendon attachments, tendons, fingers, and nails, which may result in functional damage to the joints and even disability [2, 3]. The incidence of PsA worldwide is 0.1-1% in the general population [4,5]. Differences in epidemiological estimates between studies are due to differences in geography, methodology, and target population. Currently, most new studies show an increase in the incidence of the disease [5]. Approximately 20% of people suffering from psoriasis developed PsA, often both diseases appeared simultaneously, and in 10-15% of patients, arthritis occurred first [5,6]. In people suffering from psoriasis, PsA occurs more often in adults (23.93%) than in children (8.59%), and a larger percentage of women (19.14%) than men (16.01%) [7]. According to the latest research, peripheral PsA occurs more often in women, and the axial form in men [8,9]. The peak incidence of the disease occurs in middle-aged people, but one-fourth of the recorded cases concern elderly people [10]. PsA often runs in families, there is a high risk (approximately 7.7%) of developing the disease in first-degree relatives [11]. PsA is usually seronegative, asymmetric and may be both axial and peripheral. Typical locations for it are the distal interphalangeal joints, sacroiliac joints, and the spine. Radiologically, changes such as enthesitis, tendon sheath, and digital inflammation can be observed [12]. Genetic susceptibility to PsA is closely related to the MHC genetic region in the short arm of chromosome 6 containing several alleles and HLA class I haplotypes [13]. It has been shown that people with HLA-B (27, 39, 38, 08) have a high risk of developing PsA. Moreover, HLA-B (27, 39) predisposes to faster development of PsA in people with psoriasis [14]. The pathogenesis of the disease is based on an abnormal immune response, the etiology of which is still unclear. The factors predisposing to trigger this process include genetic, metabolic (obesity), microbiological (infections, dysbiosis), biochemical (load on tendon attachments), and environmental (smoking) [15]. These factors act as triggers of the pathological process and accelerate the onset of the disease by activating DC macrophages responsible for presenting the antigen through MHC type I to T lymphocytes (CD8+) through the TLR type 2 receptor. These lymphocytes stimulate Th1 lymphocytes through IL-12 and IFNα, the response of which causes the release of TNFα and IFNγ. However, IL-6 and IL-1b in the presence of IL-23 activate Th17 lymphocytes, which stimulate the increased release of IL-17, IL-22, and CCL20 from tissues. This results in a local production of pro-inflammatory cytokines by activating the innate and adaptive immune response. The released cytokines

stimulate their transmembrane receptors, which causes a constant increase in their level and stimulates the migration of endothelial cells, fibroblasts, macrophages, dendritic cells, epithelial cells, keratinocytes, chondrocytes, osteoclasts, and osteoblasts, leading to enthesitis, synovium, and damage to articular cartilage and skin [16].

Characteristics of Tofacitinib and its regulation of the inflammatory process in psoriatic arthritis:

