Outcome Measures in Psoriatic Arthritis

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ABSTRACT. Psoriatic arthritis (PsA), an inflammatory arthritis associated with psoriasis usually seronegative for rheumatoid factor, has emerged as a more common and severe disease than previously appreciated. The disease is multifaceted. Thus the assessment of PsA requires attention to peripheral joint involvement, axial disease, dactylitis, and enthesitis, as well as the skin manifestations. In addition, the assessment of patient reported features such as patient assessment of disease activity, pain, fatigue, quality of life, and the new concept of participation are important. The assessment of damage and the assessment of tissue histology are also important outcome measures. This article summarizes these features of PsA as well as current knowledge on the instruments available for the assessment of these domains. (J Rheumatol 2007;34:1159–66)

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Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis, usually seronegative for rheumatoid factor. PsA presents with peripheral joint arthritis with or without inflammatory back disease, as well as with enthesitis, dactylitis, tendonitis, and other extraarticular features that are common to the spondyloarthropathies[1,2]. PsA has therefore been classified among the HLA-B27 associated spondyloarthropathies. However, it should be noted that fewer than half of patients with PsA have involvement of the spine, and the frequency of isolated axial involvement among patients with PsA is low. Medications used to treat PsA in the past have not provided adequate control of inflammation, and have not prevented progression of joint damage. Newer therapies have shown potential to prevent progression of joint damage[2-4].

Historical difficulties that arise when evaluating responses to therapy in PsA include lack of acceptable diagnostic classification criteria for PsA as well as accepted outcome measures for treatment response. The efficacy of newer agents has been shown in a number of recent randomized controlled trials (RCT) in both PsA and psoriasis. Data from these trials have rapidly advanced the field from a therapeutic perspective and provide a unique opportunity to better define domains and instruments that can most effectively assess

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response to treatment in RCT and longitudinal observational studies (LOS).

The issue of classification was recently addressed by the ClASsification of Psoriatic Arthritis (CASPAR) group, chaired by Dr. Philip Helliwell of Leeds, England. CASPAR included 30 rheumatologists from around the world who collected 568 patients with PsA as well as 536 controls with inflammatory arthritis [rheumatoid arthritis (RA), ankylosing spondylitis (AS), connective tissue disorders, undifferentiated arthritis, etc.] according to a standard protocol. Based on these cases, classification criteria were derived to distinguish PsA from other forms of inflammatory arthritis[5]. These criteria now require validation in other patient cohorts that include patients with and without inflammatory arthritis.

The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) was founded in 2003[6]. This group evolved from the CASPAR effort to include not only rheumatologists, but also dermatologists and other investigators. GRAPPA has set among its goals the validation and standardization of outcome assessment tools in PsA and psoriasis, for both basic clinical and therapeutic studies. Key domains for assessment of response in PsA and psoriasis in RCT and LOS were identified through an initial literature review[7] and a Delphi exercise conducted in January 2003[8]. Further refinement occurred at the GRAPPA meeting in August 2003, where a set of recommended domains was identified for assessment of patients with PsA[9]. Several instruments measuring these domains had functioned well in PsA clinical trials.

A workshop during OMERACT 7, in Asilomar, California, May 2004, was designed to identify domains appropriate for inclusion in RCT and LOS conducted in PsA[10]. Eleven domains received more than 60% of the votes and they were included in the core set of recommended domains to be assessed in RCT and/or LOS in PsA (Table 1). Several domains did not receive sufficient votes for inclusion in the core set but were nonetheless considered important from a clinical and research perspective. Thus, a research agenda was established to study these domains, and to identify appropriate instruments for assessment. It was recommended that peripheral and axial joint involvement be evaluated separately. Of note was the inclusion of "participation" as a domain that was perceived as different from health-related quality of life (HRQOL) or ability to work. It was recommended that appropriate instruments to assess participation be developed. It was also recommended that it be determined if patient global assessment of disease activity should include perception of skin and joint involvement together, or whether it should be segregated into 2 separate questions (skin and joint global assessments evaluated individually). GRAPPA set up committees to study the domains and instruments to measure these domains.

