NICE National Institute for Health and Care Excellence

NICE guidance

Tofacitinib for treating active ankylosing spondylitis

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.

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1 Recommendations

1.1 Tofacitinib is recommended as an option for treating active ankylosing spondylitis that is not controlled well enough with conventional therapy in adults, only if:

- tumour necrosis factor (TNF)-alpha inhibitors are not suitable or do not control the condition well enough and
- the company provides tofacitinib according to the commercial arrangement.

1.2 If people with the condition and their clinicians consider tofacitinib to be 1 of a range of suitable treatments (including secukinumab and ixekizumab), after discussing the advantages and disadvantages of all the options, use the least expensive. Take account of administration costs, dosage, price per dose and commercial arrangements.

1.3 Assess response to tofacitinib after 16 weeks of treatment. Continue treatment only if there is clear evidence of response, defined as:

- a reduction in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score to 50% of the pre-treatment value or by 2 or more units and
- a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more.

1.4 Take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the BASDAI and make any adjustments needed.

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

People with active ankylosing spondylitis that is not controlled well enough with conventional therapy are usually offered TNF-alpha inhibitors. If TNF-alpha inhibitors are not suitable or do not control the condition well enough, people are usually offered secukinumab or ixekizumab. Tofacitinib is an alternative to secukinumab or ixekizumab, but it might not be as safe for some people with ankylosing spondylitis, for example, people who are over 65 or who smoke.

Clinical trial evidence shows that tofacitinib is more effective than placebo for treating active ankylosing spondylitis. Tofacitinib has not been compared directly with secukinumab or ixekizumab, but an indirect treatment comparison suggests that it is as effective.

A cost comparison with secukinumab, which is most likely to be used after TNF-alpha inhibitors or when they are not suitable, suggests that tofacitinib has similar or lower costs. So, tofacitinib is recommended if it is used in the same population as secukinumab and ixekizumab.

2 Information about tofacitinib

Marketing authorisation indication

2.1 Tofacitinib (Xeljanz, Pfizer) is indicated 'for the treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for tofacitinib.

Price

2.3 The list price of a 56-tablet pack of 5 mg tofacitinib is £690.03 (excluding VAT; BNF online, accessed June 2022).

2.4 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 evaluation committee considered evidence submitted by Pfizer, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

3.1 Ankylosing spondylitis is an inflammatory rheumatic condition characterised by inflammation of the sacroiliac joints and spine as well as inflammation at peripheral sites in the body. The main symptom is back pain and stiffness, but the condition can cause pain across the body, and fatigue, and can affect mental health. The patient experts explained how ankylosing spondylitis can affect every aspect of a person's life. Treatment usually starts with conventional therapy, defined as physiotherapy followed by non-steroidal anti-inflammatory drugs. If the condition does not respond adequately to this, people will then have tumour necrosis factor (TNF)-alpha inhibitors. People may try several TNF-alpha inhibitors before having interleukin (IL)-17 inhibitors (secukinumab or ixekizumab). The patient experts said that 20% of people have ankylosing spondylitis that does not respond to the biological disease-modifying antirheumatic drugs (DMARDs) available at the time of this evaluation (TNF-alpha and IL-17 inhibitors). The main adverse effects associated with existing biological DMARDs are fatigue and an increased frequency of infections, and with IL-17 inhibitors there is an increased risk of gastritis. The patient experts explained that TNF-alpha and IL-17 inhibitors need storing at 4 degrees centigrade, which could be a particular problem when travelling. The patient experts explained that an oral treatment option would help minimise these problems and would be more convenient for people with the condition.

Decision problem

Cost-comparison analysis

3.2 Tofacitinib is licensed to treat active ankylosing spondylitis that has responded inadequately to conventional therapy in adults. NICE's technology appraisal guidance on TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis defines adequate response as at least a 50% or a 2-point improvement in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score at 12 weeks. The BASDAI is a measure of the effectiveness of treatment for ankylosing spondylitis. The clinical expert confirmed this was how adequate response was defined in practice. The company's decision problem positioned tofacitinib in 2 places:

- firstly, as a first-line DMARD after conventional therapy, with TNF-alpha inhibitors as comparators
- secondly, as a subsequent-line DMARD after TNF-alpha inhibitors, with the IL-17 inhibitors secukinumab and ixekizumab, as comparators.

