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Review

Treatment strategies for psoriatic arthritis

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ABSTRACT

The therapeutic management of psoriatic arthritis has seen major changes over the last few years, as illustrated by the recent updates of the GRAPPA and EULAR recommendations. These changes were driven by new studies establishing important benefits from early management and tight control of disease activity. The concepts underlying the treatment of psoriatic arthritis must be reappraised in the light of these new data. The objectives of this review are to discuss new concepts, to describe and assess the new drug classes introduced for psoriatic arthritis and, whenever possible, to define the specific indications of each class based on the rheumatic disease phenotype and presence of extraarticular manifestations.

1. Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory joint disease of the spondyloarthritis family for which many therapeutic advances have been achieved recently, leading to updates of the international EULAR [1] and GRAPPA [2] recommendations. Findings from studies done in the US [3], Ireland [4], Spain [5], and Sweden [6] have demonstrated a major impact of comorbidities—notably cardiovascular disease—in patients with PsA, as well as outcome benefits from early management according to a treat-to-target (T2T) strategy similar to that advocated for rheumatoid arthritis (RA). One of the challenges raised by the new treatment strategies for PsA consists in determining the best indications of drugs with novel mechanisms of action such as the anti-IL-17A antibody secukinumab, the anti-IL-12/23 antibody ustekinumab, and the phosphodiesterase 4 inhibitor (iPDE4) apremilast.

This review article starts with a discussion of the new concepts underlying the management of PsA, chiefly in the form affecting the peripheral joints. We will then review the drugs and nonpharmacological methods available for treating PsA. Finally, an overall management strategy for PsA is suggested.

2. New concepts for managing psoriatic arthritis (PsA)

2.1. Early treatment

Starting treatment early in the course of PsA is among the new concepts. Outcomes of PsA are influenced by disease duration at treatment initiation [7,8]. Thus, delaying the treatment by as little as 6 months was associated with worse functional and structural outcomes [9,10]. Patients with PsA are often seen first by primary-care physicians, who are therefore in a unique position to offer early rheumatologist referral. Similarly, dermatologists can ensure the early detection of rheumatic manifestations indicating a need for rheumatology referral in patients with psoriasis. Consequently, rheumatologists must work closely with these physicians. Questionnaires designed to assist in the reliable detection of PsA and early rheumatologist referral are being evaluated [11].

2.2. The treat-to-target (T2T) strategy

The randomized controlled open-label 48-week TICOPA trial was designed specifically to assess the T2T strategy [12]. TICOPA, which was based on the TICORA trial in RA, included 206 patients meeting CASPAR criteria for PsA with symptom onset within the last 2 years and no history of antirheumatic drug treatment. Patients were allocated at random to either standard care involving a visit about every 12 weeks and treatment adjustments as deemed fit by the rheumatologist or to a T2T strategy involving a visit every 4 weeks and decisions to modify treatment intensity based on a predefined protocol for achieving Minimal Disease Activity (MDA) criteria [13]. The ACR20 response rate after 48 weeks, chosen as the primary endpoint, was 62% in the T2T group and 44% in the

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standard-care group ($P < 0.05$) [14]. The between-group difference was increased by using more stringent response criteria: after 48 weeks, the ACR50 response rate was 51% versus 25% ($P < 0.001$) and the ACR70 response rate was 38% versus 20.5% ($P < 0.01$). The difference in structural outcomes was not statistically significant, but radiographic disease progression was minimal in both groups. Thus, the TICOPA data establish that adjusting the treatment to achieve a predefined and stringent target improves the clinical and biological control of PsA after 1 year.

2.3. Comorbidities and the need for overall patient management

In addition to diseases that share links with spondyloarthritis, several comorbidities are independently associated with PsA, such as cardiovascular disease and metabolic syndrome [15]. In addition, cutaneous psoriasis is associated with obesity [16], diabetes [16,17], fatty liver disease [18], and depression [16]. Physicians must be aware of these associations and ensure that patients with PsA receive multidisciplinary care as needed to manage the full spectrum of comorbidities.

3. Pharmacological treatments

3.1. Symptomatic drugs

3.1.1. Analgesics and nonsteroidal antiinflammatory drugs (NSAIDs)

When not contraindicated, NSAIDs are the first-line treatment of PsA in most patients, as they usually provide prompt symptom relief. NSAID therapy may suffice to control the symptoms. However, a rapid treatment effect must be obtained, and NSAID therapy alone should not be used for more than 3 months in patients with active PsA defined as arthritis (particularly with synovitis in multiple joints), structural damage, laboratory evidence of inflammation, or clinically significant extraarticular manifestations. A conventional synthetic disease-modifying antirheumatic drug (csDMARD) must be started promptly in this situation, as discussed below [1]. NSAIDs should be used in the minimal effective dosage to limit the risk of adverse effects [19,20]. Although all NSAIDs can be used, naproxen and COX-2 inhibitors may be particularly suitable due to the lower risk of cardiovascular and proximal gastrointestinal tract adverse events, respectively, compared to other NSAIDs [20]. Long-acting or sustained-release formulations deserve preference in patients whose symptoms occur chiefly at night or upon awakening. Responsiveness to NSAIDs varies widely across individuals, and several NSAIDs may therefore need to be tried before the best one is identified.

