REPORT

Psoriatic arthritis therapy: NSAIDs and traditional DMARDs

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Non-steroidal anti-inflammatory drugs (NSAIDs) and traditional disease modifying antirheumatic drugs (DMARDs) are widely used in the treatment of psoriatic arthritis (PsA), but this is based more upon clinical experience than adequate evidence from clinical trials. This report summarises the results from available trials highlighting evidence of efficacy and deficiencies with respect to effect on joints and to a lesser degree cutaneous disease. The available published data on efficacy of NSAIDs, glucocorticoids, antimalarials, sulfasalazine, gold, methotrexate, azathioprine, and ciclosporin are detailed, as well as new data on leflunomide and other novel agents. The conclusions of this review are that evidence supports marginal efficacy of sulfasalazine and perhaps gold in the treatment of peripheral psoriatic arthropathy, and methotrexate and ciclosporin are effective for treating the skin disease although evidence for improvement of the arthropathy is empirical at best. New trials with standardised and validated outcome measures are required to better assess efficacy. Evaluating newer agents, against and in combination with traditional DMARDS, may further clarify the latter's role in the future management of this condition.

I deal therapy for psoriatic arthritis (PsA) should target both rash and joint disease, treat peripheral and axial manifestations including dactylitis and enthesitis. Erosive joint damage as well as the impact on quality of life from PsA have been shown to be comparable with that in patients with rheumatoid arthritis (RA).[1][2] Therefore, both symptomatic therapy and aggressive treatment aimed at disease modification/amelioration should be the goal of effective medical management of PsA. Traditional disease modifying antirheumatic drug (DMARD) therapy, as detailed below with these aims in mind, has been poorly studied. As will be shown, there are few adequate well designed controlled randomised trials, and those that have been performed have shown disappointing efficacy. Consistently high placebo response rates are seen in PsA trials, adding to the difficulty of interpreting the results of uncontrolled trials when making management decisions for this condition. Difficulties in defining clear disease subgroups and the possible maldistribution of the subtypes of arthritis between the placebo and treatment arms further complicate the extrapolation of results to specific disease subsets. Novel biological therapies for PsA and the development of more reliable outcome measures to assess responders' symptomatic, functional, and radiological endpoints are described elsewhere in this supplement.[3–6]

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used as initial therapy, prescribed for both peripheral and axial disease. However, controlled studies assessing efficacy are limited; they confirm superiority to placebo on tender/swollen joint counts, and pain scores, but show no effect on rash (assessed by Psoriasis Area and Severity Index (PASI) score) or on the erythrocyte sedimentation rate (ESR) to suggest disease modification.[7] Worsening of skin disease with initiation of NSAID therapy has been observed for both non-specific and cyclo-oxygenase-2 specific NSAIDs[8–10] with shunting of arachidonic acid metabolites down the leukotriene pathway postulated as the mechanism, although other controlled studies suggest this is not a major clinical issue.[7] No unusual toxicity associated with the use of NSAIDs in PsA has been reported.

GLUCOCORTICOIDS

Periodic intra-articular injection of corticosteroid can be of particular value in the management of patients with oligoarticular disease or those with controlled polyarticular disease but one or two persistently actively inflamed joints. Two failed injections are a requirement for eligibility for antitumour necrosis factor (anit-TNF) therapy in recently devised guidelines.[11] In general, systemic glucocorticoids should be used judiciously because of the risk of provoking a pustular flare in the skin disease on withdrawal.[12]

CONVENTIONAL DISEASE MODIFYING ANTIRHEUMATIC DRUGS
Sulfasalazine

Sulfasalazine's efficacy in RA and other seronegative arthritides led to its use in PsA. Efficacy was initially observed in pilot studies and a number of controlled trials, with most documenting a modest degree of clinical benefit. Typical of three early controlled trials[13] involving relatively small numbers of patients was a 24 week double blind, placebo controlled study of 30 patients using a dose of 2 g/day. Significant improvement was observed in morning stiffness, number of painful joints, articular index, clinical score, and pain score, with the favourable response more pronounced in the polyarticular group.[14] A clinical response was observed as early as four weeks in one study[15] and was associated with a reduction in ESR in another.[16] Three further trials involving considerably larger numbers of patients reached similar conclusions with significant improvement noted primarily in patient reported measures. A study of 91 patients treated with a dose of 3 g/day over 24 weeks revealed significant improvement in patient global assessment,[17] and a study of 120 patients treated for a similar period demonstrated significant improvement only in reduction of pain.[18] The largest and longest of the controlled trials evaluated 221 patients treated with sulfasalazine 2 g/day over a 36 week course. This study demonstrated efficacy of sulfasalazine determined by a predefined response criterion that included improvement in tender and swollen joint counts and patient and physician global assessments. Interestingly, although the responder definition was met statistically, the only individual

