Can traditional disease-modifying anti-rheumatic drugs be withdrawn or tapered in psoriatic arthritis?

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ABSTRACT

Psoriatic arthritis (PsA) is a complex, multisystem disease with musculoskeletal and skin manifestations frequently associated with features of the metabolic syndrome. For many years, treatment strategies were largely borrowed from the rheumatoid arthritis literature, with clinical trials of traditional DMARDs in PsA often inadequate and using limited outcome measures. Nonetheless, DMARDs – in particular, methotrexate – remain the treatment of first choice for most rheumatologists treating this disease, especially for those with prominent polyarticular involvement. While there is no agreed definition of remission in PsA, a number of longitudinal studies suggests that remission can be achieved in approximately 25% of patients treated with traditional DMARDs, with drug-free remission possible in <10%. There are many unanswered questions, and this review concludes by highlighting a research agenda which aims to address some of the most critical questions for physicians and patients alike faced with deciding if treatment should be withdrawn or continued when disease remission is achieved.

Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory disease typically characterised by arthritis and psoriasis and variably associated with other extra-articular manifestations. PsA seems to be a distinctive inflammatory condition with both autoimmune and auto-inflammatory features (1). In particular, T cells play an important role in the pathogenesis of PsA with oligoclonally expanded T cells demonstrated in synovial tissue and fluid (2). While treatment strategies have improved outcomes in recent years, there is a lack of consensus regarding the role of traditional disease-modifying anti-rheumatic drugs (DMARDs) both in short-term control of active disease and in long-term disease control. This review seeks to assess the evidence both for continuing or withholding traditional DMARDs, and to set out a research agenda which might help address some of the unanswered questions.

Evidence/rationale for continuing therapy.

In the context of this complex disease, there is some evidence showing that peripheral joint involvement is progressive in the majority of PsA patients (3). In a prospective study of patients with early PsA, 47% had developed erosive changes within 2 years of diagnosis (4). Therefore, PsA has to be considered a potentially disabling disease which requires aggressive treatment, although the course in individual patients remains uncertain.

The introduction of new biological molecules for the treatment of PsA has modified the management of this disease. However, biologic agents are costly medications, to which some patients may experience adverse effects, and not all patients respond adequately. These considerations leave open the role of traditional DMARDs in treatment of PsA.

For many years, conventional approaches to treatment of PsA have included medications such as non-steroidal anti-inflammatory drugs (NSAIDs) and, if unresponsive, one or more DMARDs for the control of inflammation and/or to prevent damage. This initial approach has been endorsed by the recently published Treat-to-Target initiative in Spondyloarthropathy (5). In clinical practice, the most widely used DMARDs are methotrexate (MTX, level of evidence B), sulfasalazine (SSZ, level of evidence A), leflunomide (LEF, level of evidence A), and cyclosporine (CsA, level of evidence B). However, the efficacy of these agents in inhibiting joint erosions has

not been assessed in controlled studies (6) and the effectiveness of DMARDs in treating enthesitis and dactylitis remains poorly characterised.

Traditionally, there is a discrepancy between evidence-based data from randomised trials and the real-life approach to treat PsA patients, in routine clinical practice. In the case, for example, of MTX: a cross-sectional study using the database from the population of PsA patients included in the development of CASPAR criteria showed that MTX was the most frequently used (39% of the total population, n=433) of the traditional DMARDs. The same study also showed that use of other DMARDs was quite common: SSZ in 22%, gold salt in 11%, antimalarial drugs in 5% and, interestingly, corticosteroid in 10% of the group (7). Moreover, MTX was also a frequent second and third DMARD used in combination therapy (7). Indeed, DMARDs – and, in particular, MTX – are drugs widely accepted by many treatment recommendations, even though their traditional level of evidence is quite poor (8-11).

As PsA is a progressive disease which leads to joint damage in at least 50% of patients, continuous suppression of active joint inflammation is required in order to prevent poor long-term outcomes. Analysing the short-term data from literature, there is some evidence that DMARDs can play a role in the management. The questions are whether there is a rationale for using DMARDs to maintain disease control over long periods, and whether the short-term therapeutic benefit is continued.

