REVIEW ARTICLE

TREATMENT IN PSORIATIC ARTHRITIS: CHOICE AND DETERMINANTS OF RESPONSE

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Psoriatic arthritis (PsA) is the second most common inflammatory arthropathy after rheumatoid arthritis in early arthritis clinics. PsA presents as a symmetrical polyarthritis, like rheumatoid arthritis or an asymmetrical oligo-arthritis, with a predilection for the distal interphalangeal joints. Spinal involvement is like ankylosing spondylitis. Joint damage occurs early in up to 50% of PsA patients and has an 11% annual erosion rate in the first 2 years of the disease. There have been significant advances in understanding of PsA pathogenesis in recent years in the areas of genetics and molecular biology implicating both innate and adaptive immune systems. This has led to the introduction of evidence-based targeted therapy, primarily with tumour necrosis factor inhibitor (TNFi) agents. Therapy with disease-modifying anti-rheumatic drugs, such as methotrexate and leflunomide, remains the first-choice therapeutic intervention, even though there are few randomized controlled trials with these agents. In contrast, several successful studies of TNFi agents demonstrate excellent efficacy, in combination with methotrexate, and several novel agents are currently in development for the treatment of PsA. Before the introduction of targeted biologic medications, such as TNF inhibitors, the capacity to control disease activity was limited, with only modest effects noted in most patients with traditional oral medications such as methotrexate and sulfasalazine.

Keywords: Psoriasis, arthritis, inflammation, methotrexate, rheumatoid

Pak J Physiol 2022;18(4):31–4

INTRODUCTION

Psoriatic arthritis (PsA) is seronegative arthritis affecting both men and women with an incidence of approximately six cases per 100,000 population per annum, and 1–2 cases per 1,000 in the general population.[1] There is diversity in clinical features and the extent of psoriatic arthritis. According to Moll and Wright, psoriatic arthritis can be classified into 5 types, i.e., arthritis with specific distal interphalangeal involvement, arthritis mutilans, symmetric polyarthritis, asymmetric oligo-arthritis and spondylitis. Psoriatic arthritis may affect nails (onycholysis), ligaments, and tendons (enthesitis).[2] Classification Criteria for Psoriatic Arthritis (CASPAR) has been developed and validated as an adjunct to clinical diagnosis and a source for clinical research. The exact cause of psoriatic arthritis is unclear, but it is said that it happens due to a faulty immune system.[3] T cells and their derived cytokines degrade cartilage and bone and initiate bone resorption. In PsA there is inflammation of skin and joints. T cells are plentiful in the inflamed skin and joints. These cells in the synovium have selective T cell receptor usage suggestive of oligo-clonal expansions.[4] Antigen controlled activation of T cells results in psoriatic arthritis. The use of T cell inhibitors hints towards the involvement of T cells in inflammation of synovium and joint. HLA-DR 4 is associated with symmetric polyarthritis, HLA-B27 with axial PsA, and HLA B-38 and B-39 with polyarthritis.[5] Gene other than HLA like IL-23R is also associated with psoriatic arthritis.[6] Traumatic skin damage, streptococcal infection, and use of antibiotics are environmental factors leading to PsA.[7]

Psoriatic arthritis is highest among Caucasians of European descent.[8] In a study in North America, 1,184 patients were included with 1,037 European, 59 South Asian, 26 Chinese, 12 Black, 7 Hispanic, 12 Filipino, 2 Korean, 1 Aboriginal, and 24 mixed; the results revealed that South Asians had a lower duration, family history, psoriatic arthritis, nail psoriasis, and chances of radiographic changes as compared to European patients. South Asian patients had less severely damaged joints, and were less likely to be treated with biological agents than Europeans.[9] Another study[10] on psoriasis patients and PsA showed that the prevalence of PsA was higher in Caucasians compared to African Americans (64.5 *vs* 30%).

According to Angelo *et al*, initial therapy for PsA is with NSAIDs and DMARDs along with steroids; when patients fail to respond to this conventional therapy they are switched to biological agents.[11] Different studies around the globe have shown a difference in the understanding level of treatment among different ethnic groups, which was considered the reason for the ethnic disparity in treatment for psoriasis.[12] It was declared that black patients were not aware of biological therapy as the best psoriasis treatment. Also, these patients did not like the use of needles and feared side effects which led to avoiding biological agents by blacks. It was concluded that ethnic disparity in psoriasis treatment (biological therapy) was due to low knowledge of biological agents, fear of

needles, and adverse effects in black psoriatic patients.[13] The purpose of this article was to review and summarize various treatment choices for PsA at different stages of therapy for improvement of patients' quality of life.

