



HOW I WOULD TREAT PSORIATIC ARTHRITIS

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ABSTRACT

Psoriatic arthritis is an inflammatory arthritis that may be as common as rheumatoid arthritis. Psoriatic arthritis has a potential to cause destructive arthritis and has a significant impact on functional ability and the quality of life of an individual. Many agents are now available to treat this disease, and have been shown to be of benefit in clinical trials. This review provides an outline of the agents available and a strategy used by the authors in managing this disease in the clinic.

Keywords: Psoriatic arthritis; Psoriasis; Treatment.

RESUMO

A artrite psoriática (AP) é uma artrite inflamatória que pode apresentar uma frequência semelhante à artrite reumatoide. A AP pode causar uma artrite destrutiva e determinar um impacto significativo na capacidade funcional e na qualidade de vida do indivíduo. Actualmente estão disponíveis vários agentes para o tratamento desta patologia e que demonstraram, em ensaios clínicos, o seu benefício. Neste artigo procede-se a uma revisão dos fármacos disponíveis e apresenta-se a estratégia utilizada pelos autores no tratamento desta doença na prática clínica.

Palavras-chave: Artrite psoriática; Psoríase; Terapêutica

HOW I WOULD TREAT PSORIATIC ARTHRITIS

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Introduction

Psoriatic arthritis (PsA) is a unique inflammatory arthritis associated with psoriasis. Its prevalence in patients with psoriasis had been reported to be between 6 to 42%^{1,2}. Recent studies have reported a prevalence of about 30%³. Since the prevalence of psoriasis in the general population is about 3%, PsA may have a prevalence of about 1%. There are no currently accepted diagnostic criteria for the diagnosis of PsA⁴. Diagnosis is usually made using the clinical features and patterns described by Moll and Wright^{5,6}.

The CLASSification of Psoriatic ARthritis (CASPAR) Study, an international study to validate classification criteria and devise a new set of criteria was recently completed⁷. It demonstrated that most of the previously reported criteria had greater than 90% sensitivity and specificity and thus had face and content validity against physician diagnosis of the condition. However, CASPAR has also developed a new set of classification criteria, which will likely facilitate research in this condition.

PsA has been classified as a spondylarthritis (SpA). It has peripheral erosive arthritis, sacroiliitis and spondylitis, in addition to other characteristic features such as distal interphalangeal joint involvement, periosteitis and new bone formation, and flail and ankylosed joints in addition to skin disease that makes the disease unique, and management a challenge^{8,9}. PsA is more severe than what was thought previously. At presentation, most patients have polyarthritis, and about 20% have evidence of

joint damage¹⁰. PsA progresses over time in many patients leading to further joint damage, deformities and functional limitation¹¹. More than half of patients followed up for more than 10 years had more than 5 deformed joints¹². Patients presenting with oligoarthritis progress over time to have polyarthritis¹³. Radiological damage also progresses with time, both in the peripheral joints and the spine¹⁴. Almost a fifth (11-19%) of patients seen in a clinic setting are in ACR functional class III or IV¹⁵. The health related quality of life as measured by questionnaires such as Health Assessment Questionnaire (HAQ) and Medical Outcomes Study Short-Form 36 (SF-36) demonstrates significantly higher levels of disabilities and pain than healthy controls, and to a level similar to that of patients with rheumatoid arthritis (RA)^{16,17,18,19}. Patients with previous active and severe disease are also at an increased risk of death compared to the general population^{20,21}. Thus, PsA has a potential to cause destructive arthritis and has a significant impact on functional ability and the quality of life of an individual.

Assessment of Psoriatic arthritis

The assessment of PsA should include assessment of peripheral arthritis, spondylitis, dactylitis, tendonitis and enthesitis as well as psoriasis in addition to measures of physical function and disability. A comprehensive PsA assessment tool has not yet been developed. A review of currently available measures has been published recently²². Researchers have tended to use 'modified' tools used for the assessment of RA and SpA. The ACR 68/66 joint count is used to assess peripheral arthritis^{23,24}. Assessment of the spine would require assessing sacroiliac joint tenderness and measuring back movements²². Both the presence and degree of inflammation of a digit with dactylitis should be assessed as was done in a recent trial²⁵. The Maas-tricht Ankylosing Spondylitis Enthesitis Score (MA-

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SES) may be used to assess enthesitis²⁶. Whether these instruments are valid for psoriatic arthritis remains to be determined. The Psoriasis Area Severity Index (PASI) is one of the instruments used to measure activity of psoriasis²⁷. Inflammatory markers such as the erythrocyte sedimentation rate (ESR) and C reactive protein (CRP), are elevated in only about one half of patients with PsA, and may not always correlate with disease activity. However, these should be assessed, since a high ESR at presentation has been associated with early mortality²¹. The HAQ²⁸ and SF-36²⁹ questionnaire are used to assess physical function and health status and have been validated in psoriatic arthritis¹⁶.

