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Intervention:	*Golimumab for the treatment of rheumatoid arthritis after failure of previous disease-modifying antirheumatic drugs*
Date of NICE Meeting:	28/09/2010
Paper No:	CSAS RER ( )

This rapid evidence review (RER) has been undertaken by CSAS to provide an independent review of the evidence.

CSAS will use the RER to inform the PCT submission to NICE Technology Appraisal Committee and will use the knowledge gained to draft a submission for the ACD should the opportunity arise.

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CONSIDERATIONS FOR PCTS:

If recommended for use in the NHS it is unclear what the implementation issues might be for PCTs in ensuring access to golimumab for rheumatoid arthritis. The manufacturer's submission is expected to contain further information on the acquisition cost of golimumab. This drug has marketing approval for self-administration by patients and if it is suitable, the training procedures currently in place for etanercept self-injection should be relevant for golimumab. Golimumab plus methotrexate appears to be effective compared to methotrexate alone, but it is unknown how it compares with alternative TNF-α inhibitors for rheumatoid arthritis.

The reduced frequency of golimumab injections, compared to other TNF-α inhibitors, may be preferred by patients. However, the drug has not been shown to have better outcomes (i.e. to be more effective or less harmful) than other TNF-α inhibitors, as there have been no head to head trials. The cost effectiveness of golimumab for this indication is unknown.

KEY POINTS:

- Golimumab, a TNF-α inhibitor is given monthly by subcutaneous injection, with concomitant methotrexate. It can improve symptoms of rheumatoid arthritis. Symptoms were improved by 20% (an ACR20 response) at 14-24 weeks in 50.9% of patients given golimumab 50mg plus methotrexate in a non-weighted analysis of pooled data from 4 RCTs included in a Cochrane review. This compared with 34.0% achieving a similar symptom improvement in the placebo plus methotrexate groups. The relative risk [RR] was 1.53 (95% CI 1.23 to 1.91), the absolute risk reduction was 16.9% and the number needed to treat for one additional person to benefit was 6.
- There are no clinical trials that have directly compared golimumab with other recommended TNF-α inhibitors (adalimumab, etanercept, or infliximab). Indirect comparisons suggest that a similar proportion of patients respond to golimumab as to the other TNF-α inhibitors, but this indirect comparison should be interpreted with caution as the characteristics of patients and the prior and concomitant treatment regimens included in these studies may have differed.
- A Cochrane review has conducted a meta-analysis that suggests that, at least in the short term, golimumab has a similar safety profile to methotrexate monotherapy, with similar rates of adverse events, serious infections, cancer, tuberculosis or deaths.
- The cost of golimumab is not currently listed within the British National Formulary. The current yearly drug costs of TNF-α inhibitors that are approved for this indication are approximately £9,295 for etanercept, £9,295 for adalimumab and between £8,813 and £10,072 for infliximab.
- The 50mg dose of golimumab appears to be as effective as the higher 100mg dose for most patients.
- Golimumab is administered once monthly by subcutaneous injection. The lower frequency of injections with golimumab compared to etanercept or adalimumab, and its subcutaneous rather than intravenous administration (as for infliximab) may be preferred by patients. The product sheet from the company suggests self-administration is possible in selected patients.

SUMMARY:

- Golimumab (Simponi®, Centocor) is a high affinity, fully humanised monoclonal antibody that inhibits TNF-α. It has EMEA marking authorisation for use in moderate to severe rheumatoid arthritis in combination with methotrexate.
- Golimumab is administered once monthly by subcutaneous injection, it has EMEA marketing authorisation to be given as a 50mg dose (or as a 100mg dose in patients over 100kg).
- A Cochrane meta-analysis that included four RCTs found golimumab to be more effective than placebo in the treatment of rheumatoid arthritis after 16 to 24 weeks. At 24 weeks 50.9% of patients receiving 50mg golimumab and 51.7% receiving 100mg golimumab saw a 20% improvement in their symptoms compared with 34.0% in the placebo group. Patients receiving 50mg golimumab were 53% more likely than patients receiving placebo to achieve this improvement (RR 1.53, 95% CI 1.23 to 1.91).
- The Cochrane meta-analysis found that was no difference in the proportion of patients that experienced adverse events between patients receiving golimumab or placebo.
- Rheumatoid arthritis affects 0.8% of the population. It is estimated that for an average PCT of 300,000 people there would be 2,400 individuals with RA and that out of these 48 would be eligible for and receive TNF-α inhibitors. However, these figures are based on current usage of these drugs and may under-estimate of the number of eligible patients.
- The cost of golimumab is not currently listed within the British National Formulary. The current yearly cost of TNF-α inhibitors that are approved for this indication are approximately £9,295 for etanercept, £9,295 for adalimumab and between £8,813 and £10,072 for infliximab
- No clinical trials have been carried out directly comparing the effectiveness of golimumab for rheumatoid arthritis against other TNF inhibitors.
- The lower frequency of golimumab subcutaneous injections (monthly) compared to the other subcutaneous TNF-α inhibitors may be preferred by patients.

1 Context

1.1 Introduction

Rheumatoid arthritis (RA) is a chronic and progressive inflammatory arthritis in which the synovial tissue becomes inflamed leading to tenderness and stiffness and progressive destruction of the joints.