To address these points there are some data promoting a possible role of continuing this medication for long period of time. In a 2009 Italian retrospective study from a combined dermatologic-rheumatologic PsA clinic on long-term continuation of MTX in PsA (12), authors showed that, out of 174 patients, 104 (59.8%) were still taking MTX after three years of treatment. The reasons for discontinuation in the remaining 70 patients were: 34 (19.5%) lost to follow-up, 18 (10.3%) adverse events, 14 (8%) inefficacy and 4 (2.3%) deaths (none related to the therapy). Of note, MTX was effective in controlling joint inflammation but not in preventing joint damage. No serious side effects were recorded. Overall MTX was shown to have a good three-year performance in routine clinical practice of patients with peripheral PsA, and the authors concluded that MTX might be considered the non-biologic DMARD of choice for the treatment of this condition (12).

Recently, the role of MTX as a co-medication in TNF-inhibitor (TNFi) treatment for PsA has been evaluated using the Norwegian DMARDs registry (13). The study analysed 440 patients, 170 on TNFi only and 270 on combination therapy MTX-TNFi. The two groups showed similar baseline characteristics, with a higher number of swollen joints for the combination treatment group. Results showed that TNFi drug survival of the group on co-medication with MTX was superior to those not on MTX. The effect was mainly seen in those on Infliximab, leaving open the possibility of a role for MTX in inhibiting development of drug antibodies when patients are treated by monoclonal antibodies (13). In 2010, two years earlier, a study was carried out in Norway to assess the effectiveness and 2-year retention rate of MTX in MTX-naïve PsA patients, from the Norwegian registry (14). The study, designed as longitudinal observational multi-centre, comparing 430 PsA with a large group of patients with rheumatoid arthritis (RA), showed that after 6 months of MTX treatment PsA patients improved in most disease activity measures and patient reported outcomes. Moreover the two year retention rate was 65% confirming that MTX continues to be effective in the treatment of PsA (14).

A randomised placebo-controlled trial of methotrexate in PsA patients has been carried out in UK (15). This study enrolled 221 patients; 109 received MTX (maximum 15 mg/week) and 112 placebo. At 6 months no differences were found between the two groups for primary and secondary outcome measures, and the authors concluded that there was no evidence for efficacy of MTX in treating active PsA, furthermore raising the question as to whether MTX should be classified as a DMARD in this setting (15).

A tight control study in PsA (TICOPA) in DMARD-naïve patients has just been published as a study protocol, with the aim of assessing whether a "tight control" management protocol and predefined objective targets for treatment (minimal disease activity) can improve clinical outcome compared to standard care alone (16). This ongoing study should provide some results on the role of MTX and of other DMARDs in the treatment of PsA while also providing a possible rationale for the continuation of this therapy without switching to biological agents.

In relation to other DMARDs, sulfasalazine was compared to placebo in 6 studies in the 1990s, when this molecule was considered the "gold standard" for the treatment of rheumatoid arthritis and PsA in Europe (17). Some efficacy for sulfasalazine was recorded in these studies for peripheral arthritis only, with no benefit on the axial component of disease (17). Interestingly, there was no benefit demonstrated in terms of prevention of radiological progression. There is little or no information on the efficacy of sulfasalazine for the treatment of enthesitis or dactylitis.

Cyclosporine A (CsA) is an immunosuppressive agent that inhibits, in stimulated T cells, interleukin 2 (IL-2) production and IL-2 receptor expression. A small number of studies have compared the efficacy and safety of CsA to other DMARDs. Spadaro *et al*. in 1995 published a prospective, randomised controlled trial of PsA patients treated with MTX or Cyclosporine (CsA), showing mild efficacy for MTX (18). Interestingly, both DMARDs were effective at 12 months, even if the rate of withdrawal was higher in the CsA arm. This well designed study included only a small number of patients (total 35). Another multi-center Italian study compared the efficacy and safety of CsA to symptomatic therapy alone or in combination with sulfasalazine (19). This open trial showed that CsA was more efficacious on pain score, swollen and tender joint count compared to symptomatic therapy or sulfasalazine (19).

Leflunomide (LEF) is a selective pyrimidine synthesis inhibitor which inhibits T-cell activation and prolifera-

tion. Recently results from a large European prospective observational study showed that LEF was effective and well tolerated at 24 weeks in 514 PsA treated in clinical practice (20).

