Resistant Cases of Psoriatic Arthritis: How to Manage Them

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ABSTRACT. Psoriasis is a chronic, genetically determined and immunomediated inflammatory skin disease that affects 2%–3% of the Caucasian population. Psoriatic arthritis (PsA), which occurs in up to one-third of patients with psoriasis, has a heterogeneous pattern expressed by various manifestations, including mono-oligoarthritis, an erosive and destructive polyarthritis indistinguishable from rheumatoid arthritis (RA), and spondyloarthropathy with axial involvement or enthesitis. Early detection of inflamed joints or axial involvement in patients with PsA is important in order to reduce inflammation and prevent joint destruction, deformity, and functional disability. The treatment of moderate-severe PsA has tended to include the same disease modifying antirheumatic drugs used to treat RA, but there is much less evidence supporting their efficacy and essentially none demonstrating that they slow radiographic joint destruction in PsA. A number of clinical trials have shown that tumor necrosis factor antagonists are generally safe and efficacious in the treatment of PsA, and can inhibit the progression of radiographic damage. (J Rheumatol 2009;36 Suppl 83:73-75; doi:10.3899/jrheum.090232)

Key Indexing Terms:
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Psoriasis is a chronic, genetically determined and immunomediated inflammatory skin disease that affects approximately 2%-3% of the Caucasian population and can lead to significant physical and psychological distress for patients[1]. Psoriatic arthritis (PsA), which occurs in up to one-third of patients with psoriasis, is a persistent synovial inflammation that causes damage to articular cartilage and osteolysis[2]. It is generally characterized by a heterogeneous range of manifestations, including mono-oligoarthritis, an erosive and destructive polyarthritis that is indistinguishable from rheumatoid arthritis (RA), and spondyloarthropathy with axial involvement or enthesitis[2]. Further, the disease pattern not only differs between patients, but often also within the same patient over time.

It is estimated that 20% of patients with PsA develop severely destructive disease[2]. It is important to detect inflamed joints or axial involvement early in PsA patients in order to be able to reduce the inflammation and prevent joint destruction, deformity and functional disability[3] and, as PsA is often only diagnosed years after the appearance of psoriatic skin disease, dermatologists are strongly encouraged to seek its signs and symptoms at every patient visit. Once PsA is diagnosed, treatment should be started in order to alleviate its signs and symptoms, and inhibit structural damage.

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Various genetic, immunological, environmental, and vascular factors seem to be important in the etiology, expression, and prognosis of PsA[4]. Epidemiological studies have shown that some comorbidities, such as metabolic syndrome and insulin resistance, occur more frequently than expected and, like those with RA, PsA patients are at increased risk of death[5]. The relationship between psoriasis, metabolic syndrome, and cardiovascular disease is probably due to the underlying chronic inflammatory nature of psoriasis and increased levels of proinflammatory factors such as tumor necrosis factor–α (TNF–α)[6]. A therapeutic approach targeting both cutaneous and systemic inflammation may therefore be beneficial in the effective management of psoriasis and related comorbidities.

SEVERE PSORIASIS AND PSORIATIC ARTHRITIS: TREATMENT

The treatment of severe psoriasis is quite challenging because of its chronic and relapsing course, and the consequent difficulties in treatment planning[2]. Biological agents are perhaps the most promising of the available treatments[7]. Efalizumab, a recombinant humanized anti-CD11a monoclonal antibody that blocks the activation, adhesion, and trafficking of T cells, has been approved in more than 50 countries for the treatment of adult patients with moderate severe chronic plaque psoriasis[8]; it is well tolerated even by patients with considerable comorbidities[9], and many clinical trials lasting for periods of 12-24 weeks have demonstrated its efficacy and safety[10].

In the case of psoriasis, biological agents are designed to interfere specifically with the skin disease, but some of them (particularly those targeting TNF–α) are also

