Clinical Commissioning Policy
Baricitinib for use in monogenic interferonopathies (adults and children 2 years and over) (210506P) [URN 1930]

Publication date: July 2021 **Version number:**1.0

Commissioning position

Summary

Baricitinib is recommended to be available as a treatment option through routine commissioning for adults and children 2 years and over with monogenic interferonopathies within the criteria set out in this document.

The policy is restricted to adults and children 2 years and over. There is insufficient evidence to confirm safety and efficacy in younger children, therefore it is not recommended to be used in children under 2 years.

Executive summary

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain language summary

Monogenic interferonopathies are a group of conditions where there is too much interferon activity because of a problem with a single gene. Interferons are proteins that are produced by the immune system, usually in response to viruses. There are a wide range of potential symptoms such as severe skin rashes, gangrene, arthritis, breathing difficulty, abnormal blood counts and can also affect the brain, with an adverse impact on development and function. These conditions can lead to poor quality of life, the requirement for frequent hospital admissions and can eventually be fatal.

The current treatment for monogenic interferonopathies is to treat the symptoms, which is often with corticosteroids. There are no treatments that are currently used which stop the progression of the disease. Baricitinib is a tablet that can help to treat monogenic interferonopathies and can slow down the progression of the disease.

What we have decided

NHS England has carefully reviewed the evidence to treat monogenic interferonopathies with baricitinib. We have concluded that there is enough evidence to make the treatment available for adults and children 2 years and over at this time.

Further safety data published subsequent to the evidence review in a peer-reviewed letter in the New England Journal of Medicine (Vanderver et al. 2020) provides evidence of safety and efficacy in children 2 years and over. However, there is insufficient evidence of safety and efficacy for children under 2 years to be included within the policy.

Links and updates to other policies

This document does not update any other policies.

Committee discussion

The Clinical Panel considered that the evidence base presented demonstrated modest evidence of benefit for the use of baricitinib for the treatment of monogenic interferonopathies.

See the committee papers (link) for full details of the evidence.

Safety data published subsequent to the evidence review

Clinical Panel considered evidence describing safety data (Vanderver et al. 2020). It describes an uncontrolled prospective cohort study of 35 patients with Aicardi-Goutières syndrome (AGS) across two countries. The patients have a mean age at the point of administering baricitinib of 5.9 years. This letter is published with peer reviewed appendices detailing study protocols, methods, results and analysis. It presents safety data in an extended age group, including number and cause of hospitalisations, number and cause of deaths, dose adjustments and blood test abnormalities. It concludes that the primary risks associated with baricitinib among patients with AGS are thrombocytosis, leukopaenia and infection.

Monogenic interferonopathies

Interferons are a group of cytokines that are produced by the immune system in response to viral infections. Sometimes the genes that encode these interferons are mis-programmed and produce uncontrolled amounts of interferons or where sensitivity to interferon is abnormally increased, which can lead to a group of diseases known as interferonopathies. Monogenic interferonopathies are those that are caused by a defect to a single gene.

There are an expanding group of monogenic interferonopathies, which often share a similar mechanistic pathological process and overlap of the phenotype (Volpi et al. 2016). Some well-recognised phenotypes of monogenic interferonopathies are Aicardi-Goutières syndrome (AGS), familial chilblain lupus (FCL), stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI) and proteasome-associated autoinflammatory syndrome (PRAAS), which includes chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperatures (CANDLE) syndrome, joint contractures, muscle atrophy, microcytic anaemia and panniculitis-induced lipodystrophy (JMP) syndrome and Nakajo-Nishimura syndrome.

The clinical phenotype of an interferonopathy is mixed, but combinations of the features listed below are enough to suspect an interferonopathy:

- Skin manifestations such as nodular erythema or violaceous plaques in cold-sensitive acral (peripheral) areas
- Vasculopathy such as a chilblain-like rash, microangiopathic vasculopathy or gangrene/ulcers/infarcts in acral areas

- Lipodystrophy
- Joint manifestations such as contractures or non-erosive arthritis
- Patchy myositis
- Central nervous system (CNS) manifestations such as basal ganglia calcifications, leukoencephalopathy or white matter disease
- Pulmonary involvement such as interstitial lung disease, pulmonary fibrosis or pulmonary hypertension
- Leukopaenia or lymphopaenia with flare ups
- Infantile onset with severe and intractable diarrhoea and evidence of trichorrhexis nodosa.