3.1.2. Local glucocorticoid injections

Local glucocorticoid injections may constitute a useful short-term intervention in patients with arthritis in a small number of joints or persistent enthesitis despite appropriate NSAID or DMARD therapy [1]. The number of injections should be kept small, to prevent adverse events related to systemic glucocorticoid exposure. A need for repeating the injections usually indicates that a csDMARD or biologic should be added to the long-term regimen.

3.1.3. Oral glucocorticoid therapy

Oral glucocorticoid therapy should be used with caution and only when absolutely necessary, in the minimal effective dosage. One indication is symptom relief while waiting for synthetic or biologic DMARD therapy to become effective in patients with highly active PsA [1]. Oral glucocorticoid therapy can induce many complications, particularly when taken for long periods. Furthermore, a flare of psoriasis may occur upon treatment discontinuation, although this possibility has been challenged.

3.2. Disease-modifying antirheumatic drugs (DMARDs)

3.2.1. Conventional synthetic DMARDS (csDMARDs)

3.2.1.1. Methotrexate. Only three randomized placebo-controlled trials of methotrexate in PsA are available [21–23]. None found that methotrexate was better than the placebo. However, two of them are several decades old [21,22] and have major methodological flaws, including very small sample sizes of 37 [21] and 21 [22] patients. The only recent trial (MIPA [23]) included 221 patients and showed no significant improvement in the primary endpoint (PsARC response) with up to 15 mg/week of methotrexate compared to the placebo (39% vs. 27%, $P = 0.063$). Nevertheless, this result does not convincingly rule out an effect of methotrexate, because the trial has several methodological weaknesses such as the low methotrexate dosage given (15 mg/week vs. 20–25 mg/week in standard care), an 8-week methotrexate-titration period, and moderate disease activity at baseline that limited the ability to detect a significant effect.

In contrast, non-randomized trials replicating the conditions of everyday practice support a symptomatic effect of methotrexate [24,25]. Furthermore, in the Norwegian registry NOR-DMARD, the 2-year methotrexate continuation rate was 65% [26]. More recently, in the TICOPA trial, after 3 months of single-drug methotrexate therapy, 40.8% of patients were ACR20 responders and 22% had achieved MDA [27]. Furthermore, methotrexate is a well-established treatment for cutaneous psoriasis [28] and is therefore, the first-line treatment of PsA in patients with cutaneous psoriasis. Treatment initiation should be prompt in patients who have arthritis in multiple joints, radiographic changes, laboratory evidence of inflammation, or dactylitis [1]. A maximum dosage of 0.3 mg/kg/week is often suggested, in the absence of underlying evidence. A starting dosage of 15 mg/week is often chosen. The dosage is then adjusted based on tolerance and effectiveness up to a maximum of 25 mg/week. Parenteral administration, usually via the subcutaneous route, provides better bioavailability and may be preferred initially or used after a period of oral administration [1]. The safety profile, precautions for use, and laboratory tests needed for monitoring are the same as those well established for rheumatoid arthritis.

3.2.1.2. Leflunomide. Leflunomide was proven clinically effective on the joint manifestations of PsA in a randomized controlled trial [29]. In this large prospective observational study of everyday practice 380 of 440 patients achieved the primary endpoint of a PsARC response 24 weeks after the introduction of leflunomide. Effects on the skin manifestations were marginal. In the TOPAS study the PsARC response rate was 58.9% with leflunomide and 29.7% with the placebo ($P < 0.0001$). [30]. Gastrointestinal adverse events and the development or loss of control of hypertension are adverse events that can limit the continued use of leflunomide.

3.2.1.3. Sulfasalazine. Several randomized trials have shown greater clinical efficacy of sulfasalazine compared to a placebo in PsA with peripheral arthritis [31,32]. Sulfasalazine is thus among the csDMARDs indicated in PsA. Glucose-6-phosphate dehydrogenase deficiency must be ruled out before prescribing sulfasalazine in high-risk populations [1].

3.2.1.4. Ciclosporin. Ciclosporin has not been assessed as single-drug therapy in placebo-controlled trials. The efficacy of ciclosporin in cutaneous psoriasis is well established. An open-label trial suggested efficacy in PsA [34] In double-blind trials, ciclosporin combined with methotrexate was effective in nonresponders to

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