The inflammation is associated with an increase in the number of synovial cells, infiltration by white blood cells and formation of new blood vessels. There is also an increase in fluid-containing inflammatory cells in the joint cavity. Thinning of the bone occurs around the joint and erosions of the bone occur where synovial tissue meets cartilage and bone.[1]

The American College of Rheumatology criteria for the diagnosis of RA require four of the following features to be present: morning stiffness in joints exceeding 1 hour; physician-observed arthritis of three or more areas with soft tissue swelling; arthritis involving hand joints; symmetrical arthritis; rheumatoid skin nodules; a positive blood test for rheumatoid factor; and radiographic changes typical of rheumatoid disease.[1]

Rheumatoid arthritis is a progressive condition but its course is variable. Factors that are associated with a poor prognosis are the presence of rheumatoid factor or anticyclic citrullinated peptide (CCP) antibodies, high erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) levels, early radiographic evidence of erosions and the presence of swollen and tender joints.[1]

It is estimated that within 2 years of diagnosis, patients have moderate disability and after 10 years approximately 30% are severely disabled. Life expectancy is reduced.[1]

Patients are given combinations of non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, corticosteroids and disease modifying anti-rheumatic drugs (DMARDs) including methotrexate.[1]

The cytokine tumour necrosis factor TNF-α is thought to play a role in the rheumatoid arthritis (RA) inflammation and the TNF-α inhibitors adamilumab (Humira, Abbott Laboratories), etanercept (Enbrel, Wyeth Pharmaceuticals) and infliximab (Remicade, Schering-Plough Ltd) are approved by the NHS for adult patients who have a disease activity score (DAS28) greater than 5.1 confirmed on at least two occasions 1 month apart and have undergone trials of two DMARDs.[1]

1.2 Existing national guidance

- NICE Technology Appraisal 126. Rituximab for the treatment of rheumatoid arthritis (refractory). August 2007[2]
- NICE Clinical guideline 79. Rheumatoid arthritis: the management of rheumatoid arthritis in adults. February 2009[3]
- NICE Technology Appraisal 130. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. October 2007[1]
- NICE Technology Appraisal 141. Abatacept for the treatment of rheumatoid arthritis. April 2008[4]
- NICE Technology Appraisal 186. Certolizumab pegol for the treatment of rheumatoid arthritis. February 2010[5]

2 Epidemiology

It is estimated that rheumatoid arthritis affects between 0.5 and 1% of the population, and that 15% have severe disease. Rheumatoid arthritis (RA) affects three times as many women as men; the estimated incidence of RA in men is 0.015%, in women is 0.036%, and it has a peak age of onset of between 40 and 70 years.[1]

3 The intervention

Golimumab (Simponi®, Centocor) is a high affinity, fully humanised monoclonal antibody that inhibits TNF-α. TNF-α is a cytokine that mediates the inflammatory response of immune cells.[6]

Golimumab is currently licensed by the EMEA for rheumatoid arthritis (RA) in combination with methotrexate (MTX). The combination is indicated for the treatment of active moderate to severe rheumatoid arthritis in adult patients when the response to DMARD therapy MTX has been inadequate. Golimumab is also licensed for the treatment of severe, active ankylosing spondylitis in adult patients when the response to conventional therapy has been inadequate.[6]

Golimumab is also licensed by the EMEA for the treatment of active and progressive psoriatic arthritis (PsA) alone or in combination with MTX when the response to previous DMARD therapy has been inadequate. It is currently not approved for use in the NHS for this indication.[6]

The European Public Assessment Report published by the EMEA (19 April 2010) states that golimumab 'is given as a once monthly 50mg injection, given on the same day of each month, as an injection under the skin. The doctor may consider increasing the dose to 100mg in patients weighing more than 100kg, if they do not respond to treatment after

three or four doses. After training, patients may inject themselves with Simponi if their doctor agrees.'[6]

4 Findings

We found one Cochrane review[7] that had compared the efficacy and safety of golimumab (alone or in combination with DMARDs or biologics) to placebo (alone or in combination with DMARDs or biologics) in randomised or quasi-randomised clinical trials in adults with rheumatoid arthritis. The review contains data published up to November 2009. The review contains data from four published RCTs, these are Emery et al 2009[8] (GO-BEFORE), Kay et al 2008[9] (NCT00207714), Keystone et al 2009[10] (GO-FORWARD, NCT00264537), and Smolen et al 2009[11] (GO-AFTER NCT00299546). We have extracted the data included in this review and presented the relevant meta-analyses. We have additionally referred to the original published articles. The four RCTs included in the Cochrane review assessed golimumab alone or in combination with DMARDS, compared to placebo. There were no trials that had compared the effectiveness of golimumab against other TNF-α inhibitors for this indication. All of these trials assessed golimumab administered by subcutaneous injection every 4 weeks. We found an additional RCT that was published after the publication date of this Cochrane review, Kremer et al 2010.[12] This RCT assessed the use of golimumab given as an intravenous infusion every 12 weeks.

Golimumab has been licensed by the EMEA for rheumatoid arthritis in combination with methotrexate[6], therefore only data relating to this combination treatment has been presented in this summary. Likewise, the frequency of injection that has been licensed by the EMEA is once monthly, therefore data relating to higher frequency (fortnightly) golimumab treatment regimens has been omitted. However one study (Kremer et al 2010)[12] that has assessed a less frequent three monthly intravenous infusion regimen with a dose that was dependent on the patient's weight has been included. The suggested dose of golimumab for RA is 50mg, however in patients weighing more than 100kg the dose may be increased to 100mg. Data from studies relating to both doses has been included in this summary.

Owing to the volume of data, much has been tabulated. The primary data has been presented for the proportion of patients achieving ACR20 and ACR50 up to 24 weeks from the primary literature. The Cochrane Review meta-analyses of other outcome measures are presented alongside the risk ratios for golimumab compared to placebo.

In order to provide an illustrative comparison we have extracted the risk ratios from the NICE technology appraisal guidance on the use of the TNF-α inhibitors adalimumab, etanercept and infliximab for rheumatoid arthritis.[1] This data is presented as risk ratios. However, as this technology appraisal used data from separate placebo controlled trials with potentially different populations (for example, patients may have received TNF-α

monotherapy rather than TNF-α plus MTX or differing prior treatment regimen to the golimumab trials) the comparisons are indirect and should be interpreted with caution.