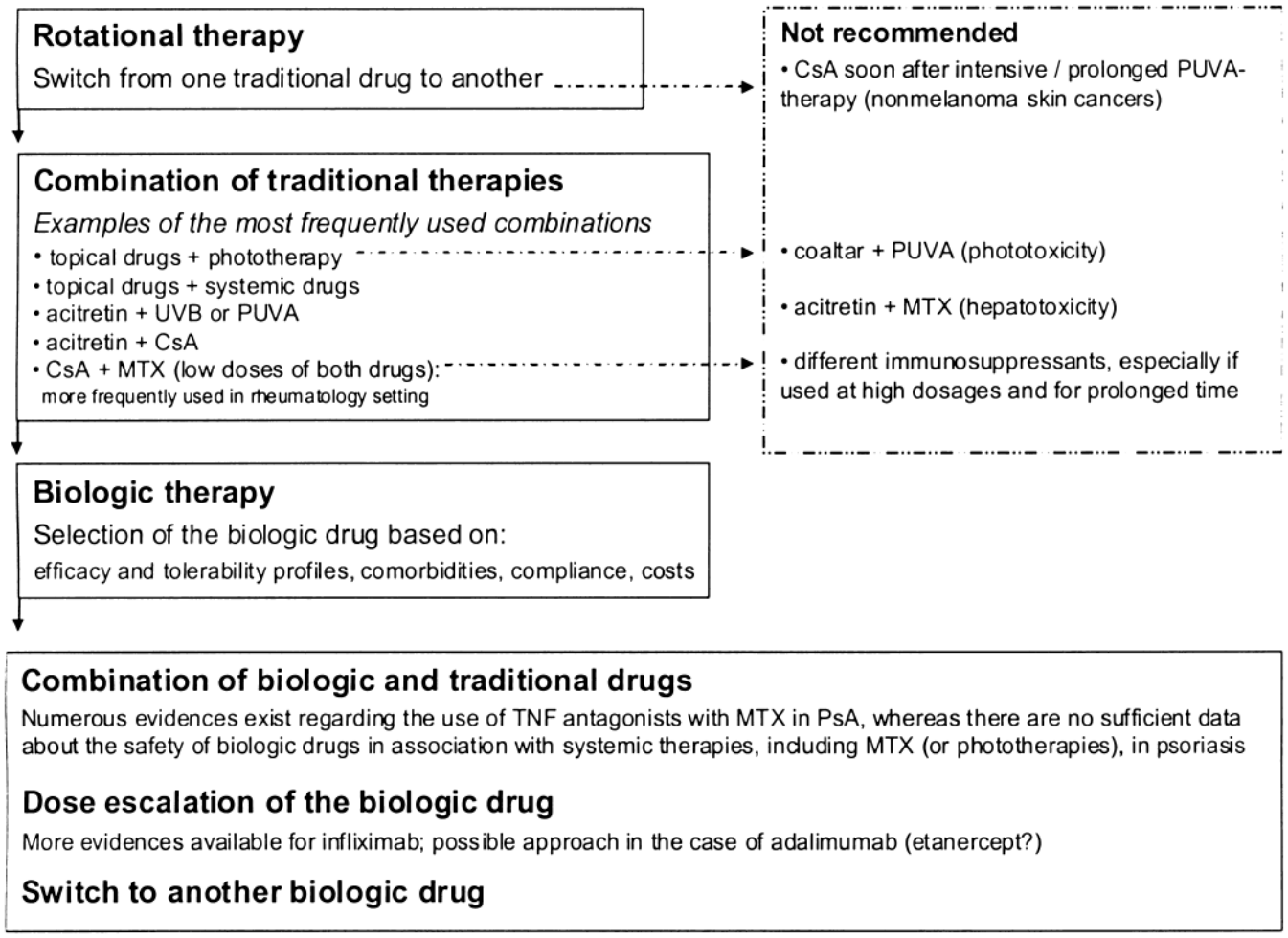

Figure 1. Management of psoriasis resistant to standard treatments: possible sequential steps that may be considered in refractory cases. CsA: cyclosporin A; MTX: methotrexate; PsA: psoriatic arthritis; PUVA: psoralen + UVA; TNF: tumor necrosis factor; UV: ultraviolet (radiation).

effective in treating moderate-severe PsA, which has so far tended to be treated by the same disease modifying antirheumatic drugs (DMARD) as those used for RA, although there is much less evidence supporting their efficacy, and essentially none demonstrating that they slow radiographic joint destruction in PsA[11]. The inefficiency of current DMARD and nonsteroidal antiinflammatory drugs (NSAID) in stopping the progression of joint disease has led to biological agents emerging as a possible alternative.

A number of studies have shown that PsA patients have high TNF levels in their synovial fluid and synovium, which supports the rationale for using TNF inhibitors[12]. It has been demonstrated that anti-TNF agents (particularly etanercept, but also infliximab and adalimumab) are effective for the many aspects of PsA, slowing down radiographic progression and improving the patients' quality of life[10].

Clinical trials have shown that etanercept is safe, efficacious, and well tolerated in moderate-severe PsA[13,14]. Atzeni, *et al*[15] studied 11 patients with PsA treated with etanercept and found that increased serum cortisol levels in relation to other adrenocortical hormones such as androstenedione and ACTH was accompanied by clinical improvement. Most of the studies and case reports concerning the use of etanercept in PsA have also reported improvements in the concomitant psoriatic skin lesions, and one study found that patients with psoriasis and mutilating PsA responded excellently to etanercept after withdrawal of cyclosporin A had induced a generalized pustular exacerbation and aggravation of arthritis[16].

Infliximab has been found to reduce epidermal hyperplasia and inflammation in patients with severe psoriasis[17]; it was also well tolerated, although the improvement in the Psoriasis Area and Severity Index score is associated with a mild infusion reaction. Further, clinical trials in patients with resistant PsA have shown that infliximab improves joint manifestations as well as skin disease, and anecdotal reports, case reports, clinical trials, and post-marketing reports of practice have shown the efficacy of infliximab and other anti-TNF agents in treating both psoriasis and PsA[18].

Adalimumab may also be effective in patients who are refractory to DMARD or other systemic drugs, including other anti-TNF agents[19]. The clinical and radiographic efficacy of adalimumab improving joint and skin manifestations, reducing disability, and inhibiting radiographic progression has been demonstrated during both short- and long-term treatment[20], and it also has a good safety profile.

However, some patients with severe PsA are resistant to anti-TNF agents or develop adverse events and require alternative treatment. One recent study has shown the presence of B cell lymphoid aggregates in PsA synovial tissues[21], and it has been reported that psoriasis partially remitted following rituximab therapy for non-Hodgkin lymphoma[22]. Finally, Cohen has described a case in which a patient with severe PsA treated with rituximab showed a dramatic clinical improvement and possible structural effect[23]. Consequently, rituximab seems to offer a new opportunity for treating PsA and psoriasis, although this will need to be confirmed by clinical trials. Possible approaches to management of psoriasis resistant to standard treatment are summarized in Figure 1.

In conclusion, biological agents are an optimal and well tolerated means of treating patients with psoriasis and PsA refractory to traditional therapy; they also lead to a significant improvement in the quality of life. However, the results depend on an early diagnosis, which requires cooperation between dermatologists and rheumatologists.

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