Tofacitinib is a member of the Janus kinase inhibitor class approved by the FDA for the treatment of psoriatic arthritis who have had an inadequate response to or have not tolerated prior therapy [17]. Tofacitinib, according to the latest data, has been approved by the EMA and FDA for the treatment of psoriatic arthritis. The EMA recommends a dose of 5 mg twice daily for PsA. However, the FDA also recommends a dose of 5 mg twice daily or a dose of 11 mg once daily in a long-acting preparation. It is an oral drug with a low molecular weight of 504.5 Da, which is both absorbed and eliminated quickly from the body after administration. It can reach maximum plasma concentrations within 30-60 minutes. The half-life of the molecule is approximately 3 hours with hepatic clearance - 70% and renal clearance - 30%. Its half maximal inhibitory concentration for various Janus kinase inhibitors is: JAK1(3.8 nM), JAK2(10.7 nM), JAK3(1.4 nM), TYK2(24 nM) [18, 19, 20]. Its action is based on partial and reversible inhibition of JAK phosphorylation and intracellular activation. JAK/STAT is an intracellular protein relay system used by many cytokines and growth factors to express genes responsible for cell activation, proliferation and differentiation. The receptors of these compounds do not exhibit enzymatic activity, but they cooperate with cytoplasmic proteins that act as kinases. After the formation of a complex between the ligand and the membrane receptor, the tyrosine kinase associated with it is activated. This kinase first autophosphorylates and then re-phosphorylates the cytoplasmic domains of the receptor, to which STAT proteins then attach. These proteins dimerize to sequentially detach from the receptor and transport to the cell nucleus, where they activate the gene transcription process by binding to DNA at the promoter gene site [21]. They thus influence the structure of chromatin and regulate the expression of inflammatory mediator genes [22]. The components of cytokine-dependent effects include four receptors: JAK1, JAK2, JAK3 and TYK2. Tofacitinib exhibits inhibitory effects on both JAK1 and JAK3 with functional specificity over JAK2, thereby inhibiting their-dependent pro-inflammatory cytokine production signaling pathways. This action leads to the inhibition of the inflammatory process [23, 24]. This drug modulates the production of many cytokines that are important in the pathogenesis of psoriatic arthritis. The specific effects of tofacitinib depend on the receptor on which it directly acts [25]. JAK inhibition by tofacitinib relies on competitive binding to a highly conserved ATP binding site. This molecule acts mainly through JAK1 and JAK3 with 5 to 100-fold selectivity for JAK2 and even less selectivity for TYK2 [26, 27]. After blocking: JAK1 inhibits IL-6, IL-22, IFN- α, IFN- γ; JAK1/3 inhibits IL2, IL-7, IL-15, IL-21; JAK2 inhibits erythropoietin, a colony-stimulating factor for macrophages and granulocytes; JAK2/TYK2 inhibits IL12 and IL-23 [26]. Many cytokines that play an important role in the pathogenesis of PsA use JAKs to further transmit signals [25].

Tofacitinib in the treatment of psoriatic arthritis:

The results of two phase III studies evaluating tofacitinib treatment in patients with PsA have been published. The OPAL Broaden study is a phase III study in which PsA patients showed an unsatisfactory response to synthetic DMARDs (methotrexate, leflunomide,

hydroxychloroquine, sulfasalazine) and had never been treated with TNF-I. The study lasted 12 months and included a double-blind trial, an active control group, and a placebo. Patients were randomized to receive: tofacitinib 5 mg twice daily orally; tofacitinib 10 mg twice daily orally; adalimumab 40 mg subcutaneously once every two weeks; placebo with a blinded switch to tofacitinib 5 mg after 3 months; placebo with a blinded switch to tofacitinib 10 mg after 3 months. Throughout the entire study period, all groups additionally took synthetic DMARDs at a constant dose. The primary endpoint of the study was the percentage of patients who, after 3 months of treatment, improved by at least 20% compared to the baseline value according to ACR20 (American College of Rheumatology). These criteria define a minimum of 20% improvement in the number of painful or swollen joints; three of the following additional parameters: assessment of arthritis according to the patient and doctor using the VAS scale, assessment of the level of joint pain by the patient according to VAS measurement, level of disability measured using HAQ-DI, CRP level. Measurement of ACR50 and ACR70 response and PASI score of 75% improvement from baseline were secondary endpoints. They also included measurements of the Leeds enthesitis index score, Spondyloarthritis Research Consortium of Canada enthesitis index score, minimal disease activity score, Chronic Illness Therapy-Fatigue (FACIT-F) scores, Medical Outcomes Study 36-Item Short-Form Health Survey version 2 (SF-36) and the Dactylitis Severity Score, as well as the Psoriatic Arthritis Response Criteria, DAS-28 and level of CRP. Videos were recorded presenting the condition of the hands and feet at the beginning of the examination and its end. Radiographic changes were assessed using the modified Sharp total scale for PsA. This study showed that patients receiving tofacitinib treatment at both 5 mg and 10 mg doses achieved a higher ACR20 response rate (50% and 61% respectively) compared to the placebo group (33%) after 3 months. However, only the group receiving a higher dose of tofacitinib (10 mg) achieved a higher ACR20 index (61%) compared to adalimumab (52%). After 3 months, there was an improvement in the HAQ-DI score, the average change of which for the group treated with tofacitinib at a dose of 5 mg was -0 .35, and at a dose of 10 mg -0.40 compared to the placebo group, where this index was -0.18. Tofacitinib according to HAQ-DI only at a higher dose (10 mg) gave better improvement than adalimumab (-0.38) [28, 29, 33]. Patients in the tofacitinib group achieved a higher PASI75 response comparably, regardless of dose, than patients receiving placebo [30]. All secondary endpoints showed improvement compared to placebo but with the hierarchical statistical faltering on the Leeds Enthesitis Index for tofacitinib 5mg bid, significance testing was not performed for other secondary endpoints lower in the testing hierarchy [28, 29]. After 12 months, 91-98% of people participating in the study met radiological criteria for freedom from progression according to the modified total Sharp scale. In all groups treated with tofacitinib, CRP levels decreased, but this decrease was slower in the group receiving tofacitinib at a dose of 5 mg [31].The remaining changes in parameters assessed in secondary endpoints after 12 months were numerically similar to the results obtained after the 3rd month of the study, but could not be compared with placebo because the placebo groups switched to tofacitinib after 3 months of the study [28,30].