Table 1. Results of voting at OMERACT 7.

No.	Item	Score, %
1	Joint activity	99
2	Patient global	96
	All 3 components	76
3	Pain assessment	94
4	Physical function	91
5	Skin disease	86
6	Quality of life	78
7	Structural damage	66
8	Acute phase reactant	64
9	Axial involvement	61
10	Participation	61
11	Enthesitis	60
12	Fatigue	48
13	Dactylitis	48
14	Physician global	51
15	Tissue histology	38
16	MRI	34
17	Morning stiffness	25
18	Damage joint count	20

As background for planned discussions at OMERACT 8, GRAPPA committees' activities over the past 18 months are reviewed in subsequent sections.

Assessment of peripheral joint involvement

Although there are no widely validated and accepted measures to assess peripheral joint involvement in PsA, several instruments have been utilized in recent RCT, and these instruments have distinguished active treatment from placebo[11]. These measures include the American College of Rheumatology (ACR) response criteria developed for RA[12], the Psoriatic Arthritis Response Criteria (PsARC) developed by Dan Clegg for the sulfasalazine study in PsA[13], and the Disease Activity Score (DAS) response criteria, also developed for RA[14]. All these measures include assessment of tender joint count (TJC) and swollen joint count (SJC), as well as patient and physician assessments of global disease activity.

The ACR20 response criteria require ≥ 20% [≥ 50% or ≥ 70%] improvement in both the TJC and SJC, as well as a 20% improvement in 3 of the following 5 items: patient and physician global assessments of disease activity [visual analog scale (VAS)], physician global assessment (VAS), patient reported pain score (VAS), Health Assessment Questionnaire (HAQ), and either erythrocyte sedimentation rate or C-reactive protein. For some RCT in PsA studies the assessed joint counts were increased to 78 in order to include the distal interphalangeal (DIP) joints of the feet. To achieve an ACR50 or ACR70, the same guidelines are used but the level of response is 50% or 70% improvement, respectively.

A measure that has come to be called the PsARC (Psoriatic Arthritis Response Criteria)[13] was specifically created, although not formally validated, for a study of sulfasalazine in PsA. The PsARC measures tender joint scores (TJS), swollen joint scores (SJS), physician global assessment of disease activity (0–5 point Likert scale), and patient global assessment (0–5 point scale). A response in the joint counts is determined

by a reduction of ≥ 30% in TJS and/or SJS and reduction of 1 in Likert global assessment scores, whereas a response in the Likert scale is determined by a reduction by 1 score. An overall response is indicated by an improvement in 2 of the 4 items, one of which must be a joint count, without worsening in any of the 4 items. In some RCT, the PsARC included 78 joints, while in others the traditional 68 joint count was used. Although PsARC is based on joint scores that may introduce additional variability, it was noted that the joint count and joint score in PsA are similar, thus PsARC with TJC or TJS should be similar.

Recent RCT in PsA have incorporated each of the instruments outlined above as either primary or secondary outcome measures of response[15]. The DAS includes 44 SJC and TJC, using the Ritchie index and the DAS28, a 28 tender and swollen joint, and patient global assessment of well-being[14]. Scores are calculated based on formulae utilizing square roots and change from baseline. The DAS defines disease activity at one point in time, e.g., baseline, and EULAR DAS response criteria include the change from baseline and the achieved level of DAS. Application of the DAS to PsA might be limited because DIP joints are excluded, therefore requiring revalidation. Nonetheless, both DAS and DAS28 were prespecified as secondary outcomes in the Infliximab Multinational Psoriatic Arthritis Trial (IMPACT), and both measures distinguished infliximab from placebo-treated patients at 16 weeks[16]. However, application of DAS28 criteria reduced the number of patients evaluable for change by 25%. In a trial comparing cyclosporine plus methotrexate to methotrexate alone in PsA, high resolution ultrasound was used to detect synovitis, in addition to the traditional measures, and proved to be responsive in the combination arm, with close correlation to SJC[17].

