



Clinical Commissioning Policy Statement: Biologic Therapies for the treatment of Juvenile Idiopathic Arthritis (JIA)

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Document Status

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1 Executive Summary

Policy Statement

NHS England will routinely commission Biologic Therapies for the treatment of Juvenile Idiopathic Arthritis (JIA) in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

Equality Statement

NHS England has a duty to have regard to the need to reduce health inequalities in access to health services and health outcomes achieved as enshrined in the Health and Social Care Act 2012. NHS England is committed to fulfilling this duty as to equality of access and to avoiding unlawful discrimination on the grounds of age, gender, disability (including learning disability), gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, gender or sexual orientation. In carrying out its functions, NHS England will have due regard to the different needs of protected equality groups, in line with the Equality Act 2010. This document is compliant with the NHS Constitution and the Human Rights Act 1998. This applies to all activities for which NHS England is responsible, including policy development, review and implementation.

Plain Language Summary

Juvenile Idiopathic Arthritis (JIA) is the commonest rheumatic disease of childhood. It is characterised by relapsing and remitting episodes of inflammation of the synovial membrane of the joints (synovitis) which, unless treated, leads to damage and deformity of the affected joints and subsequent disability.

2 Introduction

The purpose of this policy is to provide guidance for the use of biologics in patients with JIA until NICE guidance is published.

JIA is not the same as rheumatoid arthritis or other forms of inflammatory arthritis and, although there are similarities with adult forms of arthritis, JIA should be considered separately in both children and adults. JIA is an 'umbrella' term which covers a number of different sub-types listed here:

- Oligo-articular JIA
- Extended Oligo-articular JIA
- Poly-Articular JIA (RF –ve)
- Poly-Articular JIA (RF +ve)
- Systemic-Onset JIA
- Psoriatic JIA
- Enthesitis-Related Arthritis

In addition there are forms of inflammatory arthritis indistinguishable from JIA, but not listed under the umbrella term 'JIA'. These include:

- Arthritis associated with Inflammatory Bowel Diseases (Crohn's and Ulcerative Colitis),
- Arthritis found commonly in Down's Syndrome and other similar chromosome disorders.

The treatment of these is effectively identical to that of JIA and should be included accordingly.

Drug therapy is dependent upon the number and type of joints involved, as well as the presence of any extra-articular manifestations.

The commonest extra-articular complication of JIA is inflammation of the eye (uveitis). Uveitis may predate the onset of arthritis and can be severe even if the degree of arthritis is of a milder course. Unless treated properly uveitis can rapidly cause irreversible damage to the eye leading to permanent blindness.

3 Definitions

JIA is the commonest rheumatic disease of childhood.

Biologic therapies are treatments which utilise either monoclonal antibodies or soluble cytokine receptors, to specifically target individual components of the immune system.

4 Aims and Objectives

The aim of drug therapy in patients with JIA is to induce and maintain a complete remission of all symptoms, and thus to allow a child to achieve normal growth, development, and allow full participation in school, career, sport and all other aspects of normal life. The initial aim is induction of complete disease remission using corticosteroids – either intravenously or intra-articular. Oral corticosteroids are avoided where possible to avoid side effects (can affect growth or increase risk of osteoporosis) but may be needed for short periods of time.

In patients with mild disease limited to <5 joints it may be possible to induce remission which lasts for >6months with intra-articular steroids, particularly if using the long-acting corticosteroid Triamcinolone Hexacetonide. Patients with more severe disease may need intravenous steroids to induce remission, although intra-articular steroids are used in some patients as an alternative.

To maintain remission, those patients whose arthritis affects a cumulative total of 5 or more joints, or severely affecting crucial joints such as the spine, ankles, hips, and wrists, should initially be treated with Methotrexate (MTX). This accounts for around half of all children who develop JIA – i.e. around 6000 children in the UK at any one time. Methotrexate has been the first line Disease-Modifying Anti-Rheumatic Drug (DMARD) for the treatment of JIA for over 30 years. Whilst effective in reducing the amount and severity of arthritis it only induces complete remission in 30-50% of patients. Those with JIA arthritis that remains active despite optimal dosing, or who are intolerant of Methotrexate need treating with a 'Biologic'.