  The committee noted that tofacitinib could be used after IL-17 inhibitors, but that in this position it was not eligible for evaluation using a cost-comparison analysis. The clinical expert said that the most likely use of tofacitinib in clinical practice would be in the same position as the IL-17 inhibitors secukinumab and ixekizumab.

MHRA safety warning

3.3 The Medicines and Healthcare Regulatory products Agency (MHRA) has released a safety warning for tofacitinib. The safety warning states that, based on evidence from a rheumatoid arthritis population, tofacitinib is associated with an increased risk of cardiovascular events and malignancies in people with specific risk factors. The risk factors are: age over 65 years, current or previous smoking, and other cardiovascular or malignancy risk factors. From now, people with the risk factors are referred to as the 'MHRA risk factor population'. The company's positioning was consistent with the marketing authorisation. But the ERG

noted that tofacitinib was very unlikely to be used as a first-line DMARD after conventional therapy because of the MHRA safety warning. For this reason, NICE agreed with the company at the scrutiny stage that the cost comparison would proceed in the subsequent-line position (see section 3.2). The committee agreed that the relevant population for the cost-comparison analysis was people who have already had a TNF-alpha inhibitor. The company considered both ixekizumab and secukinumab as comparators in this position in the treatment pathway. The clinical expert explained that clinicians were likely to choose secukinumab over ixekizumab. The committee understood that ixekizumab was recommended more recently than secukinumab (see NICE's technology appraisal guidance on secukinumab for active ankylosing spondylitis and ixekizumab for treating axial spondyloarthritis). It understood that it was likely that secukinumab was the more established treatment in NHS clinical practice. The committee considered both comparators but concluded that secukinumab was the most relevant comparator for the cost comparison and represented the decision problem that had the most validity to NHS clinical practice.

Clinical effectiveness

Tofacitinib compared with placebo

3.4 Tofacitinib has been compared with placebo in 2 randomised controlled trials, A3921119 and A3921120, enrolling a total of 374 people. These trials showed that tofacitinib was statistically significantly superior to placebo for the following outcomes:

- Assessment in Spondyloarthritis international Society 20% and 40% (ASAS20 and ASAS40 respectively) response
- Bath Ankylosing Spondylitis Functional Index (BASFI)
- BASDAI 50% improvement.

People having tofacitinib also had statistically significantly higher scores in the:

- Ankylosing Spondylitis Quality of Life (ASQoL) measure

- SF-36v2 quality of life measure
- FACIT-F measure of fatigue in chronic illness.

A3921119 only enrolled people who had not previously had a biological DMARD, whereas 23% of people in A3921120 had previously had a biological DMARD. In A3921120, tofacitinib showed statistically significantly higher ASAS20 and ASAS40 scores than placebo in both the subgroup who had not had biological DMARDs and the subgroup who had. But there was greater uncertainty around the effect estimates in the subgroup who had previously had biological DMARDs. The committee concluded that tofacitinib was more clinically effective than placebo.

Network meta-analyses

3.5 The company did a series of network meta-analyses comparing tofacitinib with secukinumab and ixekizumab. These used multiple measures of efficacy, quality of life, serious adverse events and discontinuation in the acute phase, defined as 12 to 16 weeks. When possible, results were provided for both the subgroup who had previously had biological DMARDs and the subgroup who had not, and with fixed effect and random effects models. The network meta-analyses did not find any significant differences between tofacitinib and secukinumab or ixekizumab for any of the outcomes compared. The ERG considered that, in a cost-comparison analysis, uncertainty (characterised by wide 95% confidence intervals) could favour the new technology. This is because the increasingly wide confidence intervals are more likely to include results which suggest equivalence with the comparator. The ERG preferred the fixed effect models which were associated with less uncertainty. The ERG also noted that the network meta-analyses results supported the assumption of equivalent efficacy between tofacitinib and secukinumab or izekizumab, irrespective of the final model selected. The committee concluded that there was uncertainty in the estimates but that the network meta-analyses did not contradict the company's assumption that tofacitinib was clinically equivalent to the comparators.