A study compared responsiveness and discriminative capacity of ACR criteria, PsARC, DAS, and DAS28 in 2 phase-2 PsA trials, one with etanercept and the other with infliximab[18]. When retrospectively applied, DAS28, or EULAR "good or moderate" responses, based on changes from baseline, proved to be the most responsive and discriminant instrument, followed by DAS44, ACR20, and PsARC. All instruments showed adequate performance capability, although the ACR20 was more responsive and discriminant than ACR50 or ACR70 criteria. Preliminary analyses of the data were presented at OMERACT 7 and have subsequently been published and presented in more detail at OMERACT 8[18].

Discussions at OMERACT and subsequent GRAPPA meetings recommended that a 68 joint count be used, as it includes a majority of joints affected in PsA. Concern was expressed that adaptation of a lower joint count would exclude a number of patients eligible for RCT. Nonetheless, it was decided not to include the distal joints of the feet (78 tender joint count) as it may be difficult to distinguish PIP from DIP joint inflammation in the toes. It has been suggested that if either the PIP or DIP of the toe is involved it should be marked as a PIP.

The 68 joint count has been shown to be reliable[19,20] but not as reproducible in PsA as in RA[19,21]. At a recent international study (INSPIRE) the intraclass correlation coefficient (ICC) among 20 observers with regards to peripheral joint assessment was 0.76.

Assessment of dactylitis

Dactylitis is a hallmark clinical feature of PsA occurring in 16–48% of reported cases. Acute dactylitis may be a clinical indicator of disease severity, although chronic, nontender, diffuse, dactylitic swelling may be less clinically significant[22]. Rothschild, *et al* defined dactylitis as "uniform swelling such that the soft tissues between metacarpophalangeal and proximal interphalangeal, proximal and distal interphalangeal, and/or distal interphalangeal joint and digital tuft are diffusely swollen to the extent that the actual joint swelling could no longer be independently recognized"[23].

In previous RCT, dactylitis was measured by either its presence or absence and, if present, a tenderness score. This relegates determination of dactylitis to the clinician and its discrimination as necessarily subjective. Nonetheless, improvement in dactylitis using such measures was noted in the IMPACT and IMPACT2 trials[16,24].

The Leeds Dactylitis Instrument (LDI) is designed to provide a less subjective measure of the affected digit. It uses a measurement of diameter for digits on both sides and identified a 10% difference in diameter to define dactylitis. If the same digits are affected bilaterally, there are normative values that allow determination of the presence of dactylitis. The instrument includes a tenderness score. The LDI has demonstrated good inter- and intraobserver reliability[25]. In an open-label observational study employing several methods of assessing dactylitis, including the LDI, all measures detected improvement over 6 months with effect sizes for simply counting tender digits, and LDI of 1.16 and 0.79, respectively[26]. However, considering the hypothesized underlying pathophysiology of dactylitis, the LDI provides the best approximation to the underlying pathology and may better fulfill the "truth" criterion of the OMERACT filter.

Assessment of enthesitis

Enthesitis is another common feature in PsA. Instruments quantifying enthesitis have been developed and used exclusively in AS; the ASsessments in AS (ASAS) Working Group identified it to be an important domain to evaluate treatment associated improvements. The Newcastle Enthesitis Index (NEI) developed by Mander, *et al*[27] specifies 66 sites for assessment. The ASAS Working Group felt it was too time-consuming and perhaps too subjective to be used in RCT, and that many patients with AS have NEI scores of zero. A modified enthesitis index was developed — the Maastricht AS Enthesitis Score (MASES), assessing 13 sites[28]. The Spondyloarthritis Research Consortium of Canada (SPARCC) study[20] in patients with PsA used another modified index

applied only to 8 sites and reliability was variable. A simple enthesitis measure evaluating only the Achilles tendon and plantar fascia was found to be useful and able to discriminate between effective therapy and placebo in the IMPACT and IMPACT2 trials[16,24].