4.1 Evidence of effectiveness

The participant characteristics in the five RCTs that have assessed golimumab for RA are as follows:

Kay et al 2008 (NCT00207714)[9]

Patients had active rheumatoid arthritis for at least three months prior to screening and had been unresponsive to MTX at a dosage of at least 10mg a week for ≥3 months, and at a stable dosage for ≥4 weeks before receiving their first dose of study medication. In this trial persistent disease activity was defined as ≥6 swollen joints, ≥6 tender joints, and at least 2 of the following 3 criteria: C-reactive protein (CRP) level ≥1.5mg/dl, erythrocyte sedimentation rate (ESR) of ≥28mm in the first hour according to the Westergren method, and morning stiffness of ≥30 minutes.

The patients were randomised to receive placebo plus MTX (n=35); 50mg golimumab plus MTX (n=35); or 100mg golimumab plus MTX (n=34). At week 18 the placebo group switched to receive open label treatment with infliximab. Medications were continued until week 48.

Keystone et al 2009 (NCT00264537) GO-FORWARD study[10]

Prior to the trial the patients had been on a stable MTX dose of 15mg/week or greater, but 25mg/week or less during the 4 week period immediately prior to screening. Patients had active RA, defined as four or more swollen joints (out of 66 in total) and four or more tender joints (out of 68 in total) and at least 2 of the following: (1) CRP of ≥1.5mg/dl (normal range 0-0.6 mg/dl) or ESR by the Westergren method ≥28mm/h; (2) ≥30 minutes of morning stiffness; (3) bone erosion determined by X ray and/or MRI; or (4) anticyclic citrullinated peptide antibody or rheumatoid factor positive test results. Patients had not previously used any other TNF-α agent.

The patients were randomised to receive placebo plus MTX (n=133), 50mg golimumab plus MTX (n=89), or 100mg golimumab plus MTX (n=89). After 16 weeks, those patients who did not achieve at least a 20% reduction in swollen and tender joint counts had their medication adjusted (early escape). Patients in the placebo group who did not meet these criteria switched to receiving 50mg golimumab every 4 weeks, those in the 50mg golimumab group switched to 100mg golimumab every 4 weeks, those already in the 100mg golimumab group did not switch their medication. The MTX dose in these groups remained the same after the switch. The primary outcome was assessed prior to the early escape.

Smolen et al 2009 (NCT00299546) GO-AFTER study[11]

The patients had active RA (persistent disease activity with at least four swollen and four tender joints) according to ACR criteria at least 3 months before screening. Patients had previously received TNF-α inhibitors but had been discontinued for any reason. The last dose of TNF-α inhibitor had to have been given at least 8 weeks (adalimumab, etanercept) or 12 weeks (infliximab) prior to the first use of the study drug. The patients could continue on stable doses of methotrexate, sulfasalazine, hydroxychloroquine, oral corticosteroids, or non-steroidal anti-inflammatory drugs during the trial. About two thirds of the participants were taking methotrexate.

Patients were randomised to receive placebo (n=155), 50mg golimumab (n=153) 100mg golimumab (n=153). After 16 weeks, those patients who did not achieve at least a 20% reduction in swollen and tender joint counts had their medication adjusted (early escape). Patients in the placebo group who did not meet these criteria switched to receiving 50mg golimumab every 4 weeks, those in the 50mg golimumab group switched to 100mg golimumab every 4 weeks, those already in the 100mg golimumab group did not switch their medication. The MTX dose in these groups remained the same after the switch.

Emery et al 2009 (GO-BEFORE study)[8]

Participants had active RA but were naive to MTX but just over half of the participants (53.1%) had previous DMARD treatment. Participants were adults that had met ACR criteria for RA for at least 3 months before administration of the initial study agent, and had not received more than 3 weekly doses of oral MTX as treatment of RA. Patients had active RA, with at least 4 tender joints at both screening and baseline and met at least 2 of the following criteria at screening and/or baseline: 1) CRP level ≥1.5mg/dl or ESR ≥28 mm/hour according to the Westergren method, 2) morning stiffness lasting 30 minutes or longer 3) bone erosion by radiography and/or magnetic resonance imaging prior to initiation of treatment with the study agent, or 4) anticyclic citrullated peptide or rheumatoid factor positivity. There were 160 patients randomised to receive placebo plus MTX, 159 patients to receive 50mg golimumab plus MTX, and 159 to receive 100mg golimumab plus MTX. The dosage of MTX started at 10mg/week at the start of the study and escalated by 2.5 mg every 2 weeks to 20 mg/week at week 8.

Kremer et al 2010[12]

Patients had active RA despite treatment with MTX for ≥3 months prior to screening and at stable a dose of 15-25mg/week for ≥4 weeks prior to screening. The patients maintained this stable dose over the course of the study. Persistent RA was defined as ≥4 swollen joints and ≥4 tender joints and ≥2 of the following criteria at baseline and/or at the time of screening: CRP level ≥1.5mg/dl or an ESR of ≥28mm/hour according to the Westergren method, morning stiffness lasting ≥30 minutes, bone erosion by radiography and/or MRI, or positivity for anticyclic citrullated peptide or rheumatoid factor.

