Anti-TNF agents for rheumatoid arthritis

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Rheumatoid arthritis (RA) is a chronic inflammatory, autoimmune disease with a prevalence of approximately 1% and an annual incidence of 0.04%. Up to 50% of patients with RA are unable to work 10 years after diagnosis. The disease is associated with significant morbidity and mortality with associated medical costs to the UK of between £240 M and £600 M per year.

Non steroidal anti-inflammatory drugs (NSAIDs) have little effect on the underlying course of RA, but they have some anti-inflammatory and analgesic properties. Disease modifying antirheumatic drugs (DMARDs) have been shown to slow progression of RA and are currently recommended early in the course of treatment of RA which is when disease progression is most rapid.

Etanercept and infliximab belong to a new group of parentally administered antitumour necrosis factor (TNF) drugs.

Etanercept is licensed in the UK for the treatment of active rheumatoid arthritis in patients who have not responded to other DMARDs and in children with polyarticular-course juvenile arthritis who have not responded to or are intolerant of methotrexate. In adults it produces significant improvements in all measures of rheumatic disease activity compared to placebo. In patients whose disease remains active despite methotrexate treatment, further improvement in control is obtained with the addition of etanercept without an increase in toxicity. In one small trial, etanercept was found to be more effective than placebo in a selected group of children.

Infliximab is a monoclonal antibody which is currently licensed in the UK for Crohn's disease and, in combination with methotrexate for the treatment of rheumatoid arthritis in patients with active disease when the response to disease-modifying drugs, including methotrexate, has been inadequate. In clinical trials infliximab produced significant improvements in all measures of rheumatic disease activity compared with placebo. Infliximab in combination with methotrexate was shown to be superior to methotrexate or infliximab alone.

There are currently no predictors of a good response to anti-TNF drugs and a percentage of patients fail to respond to treatment (25% to 38% of etanercept patients; 21% to 42% of infliximab patients). Infliximab monotherapy induces the production of anti-infliximab antibodies, which may reduce its effectiveness. Adding methotrexate to infliximab therapy may prevent this response.

Anti-TNF drugs may affect host defences against infection and malignancy; whether these agents affect the development and course of malignancies and chronic infections is unknown and safety and efficacy in patients with immunosuppression or chronic infections has not been investigated. With infliximab, upper respiratory tract infections, general infections and those requiring antimicrobial treatment were more common in patients than placebo. Likewise, upper respiratory tract infections were more common in patients treated with etanercept than with placebo. Injection site reactions occur with both infliximab (16%–20%) and etanercept (37%).

There are approximately 600 000 patients with RA in the UK, and of these between 2% and 3.5% may have severe disease which has failed to respond to conventional treatment and who might be eligible for anti-TNF therapy. If between 50% and 70% of patients treated with anti-TNF drugs respond and continue on long-term treatment then the recurrent annual cost to the NHS could be between £48 M and £129 M.

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory, autoimmune disease that affects joints and other tissues. It has a prevalence of approximately 1% and an annual incidence of 0.02–0.04% or between two and four cases per 10 000 adult population [1–3]. Onset commonly occurs between the ages of 25 and 50 years. Generally half of patients are unable to work 10 years after disease onset [4]. The estimated annual cost of RA to the NHS is between £240 M and £600 M [5].

The synovial joints are most commonly affected but the inflammatory process can affect almost every tissue in the body. Onset is usually insidious and affects multiple joints. Synovial thickening occurs in most joints and joint inflammation and cartilage destruction lead to loss of mobility. These changes are commonly seen within the first 2 years of disease onset [6–7].

RA is associated with substantial morbidity and mortality and the diminished survival of these patients is similar to that seen in patients with diabetes or coronary heart disease [8–9]. In one follow up study median life expectancy was reduced by 7 years in men and 3 years in women [8].

Rheumatoid arthritis generally follows one of three routes of disease progression, progressive, intermittent or malignant. About 70% of patients with RA have progressive disease, which follows a chronic pattern with periods of exacerbation and remission. A further 25% of patients have intermittent disease which is characterized by brief attacks of inflammation with intermittent remissions in which there is little or no disease activity. The remaining 5% of patients have a malignant form of disease with extra-articular manifestations such as vasculitis.

