Scottish Medicines Consortium

tocilizumab, 20mg/ml concentrate for solution for injection (RoActemra®) No. (593/09)
Roche

04 December 2009

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

tocilizumab, (RoActemra®) is accepted for restricted use within NHS Scotland.

Licensed indication under review: in combination with methotrexate, for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs or tumour necrosis factor antagonists. In these patients, toculizumab can be given as monotherapy in case of intolerance to methotrexate or where continued treatment with methotrexate is inappropriate.

Addition of tocilizumab to disease-modifying anti-rheumatic drugs resulted in an increased response rate for reduction of disease activity.

Restriction: It is restricted for use in combination therapy within NHS Scotland. The manufacturer did not present an economic case for monotherapy. Toculizumab should be used in accordance with the British Society of Rheumatology guidelines for prescribing TNF-α blockers in adults.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

In combination with methotrexate, for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs or tumour necrosis factor antagonists. In these patients, tocilizumab can be given as monotherapy in case of intolerance to methotrexate or where continued treatment with methotrexate is inappropriate.

Dosing information

8mg/kg body weight, but no lower than 480mg, given once every four weeks administered as an intravenous infusion over 1 hour.

Product availability date

October 2009

Summary of evidence on comparative efficacy

Tocilizumab is a humanised anti-interleukin-6 (IL-6) receptor antibody that blocks the action of IL-6: one of a number of pro-inflammatory cytokines considered to play a central role in maintaining inflammation in rheumatoid arthritis (RA) that also include IL-1 and tumour necrosis factor alpha (TNF-α).

The health economic analysis presented by the manufacturer is based on studies involving the use of tocilizumab in combination with other disease-modifying anti-rheumatic drugs (DMARDs). No economic case has been made for monotherapy.

The pivotal clinical development programme consisted of five double-blind randomised phase III studies. Three were conducted in patients with inadequate response (IR) to either methotrexate (two studies) or to one of a range of specified non-biologic DMARDs including, but not restricted to, methotrexate. Inadequate response could include significant safety issues as well as lack of efficacy. One study enrolled patients with IR to anti-TNF-α therapy and the fifth study was in patients who were methotrexate naïve or had discontinued methotrexate for reasons other than toxicity or lack of efficacy.

In four placebo-controlled studies, tocilizumab or placebo was combined with other DMARD therapy, while in the methotrexate-naïve, active comparator study tocilizumab monotherapy was compared to methotrexate monotherapy. All studies enrolled patients with active moderate to severe RA of at least 3-6 months' duration, a swollen joint count of at least six of 66 joints assessed and a tender joint count of at least eight of 68. Permitted previous and concomitant therapy included oral (but not intra-articular) corticosteroids and non-steroidal anti-inflammatory drugs. Patients with previous unsuccessful treatment with an anti-TNF-α agent were excluded from all studies, except for the study that actively recruited patients IR to anti-TNF-α, and DMARDs other than those under investigation were not permitted.

The primary outcome in all studies was the proportion of patients achieving 20% improvement in disease activity according to criteria of the American College of Rheumatology (ACR-20) at 24 weeks. This is defined as $\geq$20% decrease from baseline in the number of tender and swollen joints, plus a 20% improvement in at least three of the following outcomes: patient's and physician's global assessment of disease activity, patient's

assessment of arthritis pain, Health Assessment Questionnaire-Disability Index (HAQ-DI) and serum CRP or ESR at week 24. The primary analysis was in the intention-to treat (ITT) population except in a non-inferiority analysis in the monotherapy study that used the per-protocol (PP) population. Secondary outcomes included the 50% and 70% equivalents of ACR-20 (ACR-50, ACR-70), and other measures of disease activity including a Disease Activity Score based on assessment of 28 joints (DAS28) assessed for responses indicative of low disease activity and remission. Other endpoints included assessments of pain, disability, fatigue and general mental and physical health. To adjust for multiple statistical testing, secondary outcomes were tested for significance in a sequential hierarchical manner.