The term 'Biologics' refers to a range of relatively new treatments which utilise either monoclonal antibodies, or soluble cytokine receptors, to specifically target individual components of the immune system. Currently all of them need to be given either intravenously or subcutaneously. Many are given in co-administration with MTX to optimise their effect. It is estimated that up to a third of all children who start treatment with MTX need to progress to a biologic.

Current data from the biologics Registries and their databases in the UK includes children from all over the UK who are receiving biologics for JIA. According to these databases, 890 children in England alone, are receiving a biologic for JIA; most, but not all, are receiving NICE approved biologics for JIA. Given that registration to the database is recommended but not mandatory, it is likely that this number of 890 is an underestimate. We would suggest 950 children with JIA in England to be currently on a biologic treatment as a pragmatic estimate.

5 Epidemiology and Needs Assessment

JIA has an annual incidence of 1:10,000 children and an overall prevalence in childhood of 1:1000. The term Juvenile refers to the *age at onset* and historical data suggests that around half of children with JIA continue to have active arthritis as adults ⁽¹⁾.

- Estimated 12,000,000 children <18yrs in England and Wales
- At any one time there are >12,000 children with JIA

- Estimated half of these will go on to have arthritis in adulthood
- Estimated 1 in 3 will not have arthritis in adulthood but will have sustained permanent damage to one or more joints

6 Evidence Base

Clinical Efficacy and Safety

Current 'Biologics' and the references detailing their efficacy and safety are listed below:

- Tumour Necrosis Factor (TNF) Inhibitors: Etanercept^(6, 7), Adalimumab^{(8) (14)}, Infliximab^(9, 15), Golimumab, Certolizumab. (All types of JIA)
- Interleukin-1 Inhibitors: Anakinra^(4,10), Riloncept^(4, 11), Canakinumab^(4,12) (Systemic-Onset JIA only)
- Interleukin-6 Inhibitors: Tocilizumab^(4,13, 14, 15) (All types of JIA)
- T-cell co-stimulation inhibitors: Abatacept^{(16) (18)} (All types of JIA)
- B-cell inhibitors: Rituximab⁽¹⁷⁾ (Poly-Articular RF+ve JIA only)

Poly-articular-course JIA:

High quality randomised, placebo-controlled, double blind trials demonstrate efficacy and safety of Etanercept, Infliximab, Adalimumab, Tocilizumab, and Abatacept.

These are summarised in a recent systematic review⁽¹⁸⁾. The review identified seven RCTs, one each for Etanercept, Infliximab, Adalimumab, Abatacept, and Anakinra, and one each looking at Etanercept or Infliximab as first-line therapies. It found that there was strong evidence to support the efficacy and safety of biologics over the short-term. Long-term data is available for Etanercept, for other treatments it is sparse⁽¹⁸⁾.

- There are no data from comparative trials between different agents or for sequential use of biologics, therefore the suggested treatment pathway in Appendix A is based on the consensus of the British Society for Paediatric and Adolescent Rheumatology Clinical Affairs Committee pending further NICE

guidance which is planned. These recommendations are consistent with the recent systematic review ⁽¹⁸⁾

Systemic-Onset JIA:

- High-quality randomised placebo-controlled, double-blind trials demonstrate efficacy and safety of Tocilizumab, Anakinra, and Canakinumab in Systemic-onset JIA. There is no data from comparative studies, but the use of all these agents is covered in the recent update by the American College of Rheumatology ⁽⁴⁾

The use of Golimumab, Certolizumab and Canakinumab are beyond the scope of this policy.

