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Publication date
2005

Published in
Annals of the Rheumatic Diseases

[Link to publication](#)

Citation for published version (APA):

Mease, P. J., Behrens, F., Boehncke, W.-H., Feldman, S. R., FitzGerald, O., Gladmann, D. D., Helliwell, P. S., Nash, P., Olivieri, I., Taylor, W. J., & Tak, P. P. (2005). Discussion: Assessment of psoriatic arthritis. *Annals of the Rheumatic Diseases*, 64(Suppl1), ii69-ii73.

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Ann Rheum Dis 2005;64:69-73
doi:10.1136/ard.2004.031690

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DISCUSSION

Discussion: Assessment of psoriatic arthritis

P J Mease with contributions from F Behrens, W-H Boehncke, S R Feldman, O FitzGerald, D D Gladman, P S Helliwell, P Nash, I Olivieri, W J Taylor, P-P Tak

Ann Rheum Dis 2005;64(Suppl II):ii69-ii73. doi: 10.1136/ard.2004.031690

Many of the following questions reflect items on the research agenda of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) for Outcome Measures in Rheumatology (OMERACT) 8 (May 2006) and will have task forces addressing them in the form of research projects, questionnaires, and consensus exercises.

Which joints should be included in psoriatic arthritis (PsA) assessment: carpometacarpal joints, distal interphalangeal (DIP) joints, feet DIPs? Should we perform 76, 68, 44, or 28 joint counts? Can feet DIPs be distinguished from proximal interphalangeal (PIP) joints clinically and/or radiologically? Can they be distinguished from osteoarthritis radiologically? Should we count or score?

Mease: When we set about to assess joints in the original etanercept trial, our assumption was that we needed to capture a larger number of joints than in typical rheumatoid arthritis (RA) trials, including the DIP joints of both hands and feet, as well as the carpometacarpal (CMC) joints which can be commonly affected, thus using a 76/74 joint count. Some have countered that it is difficult in many patients to assess the DIP joints of the feet, especially the smaller ones, and that assessment of the CMC joint may not be valid. Further, radiologists have grumbled that it is often difficult to distinguish the DIP joints, especially in the feet. Thus the perennial question is: Is it sufficient to count the joints, or does it add more information to score relative degree of tenderness and swelling in each joint? The Erlangen analysis of raw data from the etanercept and infliximab phase II trials suggests that counts are as distinguishing as scores, and that 76, 68, 44, and 28 joint counts are all adequate to detect differences between treatment and placebo. The only caveat is that it is worthwhile to assess at least 68 joints at study entry in order to qualify a patient, especially oligoarticular patients. FitzGerald would omit the second through fifth proximal interphalangeal (PIP) joints of the toes as difficult to assess.

Gladman: However, this may be important not only at study entry. If a patient happens to have a number of feet or distal joints involved and they are not included in the 44 or 28 joint count, how can they be followed during a trial? Therefore, it seems reasonable to perform a 68 joint count, even though it may take a couple more minutes per patient, to collect all appropriate information on these patients and to achieve proper analysis at the end of a trial.

Helliwell: I think we should include the DIPs and PIPs of the feet in a clinical assessment. It is possible to distinguish these joints clinically. It is also possible to separate them reliably radiologically but only using an oblique view of the forefoot. This has become apparent when reading the CASPAR x ray films. And I suspect that erosive disease in the DIP joints of the foot will be very specific for PsA. (Typical erosive osteoarthritis of the DIP joints of the forefoot is seldom, if

ever, seen—but that is another study to do. On the other hand it may be impossible to distinguish erosive osteoarthritis of the hand DIPs from PsA changes.) If only normal views of the forefoot are used, it is helpful to take the images with the foot weight bearing.

