Psoriatic arthritis: treatment strategies using anti-inflammatory drugs and classical DMARDs

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SUMMARY

Psoriatic Arthritis (PsA) is a chronic inflammatory disease typically characterized by arthritis and psoriasis variably associated with other extra-articular manifestations. PsA has been considered a milder and less disabling disease compared with rheumatoid arthritis (RA), even if some studies showed that PsA had joint erosions and damage. In addition, about 20-40% of PsA patients have axial skeleton involvement that may lead to functional limitation and deformity. The treatment of PsA ranged from initial treatment with non-steroidal anti-inflammatory drugs (NSAIDs) to one or more disease-modifying anti-rheumatic agents (DMARDs) for the suppression of inflammation in patients with recalcitrant peripheral joint disease. In clinical practice, the most widely used DMARDs are methotrexate (level of evidence B), sulfasalazine (level of evidence A), leflunomide (level of evidence A), and ciclosporin (level of evidence B). However, the efficacy of these agents in inhibiting joint erosions has not been assessed in controlled studies. Finally, the effectiveness of DMARDs in treating enthesitis and dactylitis is controversial.

The present paper revised the evidence-based results on treatment with "conventional" therapy for PsA. The revision was based on all the subsets of the diseases, namely the various manifestations of the articular involvement (peripheral, axial, enthesitis, dactylitis) as well as the skin and nail involvement.

Key words: *Psoriatic arthritis, biomarkers, joint damage*

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INTRODUCTION

Psoriatic Arthritis (PsA) is a chronic inflammatory disease typically characterized by arthritis and psoriasis variably associated with other extra-articular manifestations (1).

PsA has been considered a milder and less disabling disease compared with rheumatoid arthritis (RA), even if some studies showed that PsA had joint erosions and damage (2). In addition, about 20-40% of PsA patients have axial skeleton involvement ("psoriatic spondylitis"), which may lead to functional limitation and deformity (3). Therefore, PsA has to be considered a potentially disabling disease requiring aggressive treatment, although the lack of population-based studies using standardized classification criteria precludes a confident estimate of the precise prevalence of severe PsA.

The treatment of PsA has been dealt by different medication, from initial treatment with non-steroidal anti-inflammatory drugs (NSAIDs) to one or more disease-modifying anti-rheumatic agents (DMARDs) for the suppression of inflammation in patients with recalcitrant peripheral joint disease. In clinical practice, the most widely used DMARDs are methotrexate (level of evidence B), sulfasalazine (level of evidence A), leflunomide (level of evidence A), and ciclosporin (level of evidence B). However, the efficacy of these agents in inhibiting joint erosions has not been assessed in controlled studies (4). Finally, the effectiveness of DMARDs in treating enthesitis and dactylitis is dubious.

The recent 2010 update of the recommendations of the Italian Society for Rheumatology for the use of biologic (tumor necrosis factor-α blocking) agents in the treatment of psoriatic arthritis has taken into account the treatment strategies using

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NSAIDs and classical DMARDs showing, in particular, that they still represent the first choice for patients with PsA with peripheral arthritis (5).
The present paper revised the evidence-based results on treatment with "conventional" therapy for PsA. The revision was based on all the subsets of the diseases, namely the various manifestations of the articular involvement (peripheral, axial, enthesitis, dactylitis) as well as the skin and nail involvement.

Non steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are a broad group of medications widely used in the treatment of pain conditions, such as arthritis. Usually, they are the first choice of treatment for conditions like PsA, either prescribed by the general practitioner or by the rheumatologist at any stage of the disease.
Few studies have been published for the efficacy of NSAIDs of PsA treatment. In fact, even the use of these medication is very common in the real clinical practice, data from clinical trials are very poor. In 1976 a double-blind crossover study comparing azapropazone (1200 mg per day) with indomethacin (100 mg per day) was carried out in 34 PsA patients and 16 with Reiter's disease.
Main results showed that azapropazone seemed to be more effective in cases with PsA and indomethacin in Reiter's patients. However, indomethacin caused more side-effects than azapropazone while neither drug seemed to influence the skin manifestations of either diseases (6).
Another trial was carried out in 1982, comparing two different NSAIDs (indomethacin and diclofenac) by using a run-in period during which the dosage of one of trial drugs was adjusted to suit the individual patient. No significant differences were observed among the clinical improvements due to both drugs during the course of the study (7).
In 1985 in Leeds (UK), a double-blind controlled trial study of etetrinate and ibuprofen was carried out in a group of PsA patients. This study showed, in particular, that etetrinate improved skin lesions while the articular index, used by researchers during this study as outcome measure, improved in both groups treated (8).
More recently, a Cox-2 inhibitor was assessed for the efficacy of Ankylosing Spondylitis (AS), showing in particular the possibility to slow the disease progression in terms of radiological progression (9). However, even if this study was carried out on a different disease (Ankylosing Spondylitis), it is the only scientific contribution on the axial component of seronegative spondyloarthritis.
Finally, the potential side effects of NASAIDs, such as gastrointestinal risk, cardiovascular and renal toxicity have never studied in PsA. Only the role of NSAIDs on possible induction of skin flares has been considered (10).