Unlike the other studies in which the patients received subcutaneous injections of golimumab every 4 weeks, in this trial patients were randomised to receive either 2mg/kg or 4mg/kg golimumab by intravenous infusion every 12 weeks (with and without MTX). There were 129 patients that received placebo plus MTX, 129 patients received 2mg/kg golimumab plus MTX, and 128 patients received 4mg/kg golimumab plus MTX. NICE costing guidelines have used an average adult weight of 70kg when costing for drugs dosed by bodyweight. An individual of average weight would therefore have received 140mg or 280mg golimumab in this study. These doses were administered once every 12 weeks rather than monthly. (This would equate to roughly a 47mg or 93mg dose every 4 weeks).

After 16 and 24 weeks, those patients who did not achieve at least a 20% reduction in swollen and tender joint counts had their medication adjusted (early escape). Patients in the placebo group who did not meet these criteria at 16 or 24 weeks switched to receiving 4mg/kg golimumab every 12 weeks, those in the 2mg/kg golimumab group switched to 4mg/kg golimumab group if they did not meet these criteria by week 24. Those already in the 4mg/kg golimumab group did not switch their medication.

The American College of Rheumatology criteria (ACR20, 50 and 70) require a 20, 50 or 70% improvement in tender joint count, swollen joint count, global assessments, pain, disability and circulating inflammatory markers respectively. The proportion of participants achieving ACR20 and ACR50 in these five RCTs is shown below in Table 1.

Table 1: Proportion of RA patients (%) achieving ACR20 and ACR50 response with golimumab (plus concomitant MTX)

Study	*ACR20 (12-16 weeks)†*	*ACR20 (24 weeks)*	*ACR50 (12-16 weeks)†*	*ACR50 (24 weeks)*
Kay et al 2008 104 participants	(16) Placebo 37.1% 50mg golimumab 60% (P=0.056) 100mg golimumab 55.9% (P=0.119)	n/a	(16) Placebo 5.7% 50mg golimumab 37.1% (P=0.001) 100mg golimumab 29.4% (P=0.009)	n/a
Keystone et al 2009 311 participants	(14) Placebo 33.1% 50mg golimumab 55.1% (P=0.001) 100mg golimumab 56.2% (P<0.001)	Placebo 27.8% 50mg golimumab 59.6% (P<0.001) 100mg golimumab 59.6% (P<0.001)	(14) Placebo 9.8% 50mg golimumab 34.8% (P<0.001) 100mg golimumab 29.2% (P<0.001)	Placebo 13.5% 50mg golimumab 37.1% (P<0.001) 100mg golimumab 32.6% (P<0.001)
Smolen et al 2009 461 participants♣	(14) Placebo 18% 50mg golimumab 35% (P=0.0006) 100mg golimumab 38% (P=0.0001)	Placebo 17% 50mg golimumab 34% (P=0.0005) 100mg golimumab 44% (P<0.0001)	(14) Placebo 6% 50mg golimumab 16% (P=0.0062) 100mg golimumab 20% (P=0.0003)	Placebo 5% 50mg golimumab 18% (P=0.0003) 100mg golimumab 20% (P=0.0001)
Emery et al 2009 478 participants	n/a	Placebo 49.4% 50mg golimumab 61.6% (P=0.028) 100mg golimumab 61.6% (P=0.028)	n/a	Placebo 29.4% 50mg golimumab 40.3% (P=0.042) 100mg golimumab 36.5% (P=0.177)
Kremer et al 2010 386 participants	(14) Placebo 27.9% 2mg/kg golimumab 55% (P<0.001) 4mg/kg golimumab 51.6% (P<0.001)	Placebo 24.8% 2mg/kg golimumab 37.2% (P=0.032) 4mg/kg golimumab 50.0% (P<0.001)	(14) Placebo 13.2% 2mg/kg golimumab 21.7% (P=0.073) 4mg/kg golimumab 21.1% (P=0.093)	Placebo 9.3% 2mg/kg golimumab 18.6% (P=0.032) 4mg/kg golimumab 25% (P<0.001)

♣Only about two thirds of the population were receiving concomitant MTX; †Brackets at the top of the entry denote week at which measurement made; P values are for comparison versus placebo

Other outcome measures included in the studies were:

Disease Activity Score (DAS): Includes counts of tender and swollen joints (53 and 44 joints respectively), an evaluation of general health by the patient (on scale of 0 to 100), and a measure of circulating inflammatory markers (CRP or ESR).[1]

The DAS28 uses only 28 joints for assessment. Using the DAS28 criteria a score greater than 5.1 indicates high disease activity, 3.2 to 5.0 moderate disease activity and less than 3.2 low disease activity. A patient scoring less than 2.6 is defined as being in remission.[1]

The European League Against Rheumatism (EULAR) uses response criteria that are based on the DAS measure. A decrease in the DAS score of 0.6 or less is considered to show a poor EULAR response, while decreases greater than 1.2 points indicate a moderate or good EULAR response, dependent on whether the individual's DAS 28 score at the end point is above or below 3.2 respectively.[1]

The Stanford Health Assessment Questionnaire (HAQ) is one component of the ACR criteria and is a measure of the ability to perform daily activities. The scale ranges from 0 (least disability) to 3(most severe disability).[1]

The Sharp score assesses radiological damage by measuring erosions and joint space narrowing in 44 different joints and reporting an aggregated score ranging from 0 to 448.[13]

The meta-analytical results from the Cochrane systematic review that assessed golimumab for rheumatoid arthritis are listed in Table 2. The authors' conclusions in this review were "with an overall high grade of evidence, at the FDA approved dose [50mg subcutaneous injection once every 4 weeks], golimumab is significantly more efficacious than placebo in treatment of patients with active RA, when used in combination with methotrexate. The short-term safety profile, based on short-term RCTs, is reasonable with no differences in total adverse events serious infections, cancer, tuberculosis or deaths".[7,14] Safety of golimumab is further discussed in section 4.4.

