NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Etanercept, abatacept, adalimumab and tocilizumab for treating juvenile idiopathic arthritis (including review of TA35)

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of etanercept, adalimumab, tocilizumab and abatacept within their licensed indications for treating juvenile idiopathic arthritis[1].

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.

- Oligoarthritis is the most common type of JIA, accounting for 50% of new diagnoses in Europe each year. It is diagnosed when 4 or fewer joints are affected in the first 6 months of disease.

- Polyarthritis is diagnosed when 5 or more joints are affected. It can be described as either polyarticular onset disease (5 or more joints are affected at presentation or within the first 6 months) or polyarticular course (5 or more joints affected after the first 6 months). If oligoarthritis progresses and affects more than 4 joints after the first 6 months, it is called extended oligoarthritis. Around 40% of people with JIA have polyarthritis, and polyarticular onset disease accounts for 25% of new diagnoses. Polyarthritis can be further divided into

[1] Golimumab is not included in the remit of this appraisal as the manufacturer is no longer pursuing a licence for this indication.

rheumatoid factor positive arthritis and rheumatoid factor negative arthritis.

- Systemic JIA accounts for 5 to 10% of new diagnoses and is diagnosed when arthritis is part of a general illness involving fever, tiredness, rash, loss of appetite and weight loss.

- Enthesitis-related arthritis accounts for 2 to 10% of new diagnoses and is diagnosed when areas where tendons attach to the bones (entheses) are affected.

- Psoriatic arthritis accounts for 2 to 15% of new diagnoses and is diagnosed when there is joint pain associated with psoriasis (a skin condition).

JIA has an annual incidence of 0.1 per 1,000 children in the UK (equivalent to 1000 children diagnosed per year). The prevalence of JIA is approximately 1 per 1,000 children. This equates to about 10,000 children affected in the UK, 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). Other treatments such as abatacept (a T-cell activation inhibitor), adalimumab (a TNF inhibitor), etanercept (a TNF inhibitor) and tocilizumab (an interleukin inhibitor) may also be used. NICE has recommended etanercept (technology appraisal guidance 35) for the treatment of active polyarticular JIA in children aged 4 to 17 years whose condition has not responded adequately to methotrexate or who have been unable to tolerate treatment with methotrexate. NICE has also recommended tocilizumab (technology appraisal guidance 238) for the treatment of children and young people with systemic JIA if their disease has not responded to NSAIDs, systemic corticosteroids and methotrexate.

The decision to review NICE technology appraisal guidance (TA) 35 was based on the following information:

- Although there have been no major developments in the evidence base for TA35, this guidance is now out of date. This is because the licensed therapeutic indication for etanercept has changed and is now broader than that covered by 1.1 of TA35. In addition to active polyarticular juvenile idiopathic arthritis, etanercept is now licensed for extended oligoarthritis (from the age of 2 years), psoriatic arthritis (from the age of 12 years) and enthesitis-related arthritis (from the age of 12 years). The lower age range for treating polyarticular disease has been reduced from 4 years to 2 years and the marketing authorisation no

longer specifies an upper age limit of 17 in the therapeutic indications section of the summary of product characteristics.

- Other biological agents (abatacept, adalimumab and tocilizumab) have been licensed for the treatment of polyarticular juvenile idiopathic arthritis since TA35 was published.

The technologies

Etanercept (Enbrel, Pfizer) is a recombinant TNF inhibitor. It is administered by subcutaneous injection. Etanercept has a UK marketing authorisation for

- polyarthritis (rheumatoid factor positive or negative and extended oligoarthritis) in children and adolescents from the age of 2 years who have an inadequate response to, or who have proved intolerant of, methotrexate.

- psoriatic arthritis in adolescents from the age of 12 who have had an inadequate response to, or who have proved intolerant of, methotrexate.

- enthesitis-related arthritis in adolescents from the age of 12 who have an inadequate response to, or who have proved intolerant of, conventional therapy.

Abatacept (Orencia, Bristol-Myers Squibb) is a selective co-stimulation modulator which prevents T-cell activation. It is administered by intravenous infusion. Abatacept in combination with methotrexate has a UK marketing authorisation for moderate to severe active polyarthritis in paediatric patients from the age of 6 years who have had an insufficient response to other disease-modifying anti-rheumatic drugs (DMARDs), including at least 1 tumour necrosis factor (TNF) inhibitor.

Adalimumab (Humira, AbbVie) is a recombinant TNF inhibitor. It is administered by subcutaneous injection. Adalimumab has a UK marketing authorisation for

- active polyarthritis in people from the age of 2 years who have had an inadequate response to 1 or more DMARDs.

- active enthesitis-related arthritis in patients from the age of 6 years who have had an inadequate response to, or who are intolerant of, conventional therapy.

Adalimumab should be given with methotrexate except where methotrexate is not tolerated or is considered inappropriate.

Tocilizumab (RoActemra, Roche) is a humanised monoclonal antibody that inhibits the cytokine interleukin-6. It is administered by intravenous infusion. Tocilizumab has a UK marketing authorisation for active systemic onset

arthritis and polyarthritis (rheumatoid factor positive or negative and extended oligoarthritis) in patients from the age of 2 years who have not responded to other NSAIDs and corticosteroids. Tocilizumab should be used in combination with methotrexate except in patients for whom methotrexate is inappropriate.

Interventions	Etanercept, abatacept, adalimumab and tocilizumab within their licensed indications
Population	People with the following forms of juvenile idiopathic arthritis: • polyarthritis (rheumatoid factor positive, rheumatoid factor negative and extended oligoarthritis, both onset and course) • enthesitis related arthritis, and • psoriatic arthritis[2].
Comparators	• Disease modifying anti-rheumatic drugs (DMARDs) (such as methotrexate), if DMARDs can be tolerated • Best supportive care, if DMARDs are not tolerated • Etanercept, abatacept, adalimumab and tocilizumab should be compared with each other within their licensed indications where appropriate Biosimilars are not expected to be in established NHS practice at the time of appraisal and are not included as comparators.

[2] An appraisal of treatments for systemic juvenile idiopathic arthritis will be considered separately when a review proposal for TA238 is developed.

Outcomes	The outcome measures to be considered include: • disease activity • disease flares • physical function • joint damage • pain • corticosteroid reducing regimens • extra-articular manifestations (such as uveitis) • body weight and height • 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. 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 patient access schemes for the intervention or comparator technologies should be taken into account.
Other considerations	Where the evidence allows, subgroups by type of JIA will be considered: oligoarthritis, polyarthritis (rheumatoid factor positive, rheumatoid factor negative, and extended oligoarthritis), enthesitis-related arthritis and psoriatic arthritis, patients with JIA and extra-articular manifestations, such as uveitis. 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 and NICE Pathways	Related Technology Appraisals: Technology Appraisal No. 35, Mar 2002, 'Etanercept for the treatment of juvenile idiopathic arthritis'. Currently

	being updated. Related NICE Pathways: NICE Pathway: Musculoskeletal conditions, Pathway created Dec 2013. http://pathways.nice.org.uk/pathways/musculoskeletal-conditions
Related National Policy	NHS (2012) Manual for prescribed specialised services. Page 318. http://www.england.nhs.uk/wp-content/uploads/2012/12/pss-manual.pdf