NICE National Institute for Health and Care Excellence

NICE guidance

Tofacitinib for treating active psoriatic arthritis after inadequate response to DMARDs

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 are 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.

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 psoriatic arthritis in adults, only if:

- it is used as described in NICE's technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (recommendations 1.1 and 1.2) or
- the person has had a tumour necrosis factor (TNF)-alpha inhibitor but their disease has not responded within the first 12 weeks or has stopped responding after 12 weeks or
- TNF-alpha inhibitors are contraindicated but would otherwise be considered (as described in NICE's technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis).

  Tofacitinib is only recommended if the company provides it according to the commercial arrangement.

1.2 Assess the response to tofacitinib after 12 weeks of treatment. Only continue treatment if there is clear evidence of response, defined as an improvement in at least 2 of the 4 Psoriatic Arthritis Response Criteria (PsARC), 1 of which must be joint tenderness or swelling score, with no worsening in any of the 4 criteria. People whose disease has a Psoriasis Area and Severity Index (PASI) 75 response but whose PsARC response does not justify continuing treatment should be assessed by a dermatologist, to determine whether continuing treatment is appropriate based on skin response (as described in NICE's technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis, recommendation 1.3).

1.3 When using the PsARC healthcare professionals should take into account any physical, sensory or learning disabilities or communication difficulties that could affect a person's responses to components of the PsARC and make any adjustments they consider appropriate.

1.4 When using the PASI, healthcare professionals should take into account skin colour and how this could affect the PASI score, and make the clinical adjustments they consider appropriate.

1.5 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

NICE recommends several treatments for treating psoriatic arthritis. Tofacitinib is the first of a new class of drugs for treating psoriatic arthritis (Janus kinase inhibitors).

Clinical trial evidence shows that tofacitinib is more effective than placebo at treating joint and skin symptoms. An indirect comparison suggests that tofacitinib is likely to improve symptoms about as well as some of the current treatments used in the NHS for psoriatic arthritis.

Overall, the cost-effectiveness estimates of tofacitinib are within the range normally considered to be an acceptable use of NHS resources when it is used after 2 conventional disease-modifying anti-rheumatic drugs (DMARDs), or after treatment with a TNF-alpha inhibitor after 2 conventional DMARDs. Therefore, it can be recommended.

2 Information about tofacitinib

Marketing authorisation indication	Tofacitinib (Xeljanz, Pfizer), in combination with methotrexate, is indicated 'for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying anti-rheumatic drug (DMARD) therapy'.
Dosage in the marketing authorisation	The recommended dose of tofacitinib is 5 mg taken orally twice daily. No dose adjustment is needed when tofacitinib is used with methotrexate. Treatment 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 [accessed July 2018]). The company has a commercial arrangement. This makes tofacitinib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee (section 5) 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.

The condition

Psoriatic arthritis can substantially decrease quality of life

3.1 The patient experts explained that psoriatic arthritis can affect people from a young age (peak onset is 30 to 50 years) and is a lifelong condition. Symptoms including joint stiffness, fatigue and pain can make day-to-day activities difficult and have a serious negative effect on people's quality of life. The patient experts also emphasised that, because psoriatic arthritis can develop at a young age, it often affects people's relationships and career aspirations. Most people develop joint symptoms a few years after skin psoriasis and adding a painful joint disease to the skin symptoms can have a substantial psychological impact. The committee concluded that psoriatic arthritis can substantially decrease quality of life.

Treatment pathway and current management

Tofacitinib will be used in people who have had at least 2 DMARDs

3.2 The marketing authorisation for tofacitinib (with methotrexate) indicates treatment for people whose disease has had an inadequate response or cannot tolerate 1 or more disease-modifying anti-rheumatic drugs (DMARDs). The company did not submit any clinical- or cost-effectiveness analyses for the population who have had 1 conventional DMARD because this is not in line with British Society for Rheumatology guidelines and previous NICE technology appraisal guidance. These recommend people have 2 conventional DMARDs before non-conventional DMARD therapies. In previous technology appraisals, clinical experts confirmed that in the NHS, people usually have 2 DMARDs before moving on to non-conventional DMARDs. The committee concluded that tofacitinib would be used in people who have had at least 2 DMARDs and that the company's positioning of tofacitinib in the treatment pathway was in line with clinical practice, and therefore appropriate.