An international study to examine interrater reliability of these instruments in AS and PsA has recently been conducted in Toronto, Canada[29]. The International Spondyloarthritis Interobserver Reliability Exercise (INSPIRE) measured reliability for Mander, MASES, SPARCC (18 sites), and the Berlin index[30]. Agreement statistics were acceptable for all of these, with ICC ranging from 0.56 (MASES) to 0.81 (SPARCC) in PsA.

Further, these indices have been examined for responsiveness in an open-label observational study in Leeds[26]. PsA patients with active enthesitis were evaluated at baseline, 2 weeks, and 1, 3 and 6 months after initiating disease modifying antirheumatic drug treatment, mostly with methotrexate. Preliminary results indicate that all measures show a response to treatment, with effect sizes ranging from 0.40 (Mander index) to 1.19 (Berlin index). Using an iterative process of data reduction, the authors were able to derive a new index for PsA consisting of only 6 sites: both lateral epicondyles, both medial epicondyles, and both Achilles tendon insertions. This Leeds Enthesitis Index also showed good responsiveness, with an effect size of 1.19.

Assessment of axial involvement

The frequency of spinal involvement in PsA has varied between 20% and 70%, depending on features used to define disease. Psoriatic spondylitis is not as severe as that of AS, presenting with less pain, and lower sacroiliac grade and fewer syndesmophytes on radiographs[31]. For the clinical assessment of axial disease in AS, the ASAS Working Group has selected 4 measures: the occiput-to-wall distance, chest expansion, modified Schober, and lateral spinal flexion. Instead of lateral flexion, the Bath AS Metrology Index (BASMI) comprising 5 instruments can be used.

The INSPIRE study tested the interobserver reliability of these measurements in AS and PsA. Substantial to excellent reliability (ICC > 0.6) was noted for: occiput-to-wall distance, cervical rotation, chest expansion, lateral bending (using either the BASMI, Domjan, or the INSPIRE method), and hip mobility for PsA[32,33].

Radiographic features thought specific to PsA include asymmetrical sacroiliitis, nonmarginal syndesmophytes, asymmetrical syndesmophytes, paravertebral ossification, and more frequent involvement of cervical spine compared to AS[34,35]. There are 3 validated scoring methods developed for assessment of spine and sacroiliac involvement in AS: Bath AS Radiology Index (BASRI), Stoke AS Spine Score (SASSS), and a modification of SASSS (m-SASSS)[36]. The ASAS international working group has selected the m-SASSS as the preferred method for assessment of spinal damage in AS based on the different aspects of the OMERACT filter[36]. Whether the methods used to quantify sacroiliitis and spondylitis in AS are valid in PsA is not clear, since they have not been tested.

A multicenter prospective study to identify the relationship between clinical measures and radiological changes in patients with PsA (classified according to CASPAR criteria[5]) with clinical and radiological evidence of axial involvement is currently under way in Italy. Patients are consecutively recruited during followup at outpatient clinics; demographic, clinical, physical function data, and standard blood tests are collected according to a predefined protocol. Radiographs of cervical, dorsal, and lumbar spine and pelvis are performed at baseline, 12 and 24 months, and 5 years. Radiographs are independently scored by 2 readers (after specific training) using the BASRI and m-SASSS methods.

