NICE National Institute for Health and Care Excellence

NICE guidance

Tofacitinib for moderate to severe 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

1 Recommendations

1.1 Tofacitinib, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to intensive therapy with a combination of conventional disease-modifying anti-rheumatic drugs (DMARDs), only if:

- disease is severe (a disease activity score [DAS28] of more than 5.1) and
- the company provides tofacitinib with the discount agreed in the patient access scheme.

1.2 Tofacitinib, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to, or who cannot have, other DMARDs, including at least 1 biological DMARD, only if:

- disease is severe (a DAS28 of more than 5.1) and
- they cannot have rituximab and
- the company provides tofacitinib with the discount agreed in the patient access scheme.

1.3 Tofacitinib can be used as monotherapy for adults who cannot take methotrexate because it is contraindicated or because of intolerance, when the criteria in sections 1.1 or 1.2 are met.

1.4 Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy. After an initial response within 6 months, withdraw treatment if at least a moderate EULAR response is not maintained.

1.5 When using the DAS28, healthcare professionals should take into account any physical, psychological, sensory or learning disabilities, or communication difficulties that could affect the responses to the DAS28 and make any adjustments they consider appropriate.

1.6 These recommendations are not intended to affect treatment with tofacitinib that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Clinical trial evidence shows tofacitinib plus conventional DMARDs is more effective than conventional DMARDs alone for treating moderate and severe active rheumatoid arthritis that has not responded adequately to conventional or biological DMARDs.

Clinical trial evidence also shows that tofacitinib plus methotrexate is not worse in effectiveness than the biological DMARD adalimumab plus conventional DMARDs in people whose disease has responded inadequately to conventional DMARDs. Because there are no trials comparing tofacitinib with other biological DMARDs, the company did an indirect comparison. This shows that tofacitinib works as well as most of the biological DMARDs which NICE has already recommended in this indication.

Based on the health-related benefits and costs compared with conventional and biological DMARDs, tofacitinib plus conventional DMARDs is recommended as a cost-effective treatment for severe active rheumatoid arthritis, in line with previous recommendations in:

- NICE technology appraisal guidance on baricitinib
- certolizumab pegol (after a TNF-alpha inhibitor)
- adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept (after conventional DMARDs)
- tocilizumab
- golimumab (after DMARDs)
- adalimumab, etanercept, infliximab, rituximab and abatacept (after a TNF-alpha inhibitor).

  Tofacitinib for moderate active rheumatoid arthritis that has responded inadequately to conventional DMARDs is not cost effective based on what NICE normally considers acceptable, that is, £30,000 per quality-adjusted life year gained.

2 The technology

Information about tofacitinib

Marketing authorisation	Tofacitinib (Xeljanz, Pfizer) in combination with methotrexate has a marketing authorisation in the UK for the 'treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs'. Tofacitinib can be given as monotherapy in patients who are intolerant to methotrexate or when treatment with methotrexate is inappropriate.
Recommended dose and schedule	The recommended dose of tofacitinib is 5 mg twice daily. A dose of 5 mg once daily is appropriate for patients with severe renal impairment (creatinine clearance less than 30 ml/min). A dose of 5 mg once daily is appropriate for patients with moderate hepatic impairment (Child–Pugh B). Tofacitinib should not be used in patients with severe hepatic impairment (Child–Pugh C). Tofacitinib should be interrupted if a patient develops a serious infection, until the infection is controlled.
Price	The list price of a 56-tablet pack of 5 mg tofacitinib is £690.03 (excluding VAT; British national formulary [BNF] online [2017]). The average cost per patient for the first 6 months is estimated at £4,050.60 based on the list price. The average cost per patient for subsequent years is estimated at £9,001.19 based on the list price. The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of tofacitinib, with the discount applied at the point of purchase or invoice. 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.