Patients can present with severe skin inflammation that results in severe chilblains, which can be made worse by cold weather. These can progress to major and debilitating skin ulcers, gangrene and autoamputation of the tips of digits and sometimes the whole digit. These patients may already have poor quality of life due to growth and developmental delay, strokes, encephalopathy, febrile illness, severe and progressive lung disease and muscle inflammation. Some patients have less severe skin disease; however, they can experience frequent flare ups of chilblains that affect their ability to carry out activities of daily living or have inflammation of their lungs, muscles and joints resulting in progressive breathlessness, requiring oxygen, intensive care admissions, weakness and muscle and joint pain.

Due to the many different types of monogenic interferonopathies, the natural history of each condition and in each patient can be vastly different. Symptoms of AGS usually appear within the first six months of life, although some have later onset; between six and twelve months. The course of AGS is severe and progressive, where death occurs in around a quarter of patients before 17 years of age.

A diagnosis of an interferonopathy is supported by the presence of a supportive clinical phenotype, and evidence of significant dysregulation of the interferon (IFN) pathway . The IFN pathway can be assessed by measuring the expression of interferon-stimulated genes (ISGs) in peripheral blood or measurement of interferon protein directly by digital enzyme-linked immunosorbent assay (ELISA). At least one of these measurements must be abnormal in two readings at least one month apart. A diagnosis is confirmed by a specialist multidisciplinary team (MDT).

Current treatments

Treatment is currently based on symptom management, of which the current first line treatment is corticosteroids. Most patients do not receive any disease-modifying drugs and acquire disease-related morbidities. Some patients are initially thought to have other autoimmune disorders and are treated with high doses of methylprednisolone, oral prednisolone, or other disease-modifying anti-rheumatic drugs (DMARDs) with inevitably poor response to treatment. DMARDs that have been tried and shown to be mostly ineffective include methotrexate, mycophenolate mofetil and azathioprine, along with biologics such as infliximab, etanercept, anakinra, tocilizumab and rituximab. If patients get worsening symptoms despite corticosteroids, they may be treated with any of the DMARDs or biologics listed here, despite poor evidence of their effectiveness.

New treatment

The new treatment is the off-label use of baricitinib, a Janus kinase (JAK) inhibitor, as first line disease-modifying treatment for adults and children 2 years and over with a diagnosis of any monogenic interferonopathy. This could be used concurrently with other symptom control treatments such as corticosteroids.

Interferons and other cytokines function by binding to and activating cytokine receptors, which use JAK enzymes for signal transduction. JAK inhibitors inhibit the activity of these enzymes and in turn block cytokine signalling and upregulation. Baricitinib is given in tablet form and is a life-long treatment for patients with this condition.

Epidemiology and needs assessment

The overall incidence and prevalence of monogenic interferonopathies are not known. AGS is the most common monogenic interferonopathy with an estimated prevalence in England of 1 in 110,000 (unpublished data from Leeds Genetics Laboratory). FCL, PRAAS and SAVI have an estimated prevalence of less than 1 in 1,000,000 (Orpha.net no date, Touitou et al. 2013 and Orpha.net 2019). It is estimated that around 100 patients per annum will meet the inclusion criteria.

Evidence summary

NHS England has concluded that there is sufficient evidence to support a policy for the routine commissioning of this treatment for the indication.

Two studies were included in the evidence review. Sanchez et al. (2018) is an uncontrolled prospective cohort study (in the United States, Canada, Germany, Israel, Spain, Turkey and the United Kingdom) that assessed the safety and efficacy of baricitinib in 18 people with CANDLE, SAVI and other interferonopathies. Zimmermann et al. (2019) is a case series (in Germany) that reported outcomes in 3 people with FCL who were treated with baricitinib.

