NICE National Institute for Health and Care Excellence

NICE guidance

Tocilizumab for the treatment of rheumatoid arthritis

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces TA198.

This guidance is partially replaced by TA375.

1 Recommendations

1.1 Tocilizumab in combination with methotrexate is recommended as an option for the treatment of rheumatoid arthritis in adults if:

- [this part of the recommendation has been replaced by the recommendations in NICE's technology appraisal guidance on adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed]
- the disease has responded inadequately to DMARDs and a TNF inhibitor and the person cannot receive rituximab because of a contraindication to rituximab, or because rituximab is withdrawn because of an adverse event, and tocilizumab is used as described for TNF inhibitor treatments in NICE's technology appraisal guidance on adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor, specifically the recommendations on disease activity or
- the disease has responded inadequately to 1 or more TNF inhibitor treatments and to rituximab
- and the manufacturers provide tocilizumab (branded or biosimilars) with the discount agreed as part of the patient access scheme.

1.2 People currently receiving tocilizumab for the treatment of rheumatoid arthritis who do not meet the criteria in section 1.1 should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

1.3 Take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the disease activity score and make any appropriate adjustments.

2 The technology

2.1 Tocilizumab (RoActemra, Roche) is a humanised monoclonal antibody that inhibits cytokine interleukin-6 (IL-6). Reducing the activity of IL-6 may reduce inflammation in the joints, prevent long-term damage, improve quality of life and function, and relieve certain systemic effects of rheumatoid arthritis. Tocilizumab, in combination with methotrexate, has a UK marketing authorisation for the treatment of moderate to severe active rheumatoid arthritis in adults whose disease has not responded adequately to, or who were intolerant to, previous therapy with 1 or more DMARDs or TNF-alpha antagonists. In these people, tocilizumab can be given as monotherapy in case of intolerance to methotrexate or if continued treatment with methotrexate is inappropriate. Tocilizumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with methotrexate.

2.2 Tocilizumab is contraindicated in people with active, severe infections. The summary of product characteristics (SPC) lists the following as the most commonly reported adverse drug reactions associated with tocilizumab treatment: upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased alanine transaminase. For full details of side effects and contraindications, see the SPC.

2.3 Tocilizumab is administered as an intravenous infusion, given over 1 hour. The recommended dosage is 8 mg/kg, given once every 4 weeks. For people whose body weight is more than 100 kg, doses exceeding 800 mg per infusion are not recommended. Tocilizumab is available in 3 vial sizes, which are priced at £102.40 for an 80-mg vial, £256 for a 200-mg vial and £512 for a 400-mg vial (BNF edition 59, excluding VAT). The cost for tocilizumab as reported by the manufacturer is £9,295 per year for a patient weighing approximately 70 kg. Costs may vary in different settings because of negotiated procurement discounts.

2.4 The Department of Health and the manufacturer of branded tocilizumab (RoActemra, Roche) have agreed that tocilizumab will be available to the NHS with a patient access scheme in which a discount from the list price is applied to

original invoices. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS. The manufacturer has agreed that the patient access scheme will remain in place until any review of this NICE technology appraisal guidance is published. NHS England has completed a national procurement for tocilizumab, which includes the biosimilar versions of tocilizumab. Prices paid for the originator or biosimilar tocilizumab should be in line with the national procurement outcome and should be no higher than that provided through the original commercial arrangement.

3 The manufacturer's submission

The Appraisal Committee considered evidence submitted by the manufacturer of tocilizumab, a review of this submission by the Evidence Review Group (ERG), and 2 additional analyses by the Decision Support Unit (DSU).

Clinical effectiveness

3.1 In the submission, the manufacturer presented evidence on the clinical effectiveness of tocilizumab in combination with DMARDs for 2 populations: people whose rheumatoid arthritis had responded inadequately to previous DMARDs but before treatment with a TNF-alpha inhibitor (the 'DMARD-IR' population) and people whose rheumatoid arthritis had responded inadequately to previous TNF-alpha inhibitors but before treatment with rituximab (the 'TNF-IR' population). The manufacturer also presented evidence on the clinical effectiveness of tocilizumab as monotherapy. The submission focused on the tocilizumab 8 mg/kg treatment arms of the included studies because this is the recommended dose in the SPC. Some of the studies also included doses other than the licensed dose. Results for doses other than the licensed dose are not considered in this appraisal.

Tocilizumab plus methotrexate as a treatment option after an inadequate response to conventional DMARDs

3.2 The main clinical-effectiveness evidence for the DMARD-IR population came from 3 randomised controlled trials (RCTs). All 3 RCTs were double-blind, placebo-controlled parallel-group studies in adults with moderate to severe active rheumatoid arthritis whose condition had responded inadequately to treatment with methotrexate (OPTION and LITHE) or traditional DMARDs (TOWARD). The OPTION trial assessed the effects of tocilizumab 8 mg/kg plus methotrexate (n=205) compared with placebo plus methotrexate (n=204). The LITHE trial assessed the effects of tocilizumab 8 mg/kg plus methotrexate (n=398) compared with placebo plus methotrexate (n=393). The TOWARD trial assessed the effects of tocilizumab 8 mg/kg plus DMARDs (n=805) compared with placebo

plus DMARDs (n=415).

3.3 The primary outcome in the RCTs was the proportion of people with an American College of Rheumatology (ACR) 20 response at week 24. This was defined as at least a 20% improvement in both the tender joint count and the swollen joint count and at least a 20% improvement in 3 of the other 5 core set measures included in the ACR score. In all 3 RCTs, the same outcome measure and data collection instruments were used. The manufacturer stated that the RCTs had similar patient populations. This was demonstrated by general demographics and the effect of various factors on the ACR20 response rate, which was examined by logistic regression analysis. No statistically significant differences were found in treatment effects between studies and the manufacturer inferred that pooling the results of the 3 RCTs for the primary outcome was appropriate. The manufacturer's submission stated that the adjusted odds ratio for the ACR20 response of tocilizumab 8 mg/kg plus DMARD compared with placebo plus DMARD was approximately 4.2. Averaged ACR20 response rates, described as pooled results, were 59.2% in the tocilizumab 8-mg/kg arm compared with 25.8% in the placebo arm ($p \leq 0.0001$) at week 24.

3.4 Secondary outcomes of the RCTs, measured at 24 weeks, were pooled across the 3 RCTs by the manufacturer. Pooled ACR response rates were: 37.0% compared with 9.6% for ACR50 response rates ($p < 0.0001$), 18.5% compared with 2.4% for ACR70 response rates ($p \leq 0.0001$), and 4.2% compared with 0.3% for ACR90 response rates ($p \leq 0.0001$), for the tocilizumab 8-mg/kg plus DMARD arms and placebo plus DMARD arms respectively. The manufacturer also presented averaged disease activity score 28 (DAS28) results from the 3 RCTs. Approximately half of all people in the RCTs reached low disease activity, defined as DAS28 of less than 3.2. Approximately one-third of people in the RCTs went into remission, defined as DAS28 of less than 2.6. The proportion of participants going into remission while on tocilizumab was reported to increase during the study period. There was a greater decrease (improvement) in averaged health assessment questionnaire (HAQ) results from baseline HAQ score in the tocilizumab groups than in the placebo groups. In the pooled population at week 24, the proportion of participants with a clinically relevant improvement in HAQ (defined as a decrease of at least 0.25 in an individual's total score) was higher in the tocilizumab groups (68%) than in the placebo groups (52%).

3.5 Additionally, European quality of life (EuroQoL) health-state questionnaire (EQ-5D) scores were collected in the OPTION and LITHE RCTs. In the OPTION RCT, the baseline mean EQ-5D was 0.393 (standard deviation 0.327) in the tocilizumab 8 mg/kg plus methotrexate arm, and 0.391 (standard deviation 0.329) in the placebo plus methotrexate arm. At follow-up, the mean EQ-5D was 0.671 (standard deviation 0.237) in the tocilizumab 8 mg/kg arm and 0.534 (standard deviation 0.318) in the placebo arm. The manufacturer did not provide EQ-5D results from the LITHE RCT separately by treatment arm.

3.6 Two single-arm extension studies assessed maintenance of clinical benefit of tocilizumab beyond 24 weeks. Overall, response rates for those remaining on tocilizumab plus DMARD treatment were maintained or continued to improve with duration of treatment, with an increasing proportion of people achieving higher ACR scores over time. The manufacturer reported that improvements in HAQ scores were observed for up to 132 weeks in the pooled tocilizumab 8 mg/kg plus DMARD arm.