Skin assessment

Since psoriasis is a major component of disease in PsA, it is most important to evaluate skin as well as joint manifestations. A number of measures to assess the extent and severity of skin involvement have been recently reviewed in detail[37]. Of 2 general approaches, one is subjective: patient and/or physician global assessment of disease activity; and the other objective: photographs, calculation of involved body surface area, and degree of induration (thickness of lesion). Specific tools include Psoriasis Area Severity Index (PASI)[38], Lattice System Psoriasis Global Assessment (LS-PGA)[39], and National Psoriasis Foundation Psoriasis Score (NPF-PS)[40] , described in detail[10]. During OMERACT 7 it was recognized that the PASI score presents substantial methodologic challenges. Collaborative work between rheumatologists and dermatologists to better refine assessment of the extent and severity of skin involvement in psoriasis and PsA will be required. Also, regulatory requirements for improvements in PASI scores ≥ 75% and ≥ 90% are largely empirically defined, and these should be reevaluated utilizing evidence from recent RCT. Assessments of skin involvement in PsA and psoriasis were reviewed in detail at a meeting of the International Psoriasis Council (IPC) in February 2006. Despite the deficiencies noted for the PASI score, it has functioned well in RCT with new biologic therapies, both in psoriasis alone and in PsA. The IPC is currently considering development of another instrument for the evaluation of skin psoriasis for both RCT and longitudinal observational cohorts.

Nail assessment

Nail involvement in patients with psoriasis and PsA is a common, important problem. While a number of studies have evaluated the effectiveness of various treatments for nail psoriasis, the lack of a standardized assessment tool precludes any comparison or even meaningful interpretation of results. Recently, the NAil Psoriasis Severity Index (NAPSI) was developed. This measure incorporates all clinically relevant

aspects of psoriatic nail disease, and has recently been used in several studies as an outcome measure. However, the NAPSI has not yet been validated. In preliminary observations, the NAPSI was found to have significant interobserver variability. Therefore, based on discussions raised in focus groups, modifications were made to enhance its face validity and feasibility[41]. This modification of the NAPSI needs to be validated with larger numbers of patients, with patients with heterogeneous levels of disease activity, and with patients who have psoriasis without PsA. The m-NAPSI also needs to be tested longitudinally to assess its discriminant validity.

Patient global assessment of disease activity

Following OMERACT 7, the patient's perception of skin and joint involvement in PsA became an important component of the research agenda, and this topic was discussed at followup GRAPPA meetings. It was proposed that separate questions should be developed for individual assessment of skin and joints in a global disease activity instrument. GRAPPA members decided that an exercise utilizing VAS reports should help determine if separate global activity scores were preferable to a single measurement[42].

A study by Alberto Cauli of Italy has been designed to test whether a single VAS score (patient and/or physician reported) for global disease activity in psoriasis and PsA is valid and reliable in RCT or LOS compared to separately assessed VAS scores for joint and skin involvement. Psychological impact of disease is frequent in psoriasis and PsA; therefore, patient scoring of disease activity may derive from mental as well as physical factors. A further objective is to query whether involvement of specific joints, dactylitis, and/or enthesitis and/or skin areas influence patient (or physician) perceptions of disease activity.

HRQOL

Measures of HRQOL, particularly the Medical Outcomes Study Short Form-36 Health Survey (SF-36), have been used in PsA[43]. Recent RCT with anti-tumor necrosis factor (TNF) agents and leflunomide in PsA have shown significant improvements in SF-36[24,44-47]. Other measures of HRQOL have been employed in PsA trials, including the Dermatology Life Quality Index (DLQI) and EuroQOL Feeling Thermometer. The PsAQoL is the first disease-specific patient-derived measure extensively validated for use in PsA, and it should now be tested in new RCT[48]. These measures and others used in RCT have been reviewed in a recent publication[49].

Physical function and participation

Measures of physical function, including the HAQ Disease Index and the SF-36 physical function subscale, have been validated in PsA[43,44]. Both these measures improve significantly in the context of anti-TNF studies and discriminate well between placebo and effective treatment, although the SF-36 physical function scale appears to show better sensitivity to change[24,43-47].

An important domain recommended for assessment at OMERACT 7 was "participation," a term from the World Health Organization (WHO) International Classification of Functioning, Disability and Health (ICF)[50]. Conceptually it refers to "involvement in life situations" distinct from "activities," which refers to "execution of a task or action by an individual." Operationally, a significant overlap exists between these 2 concepts. At times, it is difficult to know whether participation or activity is being represented. In fact, the manual that lists the hundreds of items that make up the ICF system combines activities and participation into a single chapter and does not differentiate between them.