Patients with Inadequate Response to DMARDs

In two studies, patients with IR to methotrexate were randomised to intravenous (IV) placebo or tocilizumab 4mg/kg or 8mg/kg every four weeks in combination with oral methotrexate 10 to 25mg per week. DMARDs other than methotrexate were withdrawn. In the third study, patients with IR to a stable dose of permitted non-biologic DMARDs were randomised to IV placebo or tocilizumab 8mg/kg every 4 weeks, added to their existing DMARD therapy.

The proportion of patients achieving ACR-20, ACR-50 and ACR-70 responses at 24 weeks was significantly higher for all tocilizumab groups than for placebo in all trials. Outcomes for ACR-20 at the licensed dose are shown below. In a pooled analysis of these three trials the odds ratio (OR) ACR20 for response rates in tocilizumab + DMARD versus placebo + DMARD was 4.1 (95% confidence intervals [CI] 3.45, 4.9).

Table: Proportion of patients achieving ACR20 response at 24 weeks in three studies in patients inadequately responsive (IR) to disease modifying drugs.

	IR to methotrexate	**IR to methotrexate**	**IR to DMARDs***
	ACR 20 n/N (%)	**ACR 20 n/N (%)**	**ACR 20 n/N (%)**
Placebo group	54/204 (26%)	106/393 (27%)	101/413 (25%)
Tocilizumab group	120/205 (59%)	223/398 (56%)	448/803 (61%)

*Disease modifying anti-rheumatic drugs

One of the methotrexate-IR studies was the only pivotal study with a duration beyond 24 weeks, and was continued to assess joint damage during 52 weeks of double-blind therapy and a further 52 weeks of open-label therapy with tocilizumab alone. A total of 791 patients were randomised to placebo or the licensed dose of tocilizumab. In the first year the total Genant-modified Sharpe score increased by 1.1 points in the placebo combination group (n=393 assessed) and by 0.3 points in the tocilizumab 8mg/kg combination group (n=398), both from a baseline of 29 points. This represented a significantly reduced rate of progression in the tocilizumab group compared with placebo, and the rate of progression in the second year was similar to that for tocilizumab in the first. At one year, joint-space narrowing and erosion scores were also significantly in favour of tocilizumab.

In all three studies, most secondary endpoints were significantly in favour of tocilizumab over placebo.

Patients with Inadequate Response to Anti-TNF-α Agents

Patients with IR to anti-TNF-α therapy were randomised to IV placebo or tocilizumab 4mg/kg or 8mg/kg every four weeks in combination with oral methotrexate 10 to 25mg per week . ACR-20 response rates at 24 weeks were 10% (n=158), 30% (n=161) and 50% (n=170) respectively and differences between tocilizumab and placebo were significantly in favour of tocilizumab for ACR-20, ACR-50 and ACR-70 as well as for most other secondary outcomes.

Monotherapy study

Patients were randomised to IV tocilizumab 8mg/kg every four weeks (n=265) or oral methotrexate 7.5 to 20mg/week (n=259, escalating dose). In the primary analysis, non-inferiority of tocilizumab would be concluded if the lower limit of the 95% CI for the difference in the proportion of ACR-20 responders in the PP population was not less than -0.12. ACR-20 rates were 71% for tocilizumab and 52% for methotrexate representing a weighted difference of 0.21 (95% CI 0.13, 0.29), thus meeting non-inferiority criteria. A secondary sequential analysis established superiority of tocilizumab over methotrexate in the ITT population, with similar response rates to those in the PP analysis. Most secondary endpoints also favoured tocilizumab, with 95% CI indicating statistical superiority.

Long-term extension studies

Patients from all five pivotal trials could be entered into one of two ongoing open-label extension studies. Preliminary data indicate that short-term responses are maintained over time with median treatment duration of around a year.

Summary of evidence on comparative safety

In the direct comparison between methotrexate and tocilizumab monotherapy, the overall incidence of adverse events was similar in both treatment groups (78% and 80% for methotrexate and tocilizumab, respectively), as was the incidence of serious adverse events (2.8% and 3.8%, respectively). The incidence of adverse events considered to be related to study treatment was slightly higher in patients treated with tocilizumab (57%) than in patients receiving methotrexate (50%). The majority of adverse events were mild or moderate in intensity with <7% of patients in each group experiencing severe events.

