Tacrolimus: an effective treatment in refractory psoriatic arthritis following biologic failure

Sirs,
Psoriatic arthritis (PsA) treatment options have increased markedly in recent years due to the development of novel biologic treatments. However, some patients either fail to respond or are unable to tolerate these. In refractory cases cyclosporine, a calcineurin inhibitor has been shown to be an effective treatment (1). However use may be associated with dose-limiting toxicities including nephrotoxicity and hypertension (2). Tacrolimus is an alternative calcineurin inhibitor and has previously been shown as being efficacious in Asian patients with PsA (3). However, applicability in diverse populations has not been established.

We present the case of a 48-year-old Caucasian woman with recalcitrant PsA and Crohn’s disease. Attempts to manage her severe PsA with several different anti-tumour necrosis factor-α (anti-TNF-α) biologies either proved ineffective or were associated with severe dose-limiting toxicities. Her disease continued to remain active until the use of tacrolimus successfully controlled all her PsA manifestations with no adverse effects.

The patient presented 10 years previously with arthralgias and swelling of her wrists, metacarpophalangeal joints and knees. She was diagnosed with a symmetrical inflammatory arthropathy (cyclic citrullinated peptide antibody <0.5 units/mL; rheumatoid factor <20IU/mL), considered most likely to be rheumatoid or the rheumatoid subtype of PsA. Initially her symptoms were well managed by a regimen of weekly methotrexate (17.5 mg once weekly) and folic acid. Several months after presentation mild psoriasis was noted and her diagnosis was changed to PsA, fulfilling the CASPAR criteria (4).

Her joint disease remained in remission for four years, after which she wished to try a period without medication. Following treatment cessation her disease recurred, resulting in progressive functional impairment. After restarting methotrexate (17.5 mg once weekly), her PsA continued to remain active and treatment was escalated.

Initially another disease-modifying antirheumatic drug (DMARD), sulphasalazine (2 g/daily) was tried but showed little efficacy. In view of her worsening symptoms she was switched to the anti-TNF-α biologic, adalimumab (40 mg fortnightly). This showed moderate early efficacy. However after two months, she developed severe headaches, requiring termination of treatment. An alternative anti-TNF-α biologic, etanercept (50 mg once weekly) was substituted resulting in initial efficacy.

Unfortunately after 6 months of treatment, she developed severe abdominal pain and rectal bleeding. Following emergency hospital admission she was diagnosed with Crohn’s disease. Due to a lack of efficacy of etanercept in inflammatory bowel disease she was switched to a different anti-TNF-α, certolizumab pegol (200 mg fortnightly) in the hope of managing both diseases. Despite providing satisfactory relief of her bowel symptoms, her PsA progressed further causing a progressive impairment in her functional activities warranting substitution to a fourth anti-TNF-α biologic, infliximab (5 mg/kg every 8 weeks).

Infliximab was efficacious in suppressing joint, skin and gut disease. However after five months, she developed drug-induced lupus (positive histone antibodies) with an erythematous scaling rash. At this time all pharmacotherapy was stopped.

Off treatment her PsA symptoms rapidly deteriorated, although her Crohn’s disease remained quiescent. With therapeutic options becoming increasingly limited, a combination of the DMARD, hydroxychloroquine (400 mg/daily) and the calcineurin inhibitor, cyclosporine (100 mg/daily) was trialled. This combination proved effective, reducing symptoms, clinical signs and inflammatory markers including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) (Fig. 1). However, after three months she developed severe hypertension as a likely consequence of cyclosporine therapy, necessitating withdrawal. Changing to leflunomide was considered a relative contraindication in light of the hypertension that was induced by cyclosporine. On hydroxychloroquine monotherapy her blood pressure slowly normalised, but disease activity progressively increased.

With the therapeutic armamentarium almost empty, consideration was given to alternative treatments.

Tacrolimus is a macrolide immunosuppressive originally isolated from *Streptomyces tsukubaensis* (5). It suppresses T-cell activation by inhibiting calcineurin in a similar manner to cyclosporine. However, it is over 30–100 times more potent and considered less vasoconstrictive and fibrogenic (5). Use of tacrolimus is well established in a plethora of rheumatological conditions including rheumatoid arthritis (6), recalcitrant plaque psoriasis (7) and systemic sclerosis (8). One previous
This case demonstrates for the first time the efficacy of tacrolimus in suppressing both articular and extra-articular manifestations of PsA. Specifically, this case illustrates the successful use of tacrolimus in patients where multiple DMARDs and anti-TNF-α biologics have been unsuccessful. Tacrolimus is an effective alternative to cyclosporine in patients with multiple biologic failure, offering significant advantages in terms of adverse effect profile. Furthermore, this case demonstrates how therapeutic drug monitoring of tacrolimus levels can be used as an effective tool to ensure efficacious dosing in rheumatological conditions. Further studies are required to establish the optimal place of tacrolimus in PsA management and to validate therapeutic drug monitoring in rheumatological conditions.

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References