3 Committee discussion

The appraisal committee considered evidence submitted by Pfizer and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Treatment pathway

Tofacitinib can be used at 4 different points in the pathway

3.1 Tofacitinib's marketing authorisation covers its use at 4 points in the treatment pathway, specifically in adults with:

- moderate, active rheumatoid arthritis that has not responded adequately to conventional disease-modifying anti-rheumatic drugs (DMARDs)
- severe, active rheumatoid arthritis that has not responded adequately to conventional DMARDs
- severe, active rheumatoid arthritis that has not responded adequately to biological DMARDs, including at least 1 tumour necrosis factor-alpha (TNF-alpha) inhibitor
- severe, active rheumatoid arthritis that has not responded adequately to biological DMARDs, including at least 1 TNF-alpha inhibitor and when rituximab is contraindicated or withdrawn because of adverse events.

  The committee also noted that the marketing authorisation includes the use of tofacitinib alone or with methotrexate.

NICE technology appraisal guidance exists for these points in the rheumatoid arthritis treatment pathway

3.2 NICE currently recommends the use of the biological DMARDs in its technology appraisal guidance on baricitinib, adalimumab, etanercept, infliximab,

certolizumab pegol, golimumab, tocilizumab and abatacept (of which adalimumab, certolizumab pegol, etanercept, golimumab and infliximab are TNF-alpha inhibitors), in combination with methotrexate, in people with severe rheumatoid arthritis that has not responded to intensive treatment with combinations of conventional DMARDs. Disease severity is assessed using the disease activity score (DAS28). A DAS28 of more than 5.1 indicates severe disease (between 3.2 and 5.1 indicates moderate disease, less than 3.2 but more than 2.6 indicates mild disease and less than 2.6 indicates disease remission). For people who meet these criteria but cannot take methotrexate, the guidance recommends that baricitinib, adalimumab, certolizumab pegol, etanercept or tocilizumab may be used as monotherapy. The guidance recommends treatment should start with the least expensive drug (taking into account administration costs, dose needed and product price per dose) and should only be continued according to European League Against Rheumatism (EULAR) response at 6 months.

3.3 For people with severe rheumatoid arthritis who have already had at least 1 TNF-alpha inhibitor that hasn't worked, NICE technology appraisal guidance on adalimumab, etanercept, infliximab, rituximab and abatacept and golimumab recommends the biological DMARD rituximab in combination with methotrexate for treating severe active rheumatoid arthritis. But, if rituximab is contraindicated or withdrawn because of an adverse event, NICE technology appraisal guidance recommends tocilizumab, certolizumab pegol, baricitinib, abatacept, adalimumab, etanercept, infliximab or golimumab, in combination with methotrexate. If methotrexate is contraindicated or withdrawn because of an adverse event, NICE's guidance on abatacept, adalimumab, etanercept, infliximab, golimumab, tocilizumab, certolizumab pegol or baricitinib recommends adalimumab, etanercept, tocilizumab, certolizumab pegol or baricitinib as monotherapy. NICE technology appraisal guidance also recommends tocilizumab in combination with methotrexate when neither TNF-alpha inhibitors nor rituximab have worked.

A range of treatment options is important in rheumatoid arthritis

3.4 The committee heard from the patient experts that rheumatoid arthritis is a lifetime condition that can severely reduce quality of life. The clinical experts stated that conventional DMARDs such as methotrexate are inadequate for many

people. They added that the disease sometimes does not respond adequately to the first biological DMARD prescribed. Both the clinical and patient experts said it would be helpful to have new treatments that can be used at various points in the treatment pathway, alongside biological DMARDs after failure of conventional DMARDs. The clinical and patient experts agreed that methotrexate is often not well tolerated; the clinical experts noted that up to a third of people who are prescribed methotrexate with biological DMARDs do not take the drug because of side effects. The committee concluded that a range of treatment options is important in rheumatoid arthritis.