3.7 No head-to-head studies were identified that provided evidence on the clinical effectiveness of tocilizumab compared with TNF-alpha inhibitors and abatacept for the DMARD-IR population. Therefore, the manufacturer conducted a mixed treatment comparison. A total of 18 RCTs (including OPTION, LITHE and TOWARD) were identified for inclusion. All studies were randomised, placebo-controlled, double-blind trials and all had a follow-up period of either 24 or 30 weeks. Participants were predominantly female (approximately 80%), older than 50 years, had experienced more than 6 years' duration of rheumatoid arthritis, were previously treated with an average of 2 or more DMARDs, and more than half had used non-steroidal anti-inflammatory drugs or glucocorticoids concomitantly. The manufacturer reported that the baseline characteristics across the trials were comparable to ACR core parameters. Results for TNF-alpha inhibitors were pooled, because it was assumed there was no difference in efficacy between these drugs. This assumption was reported to be informed in NICE's previous technology appraisal guidance on adalimumab, etanercept and infliximab for rheumatoid arthritis (TA130; now replaced by NICE's technology appraisal guidance on adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept).

3.8 The mixed treatment comparison suggested that tocilizumab showed efficacy

(measured by ACR20 and ACR50 response rates) comparable to all included biological treatments. For the ACR70 response rate, tocilizumab treatment was associated with a higher response rate than the TNF-alpha inhibitors and abatacept (relative risks of 1.77 and 1.98 respectively). In the base-case comparison, there was a greater than 99% probability that tocilizumab was more efficacious than biological treatments (that is, etanercept, infliximab and adalimumab), as measured by ACR70 response rates. The manufacturer stated that homogeneity at each ACR response level was assessed using Cochran's Q-statistic (ACR20: 44.1857, p=0.0002; ACR50: 41.6878, p=0.0004; ACR70: 25.5752, p=0.0603). Based on these results, the manufacturer used random-effects methods to estimate ACR20 and ACR50 response rates, and fixed-effect methods to estimate ACR70 response rates. As well as the base-case mixed treatment comparison, the manufacturer also presented 3 scenario analyses, which included or excluded data from certain trials included in the base case. The manufacturer stated that overall, the results from these alternative scenarios were consistent with the initial findings.

Tocilizumab plus methotrexate as a treatment option after an inadequate response to a TNF-alpha inhibitor

3.9 The main clinical-effectiveness evidence for the TNF-IR population came from 1 RCT, known as RADIATE. RADIATE was a double-blind, placebo-controlled, parallel-group study in adults with moderate to severe rheumatoid arthritis. The participants' rheumatoid arthritis had responded inadequately to previous TNF-alpha inhibitor therapy. RADIATE assessed the effects of tocilizumab 8 mg/kg plus methotrexate (n=170) compared with placebo plus methotrexate (n=158).

3.10 The primary outcome of the RADIATE trial was ACR20 response rate. At 24 weeks, 50% of people in the tocilizumab arm compared with 10% of people in the placebo arm had experienced an ACR20 response (p<0.0001). Additionally, at 24 weeks, 28.8% compared with 3.8% had experienced an ACR50 response (p<0.0001), and 12.4% compared with 1.3% had experienced an ACR70 response (p<0.0002), for the tocilizumab arm and the placebo arm respectively. At week 24, the mean change from baseline in DAS28 was -3.16 for tocilizumab and -0.95 for placebo. The manufacturer stated that the remission rates were similar to those seen in the DMARD-IR population at 24 weeks. The mean decrease in

HAQ from baseline at 24 weeks for the tocilizumab group was 0.39, compared with 0.05 for the placebo group.

3.11 Two single-arm extension studies assessed the maintenance of clinical benefit of tocilizumab plus DMARDs beyond 24 weeks. Response rates to therapy with tocilizumab were maintained or continued to improve with duration of treatment (as in the DMARD-IR population). Results similar to those for the DMARD-IR population were reported and the manufacturer noted that the pattern of improvement in mean HAQ score was also observed for up to 132 weeks.

Tocilizumab as a monotherapy

3.12 One RCT (AMBITION) assessed the effects of tocilizumab 8 mg/kg alone (n=288) compared with methotrexate alone (n=284). This was a double-blind, placebo-controlled trial that included a sub-study tocilizumab arm in which placebo was given first for 8 weeks and then tocilizumab was given for 16 weeks. Most of the people in the AMBITION RCT had not received treatment with methotrexate before or had stopped methotrexate treatment for reasons other than toxicity or lack of efficacy.

3.13 The ACR20 response rate at 24 weeks in the intention-to-treat population was 69.9% in the tocilizumab arm compared with 52.5% in the methotrexate arm. The weighted difference in ACR20 response was 0.19 (95% confidence interval 0.11 to 0.27). The manufacturer concluded that treatment with tocilizumab was non-inferior to treatment with methotrexate. The manufacturer also stated that the trial population of AMBITION was not in accordance with the SPC of tocilizumab. This was because the AMBITION trial had recruited people who had not received any previous treatment with methotrexate; the SPC states that tocilizumab can be given as monotherapy in case of intolerance to methotrexate or if continued treatment with methotrexate is inappropriate.

Adverse events

3.14 The manufacturer reported that adverse events associated with the mechanism of IL-6 receptor (IL-6R) inhibition were observed in all tocilizumab treatment

groups. These adverse events included transient hepatic transaminase elevations, asymptomatic elevations of indirect bilirubin, transient neutropenia, and lipid elevations that appear to occur in association with marked decreases in acute phase proteins. In addition, serious infections associated with the immunomodulatory effects of tocilizumab were comparable with the incidence of serious infections with TNF-alpha inhibitors. Adverse events reported more frequently with tocilizumab 8 mg/kg monotherapy than in the methotrexate group were abdominal pain and discomfort, headache, dizziness, rash, pruritus and elevated blood pressure, neutropenia, leukopenia and hyperlipidaemia. Most of these events were mild and transient. The manufacturer reported that there was no increase in the severity or frequency of adverse events with prolonged exposure to the tocilizumab 8 mg/kg dose.

Follow-up data

3.15 In addition to the original submission, the manufacturer of tocilizumab provided updated data with a maximum of 180 weeks of follow-up. The response rates of all people who received at least 1 dose of tocilizumab in the OPTION, AMBITION, RADIATE and TOWARD trials were analysed. A total of 3,986 people were included in the long-term analyses. Approximately 14% of people discontinued tocilizumab treatment for safety reasons (including intercurrent illness). The manufacturer stated that tocilizumab increased or maintained ACR response rates in the DMARD-IR, TNF-IR and tocilizumab monotherapy populations. This was demonstrated by the increased proportion of people with ACR50 and ACR70 responses and with an ACR70 response maintained for 24 consecutive weeks. The manufacturer also used the long-term follow-up data to re-estimate the HAQ progression with tocilizumab. The manufacturer stated that there was a negative trend (an improvement) in HAQ progression for both the DMARD-IR and TNF-IR populations.

Cost effectiveness

3.16 The manufacturer did not identify any economic evaluations of tocilizumab and developed an economic model for the submission. This was an individual sampling model with a hypothetical homogenous cohort. The model used a

lifetime horizon for costs and benefits. It considered the DMARD-IR and TNF-IR populations separately. No evidence on the cost effectiveness of tocilizumab monotherapy was presented.

3.17 The manufacturer's initial economic model compared a treatment sequence that included tocilizumab with the same treatment sequence without tocilizumab for 2 populations. For the DMARD-IR population, tocilizumab plus methotrexate was the first biological treatment and if the condition did not respond or if the ACR20 response rate was no longer achieved then etanercept plus methotrexate was the next treatment. This was followed by rituximab plus methotrexate, then leflunomide, then gold, then ciclosporin until people withdrew from the last treatment (ciclosporin) and moved on to palliative care. The sequence was the same for the comparator arm, but excluded tocilizumab plus methotrexate at the beginning. For the TNF-IR population, the sequence was the same as the DMARD-IR population, except for the omission of etanercept plus methotrexate (that is, the first treatment in the comparator arm was rituximab plus methotrexate).