However, in the second phase III study OPAL Beyond [29], which lasted 6 months and was also conducted using a double-blind and placebo-controlled method, participants were randomly assigned to four groups with different treatment programs in a ratio of 2:2:1:1. These were the groups receiving: 5 mg tofacitinib; 10 mg tofacitinib; placebo for the first 3 months, then tofacitinib 5 mg; placebo for the first 3 months, then tofacitinib at a dose of 10 mg. The study participants were carefully selected: they had to have been diagnosed with PsA for at least 6 months, meet the CASPAR criteria, and present active plaque psoriasis and

arthritis in screening tests. In addition, they must have been treated with at least one TNF inhibitor in the past without significant improvement. During this study, patients also took various DMARDS at a constant dose. The primary endpoints were the proportion of study participants achieving a minimum 20% improvement on the ACR20 and the change from baseline in the HAQ-DI score at 3 months. The study results clearly demonstrated the effectiveness of tofacitinib compared to placebo. The ACR20 response was 50% in the 5 mg group and 47% in the 10 mg group, compared with a 24% response in the placebo group. Mean changes from baseline in the HAQ-DI score were -0.39 and -035 compared to -0.14. A 43% PSAI75 response was achieved at 3 months in the tofacitinib 10 mg group, but not in the 5 mg dose, compared to the placebo group. In the groups taking the drug throughout the study period, numerically similar improvement results were observed after its completion as those 3 months after the study. ACR50 response rates were better in both dosing groups than in the placebo groups. However, this was not achieved with the ACR70 response. Secondary endpoints at 3 months showed a positive trend, comparable to primary changes. The study clearly showed that tofacitinib, both at 5 mg and 10 mg, was more effective in improving disease activity in patients than placebo, as evidenced by the minimal disease activity after 3 months, which was 23% and 21% compared to placebo 15% [29,30,33].

To sum up, phase III studies conducted on patients with active psoriatic arthritis demonstrate the effectiveness of therapy with the Janus kinase inhibitor tofacitinib [30]. In the OPAL Broaden and OPAL Beyond studies, patient-reported outcomes: pain, fatigue, physical function, and self-rated disease improved for up to 3 months and remained stable until the end of the study [28, 29]. A randomized, controlled, double-blind phase III study was conducted in China in patients with PsA previously treated conventionally with DMARDs without significant response to treatment. The study lasted 6 months. Participants were randomly divided into two groups, one received tofacitinib 5 mg twice daily, the other placebo, which was replaced with tofacitinib 5 mg twice daily 3 months after the start of the study. The primary endpoint was the proportion of patients achieving ACR50 at 3 months. 38.2% of patients who took the drug achieved ACR50, while in the placebo group only 5.9%. In the group that took tofacitinib from the beginning of the study, the improvement in ACR was maintained throughout the study period. Already after the first month of using the drug, significant improvement was noticed. According to PASI75, in the 1st and 13th month after the start of the study, an improvement was observed in the group taking tofacitinib compared to placebo. The CRP level was significantly reduced after 3 months compared to the placebo group. There was also improvement in quality of life, physical and mental health, pain, enthesitis, and finger inflammation, and a reduction in the number of swollen and painful joints. More patients (32.4%) achieved MDA after treatment with tofacitinib compared to placebo (5.9%) [32]. The number of studies evaluating the use of tofacitinib treatment in PsA is limited. Most of it is post hoc analysis by OPAL Broaden and OPAL Beyond. To sum up, current studies demonstrate the effectiveness of tofacitinib in the treatment of all disease symptoms of PsA [34].