The following biologics are currently licensed and/or NICE approved:

In children:

- Licensed and/or NICE approved for -
 - JIA: Etanercept and Tocilizumab are licensed and approved by NICE for use in children with JIA;
 - Poly-articular JIA: Etanercept is approved by NICE
 - Systemic-Onset JIA: Tocilizumab is approved by NICE for Systemic-Onset JIA
- Licensed but not NICE approved for-
 - JIA: Adalimumab, Abatacept, and Canakinumab.

In adults:

- Licensed and NICE approved
 - Rituximab, Infliximab, Adalimumab, Certolizumab and Abatacept are licensed and NICE-approved in adults with inflammatory arthritis.
- Licensed but not NICE approved

- Golimumab is licensed but not currently NICE-approved in adults with inflammatory arthritis and there is no guidance for use in JIA
- Anakinra is licensed but currently not NICE approved for children with some autoinflammatory syndromes (Cryopyinopathies) – Systemic Onset JIA is now regarded as an autoinflammatory syndrome.

7 Rationale behind the Policy Statement

Patients with JIA arthritis that remains active despite optimal dosing, or who are intolerant of methotrexate need to be treated with a biologic.

8 Criteria for Commissioning

This policy has been agreed on the basis of NHS England's understanding of the likely price of care associated with enacting the policy for all patients for whom NHS England has funding responsibility, as at the time of the policy's adoption. Should these prices materially change, and in particular should they increase, NHS England may need to review whether the policy remains affordable and may need to make revisions to the published policy.

9 Patient Pathway

All types of JIA

Treatment pathways for JIA are detailed in Appendix A.

Initiation of treatment with DMARDs and Biologics should only be undertaken at a specialist centre within a clinical network, and should always involve a consultant paediatric rheumatologist and a paediatric-trained Clinical Nurse Specialist (CNS).

MTX is the first-line DMARD for children with JIA.

Biologics should not be used unless a patient is intolerant to, or has failed optimised treatment with MTX; this is defined as 15mg/m² given subcutaneously once-weekly

for at least 3 months; higher doses have no evidence to suggest increased efficacy⁽²⁾. For full details see 'Treatment Failure Definition' below. The only exceptions to this would be:

- The 1st-line use of Anti-TNF in patients with Axial disease or sacroiliitis (as in Appendix A). This is accepted and NICE-approved practice in adults with Spondyloarthropathy⁽³⁾.
- Patients with Systemic-Onset JIA who show signs of Macrophage Activation Syndrome (MAS). This uncommon, but potentially fatal, complication is usually treated with high-dose steroids. Where MAS is severe or steroid resistant, treatment with Anakinra may be life-saving and should not be delayed⁽⁴⁾.

The Biologic therapy should be initiated by the consultant paediatric rheumatologist following full discussion with the child, carers, and the specialist multidisciplinary team (MDT). The decision will be based primarily on the JIA subtype and will usually follow the flow diagram in Appendix A. However when choosing between individual Anti-TNF drugs, or between biologics for Systemic-Onset JIA, it may be necessary to consider the mode of administration, required dosing frequency, presence of extra-articular complications such as uveitis, adherence and response to previous medications. In the case of Systemic-Onset JIA, the potentially fatal complication of Macrophage Activation Syndrome (MAS) may necessitate the use of Anakinra⁽⁴⁾, with evidence of this drug being rapidly effective and life saving.

Clinical Trials

It is a fundamental principle that children should have access to participate in clinical trials. The evidence for many of the treatments used in paediatric rheumatology is incomplete and further evidence base to inform clinical practice is needed.

- The suggested pathways in Appendix A should be taken as a guide. Clinical trials may be available in the future, at any of the decision points in those pathways.
- Children and young people from all clinical networks in England should be offered the opportunity to participate in any trial for which they are eligible.
- Ineligibility or inability to participate in clinical trials must not impede a child's access to appropriate care along those pathways.

- At the end of any trial there should be no delay in deciding appropriate future treatment, if ongoing access to the trial drug is not available a suitable alternative must be offered.