Patients and clinicians would welcome an additional effective treatment option

3.3 The clinical experts explained that choice of therapy would depend on the patient's symptoms and characteristics, their previous treatments and tolerability of the drug. They explained that tofacitinib has a different mechanism of action. It would be a useful treatment option because there are only a limited number of non-conventional therapies that are not tumour necrosis factor (TNF)-alpha inhibitors. The clinical experts also highlighted that most non-conventional DMARDs are given subcutaneously, and that it is valuable to have other oral treatment options available. The patient experts explained that because the disease can stop responding to non-conventional DMARDs over time, and because psoriatic arthritis is a lifelong disease, all treatment options can be exhausted by some people. The patient expert also explained that each patient might have different symptoms of psoriatic arthritis and certain treatments can improve some symptoms more than others. The committee concluded that patients and clinicians would welcome an additional treatment option.

Clinical trial evidence

Tofacitinib reduces joint and skin symptoms compared with placebo

3.4 The main source of clinical-effectiveness evidence for tofacitinib came from 2 randomised, double-blinded, placebo-controlled trials. OPAL Broaden included patients who had had previous treatment with a conventional DMARD but had not had previous treatment with a TNF-alpha inhibitor. It compared tofacitinib with placebo and adalimumab. OPAL Beyond included patients who had previously had a TNF-alpha inhibitor but had stopped treatment because their disease had had an inadequate response or they could not tolerate treatment. OPAL Beyond compared tofacitinib with placebo. In both trials, a statistically significant proportion of people having tofacitinib had reductions in joint symptoms as assessed by the American College of Rheumatology (ACR) 20 at 3 months, compared with placebo. The results also showed higher rates of Psoriatic Arthritis Response Criteria (PsARC) and Psoriasis Area and Severity Index (PASI) responses at 3 months with tofacitinib compared with placebo in both trials. Also, a statistically significantly higher proportion of people having tofacitinib also saw improvements in their ability to do daily activities compared with placebo, as assessed by the health assessment questionnaire disability index (HAQ-DI). The committee was aware that there was limited evidence on

radiographic progression for tofacitinib. However, the clinical experts stated that the symptoms of psoriatic arthritis gave an indication of disease progression, and that if treatment was able to control symptoms they would expect to see a delay in the progression of joint destruction. The clinical experts also commented that there were good data available for tofacitinib's effect on progression in people with rheumatoid arthritis. The committee recognised that the symptoms of psoriatic arthritis were the main outcomes relevant to the cost-effectiveness analysis. It concluded that tofacitinib improved joint and skin symptoms compared with placebo.

The OPAL trials are generalisable to NHS clinical practice

3.5 The ERG considered that the OPAL trials were well conducted, and that the study design was similar to trials of other NICE recommended treatments for psoriatic arthritis. However, it did highlight that some patients in the trials had tofacitinib with conventional DMARDs other than methotrexate, and that this was outside the marketing authorisation for tofacitinib. The committee was aware that about 18% of OPAL Broaden and 24% of OPAL Beyond patients had other conventional DMARDs, but the clinical experts advised that this distribution reflects current NHS clinical practice. The patient experts commented that the mean age of patients in the trial was slightly higher than they would expect to see in clinical practice, but the clinical experts considered that this was unlikely to affect the generalisability of the trial results. The committee concluded that the results of the OPAL trials were generalisable to the NHS.

