

## **Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (review of TA104 and TA125)**

Personal Statement from Dr Eleanor Korendowych

This statement is based on my knowledge and experience of the use of anti-TNF therapy in Psoriatic Arthritis (PsA). I am the clinical and research lead for PsA at the Royal National Hospital for Rheumatic Diseases in Bath where I was appointed as a Consultant in 2005. I am a member of GRAPPA (Group for research and assessment of Psoriasis and Psoriatic Arthritis) and have strong collaborative links within the UK and internationally with other leaders in the field, together with my colleague in Bath, Professor Neil McHugh. The RNHRD has a large research database and patient cohort with PsA and currently has longitudinal prospective clinical data collected over the last 20 years on over 500 patients. I started a dedicated PsA anti-TNF clinic with a PsA nurse specialist in 2006 and we currently have over 60 patients on anti-TNF therapy. I also have regular PsA clinics for patients with PsA who are not on anti-TNF therapy. I personally assess all patients for eligibility for anti-TNF and review them at regular intervals during treatment. I have many years of experience in the collection of outcome data in PsA including joint scores, PASI, nail scores and radiological scoring which formed part of my PhD on the immunogenetics of PsA.

There is no doubt that PsA is a serious disease with significant morbidity, increased mortality largely due to cardiovascular risk and considerable psychosocial consequences related to the associated skin disease. The prognosis is comparable to Rheumatoid Arthritis in terms of joint destruction but there is the added complication of psoriatic skin disease for the majority of patients. In addition, patients with PsA appear to be more at risk of some complications of traditional treatments such as liver toxicity with methotrexate.

PsA is a spectrum of disease that can vary from single joint or limited joint disease to a severely destructive arthropathy known as arthritis mutilans. It can also affect the spine to give a pattern similar to Ankylosing Spondylitis (AS) both in the presence or absence of peripheral joint disease. PsA also involves the entheses and can present with widespread enthesitis in the absence of classic joint disease. Traditionally patients have been classified into subgroups, but in practice, patients can 'move' between subgroups as their disease varies in its degree of activity. Most experts would not see any need to sub-classify patients as there is no evidence for any differential effects of treatment. The exception may be the associated spondyloarthropathy which appears to respond differently to the peripheral disease with regards to medication. However, more work is needed as most of the trials do not have the data to address this issue.

PsA is a difficult disease to study by virtue of its complexity, wide variation in clinical phenotype, lack of serological diagnostic, prognostic or response markers, complicated outcome measures and tendency to significant natural disease fluctuations. This is reflected in the relative paucity of studies of the traditional DMARDs, particularly methotrexate, for the treatment of PsA. Much of the evidence base for current practice in PsA is based on small poor quality

trials and many physicians 'borrow' evidence from RA assuming that the efficacy and tolerability will be similar. Sulfasalazine has somewhat more evidence and leflunomide probably has the best trial evidence of all the non-biological agents. In practice, the main DMARDS utilised are methotrexate, sulfasalazine and leflunomide. Although these can be beneficial for patients, it is relatively rare for patients to achieve full remission and treatment is often complicated by side effects and tolerability issues. There is no direct evidence to suggest that any one DMARD is more efficacious than another. In practice, most physicians will use methotrexate or leflunomide first line if there is significant skin disease as sulphasalazine does not tend to help psoriasis.

The efficacy of anti-TNF therapy in PsA has been well established in the published trials for all three agents approved by NICE (infliximab, etanercept and adalimumab). All the published trials are of good quality. As with all clinical trials the patient population studied may not necessarily reflect clinical practice particularly in terms of disease longevity and previous medication exposure. However, a number of 'real life' experiences of anti-TNF treatments have been published at Rheumatology conferences including our own and these would all support the results shown in the published trials. The trials provide good evidence for reducing disease activity (both in the joints and the skin), preventing radiographic progression and improving physical function, quality of life and pain levels in all agents. There have been no head to head trials of the agents and differing recruitment methods would not allow any direct comparison of the agents in terms of efficacy or tolerability. In practice, I have used all three agents very successfully and there would not appear to be any significant differences between the agents. Choice of agent is often driven by patient choice and convenience but there can be clinical reasons for choosing a specific agent.

