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TUMOUR NECROSIS FACTOR INHIBITORS - INFLIXIMAB AND ETANERCEPT in the SPONDYLOARTHROPATHIES

A Position Statement of the NSW Therapeutic Assessment Group Inc.

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EXECUTIVE SUMMARY

The spondyloarthropathies are a group of chronic inflammatory disorders of the joint, including ankylosing spondylitis, psoriatic arthritis, reactive arthritis, arthritis related to inflammatory bowel diseases such as Crohns' disease and ulcerative colitis, and arthritis associated with acute anterior uveitis. Targets of anti-inflammatory therapy are inflammatory back pain (sacroiliitis, spondylitis), peripheral arthritis and enthesitis.

Infliximab is a chimeric monoclonal antibody that binds with high affinity to TNF alpha. It is currently licenced in Australia for moderate to severe Crohn's disease in patients who have an inadequate response to conventional therapies, and for treatment of rheumatoid arthritis (RA) in adults. In June 2003 approval was given by ADEC for treatment of ankylosing spondylitis- for the reduction of symptoms and improvement in physical function in patients with active disease at a maintenance dose of 5mg/kg by IV infusion every six weeks.

Etanercept is a recombinant human TNF receptor fusion protein which acts competitively to inhibit the binding of TNF to its active cell surface receptor. It is licenced in Australia for treatment of active adult RA in patients who have had inadequate response to one or more disease modifying antirheumatic drugs (DMARDs), and can be used in combination with methotrexate in patients who do not respond to methotrexate alone. Etanercept is also licenced for treatment of active polyarticular- course juvenile chronic arthritis in patients (4 to 17 years) who have had inadequate response to one or more DMARDs. In June 2003, ADEC approved etanercept for treatment of the signs and symptoms of active and progressive psoriatic arthritis when the response to previous disease-modifying antirheumatic therapy has been inadequate. A licenced indication for ankylosing spondylitis was granted by the FDA on July 24 2003.

Adverse events that have been noted in post marketing surveillance of both infliximab and etanercept therapy include invasive fungal diseases, demyelinating diseases and lymphoproliferative disorders. Mycobacterial infections have been reported with infliximab. Long term data on adverse events is not available at present.

Clinical evidence supports a trial of infliximab in patients with inadequately controlled psoriatic arthritis and ankylosing spondylitis.

Clinical evidence supports a trial of etanercept in inadequately controlled psoriatic arthritis and ankylosing spondylitis.

There is no evidence that either TNF alpha agent should be used before the other can be tried

Combination of either infliximab or etanercept with methotrexate may allow lower doses to be used, thus reducing potential for toxicity.

These agents should be reserved for patients in whom more conventional therapies have failed. There is a need to identify those patients most likely to benefit from TNF alpha inhibition, from the perspectives of cost and also possible long-term side effects.

1. INTRODUCTION

The spondyloarthropathies (SpA) are a group of chronic inflammatory disorders of the joint which are associated with the HLAB27 gene¹. Entities belonging to this group are ankylosing spondylitis (AS), psoriatic arthritis (PA), reactive arthritis, arthritis related to inflammatory bowel diseases such as Crohns' disease and ulcerative colitis, and arthritis associated with acute anterior uveitis. Within the group considerable overlap between the different disease entities can occur, for example during the course of AS, 40% of the patients will develop acute anterior uveitis.² Notably, the SpA lack rheumatoid factor or other autoantibodies and complement consumption attributable to immune complexes³.

Disease pathogenesis differs between rheumatoid arthritis (RA) and SpA. In RA, cartilage and bone destruction secondary to synovitis within synovial joints is the primary disease manifestation and it correlates with loss of function. By contrast, AS and the SpA have a predilection for the spine (particularly the sacro-iliac joints) and large synovial joints, where prominent reparative processes with bone sclerosis and new bone formation usually occur.

Targets of anti-inflammatory therapy in the spondyloarthropathies are inflammatory back pain (sacroiliitis, spondylitis), peripheral arthritis and enthesitis (inflammation at sites where ligaments, tendons or joint capsules attach to bone) and uveitis. Additional targets are psoriatic skin disease and colitis.