There is a lack of standardized validated instruments to assess clinical response. In recent clinical trials in psoriatic arthritis the ACR 20% response borrowed from RA has been used as the primary outcome with ACR50 and ACR70 as well as the as the PsA Response Criteria (PsARC) as secondary outcomes. In other studies PsARC has been used as the primary outcome^{30,31}. There are no criteria to assess response of spondylitis in psoriatic arthritis. There is also no global response criterion that includes all the varied disease manifestations mentioned previously.

Management of PsA

Patients should ideally be under care of a multidisciplinary team comprising rheumatologists, dermatologists, physiotherapists and occupational therapists. However, if the primary problem is skin disease and the arthritis is mild and non-erosive, he/she may be managed by a dermatologist after a comprehensive rheumatologic evaluation including radiographic evaluation. Periodic assessment by a rheumatologist in such cases would be ideal. On the other hand, if the primary problem is joint disease, the rheumatologist should primarily manage the patient, with the dermatologist confirming the diagnosis of psoriasis and providing input if skin disease remains an issue.

Symptom Modifying Therapy

Non-steroidal anti-inflammatory drugs (NSAIDs)
NSAIDs are useful in the treatment of PsA and give symptomatic relief. However, NSAIDs do not prevent disease progression³², and may worsen skin le-

sions³³. Their place in the management of PsA would be for sole treatment for mild non-erosive disease and for symptomatic management of pain, inflammatory swelling and morning stiffness. With the recent reports of increased risk of heart attacks and stroke with long term use of COX-2 inhibitors^{34,35,36,37}, non-selective NSAIDs like naproxen, ibuprofen, diclofenac, indomethacin or aspirin (with or without misoprostol/H2-blockers/proton pump inhibitors) would be preferred. If symptoms persist after adequate trial with two different NSAIDs, Disease Modifying Anti Rheumatic Drug (DMARD) use should be considered.

Steroids

Intra-articular steroid injections (triamcinolone, methylprednisolone) are often used for rapid relief of symptoms in cases of mono- or oligoarthritis. Systemic steroids are used occasionally for symptom relief when there is polyarthritis or when there is inadequate response to NSAIDs. However, it needs to be used with extreme caution with slow taper, since psoriasis worsens in many instances and could occasionally evolve into pustular psoriasis³⁸. We try to avoid use of systemic corticosteroids in our patients with psoriatic arthritis.

Disease Modifying Therapy

Traditional DMARDs (t-DMARDs)

In patients with persistently active or erosive disease, t-DMARDs are the first line of treatment and should be used early in the course of disease. Most drugs belonging to this class work for both the joints and skin. However, there have been few randomized control trials with these drugs in PsA³⁹.

Methotrexate (MTX)

Although there are only a few studies on its efficacy, MTX is the most widely used DMARD in PsA. It has a good risk-benefit ratio, based primarily on its use in rheumatoid arthritis, and has a relatively rapid onset of action. There are only 2 randomized controlled trials (RCT) of its use in PsA^{40,41}. The first study included 21 patients and used intravenous methotrexate (1-3mg every 10 days). Although the drug reduced joint counts and the ESR compared to placebo, there were 3 deaths⁴⁰. The other trial in 35 patients, using oral MTX (7.5-15mg/week) for 12 weeks, demonstrated improvement only in physician global improvement. The

side effects were mild and all patients completed the trial. However the study was underpowered to demonstrate effect⁴¹. Retrospective uncontrolled studies have demonstrated good results with use of MTX in PsA^{42,43}. However, a nested case-control study showed that it did not prevent radiologic progression over 2 years in patients with PsA treated after average disease duration of 9 years⁴⁴. Over the last decade, MTX has been used increasingly at higher average dosages, parenterally if doses higher than 15 or 17.5mg/week are required, and earlier in the disease course. The concern of liver toxicity has also diminished. It has thus become the cornerstone of therapy in clinical practice⁴⁵.

Sulfasalazine (SSZ)

SSZ has documented efficacy in the treatment of RA and peripheral arthritis of spondylarthritis in general. However, its efficacy in PsA is modest. There are 5 published RCTs of SSZ in PsA^{30,46,47,48,49}. In the first three trials^{46,47,48}, the number of patients treated was small and an improvement in patient global assessment was reported. In the larger trials^{30,49} there was an improvement in patient global assessment, and a marginal improvement in PsARC. A nested case control study showed no difference between treated patients and controls either in effectiveness or in progression of joints damage⁵⁰.