There are currently no reliable biomarkers that predict who is more likely to get progressive disease although a high number of swollen joints at presentation, early radiographic changes and the presence of anti-CCP antibodies (approximately 8%) may help define those whom we should be treating early with anti-TNF therapy. There are also no factors that help predict who is likely to respond to anti-TNF therapy and if so to which agent. There is certainly mounting evidence that if patients do not respond to the first agent they are very likely to respond to a second or indeed third agent. This is probably best shown by the data collected by the British Society for Rheumatology Biologics Registry (BSRBR), which has data collected nationally and prospectively on 566 patients with PsA (Saad et al, *Arth Res Ther* 2009 11(2) R52). Seventy-five percent of patients remained on their first anti-TNF drug for at least 12 months (9.5% discontinued due to inefficacy, 10% due to adverse events and 5% due to other reasons). Of the 178 patients who started a 2<sup>nd</sup> agent, 74% were still on this medication after 12 months. This therefore demonstrates a high level of persistence with anti-TNF therapy both with the first and the second agent indicating both good efficacy and tolerability. This data would certainly reflect my own clinical observations.

There is less data as to the added benefit of continuing with a traditional DMARD in addition to the anti-TNF agent and more work is needed to fully

answer this question. The data that there is would suggest some benefit and it would be my practice to continue with the DMARD unless the patient experiences a complete remission allowing slow withdrawal of the DMARD. The definition of remission or minimal disease activity (MDA) and how we decide on response to treatment has not yet been optimised for PsA. The NICE guidelines currently recommend the Psoriatic Arthritis Response Criteria (PsARC) for assessment at 12 weeks. This works well in my opinion but many centres are probably still not collecting all the data required to complete this (a 76/78 joint count and physician and patient global scores) largely due to lack of nursing and medical time and expertise in the more extensive joint count (RA uses a 28 joint count). In addition, it is only applicable at one time point and cannot be used as an ongoing assessment of disease activity much as the Disease Activity Score (DAS) is used in RA. There are problems with applying the DAS in PsA particularly the exclusion of the feet and the need for raised inflammatory markers, which are often not elevated even in active PsA.

There is a need for a composite response measure ideally that encompasses both the skin and the joints. This is currently under development. Ideally a patient will respond both in terms of their joints and their skin, but there are some whose joints improve but the skin does not or worsens and vice versa. This will require more collaborative working between Rheumatologists and Dermatologists and improved assessment of our current outcome measures to ensure we are measuring what is most important to the patient. Often a patient will accept a degree of inefficacy in one element provided their primary concern (be that joints or skin) improves significantly. The current outcome measure does not take into account any element of spondyloarthritis or enthesitis. Most physicians will use the measures utilised in AS such as the BASDAI to assess response but this requires more work. Hopefully the new composite outcome measure will cover all elements of the disease entity to optimise assessment of response to treatment.

In terms of safety, all three anti-TNF agents compare favourably with the traditional DMARDS. Again, the BSRBR has provided reassuring data on a cohort of 596 patients with PsA. They have reported no significantly increased rate of adverse events compared with a control cohort of patients with seronegative arthritis receiving DMARDS. The data on persistence with a 1<sup>st</sup> and 2<sup>nd</sup> agent also confirms an acceptable rate of adverse events similar to that expected with any of the standard treatments for inflammatory arthritis. My personal experience has been that all three agents have a similar adverse event profile and that the development of problems with one agent does not necessarily herald an increased probability of side effects with a further agent. In addition, minor side effects are often better tolerated by the patients due to the high level of efficacy of the treatment. Most adverse events seem to be experienced within the first 3 months.

There are a small number of patients who achieve an excellent initial response but disease control becomes less good over time (sometimes after 2-3 years of treatment). Switching agents is very often successful. With time, there will be a number of patients who will need an alternative agent to the three agents currently approved by NICE. The promising results with further

agents targeting both TNF and other elements of the inflammatory pathway will hopefully provide viable alternatives for treatment in the future. For now, the current anti-TNF agents approved by NICE continue to allow patients with PsA access to a level of function and quality of life that would have been unattainable in the pre-biologic era.