Overall, the data obtained from literature, from both clinical trials and clinical care settings, support the wide use of non-biologic DMARDs for PsA, but with sub-optimal evidence. MTX appears to be the most widely-used DMARD for PsA with peripheral joint involvement, despite the negative studies published. Sulfasalazine has been the most studied medication, but has shown only modest efficacy. Cyclosporine appears to have some efficacy, in particular for patients with severe skin involvement, but its use is limited by toxicity. LEF is the only DMARD that has shown good effect in clinical studies, including usual clinical care and randomised controlled trials, suggesting that it has a potential role as traditional non-biologic DMARD of choice in the treatment of PsA. It should be remembered, however, that MTX studies have been poor overall, and that the absence of evidence for its use does not necessarily equate to the absence of beneficial effect. MTX remains the "experts" DMARD of first choice in treatment of PsA, especially for patients with dominant peripheral joint involvement.

Stopping traditional DMARDs in psoriatic arthritis

In the recently published European League against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies (21), it was stated that: " The primary goal of treating patients with psoriatic arthritis is to maximise long-term health-related quality of life, through control of symptoms, prevention of structural damage, normalisation of function and social participation; abrogation of inflammation, targeted at remission, is an important component to achieve these goals." While no remission criteria have been standardised for PsA, data from several clinical series (22-25) and from the Swedish Early Psoriatic Arthritis Register (26, 27) reported a frequency of clinical remission (using different remission criteria) ranging from 17.6% to 58%, with the highest rate observed in patients treated with anti-TNF-α agents (24, 25). This wide range may be partly explained by the absence of validated criteria for remission in PsA, which has led to the use of different sets for remission assessment, as well as the different methods of selecting patients (28, 29). The concept of remission implies disease control to such an extent that sequelae of disease are avoided (28, 29). While some would accept continued treatment as part of the state of remission, others would consider remission as requiring the lack of need for continued treatment: treatment-free remission.

In clinical practice, once a patient achieves remission, the idea of stopping therapy is a natural one to consider for patients and physicians alike. The rationale for stopping therapy is that although most of the medications have good safety profiles, it is always better not to be taking a medication if it is no longer required. Several questions arise for the treating physician when the patient is in sustained remission, and these questions are often also raised by the patients themselves: Can the medication be stopped? If the medication is stopped, is there a risk that the disease will flare? If the disease flares, will it be possible to achieve remission again once the therapy is restarted? While some of these questions have been addressed by several different studies in rheumatoid arthritis, little information is currently available in PsA.

In 2001, Gladman *et al*. (22) reported that 69/391 (17.6%) patients with PsA, on ongoing treatment and with a mean disease duration of 12.7 years, achieved clinical remission with a mean remission duration of 2.6 years. Of these patients, 20 (29%) were in drug-free remission (22). In this study, remission was defined as a period of at least three consecutive visits with absence of any actively inflamed joints, independent of other clinical and laboratory parameters (22). Kane *et al*. reported a remission rate of 26% at one year and of 21% at 2 years with a DMARDs-free remission rate of only 12% at one year and 11% at two years in 129 patients with early disease (mean disease duration: 9 months) (4). In that study, remission was defined by the absence of fatigue, morning stiffness <15 min, no joint pain, complete absence of joint tenderness or swelling on physical examination (including enthesitis and dactylitis) and normal erythrocyte sedimentation rate (4).

More recent results from Canada (23) indicate that among 232 patients seen in different clinical practices in 5 provinces of Canada, 26% were classified as in remission based on joint counts, patient global assessment, physician global assessment, and acute-phase reactants. Around 30% of patients were taking biologic agents, but the percentage of patients taking traditional DMARDs was not provided (23). Theander *et al*. reported results from the Swedish Early Psoriatic Arthritis Register (26). After 5 years of follow-up, 17.9% of 179 patients with less than 2 years of disease duration achieved remission (no swollen or tender joints and normal ESR and CRP), and 40% achieved minimal disease activity (MDA) as defined by Coates *et al*. (30). Independent predictors of MDA at the 5-year follow-up were: shorter symptom duration, greater general well-being (global visual analogue scale), and low Health Assessment Questionnaire (HAQ) score at baseline. Around 8% of patients were taking biologic agents, but on multivariable analysis DMARDs or biologics did not influence disease outcome (30).

