NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Tofacitinib for treating juvenile idiopathic arthritis

Final scope

Final remit/appraisal objective

To appraise the clinical and cost effectiveness of tofacitinib within its marketing authorisation for treating juvenile idiopathic arthritis.

Background

Juvenile idiopathic arthritis (JIA) describes a group of conditions that involve joint inflammation which lasts for more than 6 weeks in people under 16 years of age. JIA causes pain, swelling and limitation of movement, which can change from day to day. When the condition becomes more active and the symptoms worsen, this is known as a 'flare'. In more severe cases, JIA can cause growth retardation, joint contractures, joint disease requiring joint replacements, eye problems and other extra-articular manifestations (such as inflammatory bowel disease and psoriasis), and permanent disability.

JIA can impair personal and social functioning and development. Children often miss out on schooling and other childhood activities, and as adults they may be limited in their ability to work. JIA may also have a considerable impact on the family of the child, including parents and carers who may need to miss work to take children to appointments. About 50% of children with JIA will not achieve remission from the condition, despite treatment, and will need further rheumatological care as adults[1].

A classification system for JIA has been developed by the International League of Associations for Rheumatology (ILAR)[2]. There are 7 categories of JIA:

- Systemic JIA, also known as Still's disease, accounts for 6% of new diagnoses[3] and is diagnosed when arthritis is part of a general illness involving fever, tiredness, rash, loss of appetite and weight loss.

- Oligoarthritis is the most common type of JIA, accounting for 51% of new diagnoses in Europe each year[3]. It is diagnosed when 4 or fewer joints are affected in the first 6 months of disease.

- Polyarticular-onset JIA, also known as polyarthritis, accounts for 24% of new diagnoses[3] and is diagnosed when 5 or more joints are affected in the first 6 months of disease. After 6 months from diagnosis, if 5 or more joints become affected it is then referred to as polyarticular-course JIA. Polyarthritis can be further divided into rheumatoid factor (RF) negative arthritis and rheumatoid factor positive arthritis. Polyarthritis includes people who are diagnosed with oligoarticular JIA but who then have more joints affected after 6 months (also known as extended oligoarticular JIA).

- Psoriatic arthritis accounts for 6% of new diagnoses[3] and is diagnosed when there is arthritis in association with psoriasis (a skin condition).

- Enthesitis-related arthritis accounts for 6% of new diagnoses[3] and is typically diagnosed when areas where tendons attach to the bones (entheses) are affected.

- JIA that does not correspond to any of the above categories, or to more than one, is termed undifferentiated arthritis. Around 7% of new diagnoses fit into this category[3].

JIA has an annual incidence of 0.1 per 1,000 children in the UK[4] (equivalent to around 1,000 children diagnosed per year[5]). The prevalence of JIA is approximately 1 per 1,000 children[4]. It is estimated that around 12,000 children and young people have JIA in the UK[4], however the condition may continue into adulthood, so there are also adults who have JIA.

Treatment aims to control joint pain and inflammation; reduce joint damage, disability and loss of function; and maintain or improve quality of life. Standard treatment for JIA includes the use of the disease-modifying anti-rheumatic drugs (DMARDs), usually methotrexate, alongside intra-articular and systemic corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDS).

NICE has recommended abatacept, adalimumab, etanercept and tocilizumab (technology appraisal guidance 373), within their marketing authorisations, as options for treating polyarticular JIA, including polyarticular-onset, polyarticular-course and extended oligoarticular JIA. That is:

- for abatacept, people 6 years and older whose disease has responded inadequately to other DMARDs including at least 1 TNF inhibitor

- for adalimumab, people 2 years and older whose disease has responded inadequately to 1 or more DMARD

- for etanercept, people 2 years and older whose disease has responded inadequately to, or who are intolerant of, methotrexate

- for tocilizumab, people 2 years and older whose disease has responded inadequately to previous therapy with methotrexate.

Adalimumab and etanercept are recommended, within their marketing authorisations, as options for treating enthesitis-related JIA, that is, for people 6 years and older (adalimumab) and 12 years and older (etanercept) whose disease has responded inadequately to, or who are intolerant of, conventional therapy. Etanercept is also recommended, within its marketing authorisation, as an option for treating psoriatic JIA, that is, in people aged 12 years and over whose disease has responded inadequately to, or who are intolerant of, methotrexate. NHS England's Clinical Commissioning Policy Statement (Biologic Therapies for the treatment of Juvenile Idiopathic Arthritis) outlines that other biologic therapies may be used in clinical practice including infliximab (when there is a history of poor adherence or intolerance to subcutaneous injections and a history of JIA uveitis), anakinra (in systemic JIA) and rituximab (in RF positive polyarticular JIA).