3.18 The probabilities of response were derived from the adjusted ACR response rates (adjusted for placebo differences across trials) from the base-case mixed treatment comparison. There were 4 categories of response: non-response, ACR20 response, ACR50 response, and ACR70 response. People were assigned a predefined drop in HAQ score (that is, an improvement in physical function) based on their ACR responses. Data from 4 RCTs (OPTION, TOWARD, LITHE and RADIATE) were analysed to estimate the relationship between ACR response and HAQ score in the first 24 weeks. People whose condition responded were assumed to have a constant probability of withdrawal owing to lack of efficacy. The probability of withdrawing from treatment was the same for the biological treatments (infliximab, etanercept, adalimumab, rituximab and tocilizumab) and was calculated as the average of 2 withdrawal rate estimates for etanercept and infliximab. At the point of switching to the next treatment, people were assumed to experience an increase in their HAQ score (rebound) equal to the initial HAQ improvement. After the initial 24-week period the HAQ score with tocilizumab plus methotrexate was assumed to decrease linearly (improve) based on the observational extensions to the RCTs. Because of substantial uncertainty in the data for weeks 132 to 156, this continued improvement was only assumed for the first 3 years in the DMARD-IR cohort and 2.5 years in the TNF-IR cohort. Beyond

this (3 years after initial treatment in the DMARD-IR cohort and 2.5 years after initial treatment in the TNF-IR cohort), the HAQ score was assumed to stay constant (that is, zero HAQ improvement) with tocilizumab plus methotrexate treatment. After the initial 24-week treatment period, no change in HAQ score was assumed (zero HAQ improvement) for biological treatments such as etanercept and rituximab. After the initial 24-week treatment period, an increase in HAQ score (that is, a worsening of physical function) was assumed for traditional DMARDs. The manufacturer also carried out sensitivity analyses using an assumption of zero HAQ progression (no improvement or worsening) while on treatment.

3.19 Tocilizumab plus methotrexate was assumed to be given for a minimum of 6 months and the administration cost of each infusion of tocilizumab was assumed to be £142 (see section 3.25 for subsequent considerations of administration costs). The costs of treating any adverse events were not included in the economic model presented by the manufacturer. The manufacturer reported that EQ-5D scores from the tocilizumab OPTION and LITHE trials were mapped to HAQ scores using a quadratic regression model. Alternative mapping equations as used in NICE's previous technology appraisal guidance on adalimumab, etanercept and infliximab, and other submissions to NICE were examined in scenario analyses. Utility weights were derived from the EQ-5D scores using the UK time trade-off tariff. Adverse events associated with tocilizumab treatment were assumed to generate an insignificant burden on people's quality of life, and therefore were not included in the model.

3.20 For the DMARD-IR population, the treatment sequence including tocilizumab plus methotrexate compared with the sequence without tocilizumab produced incremental costs of £23,253 and incremental quality-adjusted life years (QALYs) of 1.17. This resulted in a base-case incremental cost-effectiveness ratio (ICER) of £19,870 per QALY gained. For the TNF-IR population, the treatment sequence including tocilizumab plus methotrexate compared with the sequence without tocilizumab produced incremental costs of £26,640 and incremental QALYs of 1.21. This resulted in a base-case ICER of £22,003 per QALY gained. Probabilistic sensitivity analyses suggested that the addition of tocilizumab and methotrexate to the treatment sequences had a 56.4% and 22.4% probability of being cost effective (for the DMARD-IR and TNF-IR populations respectively) if the maximum acceptable amount to pay for a QALY gained is £20,000. All scenario analyses

presented by the manufacturer resulted in ICERs of less than £30,000 per QALY gained. The ICERs increased to £24,905 and £24,739 per QALY gained for the DMARD-IR and TNF-IR populations respectively, using an assumption of no change in HAQ score (that is, no continued improvement on tocilizumab after the initial ACR response).

Evidence Review Group comments

3.21 The ERG highlighted the following key areas of concern with the manufacturer's submission.

- The selection of the studies and the pooling of the TNF-alpha inhibitors in the mixed treatment comparison.
- The long-term estimates of HAQ score.
- Mapping HAQ scores to EQ-5D to derive utility estimates for the economic model.
- The rebound effect on discontinuation (defined as an increase in a person's HAQ score when treatment is withdrawn).
- The non-inclusion of adverse events in the economic model.

3.22 The ERG explored the combined adjusted ACR response rates for TNF-alpha inhibitors used in the mixed treatment comparison (DMARD-IR population) and considered that etanercept appeared less efficacious in the comparison than the literature suggested. The ERG commented that the reason for the apparent low efficacy of etanercept compared with both tocilizumab and the other TNF-alpha inhibitors was a single large trial with a very high response rate in the placebo arm (the Klareskog trial). The ERG noted that this trial only included people who were likely to benefit from methotrexate and had an aggressive dosing schedule of methotrexate if the signs and symptoms of rheumatoid arthritis reappeared. When the ERG removed the Klareskog trial from the analysis, etanercept appeared more efficacious than tocilizumab and all the other treatments in the comparison. The ERG then questioned the validity of assuming that all TNF-alpha inhibitors had the same efficacy in the model, because this lowered the estimate

of the effectiveness of the TNF-alpha inhibitor used in the model.

3.23 The ERG commented that the follow-up period of 24 weeks in the 5 included tocilizumab studies could be considered too short. It noted that the longer-term data on tocilizumab came from single-arm studies with no comparator of placebo, conventional DMARDs or biological agents, so the long-term effectiveness of tocilizumab was unclear. The manufacturer estimated the medium-term HAQ progression (up to 3 years for the DMARD-IR population and 2.5 years for the TNF-IR population) using linear functions. However, the ERG suggested that an exponential function was equally plausible. The ERG noted that any functions fitted to the data needed to be constructed carefully because even small changes to the predictions would have a significant impact on the ICER.

3.24 The ERG was also concerned about the way the relationship between HAQ and EQ-5D was modelled. The manufacturer's submission used a quadratic equation for this. The quadratic model predicted that EQ-5D scores would be lower at high HAQ scores compared with a linear model. In addition, literature has shown that EQ-5D and HAQ are closely correlated at baseline and that when quality of life worsened over time the EQ-5D became more variable (resulting in a weaker correlation). The ERG noted that the modelled relationship between HAQ and EQ-5D scores resulted in negative utilities for health states (that is, health states that are considered to be worse than death). The ERG stated that using negative utility values is questionable because a certain amount of disability (because of irreversible characteristics such as damaged joints) may remain despite optimal control of inflammatory disease. The ERG concluded that algorithms for modelling the relationship between HAQ and EQ-5D should only be used when there are no direct utility scores; however, the trials for tocilizumab (OPTION and LITHE) measured EQ-5D directly.

3.25 The manufacturer assumed the cost of administering each infusion of tocilizumab was £142. This was derived by adjusting for inflation the cost of an infusion as used in NICE's previous technology appraisal guidance on adalimumab, etanercept and infliximab. However, the ERG commented that this cost should have been adjusted for inflation from 2001 and not from 2004 as was presented by the manufacturer.

3.26 The manufacturer's submission assumed that the rebound after withdrawal from

treatment was equal to the initial HAQ improvement only. The manufacturer's submission also assumed that the HAQ score for people treated with tocilizumab improved over the course of treatment, but that for other treatments the HAQ score either remained the same (biological treatments) or worsened (conventional DMARDs and palliative care). Therefore, it was assumed that the short- to medium-term HAQ benefit was retained in the long term. NICE's previous technology appraisal guidance on adalimumab, etanercept and infliximab accepted a similar assumption that people would lose their initial HAQ improvement when treatment was withdrawn, and also that biological treatments delayed disease progression more than conventional DMARDs. However, whereas the HAQ score representing underlying disease progression for all biological treatments in NICE's previous technology appraisal guidance on adalimumab, etanercept and infliximab remained the same or worsened only slightly while on treatment, the manufacturer assumed that HAQ score improvement was possible for tocilizumab only. The ERG commented that the assumptions about rebound effect and HAQ progression disproportionately favoured tocilizumab by not only allowing the drug to delay disease progression, but also by allowing for a lasting improvement of the condition.

3.27 In addition, the ERG considered that excluding adverse events in the manufacturer's model was questionable because biological treatments are known to be associated with adverse events. It reported that it was unclear whether the adverse-event rate is higher or lower for tocilizumab than for other biological treatments. The manufacturer's submission states that the mean and median duration of treatment with tocilizumab in the clinical trials was 1.08 years. The ERG commented that the risks of longer-term treatment with tocilizumab were unknown.