Predictors of poor response to treatment in RA include more than 20 joints affected, functional disability within 1 year of onset of disease, extra-articular involvement and persistently abnormal markers of inflammation (ESR, CRP) [9].

Current management options

Treatment of RA generally involves a multimodal approach. Pharmacological treatment is used to control inflammation together with physiotherapy and surgery.

Non-steroidal anti-inflammatory drugs (NSAIDs) reduce inflammation and pain, but do not necessarily reduce cartilage erosion nor alter disease progression. Disease modifying antirheumatic drugs (DMARDs) delay disease progression, reduce cartilage erosion and provide analgesia and are now advocated in the early stages of the disease [5, 10, 11].

The DMARDs include the antimalarials, sulphasalazine, gold, D-penicillamine, corticosteroids, methotrexate, azathioprine, cyclophosphamide, chlorambucil, and cyclosporin. Each of these agents has a different mechanism of action, clinical efficacy and adverse effect profile. Clinical trials have demonstrated little difference in activity between methotrexate, D-penicillamine, injectable gold, auranofin, and hydroxychloroquine [12–13]. One meta-analysis suggested that there was no overall benefit from combination therapy, with a consequential increase in toxicity [12]. However, other studies have demonstrated increased efficacy compared with single agent therapy, both in early and late stage disease [14]. Specialist opinion is that combination treatment in selected patients can be very effective.

In practice, initial treatment of RA is generally with a single agent, usually sulphasalazine. If a satisfactory response is not achieved with a single agent after a period of between 3 and 6 months, then combination treatment is given, normally with the addition of methotrexate. Patients who fail to respond to such combination treatments are offered other therapeutic options, for example cyclosporin. However, some patients fail to respond to existing DMARDs, either due to disease resistance or drug toxicity.

In this review we report on the efficacy and place in treatment of two TNF-alfa modifiers, etanercept (Enbrel®, Wyeth) and infliximab (Remicade®, Schering-Plough).

Assessment of drug effectiveness

In the past, the outcome criteria used in clinical trials to determine the effectiveness of new anti-RA agents has varied making the comparison between agents and between clinical trials difficult. Two well accepted composite measures of disease improvement have emerged; the Paulus Index and the American College of Rheumatology Index (ACR) (Table 1). The ACR Index is rapidly becoming the gold standard in the assessment of disease severity in RA; a 20% improvement in the index (ACR20) is measurable but is not clinically significant, a 50% improvement (ACR50) is clinically important and a 70% improvement (ACR70) is 'spectacular' [15].

A large number of outcome variables used to assess efficacy in clinical trials, especially in RA, are self reported by patients (e.g. pain scores, patients' assessment of disability, patients' assessment of disease status, duration of morning stiffness, etc.). These are subject to expectation bias which may account for the high response rates in placebo treated patients [16]. Bias may also occur when there is unintentional unblinding e.g. due to injection site reactions (e.g. etanercept, infliximab).

Table 1 Health assessment scales

Scale	*Description*
Paulus index	A composite index for estimating improvement in RA in response to DMARDs. An improvement by 20% in each of 4 of 6 possible measures is required to demonstrate a Paulus 20 response. The measures are: improvement in tender and swollen joint counts; morning stiffness; patients' disease assessment; physicians' disease assessment; and erythrocyte sedimentation rate (ESR) [31].
ACR	Revised criteria (1987) for RA classification by the American College of Rheumatology are: i) Morning stiffness ≥ 1 h ii) Soft tissue swelling (arthritis) of 3 or more joints observed by physician iii) Swelling of proximal interphalangeal, metacarpophalangeal or wrist joints iv) Symmetric swelling (arthritis) v) Rheumatoid nodules vi) Presence of rheumatoid factor vii) Radiographic erosion and/or periarticular osteopenia in hand or wrist joints. Criteria 1–4 must have been present for at least 6 weeks.
ACR patient classification	i) Class I patients able to perform usual activities of daily living ii) Class II able to perform self-care, vocational activities, but limited avocational activities iii) Class III able to perform self-care, not others iv) Class IV limited ability in self-care
ACR20/50/70 response	20%/50%/70% reduction in tender joint count and swollen joint count (≥ 28 joints assessed) and a 20%/50%/70% improvement in at least three of the following i) Patients' assessment of pain ii) Physician's assessment of disease status iii) Patients' assessment of disease status iv) Patients' assessment of disability (functional questionnaire) v) Acute phase reactant measures (ESR) It has been suggested that a 50% improvement is a more direct indication of suppression of active disease than 20% [32].
Health assessment Questionnaire (HAQ)	A disease specific questionnaire, 20 questions divided into 8 functional categories (2–3 questions per category, i.e. walking, dressing, grooming, etc.), 0 = without difficulty, 3 = unable to do [33].