Taylor: Determining the least amount of data to collect to show a statistical difference between placebo and active treatment is not the only criterion for which data to collect in a clinical trial. The meaningfulness of the absolute difference detected is also important. For this reason, I do not agree that 28 joint counts are sufficient. If the 66/68 joint is used to assess disease activity at entry (which I agree with), then I can't see the rationale for not assessing these joints at the study endpoint. I believe that it is possible to distinguish clinically toe DIP from toe PIP joints, and an oblique view of the feet is adequate to visualise toe DIP joints. I think counts are as informative as scores and more reliable. Radiological distinction of osteoarthritis in the DIP joints is a nice question for a reanalysis of CASPAR radiological data; I personally feel that it is usually possible. It is also necessary to consider what the context of the distinction is—if for scoring change over time in a six month trial, then the distinction probably isn't so important since the evolution of osteoarthritic changes is probably much slower than that timeframe; in other circumstances, osteoarthritic change will be more relevant.

Behrens: I think DIPs at the feet can be clinically distinguished from PIPs, and they should be included in the joint count (count better than score). As we know from Antoni's data, the disease activity score (DAS) 28 works in PsA randomised controlled trials, but if we need a 68 or 76 joint count for inclusion of PsA patients with mild activity, we have to use these joint counts during the whole trial. If we use the PsA response criteria (PsARC) (30%), should we also calculate a "PsARC 50" and "PsARC 70"?

Olivieri: The DIP joints of the feet can be evaluated radiologically using an oblique view. The 68 joint count should be performed at the beginning and during the study.

How should a patient be globally assessed?

Mease: In general, the way this question is asked is as follows: "In all of the ways your disease affects you, how would you rate the way you feel at this time?". Patients may have some uncertainty about what represents "your disease". Might they primarily focus on the arthritis component, the skin component, or multiple other elements including psychological status, fatigue, etc? Theoretically, PsA represents both the joint and skin disease, so from that point of view, the patient should take both into account. If a therapy affects

Abbreviations: BADSAI, Bath Ankylosing Spondylitis Disease Activity Index; CMC, carpometacarpal (joint); DAS, disease activity score; DIP, distal interphalangeal (joint); PIP, proximal interphalangeal (joint); PsA, psoriatic arthritis; RA, rheumatoid arthritis

primarily the joints but not the skin, then theoretically the patient would not experience as much change as a patient who experiences both joints and skin improving significantly, and would register less change accordingly. However, they may not be thinking in such a complex way and may focus on primarily one area when rendering their response. Should we break the question into two: “In all the ways your joint disease affects you ...?” and “In all the ways your skin disease affects you ...?” This would allow some distinction if a drug only affects one parameter and not the other. Should there be these two questions and a third “Now consider all the ways in which your whole disease affects you ...?”.

Gladman: This is an important question not only for the patient global but also for the physician global.

Taylor: This is certainly a research question. I would think it will be necessary to ask all three questions, see how they relate and how much additional information is provided in a clinical trial and perhaps supplement with a qualitative study of what patients are actually thinking about when they answer these questions.

Behrens: If the primary efficacy endpoint is a response in joint parameter (skin parameter) there should be two questions: “In all the ways your joint (skin) disease ...?” and “In all the ways your disease ...?”.

How should we assess the spine clinically? Should we assess the spine radiologically? Sacroiliac (SI) joints only or with the spine? Will the BASDAI, BASFI, BASMI pass the OMERACT filter (truth/validity, discrimination, feasibility) in PsA?

Mease: Axial involvement in general occurs in approximately 40% of patients with PsA according to Gladman, whereas sacroiliitis is seen in approximately 25% of patients according to separate studies by Veale and Gladman. Clegg noted 78% of patients in the sulfasalazine PsA trial had sacroiliitis, which appears to be an unusually high percentage. There is no accepted method to assess axial involvement in PsA. Measures developed by the ASessment in Ankylosing Spondylitis (ASAS) working group, such as the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), have been used in patients with PsA enrolled in a spondyloarthropathy study, although these instruments have not been validated in this subset of patients. In fact, both Taylor and Harrison¹ and Brockbank *et al*² have shown that these do not function well in patients with PsA. Axial assessments have not been done in most PsA clinical trials out of concern about the infrequency and heterogeneity of axial involvement. Further, methodology to assess radiological change in the spine in patients with PsA has not been developed. This remains a major research agenda.