Table 2: The risk ratios for pooled analysis of 4 RCTs included in Cochrane review (only outcomes that were measured in all 4 RCTs are included)

Outcome	*No. of participants*	*Risk ratio [95% CI]*
50mg golimumab plus MTX versus placebo plus MTX (14-24 weeks)		
ACR20	919	1.53 [1.23,1.91]
ACR50	919	2.57 [1.34,4.94]
Good EULAR response	919	1.47 [1.15,1.89]
DAS remission	919	5.12 [1.67 to 15.66]
Adverse event	918	1.05 [0.93, 1.18]
Serious adverse event	918	1.05 [0.62, 1.78]
Infections	918	1.03 [0.84, 1.25]
Serious infections	918	1.06 [0.40, 2.86]
Tuberculosis	918	3.04 [0.12, 74.01]
Cancer	918	0.81 [0.16, 4.18]
Withdrawals	917	0.50 [0.31, 0.81]
Death	917	1.02 [0.11, 9.71]
100mg golimumab plus MTX versus placebo plus MTX (14-24 weeks)		
ACR20	918	1.56 [1.22, 2.01]
ACR50	918	2.43 [1.25, 4.74]
Good EULAR Response	918	1.42 [1.11, 1.82]
DAS remission	918	6.28 [1.37, 28.78]
Adverse events	915	1.06 [0.98, 1.15]
Serious adverse event	915	1.04 [0.40, 2.70]
Infections	915	0.96 [0.78, 1.18]
Serious infections	915	1.80 [0.56, 5.80]
Tuberculosis	915	Not estimable
Cancer	915	1.36 [0.33, 5.56]
Death	917	1.01 [0.11, 9.68]

The NICE technology appraisal guidance 130 assessed the TNF-α inhibitors adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis.[1] It included data from nine RCTs assessing adalimumab, 11 assessing etanercept and nine assessing infliximab. Out of these, 20 studies were used in the final meta-analysis. Four of the studies included patients that had a disease duration of 3 years or less and were MTX naive. The other 16 studies included patients where conventional DMARDs were inadequate.[1]

Adalimumab

Data were meta-analysed from five studies that included patients for whom conventional DMARDs had previously provided an inadequate response. The treatment follow up in these studies was between 12 and 52 weeks. ACR20 response (RR 2.11, 95% CI 1.84 to 2.42), ACR70 response (RR 5.22, 95% CI 3.45 to 7.89), HAQ score (WMD -0.31, 95% CI -

0.46 to -0.26]) and modified Sharp score per year (WMD-2.20, 95% CI, -3.33 to -1.07). It was not stated in the guideline document whether the patients in each trial included in this meta-analysis received ongoing MTX plus the experimental adalimumab treatment regimen.

Etanercept

Data were meta-analysed from ten studies where patients were given etanercept the licensed dose of 25mg twice weekly or equivalent. Two of the studies included patients who had an inadequate response to methotrexate. Eight studies included patients for who conventional DMARDs had provided an inadequate response. Three of these eight studies compared etanercept to placebo, while the other five studies etanercerpt was added to existing treatment regimen of methotrexate (three studies), unspecified DMARD (one study) or sulfasalazine (one study). In the meta-analysis of data from eight studies which included patients that did not respond to conventional DMARDs, etanercept was more effective than placebo or comparator treatments: ACR20 response (RR 3.59, 95% CI 2.89 to 4.46), ACR70 response (RR 9.44, 95% CI 3.98 to 22.38) and HAQ score (WMD -0.50, 95% CI -0.59 to -0.42).

Infliximab

Four studies assessing infliximab for RA were appraised. Two of these studies compared infliximab plus methotrexate with methotrexate alone. The previous treatment regimen was not defined. Addition of infliximab to methotrexate was more effective than methotrexate alone for the ACR20 response (RR 1.17, 95% CI, 1.02 to 1.34), ACR 70 response (RR 1.57, 95% CI, 1.20 to 2.05), HAQ score (WMD -0.17, 95% CI, -0.29 to -0.06) and modified Sharp score per year (WMD -3.28, 95% CI, -4.55 to -2.01). The other two studies added infliximab to an ongoing methotrexate regimen where there was an inadequate response, meta-analysis of these studies showed that adding infliximab improved outcomes: ACR20 response (RR 2.30, 95% CI, 1.90 to 2.78), ACR70 response (RR 3.16, 95% CI, 1.89 to 5.27), HAQ score (WMD -0.27, 95% CI -0.35 to -0.19) and modified Sharp score per year (-5.70, 95% CI -8.58 to -2.82).

4.2 Evidence of cost-effectiveness

We could not find a review of the cost-effectiveness of golimumab, however we found an economic evaluation of the cost-effectiveness of adalimumab, etanercept and infliximab for the treatment of RA.[15] We have included details from this review to highlight the likely considerations that may be applied to golimumab when assessing its cost effectiveness.

This review included data from 10 published economic evaluations. The study found that

"Adalimumab, etanercept and infliximab are effective treatments compared with placebo for RA patients who are not well controlled by conventional DMARDs, improving control of symptoms, improving physical function and slowing radiographic changes in joints."[15]

The authors say that the ten published economic evaluations varied. However, using their model the authors found that "TNF inhibitors are most cost-effective when used as last active therapy, with the ICER for etanercept (£24,000 per QALY) being significantly lower than the ICER for adalimumab (£30,000 per QALY) or infliximab (£38,000 per QALY). Other things being equal, etanercept would be, therefore, the TNF inhibitor of choice based on this evidence". However, they say that the most appropriate choice of TNF inhibitor may also depend on patient preference as to route of administration.