Network meta-analysis

It is appropriate to have separate network meta-analyses for people who have, and who have not, had previous biological DMARDs

3.6 The company presented 2 sets of network meta-analyses to give evidence of tofacitinib's effectiveness in people who had, and had not, previously had biological DMARDs. The network meta-analyses of trials including people who had not had a previous biological DMARD compared tofacitinib's effectiveness with placebo, adalimumab, apremilast, etanercept, infliximab, ustekinumab, golimumab, secukinumab and certolizumab pegol. Although ustekinumab is not recommended in the population with inadequate disease response to 2 previous conventional DMARDs, it was included in the network meta-analysis to provide

evidence for the population in whom treatment with a TNF-alpha inhibitor is contraindicated or not tolerated. The network meta-analyses of trials including people who had had a previous biological DMARD compared tofacitinib with placebo, ustekinumab and secukinumab. The network meta-analyses explored the effectiveness of treatments on PsARC response, PASI 75 response, and change in HAQ-DI score dependant on PsARC response. The committee was aware that doing separate network meta-analyses for the no previous biological DMARD and previous biological DMARD populations was consistent with the approach used in NICE's technology appraisal guidance on certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs (TA445), and concluded that this approach was appropriate.

The company's network meta-analysis for PsARC outcomes in patients who have not had previous biological DMARDs is acceptable

3.7 The company highlighted that the PsARC response rate for the placebo arm in the OPAL Broaden trial was the highest of all the trials included in the network meta-analysis (45%). Because of differences in placebo response rates between the trials, the company adjusted its network meta-analysis of PsARC response in the no previous biological DMARD population. The committee agreed that this approach was consistent with the assumptions used in TA445. The ERG highlighted that the company had incorrectly implemented its network meta-analysis and presented updated results based on the correct implementation, which the company accepted. In its preferred network meta-analysis model, the ERG also adjusted for placebo response rates. However, instead of assuming independent treatment effects, the ERG preferred to assume class effects between treatments because these models provided a better fit to the data. The committee noted that the choice between the company and ERG approach to the network meta-analysis only had a small effect on the cost-effectiveness results. The committee preferred to use assumptions that were consistent with TA445, and concluded that the company's approach was acceptable (when correctly implemented).

Tofacitinib has similar effectiveness to other non-conventional DMARDs

3.8 The results from the company's network meta-analysis in the no previous biological DMARD population show that tofacitinib was less effective at improving PsARC outcomes compared with biological DMARDs, but had similar

effectiveness to apremilast. The exact results from the company's analysis are academic in confidence. The results also showed that tofacitinib was more effective at improving PASI and HAQ-DI outcomes than improving PsARC response in the no previous biological DMARD population. The results from the network meta-analysis in the previous biological DMARD population show that tofacitinib 5 mg had similar effectiveness to ustekinumab in improving PsARC response. The clinical experts observed that, in this population, tofacitinib was less effective at improving PASI outcomes than ustekinumab and secukinumab. They also commented that their clinical experience of tofacitinib suggested it was not as effective at improving skin symptoms as TNF-alpha inhibitors. However, based on the academic in confidence results, on balance, the committee concluded that tofacitinib had similar effectiveness to other NICE recommended non-conventional DMARDs.

Tofacitinib has an acceptable safety profile

3.9 The clinical experts highlighted that people taking tofacitinib have an increased risk of herpes zoster infection, although the event rate is lower for psoriatic arthritis compared with rheumatoid arthritis. They explained that this adverse effect was specific to the class of Janus kinase inhibitors rather than tofacitinib alone. The clinical experts also highlighted that because tofacitinib is given with methotrexate, people who develop herpes zoster may experience more severe symptoms of the infection. However, the ERG considered that the adverse events profile of tofacitinib was similar to adalimumab, and that its tolerability was reflected in the low rate of withdrawals from adverse events in the OPAL trials. In the appraisal of tofacitinib for rheumatoid arthritis, clinical experts suggested that herpes zoster was a manageable infection. Therefore it concluded that tofacitinib has an acceptable safety profile that was similar to other non-conventional DMARDs.