METHODOLOGY

A literature search was performed for data published between 1st January 1950 and 31st December 2021 in databases like PubMed, Google Scholar, and Medline using keywords such as psoriatic arthritis, CASPAR, Psoriasis Area and Severity Index (PASI), American College of Rheumatology 20% improvement criteria (ACR20), Disease-modifying anti-rheumatic drugs (DMARDs), biological agents, immunomodulators, biosimilars to Biological agents, human monoclonal antibodies, Ustekinumab, Secukinumab, phosphodiesterase inhibitors, Apremilast, Tumour Necrosis Factor (TNF) inhibitors, Adalimumab, etanercept, infliximab, certolizumab pegol, Golimumab, Tofacitinib, Ixekizumab, CT-P13 (infliximab biosimilars), switching biological agents in PsA, Abatacept, literacy, socioeconomic status, environment, comorbidities, psoriatic arthritis in pregnancy, psoriatic arthritis in lactation, juvenile idiopathic arthritis, juvenile psoriatic arthritis and psychological state of psoriatic arthritis patients.

The inclusion criteria were all types of articles related to treatment in PsA in English language. The exclusion criteria were the articles not in English language and for which full-text was not available.

PSA treatment recommendations from organizations including the European League against Rheumatism (EULAR), Outcome measures in Rheumatology (OMERACT) panels, Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), and other National Rheumatology societies were evaluated to identify consensus guidelines on switching between DMARD therapies.

The side-effects of all available treatments for PsA, and reasons stated for its discontinuation were evaluated. Very rarely talked about topics like paediatric PsA and PsA in pregnant women were also discussed in this literature review.

RESULTS

A total of 200 studies were found, 11 studies were duplicate and discarded. Five studies were not following the inclusion criteria, and 19 were not in English language, hence excluded. Finally, 7 studies[14–20] were included for literature review and we have discussed the most effective first-line agent in PsA. Comparison of different agents used in PsA with comorbid conditions and adverse effects have been discussed. Our literature review was in accordance with the treatment guidelines of Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). [21] Also, treatment choice was according to comorbid conditions like hypertension, diabetes, hyperlipidaemia, cardiovascular disease, metabolic disease.

DISCUSSION

Initially, patients with PsA were treated with drugs used in rheumatoid arthritis, e.g., methotrexate, leflunomide, sulfasalazine. Since last 15 years, biological Disease-modifying anti-rheumatic drugs (DMARDs) like TNF inhibitors, interleukin inhibitors and phosphodiesterase-4 (PDE4) inhibitors revolutionized the whole format of PsA treatment. DMARDs like methotrexate acts by inhibiting aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase leading to intracellular accumulation of AICAR, and increased adenosine release which binds to cell surface receptors and suppresses many inflammatory and immune reactions. Leflunomide is an immunomodulator drug that achieves its effects by inhibiting mitochondrial enzyme dihydroorotate dehydrogenase, which plays a key role in *de novo* synthesis of uridine monophosphate required for the synthesis of DNA and RNA.[22]

Pharmacogenetic studies assessing methotrexate response, specifically in PsA are sparse. The gene polymorphisms which influence the metabolism of methotrexate may be classified into those that influence methotrexate transport across the cell membrane and those that influence enzymes in the cellular pathway of methotrexate.[23] Cyclosporine and sulfasalazine act by inhibition of prostaglandins, resulting in local anti-inflammatory effects that is used to treat PsA.[24,25] Apremilast is an inhibitor of PDE4, an enzyme that breaks down cAMP. In inflammatory cells, PDE4 is the dominant enzyme responsible for this action. It is a synthetic DMARD that acts upon different inflammatory mediators (IL-2, IL-12, TNF alpha, and inductively nitric oxide synthase) and suppresses them, it is currently approved by Food and Drug Administration and European Medicines Agency for treatment of active psoriatic arthritis patients.[26]

Patients who fail to respond to NSAIDs and conventional DMARDs may be started on biological agents after 3–6 months of use such as monoclonal antibodies, i.e., TNF inhibitors. As per IMPACT-2 (Improving Mood-Promoting Access to Collaborative Treatment-2) trial, infliximab efficacy was evaluated in patients who failed to respond to conventional DMARDs, as early as week-14.[27] Similarly, another 2-year study revealed that infliximab stopped bone damage in PsA patients by 54 weeks of use.[28] On the other hand, etanercept (ETN) was evaluated in a short duration study which showed clinical improvement by 12 weeks and radiographic improvement by 24 weeks. Other long-term studies on the use of ETN in spondyloarthropathies revealed that it reported fewer adverse effects as compared to other TNF inhibitors.[29]