Clinical efficacy of individual agents

Several anti-TNF alfa products are either in development or undergoing clinical trials. Etanercept is licensed in the UK for the treatment of active RA in patients who have not responded to other DMARDs and in children with poly articular juvenile arthritis who have not responded to or are intolerant of methotrexate. Infliximab, is licensed in the UK for the treatment of Crohn's disease and in combination with methotrexate for the treatment of rheumatoid arthritis in patients with active disease when the response to disease-modifying drugs, including methotrexate, has been inadequate.

Tumour necrosis factor (TNF) is a pro-inflammatory agent which is formed in the macrophages and T cells and is responsible for joint destruction and synovitis. There are two cell-surface TNF receptors (TNF_R), p55 and p75, which mediate the activity of TNF on effector cells. There are also soluble TNF receptors which act as regulators of the inflammatory response by inhibiting TNF activity.

Etanercept

Etanercept is a recombinant human TNF dimeric receptor fusion protein, which consists of the extracellular portion of two p75 receptors fused to the Fc portion of IgG1. To date, there are four published, double-blind, randomized trials in which the clinical efficacy of etanercept has been investigated, three in adults and one in children.

A multicentre, double-blind, phase II trial involved 180 patients who had refractory RA [17]. All patients had been unsuccessfully treated with between one and four DMARDS (azathioprine, hydroxychloroquine, oral/parenteral gold, methotrexate, penicillamine, and sulphasalazine) and had at least 12 tender joints, 10 swollen joints (71 joints evaluated for swelling and 68 for tenderness) and ESR ≥ 28 mm h^{-1} or CRP ≥ 2 mg dl^{-1}, and morning stiffness for more than 45 min. All patients underwent a 4-week washout period of DMARDs. Corticosteroids (≤ 10 mg day^{-1}), NSAIDs and analgesics (coproxamol, cocodamol, etc.) were permitted during the trial provided that dose had remained stable 4 weeks prior to the trial. The patients were randomised to one of the four treatment groups, etanercept 0.25 mg, 2 mg or 16 mg m^{-2} or placebo, administered as a subcutaneous injection twice weekly for 3 months. The degree of disease activity was assessed at trial onset. The primary endpoints were change from baseline in the swollen joint and tender joint count. Secondary endpoints included level of pain (visual analogue scale), duration of morning stiffness, CRP,

ESR levels, quality of life and the patient and physician's global assessment (HAQ, 45 = best, 245 = worst). ACR20 to ACR50 improvements in disease activity were also measured at 3 months.

Etanercept produced statistically significant improvements in all measures of disease activity compared with placebo. After 3 months of treatment the total tender or swollen joint count was reduced by 61% in the etanercept 16 mg group compared with 25% reduction in the placebo group ($P<0.001$). Similarly, 57% of patients in the 16 mg group had an ACR50 improvement compared with 7% of patients in the placebo group ($P<0.001$). ACR20 improvement in symptoms was noted by 75% of patients in the 16 mg group compared with 14% of patients in the placebo group ($P<0.001$). Etanercept produced improvements in pain, falls in ESR and CRP and improved patients' global assessments with respect to quality of life markers. However, these measures of disease activity began to return to baseline values after termination of treatment, although the time course of this was not reported.