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Abbreviations: DMARD, disease modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; NSAID, non-steroidal anti-inflammatory drug; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; RA, rheumatoid arthritis

measure within the definition that achieved statistical significance was the patient global assessment.[19] The action of sulfasalazine appears to be confined to peripheral arthritis with no evidence of benefit in axial disease[20] and only rare reports of either cutaneous improvement or exacerbation.

Methotrexate

The efficacy of methotrexate in PsA was first demonstrated in 1964 in a double blind, placebo controlled study of 21 patients who had active skin disease and peripheral arthritis.[21] Parenteral methotrexate (1–3 mg/kg divided in three doses at 10 day intervals) was compared with placebo with an observation period of approximately three months. Significant improvement was seen in joint tenderness and range of motion, extent of skin involvement, and ESR. After completion of therapy, however, most patients experienced a recurrence of skin and joint disease within one to four months. Adverse effects were common but did not require cessation of therapy. A randomised, double blind, placebo controlled trial comparing oral low dose pulse methotrexate (7.5 mg or 15 mg/week) with placebo over 12 weeks did show better patient tolerance; however, efficacy of this regimen was not established, as the only response measure to attain statistical significance was the physician assessment of arthritis activity.[22] The study results were blunted because one arm was lower than currently used dose of methotrexate, and because fewer patients were recruited than called for by the power calculations.[22] In a retrospective report of 40 patients over 12 years of treatment with a mean methotrexate dose of 11.2 mg/week, 38 patients had an excellent or good articular response, 36 had cutaneous resolution, and only two patients withdrew because of toxicity (leucopenia and stomatitis).[23] In seven patients who underwent 11 liver biopsies during the study, one patient was found to have micronodular cirrhosis at a cumulative methotrexate dose of 400 mg (with an unchanged biopsy at a cumulative dose of 1080 mg). In a 24 month study of 38 patients, patients treated with methotrexate did not show any improvement in radiographic progression compared with matched controls.[24] Whether the use of methotrexate in psoriasis and PsA results in more frequent or severe toxicity compared with RA is unknown. A retrospective study of 104 patients followed over two decades did not suggest increased toxicity.[25] No consensus exists as to the indications for liver biopsy either before treatment or at specified intervals during treatment.

Oral and parenteral gold

A beneficial response in some assessment measures has been demonstrated with both oral and parenteral gold in PsA. In a six month double blind, placebo controlled study of auranofin (6 mg/day) involving 238 patients, the auranofin treated group showed a modest but significant improvement in physician global assessment and occupational/daily function scores compared with the placebo group, but no significant difference was seen in morning stiffness or joint tenderness/swelling scores.[26] The rate of withdrawal from auranofin because of adverse drug reactions was 10%. An uncontrolled study of 14 patients treated with injectable gold showed either remission or improvement (50% reduction in number of inflamed joints) in 71% of patients.[27] Toxicity was similar to that observed with parenteral gold in RA. A double blind comparison of auranofin (6 mg/day), intramuscular gold sodium thiomalate (50 mg/wk), and placebo showed significant improvement in the Ritchie articular index, the visual analogue pain score, and the erythrocyte sedimentation rate (ESR) over 24 weeks in the parenteral gold group but no significant difference in the auranofin group as compared with the placebo group.[28] Radiographic disease progression was not prevented in a small controlled two year

study of parenteral gold.[29] Neither significant flare nor improvement in cutaneous psoriasis with oral or parenteral gold has been observed. When comparisons are made retrospectively[30] as well as prospectively[31] between methotrexate and gold therapy, patients with PsA treated with methotrexate are nine times more likely to respond and five times less likely to discontinue therapy than patients treated with gold—with mean treatment survival of 16 months with methotrexate compared with six months with gold.