In patients with a monogenic interferonopathy (as described above), what is the clinical effectiveness of baricitinib compared with current standard treatment?

Critical outcomes

The critical outcomes for decision making are quality of life, clinical severity of symptoms and physician and patient global assessment of wellbeing. The quality of evidence for all these outcomes was assessed as very low certainty using modified GRADE.

Quality of life

The study by Sanchez et al. (2018) found that median quality of life measurements (Pediatric Quality of Life Inventory [PedsQL]) improved numerically from baseline in 18 people with CANDLE, SAVI and other interferonopathies who were taking baricitinib for a median 2.8 years. However, the improvements were not statistically significant (results reported graphically, p value not reported).

Clinical severity of symptoms

In the cohort study by Sanchez et al. (2018) (n=18) after a median 2.8 years, disease-specific daily symptom (DDS) scores improved from baseline by an amount considered to be clinically meaningful in 12/18 (67%) people treated with baricitinib (8/10 [80%] with CANDLE, 3/4 [75%] with SAVI and 1/4 [25%] with other interferonopathies, no statistical analyses). In this study, 5/10 (50%) people with CANDLE experienced remission with no disease symptoms (DDS<0.15, no statistical analysis). No people with SAVI or other interferonopathies experienced remission.

In the study by Zimmermann et al. (2019) (n=3), after 3 months' treatment with baricitinib, a statistically significant improvement was seen in the area and severity of cutaneous lesions (mean Revised Cutaneous Lupus Area and Severity Index [RCLASI] score reported graphically, p=0.01). One patient had complete remission of skin and joint pain. In the other 2 patients, pain was partially reduced (individual visual analogue scale [VAS] scores reported graphically, all p<0.001).

Physician and patient global assessment of wellbeing

In the study by Sanchez et al. (2018) (n=18), during treatment with baricitinib, the median score for physicians' global assessment improved by a statistically significant 87.5 mm (from 90 mm at baseline to 2.5 mm at a median 2.8 years, p<0.001). Over the same period, the median score for patient or carers' global assessment improved by 22 mm (from 48 mm to 26 mm). However, this improvement was not statistically significant.

Important outcomes

The important outcomes for decision making are direct measurement of interferon (IFN), reduction in corticosteroid use, growth improvement in children and change in inflammatory markers. The quality of the evidence for all these outcomes was assessed as very low certainty using modified GRADE.

Direct measurement of IFN

Sanchez et al. (2018) (n=18) found that serum levels of the chemokine IP-10 and a 25-gene IFN response gene score (measures of IFN) decreased by a statistically significant amount during treatment with baricitinib. Median serum IP-10 reduced from 9196.7 at baseline to 1857.6 at a median 2.8 years, p<0.005. Median 25-gene IFN reduced from 417.5 at baseline to 113.3 at a median 2.8 years, p<0.01. The IFN score normalised in 5 people with CANDLE who experienced remission.

In the study by Zimmermann et al. (2019) (n=3), a statistically significant reduction was seen in the interferon-stimulated genes (ISG) score (a measure of IFN) after 3 months' treatment with baricitinib (mean reported graphically, p=0.01).

Reduction in corticosteroid use

Of the 14 people in the study taking corticosteroids at baseline in Sanchez et al. (2018), 10 (71%) successfully reduced their dose and fulfilled the corticosteroid improvement criteria while taking baricitinib (no statistical analysis). Median corticosteroid dose reduced by a statistically significant 0.33 mg/kg/day (from a prednisone equivalent dose of 0.44 mg/kg/day at baseline to 0.11 mg/kg/day at a median 2.8 years, p<0.005).

Growth improvement in children

In 13 children with growth potential at baseline in the study by Sanchez et al. (2018), mean height Z-scores improved from −4.03 to −3.19 when they took baricitinib (statistically significant, p=0.015). The authors reported that this is clinically significant. 'Catch up growth' was seen in 9 children who were able to reduce their corticosteroid dose below 0.16 mg/kg/day.