Adalimumab (ADA) is an anti-TNF monoclonal antibody evaluated by a short term (24 weeks) and later a long term (48 weeks) study revealing ADA as an efficacious and safe agent which resulted in clinically improvement in both arthritic and dermal features.[30,31] Golimumab (GOL) is a humanized IgG anti-TNFα agent which was evaluated via GO-REVEAL trial showed promising results in all the parameters of PsA and the symptoms were improved as soon as by 14th week with minimal side effects.[32] Certolizumab pegol is an anti-TNF monoclonal antibody, it does not cause complement/antibody-induced cytotoxicity. It is pegylated to prolong half-life to 14 days and increase stability and solubility while the immunogenicity is reduced. Its efficacy was assessed via RCT double-blind (RAPID-PsA) trial, revealing improved disease parameters by the 24th week.[33]

More than 75% of cases of PsA in women present before 40 years of age that is during the reproductive years. Psoriatic arthritis does not affect the chances of conceiving much. Foetal risks in pregnant women with PsA derive both from maternal disease and medication used to control the illness. Cytokine excess causes endothelial dysfunction, resulting in systemic and placental vasculopathy through placental aggregation, intermittent vasospasm, and activation of the coagulation system. Placental vasculopathy leads to reduced birth weight of the baby and intrauterine growth retardation. Treatments for PsA have side-effects, particularly in pregnant women. Topical treatments like emollients are considered the first line for the treatment of psoriasis in pregnant women.[34] Among DMARDS, methotrexate is not safe in pregnant psoriatic patients as it may lead to malformations in the developing foetus. Sulfasalazine and cyclosporine are considered safe in pregnancy. Leflunomide reported teratogenicity in pregnant animals due to which it is better avoided in pregnant psoriatic/PsA patients. TNF inhibitors like infliximab and Adalimumab although do not cause foetal malformations, but they do cross the placenta and their level peaks in the 2nd and 3rd trimester.[35] Since the half-life of these agents is longer in newly born babies there are greater chances of BCG infection in neonates. Live attenuated BCG vaccine given to a 4.5-month-old baby may result in fatal infection if the mother of the child had taken infliximab during pregnancy.[36] Study conducted by OTIS group collected data from females exposed to etanercept, adalimumab, and certolizumab compared them to women with the same autoimmune diseases but with no history of exposure to the above-mentioned drugs concluded in non-association of these drugs with VATER or any other defect. Extensive literature is not available on the use of Ustekinumab in pregnancy. Although there are few reports published in the literature, 42 unpublished cases of drug exposure during pregnancy were identified. In all pregnant women, Ustekinumab was discontinued to limit foetal exposure, but patients still aborted.[37]

Psoriasis and PsA are not uncommon among paediatric population. As classified by the criteria of the International League of Associations for Rheumatology, juvenile PsA is arthritis that starts before 16 years of age, lasts for at least 6 weeks, and is either associated with psoriasis or with dactylitis/nail pitting or onycholysis or psoriasis in a first-degree relative. No randomized control trials have been conducted in juvenile psoriatic arthritis. Recommendations are therefore extrapolated from trials of therapy in children with polyarticular course juvenile idiopathic arthritis. Kumar *et al*[38] first reported the successful use of MTX in 7 children aged 3–16 years with severe psoriasis and did not find any significant side-effects or biochemical and haematological alterations. Because of the paucity of safety and efficacy data in children, Paediatric rheumatologists often rely on adult literature.

Overall TNF inhibitors have generally been found safe and effective in Paediatric use. Gartlehner *et al*[39] revealed that TNF inhibitors like Adalimumab, Etanercept, and Infliximab are effective in adult and juvenile psoriatic arthritis. Adalimumab, a fully humanized monoclonal antibody consisting of a variable region directed against TNF created from a phage display of human components, is approved for use in Rheumatoid arthritis, Psoriatic arthritis, Ankylosing spondylitis, Juvenile idiopathic arthritis, and Crohn's disease.[40]

CONCLUSION

There is a need to treat inflammatory PsA with the right treatment modality to prevent long-term joint damage and disability. It will be imperative to encompass known demographic, serological, immunological and genomic biomarkers, and correlate with robust outcome measures when assessing additional benefits of prospective genetic testing.

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Received: 7 Feb 2022 **Reviewed:** 16 Dec 2022 **Accepted:** 23 Dec 2022

Contribution of Authors:

LA: Concept, Data collection and analysis
MAK: Data collection and writing
SI: Data collection
MA: Data analysis and result compilation

Conflict of Interest: None
Funding: None