The authors say that "the next most cost-effective use of TNF inhibitors is third line, as recommended in the 2002 NICE guidance, which gives ICERs around £30,000 per QALY using early RA effectiveness data. Using data for late RA, however, gives an ICER of around £50,000 per QALY for etanercept, with higher figures for adalimumab and infliximab. First-line use gives ICERs around £50,000 per QALY for adalimumab and etanercept as monotherapies with much higher figures for combinations with methotrexate. Sequential use of TNF inhibitors was modelled, with the TNF inhibitors starting as third line therapy and using the 'late RA' values for the TNF inhibitors. The results are similar to those using the given TNF inhibitor as the sole TNF inhibitor in third place, except that the two other TNF inhibitors are somewhat less cost-effective if used after etanercept".

4.3 Other data sources (e.g. audit)

Rheumatology (BSR) biologics register was established in 2001 for follow safety and efficacy of the use of TNF-α inhibitors in patients with RA it is likely that patients taking golimumab for RA would be followed in this register.

4.4 Safety

The four RCTs included in the Cochrane review assessed adverse events in patients taking placebo or golimumab from 16 to 24 weeks. Kremer et al 2010 assessed adverse events up to 48 weeks. The data on adverse events is summarised in table 3 below. Adverse events are given for the time period before "early escape" for those trials where this was a possibility. The Cochrane review found that there was no difference in risk for an adverse event with golimumab 50mg or 100mg compared with placebo (see Table 2 above).

We did not identify data on the long term safety profile of golimumab. The British Society of Rheumatology (BSR) biologics register was established in 2001 to monitor the safety and efficacy of the use of biologic agents, including TNF-α inhibitors, in patients with RA.[1] The register aimed to recruit enough people so that it could detect a doubling of the risk of lymphoma; sample size calculations estimated that 4,000 patients not treated with TNF-α inhibitors (controls) and 4,000 treated with each inhibitor would be required. Between October 2001 and 31 December 2004 the register recruited 8,455 patients on TNF-α inhibitors and a control cohort of 1,199 patients. Data from this register has shown no overall increase in mortality, cancer or serious adverse events in the TNF-α inhibitor group compared with controls without exposure to these drugs.[1]

The FDA label for golimumab gives the following warnings for golimumab (Simponi)[14]:

- "Serious infections leading to hospitalization or death including tuberculosis (TB), bacterial sepsis, invasive fungal, and other opportunistic infections have occurred in patients receiving Simponi.
- Simponi should be discontinued if a patient develops a serious infection or sepsis.
- Perform test for latent TB; if positive start treatment for TB prior to starting Simponi
- Monitor all patients for active TB during treatment even if initial latent TB test is negative.
- Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which Simponi is a member."

Table 3: The safety profile for golimumab* plus MTX versus placebo plus MTX

	Study (number of weeks treatment)				
	Keystone et al 2009 (16 weeks)	*Smolen et al 2009 (16 weeks)*	*Kay et al 2008 (20 weeks)*	*Emery et al 2009 (24 weeks)*	*Kremer et al 2010 (16 weeks)*♣
Adverse events	Placebo 60.9% 50mg 68.5% 100mg 69.7%	Placebo 70% 50mg 61% 100mg 73%	Placebo 85.3% 50mg 91.9% 100mg 87.9%	Placebo72.5% 50mg 81.6% 100mg 76.1%	Placebo 67.4% 2mg/kg 68.0% 4mg/kg 70.6%
Serious adverse events	Placebo 2.3% 50mg 5.6% 100mg 9.0%	Placebo 7% 50mg 5% 100mg 3%	Placebo 5.9% 50mg 10.8% 100mg 6.1%	Placebo 6.9% 50mg 6.3% 100mg 6.3%	Placebo 1.6% 2mg/kg 3.9% 4mg/kg 4.0%
Infections	Placebo 24.1% 50mg 28.1% 100mg 28.1%	Placebo 28% 50mg 27% 100mg 25%	Placebo 38.2% 50mg 32.4% 100mg 28.1%	Placebo 32.5% 50mg 34.2% 100mg 31.4%	Placebo 33.3% 2mg/kg 30.5% 4mg/kg 40.5%
Malignancies	Placebo 0% 50mg 0% 100mg 1.1%	Placebo 0% 50mg 1% 100mg 1%	Placebo 0% 50mg 0% 100mg 3.0%	Placebo 1.3% 50mg 0.6% 100mg 0.6%	Not stated
Most common adverse events	Not stated	Upper respiratory tract infection (URTI): Placebo 6% 50mg 6% 100 11% Naso-pharyngitis: Placebo 6% 50mg 5% 100mg 5% Diarrhoea: Placebo 4% 50mg 3% 100mg 7%	Nausea: Placebo 2.9% 50mg 5.4% 100mg 18.2% Headache: Placebo 20.6% 50mg 16.2% 100mg 21.2% Injection site erythema: Placebo 11.8% 50mg 13.5% 100mg 9.1% Worsening of RA: Placebo 20.6% 50mg 16.2% 100mg 12.1%	Nausea: Placebo 10% 50mg 13.9% 100mg 15.1% ALT increased†: Placebo 6.3% 50mg 12.7% 100mg 7.5% AST increased†: Placebo 3.8% 50mg 8.2% 100mg 6.3% URTI: Placebo 8.8% 50mg 8.2% 100mg 11.9%	Not stated for 16 week assessment

*50mg or 100mg subcutaneous golimumab monthly unless otherwise stated; ♣ intravenous golimumab infusion every 12 weeks; †ALT or AST increased by at least 100% from baseline with value >150IU/litre; ALT alanine aminotransferase, AST aspartate aminotransferase, URTI upper respiratory tract infection

4.5 Summary of Section 4

Golimumab plus methotrexate is effective compared to methotrexate alone for the treatment of rheumatoid arthritis, with between 34% and 61.6% of patients achieving a 20% improvement in their symptoms over 24 weeks compared to the equivalent improvement in 17% to 49.4% of patients receiving methotrexate alone.