Definitions

1. **Definition of 'Response'**: Response to therapy should be assessed after 3 months of therapy and re-assessed every 3 months whilst treatment continues. It should document the current status of every synovial joint as either:

- Active synovitis
- No active synovitis but decreased range of movement
- No synovitis and full range of movement

In addition the presence of absence of extra-articular complications including Psoriasis, Inflammatory Bowel Disease, Uveitis, Fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributed to JIA should be noted.

2. **Definition of 'clinical inactive disease'** ⁽⁵⁾ (all must be met)

- No joints with active arthritis
- No fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributed to JIA
- No active uveitis
- ESR or CRP level (both if both tested) within normal limits for the laboratory where tested or, if elevated, not attributable to JIA
- Physician's global assessment of disease activity score as lowest possible on whichever scale is used
- Duration of morning stiffness ≤ 15 min

3. **Definition of 'clinical remission on medication'** ⁽⁵⁾

Satisfaction of the definition of clinical inactive disease for at least 6 continuous months while on therapy for JIA.

4. Definition of 'clinical remission off medication' ⁽⁵⁾

Satisfaction of the definition of clinical inactive disease for at least 12 continuous months while off all therapy for JIA.

5. Treatment failure definition:

- Persistent synovitis in 2 or more joints
- Within 12 months; 2 or more separate episodes of corticosteroid use to control flares of disease
- Development/worsening of erosive disease due to ongoing synovitis
- Intolerance of therapy – including inability to tolerate the injections
- Ongoing evidence of active uveitis, even in the presence of quiescent joint disease.

6. Biologic 'Switching'

Patients who do not achieve, or who fail to maintain, good control of their disease will need to switch to an alternative 'Biologic' from the list above. The decision will be based primarily on the JIA subtype and will usually follow the flow diagram in Appendix A. Evidence to support the sequential use of biologics is based on reported use in international Registries ⁽¹⁸⁾; there are no RCTs for sequential use of therapies. The choice between the different anti-TNF agents for JIA is based on clinical factors (presence of, or history of JIA related uveitis), patient factors (history of poor adherence or intolerance of subcutaneous injections, geographical location and distance from day unit centres. The use of Infliximab (given as an intravenous infusion usually on a monthly basis) is often recommended by paediatric rheumatologists if there has been a history of poor adherence or intolerance to subcutaneous injections and there is a history of JIA uveitis. The use of Adalimumab is often recommended by paediatric rheumatologists if there has been a history of JIA uveitis.

Children with ongoing arthritis and who fail anti-TNF agents may be recommended to receive other biologics – Tocilizumab, Abatacept (rheumatoid

factor negative (RF-ve) polyarticular JIA, or Rituximab (rheumatoid factor positive (RF+ve) polyarticular JIA).

Tocilizumab is NICE approved for Systemic Onset JIA. Anakinra may be recommended by paediatric rheumatologists in children with Systemic Onset JIA and with potentially life threatening Macrophage Activation Syndrome.

Children who fail to achieve good control with 3 or more different 'Biologics,' consideration should be given to referral to a specialist centre to discuss the options for Bone-Marrow transplantation or Autologous Stem cell rescue.

10 Governance Arrangements

For all medicines that are unlicensed or used for an unlicensed indication each hospital trust must assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics committee or similar and NHS England may ask for assurance of this process.

11 Mechanism for Funding

From April 2013 NHS England will be responsible for commissioning in line with this policy on behalf of the population of England.

12 Audit Requirements

All children who commence treatment with a Biologic should be offered the option of enrolling in the appropriate long-term national Registries. These Registries are designed to provide long-term safety data for all these drugs and enrolment of data to the Registries is strongly recommended.

13 Documents which have informed this Policy

See Section 16

14 Links to other Policies

This policy follows the principles set out in the ethical framework that governs the commissioning of NHS healthcare and processes for the management of individual funding requests (IFR).

15 Date of Review

This policy will be reviewed once further guidance from NICE is received.

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Appendix A

Suggested Treatment Flow-chart for JIA

See attachment.