A second study recruited 89 patients with persistent RA, who were classified as being class I, II or III (ACR) and had active disease defined as ≥ 6 swollen joints and ≥ 6 tender joints for at least 6 months [18]. All patients had previously received methotrexate for at least 6 months prior to the trial, and this was continued during the trial at a mean weekly dose of between 18 and 19 mg. In addition to methotrexate, patients were randomised to receive either a subcutaneous injection of etanercept 25 mg or placebo twice weekly for 24 weeks. Patients were permitted to take NSAIDs and prednisolone (≤ 10 mg daily) during the trial, provided that doses remained stable. The primary outcome was ACR20 at 24 weeks; other endpoints included ACR20 at 12 weeks, ACR50 and 70 at 12 and 24 weeks, number of tender and swollen joints, and physician's global assessment.

Three percent of patients treated with etanercept failed to complete 24 weeks of the study. The number of patients achieving ACR20 was significantly higher in the etanercept group compared with placebo at both 12 weeks (66% *vs* 33%, $P=0.003$) and 24 weeks (71% *vs* 27%, $P<0.001$). At 24 weeks the median tender joint count (75% *vs* 39%) and median swollen joint count (78% *vs* 33%) were reduced by etanercept compared to placebo groups. An ACR50 improvement at 24 weeks was achieved in 39% of the etanercept group and 3% in the placebo group ($P<0.001$).

A phase III randomised double blind study recruited 234 patients with class I, II, or III RA (defined by ACR criteria) who had inadequate response to DMARDs (87% had previously received methotrexate), and who also had ≥ 12 tender joints and ≥ 10 swollen joints, and either raised ESR ≥ 28 mm h^{-1}, raised CRP ≥ 2 mg dl^{-1} or morning stiffness ≥ 45 min [19]. Patients were randomised to receive either etanercept 10 mg, 25 mg or placebo by subcutaneous injection twice weekly for 26 weeks. Administration of DMARDs was not permitted during the trial and a 1 month washout period was required. NSAIDs and oral corticosteroids (equivalent to prednisolone ≤ 10 mg daily) at stable doses were permitted. The primary endpoints were either an ACR20 or ACR50 improvement in disease at 3 and 6 months. ACR70 and Paulus assessments were also included as secondary endpoints. The drop out rates at 6 months were 24%, 32% and 67% for etanercept 25 mg, 10 mg and placebo, respectively ($P<0.001$ etanercept *vs* placebo). At 3 months of treatment the number of patients achieving an ACR20 was 62% and 23% for etanercept 25 mg and placebo, respectively ($P<0.001$). After 6 months ACR20 was achieved in 59% (25 mg group), 51% (10 mg group) and 11% (placebo group) ($P<0.001$ etanercept *vs* placebo), and similarly ACR50 was achieved in 40% (25 mg group), 24% (10 mg group) and 5% (placebo group) ($P<0.001$ etanercept *vs* placebo). ACR70 was achieved in 15% (25 mg group), 9% (10 mg group) and 1% (placebo group) after 6 months of treatment ($P=0.031$ etanercept 10 mg *vs* placebo and $P<0.001$ for 25 mg *vs* placebo). The mean tender joint count was reduced by 56% in the 25 mg group, 44% in the 10 mg group and 6% in the placebo group ($P<0.05$ etanercept *vs* placebo). Minimal disease, defined as 0–5 tender or swollen joints was achieved in 17% of the 25 mg group, 14% of the 10 mg group and 3% of the placebo group ($P<0.005$ etanercept *vs* placebo).

Table 2 Percentage improvements in ACR response from baseline for infliximab and placebo at 30 weeks [25].