Cantini *et al*. studied all consecutive new outpatients with peripheral PsA requiring second-line drugs observed between January 2000 and December 2005 at the Rheumatology Unit of the Hospital of Prato, Italy (24, 25). 236 patients were included, mean disease duration of 13 months (SD 7 months), of whom 20% of patients on classical DMARDs achieved remission. Remission was defined by very stringent criteria (fatigue and pain <10, measured by visual analogue scale 1–100 mm, morning stiffness <15 min, absence of tender and swollen joints, and normal ESR). Treatment was suspended in those patients who achieved remission after 2003. Mean duration of remission after therapy interruption was 12 (SD 2.4) months (24, 25).

Another concern for patients who have no clinical disease activity is that they might still have subclinical disease as measured by highly sensitive imaging techniques such as ultrasound or MRI. Recently Dejaco *et al*. studied, with ultrasound and Power Doppler (PD), patients who were in remission by different criteria, and found PD signals in around 60% of patients (31). Whether or not such patients with sub-clinical inflammation experience sequelae of disease such as progression in joint damage remains to be proven. Until it is shown that persistent imaging evidence of joint inflammation is associated with a relevant outcome, such activity should not preclude the patient being defined as in remission.

In summary, remission is a reasonable and achievable target in patients with PsA treated with traditional DMARDs (approximately 25% of those treated), and early treatment is one of the factors associated with a greater chance of achieving remission. With traditional DMARDS, there are data to suggest that a few patients (fewer than 10%) in whom early treatment is withdrawn remain in sustained remission. While rheumatologists and patients are actively discussing treatment-reduction or withdrawal strategies in patients achieving remission, much additional work is required to help guide this choice, in particular for patients on combination therapies with drugs such as TNF inhibitors.

Research agenda

The above summary indicates a significant gap in the literature, which if addressed would help inform physicians and patients facing difficult decisions about need for treatment continuation. The following research agenda is proposed:

1. There is a need to have an accepted definition of the state of remission in PsA. Coates and colleagues have made progress regarding a definition of minimal disease activity (MDA) (30). MDA is a legitimate target for treatment, but data using stringent definitions of remission (22-27) suggest that remission can be achieved in approximately 25% of PsA patients treated with traditional DMARDs. As proposed in the EULAR treatment guidelines (21), treatment should target remission; we believe that is correct, indicating that the need for an agreed-upon, validated definition of remission is paramount. Using randomised controlled trial (RCT) and other datasets from clinical settings, it may well be possible to develop such an instrument without having to resort to additional data collection.

2. Most of the instruments currently used to assess treatment response in PsA RCTs are derived from studies in rheumatoid arthritis (*e.g*. ACR responses, EULAR responses). These measures have proven useful in separating active treatment from placebo, but they appear less effective when two similar, active treatments are compared (32). The measures are largely measures of joint inflammation only; other components of PsA including skin, entheseal, dactylitic, axial and nail responses are not included. A number of new, composite measures of disease activity have recently been proposed including the Composite Psoriatic Disease Activity Index (CPDAI) (33), the Psoriatic ArthritiS Disease Activity Score (PASDAS) and the Arithmetic Mean Desirability Function (AMDF) (34). Following presentation of data at the OMERACT 13 meeting, it was agreed that these three instruments should be taken forward for testing in further RCT datasets. It is hoped that, before long, a recommended composite score for use in future RCTs will emerge, and it is also then possible that this composite score can be used to generate an agreed definition of remission. This agreed definition is likely to prove more meaningful to patients, as it will reflect all of the ways that patients are affected by their disease.

3. At this point, it is not known whether control of composite disease activity delays or halts disease progression or improves long-term outcome or survival. These questions can be addressed in long-term follow-up studies or in registries. The issues of long-term outcome or survival are perhaps especially important as we increasingly become aware of the significant percentage of patients with features such as obesity, hypertension, insulin resistance and hyperlipidaemia. All of these factors likely contribute to accelerated atherosclerosis with an excess of cardiovascular-related mortality in PsA, noted in previous studies. Will control of composite disease activity alone be sufficient to reduce cardiovascular complications or – more likely – will we need to be much more proactive in addressing metabolic syndrome features in order to achieve significant improvements in patient long-term outcomes?