Manufacturer's response to consultation

3.28 In response to 3 rounds of consultation for the original technology appraisal guidance on tocilizumab for rheumatoid arthritis (TA198), the manufacturer presented revised ICERs for the DMARD-IR and TNF-IR populations incorporating some of the ERG's suggested changes. The manufacturer also provided ICERs for positioning tocilizumab after an inadequate response to rituximab, and tocilizumab for people who are intolerant to rituximab or for whom rituximab is

contraindicated. The clinical-effectiveness data for tocilizumab used in these positions were taken from the RADIATE trial. All of the revised and new ICERs incorporated degraded ACR response rates for tocilizumab, etanercept and rituximab when they are used later in the treatment sequence. Estimates for etanercept were based on treatment response to a second or third TNF-alpha inhibitor reported from the South Swedish Arthritis Treatment Group. These downgraded the efficacy of etanercept from 62%, 38% and 16% to 49%, 26% and 7% for ACR20, ACR50 and ACR70 response rates respectively when used after 1 biological treatment. For tocilizumab when used after 2 biological treatments, degraded rates were based on the subgroup of people from the RADIATE trial whose rheumatoid arthritis had responded inadequately to more than 1 TNF-alpha inhibitor. Based on these data, tocilizumab response rates changed from 62%, 31% and 12% to 50%, 31% and 15% for ACR20, ACR50 and ACR70 response rates respectively. For rituximab used after 2 biological treatments, the manufacturer provided downgraded response rates based on a subgroup of people whose rheumatoid arthritis had responded inadequately to more than 1 TNF-alpha inhibitor from a trial comparing rituximab plus methotrexate with placebo plus methotrexate (REFLEX). Based on these data, the rituximab response rates were downgraded from 46%, 23% and 14% to 42%, 22% and 10% respectively.

3.29 The revised ICERs were based on the adjusted ACR rates from the mixed treatment comparison, and included a long-term HAQ improvement for tocilizumab and a stable HAQ score (that is, zero HAQ progression) for all other biological treatments. This was not the case for the ICER for tocilizumab given after rituximab, for which no HAQ improvement for treatment with any biological treatment, including tocilizumab, was assumed. All of the revised ICERs were calculated using the HAQ to EQ-5D mapping and included negative utilities that represented states worse than death. The ICERs were subject to the assumption that a person would experience the same adverse events during treatment as during palliative care, and that the cost of administration of tocilizumab was £154.

3.30 The manufacturer's revised ICER for the DMARD-IR population increased from £19,870 to £21,733 per QALY gained and increased from £22,003 to £23,285 per QALY gained for the TNF-IR population. The ICER for tocilizumab used after rituximab was £23,735 per QALY gained. The ICER for tocilizumab for people who

are intolerant to rituximab or for whom rituximab is contraindicated was £20,242 per QALY gained.

Decision Support Unit report 2010

3.31 In 2010, the DSU was asked to undertake additional cost-effectiveness analyses to validate the manufacturer's ICERs submitted following the third round of consultation, and to conduct sensitivity analyses to address the Appraisal Committee's concerns about key parameter assumptions. The 2010 report highlighted a key issue with the calculation of the ICERs presented by the manufacturer. This concerned the 'pair-wise' calculation of sequences containing tocilizumab plus methotrexate with the same sequence excluding tocilizumab rather than an 'incremental' comparison of all strategies containing tocilizumab plus methotrexate with each other and with a base-case strategy without tocilizumab. The DSU considered that the incremental approach was the most appropriate, not only to determine whether tocilizumab plus methotrexate was cost effective, but also in what circumstances, given the availability of a number of other treatments that are used sequentially. The DSU's 2010 report explained that an ICER calculated through a pair-wise comparison does not demonstrate that the sequence can be considered cost effective because there are a series of mutually exclusive sequences available and only 1 can be selected at any 1 time.

3.32 For etanercept, the mixed treatment comparison analysis combined all TNF-alpha inhibitors (etanercept, infliximab and adalimumab) but excluded the Klareskog trial of etanercept that the Committee had requested to be removed because of its unusually high placebo response rate. The DSU noted in the 2010 report that the adjusted mixed treatment comparison rates were lower than the unadjusted trial ACR, or point estimate, rates for etanercept. The adjusted etanercept ACR20, ACR50 and ACR70 response rates were 62%, 38% and 16% respectively and the unadjusted ACR20, ACR50 and ACR70 response rates were 71%, 39% and 17% respectively. In 2010, the DSU reported that the unadjusted rates in the model were taken from a single etanercept trial, without justification for the sole use of this particular trial. The DSU provided an alternative set of unadjusted response rates for etanercept, which were based on the 2 etanercept trials from the mixed treatment comparison (rather than the single trial chosen by the manufacturer). The DSU stated in the 2010 report that this appeared to represent the most

robust data. The resulting unadjusted ACR response rates were 73%, 47% and 22% for ACR20, ACR50 and ACR70 respectively. For rituximab, the adjusted mixed treatment comparison ACR response rates were also lower than the unadjusted ACR trial response rates. The percentage of people reaching an ACR20, ACR50 and ACR70 response rate was 51%, 27% and 12% respectively in the unadjusted analysis and 46%, 23% and 14% respectively in the adjusted analysis. The unadjusted data were taken from the REFLEX trial.

3.33 The DSU highlighted in the 2010 report that the opposite effect was observed with the adjusted and unadjusted ACR rates for tocilizumab, that is, the adjusted rates from the mixed treatment comparison were higher than the unadjusted rates. For tocilizumab given as the first biological treatment in the sequence, the adjusted rates were 63%, 41% and 26% for ACR20, ACR50 and ACR70 response rates respectively and the unadjusted rates for tocilizumab, which were based on a separate meta-analysis of OPTION, TOWARD and LITHE (submitted as part of the manufacturer's licence application), were 59%, 37% and 19% respectively. For tocilizumab used as the second biological treatment in a sequence (that is, after a TNF-alpha inhibitor), the mixed treatment comparison had the same effect of increasing the tocilizumab ACR response rates. The adjusted rates were 62%, 31% and 12%, whereas the unadjusted rates were 50%, 29% and 12% for ACR20, ACR50 and ACR70 response rates respectively. The unadjusted rates for tocilizumab used as the second biological treatment in the sequence were taken from the RADIATE trial.

3.34 The DSU also commented on the degradation rates provided by the manufacturer. These rates were all from single data sources, without justification given for the selection of the sources. The DSU highlighted that the degraded response rates for etanercept were based on the reported ACR rates for the TNF-alpha inhibitors as a group and may not have been generalisable to etanercept. The DSU also noted that the degraded ACR70 response rate for tocilizumab used after 2 biological treatments assumed by the manufacturer (15%) was marginally better than when used after a single biological treatment (12%). The DSU stated that this appeared to be counterintuitive and that it would be more appropriate to assume the same ACR70 response rate when tocilizumab is given after 2 biological treatments as for when it is given after 1.

3.35 In the 2010 report, the DSU considered 4 separate approaches that varied the

ACR response rates and degradation rates used to calculate the incremental ICERs (approaches to evidence synthesis).

- Approach 1 was the same as the manufacturer's revised base case and used the adjusted mixed treatment comparison results with the degradation rates supplied by the manufacturer.
- Approach 2 used the unadjusted single trial ACR response rates for etanercept when used first in the treatment sequence as supplied by the manufacturer. All other estimates remained the same as in approach 1.
- Approach 3 used the unadjusted trial ACR response rates for all treatments in the sequence as supplied by the manufacturer. In addition, this approach replaced the degraded effect for tocilizumab when used after 2 biological treatments with the same effect assumed after 1 biological treatment to account for the counterintuitive change in response rate assumed by the manufacturer (see section 3.34).
- Approach 4 was the same as approach 3, except that the DSU used the alternative unadjusted ACR response rates for etanercept from the 2 trials (described in section 3.32).

3.36 For each of the 4 approaches to evidence synthesis, the DSU undertook 4 sets of sensitivity analyses to assess the robustness of the ICER results to other key parameter assumptions in the 2010 report. These were:

- employing the same set of parameter assumptions employed by the manufacturer in its base case
- assuming no long-term HAQ improvement with tocilizumab
- assuming no long-term HAQ improvement with tocilizumab and excluding negative utilities from the HAQ to EQ-5D mapping
- assuming no long-term HAQ improvement with tocilizumab and doubling the administration costs for tocilizumab to £308.60 per infusion.

3.37 The DSU in the 2010 report calculated the incremental ICERs for each approach using the 4 sensitivity analyses and presented the incremental results separately for each of the 16 possible analyses. In each incremental analysis, the treatment

strategies compared with each other were:

- etanercept followed by rituximab (strategy 1)
- tocilizumab, followed by etanercept, followed by rituximab (strategy 2)
- etanercept, followed by tocilizumab, followed by rituximab (strategy 3)
- etanercept, followed by rituximab, followed by tocilizumab (strategy 4).