Index	*Placebo*	*Infliximab* (P *values vs placebo)* *3 mg kg^{-1}/4 weeks*	*3 mg kg^{-1}/8 weeks*	*10 mg kg^{-1}/4 weeks*	*10 mg kg^{-1}/8 weeks*
ACR20	20%	53% ($P<0.001$)	50% ($P<0.001$)	58% ($P<0.001$)	52% ($P<0.001$)
ACR50	5%	29% ($P<0.001$)	27% ($P<0.001$)	26% ($P<0.001$)	31% ($P<0.001$)
ACR70	0%	11% ($P<0.001$)	8% ($P=0.002$)	11% ($P=0.007$)	18% ($P=0.002$)

Table 3 Comparative costs of DMARDs

Drug	*Dose*	*Cost for 1 years (£)**
Methotrexate	7.5–20 mg weekly	22–59
Sulphasalazine EC	500 mg qds	126
Cyclosporin	3 mg kg^{-1} day^{-1} (70 kg)	1,957
Gold	50 mg i.m. monthly	112
Hydroxychloroquine	200 mg bd	55
Penicillamine	500 mg daily	125
Leflunomide	20 mg daily	566
Etanercept	25 mg s.c. twice weekly	8,082
Infliximab	3 mg kg^{-1} at 0, 2, 6 and every 8 weeks (9 doses per in subsequent years) (<67 kg–>67 kg)	8122–12 182 1st year 5866–8798 subsequent years

*Drug Tariff/MIMS June 2000.

Paulus 20% responses were achieved in 68%, 64% and 16% of patients in etanercept 25 mg, 10 mg and placebo, respectively ($P<0.001$ etanercept *vs* placebo).

In a two part study 69 children (4–17 years old) with active polyarticular juvenile rheumatoid arthritis despite treatment with NSAIDs and methotrexate were given etanercept (0.4 mg kg^{-1} subcutaneously twice weekly) for up to 3 months [20]. Stable doses of NSAIDs and low dose corticosteroids were permitted during the study. Patients whose condition had improved (defined as a 30% improvement in at least three of the following variables: global assessments by physician and patient or parent, number of swollen joints, number of joints with limited motion, functional ability, and ESR) were then randomised to receive either etanercept or placebo until disease flare (change of 30% in three of the disease variables from baseline at entry into double blind trial and a minimum of two active joints) occurred or 4 months had elapsed. Fifty-one patients entered the double-blind phase with a significantly higher number of patients in the placebo group using corticosteroids. By the end of the open label study 74% of patients had an improvement and in some patients this occurred 2 weeks after starting treatment, 64% had a 50% improvement and 36% had a 70% improvement. In the double-blind phase significantly fewer patients receiving etanercept had a disease flare compared with placebo (28% *vs* 81%, $P=0.003$). The median time to flare was 116 days in the etanercept group and 28 days in the placebo group ($P<0.001$). After 7 months of treatment 80% of patients in the etanercept group had improved compared with 35% of the placebo patients ($P<0.01$). 72% of patients receiving etanercept had a 50% improvement compared with 23% of placebo patients and 44% *vs* 19% had a 70% improvement.

Infliximab

Infliximab or chimeric A2 is a mouse-derived IgG1κ monoclonal antibody which neutralizes the biological activity of human tumour necrosis factor alpha (TNFα). Infliximab inhibits the binding of TNFα to its target receptors and also inhibits the production of other pro-inflammatory cytokines, namely interleukin and granulocyte colony stimulating factor. Small studies have demonstrated clinical benefit from infliximab in RA [21–22].

In a small, double-blind study, 73 patients with active RA (as defined by ACR with ≥ 6 tender or painful joints, morning stiffness ≥ 45 min, ESR ≥ 28 mm h^{-1} for 6 months duration while receiving at least one DMARD) were randomised to receive either infliximab low dose (1 mg kg^{-1}), high dose (10 mg kg^{-1}) or placebo as a single infusion [22]. NSAIDs and oral corticosteroids (≤ 12.5 mg daily) were permitted during the trial, provided that doses remained stable. At 4 weeks significantly more patients receiving infliximab had a response, using the Paulus 20% criteria (Table 1) (8%, 44%, 79% for placebo, low dose and high dose, respectively, $P=0.0083$ for low dose *vs* placebo and $P<0.0001$ for high dose *vs* placebo). Analysis of the Paulus 50% response showed improvement in 8% of placebo patients and 28% and 58% from the low dose and high dose groups, respectively ($P=0.138$ low dose *vs* placebo, $P=0.0005$ 10 mg *vs* placebo). Reductions in levels of CRP and ESR were not statistically significant at 4 weeks in the low dose group, nor was the improvement in morning stiffness. However, a statistically significant difference was observed in these markers with the high dose group (ESR, $P<0.001$ *vs* placebo, CRP, $P<0.001$ *vs* placebo).