Helliwell: As you know the “Italians” have volunteered to tackle this issue, but Will Taylor, Hans Zmierzak, and I are preparing a paper on this issue. As with ankylosing spondylitis, we feel clinical and radiological criteria are necessary. It may be possible to develop a scoring system for assessing spinal involvement based on the “typical features” of ankylosing spondylitis and PsA and then test the sensitivity/specificity in the usual way. This is another potential spin-off of the CASPAR data.

Taylor: There are two related issues—one is to define who has axial disease (classification) and the other is how to measure its severity. The ASAS group eventually came down to measuring morning stiffness (length and intensity) from two items of BASDAI to measure axial inflammation, which I

think is a little inadequate. The BASDAI has been evaluated in cohort studies of PsA,¹ but we found it less valid than the Dougados Articular Index, which is a kind of “axial joint count”. In terms of radiological evaluation, since the manifestations are not that dissimilar from ankylosing spondylitis (mainly distributed differently), I don’t think that it is necessary to invent new radiological scoring methods, but existing ankylosing spondylitis methods do need to be evaluated in PsA studies.

Oliveri: The radiological score methods suggested for primary ankylosing spondylitis should be tested in patients suffering from psoriatic spondylitis.

How should we assess enthesal involvement—Mander, Maastricht, present/absent? How does one examine an enthesal site? By imaging? What about distinction from fibromyalgia?

Mease: Enthesal inflammation is a key feature of PsA. This may be isolated to tendon insertions, such as the Achilles’ tendon or plantar fascia, or be more diffuse, including multiple ligamentous attachments around the thorax, pelvis, and joints. In the diffuse form there may be some difficulty in distinguishing PsA enthesitis from fibromyalgic tender points. In the IMPACT I trial of infliximab, enthesitis at the Achilles’ tendon or plantar fascia was judged as present or absent, and showed improvement with treatment. A previously developed index, the Mander index, has been considered cumbersome because of the large number of sites assessed. A more recent enthesal assessment tool is the one developed by the group in Maastricht, which asks for palpation of just 13 sites. This has been validated in patients with ankylosing spondylitis and may be worthwhile to use in PsA. Distinctive magnetic resonance imaging (MRI) and ultrasound findings have been demonstrated at enthesal sites and adjacent bone, which have shown improvement with antitumour necrosis factor (anti-TNF) therapy.

FitzGerald: I would suggest a more simplified Maastricht count, that is two lateral epicondylar, two superior border of patella, two inferior border of patella, two Achilles’, and two plantar fascia insertion (10 total).

How should we assess dactylitis—as present/absent or quantitatively?

Mease: Dactylitis is a characteristic manifestation of PsA, present in nearly half of patients. It is felt to be a combination of synovitis in joints of the affected digit and inflammation of the ligamentous insertions along the shaft of the digital bone. Tentative scoring systems have employed a simple 0–3 scale of severity, based on the clinician’s judgment of relative severity. Other quantitative assessments have been proposed. Is it important to assess dactylitis? Can dactylitis respond to treatment? A simple scoring of “present” or “absent” was done in the IMPACT I trial with infliximab, in which statistically significant improvement of dactylitis was demonstrated.

FitzGerald: I would suggest a 0–2 scale (0 = none, 1 = present but minimal, 2 = present and maximal). This would give a score range of 0–20. I would also suggest that, where dactylitis is present, the joints in that digit should not be scored separately. This would avoid double counting. In considering entry to clinical trials, minimal swollen joint, tender joint and dactylitis counts could be agreed.

Helliwell: A quantitative measure of dactylitis has been developed. The paper on reliability is in preparation at the moment. A study looking at the responsiveness of this instrument and the various enthesal measures (Mander,

MASES, and “modified Gladman”) is planned for the new year.

Gladman: It is clearly important to assess dactylitis since it is associated with worse radiological outcome than digits without dactylitis. The assessments should include differentiation between acute dactylitis, which may respond to treatment, and chronic dactylitis, which may not. Again, an appropriate tool is required. It may be that a yes/no question is sufficient, but that needs to be ascertained in a study.