Human tumour necrosis factor (TNF alpha) is a pro-inflammatory and immunoregulatory cytokine that, when overexpressed, mediates chronic inflammation⁴. Cellular responses to TNF alpha include: up-regulation of other inflammatory cytokines such as interleukin-1 and IL 12; upregulation of chemokines such as IL-8; priming and activation of neutrophils; up-regulation of adhesion molecules and tissue factor by endothelial cells and induction of proliferation and increased synthesis of IL-6 and metalloproteinases by fibroblasts.

Infliximab is a chimeric monoclonal antibody that binds with high affinity to TNF alpha. It is currently licenced in Australia for: -

- **moderate to severe Crohn's disease** in patients who have an inadequate response to conventional therapies.
- **treatment of rheumatoid arthritis (RA) in adults**, specifically reduction of signs and symptoms and prevention of structural joint damage (erosions and joint space narrowing) in adult patients with active disease despite treatment with methotrexate .
Infliximab should be given in combination with methotrexate, as efficacy and safety have been demonstrated only in combination with methotrexate.
- **treatment of ankylosing spondylitis**; for the reduction of symptoms and improvement in physical function inpatients with active disease at a maintenance dose of 5mg/kg by IV infusion every six weeks.

Etanercept (Enbrel[®]) is a recombinant human TNF receptor fusion protein which acts competitively to inhibit the binding of TNF to its active cell surface receptor. It is currently licenced in Australia for

- **treatment of active, adult RA** in patients who have had inadequate response to one or more DMARDs. It can be used in combination with methotrexate in patients who do not respond to methotrexate alone.
- **treatment of active polyarticular- course juvenile chronic arthritis** in patients (4 to 17 years) who have had inadequate response to one or more DMARDs. It has not been studied in children less than 4 years of age.
- **treatment of signs and symptoms of active and progressive psoriatic arthritis** in adults when the response to previous disease-modifying antirheumatic therapy has been inadequate. (Not indicated for treatment of psoriasis not associated with manifestation of arthritic disease.)

The FDA granted a licenced indication for etanercept for ankylosing spondylitis on July 24 2003.

The Pharmaceutical Benefits Advisory Committee recommended in December 2002 that etanercept be listed on the Pharmaceutical Benefits Scheme under section 100 on the basis of “high but acceptable cost-effectiveness ratios”. In adults, this listing is for treatment of patients with severe active rheumatoid arthritis who have a record of rheumatoid factor positive status and who have failed other treatment options. In children listing is for the treatment of patients aged 4-17 years with active polyarticular-course juvenile chronic arthritis, who have failed other treatment regimens.

Clinical evidence for RA and Crohns will not be considered in this paper. Guidance documents for use of infliximab and etanercept in treatment of RA & juvenile idiopathic arthritis, and infliximab for Crohns disease have been produced by the National Institute for Clinical Excellence (UK). The Canadian Coordinating Office for Health Care Technology (CCOHTA) has published overviews on etanercept for RA and infliximab for Crohns disease. These are included in the reference list at the end of this document.

2. CLINICAL EVIDENCE

2.1 Psoriasis and psoriatic arthritis (PA)

Although the cause and pathogenesis of psoriasis are unknown, genetic factors, immunological factors and environmental agents are believed to have a role.⁵ Although no autoantigen has been identified, there is probably enough circumstantial evidence to categorise the disease as autoimmune in nature.⁶ Several studies have demonstrated that TNF may be implicated in the pathogenesis of psoriasis^{7 8 9 10}.

The currently accepted definition of PA by Moll and Wright¹¹ is ‘an inflammatory seronegative arthritis accompanied by psoriasis’. They define 5 types of psoriatic arthropathy: asymmetrical oligoarticular arthritis, distal interphalangeal, mutilating, symmetrical polyarthritis and spinal form. It is not known why a subset of patients with psoriasis also experience joint manifestations. In approximately 75% of patients with PA, the appearance of skin lesions precedes arthritic symptoms¹². The onset and severity of PA may not correlate with onset and severity of psoriasis in any given

patient¹³. Treatment for PA depends on the extent of joint manifestations- mild symptoms may respond to physiotherapy and NSAIDs¹⁴. More severe disease is likely to require steroids or DMARDs. Evidence for MTX and other DMARDs is limited¹⁵; the use of these agents is largely predicated on the knowledge of their effectiveness in rheumatoid arthritis (RA).