Change in inflammatory markers

Sanchez et al. (2018) (n=18) found that levels of the inflammatory markers C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) decreased during baricitinib treatment. However, the differences from baseline were not statistically significant. Median CRP reduced from 15.9 mg/L at baseline to 2.9 mg/L and median ESR reduced from 53 mm/hour at baseline to 37 mm/hour after a median 2.8 years.

In patients with a monogenic interferonopathy, what is the safety of baricitinib compared with current standard treatment?

Important outcomes

The important outcomes for decision making are withdrawal from treatment due to: adverse events, serious adverse events, treatment-related adverse events, upper respiratory tract infections and raised liver transaminases. The quality of the evidence for all these outcomes was assessed as very low certainty.

Withdrawal from treatment due to adverse events

In the study by Sanchez et al. (2018) (n=18), 1 person without a genetic diagnosis stopped baricitinib because of osteonecrosis and an unsatisfactory treatment response. One person with CANDLE developed BK viremia and azotemia and stopped treatment because of acute kidney injury. These people later died due to worsening disease.

Serious adverse events

In Sanchez et al. (2018) (n=18), 15 people (83%) had at least 1 serious adverse event. In most instances, these resolved without interrupting baricitinib treatment. No deaths were reported during the study (median 2.8 years). In Zimmermann et al. (2019) (n=3), baricitinib was reportedly well-tolerated and no serious adverse effects occurred over 3 months.

Treatment-related adverse events

In the study by Sanchez et al. (2018) (n=18), 16 people (89%) taking baricitinib experienced treatment-related infections (most commonly upper respiratory tract infections [see below]) over a median 2.8 years. The adverse events seen in the study were generally consistent with those listed in the summary of product characteristics for baricitinib, except for viral reactivation with BK virus (BK viremia and viruria, n=9 and n=15 respectively), which was considered unique to the study population compared with people with rheumatoid arthritis (the licensed indication). Note that, although these adverse events were new or worsened after starting baricitinib treatment, they may not be solely caused by baricitinib and may be related to the disease or concomitant treatment.

Upper respiratory tract infections

In Sanchez et al. (2018) (n=18), 15 people (83%) experienced upper respiratory tract infections over a median 2.8 years and, in Zimmermann et al. (2019) (n=3), 2 people experienced repeated mild upper respiratory tract infections over 3 months.

Raised liver transaminases

Liver transaminases were raised in 9/18 people (50%) in the study by Sanchez et al. (2018).

In patients with a monogenic interferonopathy, what is the cost-effectiveness of baricitinib?

No cost-effectiveness evidence was found for baricitinib for people with monogenic interferonopathies.

From the evidence selected is there any data to suggest that there are particular subgroups of patients that would benefit from treatment with baricitinib more than others?

Although, Sanchez et al. (2018) reported that outcomes seemed better in the subgroup of people with CANDLE compared with SAVI and other interferonopathies, this is of very low certainty. There are no statistical analyses reported and these results are likely to be subject to confounding and bias because the numbers of people in each subgroup were very small (n=10, 4 and 4 respectively).

From the evidence selected, what are the criteria used by the research studies to confirm a diagnosis of monogenic interferonopathy?

It is unclear what criteria were used by the research studies to confirm genetic diagnoses of monogenic interferonopathies. In the study by Sanchez et al. (2018), for people for whom a genetic diagnosis of a monogenic interferonopathy had not been made, inclusion criteria included no response to at least 1 biologic therapy and treatment with or no response to corticosteroids.

Discussion

The key limitation to identifying the effectiveness of baricitinib compared to standard treatment for monogenic interferonopathies is the lack of reliable comparative studies. It should be noted that these are rare conditions and, therefore, conducting prospective comparator studies may be unrealistic. The included studies are small uncontrolled observational studies, which are subject to bias and confounding and are low quality. The quality of the evidence for all the outcomes was assessed as very low certainty.

The methods and results of the studies are reported well, but it is unclear how precise the results are. The outcomes considered are relevant to people with monogenic interferonopathies. However, it is difficult to discuss the clinical relevance of some of the outcomes because they do not have published minimal clinically important differences. Also, results for some outcomes should be interpreted with caution because they are disease-orientated outcomes, such as blood test results, which may not result in benefits in patient-orientated outcomes, for example, quality of life or symptom severity.