Behrens: It is important to assess dactylitis (in agreement with Gladman response), and scoring with present and absent is not sufficient.

Olivieri: Recent ultrasonography and MRI studies on both finger and toe dactylitis have established that the sausage shaped appearance is due to flexor tenosynovitis and that the enlargement of joint capsule is not a sine qua non condition. Flexor tenosynovitis was always present, but joint synovitis occurred in 17–62% of the sausage-like digits. A recent MRI study of ours has demonstrated using fast spin echo T2-weighted sequences with fat saturation that in psoriatic dactylitis there is no evidence of enthesitis of flexor digitorum tendons and joint capsule. Number of digits with dactylitis is better than yes/no scoring.

How should we assess the skin—in categories or continuously? Psoriasis Area and Severity Index (PASI) 75 or 50?

Mease: A number of skin assessment tools have been employed in psoriasis and PsA trials, as outlined by Feldman and Krueger in this supplement.³ The PASI continues to be a commonly used instrument for overall measurement of skin response, although it is acknowledged that it does not perform as well in patients with a low amount of skin disease burden and is considered somewhat cumbersome to use in regular clinical practice. A PASI 50 response is considered by patients and clinicians to be a significant response; PASI 75 remains a threshold that the US Food and Drug Administration (FDA) prefers to see achieved by new therapies. It remains ironic that the PASI 75 is the primary endpoint in most psoriasis studies, whereas the American College of Rheumatology (ACR) 20 is in arthritis studies, despite the fact that the former represents a much greater degree of improvement in disease burden than the latter, and therefore a higher “bar” to cross. Despite this difference, it is true that the ACR 20 performs better in terms of responsiveness and discrimination than the ACR 50 and 70 in PsA studies, according to recent data analysis from both etanercept and infliximab trials. Hence, as a marker of response, ACR 20 is highly useful, even though as clinicians, we prefer to shoot for at least an ACR 50 response in our patients. More easily applied skin measures include the target lesion score and static global. The National Psoriasis Foundation (NPF) and the Lattice scoring systems await in the wings, needing to be used in clinical trials to gain a better sense of their potential utility. The FDA has generally favoured categorical evaluation—that is, capturing the status at that moment in time.

Boehncke: The PASI has been the most widely used means of evaluating skin involvement over the past years in Europe. At least in the setting of a phase 1–3 study, one should use this parameter. (That does not exclude using another one in parallel in the same study.) Comprehensive data sets should contain PASI 75, PASI 50, and the change of PASI throughout the study period. The PASI may be a bit more of a problem in phase IV.

How should we assess fatigue?

Mease: There is increased interest in assessment of fatigue because it is common and is increasingly recognised to have a major impact on patients’ sense of wellbeing. Fatigue can be related to cytokine activation due to inflammation and due to psychoemotional factors. Patients will often describe fatigue, in addition to pain, as being one of the main things they would like to change with therapy. The new biological agents, such as the anti-TNF medications, can yield a significant improvement in this symptom. Historically, one would have hoped that the element of fatigue would be captured in a patient’s assessment of overall global health or wellbeing. However, it is now appreciated that fatigue is a domain worthy of more specific enquiry. Several assessment instruments have been developed which explore various dimensions of fatigue such as physical or emotional. Examples of these include the MFI (Multidimensional Fatigue Inventory), the FACIT (Functional Assessment of Chronic Illness Therapy) Measurement System, the Fatigue Severity Scale, and the MAF (Mutidimensional Assessment of Fatigue) scale. These could all be tested against a simple visual analogue scale measure of fatigue. Fatigue has not typically been assessed in PsA trials.

How should we assess quality of life, function, and “participation”?