2.1.1 Infliximab

A number of case reports and small case series have been published, however no double blind trials could be found which focussed on PA rather than psoriasis. Antoni et al¹⁶ treated 10 patients with severe PA with infliximab 5mg/kg at weeks 0, 2 and 6, with MRI objectively measuring joint inflammation at weeks 0 and 10. Based on patient response, treatment was individualised after week 10. Nine patients completed 54 weeks of treatment, with no discontinuations due to adverse events. Disease activity measures included the American College of Rheumatology ACR 20, ACR 50 and ACR 70¹⁷. The ACR criteria for arthritis improvement from baseline are defined as a 20%, 50% or 70% improvement in the number of swollen and tender joints, with a corresponding improvement in 3 of 5 additional categories (Patient Global VAS, Physician Global VAS, Health Assessment Questionnaire, ESR or CRP, and Patient VAS of pain). Eight patients attained ACR 70 responses by week 10, with 6 patients maintaining this response at the 54- week follow-up.

Six patients with progressive joint disease and psoriatic skin lesions unresponsive to methotrexate therapy were treated with infliximab 5mg/kg at weeks 0, 2 and 6 in an open label study¹⁸. All patients had polyarticular disease, with clinical and serological activity. At week 10 all patients showed sustained response. Median swollen joint count improved by 88%.

O'Quinn et al published case reports¹⁹ of single infusions of infliximab 5-10 mg/kg (with paracetamol and diphenhydramine pretreatment) in 2 patients. The first patient had a 17 year history of widespread psoriasis vulgaris, 7 year history of erythroderma and also PA of the distal interphalangeal (oedema and pain with active motion) and sacroiliac joints. Ten days after IV infusion of infliximab 10mg/kg, plaques were noticeably thinner to palpation, and the patient reported resolution of pain in the distal interphalangeal and sacroiliac joints. Fingers were clinically normal on examination with no pain on active motion. The second patient was a 33 year old woman with an 8 year history of psoriasis vulgaris, psoriatic arthritis (oedema, warmth and nearly incapacitating pain in the phalangeal joints) and inflammatory bowel disease. Within 24 hours of an intravenous infusion of infliximab 5mg/kg, the patient reported decreased erythema in the psoriatic plaques, and rapid resolution of abdominal symptoms. After two weeks, examination showed complete clearing of plaques, no erythema and minimal discomfort on active motion of interphalangeal joints.

Mang²⁰ presented a case report of a 41 year old male patient with a 23 year history of histologically proven chronic psoriasis and PA (acute mutilating psoriatic arthritis on bone scintigraphy and X-ray of the hands). He was given an IV infusion of infliximab 3mg/kg repeated at 3-4 weekly intervals. After 10 infusions, complete remission of psoriasis occurred and at 8 months, X-ray and bone scintigraphy showed a marked decrease in the uptake of tracer, indicating a decrease in joint inflammation.

2.1.2 Etanercept

The FDA approval for a licenced indication for etanercept in PA includes safety and efficacy data in 205 patients with at least 3 swollen and 3 tender joints, and plaque psoriasis with qualifying target lesion of at least 2 cm². The double blind placebo controlled study investigated the effects of etanercept 25mg or placebo administered subcutaneously (SC) twice weekly for 6 months. Compared to placebo, treatment with etanercept resulted in significant improvements in all measures of disease activity in psoriatic arthritis at 6 months ($p < 0.001$). The measures of arthritis disease activity included assessment of 78 joints for tenderness, 76 joints for swelling, physician and patient global assessments, patients assessment of pain and disability, and C-reactive protein serum concentration.