Adverse events leading to discontinuation and dose modification were reported by slightly more patients in the methotrexate group (5.3% and 22%, respectively) than in the tocilizumab group (3.8% and 19%, respectively). Three patients in the tocilizumab group and one treated with methotrexate died during the study: one death was considered to be possibly related to treatment (gastrointestinal perforation in a patient treated with tocilizumab).

Adverse events that occurred at a higher frequency in the tocilizumab group during the 24 week study included headache (7.3% versus 2.5% in the methotrexate group), skin and subcutaneous tissue disorders (15% versus 11%), hypertension (5.6% versus 2.1%), respiratory disorders (9.0% versus 6.7%) and psychiatric disorders (6.9% versus 3.9%).

Serious or severe infections were reported by five patients in the tocilizumab group compared to three patients in the methotrexate group. In addition, two patients receiving tocilizumab as escape therapy experienced a serious infection. Infections were the most common serious adverse events in a pooled analysis of all five studies and were more common with tocilizumab than with comparators. This analysis highlighted safety signals in common with those from the study above.

Summary of clinical effectiveness issues

Tocilizumab is indicated in combination with methotrexate for patients who have inadequate response (IR) to previous therapy with one or more DMARDs or tumour necrosis factor antagonists. In these patients, tocilizumab can be used as monotherapy in patients with intolerance to methotrexate or where continued treatment with methotrexate is inappropriate. In placebo-controlled studies it has been assessed in combination with methotrexate in patients with intolerance or inadequate efficacy during methotrexate or anti-TNF-α therapy. In patients with inadequate response/intolerance to other non-biologic DMARDs it has been assessed in combination with continued DMARD therapy that could include, but was not restricted to, methotrexate.

Tocilizumab monotherapy has been licensed as a second-line treatment in case of intolerance to methotrexate or where continued treatment with methotrexate is inappropriate. One study directly compared tocilizumab monotherapy with methotrexate monotherapy, however the population in this study differed from that for the licensed indication consisting of patients naïve to methotrexate or who had discontinued for reasons other than intolerance or lack of efficacy.

Guidelines for biologic therapy advise their use in patients with active RA defined as a DAS28 score >5.1 points on two occasions at least one month apart. While all pivotal studies for tocilizumab recruited patients with active RA it is not clear whether the definition of active disease included this requirement, however mean baseline scores were ≥6.5 for the licensed dose of tocilizumab and for comparators in all studies. It is not clear how tocilizumab fits in with those guidelines.

The endpoints used in the pivotal studies are relevant to benefits experienced by patients in clinical practice and are routinely measured in RA clinical studies. All studies assessed the rates of remission in disease activity at 24 weeks (as assessed in 28 joints), and one study measured radiographic progression for up to two years. In common with most endpoints these showed a significant advantage for tocilizumab over comparators, though measures of joint progression may have been influenced by crossover of patients from placebo to tocilizumab, particularly in the second year.

Tocilizumab is administered as an intravenous infusion over an hour. Other intravenous biologic agents (infliximab and rituximab) require administration within an infusion suite under close supervision, with resuscitation facilities available. The Summary of Product Characteristics states that serious hypersensitivity reactions have been reported in association with infusion of tocilizumab in approximately 0.3% of patients. It warns that appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during administration.

Summary of comparative health economic evidence

A cost-utility analysis was performed using a patient simulation model comparing adding tocilizumab in combination with methotrexate to a sequence of treatments for patients with moderate to severe RA who had inadequate response to first line DMARDs or to anti-TNF-α drugs. For the DMARD and anti-TNF-α cohorts, tocilizumab was positioned ahead of etanercept and rituximab respectively followed by a sequence of traditional DMARDs (ciclosporin, gold and sulfasalazine) and palliative care. The comparators seem appropriate.

