

Health Technology Appraisal: etanercept, infliximab and  
adalimumab for the treatment of psoriatic arthritis (rev 104,  
125)

Personal view of etanercept, infliximab and adalimumab for psoriatic  
arthritis

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## **A. Introduction and clinical manifestations**

### *Epidemiology and burden of disease*

Psoriatic arthritis is second only to rheumatoid arthritis in frequency in cases of inflammatory arthritis seen in out-patient clinics in the UK. New, validated classification criteria have facilitated both clinical and epidemiological studies (Taylor et al. 2006). Most epidemiological surveys have been carried out on populations of people with psoriasis seen in secondary care where the prevalence has been found to be as high as 39%, although a lower prevalence is more likely (Leonard, O'Duffy, & Rogers 1978). More recent figures are available from a UK based community survey of people with psoriasis where the prevalence of psoriatic arthritis in this population was found to be 14% (Ibrahim G, Waxman, & Helliwell 2009). Of interest, in this latter survey almost half the people identified had established disease and were not known to have the disorder. The reasons for this are as yet unclear but may be several. Firstly, the articular complaints may not have been presented to a health professional. Secondly, if presented, the health professional may have wrongly attributed them to some other diagnostic category, such as osteoarthritis (the mean age of this group was 54 years). This may also have been an error of omission, given that psoriatic arthritis is less frequent and less recognisable than, for example, rheumatoid arthritis.

The peak age of onset of psoriatic arthritis (20 – 40 years) is younger than that found in rheumatoid arthritis (50 – 60 years). This is in most cases later than the onset of psoriasis which appears for the most part between 5 – 15 years. In a minority of cases psoriatic arthritis may also be first diagnosed at the extremes of life.

Although there is a wide spectrum of disease expression (see below) there is no doubt that disability, quality of life and mortality are adversely affected in this disorder. In this context it is important to note that the skin disease may be an important contributor to these outcomes (Sokoll & Helliwell 2001). More recent work emerging from several centres has focussed on the increased cardiovascular morbidity in psoriatic arthritis, with two fold increases of the chance of having a major cardiovascular event, such as a myocardial infarction (Gelfand et al. 2006). A higher risk of suicide has also been demonstrated (Gladman et al. 1998).

### *Clinical sub-groups*

Psoriatic arthritis is a heterogeneous disease. Wright and Moll originally described 5 subgroups reflecting the diverse clinical manifestations of this disorder: distal interphalangeal joint predominant (5%), asymmetrical oligoarthritis (70%), symmetrical polyarthritis (15%), predominant spondylitis (5%), and, the most severe form, arthritis mutilans (5%). The precise composition and relative frequency of these subgroups has since been the subject of some debate. Most of the published series in the last 20 years have reported the symmetrical polyarthritis sub-group to be the most frequent, at about 60%. The reason for this discrepancy is not entirely clear although it is unlikely that the disease has changed since the original Moll and Wright description. It is more likely that Moll and Wright were using more specific, but un-stated, criteria to identify their cases, although a recent review of the cases catalogued by Dr John Moll reveal a predominance of the polyarticular pattern (unpublished data from Helliwell and Healy).

Recognising that the disease can involve both axial and peripheral sites is not disputed but the utility and practicability of dividing the cases with predominant peripheral arthritis remains unclear (Helliwell et al. 1991; Veale & Fitzgerald 1992). The situation is confounded

by such factors as the precise method for ascertaining joint involvement and recognising that the disease pattern will change over time both with evolution of the disease (Jones et al. 1994) and with treatment (Kane et al. 2003).

From a practice and treatment point of view it seems appropriate to make the following distinctions: (1) Axial disease (spondylitis) (2) Peripheral disease (oligoarthritis and polyarthritis) (3) Unique disease features (dactylitis, enthesitis, distal interphalangeal joint involvement) (4) Unusual presentations (onychodermatoperiostitis, SAPHO (synovitis, acne, pustulosis, hyperostosis, osteomyelitis) syndrome).

## **B Conventional Treatments**

The heterogeneous nature of psoriatic arthritis demands different approaches and ingenuity to enable appropriate disease control with minimum adverse effects. Further, the presence of skin disease, which may be of more importance to the patient, has to be considered when choosing different options. To facilitate disease management some clinicians now conduct combined clinics with dermatological colleagues: this enables a considered judgement of drug treatment options, addresses the main concerns of the patient and reduces the number of hospital out-patient visits to a minimum. However, this option is unpopular with hospital managers.

It is also worth noting that most clinical trial data in psoriatic arthritis is hampered by a lack of appropriate outcome measures for this disorder (Gladman et al. 2004). There is some evidence that 'borrowed' tools from other disorders are inappropriate for psoriatic arthritis where axial and peripheral disease co-exist (Taylor & Harrison 2004). Current work undertaken by the Group for Research and Assessment of Psoriasis and Psoriatic arthritis (GRAPPA) will provide more specific composite outcome measures for this disorder in the future.

### *Initial treatments*

Many patients are referred from dermatology colleagues with vague symptoms of myalgia and arthralgia. Often, as would be expected with patients referred to secondary care, their skin disease is severe and extensive. These patients comprise a significant but commonly unrecognised group of patients who, although not fitting into the rubric of psoriatic arthritis, nevertheless have musculoskeletal symptoms associated with their skin disease. It is possible that their symptoms fluctuate with the severity of their psoriasis but no systematic data are available currently.

