

New Agents in Treatment of Psoriatic Arthritis

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ABSTRACT

Background: psoriatic arthritis is a long term inflammatory arthritis. Psoriatic arthritis is leading to bone erosion, joint destruction and associated with nail diseases, dactylitis, enthesitis, sponylylitis and uveitis.

Aim of this study was to review the new lines of treatment for psoriatic arthritis with or without skin affection.

Treatment, the underlying process in psoriatic arthritis is inflammation; so, treatments are directed to reduce and control inflammation. Although no clear correlation exists between joint inflammation and the skin in every patient, the skin and joint aspects of the disease often must be treated simultaneously. However, only certain therapies are effective for psoriasis and psoriatic arthritis. Systemic agents, can be used for both skin and joint manifestations, it includes methotrexate and ciclosporin. For the biologic agents, the tumour necrosis factor inhibitors such as adalimumab, etanercept, infliximab, golimumab and certolizumab are effective. Ustekinumab is a recently agent belonging to the group of anti-IL-12p40 antibodies and has been shown to be efficacious. Newer drugs in the treatment which have shown efficacy for both psoriasis and psoriatic arthritis consist of the anti-IL-17 agent, secukinumab, and a phosphodiesterase-4 inhibitor, apremilast. As well as the oral JaK inhibitor, tofacitinib, have very limited but promising data.

Keywords: psoriasis, psoriatic arthritis, anti- TNF, anti-IL-17, small molecules inhibitors.

INTRODUCTION

Psoriasis is a chronic immune-mediated inflammatory disorder characterized by uncontrolled proliferation of keratinocytes, activated dendritic cells, release of pro-inflammatory cytokines, and recruitment of T-cells to the skin ^[1]. Psoriasis usually presents 8–10 years before psoriatic arthritis, although some patients present with psoriatic arthritis with psoriasis. Both of them are immune-mediated chronic inflammatory diseases with a similar pathogenesis, synchronous treatment should be undertaken to minimize side effects and financial burden of medications ^[2].

The peak of psoriatic arthritis incidence occurs between 30 and 50 years of age. It is characterized clinically by edema, pain, tenderness, and stiffness of the joints, ligaments and tendons (dactylitis and enthesitis) ^[3].

Both the innate and adaptive immune systems are involved in the pathogenesis of psoriasis and PsA. T cell activation is a key component specifically, TH1 TH17 and TH22 cells are up regulated in psoriasis lesions ^[4].

Several factors must be considered in selecting therapy, including type of psoriasis, severity and extent. Not all therapies that target psoriasis can treat PsA and vice versa. In treating psoriasis alone, commonly used agents include topical corticosteroids, coal tar, vitamin D analogs (e.g., calcipotriol), topical tazarotene, narrow band ultraviolet B (NB-UVB) phototherapy, sporalen plus ultraviolet A (PUVA) photo-chemotherapy and

oral retinoids (e.g. acitretin). In treating psoriatic arthritis alone, non-steroidal anti-inflammatory drugs (NSAIDs), intra articular corticosteroid injections and disease-modifying anti-rheumatic drugs (DMARDs), such as sulfasalazine, are the agents commonly prescribed. It should be noted that the DMARDs and NSAIDs, although able to control symptoms, do not retard progression of radiographic joint damage ^[5].

Conventional systemic therapies effective for both psoriasis and PsA include methotrexate, ciclosporin and leflunomide. The advantage of biologic agents for the treatment of psoriasis and PsA has not precluded the use of these drugs because of their oral route of administration and lower cost ^[6]. Biologics have now been increasingly used for patients with both psoriasis and PsA when first-line therapy has failed ^[7].

The aim of the present study is to review the new lines of treatment for psoriatic arthritis with or without skin affection.

METHODS

A PubMed search (without methodological search filters or limits) on the words “psoriasis”, “psoriatic arthritis”, “pathogenesis of psoriatic arthritis” and “pharmacological & non-pharmacological treatment of psoriatic arthritis” in the title and abstract was last performed on 1 May 2017. Relevant results from the articles which were selected for review are summarized and presented in this narrative review.

