NHS England

Evidence review: Baricitinib for use in monogenic interferonopathies (adults and children 2 years and over)

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Contents

1. Introduction

This review aims to assess the evidence for the clinical effectiveness, safety and cost-effectiveness of baricitinib compared with current standard treatment in people with monogenic interferonopathies, including Aicardi-Goutières syndrome (AGS), familial chilblain lupus (FCL), chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperatures (CANDLE) syndrome, and stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI) (Volpi et al. 2016).

Treatment of monogenic interferonopathies is currently based on symptom management, with corticosteroids generally used first-line. If symptoms worsen despite corticosteroids, disease-modifying antirheumatic drugs (DMARDs) or biological medicines are sometimes used, despite poor evidence of their effectiveness (Volpi et al. 2016).

Baricitinib is a Janus kinase (JAK) inhibitor, which has a marketing authorisation for treating moderate to severe active rheumatoid arthritis in adults who have responded inadequately to, or who are intolerant of 1 or more DMARDs (Olumiant summary of product characteristics). Using baricitinib for treating monogenic interferonopathies is off label use. It is taken by mouth.

2. Executive summary of the review

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.

3. Methodology

Review questions

The review questions for this evidence review are:

1. In patients with a monogenic interferonopathy (as described above), what is the clinical effectiveness of baricitinib compared with current standard treatment?
2. In patients with a monogenic interferonopathy, what is the safety of baricitinib compared with current standard treatment?
3. In patients with a monogenic interferonopathy, what is the cost-effectiveness of baricitinib?
4. 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?
5. From the evidence selected, what are the criteria used by the research studies to confirm a diagnosis of monogenic interferonopathy?

See Appendix A for the full review protocol.

Review process

The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2019).

The evidence searches were informed by the PICO document and were first conducted on 18 March 2020. The searches were re-run to identify any additional papers on 8 June 2020.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO framework. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE Profiles.

4. Summary of included studies

Two studies were identified for inclusion. Sanchez et al. 2018 is an uncontrolled prospective cohort study that assessed the safety and efficacy of baricitinib in 18 people with CANDLE, SAVI and other interferonopathies. Zimmermann et al. 2019 reported outcomes in 3 people with FCL who were treated with baricitinib.

Table 1 provides a summary of these included studies and full details are given in Appendix E. No cost-effectiveness studies were identified.

Table 1 Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Sanchez et al. 2018 Uncontrolled prospective cohort study United States, Canada, Germany, Israel, Spain, Turkey, United Kingdom	Expanded access programme looking at the safety and efficacy of baricitinib for treating people with CANDLE, SAVI and other presumed interferonopathies 18 people: 10 with CANDLE, 4 with SAVI and 4 with other interferonopathies. One person was later found to have AGS and 1 person had a novel disease-causing mutation Mean age was 12.5 years (6 people were ≥18 years)	Open label treatment with baricitinib The dose was escalated until the 'optimal tolerated treatment dose' was reached. This was 4−10 mg/day, usually in divided doses[1]	**Critical Outcomes** • Quality of life • Clinical severity of symptoms: DDS scores • Physician and patient global assessment **Important outcomes** • Reduction in corticosteroid use

	78% were on long-term corticosteroid treatment (average 5.7 years). Corticosteroid treatment was ineffective and had been stopped in 3 people with SAVI and 1 with CANDLE. 1 to 6 conventional and/or biologic DMARDs were ineffective in all people	The median duration of treatment was 2.8 years; people took optimal doses for a median of 2.5 years At the time of safety analysis, mean baricitinib exposure was 3.5 years There was no comparator	• Direct measurement of IFN • Growth improvement in children • Change in inflammatory markers (ESR and CRP) • Adverse effects
Zimmermann et al. 2019 Prospective case series Germany	Investigated the efficacy and safety of baricitinib in 3 people (mean age 51 years) with FCL[2] and painful and mutilating erythematous ulcerative skin infiltrates on acral locations as well as arthritis All patients had previously been treated with topical corticosteroids and hydroxychloroquine, with unsatisfactory results. These treatments had been stopped at least 6 weeks before the baricitinib was started	Open label treatment with baricitinib 4 mg daily for 3 months (during the winter season) There was no comparator	**Critical Outcomes** • Clinical severity of symptoms: area and severity of cutaneous lesions, and pain[3] **Important outcomes** • Direct measurement ISG • Adverse effects

Abbreviations: AGS, Aicardi-Goutières syndrome; CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperatures syndrome; CRP, C-reactive protein; DDS, disease-specific daily symptom; ESR, erythrocyte sedimentation rate; FCL, familial chilblain lupus; IFN, interferon; ISG, interferon-stimulated genes; SAVI, stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy

[1] Twice daily in 15 people, 3 times daily in 2 people and 4 times daily in 1 person

[2] Due to TREX1 mutation

[3] The DDS score was not used in this study. Cutaneous lesions were assessed using the Revised Cutaneous Lupus Area and Severity Index (RCLASI) and pain was assessed using a visual analogue scale (VAS) score

5. Results

In patients with monogenic interferonopathies, what is the clinical effectiveness and safety of baricitinib?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Change from baseline in quality of life scores **Certainty of evidence: very low**	Improvement in quality of life is a marker of successful treatment. People with monogenic interferonopathies often have poor quality of life so this outcome is relevant to them. One uncontrolled prospective cohort study (Sanchez et al. 2018) provided evidence relating to quality of life for a median duration of treatment of 2.8 years. In this study, 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. However, the improvements were not statistically significant (p value not reported, results reported graphically). (**VERY LOW**). **This study provides very low certainty evidence that baricitinib increases quality of life in people with CANDLE, SAVI and other interferonopathies by a small, nonsignificant amount after 2.8 years of treatment.**
Change from baseline in clinical severity of symptoms **Certainty of evidence: very low**	Clinical severity of symptoms is relevant to people with monogenic interferonopathies because symptoms can be severe and disabling and affect their function, activities of daily living and quality of life. Improvement in symptoms is a marker of treatment success. One uncontrolled prospective cohort study (Sanchez et al. 2018) provided evidence relating to clinical severity of symptoms for a median duration of treatment of 2.8 years. This study mainly included people with CANDLE and SAVI. A prospective case series (Zimmermann et al. 2019) provided evidence relating to clinical severity of symptoms over 3 months in people with FCL. In the cohort study (n=18), after a median 2.8 years, 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). Overall, the median DDS score decreased by 1.05 (from 1.3 at baseline to 0.25, p<0.0001, statistically significant). 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. (**VERY LOW**). In the case series (n=3), after 3 months' treatment, a statistically significant improvement was seen in the area and severity of cutaneous lesions (mean 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 VAS scores reported graphically, all p<0.001). (**VERY LOW**). **These studies provide very low certainty evidence that baricitinib improves symptoms in people with CANDLE, SAVI, FCL and other interferonopathies. It is not known if the improvements seen are all clinically meaningful, but symptoms resolved completely in some people.**
Physician and patient global assessment of wellbeing **Certainty of evidence: very low**	People with monogenic interferonopathies often have poor quality of life and debilitating symptoms that affect their wellbeing so this outcome is relevant to them. Global assessment is a holistic measure of treatment effect, subjectively assessed by the patient and clinician, which may not be captured by individual measures. One uncontrolled prospective cohort study (Sanchez et al. 2018) provided evidence relating to global assessment of wellbeing for a median duration of treatment of 2.8 years. In this study (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, the improvement was not statistically significant. (**VERY LOW**). **This study provides very low certainty evidence that treatment with baricitinib for 2.8 years improves wellbeing in people with CANDLE, SAVI and other interferonopathies. The improvement in physicians' global assessment is likely to be clinically meaningful.**
Important outcomes	
Direct measurement of IFN **Certainty of evidence: very low**	This outcome is relevant to people with monogenic interferonopathies because these blood tests are a way of measuring whether their condition is responding to treatment or not. A reduction suggests improvement and normal levels can indicate remission. One uncontrolled prospective cohort study (Sanchez et al. 2018) provided evidence relating to IFN levels for a median duration of treatment of 2.8 years. This study mainly included people with CANDLE and SAVI. A prospective case series (Zimmermann et al.

	2019) provided evidence relating to IFN levels over 3 months in people with FCL. In the cohort study (n=18), 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. (**VERY LOW**). In the case series (n=3), a statistically significant reduction was seen in the ISG score (a measure of IFN) after 3 months' treatment with baricitinib (mean reported graphically, p=0.01). (**VERY LOW**). **These studies provide very low certainty evidence that baricitinib improves IFN levels in people with CANDLE, SAVI, FCL and other interferonopathies. The clinical significance of the improvement is unclear, except perhaps for people with CANDLE.**
Reduction in corticosteroid use **Certainty of evidence: very low**	This outcome is relevant to people with monogenic interferonopathies because corticosteroids have serious adverse effects (such as diabetes, osteoporosis and psychiatric reactions), especially when they are taken long-term at high doses. Reducing the dose reduces the risk of adverse effects. One uncontrolled prospective cohort study (Sanchez et al. 2018) provided evidence relating to reducing corticosteroid use over a median duration of treatment of 2.8 years. Of the 14 people on corticosteroids at baseline, 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). (**VERY LOW**). **This study provides very low certainty evidence that treatment with baricitinib for 2.8 years enables people with CANDLE, SAVI and other interferonopathies to reduce their dose of corticosteroid.**
Growth improvement in children **Certainty of evidence: very low**	People with monogenic interferonopathies often have chronic inflammation, which reduces their rate of growth. Improved growth is a marker of controlled inflammation in children and is a relevant outcome to them. One uncontrolled prospective cohort study (Sanchez et al. 2018) provided evidence relating to growth improvement in children over a median duration of treatment of 2.8 years.