Long-term efficacy of tofacitinib

3.6 NICE's health technology evaluations manual states that a cost-comparison analysis requires that the technology has similar health benefits to the comparator over the average time on treatment. The company network meta-analyses compared tofacitinib with secukinumab and ixekizumab for outcomes measured between 12 and 16 weeks (the acute phase) and found no significant differences. But the committee considered that the wide 95% confidence intervals in the subgroup who had previously had biological DMARDs were compatible with tofacitinib also being either much more or much less effective than the comparators. The ERG noted the lack of longer-term data on efficacy, which led to uncertainty about the assumption of long-term clinical equivalence. The ERG noted that in past cost-utility appraisals of biological DMARDs in ankylosing spondylitis, the trials had between 2 and 5 years of follow up, which showed that responses were maintained in the long term. The clinical expert said that long-term efficacy of tofacitinib (a small molecule drug) was expected to be similar to or greater than biological drugs such as secukinumab (a monoclonal antibody). This is because monoclonal antibodies can provoke an immune response against themselves which can lead to loss of efficacy over time, something that is less likely to happen with small molecule drugs. The committee considered this biologically plausible but noted that there was still uncertainty around longer-term efficacy which could also be affected by discontinuation and safety (see section 3.7 and section 3.8).

Discontinuation rates

3.7 Differences in discontinuation will lead to differences in both efficacy and costs between the technology and comparators. The company did not model discontinuation because it assumed that discontinuation of tofacitinib was the same as the comparators. The company base case was presented as first year costs and subsequent year costs. It said that time horizon was not usually relevant in a cost-comparison analysis because if a drug was cost saving in the first year, it would be cost saving in all subsequent years. The ERG commented that in past technology appraisals on ankylosing spondylitis, a flat rate annual

discontinuation was applied equally to both arms. It also questioned whether, because tofacitinib is taken orally twice daily, there could be differences in adherence (for example, if people forget to take it). However, the clinical expert said that, in their experience, if a drug is working then adherence is likely to be high. The patient experts supported this and said that the effect of the condition on all parts of life was so substantial that, if a drug was working, it would be very unlikely for someone to not take it. The patient experts also said that with injectable biologicals there is a treatment 'waning period' at the time furthest from the previous injection. This waning of treatment effect would not occur with a twice-daily oral drug. The patient expert emphasised that this lack of treatment effect waning would be highly valued, and meant that issues with adherence were unlikely. The ERG accepted this but considered that discontinuation rates should have been modelled and that a time horizon was relevant to this appraisal. It said that secukinumab had a loading dose, meaning that its costs in the first year would be higher than in subsequent years. It said that modelling of discontinuation rates over a longer time horizon would be the best way to accurately capture costs of both treatments. The committee concluded that, while it was plausible that discontinuation rates for tofacitinib and secukinumab could differ (which could favour either treatment), it had seen no evidence of this.

Generalisability of the MHRA risk factor population

3.8 The ERG noted that around half of the people in A3921120 had at least 1 of the MHRA safety warning risk factors (see section 3.3). Because of this, it was uncertain if the evidence from A3921119 and A3921120 would be generalisable to the population who would have tofacitinib in NHS clinical practice. The company highlighted evidence from A3921120 which showed that tofacitinib had similar ASAS40 responses among people who smoke, people who used to smoke and people who had never smoked. The committee considered whether any of the risk factors may be effect modifiers. The clinical expert explained that, with TNF-alpha inhibitors, treatment effect can be reduced in people who smoke, but that they were not aware of any such effect with the other MHRA risk factors. The committee noted that the small sample size meant there was uncertainty around these estimates. It said that it was not possible

to make a similar comparison in the over and under 65 years subgroups because of the lack of people over 65 in the placebo arm. The committee concluded that the trial results were likely to be broadly generalisable to the decision problem population. But it was plausible that there were differences in response between the risk factor and non-risk factor populations, which made generalisability to NHS clinical practice uncertain.

Generalisability of the biological DMARD-experienced population

3.9 The ERG noted that nobody in A3921119 and only 23% of people in A3921120 (31 people who had tofacitinib and 31 people who had placebo) had previously had biological DMARDs. The ERG considered that this could affect generalisability of the trial data to the population in clinical practice who would have had biological DMARDs. The clinical expert said that biological DMARDs often show a greater treatment effect in people who have not had them before, which then reduces on each subsequent treatment. They said that it was likely that a similar effect would be seen with tofacitinib. The committee also noted that, in previous cost-utility appraisals of biological DMARDs in ankylosing spondylitis, relatively small numbers of people had previously had biological DMARDs. The company highlighted the results of the network meta-analyses in the population who had previously had biological DMARDs. These results suggested that tofacitinib was not statistically significantly different to secukinumab or ixekizumab in all the compared measures of efficacy or quality of life. The committee noted this but remarked that the wide confidence intervals for the subgroup who had previously had biological DMARDs reflected the smaller sample size and added uncertainty. The committee said that this uncertainty could not be explored within a cost-comparison analysis appraisal.

