Cyclosporine in psoriatic arthropathy

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ABSTRACT

Psoriatic arthropathy (PsA) is an inflammatory arthropathy associated with skin or nail psoriasis with heterogeneous clinical manifestations. A pragmatic therapeutic approach to PsA is to stratify the disease manifestations according to their response to synthetic and biological agents. It is now reasonably well established that peripheral arthritis is amenable to treatment with synthetic disease-modifying anti-rheumatic drugs, while psoriatic pelvispondylitis and inflammatory tendon lesions appear to require the use of biological agents. Cyclosporine is a calcineurin inhibitor belonging to the synthetic disease-modifying anti-rheumatic drugs group. It has been shown to be effective in treating both arthritis and psoriasis. In this paper, we will briefly summarise the current knowledge about the efficacy of cyclosporine, both as a monotherapy and as an adjunctive treatment for PsA.

Introduction

Psoriatic arthropathy (PsA) is an inflammatory arthropathy associated with skin or nail psoriasis which was officially recognised as a distinct disease by the American Rheumatology Association back in 1964 (1). The onset of skin and joint manifestations is simultaneous in 15% of cases, while in 60% of patients psoriasis antedates arthritis, and in 25% of cases the reverse occurs. In addition, in a small number of cases PsA may be diagnosed in the absence of skin and nail disease when the arthritis has features consistent with PsA and one or more close relatives of the subject affected suffer from psoriasis (PsA *sine psoriasis*) (2, 3).

It is well recognised that PsA is quite heterogeneous in terms of clinical manifestations. In fact, not only can PsA cause both skin and articular lesions, but articular manifestations *per se* are also substantially diverse, ranging from arthritis proper to tendon inflammation. The first attempt to capture the wealth of joint manifestations of PsA is credited to Moll and Wright, who identified five subsets within PsA: predominant distal interphalangeal joint involvement, arthritis mutilans, symmetrical polyarthritis, asymmetrical mono- or oligoarthritis, and psoriatic pelvispondylitis (4). Subsequent analysis revealed that these subsets can overlap and, more importantly, evolve from one into another in the same patient (5). The only noticeable exception is peripheral arthritis in its various expressions and psoriatic pelvispondylitis, which tend to remain stable over time, although they may coexist in the individual subject. In addition, it also has become clear that Moll and Wright's classification did not include some subsets which are now included in the spectrum of PsA, namely asymmetric polyarthritis (6) and isolated enthesopathy (7). Since 2006 newer validated classification criteria (CASPAR, Classification Criteria for Psoriatic Arthritis) for PsA gained widespread acceptance as entry criteria in clinical trials (3).

From a therapeutic point of view, a pragmatic approach is to stratify the manifestations of PsA according to their response to synthetic and biological agents. In this regard, it is now reasonably well established that peripheral arthritis is amenable to treatment with synthetic disease-modifying anti-rheumatic drugs (DMARDs). In contrast, psoriatic pelvispondylitis and inflammatory tendon lesions (enthesitis and dactylitis, although the latter may also be associated with peripheral synovitis) appear to require the use of biological agents, since they respond to the biological but not conventional DMARDs. Both the EULAR (European League Against Rheumatism) (8) and the GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis) (9) recommendations take these considerations into account, and thus advise using synthetic DMARDs only for the treatment of peripheral arthritis and (if a

particular DMARD is known to benefit skin disease) for treating psoriasis.

Cyclosporine is a synthetic DMARD that acts by inhibiting calcineurin. Inhibition of calcineurin blocks the translocation of the cytosolic component of the nuclear factor of activated T cells (NF-AT), which in turn interferes with the synthesis of inflammatory mediators such as IL-2, IL-4 and C40 ligand that are required for B-cell help and T-cell proliferation (10). Clinically, cyclosporine has been shown to be effective in treating both arthritis and psoriasis (11). In this paper, we will briefly summarise our knowledge about the efficacy of cyclosporine in PsA.

Cyclosporine as monotherapy for psoriatic arthropathy

A small randomised clinical trial (RCT) compared cyclosporine (3–5 mg/kg/day) with methotrexate (MTX) (maximum dose 15 mg/week) in 35 patients with active PsA over a period of one year (12). The number of painful and swollen joints, the Ritchie index, the duration of morning stiffness, grip strength, C-reactive protein levels, the patient's and the physician's assessment of PsA activity, as well as the Psoriasis Area and Severity Index (PASI) improved significantly in both treatment groups. This clinical benefit remained sustained at 6 and 12 months, although after one year of therapy cyclosporine and methotrexate had to be withdrawn in 41.2% and 27.8% of the patients, respectively.

In a 24-week Italian multicentric trial cyclosporine (3 mg/kg/day) was compared to sulfasalazine (2 g/day) and standard therapy alone (non-steroidal anti-inflammatory drugs, painkillers and/or prednisone <5 mg/day) (13). In comparison to both standard therapy and sulfasalazine there was a statistically significant difference in favour of cyclosporine in terms of the mean changes in the pain score, which was the primary response variable. A significant decrease in favour of cyclosporine *versus* standard therapy alone was also observed for swollen joint count, tender joint count, joint/pain tenderness score, patient and physician global assessment by at least one point, total Arthritis Impact Measurement Scale score, and spondylitis functional index. The most common adverse event in the cyclosporine group was mild and reversible kidney dysfunction.