In a randomised double blind, single centre study, Mease et al²² treated 60 patients with psoriasis and PA (defined as 3 or more swollen joints and 3 or more tender or painful joints) with etanercept 25mg SC twice weekly, or placebo, for 12 weeks. The primary endpoint with respect to efficacy in PA was the proportion of patients who met the Psoriatic Arthritis Response Criteria (PsARC) at 12 weeks. This composite measure requires improvement in 2 factors, and no worsening in any of the following 4 factors: patient and physician global assessments and tender and swollen joint scores. A secondary endpoint was the proportion of patients with PA meeting ACR 20 criteria. For the primary endpoint, at 12 weeks, 26 etanercept-treated patients (87%) met the PsARC compared with 7 (23%) treated with placebo ($p < 0.0001$). The secondary endpoint, ACR20, was achieved by 22 (73%) of etanercept-treated patients compared with 4 (13%) placebo treated patients ($p < 0.0001$). The etanercept group at 12 weeks showed significant improvement in all measures of disease activity compared with placebo group ($p < 0.0002$)

Yazici et al^{23 24} surveyed the effectiveness of etanercept in severe, resistant PA (failure to respond to multiple DMARDs and/or immunosuppressive agents) in 10 patients for periods of up to 26 months. Etanercept was initially administered at a dose of 25mg SC twice weekly and assessment was by way of physical examination and Health Assessment Questionnaire (HAQ). Prior to commencement of etanercept, patients had a mean of 6.1 (range 3-10) actively inflamed joint areas. At 3 months, this had decreased to a mean of 1.1 areas, and 5 patients were without any active joint disease. At 12 months, 8 of 10 patients were still on etanercept (one patient was discontinued because of osteomyelitis and one swapped to infliximab due to increased disease activity). At 2 years duration of therapy, six patients were receiving etanercept 25mg SC twice weekly and two were receiving 25mg SC every 10 days. Four patients had no swollen or tender joints. Whilst acknowledging the methodological deficiencies of an open label study, the authors noted the promising results of etanercept therapy in their cohort of patients and recommended outcomes and adverse event profiles of different frequencies of etanercept administration should be explored in large, randomised trials.

Aboulafia et al²⁵ described a case report of a hospitalised patient with AIDS who was treated with etanercept, 25mg sc twice weekly, for rapidly progressive and debilitating PA (He was unable to walk and had difficulty feeding himself because of wrist pain and finger deformities). Within 3 weeks his skin lesions had improved dramatically and joint inflammations stabilised, and after 8 weeks he could walk with a cane and use his hands for activities of daily living. Despite improvement in his psoriasis and PA, etanercept was discontinued due to recurrent bacterial infections.

2.2 Ankylosing spondylitis(AS)

Ankylosing spondylitis is a chronic disease with a poorly defined aetiology and complex pathogenesis²⁶ and is characterised by progressive spinal ankylosis and deformity.

AS is associated with HLA-B27 in 90% of patients. HLA-B27 has a role in the binding of antigenic peptides and their presentation to CD8 T cells. HLA-B27 restricted cytotoxic T cells with specificity for bacteria, viral peptides or autoantigens that cause arthritis (such as peptides derived from the HLA-B27 molecule itself), have been identified in patients with AS^{27 28}. There is conflicting information about the levels of TNF alpha and its polymorphisms in AS²⁹.

There is no single laboratory marker shown to accurately reflect disease activity in response to treatment in AS³⁰. However, MRI may prove useful for assessing specific features of AS such as periosteal reactions and ectopic ossification of ligaments³¹ and thus treatment response. Objective evidence of improvement demonstrated with a 99m Tc-MDP bone scan has been reported in a patient with AS³². Non steroidal antiinflammatory drugs (NSAIDs) are the current basis of drug therapy for AS¹⁵.

2.2.1 Infliximab

Braun et al assessed the effectiveness of infliximab in 70 patients with active AS (classified according to modified New York criteria) in a multicentre placebo controlled trial³³. Patients received infliximab 5mg/kg or placebo at weeks 0,2 and 6. The primary outcome measure was regression of disease activity of at least 50%, using the Bath Ankylosing Spondylitis Disease Activity Index-BASDAI³⁴. Fifty three percent of patients treated with infliximab achieved a 50% improvement in the measure of disease activity at week 12 as opposed to 9% of placebo treated patients. Treatment was generally well tolerated but 3 patients had to stop treatment, because of systemic tuberculosis, allergic granulomatosis of the lung, or mild leucopenia.

Twenty patients from the above trial (11 placebo and 9 infliximab) were included in a study³⁵ to evaluate a scoring system for spinal changes in AS, the first report of a systematic analysis of inflammatory and structural spinal changes as assessed by MRI in patients with AS undergoing infliximab therapy. Clinical examination and MRI were performed at baseline and after 12 weeks, and a clear correlation was seen when clinical findings were compared with MRI results.