The study was approved by the Ethics Board of Ain Shams University.

MANAGEMENT OF PSORIATIC ARTHRITIS EULAR Recommendations on Psoriatic Arthritis Treatment ^[8]

1. Aim at achieving remission or minimal disease activity, by frequent monitoring and frequent adjustment of therapy.
2. NSAIDs may be used for symptomatic relief.
3. For active peripheral arthritis, consider csDMARDs early on, with MTX being preferred for patients with relevant skin disease.
4. Systemic steroids should be used with caution in lowest possible dose, Intraarticular steroids may be added to systemic DMARDs.
5. Biologic DMARDs, usually TNF inhibitors, shall be considered for patients with peripheral arthritis who failed at least one csDMARD.
6. If a TNF inhibitor is not appropriate, consider IL-12/23 or IL-17 inhibitor for patients with peripheral arthritis and one csDMARD failure.
7. If a TNF inhibitor or IL-12/23 or an IL-17 inhibitor is not appropriate, consider a PDE-4 inhibitor (apremilast) as bDMARD of choice.
8. For active enthesitis and/or dactylitis and insufficient response to NSAIDs or local glucocorticoid injections, consider TNF inhibitor as a first bDMARD of choice.
9. In patients with predominantly axial disease that is active and has insufficient response to NSAIDs, a TNF inhibitor shall be used as a bDMARD of choice (csDMARDs not recommended).
10. In patients who failed a bDMARD, switching to another bDMARD should be considered, including switching between TNF inhibitors.

CONVENTIONAL DISEASE MODIFYING ANTIRHEUMATIC DRUGS (csDMARDs)

Conventional systemic therapies effective for both psoriasis and psoriatic arthritis include methotrexate, ciclosporin and leflunomide. The advent of biologic agents for the treatment of psoriasis and psoriatic arthritis has not prevented the use of these drugs because of their oral route of administration and lower cost. Treatment with methotrexate followed by decreased antibody production and suppressed cytokine levels ^[9]. Methotrexate is beneficial both for skin and joints and has a rapid onset of action (3-4 weeks). Significant improvement was seen in joint tenderness and range of motion, extent of skin involvement, and ESR ^[10].

Use of leflunomide (100 mg/day for three days followed by 20 mg/day) in psoriatic arthritis patients improved responses in joint pain, degree of swelling,

and improved the quality of life ^[11]. Ciclosporin A has been used successfully in cutaneous psoriasis and psoriatic arthritis ^[12].

Biological agent

The most recent type of treatment is biological response modifiers which using recombinant DNA technology. Biologic medications are derived from living cells cultured in a laboratory. Biologics target specific parts of the immune system, unlike traditional DMARDs that affect the entire immune system. They are given by injection or intravenous (IV) infusion ^[13].

Biologics prescribed for psoriatic arthritis are TNF- α inhibitors, including infliximab, etanercept, golimumab, certolizumab pegol and adalimumab, as well as the IL-12/IL-23 inhibitor ustekinumab ^[14]. A treatment with anti-tumor necrosis factor (TNF) alpha should be started, if the patient fails the treatment target low disease activity after 3-6 months of DMARD therapy or if the patient suffers from enthesitis, dactylitis, or predominantly axial disease or very active disease with structural damage, extra-articular manifestations, or extensive skin involvement ^[15].

Biologics are indicated for active and radiological progressive psoriatic arthritis. According to the treat-to-target concept in rheumatoid arthritis, the EULAR recommendations for psoriatic arthritis suggest a switch to a second anti-TNF in case of lack of efficacy ^[15]. Currently, five biologics (certolizumab, etanercept, adalimumab, infliximab and golimumab) are available for the treatment for psoriatic arthritis. It is potentially demonstrated positive effects for anti-TNFs regarding PsA-associated enthesitis, dactylitis, skin psoriasis, psoriatic nail disease, and inhibition of radiographic progression. Moreover, PsA patients treated with anti-TNFs showed less progression of radiographic damage after 1-2 and 3-4 years, respectively, when compared with patients treated with methotrexate. Consequently, treatment with TNF blockers had a better radiographic outcome compared with treatment with synthetic DMARDs ^[16].