In another study on 60 patients with PsA, cyclosporine was given at a dose of 2.5–3 mg/kg/day for a period of 24 months (14). The primary endpoints were 20% and 50% improvement in disease activity according to American College of Rheumatology (ACR) responses at 6, 12, 18, and 24 months; other endpoints were 70% ACR responses at 6, 12, 18, and 24 months. Forty-nine patients completed the 24 months of treatment with cyclosporine. All the clinical variables showed significant improvement after 6 months of treatment. The PASI scores also significantly decreased. Side effects included hypertrichosis (24% of patients), gum hyperplasia (12%), gastrointestinal intolerance (9%), hypertension (21%), neurological disturbance (7%), and nephrotoxicity (17%). Three patients withdrew due to treatment failure. One patient was lost to follow-up, and seven patients withdrew due to side effects.

Karanikolas *et al*. assessed the efficacy and safety of adalimumab or cyclosporine as monotherapy or combination therapy in patients with active PsA despite methotrexate therapy in a prospective 12-month, non-randomised, unblinded clinical trial (15). Fifty-seven, 58, and 55 patients received cyclosporine (2.5–3.75 mg/kg/day), adalimumab (40 mg every other week), or a combination of both, respectively. The Psoriatic Arthritis Response Criteria (PsARC) at 12 months were met by 65% of cyclosporine-treated, 85% of adalimumab-treated, and 95% of combination-treated patients, while the ACR 50 response rates were 36%, 69%, and 87%, respectively. A significantly greater mean improvement in Health Assessment Questionnaire (HAQ) Disability Index was achieved by combination treatment compared to cyclosporine or adalimumab alone. Combination therapy improved PASI 50 response rates significantly beyond adalimumab response rate, but not beyond the effect of cyclosporine monotherapy. Side effects were broadly evenly distributed among the treatment arms; uncontrolled hypertension was recorded in only one patient receiving cyclosporine.

There are little data on the effect of cyclosporine on radiographic progression of PsA. In a 2-year open study of 24 patients (15 completers) cyclosporine (starting dose 3 mg/kg/day) appeared to control the progression of radiological damage in the peripheral joints of 60% of PsA patients (16).

Cyclosporine as adjunctive treatment for psoriatic arthropathy

A few studies have investigated the effects of cyclosporine as add-on therapy in PsA.

In a randomised clinical trial, Frazer *et al*. assessed the efficacy and safety of adding cyclosporine (2.5 mg/kg/day to maximum 4 mg/kg/day) or placebo to 72 patients with PsA who had an incomplete response to methotrexate (17). Significant improvement were noted in both groups at 12 months, consistent with the high placebo response (thrice as high as the placebo arm in rheumatoid arthritis) often seen in PsA (18). However, improvements were greater in the cyclosporine study arm for swollen joint count (decrease from a mean of 12 swollen joints at baseline to 6.7 swollen joints at 12 months *vs*. a decrease from 12 to 7.9 swollen joints in the placebo group) and the PASI (from 2 to 0.8 in the cyclosporine arm *vs*. 2.2 to 1.9 in the placebo arm). Synovitis as evaluated by ultrasonography also improved more in the subjects treated with cyclosporine (active joint count -2.5 in the cyclosporine group compared to -0.28 in the placebo arm). Hypertension was more common in the cyclosporine than in the placebo group (18% *vs*. 9%). Overall, the number of patients who withdrew from study because of adverse events was 34% in the cyclosporine arm and 6% in the placebo arm.

The rationale for combining cyclosporine with methotrexate lies in their different mechanisms of action, with methotrexate mainly targeting macrophages and cyclosporine primarily inhibiting T cells (19). Data derived from rheumatoid arthritis have confirmed that adding cyclosporine to methotrexate provides additional, sustained ben-

efit over and above that provided by placebo (20). Combined therapy with cyclosporine and methotrexate does not increase transaminases and increases non-significantly bilirubin and alkaline phosphatase levels (21). Therefore, adding cyclosporine may be considered both in the short and in the longer term in patients with arthritis who flare under methotrexate monotherapy.

In an open study of 41 patients with resistant PsA diagnosed according to the CASPAR criteria, patients were treated with etanercept plus methotrexate (7.5–15 mg weekly) or cyclosporine (3 mg/kg/day) (22). Both groups showed a clinical response (defined as significant reduction in DAS28 scores) at 3 and 6 months without between-group differences, whereas psoriasis activity (defined by the PASI) improved more in the group of patients treated with cyclosporine. Among the patients who received cyclosporine, one dropped out because of hypertension and three required initiation of anti-hypertensive medications, while two had a significant rise in serum creatinine values.

In another small open-label study of 11 patients receiving etanercept, cyclosporine (3 mg/kg/day) was added to etanercept because of insufficient control of skin psoriasis (23). The primary efficacy end point (PASI 75, *i.e.* a 75% or greater improvement in the PASI from baseline) was achieved by 9 of 11 patients at week 24. In one patient cyclosporine was discontinued owing to rising creatinine levels, while the dose of cyclosporine was reduced in another patient due to worsening of pre-existing hypertension.

Conclusions

Cyclosporine appears to be effective for the treatment of both peripheral arthritis and skin disease in PsA as monotherapy and as adjunctive therapy. The data on its effects on radiographic progression are too limited to arrive at definite conclusions. Tolerability is generally good, although close monitoring of blood pressure and renal function parameters is required (11).

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