Stone et al³⁶ enrolled 21 patients in an **open label** trial to receive infliximab 5mg/kg at 0,2, and 6 weeks. Patients were assessed at baseline and at week 14 using 9 functional indices including BASDAI and the Health Assessment Questionnaire (HAQ). The primary definition of response was at least 20% improvement in 5 of 9 indices after 3 infusions. At 14 weeks there was greater than 75% improvement in BASDAI, BASFI, patient global assessment, physician global assessment, spinal pain, total body pain and HAQ scores in the 18 evaluable patients. Eight patients underwent pre and post-infusion magnetic resonance imaging to evaluate inflammatory imaging changes, to resolve whether the clinical response correlated with changes in MRI imaging. Imaging studies were reviewed, 48 hours after infusion and compared to baseline imaging. After 2 infusions there was mild improvement in four patients, moderate improvement in three patients and one patient was stable

An **open pilot** study³⁷ of 11 patients with severe AS of relatively short duration (median 5 years) found that disease activity (measured by outcome parameters BASDAI, visual analogue spinal pain scale, Bath AS Functional Index³⁸ and Bath AS Metrology Index³⁹) was improved after treatment

with infliximab 5mg/kg at weeks 0, 2 and 6. Improvement of at least 50% in activity, function and pain scores was documented in nine out of ten patients and a median improvement in the BASDAI of 70% after 4 weeks was observed. Ten patients were enrolled into a one-year extension of the study⁴⁰, with additional infusions given only if there had been a clear-cut relapse of disease. Six patients received all 3 infusions and 4 patients withdrew prior to one year (2 had allergic reactions). A relapse (80% or greater of the baseline BASDAI value) occurred after 3-21 weeks (median 12 weeks) in 9 patients, who subsequently received the 4th infusion.

An **open-label** study of 21 SpA patients with longer disease duration has been subjected to subgroup analysis and the results published⁴¹. Eleven patients suffering from AS (classified according to modified New York criteria), received 3 infusions of infliximab 5mg/kg at weeks 0, 2 and 6. A significant reduction of tender and swollen joint count was seen from day 3 onwards. In an extension protocol of the initial pilot study, all patients were retreated every 14 weeks for a total of 12 months with an infusion of 5mg/kg. Subgroup analysis data was not presented however the authors conclude that improvement of all disease manifestations was maintained over a one-year period.

Maksymowych⁴² evaluated the use of a lower dose of infliximab, 3mg/kg, in 21 patients with AS. Doses were given at 0, 2, and 6 weeks and then every 2 months for approximately 16 months. Four patients withdrew (2 for serious adverse events: 1 with septic osteomyelitis, 1 with severe hypersensitivity after 3 and 2 infusions respectively). The mean BASDAI improved significantly from baseline to 14 weeks in the 17 evaluable patients (6.2 to 2.8; $p < 0.001$). Complete remission of peripheral joint disease was seen in 45.4% of patients (5 of 11) evaluated at 14 weeks. Only three patients required an increased dose to 5mg/kg after 14 weeks.

2.2.2 Etanercept

Gorman et al⁴³ conducted a randomised double blind controlled trial in 40 patients with active inflammatory AS (according to modified New York Clinical Criteria definition⁴⁴). They received etanercept 25mg or placebo twice weekly for 4 months, with an optional six-month open label extension. The primary outcome measure was a composite response, defined as 20% or greater improvement in at least 3 of 5 measures of disease activity, as recommended by the Assessments in Ankylosing Spondylitis Working Group⁴⁵. Response rate at 4 months was 80% in the etanercept group and 30% in the placebo group ($p = 0.004$). The most common adverse events were injection site reactions, and minor uncomplicated infections of the respiratory tract, that occurred in 10 etanercept treated patients and 12 placebo treated patients. One patient had tinnitus and increased frequency of pre-existing muscle fasciculations.

Barthel⁴⁶ has reported 2 patients treated with etanercept 25mg twice weekly who had rapid and profound symptom relief and have continued to derive benefit at 12 month follow up.