The only existing instrument that may reflect the concept of participation appears to be the WHO Disability Assessment Schedule (WHODAS)[51], based upon the ICIDH-2, an immediate precursor to the ICF. This self-report questionnaire has been used in AS[52]. A study designed to validate the WHODAS II in PsA is under development. An alternative way of examining participation has been to define "functioning" more broadly, based on the ICF model, and query which items of the ICF classification are relevant for people with PsA. This approach has been used for developing "core-sets" of ICF items, specific to individual diseases such as RA or low back pain[53,54]. The process by which a core set of items is identified is well defined and rigorous, involving 4 preliminary studies, a consensus conference, and a large-scale validation study. In collaboration with Prof. Stucki's group (ICF Research Centre, Munich, Germany) we have begun the process of identifying a core set of ICF items for people with PsA. The advantages of this approach include the ability to clearly identify items that should be measured in PsA (using the universal framework of the ICF) and where gaps in assessment remain, once existing measurement tools are linked to these items.

At present, (1) a literature review of existing measurement tools and mapping these to items in the ICF, and (2) a Delphi study of health professionals (dermatologists, rheumatologists, rehabilitation physicians, allied health professionals) to determine which items in the ICF are most relevant to PsA from a professional perspective have been completed. An empirical study to obtain a direct patient perspective regarding which ICF items are important to them and are most frequently affected by psoriasis and PsA is currently under way.

Fatigue

An important symptom domain in patients with inflammatory disease is fatigue. A variety of multidimensional instruments have been developed to assess this domain in various autoimmune diseases such as the Functional Assessment of Chronic Illness Therapy– Fatigue scale (FACIT–fatigue)[55], the Krupp Fatigue Severity Scale (KFSS)[56], the Multidimensional Assessment of Fatigue (MAF) scale[57], and the Multidimensional Fatigue Inventory (MFI)[58]. The KFSS has been validated in multiple sclerosis and systemic lupus ery-

thematosus and utilized in a single PsA RCT[59]. The FACIT–fatigue has been used in phase 3 RCT of adalimumab in RA with significant improvement of fatigue reported in all active treatment groups as well as in PsA (ADEPT)[47]. A recent study of 100 patients with PsA showed that the FACIT–fatigue scale was reproducible and correlated with the KFSS and with complaints of fatigue[60]. Assessment of fatigue in patients with RA is discussed in another section of this OMERACT report.

Assessment of damage

An important outcome measure in PsA is assessment of damage, and demonstration of the ability of treatment to prevent or inhibit structural damage[61]. Several efforts to validate radiological assessment tools in PsA have recently been published. Rahman, *et al*[62] demonstrated that the Steinbrocker method, which assigns the worst joint grade on a 0 to 4 scale as the patient's grade, demonstrates good inter- and intrarater reliability, but is not sensitive to change. However, a modification of that method, which assigns a grade to each joint on the same scale, demonstrated both intra- and interobserver reliability and sensitivity to change, as did the Larsen method. This method has been used in prognosis studies in PsA where active inflammation was shown to predict progression of damage[63]. Wassenberg, *et al*[64] developed a system that incorporates both assessment of peripheral joint disease and specific radiological manifestations in PsA. This system, the PsA Ratingen score, has not yet been tested in RCT. The Sharp scoring system[65] performed on radiographs of the hands and wrists (modified to include DIP joints) showed the ability of etanercept to prevent progression of erosions in a RCT in PsA[44]. A similar approach in the ADEPT trial also showed less progression of damage in the active treatment group[47]. The van der Heijde modification of the Sharp scoring system[66] was recently utilized in both IMPACT and IMPACT 2 studies, and also provided evidence for less progression of radiographic damage in patients receiving active treatment[67,68]. The differing characteristics of the scoring methods and their validity in PsA have been summarized in a review[61]. Plans are currently under way using radiographs from the above mentioned RCT to compare these 4 scoring methods for reliability and sensitivity to change.