Mease: Instruments developed for the assessment of quality of life and function have been used in PsA trials and generally appear to function well based on data from the analysis of the outcome measures used in the etanercept and infliximab phase II studies. These include the Health Assessment Questionnaire (HAQ), the Medical Outcome Survey Short Form 36 (SF-36), and the Dermatology Life Quality Index (DLQI), the latter developed by Andrew Finlay. These instruments need to be validated in PsA. Recently, Veale’s group has developed a PsA quality of life instrument that is more specific for PsA but which has yet to be employed in a clinical trial. At OMERACT 7, the GRAPPA group accepted the suggestion that has come from the World Health Organization to develop instruments to measure “participation”, that is, the ability and interest of a patient to fully (or not) participate in life activities. This appears to get at a more fundamental perspective on function than simple physical ability.

Feldman: The DLQI is designed to assess quality of life related to skin involvement, not joint disease. I’m not sure you’d want to validate it for PsA.

Taylor: I think the SF-36 and HAQ are pretty much validated for PsA, although I still have concerns about the ability of HAQ to truly measure physical function accurately in axial disease.

How should we assess histological and immunohistochemical changes?

Tak: Serial miniarthroscopy has been developed to obtain sufficient numbers of synovial tissue samples to minimise sampling error. Protocols have been developed for reliable immunohistological analysis by investigators participating in the OMERACT group “Synovial Tissue Analysis in Randomized Clinical Trials”. Semiquantitative analysis, counting of cells, and, more recently, sophisticated digital image analysis have been developed for reliable quantification of stained tissue sections. Studies using this approach in patients treated with TNF α blockade (D Baeten, P-P Tak) and alefacept (P-P Tak) have recently been published. They provide insight into the mechanism of action of therapy and may help to assess possible clinical efficacy in an early stage

of drug development. Future studies are planned to identify synovial biomarkers that could be used to predict clinical efficacy, similar to recent work in patients with RA.

FitzGerald: David Kane has a nice paper coming out shortly which addresses this issue in 10 patients biopsied pre and post methotrexate. Certainly, the basic markers should be looked at, but there is work to be done on which marker is best, how do we assess skin, etc. I plan to take that work forward shortly with a GRAPPA subgroup.

How does one go about developing a DAS instrument for PsA? If the DAS in RA is somewhat heavily weighted toward erythrocyte sedimentation rate (ESR), is this a problem for PsA?

Gladman: It is unlikely that we would spend the time and effort required to develop a totally new DAS. Since DAS functions well in clinical trials in PsA, as demonstrated by Antoni's recent analysis, it seems reasonable to continue to use it and determine whether it continues to function well. In addition, it may be worthwhile considering whether the other items such as dactylitis, enthesitis, and axial involvement can also be incorporated into a DAS-type instrument.

Taylor: I should have thought that a PsA DAS needs to be constructed using the same methodology as the original DAS. That is, to measure a range of potential activity indices in the context of normal clinics and to define high or low disease activity states based on physician treatment decisions. If a PsA DAS is constructed using different methodology, then it may be confusing to use a similar name. Once the DAS is constructed, the calibration of the scores should be done using trial data: Which range of scores was associated with placebo and which range was associated with active treatment?

What should be the length of clinical trials?

Mease: A minimum of three months and preferably up to six. Anti-TNF medications appear to yield benefit by approximately three months, but it may take longer to see full benefit with other drugs such as the costimulatory blockade agents or older disease modifying antirheumatic drugs (DMARDs). Length of trial should be based at least on anticipated apex of benefit. Long term safety and radiographic effects take longer to assess—that is, a minimum of one year and optimally several.

Gladman: Another issue is whether the trials should be placebo controlled or comparison trials with current medications.

How does one deal with the variability of disease activity in PsA, which is less consistent than that of RA? Similarly, how does one deal with the lack of radiological progression of some patients?

Mease: It is appropriate to raise these questions as we judge the effectiveness of therapies over time. Because of the greater degree of variability of disease expression, at any given moment of ascertainment, whether the patient is on placebo or treatment, there is a chance that the patient will be naturally be in a period of lesser disease activity not due to a specific treatment. Thus, it is harder to judge treatment effect reliably. Similarly, since a substantial number of patients may not progress radiologically in a consistent manner, it will be harder to judge true difference in effect between treated and placebo patients. Part of the way this is dealt with is to acknowledge the point and then build these variables into the power calculations when determining the appropriate N for a study.