FDA approved the TNF inhibitor certolizumab pegol (Cimzia) for the treatment of active psoriatic arthritis in adults. Approval was based on an ongoing, randomized, double-blind, placebo-controlled trial in 409 patients with active and progressive adult-onset psoriatic arthritis in which certolizumab-treated patients were significantly more likely to meet American College of Rheumatology 20%, 50%, and 70% response criteria by week 12 than placebo-treated patients. Certolizumab pegol, a PEGylated FC-free anti-TNF, Certolizumab

reduced radiographic progression and improved skin manifestations^[17].

Golimumab (Simponi) is a medication used in the treatment of active psoriatic arthritis. Golimumab is a tumor necrosis factor (TNF) inhibitor, which have proven efficacy for treating psoriatic arthritis and psoriasis. It was experienced significant improvement in the signs and symptoms of psoriatic arthritis, including the number of joints affected, pain levels, and overall assessment of disease activity^[18]. Golimumab targets and binds to the excess TNF, which found in patients with psoriatic arthritis and leads to joint pain, stiffness, and swelling. It reduces the joint symptoms of psoriatic arthritis and prevents further damage to the joints. It is administered as a 50-mg injection subcutaneously once a month. It may be given alone or in combination with methotrexate or non-steroidal anti-inflammatory drugs (NSAIDs)^[3]. The treatment recommendations for psoriatic arthritis suggest that anti-TNFs (etanercept, infliximab, and adalimumab- certolizumab and golimumab not included in this analysis) are equally effective for the treatment of peripheral arthritis, the inhibition of radiographic progression, and the improvement of skin disease^[19]. Biologics may increase the risk of minor and serious infections. Rarely, they may be associated with nervous system disorders, blood disorders or certain types of cancer.

IL-12 / IL-23 Inhibitors

Ustekinumab, a new IL-12/IL-23-antibody approved for the treatment of plaque psoriasis and psoriatic arthritis, showed reduction of joint diseases activity as well as improvement of quality of life in patients with psoriatic arthritis^[20]. U.S. Food and Drug Administration (FDA) and the European Union approved ustekinumab, an IL-12/23 inhibitor, for the treatment of active psoriatic arthritis in adults who have not responded adequately to treatment with nonbiologic DMARDs^[17].

IL-17 Inhibitors

Secukinumab (Cosentyx) is a human IgG1 monoclonal antibody that selectively binds to and neutralizes IL-17A, which is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Secukinumab was approved by the FDA for adults with active psoriatic arthritis in January 2016. secukinumab, suggesting some clinical benefits, including quality-of-life improvements^[21].

Phosphodiesterase-4 inhibitors

A first treatment option for the management of psoriatic arthritis, apremilast is a small molecule phosphodiesterase-4 inhibitor approved for use by the

FDA in 2014. By inhibiting PDE4, an enzyme which breaks down cyclic adenosine monophosphate, cAMP levels rise, resulting in the down-regulation of various pro-inflammatory factors including TNF- α and the up-regulation of the anti-inflammatory factor interleukin 10^[22]. Apremilast, an oral phosphodiesterase-4 inhibitor, is given in tablet form and taken by mouth, showed significant improvements in disease activity, skin psoriasis, and physical function as well as an acceptable safety profile in a placebo-controlled trial on patients with psoriatic arthritis^[23].