The primary data sources for clinical effectiveness over a 6-month cycle were the three tocilizumab trials in patients with inadequate response to DMARDS and one trial in patients with inadequate response to anti-TNF-α therapy. The model was driven by ACR outcomes and HAQ scores. As no comparative data were available an indirect comparison (mixed treatment comparison [MTC]) was performed. Long-term effectiveness of tocilizumab and comparators was based on trial extension studies, published evidence, clinical opinion and assumption. The tocilizumab trial extension data demonstrated a decreasing HAQ score up to 3.5 years for responders whilst on tocilizumab treatment. However, no change over time in HAQ score was assumed for anti-TNF-α or rituximab therapies. The effects of 'rebound' (increase in HAQ after treatment discontinuation), and a constant withdrawal rate due to lack of efficacy were included in the model.

The key results were a base case cost-effectiveness for tocilizumab of £20,096 and £22,254 per QALY gained for the DMARD and anti-TNF-α cohorts respectively. This was based on a difference in cost of £24,000 and a QALY gain of 1.2 over a lifetime for the DMARD cohort and £27,400 and QALY gain of 1.23 for the anti-TNF-α cohort. A main driver for these results was the additional drug cost associated with tocilizumab. In addition, tocilizumab was associated with greater drug administration costs compared to anti-TNF-α therapies or rituximab, with small cost offsets relating to less in-patient care estimated.

The economic analysis was thorough and detailed. There were a number of limitations which increase uncertainty over the base case results. These include uncertainty over the exact studies to include in the mixed treatment comparison, the appropriateness of the assumption that long-term continued improvement in HAQ score is less favourable for responders to anti-TNF-α or rituximab than tociluzimab, some uncertainties over the appropriate EQ 5D-HAQ mapping method used for utility measurement and a lack of direct use of the EQ 5D results for tocilizumab collected from the clinical trials. In addition, no account was taken of adverse events costs or disutilities, or disutility associated with possible additional IV administration burden for patients compared to some anti-TNF-α therapies.

However, despite these limitations scenario analysis and additional one-way sensitivity analysis performed by the manufacturer indicated that it was unlikely that the cost per QALY of adding tocilizumab to the treatment sequence after DMARD or anti-TNF-α therapy would exceed £30,000. Probabilistic sensitivity analysis (PSA) indicated a 95% and 87% probability of tocilizumab being cost-effective at a threshold of £30K/QALY for the DMARD and anti-TNF-α cohorts respectively. It is unlikely that adding tocilizumab would be considered cost-effective at a lower threshold of £20,000 per QALY gained (respective probabilities of 45% and 35% for the DMARD and anti-TNF-α cohorts).

Despite the uncertainties it was considered that a sufficiently robust economic case for tocilizumab has been presented for acceptance by the SMC.

Summary of patient and public involvement

Patient Interest Group Submission: National Rheumatoid Arthritis Society (NRAS).

Additional information: guidelines and protocols

The British Society of Rheumatology (BSR) published guidelines in July 2006 that emphasise that progression of RA causing irreversible damage may be rapid in the early stages of the disease, providing a narrow window of opportunity for prevention. Patients with

rheumatoid arthritis should be established on DMARDs as soon as possible after a diagnosis has been established. Disease-modifying therapy should be part of an aggressive package of care, incorporating escalating doses, intra-articular steroid injections, parenteral methotrexate and combination therapy, rather than sequential monotherapy, progressing to biologic (antiTNF-α) therapy when required. In 2009 BSR added guidelines on management after the first two years emphasising that DMARDs and biologic therapies are medium- to long-term treatments whose discontinuation may result in flare, but that an adequate response is a requirement for long-term continuation of biologics.

The National Institute for Health and Clinical Excellence (NICE) recommended in guidelines published in February 2009 that people with newly diagnosed active RA should be offered a combination of DMARDs (including methotrexate and at least one other DMARD), plus short-term glucocorticoids, as first-line treatment as soon as possible and ideally within 3 months of the onset of persistent symptoms. In people with newly diagnosed RA for whom combination therapy is not appropriate, NICE recommends starting DMARD monotherapy with greater emphasis on fast escalation to a clinically effective dose rather than on choice of DMARD. In people in whom sustained and satisfactory levels of disease control have been achieved, cautiously try to reduce drug doses to levels that still maintain disease control.