Gladman: It is for that reason that the PsARC recognises response of greater than 30%. That may be a threshold for PsA. One can actually look at the placebo arm of drug trials in PsA and see what was documented for the actual variation in joint count during the trial and then decide what the cut-off for both ACR and PsARC, and even the DAS, should be.

How does one best address assessment of patients with oligoarticular disease?

Mease: It is important to assess PsA patients with oligoarticular disease in order to see if their response to treatment is any different than patients with polyarticular disease. Results of clinical trials have not suggested a difference in this regard. A common question is whether it is "worth it" to treat patients with just a few inflamed joints with systemic medications, especially expensive ones. It is difficult to make generalisations about this since if a strategic joint is affected severely, then it may yield as much disease burden as a patient with many joints involved and thus deserve full and aggressive treatment. On the other hand, if a patient has few joints which happen not to be severely involved, then they represent a low disease burden state and lesser therapeutic paths may well be justified. Some consideration should be given to injection therapy if few joints are involved, typically with intra-articular steroids. This also may be a place for intra-articular injection of anti-TNF medications, which has been done in some patients with RA.

Gladman: Intra-articular steroids will likely be given to individuals who have persistent disease, unresponsive to the above measures. However, it is conceivable that if the anti-TNF or other biological agents are indeed disease modifiers, then they should be offered to anyone with active inflammation to prevent damage.

Helliwell: I think patients with oligoarticular disease can be some of the most difficult patients to treat with this disorder, being resistant to all conventional therapies. It remains to be seen if the newer drugs can have an impact—so these patients should be included, and stratified, in studies of treatment.

How does one best address the issue of early versus more established disease?

Mease: Kane *et al*, from the Dublin group, published observations about PsA presentation from an early arthritis clinic in 2003. This work has yielded interesting observations about the characteristics of patients with a mean disease duration of 10 months, such as the majority being polyarticular, approximately 40% with enthesopathy, 40% with DIP involvement, and 10% with inflammatory spinal pain. Other than noting that patients with polyarticular disease were more likely to be treated with DMARDs, and at the one and two year mark, a number of these patients became oligoarticular and few were in remission, there has been no controlled trial of therapy in this cohort of patients to observe if earlier intervention significantly affects long term outcome, as has been documented in RA. One tantalising question is whether earlier treatment of moderate to severe psoriasis with biologicals will hinder the ultimate appearance of PsA. We have no data at this time which either support or refute the possibility that we can prevent the appearance of PsA with therapeutic intervention before the disease appears. We also need to gain experience with therapeutic intervention in patients with very early arthritic manifestations.

Gladman: Since psoriasis appears less severe in patients with PsA participating in drug trials, one wonders whether that will be an issue. More important is the question of the role of

early therapy in PsA to prevent joint damage regardless of skin involvement. That too has not been addressed although we all believe it will be the case.

What are the advantages and disadvantages of assessing all-comers with spondyloarthropathies rather than just PsA?

Nash: Many consider the spondyloarthropathies to be one disease with variable expression. For example, those with predominantly spinal involvement are diagnosed with ankylosing spondylitis, and those with psoriasis and arthritis are said to have PsA and psoriasis. However, ultimately they are expressions of the same basic disease process, including such cardinal features as the potential for spine involvement, asymmetrical arthritis, enthesopathy, iritis, and the capability of having similar genetic patterns—for example human leucocyte antigen (HLA)-B27, and the possibility of a shared animal model, the HLA-B27 transgenic rat for research purposes. There is much to be said for this position, especially in the clinic, wherein pattern recognition of these types of common elements may lead to earlier diagnosis. (However, Gladman notes that PsA patients with spondyloarthritis are more likely to be HLA-B27 negative than patients with ankylosing spondylitis.) Responses to certain medications, such as the anti-TNFs, are also very similar. However, there are some very real differences between the different subsets of spondyloarthropathies. Unique clinical features of PsA include DIP involvement, arthritis mutilans, greater amount of peripheral arthritis, asymmetrical syndesmophytes in the spine that are distinct from those seen in ankylosing spondylitis, other unique radiological features, and certain genetic patterns that are clearly different than those seen in ankylosing spondylitis. In ankylosing spondylitis, aortic valve and upper lobe of lung pathology, as well as consistent and often severe spinal involvement are unique. The situation where the “splitters” have the greatest legitimacy is in the clinical trial situation, wherein certain outcome measures, such as the BASDAI, may not perform adequately in a disease such as PsA where spine involvement is less frequent and more heterogeneous than in ankylosing spondylitis, as suggested recently by Taylor and Harrison. Thus, in a clinical trial in which all spondyloarthropathies are assessed with the same measures there may be subgroups which are not as validly assessed as in a trial in which a single spondyloarthropathy subset is studied with measures that have been validated in that subset.