Janus Kinase inhibitors

Janus kinases (JAKs) are intracellular tyrosine kinases that participate in the cytokine signaling pathway by associating with specific cytokine receptors. Tofacitinib is an oral JAK inhibitor that can suppress IL-23 receptor expression, thereby affecting Th-17 cell differentiation while also interrupting signaling by IL-6 and IFN- γ ^[24]. Tofacitinib was FDA approved in late 2012 for the treatment of RA. It has been shown to be effective in phase II trials of moderate to severe psoriasis at doses of 5 and 15 mg twice daily at 12 weeks of therapy^[25].

Complementary and Alternative Therapies

Obesity and psoriatic arthritis

Patients with psoriatic arthritis have a high rate of obesity. Obesity itself increases the risk of developing PsA, and researchers have found that obesity can reduce the effectiveness of certain treatments for PsA, specifically those that target tumor necrosis factor (TNF-alpha)^[26].

Risks of inflammation

Psoriatic arthritis causes an increase in inflammation throughout the body. This abnormal inflammation causes several negative effects in the body. In the joints, it causes stiffness, pain, and swelling. In the blood vessels, it increases the risk of atherosclerosis, the formation of abnormal fatty masses in the arteries, and can ultimately lead to major cardiovascular events^[26]. Obesity, which leads to changes in levels of cytokines (tumor necrosis factor α (TNF α), interleukin (IL)-6) and 'adipokines' (leptin, adiponectin), is associated with a low-grade chronic systemic inflammation^[27].

On the other hand, monocytes, CD4 T lymphocytes and most proinflammatory cytokines (TNF α , IL-1 β , IL-6 and IL-18) that play a central role in the pathophysiology of major arthritides, are also involved in the induction and maintenance of the atherosclerotic process^[28]. Thus, in obese patients with PsA, the obesity-related inflammatory status may act synergistically with the immunity-related

inflammation. Further supporting this hypothesis, obesity has been shown to be a negative predictor of success of a treatment with TNF α blockers in patients with psoriatic arthritis [29]. Given that caloric restriction lowers inflammatory cytokines levels in obese subjects [30].

Certain foods May Help Ease Psoriatic Arthritis Symptoms

Fruits and vegetables, herbs and spices, omega-3 fatty acids and vitamin D [31].

Prevent and Ease Psoriatic Arthritis Symptoms

Patients can soothe their symptoms of psoriatic arthritis, or even stop them before they start with a combo of exercise, medicines, and other treatments [32].

Exercise

Movement is vital to helping the pain and stiffness of arthritis. Exercise and physical therapy are important ways to help managing psoriatic arthritis symptoms, but they can help feeling well, too. Exercise and physical therapy are typically very safe, effective ways to deal with psoriatic arthritis. probably low-impact activities like walking, swimming, or biking. When making exercise a habit, it can ease arthritis symptoms, improve moving, get stronger and more flexible, keep weight healthy, which takes pressure off joints, help heart, boost mood and give more energy. Patient can work out on his own or with the help of a physical therapist. Warm up first, so muscles can ease into it [32]. One of best options is water therapy, also called hydrotherapy or aqua therapy. It's an exercise program held in a pool [32].

Hot and Cold packs

Relaxation, avocational activities and family support

Listen to favorite music and take a break. Or focus on breath in, out... in, out for a few moments. Other thoughts are bound to come up to-do list, a conversation need to have later today. Just gently return attention to breath. Prayer, is another great resource when you're stressed. Although none of these approaches will take the sources of stress away, they'll renew and refresh mind and emotions. It's a key part of day and can help give more energy to do the things you need (and want) to do [32].

Surgical interventions

Patients with progressive joint involvement unresponsive to therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) and antirheumatic drugs (DMARDs) may require surgical intervention [33].

RECOMMENDATIONS

- 1- Clinical trials on large numbers of patients to investigate long term effect of different lines of treatments are needed.
- 2- Co- management of the patients with dermatologist is necessary.
- 3- Although biologic agents are more effective than traditional systemic agents, cost is often a limiting factor in many countries, hence, it is good to the range of treatment options available so the most suitable one could be selected for each patient.

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