There have been no direct comparative studies that have assessed the effectiveness of golimumab versus the other TNF-α inhibitors that have been approved for use in the NHS for rheumatoid arthritis (adalimumab, etanercept and infliximab). The proportions of patients that achieve the 20% improvement on golimumab compared with patients receiving placebo is similar to trials that have assessed these TNF-α inhibitors for RA.

A Cochrane review has conducted a meta-analysis that suggests that, at least in the short term, golimumab has a similar safety profile to methotrexate monotherapy, with similar rates of adverse events, serious infections, cancer, tuberculosis, and deaths. It is likely that if approved by NICE for use in the NHS for RA, a sample of patients will be included in the BSR biologics register to follow up safety and efficacy in the longer term.

5 Implementation

5.1 Current local activity and costs

Golimumab has been licensed by the EMEA to be administered in a 50mg or 100mg dose once monthly for patients who have active RA and have not responded to DMARDs. This patient population currently receive adalimumab, etanercept or infliximab. The dosages of these TNF-α inhibitors are the same as used for psoriatic arthritis except infliximab, which is infused as a 3mg/kg dose for rheumatoid arthritis and a 5mg/kg dose for psoriatic arthritis. In addition to the NICE technology appraisal for these drugs for rheumatoid arthritis[1] we have used the NICE costing template for these drugs when indicated psoriatic arthritis for additional management costs which are likely to be similar.[16]

Etanercept is administered as a 25mg twice weekly subcutaneous injection or a 50mg dose once weekly. The net price of a 25mg prefilled syringe is £89.38, and of a 50mg prefilled syringe is £178.75 (BNF59). The annual cost of using either 52 once-weekly doses or 104 twice weekly doses is £9,295, and the annual costs of outpatient visits are

£204, giving a total annual cost of £9,501. Patients who respond to etanercept are taught how to self inject by nurses; this takes three sessions at a total cost of £102. Etanercept can be used as a monotherapy or with MTX. In moderate to severe rheumatoid arthritis oral methotrexate is used in doses of up to 20mg weekly [BNF59.] The net cost of one hundred 10mg methotrexate tablets is £55.19.

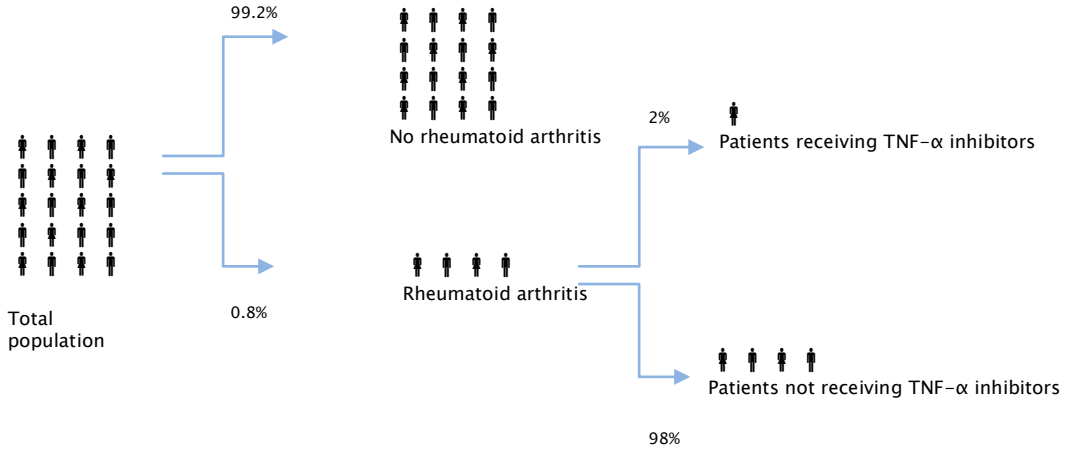
Infliximab is available as a 100mg vial, with a current net cost of £419.62. Infliximab is administered at a dose of 3mg/kg by intravenous infusion over two hours at weeks 0, 2 and 6 and thereafter every eight weeks. The NICE technology appraisal states that if there is an inadequate response or a loss of response, consideration may be given to increasing the dose of infliximab stepwise by approximately 1.5mg/kg, up to a maximum of 7.5mg/kg every 8 weeks.[1]Alternatively, administration of 3mg/kg every 4 weeks may be considered. On the standard dosage, assuming an average weight of 70kg, each dose of infliximab requires three vials at a cost of £1,259. Assuming an administration of 8 doses in the first year and 7 doses in subsequent years this would correspond to an annual cost of between £8,813 and £10,072 (although these costs may vary in different settings because of negotiated procurement costs). The cost of day case attendance is estimated to be £572. Based on these figures the annual costs of day case attendance are between £4,004 and £4,576 giving a total annual cost of between £12,817 and £14,648. Infliximab must be used concomitantly with MTX.

Adalimumab is administered as 40mg subcutaneous injections fortnightly. In monotherapy if patients experience a decrease in response the dose may be increased to 40mg every week. A prefilled 40mg pen or syringe costs £357.50, giving an estimated annual cost for 26 doses of adalimumab of £9,295. Adalimumab can be used with or without additional MTX.