Tofacitinib offers a potentially important new treatment option for people with rheumatoid arthritis

3.5 The clinical experts emphasised that tofacitinib is a novel treatment with a different mode of action to the biological DMARDs. They noted that the selective inhibition of Janus kinase 1 and 3 will affect a broad range of cytokines involved in the pathogenesis of rheumatoid arthritis. The clinical experts noted that there are subtly different adverse effects across the different classes of drugs for rheumatoid arthritis, but the adverse effects associated with Janus kinase inhibitors are unlikely to influence their desire to prescribe the drug. The patient experts noted that the potential benefits of treatment with Janus kinase inhibitors are likely to outweigh the adverse effects. The clinical experts also noted the similar kinetic action of tofacitinib compared with biological DMARDs, specifically TNF-alpha inhibitors. Both the clinical and patient experts also highlighted that tofacitinib is given orally, which has major benefits for both patients and the health system. The patient experts emphasised that this is an important factor for people who have difficulty injecting themselves because of the disease affecting their hands. The patient experts also noted that some current treatments have to be stopped if the person gets an infection, and that some treatments may cause injection site reactions. The committee recognised that rheumatoid arthritis significantly affects quality of life. It concluded that there is a need for new treatment options, particularly when there is an inadequate response to conventional or biological DMARDs.

Subgroups

The company's subgroups and comparators were appropriate

3.6 The committee was aware that the company had analysed 5 distinct subgroups for whom tofacitinib could be used:

- people with moderate rheumatoid arthritis whose disease has responded inadequately to conventional DMARDs
- people with severe rheumatoid arthritis whose disease has responded inadequately to conventional DMARDs and for whom methotrexate is a treatment option
- people with severe rheumatoid arthritis whose disease has responded inadequately to conventional DMARDs and for whom methotrexate isn't an option
- people with severe rheumatoid arthritis whose disease has responded inadequately to biological DMARDs and for whom rituximab is a treatment option
- people with severe rheumatoid arthritis whose disease has responded inadequately to biological DMARDs and for whom rituximab is contraindicated or not tolerated.

The relevant comparators varied by subgroup. The committee concluded that it was appropriate to consider the 5 groups separately and that the company had broadly included the appropriate comparators.

Clinical effectiveness

The trials were adequate and suitable for decision-making

3.7 The company's clinical evidence came mainly from 4 phase III randomised controlled trials. The trials included people with moderate to severe rheumatoid

arthritis, as defined in section 3.6. The trials were:

- ORAL Standard, which included people whose disease responded inadequately to methotrexate and who had not had biological DMARDs. Tofacitinib 5 mg was given twice daily in combination with methotrexate and the comparators were placebo and adalimumab, both in combination with methotrexate.
- ORAL Scan, which included people whose disease responded inadequately to methotrexate and who had not had biological DMARDs. Tofacitinib 5 mg was given twice daily in combination with methotrexate and the comparator was placebo plus methotrexate.
- ORAL Sync, which included people whose disease responded inadequately to conventional or biological DMARDs. Tofacitinib 5 mg was given twice daily in combination with at least 1 conventional DMARD and the comparator was placebo plus methotrexate.
- ORAL Solo, which included people whose disease responded inadequately to conventional or biological DMARDs. Tofacitinib 5 mg alone was given twice daily and the comparator was placebo.

  The primary outcomes of all the randomised controlled trials, measured at month 3 or 6, were:

- proportion of people with a 20% improvement in the American College of Rheumatology response criteria (ACR20)
- mean change from baseline in the Health Assessment Questionnaire–Disability Index (HAQ-DI)
- proportion of people with a DAS28 of less than 2.6.

  The key secondary outcomes included the proportion of people with a 50% or 70% improvement in the response criteria (ACR50 and ACR70 respectively).

  Additional clinical evidence came from ORAL Strategy, a phase III/IVb randomised controlled trial. It included people with moderate to severe rheumatoid arthritis, and measured ACR50 at month 6, as its primary

outcome. The committee concluded that the trials were adequate and suitable for decision-making.

EULAR response was derived from DAS28 score

3.8 The committee noted that because the ORAL trials did not collect the EULAR response criteria, EULAR response was derived from the DAS28 scores for each trial, at month 3 or 6. The EULAR response criteria use the individual change in DAS28 and the absolute DAS28 score to classify a EULAR response as good, moderate, or none. The committee accepted the company's estimation of the EULAR response and concluded that the trials were relevant and adequate for its decision-making.