CLASSICAL DMARDs

Methotrexate

The recent introduction of new biological molecules for the treatment of PsA has stimulated the review of evidence for the efficacy of Disease Modifying Anti-Rheumatic Drugs (DMARDs).
In fact, even in the daily clinical practice Methotrexate (MTX) is widely used, yet the evidence for the efficacy or effectiveness of this molecule on the broad spectrum of the disease (skin, nail, peripheral joint, axial, enthesitis, dactylitis) is poor, graded as level B of evidence for polyarticular disease (11). However, a cross-sectional study using the database from the CASPAR study showed that MTX, among the DMARDs, was the most used medication (39% of the total population, n=433) in the real life.
The same study showed, also, that other DMARDs were quite common: sulphasalazine was used in 22%, gold salt in 11%, antimalarial drugs in 5% and, finally, corticosteroid in 10% of the group (12).
A comparison of MTX *vs* NSAIDS was the aim of a study on a group of early PsA patients. Results showed that MTX was more rapid and effective than NSAIDS

on clinical response (swollen and tender joint counts), while no differences were observed on other disease activity indexes (CRP, ESR, VAS) (13).

More recently Marchesoni et al., in Italy, evaluated the long-term survival of MTX in PsA patients with peripheral joint involvement, in a setting of everyday clinical practice (14). This observational retrospective study, using data from dermatological-rheumatological PsA clinic, showed that, out of 174 patients, 104 (59.8%) were still taking MTX after three years of treatment. The reasons of discontinuation were in the remaining 70 patients, 34 (19.5%) lost to follow-up, 18 (10.3%) adverse events, 14 (8%) inefficacies and 4 (2.3%) deaths (none related to the therapy). In particular, MTX was effective in controlling joint inflammation but not in preventing their deterioration. No serious side effects were recorded. Overall MTX showed, in real clinical practice, to have a good three year performance in a group of patients with peripheral PsA. The authors concluded that MTX might be considered the non-biologic DMARDs of choice for the treatment of this condition (14).

Previous studies have dealt with the efficacy or effectiveness of MTX in PsA patients and, overall, there has been a small amount of evidence supporting the use of this drug. The first study, in 1964, was designed as double-blind in a small group of 21 PsA patients, using MTX IV (2 mg/kg) weekly and the efficacy was deemed using a joint index (15). In 1984, in a 12-week prospective controlled, double-blind multicenter trial comparing placebo oral pulse MTX (7.5-15 mg weekly), MTX was superior to placebo only in physician assessment of arthritis activity and in improvement of amount of skin surface area with psoriasis. However, overall low dose oral MTX (7.5-15 mg weekly) did not improve PsA (=0.39-0.89) (16).

Spadaro et al. in 1995 published a study on a prospective, controlled randomized trial of PsA patients treated with MTX or Cyclosporin (CsA), showing a mild efficacy of MTX (17). Interestingly, both DMARDs were effective at 12 months, even if the rate of withdrawn was higher in the CsA arm. This well designed study suffered only for the small number of patients (total 35).