The study by Sanchez et al. (2018) enrolled adults and children without other satisfactory treatment options. Most people (78%) had been taking corticosteroids long-term (average 5.7 years) and all people had found at least 1 conventional or biologic DMARD ineffective. During the study, the dosage of baricitinib was 4−10 mg/day (usually in divided doses), which is 1.83-fold higher than the licensed dosage of baricitinib for people with rheumatoid arthritis (4 mg/day).

Conclusion

The results of the study by Sanchez et al. (2018) suggest a high dose of baricitinib (4−10 mg/day) is associated with improvement in outcomes in adults and children with CANDLE, SAVI and other monogenic interferonopathies over a median 2.8 years. However, the quality of the evidence for all the outcomes was assessed as very low certainty and the clinical relevance of some of the outcomes used is unclear. Serious and treatment-related adverse events were common but did not lead to discontinuation of treatment.

Generally, the results of this study apply to people with poorly controlled CANDLE and SAVI and no other treatment options; they may not apply to people with less severe disease or other monogenic interferonopathies. However, these are 2 of the most common monogenic interferonopathies and experts have advised that, due to the pathways involved, baricitinib would be expected to have similar effects in similar conditions.

The results of the case series by Zimmermann et al. (2019) suggest baricitinib (4 mg daily) is associated with improved outcomes in adults with poorly controlled FCL. Statistically significant improvements were seen in cutaneous lesions and joint pain over 3 months. However, these results are unreliable and of very low certainty. Treatment with baricitinib was well-tolerated but the study was likely to have been too small and too short to detect serious and uncommon adverse events.

Implementation

Criteria

Inclusion criteria

This treatment is to be used as first-line disease-modifying treatment for adults and children 2 years and over with a diagnosis of any monogenic interferonopathy. A diagnosis of a monogenic interferonopathy is made by all of the following:

- Presence of supportive clinical phenotype
- Diagnosis is supported by a specialist MDT[1].

Children 2 years and over should also meet all of the criteria set out in the NHS England Commissioning Medicines for Children in Specialised Services policy (NHS England 2017).

Exclusion criteria

Treatment should not be initiated, or should be temporarily interrupted in patients with any of the following:

- Absolute lymphocyte count less than 0.5×10^9 cells per litre
- Absolute neutrophil count less than 1×10^9 cells per litre
- Haemoglobin less than 8g/dL

Baricitinib is contraindicated in pregnancy.

Patients should be screened for tuberculosis (TB) before starting baricitinib therapy. Baricitinib should not be given to patients with active TB. Anti-TB therapy should be considered prior to initiation of baricitinib in patients with previously untreated latent TB.

Assessment should be made by the specialist MDT as to whether the benefits outweigh the potential harms in patients with any of the following:

- Severe hepatic impairment
- Renal impairment (where creatinine clearance is less than 30mL/minute)
- Patients who are breast feeding.

Starting criteria

Patients that meet the required inclusion and do not meet any of the exclusion criteria should start baricitinib. The specialist MDT should ensure that routine blood tests (full blood count (FBC), urea and electrolytes (UE), liver function tests (LFTs), amylase, lipid profile) along with hepatitis and HIV exclusion if appropriate have been checked prior to starting treatment.

Provider organisations must register all patients using prior approval software and ensure monitoring internal trust arrangements are in place to capture patient outcomes. The patient outcome data should be available for NHS England if required.

The relevant specialist MDT (which can include specialised rheumatology, neurology, immunology or genetics service) should include paediatric clinicians for patients under the age of 18.

[1] Relevant specialist MDTs include specialised rheumatology, neurology, immunology or genetics service.

The dose of baricitinib to be used should be based on the patient's weight and eGFR. See Appendix 1 for a suggested dosing table. Doses should be reduced for patients with poor renal function.