2.3 Crohns

A subgroup of patients with Crohn's disease fulfils the criteria for spondyloarthropathy. Although infliximab has become a registered therapy for patients with Crohn's disease, the efficacy of this treatment for arthritis symptoms associated with the disease has not been properly studied. Van den Bosch⁴⁷ treated 4 patients with refractory Crohn's disease associated with spondyloarthropathy

and found that the infliximab 5mg/kg induced remission of GIT symptoms and also articular symptoms. No side effects were recorded.

2.4 Undifferentiated spondylarthropathy (SpA)

D'Agostino et al ⁴⁸ report their experience with 2 HLA- B27 positive SpA patients who had refractive (defined as 2 years) erosive calcaneal enthesitis without other articular or axial symptoms. After treatment with infliximab 3mg/kg at weeks 0, 2 and 6, both patients experienced significant remission as documented by ultrasonography.

Marzo-Ortega et al performed a descriptive longitudinal study ³¹ of 10 SpA patients to determine the effects of 6 months treatment with etanercept 25mg twice weekly, on the clinical manifestations of resistant SpA and on axial and peripheral enthesal lesions using magnetic resonance imaging (MRI). There was a statistically significant improvement in all clinical and functional parameters. Nine patients had a total of 44 MRI-detectable enthesal lesions. Overall 86% of MRI detected enthesal lesions either regressed completely or improved.

Brandt et al reported use of 2 dosage regimens of infliximab (3mg/kg or 5mg/kg) in 6 undifferentiated SpA patients with refractory disease ⁴⁹. Doses were given at 0, 2 and 6 weeks and patients observed for a total of 12 weeks. As there are no validated outcome measures in undifferentiated SpA at present the authors chose to use the core set of endpoints for AS ⁵⁰. At least 50% improvement in outcome variables was observed in the 5mg/kg group as compared with a 15% or greater improvement in the 3mg/kg group.

3 ADVERSE EFFECTS

Both infliximab and etanercept have been used in tens of thousands of patients and thus the safety databases are extensive. Since TNF influences cellular immunity and modulates inflammatory responses these agents may affect host defences against malignancies and infections ⁵¹

Infliximab has been associated with a number of adverse events; infusion reactions are reported in 19% of patients in clinical trials and consist of fever or chills, and more rarely chest pain, hypotension, dyspnoea, pruritis and urticaria. Neutralising antibodies are formed and patients can develop a serum sickness reaction days after administration. Infections are common in infliximab treated patients, possibly because many patients receive other immunosuppressive therapies ⁵¹. Mycobacterial infections have been reported, suggesting reactivation of latent tuberculosis ⁵². However in controlled clinical trials there does not appear to be an increased risk of serious infection in infliximab treated patients. ⁵¹

The approved Australian product information for Remicade[®] ⁵³ states that the drug is contraindicated in patients with severe infections eg sepsis, abscesses, tuberculosis and opportunistic infections, and patients who clinically manifest these conditions must be treated prior to therapy with Remicade[®].

Unlike infliximab, which is a chimeric monoclonal antibody, etanercept is fully humanized, resulting in substantially less immunogenicity. However, the approved Australian product information for Enbrel[®] ⁵⁴ states that treatment should not be initiated in patients with active infections, and list patients with or at risk of sepsis as a contraindication. Rare cases of

pancytopenia and very rare cases of aplastic anaemia have been reported in patients on etanercept. There have been post marketing and trial reports of worsening of congestive heart failure in patients treated with etanercept. Recently a case of mycobacterium tenosynovitis was reported in a patient receiving etanercept 25mg twice weekly for 8 months⁵⁵

Postmarketing reports to the FDA up to July 2001(all indications) have identified invasive fungal diseases⁵⁶, demyelinating diseases⁵⁷, and lymphoproliferative disorders⁵⁸ in association with infliximab and etanercept therapy. The Australian Adverse Drug Reaction Advisory Committee (ADRAC) had received up to November 2002 a total of 36 reports for infliximab (including 33 where it was the sole suspected drug). Amongst these were malignant lymphoma (1 case), bronchospasm (2) and leucocytosis(1). For etanercept, ADRAC had received 6 reports to November 2002, with one case of pneumonia and one case of purpura, where etanercept was the sole suspected drug.