Leflunomide

Leflunomide is a selective pyrimidine synthesis inhibitor that targets activated T cells lacking a salvage pathway.[32] A small, pilot, open label study of six patients with psoriatic polyarthritis showed a significant decrease in the C-reactive protein (CRP) level as well as in the tender and swollen joint count, although not in the extent of psoriasis, after three months of therapy.[33] Another study of 12 patients with polyarticular PsA who had failed at least one DMARD confirmed the clinical efficacy of leflunomide in the eight patients available for follow up, over two years of follow up.[34] Psoriatic rash improved in two thirds of the patients. These promising results led to a randomised double blind, placebo controlled study in 188 patients with active PsA (>3 tender and swollen joints) and active rash (>3% body surface area). More than half of the patients had been inadequately controlled by prior DMARD therapy including methotrexate. After six months, 59% (56/95) of patients treated with leflunomide met the primary efficacy endpoint (psoriatic arthritis response criteria; PsARC), compared with 30% (27/91) of patients treated with placebo; 24% of the former (compared with 0% of the latter) had significant PASI score improvements. Treatment was relatively well tolerated with adverse effects similar to the RA experience and no unusual toxicity.[35]

Azathioprine and 6-mercaptopurine

Both azathioprine and its derivative, 6-mercaptopurine, are purine analogues that have been used in the treatment of psoriasis and PsA. Although favourable results have been reported, the study populations have been small and no placebo controlled data are available. Eleven of 13 patients treated with 6-mercaptopurine (20–50 mg/kg per day) showed improvement in both joint and skin disease within three weeks of initiation of therapy and maintenance of this improvement on a dose of 1 mg/kg per day with minimal adverse effects.[36] A 12 month double blind crossover study of azathioprine (3 mg/kg per day) in six patients reported moderate or marked joint improvement in all six patients and cutaneous improvement in four; however, the dose of azathioprine had to be reduced in five patients because of leucopenia.[37] In view of the known toxicity of these agents, appropriate monitoring is mandatory.

Ciclosporin A

Ciclosporin A has been used with success in cutaneous psoriasis and beneficial effect in PsA. Representative of this experience is a six month open study of eight patients (seven of whom were refractory to methotrexate) with a starting dose of 3.5 mg/kg per day, which produced marked improvement in joint and skin disease in seven of the eight patients after two months.[38] One patient withdrew from the study because of lack of efficacy, and three patients required a 25% reduction in the dose of ciclosporin A because of a 50% increase in serum creatinine. A prospective controlled trial comparing ciclosporin A (3 mg/kg per day) with methotrexate (7.5 mg weekly) treated over a one year period suggested equivalent efficacy in 35 patients with PsA, although combined withdrawals due lack of efficacy and toxicity were

greater in the ciclosporin A group.[39] A single six month pilot study has employed ciclosporin A (3–5 mg/kg per day) in combination with methotrexate (10–15 mg/week) in eight patients who had failed prior second line therapy.[40] Significant improvement was described in all patients during the first month of treatment, with five patients continuing on combined therapy at the conclusion of the study period. Further studies are needed to define benefit and toxicity especially over a longer term.

Antimalarial agents

Reports of favourable response to both chloroquine (250 mg/day) and hydroxychloroquine (200–400 mg/day) in approximately 75% of patients have been offset by concerns that antimalarial drugs may have an adverse effect on the skin disease. The spectrum of suspected cutaneous toxicity includes exacerbation of plaques, photosensitivity, generalised erythroderma, evolution to pustular psoriasis, and the development of an exfoliative dermatitis. Although the reported incidence of these reactions ranges from 0% to 100%, it is important to note that more frequent reactions were observed in early trials that had few patients and primarily used regimens with quinacrine; much less toxicity has been seen in the more recent experience involving larger numbers of patients and using chloroquine or hydroxychloroquine.[41] A prospective controlled trial is needed to establish the efficacy and safety of these agents in the treatment of PsA.

D-penicillamine

A favourable effect on PsA has been observed with the use of D-penicillamine, but the available information is anecdotal and very limited. Eleven patients (two with spondylitis, four with asymmetric oligoarthritis, and five with symmetric polyarthritis) were randomised to an initial phase consisting of treatment with either D-penicillamine or placebo for four months, followed by four months of treatment with D-penicillamine for all patients.[42] The maximum dose of D-penicillamine was 750 mg/day, and no unusual toxicity was observed. Clinical benefit was seen only during D-penicillamine treatment; however, no efficacy measure attained statistically significant improvement.