Antimalarials

Chloroquine has been used in the treatment of PsA without exacerbation of psoriasis as feared by dermatologists. However, although the majority of patients demonstrated a >30% reduction in the actively inflamed joint count, the results were not different from the control group⁵¹.

Ciclosporin A (CsA)

CsA is effective in controlling psoriasis⁵². There are no RCTs comparing CsA with placebo in PsA. However, there are trials comparing it with other DMARDs. In a three arm RCT comparing CsA 3-5mg/kg/day added to standard therapy (NSAIDs and low dose prednisone) with SSZ 2g/day added to standard therapy and standard therapy alone, there was improvement in pain only in CsA treated patients. There was no demonstrable difference in the outcome measures chosen⁵³. In a 2-arm RCT comparing CsA to MTX, both arms showed improvement at 6 and 12 months. However, more patients were withdrawn from CsA arm due to toxic-

ity⁵⁴. In the most recently published RCT, CsA was compared to placebo as an add-on treatment, in patients with PsA demonstrating an incomplete response to MTX monotherapy. There was significant improvement at 12 months in the swollen joint count, C reactive protein, PASI and synovitis detected by high-resolution ultrasound. There was no improvement in the Health Assessment Questionnaire or pain scores⁵⁵. Thus, CsA may have a role in patients with partial response to MTX as an add-on treatment. However, it is toxic and is not well tolerated.

Azathioprine (AZA)

One RCT reported in an abstract form reported improvement in patients treated with AZA compared with patients on placebo⁵⁶. A nested case control study failed to show effectiveness or ability to prevent disease progression⁵⁷.

Leflunomide

Leflunomide was recently shown to be an effective treatment of PsA in a multicentre double blind controlled trial comparing it to placebo⁵⁸. Leflunomide-treated patient had a better PsARC, ACR20 response and improvement in PASI scores. The measures of quality of life also showed improvement in the leflunomide arm. It is an important addition to the therapeutic armamentarium that we have in treating psoriasis and PsA.

Other DMARDs

Although not shown to protect from progression of joint damage, Gold^{59,60} (both oral and parenteral) has been used, with intramuscular gold being more effective. With significant concern about toxicity, slow mode of action, problems with availability, and availability of more effective drugs, it is seldom used nowadays. Penicillamine use is limited due to its toxicity. There are some reports that mycophenolate mofetil may be efficacious, but there have been no RCTs to prove its role^{61, 62}. Etretinate (retinoic acid derivative) has been shown to be effective in an RCT⁶³, and two small, uncontrolled trials^{64,65}.

Biologic Agents

Anti-Tumour Necrosis Factor (TNF) Agents

Infliximab

Infliximab is a chimeric monoclonal antibody that

binds to human TNF. It is administered as an intravenous infusion at 0, 2 and 6 weeks followed by once every 8 weeks. An observational study on patients with refractory PsA, infliximab led to a marked improvement in psoriasis but only modest response in joint disease. Toxicity and rate of treatment termination was high⁶⁶. However, randomized controlled trials have demonstrated efficacy of infliximab in psoriatic arthritis. The Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT)⁶⁷ has shown that 65%, 46% and 29% of Infliximab treated patients achieved an ACR20, ACR50 and ACR70 response at week 16 compared to 10%, 0% and 0% of placebo-treated patients, respectively. Among patients who had PASI scores of ≥ 2.5 at baseline, 68% of Infliximab-treated patients achieved improvement of $\geq 75\%$ in the PASI score at week 16 compared to none of the placebo-treated patients. Sustained improvement was seen through week 50. Dactylitis and enthesitis also improved. Adverse events were similar between the treatment groups. The improvement persisted through 1 and 2 years of follow-up^{67,68}. The larger IMPACT 2 trial⁶⁹ showed similar results as the IMPACT trial with significant improvement in active PsA, psoriasis, dactylitis and enthesitis. Both IMPACT and IMPACT2 demonstrated a favourable effect of infliximab on progression of joint damage^{70,71}.

Etanercept

Etanercept is a dimeric fusion protein consisting of the extra cellular portion of the human p75 TNF receptor linked to the Fc portion of human IgG1. It binds and inactivates TNF. It is administered as a subcutaneous injection twice weekly, the usual dose being 25mg per dose. Results from the first phase II RCT³¹ in PsA showed that at 12 weeks 87% of etanercept treated patients responded compared to 23% of placebo treated patients. All components of PsARC showed improvement. 73% of patients in the etanercept arm achieved an ACR20 response compared to 13% of patients in the placebo arm. 26% of patients in the etanercept arm achieved a PASI75 response, compared to none of those treated with placebo. Injection site reactions were more common among the etanercept treated patients. The results were further confirmed in a phase III multicentre trial⁷², which also demonstrated significant sustained improvement in quality of life. There was also less radiographic progression. As in the previous trial, the only significant

difference in the safety profile between etanercept and placebo was more injection site reactions in the etanercept arm. While the RCTs suggest that etanercept exerts its effect early, a recent observational study cautions that in some patients response may be delayed and noted only after 6 months of therapy⁷³. Etanercept has also shown a potential to prevent progression of joint damage.