Costs

Additional monitoring costs

3.10 There may be additional monitoring costs for tofacitinib that were not included in the cost comparison. The company base case in the cost-

comparison model included only drug acquisition and monitoring costs. The ERG raised the issue that the costs of adverse effects and some monitoring costs had been excluded. The company did not include annual lipid monitoring in its base case but provided a scenario with these costs included. The ERG base case included these costs and also had slightly different drug acquisition costs, which were because of differences in the way the ERG and the company calculated the number of doses for secukinumab. The ERG said that the company overestimated doses of secukinumab because it assumed a 4-weekly, rather than a monthly, administration. The committee considered that amending these factors in the ERG base case did not have a large effect on the cost-comparison estimates. The ERG also considered that excluding the costs of adverse events could bias the analysis towards tofacitinib if the adverse event profile was different to the comparators in the long term. The clinical expert explained that the adverse event profile was unlikely to be different. They said that even if the incidence of some viral infections was higher with tofacitinib, this could be compensated for by an absence of inflammatory bowel issues associated with IL-17 inhibitors. The committee accepted this but also questioned whether, in light of the MHRA safety warning, there may be additional monitoring costs for tofacitinib. This includes a need for electrocardiograms or screening for malignancies, which could incur substantial additional costs for tofacitinib. The clinical expert did not think that such additional monitoring costs would apply. They said that clinicians would consider the MHRA safety warning, and the individual risk for each person, before deciding whether to use tofacitinib. This meant that it was unlikely that the MHRA warning would result in additional monitoring costs. The committee noted this but considered that there was relatively little data on adverse effects. It noted that the data presented came from a small number of people who were followed up for a relatively short time. The committee concluded that it was uncertain if tofacitinib would incur additional monitoring costs in the longer term because many of these costs were tied to long-term safety, which it also considered uncertain.

Cost-comparison estimates

Company and ERG cost-comparison estimates

3.11 The company presented a cost-comparison analysis that modelled the total costs of tofacitinib, secukinumab and ixekizumab for the first 10 years of treatment. The committee considered that the comparison with secukinumab was the most relevant and represented the most valid decision problem (see section 3.3). It considered that the available clinical evidence did not contradict the assumption of clinical equivalence between tofacitinib and secukinumab at 16 weeks. It noted there were uncertainties, including the long-term efficacy and discontinuation of tofacitinib. Because of these uncertainties, the committee considered that it would want tofacitinib to be cost neutral when compared with secukinumab. After considering the comparator patient access schemes, the committee concluded that tofacitinib was likely to be cost neutral when compared with secukinumab at time points relevant to clinical practice.

Other factors

Equality issues

3.12 No equalities issues were identified during this appraisal. But NICE's technology appraisal guidance on TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis notes that healthcare professionals should take into account any factors that could affect responses to the BASDAI and spinal visual analogue scale, including:

- physical, sensory or learning disabilities
- communication difficulties.

The committee considered this in its decision making.

Conclusion

Recommendation

3.13 The committee concluded that tofacitinib was likely to be an effective use of resources when compared with secukinumab. It considered that the short-term evidence for tofacitinib in people who had previously had a biological DMARD showed that it was plausible that tofacitinib was as effective as secukinumab. It noted that there was uncertainty about long-term effectiveness that could not be explored in the context of a cost-comparison appraisal. However, having considered that the total costs of tofacitinib were likely to be lower than or equal to the costs of secukinumab, it concluded that tofacitinib was a cost-effective treatment option. So, tofacitinib is recommended as an option for treating active ankylosing spondylitis which has not responded to conventional therapy and when TNF-alpha inhibitors have not worked well enough or are not suitable.

4 Implementation

4.1 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 integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication. Because tofacitinib has been recommended through the cost-comparison process, NHS England and integrated care boards have agreed to provide funding to implement this guidance 30 days after 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 guidance 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 draft guidance.

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 ankylosing spondylitis 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 Evaluation committee members and NICE project team

Evaluation committee members

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

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

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

Chair

Charles Crawley
Chair, technology appraisal committee B

NICE project team

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

Samuel Slayen
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