The company's economic model

The comparators included in the model are appropriate

3.10 The company submitted cost-effectiveness analyses for 3 different subpopulations:

- people whose disease did not adequately respond to at least 2 previous conventional DMARDs

- people whose disease did not adequately respond to at least 2 previous conventional DMARDs and at least 1 TNF-alpha inhibitor, and
- people who cannot have TNF-alpha inhibitors or they are not tolerated.

The clinical evidence for the no previous biological DMARD population informed the modelling of people whose disease had an inadequate response to at least 2 previous conventional DMARDs. In this subpopulation, the company compared tofacitinib with etanercept, adalimumab, infliximab, golimumab, certolizumab pegol, secukinumab, apremilast and best supportive care. The clinical evidence for the no previous biological DMARD population also informed the modelling of people who cannot have TNF-alpha inhibitors or they are not tolerated. The clinical evidence for the previous biological DMARD population informed the modelling of people whose disease had an inadequate response to at least 1 TNF-alpha inhibitor. In both these subpopulations, the company compared tofacitinib with ustekinumab, secukinumab and best supportive care. The committee concluded that the company's choice of comparators is appropriate.

PsARC response should be assessed at 12 weeks

3.11 The committee noted that the economic analysis was based on the assumption that people whose psoriatic arthritis has not shown an adequate PsARC response at 3 months (12 weeks) stop tofacitinib treatment. This matches the timing of the primary outcome assessment in the OPAL trials. The committee concluded that PsARC response should be assessed at 12 weeks to decide if tofacitinib treatment should continue.

It is appropriate to model separate subgroups to reflect psoriasis severity

3.12 The economic model was based on the assessment group's model developed in NICE's technology appraisal guidance on certolizumab pegol and secukinumab (TA445). In TA445, the assessment group modelled the cost effectiveness of 3 psoriasis subgroups (psoriatic arthritis without concomitant psoriasis, with concomitant mild to moderate psoriasis, and with concomitant moderate to severe psoriasis). The company differed from the approach used in TA445 and modelled a 'weighted average' of the severity level of psoriasis, rather than separate subgroups. The ERG explained that modelling severity of psoriasis as a weighted average would not adequately capture the costs and benefits of secukinumab, because the licensed dose of secukinumab depends on the

severity of psoriasis. The committee concluded that it is appropriate to capture differences in severity of psoriasis using separate subgroups, in line with TA445.

The company's modelling of disease progression is acceptable

3.13 After the 12-week assessment of response, the company modelled psoriasis and arthritis progression separately. The company assumed that with best supportive care, the arthritis element of the disease would progress over time, but the level of psoriasis would stay stable. The company assumed that HAQ-DI scores would stay constant while people were having tofacitinib or biological DMARDs, and would rebound and progress in line with best supportive care in people who stopped treatment. For people having apremilast, the company's model was in line with the committee preferred approach in NICE's technology appraisal guidance on apremilast for treating active psoriatic arthritis. The clinical experts explained that in practice, disease progression increases with age. The clinical experts suggested that, because people with psoriatic arthritis tend to be younger, the assumption of constant HAQ-DI scores was reasonable. To explore the uncertainty in this area, the ERG presented scenario analyses for different rates of 'on-treatment' disease progression for tofacitinib. The committee noted that the ERG's exploratory analyses showed that different assumptions about disease progression only had a small effect on the cost-effectiveness results. The committee understood that there was some evidence on radiographic progression from OPAL Broaden, but noted that the ERG did not consider the evidence strong. The committee recalled that it had accepted the same assumptions about disease progression in the NICE technology appraisal guidance on certolizumab pegol and secukinumab in this indication, without any radiographic evidence. The committee concluded that the company's modelling of disease progression was acceptable.