5.2 Economic model

The estimated prevalence of rheumatoid arthritis aged 18 and over within England is 0.8%. The eligible population is likely to be similar to the population eligible for the TNF-α inhibitors that have been approved by NICE for use within the NHS. These are individuals with active rheumatoid arthritis that have responded inadequately to DMARDs. It is estimated that after 5 years of taking DMARDs 80% of people taking gold, 65% of patients taking sulfasalazine and 43% of patients taking methotrexate discontinue treatment.[15] DMARDs may be discontinued because of toxicity, inadequate disease control, disease relapse, patient or physician preferences, complicating co-morbidity or a combination of these[15]. It has been estimated that 2% of patients with RA are currently on TNF inhibitors[15] and we have used this figure to estimate the immediate population that would be likely to potentially receive golimumab. However this is likely to be a conservative estimate of demand for TNF-α inhibitors as a whole, as more people may be eligible for TNF-α inhibitors than currently use them, and demand may increase

in the future. For an average PCT of 300,000 it would be estimated that there would be 2,400 individuals with RA and that out of these 48 would receive TNF-α inhibitors.



Formula to estimate local need for golimumab treatment:

(Total population) x 0.008 x 0.02

NB: This formula estimates the population that are initially eligible, and does not account for the proportion of eligible patients that will not respond to treatment.

Current NICE guidance recommends that in order to continue therapy with TNF-α inhibitors, disease activity needs to decrease by a DAS28 of 1.2 after 6 months of treatment.[1,15] Previous guidance also required the DAS28 score to be below 3.2, and assessed response at 3 rather than 6 months.[15] A proportion of patients taking adalimumab, etanercept or infliximab have been enrolled in the British Society of Rheumatology (BSR) biologics register to provide additional follow-up data for all three drugs. This follow-up has shown that 41% of patients classified as not responding on DAS thresholds continued with TNF inhibitors, indicating that clinicians and patients felt that a smaller improvement in DAS (mean 0.3) and other health gains were sufficient to warrant continued drug use.[15]

The cost of golimumab for the UK market is not known.

5.3 Other implementation issues (eg training, capacity)

Golimumab is approved by the FDA at a dose of 50-mg once monthly for patients with RA [14]

The European Public Assessment Report published by the EMEA (19 April 2010) states that golimumab 'is given as a once monthly 50 mg injection, given on the same day of each month, as an injection under the skin. The doctor may consider increasing the dose to 100 mg in patients weighing more than 100 kg, if they do not respond to treatment after three or four doses. After training, patients may inject themselves with Simponi if their doctor agrees.' [6]

The lower frequency of injections with golimumab (once monthly) compared to etanercept (twice weekly) or adalimumab (fortnightly) may be preferred by patients.

It is not clear whether NICE will also consider a higher dose delivered once every three months by intravenous infusion based on the data provided by Kremer et al 2010.[12]

6 Ethical issues

None identified.

7 Discussion and conclusions

The available evidence on golimumab for RA includes four RCTs that have been included in a Cochrane review meta-analysis. Additionally a RCT published after the publication of the Cochrane review has assessed a higher, but less frequent dose of golimumab against placebo. We have only included data in this review where both the treatment and placebo groups received methotrexate. The conclusion from the Cochrane review was that golimumab was more effective than placebo for rheumatoid arthritis. There is not sufficient data to assess whether golimumab is more effective than etanercept, adalimumab or infliximab. Golimumab is suitable to be administered by patients like etanercept, the lower frequency of injections compared to etanercept or adalimumab may be preferred by patients.

It is estimated that for an average PCT of 300,000 people there would be 2,400 individuals with RA and that out of these 48 would receive TNF-α inhibitors. The pooled non-weighted proportions of patients from the Cochrane meta-analysis that reached ACR20 criteria by weeks 16 to 24 were 50.9% of patients receiving 50mg golimumab, 51.7% receiving 100mg golimumab, and 34% receiving placebo. This gave a weighted relative risk of 1.53 (95% CI 1.23 to 1.91) for 50mg golimumab versus placebo and 1.56 (95% CI 1.22 to 2.01) for 100mg golimumab versus placebo. The non weighted absolute risk difference for 50mg golimumab is 16.9% compared with placebo (50.9% minus 34%). This means that about six people will need to

be treated (NNT 6) in order for the symptoms of one additional person to improve by 20% or more over 14 to 24 weeks taking golimumab 50mg in addition to methotrexate.

8 Options for PCTs

If recommended for use in the NHS it is unclear what the implementation issues might be for PCTs in ensuring access to golimumab for rheumatoid arthritis. The manufacturer's submission is expected to contain further information on the acquisition cost of golimumab. This drug has marketing approval for self-administration by patients and if it is suitable, the training procedures currently in place for etanercept self-injection should be relevant for golimumab. Golimumab plus methotrexate appears to be effective compared to methotrexate alone, but it is unknown how it compares with alternative TNF-α inhibitors for rheumatoid arthritis.

The reduced frequency of golimumab injections, compared other TNF-α inhibitors, may be preferred by patients. However, the drug has not been shown to have better outcomes (i.e. to be more effective or less harmful) than other TNF-α inhibitors, as there have been no head to head trials. The cost effectiveness of golimumab for this indication is unknown.

9 References

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10 Appendix

10.1 Search strategy

Guidelines/background

1. Guidelines finder
2. NICE
3. CRD HTA database
4. NHS Evidence
5. Google e.g.: (simponi OR golimumab) AND (~guideline OR ~algorithm) filetype:pdf

Effectiveness and cost-effectiveness

1. MEDLINE & EMBASE (via Ovid)
    1 (cnto148 or simponi or golimumab).mp.
    2 (psoriati* adj3 arthr*).mp.
    3 1 and 2
2. CRD HTA, DARE and EED database
    1 cnto148 or simponi or golimumab
3. EuroScan

Grey literature and ongoing trials

1. FDA
2. EMEA
3. MHRA
4. Scottish Medicines Consortium
5. All Wales Medicine Strategy Group
6. Manufacturers' websites as applicable
7. metaRegister of Controlled Trials (mRCT)