Colchicine

Colchicine is an alkaloid known to attenuate the inflammatory response by interfering with neutrophil chemotaxis. A pilot study showed that 11 of 22 patients treated with colchicine (0.02 mg/kg per day) had significant cutaneous clearing, while four of eight patients with arthralgias had symptomatic improvement.[43] A subsequent 16 week double blind crossover study of 15 patients compared colchicine (1.5 mg/day) with placebo.[44] With the patient global assessment as the primary efficacy measure, colchicine was judged more effective than placebo by 10/12 patients (83%) who completed the study, and significant improvement was seen in grip strength, Ritchie index, joint pain, and joint swelling during treatment with colchicine. Gastrointestinal symptoms results in withdrawal of two patients from the study and a temporary dose reduction in five others. No unanticipated clinical or laboratory toxicity was seen. A 23 week study of 25 patients comparing the therapeutic effect of colchicine (0.6–1.8 mg per day) with placebo was reported in 1993.[45] No significant difference was noted between colchicine or placebo treatment for the primary outcome measure (Lansbury joint counts) or any of the seven secondary outcome measures. No change in the psoriasis was noted during active or placebo treatment. Adverse clinical effects were reported more often during treatment with colchicine (14 patients) than with the placebo (four patients), resulting

in the early withdrawal of three patients receiving colchicine from the trial. Creatine kinase values increased, without weakness, during treatment with colchicine (five patients) and placebo (four patients). This study did not provide evidence that colchicine is of therapeutic value in the treatment of PsA. Larger studies of longer duration will be necessary to establish any role of colchicine in the management of PsA.

Retinoids

Etretinate, a vitamin A derivative, is the most commonly used retinoid in the treatment of psoriasis, and initial experience with this agent in PsA suggests a beneficial effect. In one pilot study, 40 patients treated with etretinate (50 mg/day) for a mean of 21.9 weeks experienced significant improvement in the number of tender joints, the duration of morning stiffness, and the ESR.[46] Maximal improvement for most efficacy measurements was seen at between 12 and 16 weeks. Mucocutaneous reactions consisting of dried and cracked lips, mouth soreness, and nosebleeds were seen in the preponderance of patients (39/40) and required cessation of treatment in nine patients. Other relatively frequent adverse effects were alopecia, hyperlipidaemia, myalgias, and elevated transaminase levels. Etretinate is a teratogen and should not be used in women of childbearing potential.

Photochemotherapy

The most commonly used form of photochemotherapy involves the oral administration of 8-methoxypsoralen, a photosensitising medication, followed by exposure to long wave ultraviolet A (PUVA) light, which activates the drug. A prospective study of 27 patients treated with PUVA found a 49% mean improvement in articular index of patients with peripheral arthritis, whereas no benefit was seen in patients with spondylitis.[47] In responders, improvement in the peripheral arthritis seemed to correlate with clearing of the skin disease, whereas no such relationship was observed in patients with axial disease. Extracorporeal photochemotherapy, also known as photopheresis, has been shown to diminish the in vitro viability, proliferation, and mitogen response of lymphocytes, but reports of clinical improvement in arthritis symptoms are variable and no effect on skin lesions has been observed.[48 49]

Somatostatin

Somatostatin may benefit some patients with PsA but requires prolonged intravenous infusion (48 hours) and is poorly tolerated because of nausea. In one study, patients with extensive skin lesions and polyarticular involvement seemed more responsive.[50]

Miscellaneous

Other agents that have been reported to have activity in PsA include bromocriptine, cimetidine, fumaric acid, 2-chlorodeoxyadenosine, parenteral nitrogen mustard, peptide T, radiation synovectomy with yttrium 90, dietary supplements and total lymph node irradiation. Further study is needed to define what role, if any, these regimens might have in patient management.

CONCLUSION

For a disease as prevalent as PsA, the evidence base demonstrating efficacy of therapy with traditional DMARDs is very limited. There are data that demonstrate marginal efficacy of sulfasalazine and perhaps gold in the treatment of peripheral arthropathy associated with psoriasis. Methotrexate and ciclosporin are effective for treating the rash but evidence for improvement of the arthropathy is empirical; at present these have not been systematically

studied. None of the traditional DMARDs have been shown to prevent radiological progression nor to impact significantly on axial disease, dactylitis, or enthesitis. With renewed interest in clinical research in PsA, progress will be made with definition, standardisation, and validation of outcome measures. These will result in more rigorous studies with agents such as TNF inhibitors and other novel biological therapies, including established DMARDs as comparators and/or in combination arms of large well defined randomised controlled trials. Data from future trials using traditional DMARD comparators will likely help establish the true efficacy (or lack of efficacy) of these agents.

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