3.38 For all treatment strategies, the calculation of the ICER included the costs and QALYs associated with treatment with conventional DMARDs and palliative care at the end of the sequence. All treatment strategies were in combination with methotrexate.

3.39 Using the threshold for cost effectiveness (£30,000 per QALY gained), the results of the fully incremental analysis undertaken by the DSU in the 2010 report indicated that using tocilizumab as a first-line treatment before etanercept would not be cost effective for any approach and with any set of parameter assumptions (including the manufacturer's base-case assumptions). Using tocilizumab as a second-line treatment before rituximab would only be cost effective if it is assumed that tocilizumab has long-term HAQ improvement and there is no HAQ improvement assumed with other biological treatments. However, if tocilizumab has zero HAQ improvement, then tocilizumab would only be cost effective when used as a third-line treatment after rituximab. If tocilizumab has zero HAQ improvement and the administration costs of tocilizumab are doubled, then tocilizumab is never cost effective (that is, standard care is the most cost-effective sequence). For people who have an intolerance to rituximab, or for whom rituximab is contraindicated, adding tocilizumab to the current standard care is cost effective. However, if tocilizumab does not have a different effect on long-term HAQ and the administration costs of tocilizumab are doubled, then the current standard care would be more cost effective for this population.

Rapid review of NICE's technology appraisal guidance on tocilizumab for rheumatoid arthritis: patient access scheme

3.40 In the Appraisal Committee's original guidance on tocilizumab for rheumatoid arthritis (TA198), tocilizumab plus methotrexate was recommended for the treatment of rheumatoid arthritis that has not responded adequately to 1 or more TNF-alpha inhibitors or to rituximab, or in whom rituximab is contraindicated or is withdrawn because of an adverse effect. Following publication of this guidance, the manufacturer submitted a patient access scheme in which a discount was applied to all indications for tocilizumab (see section 2.4) to be considered as a rapid review of the original guidance.

3.41 As part of the rapid review, the manufacturer did not submit any additional clinical-effectiveness data. However, the manufacturer did clarify the ACR and non-response rates for each drug for each position in the treatment sequences. This highlighted that when tocilizumab is the first biological treatment in the sequence, the non-response rate is approximately 40% compared with 27% when etanercept is the first biological treatment in the sequence.

3.42 The manufacturer submitted revised ICERs using the assumptions that the Committee agreed at the final Committee meeting before issuing NICE's original technology appraisal guidance on tocilizumab for rheumatoid arthritis, which included:

- using approach 4 to evidence synthesis (see section 3.35)
- assuming no long-term HAQ improvement with tocilizumab.

3.43 The manufacturer presented the results of an incremental analysis for the DMARD-IR population in which the following treatment sequences were included:

- etanercept then rituximab (baseline sequence)
- tocilizumab then etanercept then rituximab
- etanercept then tocilizumab then rituximab

- etanercept then rituximab then tocilizumab.

3.44 The manufacturer was requested to include an additional baseline treatment sequence of tocilizumab, followed by etanercept. In this analysis, the ICER for tocilizumab as the first treatment in the sequence was £5,716 per QALY gained. As the second treatment in the sequence, it was £30,716 per QALY gained, and as the third treatment in the sequence, the ICER was £8,134 per QALY gained. All ICERs incorporated the discount for tocilizumab agreed as part of the patient access scheme.

3.45 The manufacturer also responded to a request from the DSU as part of this rapid review to provide ICERs for the TNF-IR population in which the following treatment sequences were included:

- rituximab (baseline sequence)
- tocilizumab then rituximab.

3.46 In this analysis, the costs and QALYs associated with prior treatment with a TNF-alpha inhibitor were assumed to be the same for both treatment strategies and were therefore not modelled. The ICER for the tocilizumab sequence compared with the baseline sequence (incorporating the discount for tocilizumab agreed as part of the patient access scheme) was £22,690 per QALY gained.

Decision Support Unit report 2011

3.47 In 2011, the DSU was asked to undertake a review of whether the manufacturer had correctly implemented the Department of Health approved patient access scheme within their cost-effectiveness analysis. Additionally, the DSU critiqued the changes to the costs of tocilizumab and ensured the Committee's agreed assumptions from NICE's original technology appraisal guidance on tocilizumab had been used as the starting point within the economic analysis.

3.48 The DSU confirmed in the 2011 report that these conditions were met. However, it raised the following issues with the manufacturer's analyses:

- No results had been presented for the subgroup of people intolerant to rituximab or who have had rituximab withdrawn because of a contraindication. The ICERs were incorrect because no account had been taken of sequences that were extendedly dominated (less effective than and at least as costly as a combination of other drug sequences).
- Within the TNF-IR analysis, a sequence of rituximab followed by tocilizumab had not been included.
- The DSU also corrected for a minor inaccuracy in the unadjusted trial rates used in NICE's original technology appraisal guidance on tocilizumab. This changed the ACR20, ACR50 and ACR70 response rates for tocilizumab following 2 biologicals from 0.50, 0.31 and 0.15 to 0.50, 0.29 and 0.12 respectively.

3.49 In 2011, the DSU reported the results of their exploratory analysis for the DMARD-IR population, which included the same treatment sequences in an incremental analysis as those modelled by the manufacturer (see section 3.42). All ICERs incorporated the discount for tocilizumab agreed as part of the patient access scheme. In this analysis, 3 sequences were extendedly dominated (first: etanercept followed by rituximab; second: tocilizumab as the first treatment; third: tocilizumab as the second treatment). The ICER for tocilizumab as the third treatment in the sequence was £28,380 per QALY gained compared with £8,134 per QALY gained from the manufacturer's analysis.

3.50 The DSU provided an additional exploratory analysis in the 2011 report. This was an exploratory analysis for the rituximab-intolerant DMARD-IR population. All ICERs incorporated the discount for tocilizumab agreed as part of the patient access scheme. In this analysis etanercept alone was extendedly dominated. The ICER for tocilizumab followed by etanercept compared with tocilizumab alone was £10,698 per QALY gained, and the ICER for etanercept followed by tocilizumab compared with tocilizumab followed by etanercept was £30,121 per QALY gained.

3.51 The DSU reported the results of their exploratory analysis for the TNF-IR population, which included the same treatment sequences in an incremental analysis as those modelled by the manufacturer (see section 3.43). All ICERs incorporated the discount for tocilizumab agreed as part of the patient access

scheme. In this analysis, tocilizumab followed by rituximab was dominated (was less effective than and at least as costly) by rituximab followed by tocilizumab. The ICER for rituximab followed by tocilizumab was £18,527 per QALY gained compared with the manufacturer's estimate of £22,690 per QALY gained.

3.52 Full details of all the evidence are in the manufacturer's submissions, the ERG report, and the reports from the DSU.

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of tocilizumab, having considered evidence on the nature of rheumatoid arthritis and the value placed on the benefits of tocilizumab by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.2 The Committee understood that the main purpose of treatment for rheumatoid arthritis is to suppress inflammation, which in turn can slow disease progression and prevent irreversible joint damage. The Committee heard from the clinical specialists and patient experts that the primary concern with tocilizumab treatment was the potential for infectious complications, but that trial data suggested that most adverse events were relatively minor, and, in most cases, did not limit treatment use. The Committee noted the safety data presented by the manufacturer, which reported 27 deaths and a serious adverse event rate of 5.8%. The Committee considered that this adverse event rate was high, but heard that it was comparable with other biological treatments.

4.3 The Committee understood that NICE's previous technology appraisal guidance on adalimumab, etanercept and infliximab (TA130) recommended TNF-alpha inhibitors adalimumab, etanercept and infliximab as options for the treatment of adults whose rheumatoid arthritis has responded inadequately to 2 DMARDs (unless DMARDs are contraindicated), and with a DAS28 score greater than 5.1. The Committee noted that in NICE's previous guidance on adalimumab, etanercept and infliximab, treatment should normally be initiated with the least expensive drug (taking into account administration costs, required dose and product price per dose) and this may need to be varied in individual cases because of differences in the mode of administration and treatment schedules. It was also aware of:

- NICE's previous technology appraisal guidance on certolizumab pegol for the treatment of rheumatoid arthritis (TA186; now replaced by NICE's technology appraisal guidance on adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept)

- NICE's technology appraisal guidance on golimumab.