The technology

Tofacitinib (Xeljanz, Pfizer) is a janus kinase (JAK) inhibitor and is a targeted synthetic small molecule. Janus kinases are intracellular enzymes that transmit

signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of creating new blood cells in the body (hematopoiesis) and immune cell function. Tofacitinib is administered orally.

Tofacitinib does not currently have a marketing authorisation in the UK for treating JIA. It has been studied in a clinical trial compared with placebo in children aged 2 to 17 who have JIA (including extended oligoarthritis, polyarthritis, psoriatic arthritis, enthesitis-related arthritis and systemic JIA with active arthritis but without active systemic features). Patients in the trial who have extended oligoarthritis, polyarthritis and systemic JIA with active arthritis but without active systemic features must be intolerant to, or their disease must have responded inadequately to, 1 or more DMARD. The disease of patients in the trial who have psoriatic arthritis or enthesitis-related arthritis must have responded inadequately to NSAIDs. Stable doses of concomitant NSAIDs and/or methotrexate and/or oral glucocorticoids were permitted.

Tofacitinib has a UK marketing authorisation for the following other rheumatic diseases:

- in combination with methotrexate for treating moderate to severe active rheumatoid arthritis in adult patients whose disease has responded inadequately to, or who are intolerant to one or more DMARDs. Tofacitinib can be given as a monotherapy in case of intolerance to methotrexate or when treatment with methotrexate is inappropriate.

- in combination with methotrexate for treating active psoriatic arthritis in adult patients whose disease has responded inadequately to, or who are intolerant to prior DMARD therapy.

Intervention(s)	Tofacitinib
Population(s)	People 2 years and older with juvenile idiopathic arthritis
Comparators	For people with psoriatic arthritis or enthesitis-related arthritis whose disease has responded inadequately to NSAIDs and who have not been offered a DMARD: • methotrexate For people whose disease has responded inadequately to, or who are intolerant of, 1 or more DMARDs, and are eligible for currently available biologic DMARDs: • abatacept (people aged 6 years and older) • adalimumab (people aged 2 years and older) • etanercept (people aged 2 years and older) • tocilizumab (people aged 2 years and older) • infliximab • rituximab (rheumatoid factor-positive arthritis) • anakinra (systemic JIA, subject to ongoing NICE appraisal)

Outcomes	The outcome measures to be considered include: • disease activity (including disease flares and remission) • physical function • joint damage • body weight and height • pain • corticosteroid sparing • JIA subgroup-specific outcomes where relevant (e.g. enthesitis and dactylitis counts) • mortality • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.
Other considerations	If evidence allows, subgroups by JIA category will be considered. The availability and cost of biosimilar products should be taken into account. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations	Related Technology Appraisals: 'Tofacitinib for treating active psoriatic arthritis after

and NICE Pathways	inadequate response to DMARDs' (2018). NICE Technology Appraisal 543. 'Tofacitinib for moderate to severe rheumatoid arthritis' (2017). NICE Technology Appraisal 480. 'Abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis' (2015). NICE Technology Appraisal 373. 'Tocilizumab for the treatment of systemic juvenile idiopathic arthritis' (2011). NICE Technology Appraisal 238. Appraisals in development (including suspended appraisals): 'Anakinra for treating active Stills disease' NICE technology appraisals guidance [ID1463]. Expected publication date February 2021. Terminated appraisals: 'Canakinumab for treating systemic juvenile idiopathic arthritis' (terminated appraisal) (2013). NICE Technology Appraisal 302. Related NICE Pathways: Musculoskeletal conditions (2013) NICE pathway http://pathways.nice.org.uk/pathways/musculoskeletal-conditions
Related National Policy	NHS England (2015) Clinical Commissioning Policy Statement: Biologic Therapies for the treatment of Juvenile Idiopathic Arthritis (JIA) The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) Section 138. Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 2 to 5. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

References

1. Minden K, Kiessling U, Listing J, et al. (2000) Prognosis of patients with juvenile chronic arthritis and juvenile spondyloarthropathy. Journal of Rheumatology 27:2256–63

2. Petty R, et al. (2004) International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis: Second Revision, Edmonton, 2001. Journal of Rheumatology 31(2):390-2

3. Davies R, et al. (2016) Treatment prescribing patterns in patients with juvenile idiopathic arthritis (JIA): Analysis from the UK Childhood Arthritis Prospective Study (CAPS). Seminars in Arthritis and Rheumatism 46(2):190-195

4. NHS England (2015) Clinical Commissioning Policy Statement: Biologic Therapies for the treatment of Juvenile Idiopathic Arthritis (JIA)
5. Office for National Statistics. National population projections: 2018-based. Accessed Nov 2020