4. As mentioned above, there are data which suggest that inflammation may persist on ultrasound even in those PsA patients who are thought to be in clinical remission (31). The significance of this sub-clinical remission remains to be identified, and it certainly is possible that such ultrasound findings are not associated with subsequent clinical symptoms or with progression of radiographic damage. Similar findings have been observed in psoriasis patients who do not have clinical symptoms where again the significance remains unproven. Well-conducted, follow-up studies of cohorts of patients in clinical remission with repeated ultrasound and possibly other imaging modalities will assist in answering these important questions.

5. Finally, there are at present no data which assist physicians in identifying which individual patients in remission will remain in remission on treatment cessation. Studies are required that will aim to identify clinical, genetic or biochemical biomarkers which, if present or absent, identify subsets of patients in whom treatment withdrawal is likely to be successful. An RCT including 3 treatment arms (MTX *vs*. TNFi *vs*. Combination) followed by a planned treatment withdrawal in patients achieving remission would answer many questions critical to the management of patients with this complex disease.

References

1. HAROON M, FITZGERALD O: Pathogenetic overview of psoriatic disease. *J Rheumatol* 2012; 89 (Suppl.): 7-10.
2. CURRAN SA, FITZGERALD OM, COSTELLO PJ *et al*.: Nucleotide sequencing of psoriatic arthritis tissue before and during methotrexate administration reveals a complex inflammatory T cell infiltrate with very few clones