4.4 It noted the recommendations for the TNF-alpha inhibitors certolizumab pegol and golimumab to be used as described in NICE's previous technology appraisal guidance on adalimumab, etanercept and infliximab, including the specific considerations concerning disease activity and choice of treatment. For treatment following an inadequate response to DMARDs (including at least 1 TNF-alpha inhibitor), NICE's technology appraisal guidance on adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor recommends rituximab plus methotrexate.

4.5 The Committee discussed the treatment options for people with moderate to severe active rheumatoid arthritis. It was aware that after an inadequate response to rituximab, additional DMARDs and best supportive care would be offered. The Committee heard from the manufacturer that it was seeking a recommendation for tocilizumab as an option along with other biological treatments in the treatment pathway. The Committee concluded that there were 4 possible scenarios for including tocilizumab in the treatment pathway:

- Tocilizumab after 2 DMARDs as an alternative to TNF-alpha inhibitors.
- Tocilizumab after TNF-alpha inhibitors as an alternative to rituximab.
- Tocilizumab after TNF-alpha inhibitors when a person is intolerant to rituximab or for whom rituximab is contraindicated.
- Tocilizumab as an addition to the treatment pathway after rituximab.

Clinical effectiveness

4.6 The Committee first discussed tocilizumab given as monotherapy. It noted that the only clinical evidence for tocilizumab monotherapy came from a trial that included people who had not been previously treated with methotrexate and that tocilizumab monotherapy treatment for this population was outside the licensed indication of tocilizumab. The Committee also noted that no cost-effectiveness estimates of tocilizumab given as monotherapy had been presented by the

manufacturer. It concluded that no evidence for tocilizumab monotherapy within its licensed indication was available, and therefore no recommendations for tocilizumab as a monotherapy could be made.

4.7 The Committee considered the evidence on the clinical effectiveness of tocilizumab plus DMARDs compared with placebo plus DMARDs. The Committee concluded that tocilizumab plus methotrexate was clinically effective compared with placebo plus DMARDs when given before TNF-alpha inhibitors and when given before rituximab.

4.8 The Committee then considered the evidence for the relative efficacy of tocilizumab compared with etanercept and compared with rituximab when all treatment strategies were in combination with methotrexate. It understood that tocilizumab had not been compared head-to-head with etanercept (or any other TNF-alpha inhibitor) or rituximab, and that indirect evidence had been combined in a mixed treatment comparison for this purpose. It noted the concerns raised by the ERG and clinical specialists regarding the mixed treatment comparison. The mixed treatment comparison assumed that the TNF-alpha results could be regarded as a class; however, when merged, the overall results reduced the efficacy of etanercept. The Committee noted that the manufacturers had responded to its requests to remove the Klareskog trial of etanercept from the analysis because this was a large RCT with unusually high control-arm response rates and did not correspond with the inclusion criteria of the mixed treatment comparison. With this trial removed, the Committee noted that etanercept appeared at least equal to, and possibly had higher efficacy than, tocilizumab.

4.9 The Committee further noted the concerns of the DSU in its 2010 report regarding the adjusted ACR response rates from the mixed treatment comparison compared with the 'unadjusted' point estimates from the individual trials. It understood that the proportions of people achieving ACR20, ACR50 and ACR70 response rates for etanercept and rituximab resulting from the mixed treatment comparison were lower than the corresponding unadjusted trial ACR response rates. Conversely, the proportions of people achieving ACR20, ACR50 and ACR70 response rates were higher for tocilizumab in the adjusted mixed treatment comparison analysis than the unadjusted trial rates. The 2010 DSU report clarified that the counterintuitive results of the mixed treatment comparison had possibly arisen when the comparator response rates from all of the trials had

been pooled. The Committee considered that the mixed treatment comparison included a set of heterogeneous trials, which meant that the results were subject to considerable uncertainty, and that limited confidence could be placed in the adjusted ACR response rates in the manufacturer's revised base case. The Committee concluded that using the unadjusted trial estimates in the analyses was more appropriate.

4.10 The Committee considered the relative efficacy of tocilizumab compared with etanercept and also with rituximab using the unadjusted trial estimates of ACR rates. It considered that the evidence was not conclusive of a benefit of any 1 drug over another. The Committee concluded that no convincing evidence had been presented to demonstrate the superiority of tocilizumab over etanercept or rituximab, but that the estimates were in a similar range to etanercept and rituximab.

4.11 The Committee considered the clinical evidence for tocilizumab after treatment with rituximab. Based on previous discussions it recognised that tocilizumab plus methotrexate is clinically effective compared with placebo plus methotrexate (see section 4.7). It noted the evidence from the RADIATE trial in which a subgroup of people had rheumatoid arthritis that had responded inadequately to 2 TNF-alpha inhibitors. It understood that this was the only available evidence to consider the effectiveness of tocilizumab after rituximab. The Committee considered that it indicated a benefit of tocilizumab after 2 biological treatments. In view of this evidence and considering the comments from patient experts and clinical specialists, the Committee, on balance, agreed that tocilizumab was likely to benefit people whose rheumatoid arthritis has responded inadequately to rituximab.

Cost effectiveness

4.12 The Committee discussed the appropriate approach for determining the cost effectiveness of tocilizumab. It understood that before the 2010 DSU report the manufacturer's ICERs were based on adjusted trial response rates from the mixed treatment comparison. It also understood that the 2010 DSU report presented analyses using 4 different approaches to evidence synthesis (see section 3.35). The Committee considered, on the basis of previous discussions (see

section 4.8), that approach 1, in which the ACR response rates came from the mixed treatment comparison, was not appropriate. The remaining 3 approaches to evidence synthesis used the unadjusted trial response rates for all treatments and incorporated degradation rates. The Committee understood that approaches 2 and 3 only used the unadjusted ACR response rate from a single trial for etanercept, rather than from the 2 available trials. The Committee had a strong preference for approach 4, which used data from both of the etanercept trials. Approach 4 also corrected the counterintuitive ACR70 response rate for tocilizumab used as a third biological treatment in the treatment sequence noted by the DSU in the 2010 report. The Committee concluded that approach 4 to evidence synthesis (see section 3.35) was the most appropriate for consideration.

4.13 The Committee also discussed the 2 sensitivity analyses presented by the DSU within approach 4 in the 2010 report. The first concerned evidence supplied by the manufacturer for a long-term HAQ improvement. It understood that the data for a HAQ improvement with tocilizumab treatment came from open-label extension studies in which only the HAQ scores for people who remained on treatment were available. It noted that, for the open-label extension trial assessing the benefits of tocilizumab after the failure of conventional DMARDs (that is, before etanercept), approximately 30% of people had stopped treatment. It further noted that the confidence intervals around the mean HAQ scores at each point in time were wide. The Committee therefore considered that the manufacturer's evidence was not a robust estimate of the long-term HAQ improvement on tocilizumab and was subject to uncertainty. Furthermore, the manufacturer had not provided any comparable investigation into long-term HAQ trends for the comparator biological treatments other than rituximab. The manufacturer presented a graph of a stable HAQ trend for people on rituximab from the REFLEX trial. However, no data had been supplied by the manufacturer to support the graph. The Committee questioned the comparability of the rituximab and tocilizumab HAQ trend lines, and considered that single-arm extension trial data did not provide a direct comparison of the relative benefits between the 2 treatments. In addition, the Committee heard from patient experts and clinical specialists that it was unlikely that tocilizumab would provide a long-term HAQ benefit over and above that of any other biological treatment. Overall, the Committee could not support the assumption that there is a long-term HAQ gain with tocilizumab (that is, a HAQ improvement with tocilizumab) compared

with no HAQ improvement with other biological treatments. It concluded, on the basis of the evidence presented, that the long-term HAQ improvement on tocilizumab treatment had not been demonstrated. The Committee agreed that the analyses that assumed no long-term HAQ improvement with tocilizumab were therefore the most appropriate for consideration.

4.14 The second sensitivity analysis that the Committee considered concerned the exclusion of negative utilities (health states worse than death) from the incremental analysis. The Committee noted that the manufacturer's mapping of HAQ scores to EQ-5D utility values resulted in negative utility values. It discussed that excluding negative utility values could be considered counterintuitive and did not allow for a worsening of quality of life when a person had rheumatoid arthritis. The Committee heard from the manufacturer that it was possible that there were some people with rheumatoid arthritis who may experience negative utility values. The Committee noted that the impact of removing the negative utilities from the incremental analysis was minimal. The Committee agreed that although the exclusion of negative utility values was subject to some debate, it was not a key issue in determining the cost effectiveness of tocilizumab. The Committee therefore accepted that the calculation of some ICERs would include negative utility values but concluded that this was acceptable because of the low impact on the ICERs.