Side effects of Tofacitinib treatment:

The most common known side effects of tofacitinib are an increased risk of serious cardiovascular events; reactivation of the Varicella zoster virus often leading to the development of herpes zoster affecting more than one dermatome; severe infections, most often of the respiratory or urinary tract requiring hospitalization; infections in patients with

weakened immunity; malignancies cancer [35]. Compared to other JAK inhibitors, tofacitinib has the highest risk of serious cardiovascular events [36, 37]. In the case of patients who smoke cigarettes or have smoked in the past, especially in the elderly, special oncological vigilance should be maintained during treatment with tofacitinib due to the increased risk of lung and skin cancer. During therapy with this drug, the patient's health should be regularly monitored in order to detect early adverse events and prevent their progression [37, 38]. The safety profile of tofacitinib in psoriatic arthritis is acceptable, and the benefits outweigh the possible complications. Furthermore, this profile is comparable to the safety profile of other systemic therapies commonly used for psoriatic arthritis, apart from the high risk of herpes zoster characteristic of tofacitinib [39,40].

Conclusions:

Janus kinase inhibitors are a relatively young group of drugs that are still undergoing a number of clinical trials. Tofacitinib is the best-known member of the group. In rheumatology, it is used in the treatment of psoriatic arthritis. The effectiveness of the drug has been confirmed by many clinical studies. It inhibits the production of many cytokines simultaneously. The therapeutic effect is characterized by a rapid improvement in the clinical condition of patients. After achieving remission, the correct therapeutic procedure is to gradually reduce the dose which does not result in the loss of the therapeutic effect. Tofacitinib is an oral therapeutic option that should be considered for the treatment of psoriatic arthritis. Studies conducted on patients in whom conventional DMARD treatment did not produce the desired therapeutic effect prove that tofacitinib is an effective solution even in difficult forms of PsA. The main side effects are an increased risk of cardiovascular events and Varicella zoster virus reactivation. Monitoring people treated with this medicine increases the chances of quickly detecting early signs of side effects and preventing their further development. The safety profile of tofacitinib is acceptable, and the benefits outweigh the likely complications.

Supplementary materials:

Not applicable.

Author’s contribution:

Conceptualization, Marta Skorupska, Magdalena Joanna Czeczotka and Martyna Magdalena Martka; methodology, Justyna Śliz, Aleksandra Natalia Popławska and Krzysztof Woźniak; software, Marta Skorupska, Martyna Magdalena Martka and Krzysztof Woźniak; check, Natalia Aleksandra Popławska, Justyna Śliz and Magdalena Joanna Czeczotka; formal analysis, Marta Skorupska, Natalia Aleksandra Popławska and Krzysztof Woźniak; investigation, Martyna Magdalena Martka, Justyna Śliz and Magdalena Joanna Czeczotka; resources Justyna Śliz, Marta Skorupska and Martyna Magdalena Martka; data curation, Magdalena Joanna Czeczotka, Krzysztof Woźniak and Natalia Joanna Popławska; writing-rough preparation, Marta Skorupska, Martyna Magdalena Martka and Krzysztof Woźniak; writing- review and editing Justyna Śliz, Natalia Aleksandra Popławska and Magdalena Joanna Czeczotka; visualization, Natalia Aleksandra Popławska, Krzysztof Woźniak and Justyna Śliz; supervision, Marta Skorupska, Magdalena Joanna Czeczotka and Martyna Magdalena Martka; project administration Justyna Śliz, Marta Skorupska, Magdalena Joanna

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The authors of the paper report no conflicts of interest.

Data Availability Statement

The data presented in this study are available upon request from the correspondent author.

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