exhibiting features that suggest they drive the inflammatory process by recognizing autoantigens. *J Immunol* 2004; 1172: 1935-44.
3. MCHUGH NJ, BALACHRISHNAN C, JONES SM: Progression of peripheral joint disease in psoriatic arthritis: a 5-yr prospective study. *Rheumatology* (Oxford) 2003; 42: 778-83.
4. KANE D, STAFFORD L, BRESNIHAN B, FITZGERALD O: A prospective, clinical and radiological study of early psoriatic arthritis: an early synovitis clinic experience. *Rheumatology* 2003; 42: 1460-8.
5. SMOLEN JS, BRAUN J, DOUGADOS M *et al*.: Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: recommendations of an international task force. *Ann Rheum Dis* 2013 Jun 8 [Epub ahead of print].
6. PIPITONE N, KINGSLEY GH, MANZO A, SCOTT DL, PITZALIS C: Current concepts and new developments in the treatment of psoriatic arthritis. *Rheumatology* (Oxford) 2003; 42: 1138-48.
7. HELLIWELL PS, TAYLOR WJ, GROUP CS: Treatment of psoriatic arthritis and rheumatoid arthritis with disease modifying drugs -- comparison of drugs and adverse reactions. *J Rheumatol* 2008; 35: 472-6.
8. SORIANO ER: The actual role of therapy with traditional disease-modifying antirheumatic drugs in psoriatic arthritis. *J Rheumatol Suppl* 2012; 89: 67-70.
9. SALVARANI C, PIPITONE N, MARCHESONI A *et al*.: Recommendations for the use of biologic therapy in the treatment of psoriatic arthritis: update from the Italian Society for Rheumatology. *Clin Exp Rheumatol* 2011; 29 (Suppl. 66): S28-41.
10. LUBRANO E, SCARPA R: Psoriatic arthritis: treatment strategies using anti-inflammatory drugs and classical DMARDs. *Reumatismo* 2012; 64: 107-12.
11. KAVANAUGH AF, RITCHLIN CT; GRAPPA TREATMENT GUIDELINE COMMITTEE.: Systematic review of treatments for psoriatic arthritis: an evidence based approach and basis for treatment guidelines. *J Rheumatol* 2006; 33: 1417-21.
12. RICCI M, DE MARCO G, DESIATI F *et al*.: [Long-term survival of methotrexate in psoriatic arthritis]. *Reumatismo* 2009; 61: 125-31.
13. FAGERLI KM, LIE E, VAN DER HEIJDE D *et al*.: The role of methotrexate co-medication in TNF-inhibitor treatment in patients with psoriatic arthritis: results from 440 patients included in the NOR-DMARD study. *Ann Rheum Dis* 2013 Jan 3 [Epub ahead of print].
14. LIE E, VAN DER HEIJDE D, UHLIG T *et al*.: Effectiveness and retention rates of methotrexate in psoriatic arthritis in comparison with methotrexate-treated patients with rheumatoid arthritis. *Ann Rheum Dis* 2010; 69: 671-6.
15. KINGSLEY GH, KOWALCZYK A, TAYLOR H *et al*.: A randomized placebo-controlled trial of methotrexate in psoriatic arthritis. *Rheumatology* (Oxford) 2012; 51: 1368-77.
16. COATES LC, NAVARRO-COY N, BROWN SR *et al*.: The TICOPA protocol (TIght COntrol of Psoriatic Arthritis): a randomised controlled trial to compare intensive management versus standard care in early psoriatic arthritis. *BMC Musculoskelet Disord* 2013; 14: 101.
17. CLEGG DO, REDA DJ, ABDELLATIF M: Comparison of sulfasalazine and placebo for the treatment of axial and peripheral articular manifestations of the seronegative spondylarthropathies: a Department of Veterans Affairs cooperative study. *Arthritis Rheum* 1999; 42: 2325-9.
18. SPADARO A, RICCIERI V, SILI-SCAVALLI A, SENSI F, TACCARI E, ZOPPINI A: Comparison of cyclosporin A and methotrexate in the treatment of psoriatic arthritis: a one-year prospective study. *Clin Exp Rheumatol* 1995; 13: 589-93.
19. SALVARANI C, MACCHIONI P, OLIVIERI I *et al*.: A comparison of cyclosporine, sulfasalazine, and symptomatic therapy in the treatment of psoriatic arthritis. *J Rheumatol* 2001; 28: 2274-82.
20. BEHRENS F, FINKENWIRTH C, PAVELKA K *et al*.: Leflunomide in psoriatic arthritis: results from a large European prospective observational study. *Arthritis Care Res* 2013; 65: 464-70.
21. GOSSEC L, SMOLEN JS, GAUJOUX-VIALA C *et al*.: European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. *Ann Rheum Dis* 2012; 71: 4-12.
22. GLADMAN DD, HING EN, SCHENTAG CT, COOK RJ: Remission in psoriatic arthritis. *J Rheumatol* 2001; 28: 1045-8.
23. GLADMAN DD, CHANDRAN V, THAVANESWARAN A, ZUMMER M: Psoriatic arthritis in Canadian clinical practice: the PsA assessment in rheumatology. *J Rheumatol* 2012; 39: 1850-3.
24. CANTINI F, NICCOLI L, NANNINI C *et al*.: Criteria, frequency, and duration of clinical remission in psoriatic arthritis patients with peripheral involvement requiring second-line drugs. *J Rheumatol Suppl* 2009; 83: 78-80.
25. CANTINI F, NICCOLI L, NANNINI C *et al*.: Frequency and duration of clinical remission in patients with peripheral psoriatic arthritis requiring second-line drugs. *Rheumatology* (Oxford) 2008; 47: 872-6.
26. THEANDER E, HUSMARK T, ALENIUS GM *et al*.: Early psoriatic arthritis: short symptom duration, male gender and preserved physical functioning at presentation predict favourable outcome at 5-year follow-up. Results from the Swedish Early Psoriatic Arthritis Register (SwePsA). *Ann Rheum Dis* 2013 Jan 25 [Epub ahead of print].
27. LINDQVIST UR, ALENIUS GM, HUSMARK T *et al*.: The Swedish early psoriatic arthritis register-- 2-year follow-up: a comparison with early rheumatoid arthritis. *J Rheumatol* 2008; 35: 668-73.
28. KAVANAUGH A, FRANSEN J: Defining remission in psoriatic arthritis. *Clin Exp Rheumatol* 2006; 24 (Suppl. 43): S83-087.
29. CAPERON A, HELLIWELL PS: Remission in psoriatic arthritis. *J Rheumatol Suppl* 2012; 89: 19-21.
30. COATES LC, FRANSEN J, HELLIWELL PS: Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. *Ann Rheum Dis* 2010; 69: 48-53.
31. DEJACO CEA: Disparity Between Sonographic and Clinical Criteria of Remission in Psoriasis Arthritis. *Arthritis Rheum* 2012; 64 (Suppl.): S48.
32. FITZGERALD O, HELLIWELL P, MEASE P *et al*.: Application of composite disease activity scores in psoriatic arthritis to the PRESTA data set. *Ann Rheum Dis* 2012; 71: 358-62.
33. MUMTAZ A, GALLAGHER P, KIRBY B *et al*.: Development of a preliminary composite disease activity index in psoriatic arthritis. *Ann Rheum Dis* 2011; 70: 272-7.