Long term data on adverse events is not available at present.

4 ECONOMIC DATA

Zink⁵⁹ and Boonen⁶⁰ have identified the socioeconomic burden associated with AS. Zink et al⁵⁹ described a database containing the case mix and demographics of 25,653 German patients with inflammatory rheumatic diseases of whom 23% had seronegative spondyloarthropathies including AS, PA and reactive arthritis. Boonen et al⁶⁰ investigated the cross sectionally prevalent employment, work disability and sick leave in Dutch patients aged 16-60 years with AS who regularly visit a rheumatologist. They report an 11% decrease in employment (more pronounced for men) and a 15% increase in work disability-8.8 and 15.3 days of sick leave per patient per year in addition to the non specific absence reported for the general population.

Etanercept is listed on the Australian Pharmaceutical Benefits Scheme (PBS), under both S85 and S100. The general listing (authority required) is for adults with severe active RA who are rheumatoid factor positive and fulfil certain other criteria. The S100 listing is for paediatric patients with severe active polyarticular course juvenile chronic arthritis, and private hospital authority is required.

Infliximab has also been listed on the PBS under the Repatriation Benefits schedule, for refractory RA of specific accepted war- caused or service-related disability. Criteria include no history of opportunistic infections in the last 2 months and not history of active tuberculosis requiring treatment in the last 3 years.

However, no cost effectiveness data could be found for etanercept or infliximab in patients with spondylarthropathies.

5 PLACE IN THERAPY

In assessing the evidence for these agents the considerable variation in trial methodology when determining diagnostic criteria, failure of standard therapy, exclusion criteria and criteria for withdrawal of therapy, places limitations on conclusions that can be reached. Even in the controlled trials, changes observed were mostly subjective.

Practical considerations include

- The need to have the patient ‘infection free’ prior to commencement of therapy. European Consensus guidelines on TNF inhibitors⁶¹ recommend a chest Xray and Mantoux test prior to treatment and the Australian Rheumatology Association recommends CXR and Mantoux on all patients starting these treatments regardless of their underlying medical condition. (personal communication Dr J Bertouch)
- The relative safety and efficacy of infliximab versus etanercept in seronegative arthropathies of all types is not defined. Since it appears that most patients will require at least 5mg/kg of infliximab it is possible that this dose will produce more problems eg with infection in the longer term
- There is no data to guide the duration of therapy. It is likely that patients will rapidly relapse as soon as either infliximab or etanercept is ceased.
- The subcutaneous route of administration of etanercept allows for dosing at home or as an outpatient; administration of infliximab intravenous infusions must be done under medical supervision (generally in hospital).

6 RECOMMENDATIONS

Clinical evidence supports a trial of infliximab in patients with inadequately controlled psoriatic arthritis and ankylosing spondylitis.

Clinical evidence supports a trial of etanercept in inadequately controlled psoriatic arthritis and ankylosing spondylitis.

There is no evidence that either TNF alpha agent should be used before the other can be tried.

Combination of either infliximab or etanercept with methotrexate may allow lower doses of the DMARD to be used, thus reducing potential for toxicity and reducing cost.

These agents should be reserved for patients in whom more conventional therapies have failed. There is a need to identify those patients most likely to benefit from TNF alpha inhibition, from the perspectives of cost and also possible long-term side effects.

GUIDANCE DOCUMENTS CITED:

National Institute for Clinical Excellence Technology Appraisal Guidance No 36: Guidance on the use of etanercept and infliximab for the treatment of rheumatoid arthritis. March 2002

National Institute for Clinical Excellence Technology Appraisal Guidance No 35: Guidance on the use of Etanercept for the treatment of Juvenile Idiopathic Arthritis. March 2002

National Institute for Clinical Excellence Technology Appraisal Guidance No 40: Guidance on the use of Infliximab for Crohns Disease

Canadian Coordinating Office for Health Technology Assessment Issues in Emerging Technologies: Etanercept- Antitumour Necrosis Factor Therapy for Rheumatoid Arthritis
Canadian Coordinating Office for Health Technology Assessment Technology Overview: Clinical and Economic Assessment- Infliximab for the Treatment of Crohns Disease.

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