The same authors examined the clinical efficacy of repeated therapy with infliximab [23]. Seven patients from the original study were treated with infliximab (10 mg kg^{-1}) for a total of four drug cycles. Treatment was initiated at the point of relapse of initial treatment and the study extended by between 17 and 108 weeks. Of the seven patients only two completed four full cycles, due to adverse drug reactions (72% drop out rate). The study showed that flares of RA could be controlled with 10 mg kg^{-1} of infliximab. However, relapse after treatment withdrawal was evident.

A double-blind, multicentre, placebo-controlled trial recruited 101 patients with active RA (ACR criteria), who had failed to respond to low dose methotrexate (7.5–15 mg $week^{-1}$ for a minimum of 6 months) [24]. Patients were randomised to receive either an intravenous infusion of infliximab (1, 3 or 10 mg kg^{-1}) with or without methotrexate (7.5 mg $week^{-1}$) or placebo with methotrexate 7.5 mg $week^{-1}$ at weeks 0, 2, 6, 10, and 14; patients were followed up until week 26. All

DMARDs were withdrawn prior to the trial. Stable doses of NSAIDs and corticosteroids were permitted. The primary endpoint was the duration of treatment response, assessed using the Paulus 20% index. The median duration of response in the placebo plus methotrexate group was zero. With infliximab 1 mg kg^{-1} the median duration of response was 2.6 weeks (P=ns *vs* placebo), which extended to 16.5 weeks in patients also receiving methotrexate ($P<0.001$ *vs* placebo). Similarly with infliximab 3 mg kg^{-1} a response was achieved for a median of 17.2 weeks and 16.5 weeks when combined with methotrexate. Infliximab 10 mg kg^{-1} extended the median response period to 10.4 weeks when used alone and to more than 18.1 weeks when combined with methotrexate ($P<0.001$ *vs* placebo in both groups, P=ns between infliximab groups). A similar trend was noted with the Paulus 50% index.

A large multicentre, double-blind, study included 428 patients who had active RA (ACR criteria together with $\geq$6 swollen or tender joints and two of the following, $\geq$45 min morning stiffness, ESR $\geq$28 mm h^{-1} or CRP $\geq$2 mg dl^{-1}), and who had received methotrexate at a stable dose of 12.5 mg $week^{-1}$ for at least 3 months prior to the trial [25]. Patients were randomised to receive placebo or one of four possible infliximab regimens (3 mg kg^{-1} injection every 4 weeks or 8 weeks or 10 mg kg^{-1} every 4 weeks or 8 weeks) for 30 weeks. Methotrexate was continued during the trial at a median dose of 15 mg $week^{-1}$. NSAIDs and oral corticosteroids were permitted during the trial provided that doses remained stable 4 weeks prior to the trial. All patients were given intravenous infusions at week 0, 2 and 6 and every 4 weeks thereafter (patients randomized to 8 weekly infliximab treatment were given alternate placebo infusion). Primary endpoints were improvement in ACR20 at 30 weeks. Secondary endpoints were ACR50/70, a reduction in swollen and tender joint count (from a total of 66 and 68 joints, respectively), pain score, physicians' and patients' global assessment, HAQ, CRP and rheumatoid factor level. At 30 weeks the proportion of patients achieving ACR20 was significantly higher in all infliximab groups compared with methotrexate alone. Full details of ACR-defined responses are given in Table 2.

All infliximab regimes were significantly better than placebo in all other measures of disease activity ($P<0.001$).