Both a 2005 update of BSR guidelines and a NICE guideline (October 2007) for prescribing TNF-α blockers in adults with RA recommend biologic therapies for patients who have active RA, defined by a DAS28 score >5.1 on two occasions at least one month apart, and have failed to respond to or tolerate adequate therapeutic trials of methotrexate and at least one other standard DMARD. It is recommended that therapy should be stopped after 3 months if a response is not achieved, where response is defined as improvement in the DAS28 score of >1.2 or a DAS28 score <3.2.

Additional information: comparators

TNFα blockers etanercept, infliximab, and adalimumab; rituximab; abatacept, oral or parenteral methotrexate.

Cost of relevant comparators

Drug	Dose regimen	Cost per year
Tocilizumab	**8mg/kg once every 4 weeks**	**9,318 ****
Abatacept*	750mg (≥ 60kg to ≤100kg) every 4 weeks in year 2	£9445 ** [a]
Infliximab*	3mg/kg every 8 weeks in year 2.	£7553 to 8812 [a] **
Etanercept*	25mg twice weekly or 50mg weekly	£9,295
Adalimumab*	40mg every two weeks	£9,295
Rituximab*	1000mg followed by a second 1000mg dose two weeks later then repeat if necessary	£3,493 to £6985 [a,b]
Methotrexate*	15mg per week	£43 for tablets [c] £862 for Metoject [c]

Doses are for general comparison and do not imply therapeutic equivalence. Weight-based doses based on a body weight of 70kg.

Costs from Monthly Index of Medical Specialities (MIMS) October 2009 except for etanercept which was from eVadis on October 07 2009.

Costs exclude the concomitant use of methotrexate.

** During the initial year of therapy with infliximab, 9 doses would be required over a 54 week period. The cost would be £11,330 based on a body weight of 70kg. Cost assumes no vial sharing. During the initial year of therapy with abatacept, 15 doses would be required over a 52 week period. The cost would be £10,898. based on a 750mg dose.

a: cost does not include the cost of infusion fluid (e.g. sodium chloride 0.9%) or sundries required for administration.
b: cost assumes one to two courses given per year.
c: costs based on the use of 2.5mg tablets and 15mg/1.5ml injection

Additional information: budget impact

The gross budget impact of tocilizumab has been estimated by the manufacturer to be £1.2 million in year one increasing to £7 million by year five. This is based on an estimate of 127 patients treated in year one (assumed to be 5% of moderate to severe RA patients with inadequate response to first line DMARD or aTNF) rising to 758 patients in year five (assumed to be 15% of moderate to severe RA patients with inadequate response to first line DMARD or aTNF). An additional cost is associated with administration of tocilizumab, estimated to increase gross costs to £1.4 million in year one and £8.5 million in year five. No net cost estimates were provided but the overall net drug cost will be considerably lower than the gross costs shown given that tocilizumab would be prescribed as an alternative to alternative treatments with a similar acquisition and administration costs.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 13 November 2009.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission. The reference shaded grey is additional to those supplied with the submission.

Smolen JS, Beaulieu A, Rubbert–Roth A et al. Effect of interleukin–6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double–blind, placebo–controlled, randomised trial. Lancet 2008; 371(9617): 987–997

Genovese MC, Mckay JD, Nasonov EL et al. Interleukin–6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease–modifying antirheumatic drugs: the tocilizumab in combination with traditional disease–modifying antirheumatic drug therapy study. Arthritis Rheum 2008; 58(10): 2968–2980

Emery P, Keystone E, Tony HP et al. Il–6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti–tumour necrosis factor biologicals: results from a 24–week multicentre randomised placebo–controlled trial. Ann Rheum Dis 2008; 67(11): 1516–1523

European Medicines Agency (EMEA). European Public Assessment Report. RoActemra. EMEA/H/C/000955 www.emea.europa.eu