The company adjusted for crossover using 2 approaches considered suitable for decision-making

3.9 The committee noted that the design of the ORAL trials allowed all the patients having placebo or all patients whose condition did not respond to placebo to have tofacitinib after month 3 (response was defined as a 20% reduction in the number of tender and swollen joints). The committee heard from the ERG that, to adjust for crossover, 2 approaches were applied. The first approach estimated the treatment effect (estimate 1) by imputing the number of patients from the placebo arm whose condition did not respond at month 3 (also known as non-responder imputation without advancement penalty). The second approach estimated the treatment effect (estimate 2) by imputing the number of patients from the placebo arm whose condition did not respond at month 3 as well as the patients from the tofacitinib arm whose condition did not respond (also known as non-responder imputation with advancement penalty). The committee noted that the primary analysis for the ORAL Standard, Scan and Sync trials was based on non-responder imputation with advancement penalty (estimate 2) and therefore clinical results are reported for a combined placebo group (that is, the group who crossed over to have either 5 mg or 10 mg of tofacitinib, because the results were not provided separately for the licensed 5 mg dose). Because fewer patients from the placebo arm whose condition did not respond at month 3 later developed a

response at month 6 compared with patients from the tofacitinib arm, the ERG agreed that the true treatment effect was likely to lie between these 2 estimates, but closer to estimate 1 than to estimate 2. The committee was satisfied with the approaches used to adjust for crossover and agreed with the ERG on their estimation of the true treatment effect.

Tofacitinib with methotrexate is more clinically effective than conventional DMARDs for moderate to severe disease that has responded inadequately to conventional DMARDs

3.10 The committee considered ORAL Standard and ORAL Scan, which included people with moderate to severe rheumatoid arthritis whose disease responded inadequately to conventional DMARDs. In both trials, there was a statistically significant increase in the proportion of people having tofacitinib who met the ACR20 criteria at month 6 compared with the combined placebo group (see section 3.9): ORAL Standard 51.5% compared with 28.3% respectively, $p<0.001$; ORAL Scan 51.5% compared with 25.3% respectively, $p<0.001$. In ORAL Standard, there was also a statistically significant increase in the proportion of people having adalimumab who met the ACR20 criteria at month 6 compared with the combined placebo group: 47.2% compared with 28.3% respectively, $p<0.001$. Statistically significant improvements in the mean change from baseline in HAQ-DI scores and the proportion of patients achieving a DAS28 of less than 2.6 were also seen in ORAL Standard for tofacitinib compared with the combined placebo group (−0.55 compared with −0.24, $p<0.001$; 6.2% compared with 1.1%, p value is confidential). For ORAL Scan, no statements about statistical significance could be made for the HAQ-DI score or DAS28 outcomes. The committee considered ORAL Strategy, which included people with moderate to severe rheumatoid arthritis that responded inadequately to conventional DMARDs. For the proportion of people meeting the ACR50 criteria at 6 months, tofacitinib plus conventional DMARDs was non-inferior to adalimumab plus conventional DMARDs, and tofacitinib monotherapy was less effective than both tofacitinib and adalimumab, both in combination with conventional DMARDs. The committee concluded that in people with moderate to severe rheumatoid arthritis whose disease has responded inadequately to conventional DMARDs, tofacitinib plus conventional DMARDs is not worse in effectiveness than adalimumab plus conventional DMARDs, and is more effective than conventional DMARDs alone.