Olivieri: There is also the possibility that the clinical spectrum of PsA includes spondyloarthropathy forms (with clinical features and family history of spondyloarthropathy) and non-spondyloarthropathy forms (for example the rheumatoid-like symmetrical polyarthritis).

Gladman: Even in patients with PsA, it is important to assess the presence of spinal disease and its response to therapy. In PsA the spinal disease may not be as painful, but it may lead to deformities and damage and hence disability. If is not assessed an opportunity for early treatment will be missed.

What about the radiological assessments of the peripheral joints, and the damaged joint score discussed at the last OMERACT? What are the significant unresolved issues regarding radiological assessment of PsA, particularly in reference to measurement of disease progression?

Mease: In the article on radiographic imaging by van der Heijde *et al* in this supplement, radiological assessment

methods and results of clinical trials using them are thoroughly reviewed.⁴ A number of issues remain problematic. Unlike RA, wherein there is more predictable and consistent progression of joint destruction, which can be measured radiographically, PsA behaves more quixotically. Clinically we observe more unpredictable waxing and waning joint inflammation. In a cohort of patients in a clinical trial some patients do not worsen radiographically regardless of treatment arm. Thus, one must exercise greater caution in attempting to compare radiographic results of different trials, since even apparently well matched groups could differ in their radiographic responses due to chance alone. One must also be cautious about attempting to project likely progression of disease over time. Also, if there are fewer joints involved in a patient with PsA than in a typical RA patient, and fewer patients progress radiologically than is typical for RA, then it may be necessary to conduct trials with larger numbers of patients than in a typical RA trial in order to show statistically significant difference between treatment arms. This may particularly true in trials of drugs with less dramatic treatment effects.

A further interesting point is that we have seen the ability of the anti-TNF medicines to significantly slow radiological progression even in patients who have not achieved an ACR 20 response in a clinical trial, which has also been observed in RA. It is likely that this will also be seen with agents that may have little or no anti-inflammatory effect but may have antiresorptive and antiosteoporotic effects, such as a receptor activator of nuclear factor κ B (RANK) ligand inhibitor. Although there are unique radiological markers of PsA such as pencil in cup change and periostitis, it is not known if measurement of change in these findings has any clinical meaning or has significance regarding disease progression. There was no change in these findings in a year of observation in the etanercept phase III trial.

We do not know, as of yet, how to effectively use MRI or ultrasound assessment in the assessment of disease progression. Work on this is underway.

Gladman: The issue of clinically damaged joints has not been adequately addressed. In the Canadian SPARCC study, there was excellent agreement on the number of clinically damaged joints defined as joints with clinical deformities, ankylosed or flail joints, or joints with marked (greater than 20% of the range) restriction of movement that cannot be attributed to inflammation (joint swelling).⁵ Since it is easier to record clinical damage than perform radiographs at six month intervals, this may be an outcome measure to be included in clinical trials.

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PostScript

MATTERS ARISING

Anti-C1q antibodies in renal and non-renal SLE

We read with interest the report of Marto *et al*¹ on the occurrence of anti-C1q antibodies in systemic lupus erythematosus (SLE), particularly their finding of anti-C1q in 39.8% of patients with SLE without renal disease, 27.3% of whom went on to develop nephritis.