Adverse effects

In trials the administration of etanercept was not dose limited by toxicity. The commonest adverse events associated with the drug are injection site reaction (37%), upper respiratory tract infections (29%), headache (17%), and diarrhoea (5–12%). Recently the US FDA issued a warning to physicians after sepsis and serious infection were reported in 30 patients receiving etanercept [26]. Etanercept should be used with caution in patients with a history of recurrent infections or who are susceptible to infection e.g. diabetes [27]. The Summary of Product Characteristics (SPC) states that it is not known whether etanercept influences the development or course of malignancies of chronic infections and safety in patients who are immunosuppressed or have chronic infections is unknown.

In clinical trials up to 33% of patients treated with infliximab experienced infections (upper respiratory tract was the commonest infection) compared with 16% (mean) of placebo patients [22–25]. A delayed hypersensitivity reaction has been observed in approximately 25% of patients who are retreated with infliximab for Crohn's disease within 2–4 years of initial treatment [28]. Other adverse events experienced with infliximab include myalgia, rash (12%), fever (5%), pruritis (1%), polyarthralgia, dysphagia, facial, hand or lip oedema, headache (20%), and sore throat. Up to 20% of patients experienced an infusion-related effect (e.g. headache, fever) compared with between 7 and 10% of placebo patients. Infliximab therapy may result in the initiation of an autoimmune process in certain patients occasionally leading to a lupus-type syndrome. The development of human anti chimeric antibodies (HACA) has also been observed in approximately 10–20% of trial patients. This is effectively an immune response to infliximab itself and may result in ineffective therapy. The addition of immunosuppressive agents may limit this adverse effect although this may result in increased toxicity. The SPC states that infliximab may affect normal immune responses and may predispose a patients to opportunistic infections, it also warns that the long-term effects of infliximab in terms of development of malignancy is unknown.

Other considerations

Etanercept (Enbrel®, Wyeth) is licensed for the treatment of active RA in adults who have not responded to other DMARDs, including methotrexate, at a dose of 25 mg subcutaneously twice weekly. It is also licensed for the treatment of active polyarticular-course juvenile chronic arthritis in children aged 4–17 years who have not responded to, or are intolerant, methotrexate. The annual cost of treatment for an adult is £8080 (Table 3).

Infliximab (Remicade®, Schering-Plough) is licensed in the UK for use in Crohn's disease and, in combination with methotrexate, for the treatment of rheumatoid arthritis in patients with active disease when the response to disease-modifying drugs, including methotrexate, has been inadequate. The cost per 100 mg vial is £451; at

a dose of 3 mg kg^{-1} every eight weeks the annual cost will be between £8122 and £12 182 in the first year of treatment and between £5866 and £8798 in subsequent years. As infliximab is administered via an intravenous infusion there will be associated administration costs such as nursing time, giving sets, etc.

There are approximately 600 000 patients with RA in the UK, and of these between 2 and 3.5% may have severe disease which has failed to respond to conventional treatment who might be eligible for anti-TNF therapy [29–30]. If between 50 and 70% of patients treated with anti-TNF drugs respond then the annual cost to the NHS could be between £48 M and £129 M.

Conclusions

In adults, etanercept has been shown to significantly improve all measures of RA disease when compared with placebo. Combination treatment with etanercept and methotrexate is more effective than methotrexate monotherapy. However, there are currently no comparative data available.

Any benefits seen during treatment are quickly lost once therapy is stopped and it seems likely that long-term therapy will be required. At present, the long-term safety of etanercept has not been demonstrated and there is some concern that etanercept impairs the immune system leading to sepsis and severe infection in some patients.

In a small study, etanercept was more effective than placebo in a selected group of children with polyarticular arthritis. Larger trials of longer duration are required before the place of etanercept can be established in this group of patients.

Infliximab has been shown to significantly improve symptoms associated with RA compared with both placebo and methotrexate. One trial has suggested that combination therapy with methotrexate is more effective than either methotrexate or infliximab alone. As yet, there are no published comparative data with other DMARDS. Similarly, long-term safety data are also lacking and there are concerns about the effect that infliximab has on the immune system.

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