Reassessment

Efficacy and safety monitoring should take place, ideally face-to-face in at least the first 3 reviews, at 1 and 3 months after starting treatment and every 3 months thereafter. Efficacy will be determined by a specialist rheumatology, neurology, immunology or genetics MDT by clinical improvements. The review should also include routine blood tests (FBC, UE, LFTs, amylase and lipid profile). Hyperlipidaemia should be treated according to international clinical guidelines. Treatment should be interrupted if drug-induced liver injury is suspected. Treatment should also be interrupted if:

- Absolute lymphocyte count is less than 0.5×10^9 cells per litre
- Absolute neutrophil count is less than 1×10^9 cells per litre
- Haemoglobin is less than 8g/dL.

Dose review and escalation can be considered in exceptional circumstances up to a maximum of 10mg per day, in divided doses. Dose escalation should be made in no more than 2mg increments. Dose escalation should only be made where a second specialist rheumatology, neurology, immunology or genetics MDT[2] agrees that there are reasonable grounds to expect significant benefit in patients who do not have an initial response or only partial response to treatment. A suggested dose escalation table based on weight and renal function is provided in Appendix 2.

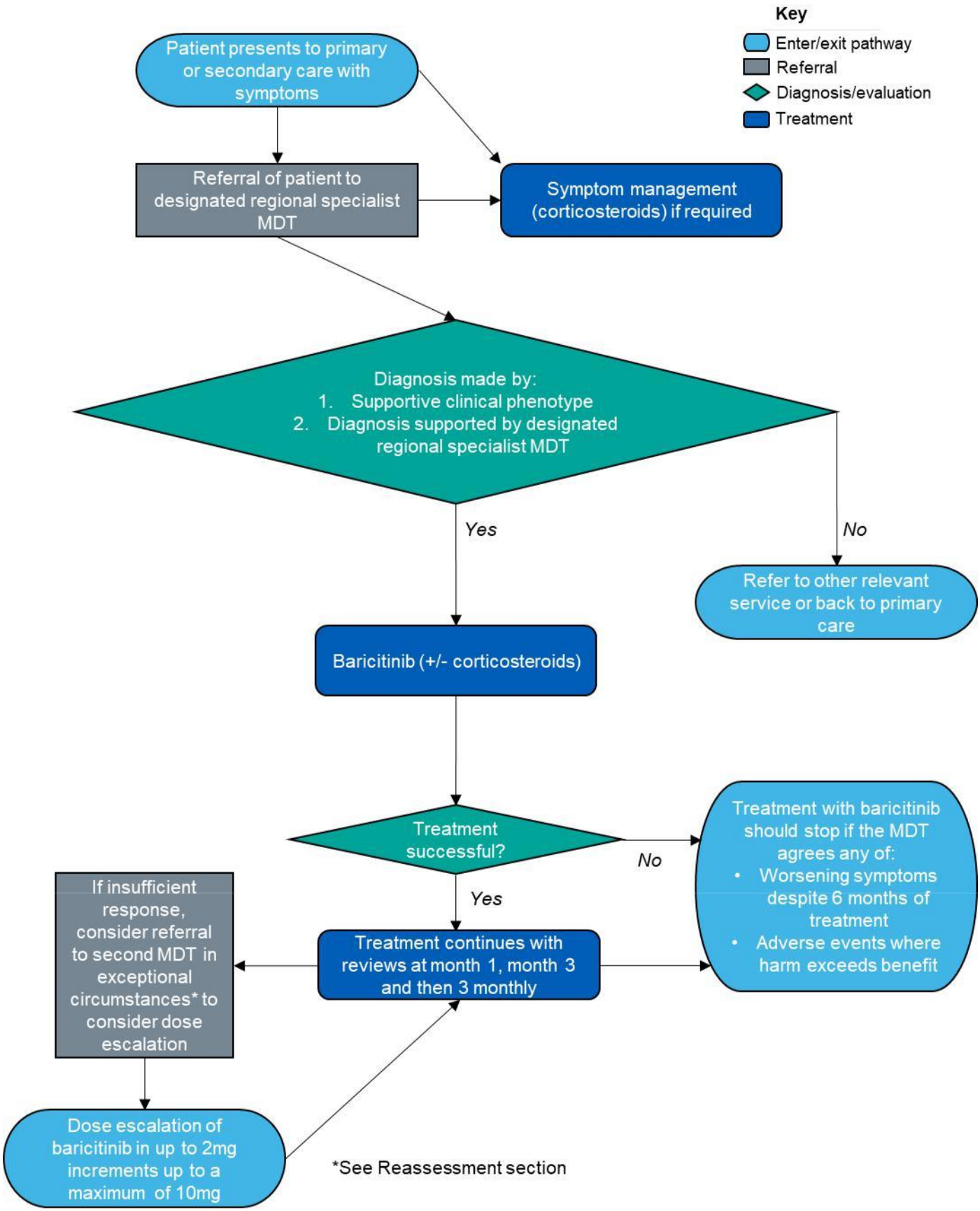
Stopping criteria

A decision to stop using baricitinib should be made by a specialist MDT using the following criteria:

- Worsening symptoms despite treatment by 6 months
- Adverse events where harm exceeds the benefit at any time during treatment.

[2] This second MDT may be at the same centre or in a different centre if required.

Patient pathway



Governance arrangements

This policy should be used in conjunction with the Paediatric Medicine: Rheumatology Service Specification (E03/S/b, NHS England, 2013) and the Specialised Immunology Service Specification (B09/S/a, NHS England, 2013).

Any provider organisation treating patients including children with this intervention will be required to 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.

Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Mechanism for funding