Tissue analysis

Kruithof, *et al* recently compared synovial immunohistologic features characterizing RA and spondyloarthropathy (SpA), including PsA[69]. Using a semiquantitative scoring system, the authors identified a number of features characteristic of RA synovium and, in the PsA subgroup alone, increased vascularity and neutrophil numbers distinguished from RA. The authors concluded that the synovitis in PsA, both oligo- and polyarticular, resembles SpA more than RA.

In the only placebo-controlled study in PsA to date to involve tissue analysis, synovial tissue and lesional skin biopsy specimens were obtained at baseline and 48 h after treatment with infliximab (n = 6) or placebo (n = 6)[70]. A significant reduction in mean T cell numbers was found in both lesional epidermis ($p = 0.028$) and synovial tissue ($p = 0.043$) after infliximab treatment, but not after placebo. Similarly, the number of macrophages in the synovial sublining was significantly reduced ($p = 0.043$). The changes in cell numbers could not be explained by induction of apoptosis at the site of inflammation.

A number of studies have explored synovial changes in PsA following treatment intervention. In an open study of treatment with methotrexate, Kane, *et al*[71] demonstrated significant reductions in T cell and macrophage numbers but vascularity remained unchanged. Adhesion molecule expression was reduced, suggesting less vascular endothelial activation. Expression of proinflammatory cytokines, most significantly IL-8, was reduced with methotrexate.

Under the leadership of D. Baeten, archival material from 52 SpA patients, including 16 with PsA, has been examined for markers of treatment response[72]. Analysis showed that changes in synovial macrophage subsets, polymorphonuclear leukocytes, and matrix metalloproteinase-3 (MMP-3) expression best reflected clinical response to treatment after 12 weeks.

Skin biopsies from a target psoriatic plaque and synovial tissue biopsies from a target joint were taken before and at Week 4 of infliximab therapy (n = 11)[73]. After 4 weeks, cell infiltrate was reduced in both skin and synovium but synovial changes were not significant. There was a significant reduction in the number of blood vessels in dermis and synovium at Week 4. A significant reduction in the expression of alpha(V)beta(3) integrin, a marker of neovascularization, and in adhesion molecules was also found. There was a trend toward reduced expression of vascular endothelial growth factor in both skin and synovium.

Finally, in a study by Kruithof, *et al*[74], synovial tissue biopsy samples were obtained in 20 patients with SpA and 6 with PsA, at Weeks 0, 12, and 52 following etanercept therapy. Histologic synovitis was downregulated, with a profound reduction in global cellular infiltration, including T cells and macrophages, but not B cells. The most prominent change was a reduction in the different macrophage subsets (CD68, CD163, MRP-8, and MRP-14). Structural changes included normalization of lining layer hyperplasia and a moderate reduction in vascularity. No effect on the microarchitecture of lymphoid aggregates was observed. In terms of matrix degradation, synovial expression of MMP-3 and MMP-9 was downmodulated in correlation with a rapid and profound decrease in serum MMP-3.

It has now been agreed that a prospective study should be undertaken to examine changes in tissue (skin and synovium) biomarkers at earlier timepoints (4 weeks) that should predict subsequent clinical responses at 12 weeks to anti-TNF therapy in PsA. Biopsies of skin and synovium will be obtained at

baseline and at 4 weeks following anti-TNF therapy or placebo. This will also help to identify marker(s) that best distinguish active treatment from placebo. Additional open studies comparing the effects of anakinra and of etanercept on clinical, immunohistologic, and magnetic resonance imaging features are completed and under way, respectively. Combined, the analysis of these studies will hopefully provide an indication of potential biomarkers of treatment response that can then be tested further in RCT.

Conclusion

The objectives of the OMERACT 8 PsA module were: (1) to achieve consensus on the core set of domains to be assessed in PsA clinical trials and in LOS; (2) to review and endorse outcome measures used to assess these domains based on evidence derived from clinical trials; and (3) to develop a new research agenda to identify other assessment tools.

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