Cost-effectiveness results

Pairwise ICERs comparing treatment to best supportive care are appropriate for decision-making

3.14 For each population, the company presented fully incremental analyses and pairwise analyses comparing all treatments to best supportive care. The ERG explained that the total costs and quality-adjusted life years (QALYs) for all therapies included in the company's analysis were very similar. Because of this, the fully incremental analyses were very sensitive to small differences in the

estimates of costs and QALYs. The ERG recommended that in this instance, pairwise incremental cost-effectiveness ratios (ICERs) would give a better reflection of the cost effectiveness of the technologies. The committee agreed that in this appraisal, pairwise comparisons with best supportive care were appropriate for decision-making.

Tofacitinib is a cost-effective treatment option for people who have, and who have not, had a previous biological DMARD

3.15 The committee considered the ICERs presented by the company and the ERG. It took into account commercial arrangements for tofacitinib and its comparators. Some of the commercial arrangements are confidential, so the exact cost-effectiveness results cannot be reported. The committee noted that:

- The company's base-case pairwise analysis showed that tofacitinib had the second lowest ICER for people who had not previously had a biological DMARD and the lowest ICER in for people who had had a previous biological DMARD, when compared with best supportive care.
- In the ERG's exploration of subgroups based on psoriasis severity:
  - tofacitinib had the lowest ICER in people with psoriatic arthritis with moderate to severe psoriasis who had not had a previous biological DMARD compared with best supportive care
  - secukinumab had a higher ICER than tofacitinib in people with no psoriasis and mild to moderate psoriasis who had not had a previous biological DMARD compared with best supportive care. However, the committee recognised that the differences in costs and QALYs between tofacitinib and secukinumab were small.
- Tofacitinib had the lowest ICER for most of the psoriasis subgroups in the previous biological DMARD populations.

  All the ICERs for tofacitinib were below £20,000 per QALY gained. The committee concluded that tofacitinib was a cost-effective treatment option for people who have had, and who have not had, a previous biological DMARD.

Conclusion

Tofacitinib is a cost-effective use of NHS resources

3.16 The committee concluded that tofacitinib (with methotrexate) was a cost-effective use of NHS resources when:

- the criteria in NICE's technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis are met; that is, the person has peripheral arthritis with at least 3 tender joints and at least 3 swollen joints, and the psoriatic arthritis has not responded adequately to trials of at least 2 conventional DMARDs, given either individually or together or
- the person has had a TNF-alpha inhibitor but their disease has not responded within the first 12 weeks or had stopped responding after the 12 weeks or
- TNF-alpha inhibitors are contraindicated but would otherwise be considered (as described in NICE's technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis).

Other factors

Clinicians should take into account factors that may affect PsARC and PASI and make any clinical adjustments needed

3.17 The committee noted that the economic analyses (in all populations) were based on the assumption that people whose psoriatic arthritis has not shown an adequate PsARC response at 3 months stop treatment with tofacitinib. The committee considered that the recommendation to stop treatment based on an inadequate PsARC response (as described in NICE's technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis) was also appropriate for tofacitinib. It noted that some people may have physical, sensory or learning disabilities or communication difficulties that could affect their responses to components of the PsARC, and concluded that this should be taken into account when using the PsARC. The committee was also aware that the PASI might underestimate disease severity in people with darker skin. The committee concluded that, when using the PASI, healthcare professionals should take into account skin colour and how this could affect the PASI score, and make the clinical adjustments they consider appropriate.

Fatigue symptoms may not have been fully captured in the QALY

3.18 The clinical experts suggested that tofacitinib might have additional benefits in treating fatigue, and that improvements in this domain might not be captured adequately by the HAQ-DI assessment and therefore the QALY. The clinical experts explained that there is a lack of adequate measures of fatigue in the psoriatic arthritis disease area. The committee agreed that there may be some health benefits that had not been captured in the QALY calculation, but that there was uncertainty about the extent of these benefits and that this would apply similarly to other treatments for psoriatic arthritis. The committee concluded that tofacitinib's effect in improving fatigue symptoms may be a potential uncaptured benefit in the analysis, and took this into account.

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 document.

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 psoriatic 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.

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.

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Accreditation