4.15 The Committee considered the administration costs of tocilizumab. It noted comments received during consultation in 2010 that, although the infusion took 1 hour, the total time taken to administer tocilizumab in an organised unit would be at least 2 hours. The Committee then discussed the 2010 DSU analysis using approach 4 with no long-term HAQ improvement and the administration costs doubled. It heard from the DSU that the decision to double the cost was not based on a robust estimate of the time taken to administer tocilizumab, but was intended to illustrate the sensitivity of the ICERs to this assumption. Although the Committee agreed that a cost based on an administration time of 1 hour represented the minimum cost to the NHS, it did not agree that the true cost would be as much as double. The Committee therefore considered that it was not appropriate to double the administration cost of tocilizumab and concluded that the manufacturer's revised estimate of £154 was acceptable.

4.16 The Committee noted that some modelling assumptions in the manufacturer's

submission had not been investigated by the DSU in the 2010 report. These included, first, any difference in the adverse events that may occur on biological treatment compared with those that might occur in palliative care. Second, that despite previous requests to the manufacturer to use directly observed EQ-5D data, the revised base-case ICERs from the manufacturer were still subject to a HAQ mapping algorithm. The Committee highlighted its concern with this, but acknowledged that the data had not been available to investigate these assumptions.

4.17 In summary the Committee concluded that the best estimate of cost effectiveness of tocilizumab in any position in the treatment pathway should be based on approach 4 to evidence synthesis in which the ACR response rates came from the trials rather than the mixed treatment comparison and used a corrected degradation factor for tocilizumab (see section 3.35). In addition, it concluded that no long-term HAQ improvements with tocilizumab should be assumed.

4.18 The Committee considered the cost-effectiveness analyses submitted by the manufacturer in 2011 that were based on the preferred approach (see section 4.17) and that incorporated tocilizumab at the discount agreed as part of the patient access scheme (see section 2.4). It also considered the DSU 2011 report when reviewing the manufacturer's submission. It discussed the manufacturer's analyses, which the DSU replicated including fully incremental calculations (see sections 3.45 to 3.47) for all 3 patient subgroups: people whose rheumatoid arthritis has responded inadequately to 1 or more conventional DMARDs (DMARD-IR analysis); people who are intolerant to rituximab, or for whom rituximab is contraindicated (DMARD-IR rituximab intolerant); people whose rheumatoid arthritis has responded inadequately to TNF-alpha inhibitors (TNF-IR analysis). The Committee accepted the DSU separate exploratory incremental analyses. It noted the DSU's comment from the 2011 report that the manufacturer's analysis had not taken into account extended dominance (when 1 or more drug sequences are less effective than and at least as costly as another sequence) and that this had an impact on the ICERs. The Committee concluded that the DSU's 2011 exploratory analyses should be used as the basis for determining the cost effectiveness of tocilizumab.

4.19 The Committee also considered the straightforward inferences that could be

made from its separate clinical effectiveness and costing conclusions. These were that for the DMARD-IR population (who had not received a TNF-alpha inhibitor or any other biological treatment) tocilizumab was similar in clinical effectiveness (see section 4.10) to the TNF-alpha inhibitors and could be considered a plausible alternative. In the case of the TNF-IR population (whose condition had failed to respond to a TNF-alpha inhibitor but who had not yet tried rituximab), the position was different. Although tocilizumab might be as clinically effective as rituximab, it was also more expensive and so the Committee concluded tocilizumab could not be considered an option unless rituximab was contraindicated, not tolerated or had failed.

4.20 The Committee considered the DMARD-IR ICERs in the DSU's 2011 exploratory analysis. It noted from the total costs and QALYs for the sequences that when tocilizumab was the first biological treatment rather than etanercept, it was associated with fewer QALYs and less cost. It understood that this was because of the percentage of non-responders on tocilizumab (approximately 40%) when taken as a first-line biological treatment, which resulted in reduced time on tocilizumab treatment and therefore lower cost of the sequence. The Committee noted that this improved the cost effectiveness of tocilizumab. However, on the basis of previous discussions (see section 4.10) the Committee was not convinced that the clinical effectiveness of tocilizumab would be superior to that of etanercept. The Committee concluded that the improved cost effectiveness of tocilizumab as the first biological treatment compared with etanercept was due to the cost of time on treatment, rather than any substantial differences in clinical or cost effectiveness between tocilizumab and etanercept.

4.21 The Committee further considered the DMARD-IR ICERs from the DSU's 2011 exploratory analysis. It noted that although tocilizumab appeared cost effective as the first biological treatment (£5,700 per QALY gained), this sequence had rituximab as the third biological treatment in the sequence, rather than the second. The Committee raised concerns that this was counterintuitive because the total drug treatment cost of rituximab is approximately half that of either tocilizumab or etanercept. On the basis of previous discussions (see section 4.11) the Committee was not convinced that the clinical effectiveness of etanercept or tocilizumab would be sufficiently superior to rituximab such that a sequence in which rituximab was third would be more cost effective than 1 in which rituximab was second. The Committee noted that a sequence in which tocilizumab was the

first biological treatment, followed by rituximab, followed by etanercept, had not been included in either the manufacturer's or the DSU's 2011 analyses. It was aware that in clinical practice this sequence would involve off-licence use of rituximab because the marketing authorisation restricts rituximab to use after an inadequate response or intolerance to other DMARDs including 1 or more TNF-alpha inhibitors. However, the Committee considered that to understand the impact on the cost effectiveness of placing tocilizumab first in the sequence, it was important to consider all possible treatment sequences. It noted that in their exploratory incremental analysis from 2011, the DSU had incorporated an alternative baseline sequence of tocilizumab followed by rituximab. The Committee accepted this sequence as a proxy for tocilizumab, followed by rituximab, followed by etanercept. It noted that when this alternative baseline sequence was included in the exploratory analysis, 3 sequences were extendedly dominated (see section 3.49) leaving the baseline sequence of tocilizumab followed by rituximab, and the sequence of etanercept, followed by rituximab, followed by tocilizumab. Comparing these 2 sequences, tocilizumab as the third biological in the sequence had an ICER of £28,400 per QALY gained, compared with tocilizumab as the first biological treatment in the sequence. It accepted that some uncertainty around the point estimates of the ICERs was likely. However, the conclusion to this analysis was consistent with the reasoning in section 4.18. The Committee concluded that tocilizumab should be recommended as an option when used in the same way as the TNF-alpha inhibitors etanercept, adalimumab, infliximab, golimumab and certolizumab pegol recommended in NICE's technology appraisal guidance on adalimumab, etanercept and infliximab; certolizumab pegol; and golimumab. The Committee understood that its recommendation would apply to people whose rheumatoid arthritis has a DAS28 score of greater than 5.1. It also understood that treatment should normally be initiated with the least expensive drug (taking into account administration costs, required dose and product price per dose) and this may need to be varied in individual cases because of differences in the mode of administration and treatment schedules.

4.22 The Committee discussed the cost effectiveness of tocilizumab when a person is intolerant to rituximab or for whom rituximab is contraindicated (that is, the DMARD-IR rituximab intolerant population). The Committee again took the view that, assuming that etanercept and tocilizumab have approximately equal effectiveness (see section 4.19) and cost, it would be reasonable for either to be

an option in this position. The Committee noted that the DSU's 2011 analyses broadly corroborated these conclusions. It noted that in this population the ICER from the DSU's 2011 exploratory incremental analysis was £30,100 per QALY gained for a sequence in which etanercept was followed by tocilizumab, and £10,700 per QALY gained for a sequence in which tocilizumab was followed by etanercept (see section 3.50). The Committee concluded that tocilizumab should be recommended as an option for the DMARD-IR rituximab intolerant population. It further concluded that this recommendation should be in line with NICE's technology appraisal guidance on adalimumab, etanercept, infliximab, rituximab and abatacept, specifically the recommendations on disease activity when a second TNF-alpha inhibitor is recommended for people in whom rituximab is contraindicated or when rituximab is withdrawn because of an adverse event.