We recently tested for anti-C1q antibodies using an enzyme linked immunosorbent assay (ELISA) kit (Buhlmann Laboratories, Basel) in the sera of 28 patients with SLE (median 13.2 U/l (range 0.6–1516)), 14 patients with rheumatoid arthritis (RA; 12.6 (2–119.6)), and 13 healthy control subjects (5.4 (3–137.2)). Although just over 40% of patients with SLE and RA had anti-C1q levels above the manufacturer's cut off point for positivity, 18.2 U/l, only patients with SLE had levels over 200 U/l.

While we agree with Marto's findings of a correlation between renal disease and anti-C1q positivity in patients with SLE ($r = 0.56$, $p < 0.05$ in our study), we also found a correlation between haematological disease and anti-C1q positivity ($r = 0.65$, $p < 0.05$), and particularly, a negative correlation between lymphocyte count and anti-C1q concentration ($r = -0.55$, $p > 0.05$). Although 11/18 patients with haematological disease also had renal disease, some of the highest concentrations of anti-C1q antibody (460 and 680 U/l) were found in patients with marked lymphopenia but no evidence of nephritis.

Increased numbers of circulating apoptotic lymphocytes have been described in SLE,^{2–4} and linked with lymphopenia and disease activity. As Marto and colleagues argue, interference with clearance of apoptotic cells is now an attractive hypothesis for the development of autoimmunity.⁵ Interference of anti-C1q with the removal of the increased numbers of apoptotic lymphocytes in these lymphopenic patients might result in the exposure of antigenic nuclear material to the immune system, and so contribute to the development of autoantibodies. Although almost all studies on anti-C1q antibodies have been directed at lupus nephritis, a larger study might be useful in examining possible relationships with other forms of the disease, including haematological manifestations.

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CORRECTION

Discussion: Assessment of psoriatic arthritis (Mease P J, Behrens F, Boehncke W-H, Feldman S R, FitzGerald O, Gladman D D, Helliwell P S, Nash P, Olivieri I, Taylor W J, Tak P-P. *Ann Rheum Dis* 2005;64(suppl 2):ii69–73.)

The author name P-P Tak is incorrect in the list of authors. The correct name is P P Tak.

Corrections printed in the journal also appear on the *Annals website* <http://www.annrheumdis.com> and are linked to the original publication

FORTHCOMING EVENTS

Second EULAR Course on Systemic Lupus Erythematosus

4–9 September 2005; San Miniato, Italy
This course for 70 young rheumatologists (age <40) has been designed to provide comprehensive, intensive training on various aspects of this disease. It will deal with the following topics:

- Treatment of SLE, molecular basis of drug action, and pharmacogenetics
- Evaluation of patients with SLE: disease activity, damage, response to treatment
- Renal disease in SLE
- Neurological disease in SLE
- Skin disease in SLE
- Particular problems in SLE: fever, vaccination, pregnancy, haematological manifestations

Contact: Organising secretariat: c/o Clinical and Experimental Rheumatology, Via Santa Maria 31, I-56126 Pisa, Italy.

Tel.: +39-050-40124

Fax: +39-050-502299

Email: slecourse@clinexrheumatol.org

Third International Conference on Neuroendocrine Immune Basis of the Rheumatic Diseases

10–12 September 2005; Genova-Santa Margherita, Italy

Topic: The clinical translation of the neuroendocrine immune mechanisms of the rheumatic diseases for a better understanding and management of their diagnosis and treatment.

Local organiser: Professor Maurizio Cutolo, Division of Rheumatology, DIMI, University of Genova, Italy

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XI Mediterranean Congress of Rheumatology

22–24 September 2005; Heraklion Crete, Greece

The meeting is organised by the Departments of Medicine, Rheumatology, and Clinical Immunology and Allergy, University of Crete. Contact: Organising Bureau (secretariat and travel office) of the Mediterranean Congress of Rheumatology

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Future EULAR congresses

21–24 June 2006; EULAR 2006; Amsterdam, The Netherlands

13–16 June 2007; EULAR 2007; Barcelona, Spain

11–14 June 2008; EULAR 2008; Paris, France