Tofacitinib alone and with methotrexate is more clinically effective than conventional DMARDs for moderate to severe disease that has responded inadequately to

conventional or biological DMARDs

3.11 The committee considered ORAL Sync (combination therapy) and ORAL Solo (monotherapy), which included people with moderate to severe rheumatoid arthritis whose disease responded inadequately to conventional or biological DMARDs. For ORAL Sync, in the tofacitinib plus methotrexate group compared with the combined placebo group, there was a statistically significant increase in the proportion of people meeting the ACR20 criteria at 6 months (52.7% compared with 31.2%, $p<0.001$) and in the mean change from baseline in HAQ-DI scores at 3 months (−0.46 compared with −0.21, $p<0.01$) respectively. The proportion achieving remission using a DAS28 less than 2.6 response at 3 months was 9.1% compared with 2.7% for tofacitinib plus methotrexate compared with combined placebo ($p=0.0038$). In ORAL Solo, the proportion of people meeting the ACR20 criteria and the mean change from baseline in HAQ-DI scores at 3 months was statistically significantly higher for tofacitinib monotherapy compared with combined placebo at 3 months (ACR20 59.8% compared with 26.7%, $p<0.001$; HAQ-DI −0.50 compared with −0.19, $p<0.001$). The proportion of patients in the tofacitinib monotherapy group compared with the combined placebo group who went into remission, based on a DAS28 response of less than 2.6 at 3 months, was not statistically significantly different (5.6% compared with 4.4%; $p=0.62$). The committee concluded that tofacitinib plus conventional DMARDs is more effective than conventional DMARDs alone, and tofacitinib alone is more effective than placebo in people with moderate to severe rheumatoid arthritis whose disease has responded inadequately to conventional or biological DMARDs.

Tofacitinib has a similar safety profile to conventional DMARDs

3.12 The committee noted that the safety profiles of tofacitinib and conventional DMARDs were similar. It heard from the ERG that a safety review by Curtis et al. (2016) showed that the incidence of herpes zoster was significantly higher in people who had previously had tofacitinib than those who had previously had biological DMARDs. The committee heard from clinical experts that this adverse effect was specific to the class of Janus kinase inhibitors rather than tofacitinib. It also heard that the higher incidence of herpes zoster in the review was not associated with a higher rate of patients stopping treatment with tofacitinib

because it is considered as a manageable infection. The committee concluded that tofacitinib's safety profile was acceptable and similar to that of conventional DMARDs.

Indirect comparison

Network meta-analyses show that tofacitinib works as well as biological DMARDs

3.13 The committee was aware that other than the direct comparison with adalimumab, the only evidence available on the comparative effectiveness of tofacitinib and the biological DMARDs was from the company's network meta-analyses. The company did separate analyses for patients whose disease responded inadequately to either conventional or biological DMARDs, using change in HAQ-DI from baseline and EULAR response outcome measures, together with estimate 1 (see section 3.9) in the base case.

At the 20- to 30-week follow-up, for patients whose disease responded inadequately to conventional DMARDs, the network meta-analysis showed that:

- tofacitinib plus conventional DMARDs gave better EULAR response rates than conventional DMARDs alone
- tofacitinib plus conventional DMARDs gave similar EULAR response rates to biological DMARDs plus conventional DMARDs
- estimates 1 were higher than estimates 2.

At the 20- to 30-week follow-up, for patients whose disease responded inadequately to biological DMARDs, the network meta-analysis provided only used estimate 2 and showed that tofacitinib plus conventional DMARDs gave similar EULAR response rates to biological DMARDs plus conventional DMARDs.

The company's and ERG's network meta-analysis results were

broadly comparable

3.14 The committee heard from the ERG that there were problems with the methods used in the company's network meta-analysis. These included:

- different models for EULAR response in the 2 populations
- a random effects model for patients whose disease responded inadequately to conventional DMARDs and a fixed effects model for patients whose disease responded inadequately to biological DMARDs
- a uniform prior in the random effects model
- using estimate 1 in their base case and
- the method of linking etanercept to the network.

Also, studies reporting EULAR responses were synthesised with converted EULAR response outcomes from studies that only reported ACR responses. At the clarification stage, the company corrected the errors in their network meta-analysis. The committee was satisfied that the corrected network meta-analysis was suitable for decision-making.