4.23 Finally, the Committee considered the DSU's 2011 exploratory analysis for the TNF-IR population. It understood that in this analysis, the costs and QALYs associated with earlier treatment on a TNF-alpha inhibitor were assumed to be the same and so the analysis comprised 2 sequences containing tocilizumab (1 in which tocilizumab is followed by rituximab, and 1 in which rituximab is followed by tocilizumab) and a baseline treatment sequence of rituximab alone. The Committee noted from this analysis that the treatment strategy that placed tocilizumab before rituximab was dominated by treating with rituximab before tocilizumab (in people who had previously only had a TNF-alpha inhibitor). The Committee accepted the ICER from this analysis as the most plausible estimate of tocilizumab following rituximab in this population (that is, £18,500 per QALY gained). The Committee also compared this ICER with the manufacturer's estimate of £22,700 per QALY gained. In view of this, the Committee concluded that tocilizumab could be considered an option after an inadequate response to treatment with rituximab but should not be recommended as an alternative to rituximab.

4.24 The Committee noted that, in clinical practice and as recommended in NICE's previous technology appraisal guidance on adalimumab, etanercept and infliximab, treatment should normally be initiated with the least expensive drug; this would not necessarily be the same drug in individual cases because of differences in the mode of administration and treatment schedules. The Committee therefore concluded that it was appropriate to recommend tocilizumab as an option following the same considerations as for the drugs

recommended as options in NICE's previous technology appraisal guidance on adalimumab, etanercept and infliximab.

4.25 The Committee concluded that it was appropriate to recommend tocilizumab plus methotrexate as an option for people whose rheumatoid arthritis has a DAS28 score greater than 5.1 and has responded inadequately to 1 or more previous DMARDs if used as described for TNF inhibitor treatments in NICE's previous technology appraisal guidance on adalimumab, etanercept and infliximab, specifically the recommendations on disease activity and choice of treatment. It concluded that tocilizumab plus methotrexate could be recommended as an option for people whose rheumatoid arthritis has responded inadequately to treatment with DMARDs and a TNF inhibitor and in whom rituximab is contraindicated or who had rituximab withdrawn because of an adverse event. The Committee concluded that, for people whose rheumatoid arthritis has responded inadequately to previous TNF inhibitors, and for whom rituximab is an option, tocilizumab plus methotrexate could not be recommended because although it might be as effective as rituximab, it was more expensive and so could not be considered unless rituximab was contraindicated, not tolerated or had failed. The Committee also concluded that tocilizumab plus methotrexate could be recommended for people whose rheumatoid arthritis has responded inadequately to treatment with 1 or more previous TNF inhibitors and rituximab. It also decided that a recommendation about tocilizumab as monotherapy could not be made because there was not enough evidence of its efficacy as a monotherapy.

5 Implementation

5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has rheumatoid arthritis and the healthcare professional responsible for their care thinks that tocilizumab is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Appraisal Committee members and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Kathryn Abel
Reader and Consultant Psychiatrist, Director of Centre for Women's Mental Health, University of Manchester

Dr David Black
Director of Public Health, Derbyshire County Primary Care Trust

Dr Daniele Bryden
Consultant in Intensive Care Medicine and Anaesthesia, Sheffield Teaching Hospitals NHS Trust

Dr Andrew Burnett
Director for Health Improvement and Medical Director, NHS Barnet, London

David Chandler

Lay member

Dr Mary Cooke
Lecturer, School of Nursing, Midwifery and Social Work, University of Manchester

Dr Chris Cooper
General Practitioner, St John's Way Medical Centre, London

Dr Christine Davey
Research Adviser, North and East Yorkshire Alliance Research and Development Unit, York

Richard Devereaux-Phillips
Director, Public Policy and Advocacy NW Europe, BD, Oxford

Professor Rachel A Elliott
Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Alan Haycox
Reader in Health Economics, University of Liverpool Management School

Professor Cathy Jackson
Professor of Primary Care Medicine, University of St Andrews

Dr Peter Jackson
Clinical Pharmacologist, University of Sheffield

Dr Janice Kohler
Senior Lecturer and Consultant in Pediatric Oncology, Southampton University Hospital Trust

Henry Marsh
Consultant Neurosurgeon, St George's Hospital, London

Professor Gary McVeigh
Professor of Cardiovascular Medicine, Queen's University Belfast and Consultant Physician, Belfast City Hospital

Professor Eugene Milne

Deputy Regional Director of Public Health, North East Strategic Health Authority, Newcastle upon Tyne

Dr Neil Myers
General Practitioner, Glasgow

Professor Stephen O'Brien
Professor of Haematology, Newcastle University

Dr Danielle Preedy
Lay member

Dr Peter Selby
Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Dr Surinder Sethi
Consultant in Public Health Medicine, North West Specialised Services Commissioning Team, Warrington

Professor Andrew Stevens
Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Dr Matt Stevenson
Technical Director, School of Health and Related Research, University of Sheffield

Professor Paul Trueman
Professor of Health Economics, Brunel University, London

Dr Judith Wardle
Lay member

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Emma Stewart

Technical Lead

Joanne Holden and Rebecca Trowman
Technical Advisers

Lori Farrar
Project Manager

7 Sources of evidence considered by the Committee

The Evidence Review Group (ERG) report for TA198 Tocilizumab for the treatment of rheumatoid arthritis was prepared by West Midlands Health Technology Assessment Collaboration:

- Meads C, Jit M, Tsourapas A, Ashfaq K, Connock M, Bayliss S, Jobanutra P, Tocilizumab for the treatment of rheumatoid arthritis, April 2009

The Decision Support Unit (DSU) report for TA198 Tocilizumab for the treatment of rheumatoid arthritis was prepared by the Centre for Health Economics, University of York:

- Palmer S, Sculpher M, Tocilizumab for the treatment of rheumatoid arthritis, May 2010

The DSU report for this appraisal Rheumatoid arthritis – tocilizumab (rapid review TA198) was prepared by the School of Health and Related Research, University of Sheffield:

- Minton J, Tappenden P, Tosh J, Tocilizumab for the treatment of rheumatoid arthritis, September 2011

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Manufacturers or sponsors were also invited to make written submissions. Professional or specialist, patient or carer groups, and other consultees, had the opportunity to give their expert views. Manufacturers or sponsors, professional or specialist, patient or carer groups, and other consultees, also have the opportunity to appeal against the final appraisal determination.

Manufacturers or sponsors:

- Roche Products

Professional or specialist, and patient or carer groups:

- Arthritis and Musculoskeletal Alliance (ARMA)
- Arthritis Care

- National Rheumatoid Arthritis Society
- British Health Professionals in Rheumatology
- British Society for Rheumatology
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

Other consultees:

- Department of Health
- Welsh Government

Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- NHS Quality Improvement Scotland
- Abbott Laboratories (adalimumab)
- AstraZeneca UK (chloroquine)
- GlaxoSmithKline (azathioprine)
- Novartis (ciclosporin)
- Pfizer (methotrexate, sulfasalazine)
- Roche Products (rituximab)
- Sanofi–Aventis (hydroxychloroquine, leflunomide, sodium aurothiomalate)
- Schering-Plough (infliximab)
- Wyeth Pharmaceuticals (etanercept)
- West Midlands Health Technology Assessment Collaboration

- National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA Programme)

The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer or sponsor consultees and commentators. They gave their expert personal view on the original TA198 Tocilizumab for the treatment of rheumatoid arthritis by attending the initial Committee discussion and providing written evidence to the Committee. They are invited to comment on the ACD.

- Dr Pavaladurai Vijayadurai, Consultant Immunologist nominated by Royal College of Pathologists – clinical expert
- Professor Peter C Taylor, Professor of Experimental Rheumatology and Honorary Consultant Rheumatologist, nominated by The British Society for Rheumatology – clinical expert
- Dr Andrew J K Oster, Consultant Rheumatologist and Associate Lecturer, School of Clinical Medicine, University of Cambridge and Director, Rheumatology Clinical Research Unit, nominated by The British Society for Rheumatology – clinical expert
- Ms Ailsa Bosworth, Chief Executive National Rheumatoid Arthritis Society (NRAS), nominated by National Rheumatoid Arthritis Society (NRAS) – patient expert
- Ms Jean Burke, Management Consultant, Comma Consulting, nominated by National Rheumatoid Arthritis Society (NRAS) – patient expert

Representatives from the following manufacturer or sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Roche Products

Update information

Minor changes since publication

June 2024: The wording of the recommendation describing the commercial arrangement (see section 1.1), and in section 2.4, was updated to include procurement information about tocilizumab biosimilars.

June 2021: Recommendation 1.3 added on equality when using the disease activity score.

January 2016: The first bullet point of recommendation 1.1 was updated by the recommendations in the NICE technology appraisal guidance on adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed.

February 2014: Implementation section was updated to clarify that tocilizumab is recommended as an option for treating rheumatoid arthritis.

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