### *Spondylitis*

Although differences between the clinical manifestations of psoriatic spondylitis and classical ankylosing spondylitis are described (Helliwell, Hickling, & Wright 1998) it is compelling to regard the issue as one of quantity rather than quality – the disease is merely less extensive in psoriatic arthritis rather than a completely different disease process. Further, recent meetings of GRAPPA and the Assessment of Spondyloarthritis (ASAS) group have supported the similarity of spondylitis with and without the presence of psoriasis thus enabling the use of similar classification criteria and treatment algorithms.

### *Peripheral arthritis*

- (a) Oligoarthritis. Moll and Wright described this as the most frequent clinical presentation of psoriatic arthritis. From a clinical point of view this can be both the easiest and the hardest group of patients to treat. Some patients will have one or two scattered joints which are symptomatically controlled by NSAIDs or by intra-articular

steroids. Others will have the most intractable symptoms from just one or two areas defying all treatment options (see case study # 2).

- (b) Polyarthritis. In many ways this sub-group is the most straightforward to treat, resembling, as it does, rheumatoid arthritis. Patients are usually rapidly progressed to DMARDs starting with sulphasalazine and progressing to methotrexate, cyclosporine and leflunomide. Each of the latter three drugs may have significant beneficial effects on the skin.
- (c) Other manifestations (dactylitis, enthesitis, and other extra-articular manifestations). Clear data on treatment of these characteristic disease features is lacking, the best evidence coming from trials of biologic drugs. It is now appreciated that a major extra-articular manifestation of psoriasis and psoriatic arthritis is an increased cardiovascular morbidity with a two fold increase in the likelihood of a major cardiovascular event, such as myocardial infarction. The impact of effective treatment on this clinical feature has yet to be assessed.

There is currently a dearth of data on the efficacy of non-biologic agents for the treatment of this disease, either used singly or in combination. A recent review of the evidence for all treatments for individual aspects of the disease (peripheral arthritis, skin involvement, spinal disease, dactylitis and enthesitis) has been published, along with treatment recommendations, both from the GRAPPA group (Ritchlin et al. 2009). Additionally, a major clinical trial of intensive 'tight control' therapy for psoriatic arthritis is currently underway in 7 centres in the UK and the results of this study are expected in 2011 (Eudract number: 2007-004757-28)

### **C. The place of biological drugs (anti-TNF drugs infliximab, adalimumab and etanercept) in clinical practice.**

Anti-TNF drugs are now firmly established in the therapeutic profile of psoriatic arthritis. No new non-biologic drugs have become available since the last appraisal of infliximab and etanercept. The anti-TNF drugs remain the best available treatment for this disorder in terms of efficacy and adverse effects – this is a personal view and not based on trial evidence. The ability of anti-TNF drugs to transform lives remains the single most compelling evidence in clinical practice – see case report # 1 below.

The use of this technology can be summarized as follows:

1. Biological drugs are never used unless conventional treatments have failed and always in line with recommendations from NICE and BSR guidelines.
2. Most often the biological drugs are used in cases of polyarticular psoriatic arthritis resembling rheumatoid arthritis. The reasons for this are threefold: clinicians feel more comfortable if a patient has a significant burden of disease, this is the most frequent sub-group and these patients have the worst prognosis.
3. Both axial and peripheral disease respond well to biological drugs.
4. Some forms of psoriatic arthritis are very difficult to treat with any drug. It is my experience that these forms of psoriatic arthritis respond very well to the biological agents, even though the arthritis itself does not conform to the stereotypic case. In

particular I refer to the severe oligoarticular forms of psoriatic arthritis (see below) and to cases of isolated severe dactylitis and enthesitis

5. In most cases it is gratifying to see that the skin manifestations of this disease also respond well to the biological drugs.
6. The choice of anti-TNF drug is limited by the previous NICE appraisal and by individual patient characteristics. In practice, infliximab and adalimumab seem to be more efficacious for the skin and etanercept appears to be safer overall.

Case history # 1. A 50 year old man with extensive skin disease, spinal ankylosis and peripheral arthritis has failed to respond to both methotrexate, sulfasalazine and leflunomide. His joints are so bad he has to travel in a motorised chair. His skin is so bad that at the school where he teaches technology his course around the school is charted by little piles of skin that he sheds. Three months after commencing etanercept his skin is almost clear for the first time in 15 years and he can now get around with one stick. His wife is so happy that his self-esteem and quality of life are very much improved.

Case history # 2. A 40 year old doctor who has a 10 year history of oligoarticular psoriatic arthritis manifest by inflammation and deformity of two distal interphalangeal joints, the proximal inter-phalangeal joint of his right index finger and recurrent dactylitis of his fingers. He has minimal skin disease. For many years he was well controlled on NSAIDs alone until three years ago when he developed intractable dactylitis of his right index finger and left thumb and severe insertional enthesitis posterior to his left heel. Treatment with methotrexate, sulphasalazine, cyclosporine, leflunomide and combinations of these were tried without success. Local steroid injections offered temporary relief but were very painful during administration. He became increasingly disabled by these few areas of disease, gave up golf and mountain biking and started working part time. Within two weeks of starting etanercept he was a 'new man', his painful heel and swollen fingers resolved and, a year later, is back doing sport and working full time. He says he has recaptured the vigour he lost when his disease was active. He has experienced no side effects.

## Summary

Psoriatic arthritis is a heterogenous disease which presents challenges to therapeutic ingenuity. The evidence base for existing, conventional DMARDs treatment is poor. The biologic anti-TNF drugs can be life changing in this disorder. The effect of these therapies on long term structural damage and extra-articular manifestations, such as cardiovascular morbidity, remains to be shown.

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