Cost effectiveness

The economic model structure was appropriate for decision-making

3.15 The company used an individual patient-based discrete event simulation model for its economic evaluation. The model simulates patients' disease progression through the sequences of treatments being compared. It was based on the model used by the assessment group during the production of NICE technology appraisal guidance on adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis. The model categorised patients based on their EULAR response (good, moderate or no response) at 6 months. Response rates were based on a regression model using ORAL trial data (for tofacitinib and tofacitinib plus methotrexate) and the

company's network meta-analysis (for the comparators). The treatment stopped if the patient did not have at least a moderate EULAR response at 6 months. The company analysed cost effectiveness for each of the subgroups described in section 3.6. The committee concluded that the model structure was appropriate for its decision-making.

The model was adequate for decision-making

3.16 After corrections by the company (at the clarification stage and a later correction of an error in the company submission), the ERG identified several issues with the company's economic analyses including:

- exclusion of relevant comparators that have previously been recommended by NICE
- using inappropriate sequences of treatment
- assuming that the efficacy for sulfasalazine is the same as the efficacy for placebo
- deterministic rounding of HAQ scores to the nearest valid HAQ score, rather than allowing HAQ scores to be sampled based on a continuous HAQ value
- excluding intravenous abatacept and subcutaneous tocilizumab from the list of comparators.

The ERG amended the company's model by using the appropriate sequencing and applying a probabilistic HAQ rounding (instead of deterministic) and stated that the other errors were unlikely to change the broad conclusions of the company's model. The committee concluded that the ERG's amended model was adequate for its decision-making.

Cost-effectiveness results

Tofacitinib is not cost effective for moderate disease after conventional DMARDs

3.17 In the moderate active rheumatoid arthritis population whose disease has responded inadequately to conventional DMARDs, the ERG's incremental cost-effectiveness ratio (ICER) for the tofacitinib sequence compared with the conventional DMARD sequence, including the confidential comparator patient access scheme, was above £30,000 per quality-adjusted life year (QALY) gained. The committee considered that tofacitinib plus conventional DMARDs was not cost effective in people with moderate rheumatoid arthritis whose disease has responded inadequately to conventional DMARDs.

Tofacitinib, with methotrexate, is cost effective for severe active disease after conventional DMARDs

3.18 In the ERG's analysis for the severe rheumatoid arthritis population whose disease has responded inadequately to conventional DMARDs, the clinical and cost-effectiveness estimates for tofacitinib plus conventional DMARDs were very similar to what had previously been seen in rheumatoid arthritis. The committee concluded that it could recommend tofacitinib plus methotrexate as a cost-effective use of NHS resources for people with severe rheumatoid arthritis whose disease has responded inadequately to conventional DMARDs, in line with the NICE recommendations on adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept.

Tofacitinib monotherapy is cost effective for severe active disease after conventional DMARDs

3.19 In the ERG's analysis for the severe rheumatoid arthritis population whose disease has responded inadequately to conventional DMARDs, tofacitinib monotherapy produced very similar clinical and cost-effectiveness estimates compared with what had previously been seen in rheumatoid arthritis. The

committee concluded that it could recommend tofacitinib monotherapy as a cost-effective use of NHS resources for people with severe rheumatoid arthritis whose disease has responded inadequately to conventional DMARDs, in line with the NICE recommendations on adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept.

Tofacitinib is not cost effective for severe disease after biological DMARDs if rituximab is a treatment option