A randomized, double-blind, placebo controlled multicentre trial of combination therapy with MTX plus CsA was carried out in 72 patients with active PsA (18). The aim the of this trial was to assess the efficacy and safety of adding CsA to the treatment of patients with PsA demonstrating an incomplete response to MTX therapy. The study showed a significant improvement of swollen joint count, C reactive protein, and PASI. Interestingly, the study evaluated the effects of combination treatment by High Resolution Ultrasound (HRUS) and the results showed a significant improvement in the arm treated with MTX and CsA on the synovitis by HRUS. Finally, the same study did not show any improvement on pain scores and Health Assessment Questionnaire (18).

Sulphasalazine

Sulphasalazine was compared to placebo in 6 studies in the 90's when this molecule was considered the gold standard for the treatment of rheumatoid arthritis and PsA (19-24). However, the efficacy of sulphasalazine was recorded in these studies on the peripheral arthritis only, with a lack of efficacy on the axial component of the disease (25). Interestingly, the efficacy observed was only on the clinical manifestations without benefits on the radiological progression of the disease. Few data have been obtained on the efficacy of sulphasalazine for the treatment of enthesitis or dactylitis. Finally, up to a third of patients enrolled for these studies showed some adverse effects of the treatment, namely gastrointestinal intolerance, dizziness and raised liver function tests (25).

Cyclosporin A

Cyclosporin A (CsA) is an immunosuppressive agent having the capability to inhibit the activity of transcription factors of the nuclear factor of activated T cell family, acting in stimulated T cells by suppressing interleukin 2 (IL-2) production and IL-2

receptor expression. CsA has been utilized in Psoriasis showing to be effective and its use for the treatment of the skin can be summarized as follow:

a) intermittent course, usually short periods of time;
b) continuous treatment;
c) crisis intervention;
d) combination of sequential and rotational therapy (26).

For the treatment of PsA by using CsA, there are in literature 3 main studies aimed to compare the efficacy and safety of CsA to other DMARDs. As reported in the section of MTX, Spadaro et al. in 1995 (17) compared CsA with MTX in a small group of PsA patient, and Fraser et al. in 2005 (18) carried out a study on combination therapy (CsA+MTX) *vs* MTX. In 2001 an Italian multicentre study was carried out to compare the efficacy and safety of CsA with a symptomatic therapy alone or in combination with sulphasalazine (27). This open trial showed that CsA was more efficacious on pain score, swollen and tender joint count compared with symptomatic therapy or sulphasalazine (17). As regards the long-term safety of CsA, an Italian study showed this important aspect of the management of severe PsA (28).

Leflunomide

Leflunomide, a selective pyrimidine synthesis inhibitor with the property to inhibit T-cell activation and proliferation was assessed for its efficacy and safety in a randomized placebo controlled trial involving 190 PsA patients with active disease (artrhritis), defined as at least 3 tender and 3 swollen joints. The DMARD showed efficacy in improving the articular involvement of PsA, as well as disability and skin psoriasis (29). As regards the side-effects, the most frequent were diarrhea, raised liver function tests, flu-syndrome and headache, and these were more common than in the group treated with placebo (29).

Other DMARDs

The treatment for PsA has "borrowed" various DMARDs already used for the treatment of rheumatoid arthritis. In particular gold salts (auranofin and sodium thiomalate) did not show to be more effective than placebo. Azathioprine may be effective, but larger controlled trials are needed.

More recently, a systematic review and meta-analysis was performed to estimate the efficacy by using the rates of withdrawn due to lack of effect, and to estimate the safety and toxicity by using withdrawal due to adverse events (30).

Antimalarials are not indicated for the treatment of PsA patients, because of their possible associations with exacerbations of psoriasis (31). Finally, few studies have been carried out on mycophenolate mofetil (MMF) in the treatment of psoriasis and PsA (32), a molecule that acts inhibiting inosine monofospahte and subsequent *de novo* guanine synthesis necessary for DNA replication on lymphocytes but not neutrophils.

CONCLUSIONS

Overall, the data obtained from literature are supporting the wide use of non-biologic DMARDs for PsA but without a good level of evidence. Indeed, MTX seems to be a quite common DMARDs for the PsA with peripheral joint involvement, mainly in established disease. Sulphasalazine has been the most studied medication even if it showed only modest efficacy.

Cyclosporine seems to be an effective medication also for the skin disease, but it showed toxicity. Finally, leflunomide is the only drug that recently has proved to be effective on both main components of the disease, suggesting its potential role as traditional non-biologic DMARDs in the treatment of PsA.

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