The mechanism for funding is via established mechanisms for high-cost tariff-exempt drugs to NHS England specialised commissioning teams.

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base, then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Definitions

Chilblains	Small, itchy swellings on the skin that occur as a reaction to cold temperatures, most commonly affecting extremities such as toes, fingers, ears and nose.
Cytokines	A group of small proteins, such as interferons, interleukins and growth factors which are produced by the immune system in response to different signals.
Enzyme-linked immunosorbent assay (ELISA)	A common biochemical test, which can detect the presence of a protein.
Interferon signature	An 'interferon signature' is a measure of the expression of interferon-stimulated genes in the bloodstream.
Leukoencephelopathy	Disorders of the white matter within the brain.
Lipodystrophy	The abnormal distribution of fat in the body.
Myositis	Any condition that causes inflammation in muscles, which can lead to weakness, swelling and pain.
Trichorrhexis nodosa	A defect in the hair shaft, characterised by thickening or weak points that causes hair to break easily.
Vasculopathy	Any disease that affects blood vessels.

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Appendix 1: Initial dosing table

Weight class	Morning dose	Afternoon dose	Evening dose	Total daily dose	Dosing frequency
eGFR ≥ 120mL/min/1.73m^2					
<20kg	2mg	2mg	2mg	6mg	TDS
20-40kg	4mg		2mg	6mg	BD
>40kg	4mg		4mg	8mg	BD
eGFR <120mL/min/1.73m^2					
<20mg	2mg		2mg	4mg	BD
20-40kg	2mg		2mg	4mg	BD
>40mg	2mg		2mg	4mg	BD

Table 1: suggested initial dosing table based on weight and renal function (eGFR). Adapted from data in Kim et al. 2018. TDS: three times daily. BD: twice daily.

Appendix 2: Dose escalation table

Weight class	Morning dose	Afternoon dose	Evening dose	Total daily dose	Dosing frequency
eGFR ≥ 120mL/min/1.73m^2					
<20kg	2mg	2mg + 2mg	2mg	8mg	QDS
20-40kg	4mg		4mg	8mg	BD
>40kg	6mg		4mg	10mg	BD
eGFR <120mL/min/1.73m^2					
<20kg	2mg	2mg	2mg	6mg	TDS
20-40kg	4mg		2mg	6mg	BD
>40kg	4mg		2mg	6mg	BD

Table 2: suggested dose escalation table based on weight and renal function (eGFR) for exceptional circumstances. Adapted from data in Kim et al. 2018. QDS: four times daily. TDS: three times daily. BD: twice daily.