Adalimumab

Adalimumab is a humanized anti-TNF α antibody and is administered subcutaneously at 2-weekly intervals. Results from the ADEPT trial, a phase III placebo controlled double-blind study, were published recently in abstract form⁷⁴. ACR 20/50/70 responses were seen in 57/39/23% of Adalimumab treated patients compared to 14/4/1% in the placebo treated patients at week 24. In those with $>3\%$ body surface area involvement with psoriasis, PASI50/75/90 response was achieved in 75/59/42% patients, respectively, compared with 12/1/0% in the placebo treated patients. Adalimumab has also been reported to lead to clinically meaningful and statistically significant improvement in quality of life⁷⁵. It has also been shown to be effective in inhibiting radiographic disease progression over 1 year⁷⁶. There was no difference in the adverse event profile between both treatment arms.

T-cell directed agents

Interactions such as those between lymphocyte function-associated antigen 1 (LFA-1) and its ligand intercellular adhesion molecule 1 (ICAM-1), and LFA-3 and CD2 are required for full T-cell activation. Molecules inhibiting these interactions have been developed recently and clinical trials with these agents in the treatment of PsA are in progress, since T-cell activation is important in pathogenesis of PsA.

Alefacept is a fully human fusion protein consisting of the first extra cellular domain of LFA-3 fused to the hinge segment and constant regions of IgG1. It inhibits antigen driven activation of T cells and also causes selective apoptosis of memory T-cells. Results from a double blind, placebo controlled RCT of alefacept in combination with MTX are now available⁷⁷. All patients had active PsA despite treatment with MTX. At 24 weeks ACR20 response was achieved in 54% of alefacept treated patients compared to 23% of patients on placebo. In patients with psoriasis involving $>3\%$ body surface area, 53% of alefacept treated patients

achieved PASI50 compared to 17% of those receiving placebo. These results were obtained at 24 weeks, although the active drug was given for only the first 12 weeks of the study. Adverse events were mild to moderate and <2% of alefacept treated patients discontinued treatment due to treatment-related adverse events⁷⁸.

Efalizumab is a humanized monoclonal IgG1 antibody against CD11a one of the subunits of LFA-1. It is effective in the treatment of psoriasis^{79,80}. Results of a phase II trial with this agent for PsA have been disappointing with only 28% of the patients achieving ACR20 response compared to 19% of the placebo treated patients⁸¹.

Management of PsA today

With the availability of a large number of agents, with good efficacy and low toxicity, we have a number of options for treating patients with PsA. However, due to concerns about costs and long-term toxicity, the newer agents are being used cautiously. The British Society for Rheumatology recently published guidelines for treatment of PsA with anti-TNF α agents⁸².

Our approach to treatment of patients with PsA is based on a step-up strategy. Patients with mild psoriasis and arthritis are treated with topical agents and NSAIDs with or without intra-articular corticosteroids. Patients with evidence of persistent synovitis despite these measures, or those have evidence of severe joint disease (3 swollen joints, erosive disease) are first given an adequate trial with at least 2 t-DMARDs (methotrexate, leflunomide, sulfasalazine or ciclosporin A). We define an adequate trial of MTX as maximum tolerated dose, given either orally or parenterally (intramuscular or subcutaneous for doses >17.5mg/wk), for at least 3 months. Leflunomide is given at a dose of 20mg daily. We prefer not to give the loading dose. SSZ up to 4grams per day for 3 months may be tried in patients who are not sensitive to sulfa. Ciclosporin is given at a dose of 3-5mg/kg with close monitoring of kidney and liver functions and blood pressure. If patients continue to have active joint disease (≥ 3 tender and ≥ 3 swollen joints) an anti-TNF agent, usually etanercept (as it is currently the only agent approved for PsA in Canada) is instituted. If there is a failure on Etanercept, Infliximab or Adalimumab is tried. Other biologics are considered if the patient still

does not respond.

If the major issue is with skin disease, we use alefacept, which has now been approved for the treatment of psoriasis in Canada.

Conclusion

Psoriatic arthritis has the potential to cause destructive arthritis and has a significant impact on the functional capacity and health related quality of life. More agents with reasonably proven efficacy are available for its management today. Biologic agents may have better efficacy than the traditional DMARDs and may prevent progression of joint damage. Further clinical studies are however required to clearly define their place in management of patients with PsA given its cost and concern for long-term safety.

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