3.20 For the severe rheumatoid arthritis population whose disease has responded inadequately to biological DMARDs and for whom rituximab is a treatment option, the only sequence recommended by NICE is rituximab followed by tocilizumab. In the ERG's analysis, ICERs were presented for alternative sequences compared with the recommended sequence. It showed that when using estimate 1, tofacitinib followed by tocilizumab was dominated by rituximab followed by tocilizumab, whereas the sequence of rituximab followed by tofacitinib gives cost savings but also loss of QALYs, resulting in ICERs that reflect 'savings per QALY lost'. For example, in the ERG's analysis, when comparing the sequence starting with rituximab followed by tofacitinib with the sequence starting with rituximab followed by tocilizumab, there was a cost saving of £15,284 in the tofacitinib sequence, but a QALY loss of −0.19, resulting in an ICER of £80,442 saved per QALY lost. When using estimate 2, the sequence of tofacitinib followed by tocilizumab was dominated by rituximab followed by tocilizumab (less costly and more effective) whereas rituximab followed by tofacitinib resulted in cost savings but also loss of QALYs (£137,483 saved per QALY lost). The committee noted that a confidential patient access scheme is in place for tocilizumab, which was not included in this analysis. The committee considered the ICERs that incorporated confidential patient access schemes for tocilizumab and tofacitinib, but the results are confidential and cannot be reported here (to protect the confidentiality of the discounts in the patient access schemes). The committee noted that when using estimate 1, the sequence of tofacitinib followed by tocilizumab remained dominated by NICE's recommended sequence, and although the ICER for rituximab followed by tofacitinib was lower, the cost savings were at a less acceptable level given the QALYs that would be lost. When using estimate 2, the sequence of tofacitinib followed by tocilizumab resulted in cost savings and loss of QALYs. The ICER for rituximab followed by tofacitinib no

longer resulted in cost savings and was dominated by the recommended sequence. Therefore there was a high degree of uncertainty around the cost-effectiveness estimates in this population. Taking into account all of the information presented, the committee concluded that tofacitinib was not a cost-effective use of NHS resources for people with severe rheumatoid arthritis whose disease has responded inadequately to biological DMARDs if rituximab is a treatment option.

Tofacitinib, with methotrexate, is cost effective for severe disease after biological DMARDs if rituximab is not a treatment option

3.21 The committee noted that adalimumab, infliximab and certolizumab pegol, all in combination with methotrexate, have not been included in the analyses despite this being recommended by NICE. The committee noted that all the comparisons produced very similar estimates of clinical and cost effectiveness compared with those previously seen in appraisals of rheumatoid arthritis. It concluded that tofacitinib plus methotrexate was a cost-effective use of NHS resources for people with severe rheumatoid arthritis whose disease has responded inadequately to biological DMARDs and for whom rituximab is not a treatment option.

The recommendations also apply to tofacitinib for severe disease after biological DMARDs if methotrexate is not a treatment option

3.22 The committee was aware that the marketing authorisation for tofacitinib includes its use as a monotherapy. But the company did not present an economic analysis for tofacitinib alone for severe disease, after biological DMARDs, in patients who cannot have methotrexate. The committee recognised the considerable uncertainty about the effectiveness of tofacitinib alone in people whose disease has responded inadequately to conventional or biological DMARDs. The committee was aware that in NICE's technology appraisal guidance on baricitinib, the committee concluded that baricitinib monotherapy has similar clinical effectiveness to baricitinib plus conventional DMARDs. The committee

heard from the clinical experts that, although the preference is to give tofacitinib plus methotrexate, if a person cannot take methotrexate, tofacitinib will be given alone. The clinical experts also noted that Janus kinase inhibitors seem to have similar clinical effectiveness. The committee concluded that its recommendations for tofacitinib plus conventional DMARDs should also apply to tofacitinib alone for people with severe rheumatoid arthritis whose disease has responded inadequately to biological DMARDs and who cannot take methotrexate because it is contraindicated or not tolerated.

4 Implementation

4.1 Section 7(6) 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.

4.2 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 determination.

4.3 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 doctor responsible for their care thinks that tofacitinib is the right treatment, it should be available for use, in line with NICE's recommendations.

4.4 The Department of Health and Pfizer have agreed that tofacitinib will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to pfizerNICEaccount@pfizer.com.

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

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.

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.

Aminata Thiam
Technical lead

Fay McCracken
Technical adviser

Kate Moore
Project manager

Update information

December 2020: Recommendation 1.3 updated to clarify when tofacitinib can be used as monotherapy. Recommendation 1.5 added to ensure equality when using the DAS28.

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