	At baseline in this study, growth and physical maturation were delayed, with mean bone age 3.5 years lower than chronological age. In 13 children with growth potential who took baricitinib, mean height Z-scores improved from −4.03 to −3.19 (statistically significant, p=0.015). The authors report 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. Mean height percentile increased from the 1.4th percentile to the 7.2nd percentile. (**VERY LOW**). **This study provides very low certainty evidence that growth improves in children with CANDLE, SAVI and other interferonopathies treated with baricitinib for 2.8 years.**
Change in inflammatory markers (CRP and ESR) **Certainty of evidence: very low**	This outcome is relevant to people with monogenic interferonopathies because these blood tests are measures of treatment response. They are markers of inflammation and, if they are raised at baseline, they are a way of assessing improvement in inflammation. One uncontrolled prospective cohort study (Sanchez et al. 2018) provided evidence relating to inflammatory markers over a median duration of treatment of 2.8 years. In this study (n=18), CRP and 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. (**VERY LOW**). **This study provides very low certainty evidence that treatment with baricitinib for 2.8 years does not significantly improve inflammatory markers in people with CANDLE, SAVI and other interferonopathies.**
Safety	
Withdrawal from treatment due to adverse events **Certainty of evidence: very low**	This outcome is important to people because it is an indicator of serious adverse effects or lack of efficacy of the treatment and could affect the person's decision to take baricitinib. One uncontrolled prospective cohort study (Sanchez et al. 2018) provided evidence relating to withdrawal from treatment over a median duration of treatment of 2.8 years. In the cohort study (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. (**VERY LOW**). **This study provides very low certainty evidence that some people with CANDLE, SAVI and other interferonopathies may need to stop taking baricitinib because of adverse effects or because the treatment is ineffective.**

Serious adverse events **Certainty of evidence: very low**	This outcome is important to people because serious adverse effects can be life threatening or require hospitalisation or intervention to prevent permanent impairment or damage. They may also result in persistent or significant disability or incapacity. Serious adverse events may or may not be directly related to treatment. One uncontrolled prospective cohort study (Sanchez et al. 2018) provided evidence relating to serious adverse events over a median duration of treatment of 2.8 years. This study mainly included people with CANDLE and SAVI. A prospective case series (Zimmermann et al. 2019) provided evidence relating to serious adverse events over 3 months in people with FCL. In this cohort study (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. (**VERY LOW**). In the case series (n=3), baricitinib was reportedly well-tolerated and no serious adverse effects occurred. (**VERY LOW**). **The cohort study provides very low certainty evidence that serious adverse events are common in people with CANDLE, SAVI and other interferonopathies taking baricitinib for 2.8 years. However, the treatment is unlikely to need stopping because of these serious adverse events. The case series was likely to have been too small and too short to detect serious or rare adverse events in people with FCL taking baricitinib for 3 months.**
Treatment-related adverse events **Certainty of evidence: very low**	Treatment-related adverse events are side effects that were new or worsened after starting baricitinib treatment. They are relevant to people with monogenic interferonopathies because they can affect their decision to start treatment with baricitinib. One uncontrolled prospective cohort study (Sanchez et al. 2018) provided evidence relating to treatment-related adverse events over a median duration of treatment of 2.8 years. In the cohort study (n=18), 16 people (89%) experienced treatment-related infections (most commonly upper respiratory tract infections [see below]). 2 people developed herpes zoster. Transient cytopenias developed in the context of infections and intermittent disease exacerbations. Viral reactivation with BK virus (BK viremia and viruria, n=9 and n=15 respectively) was also seen. Other non-infection treatment-related adverse events were also common. (**VERY LOW**). **The study provides very low certainty evidence that treatment-related adverse events (particularly infections) are common in people with CANDLE, SAVI and other interferonopathies taking baricitinib for 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, 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 **Certainty of evidence: very low**	This outcome is relevant because it is one of the most common adverse effects of baricitinib and can sometimes be serious, requiring hospitalisation. One uncontrolled prospective cohort study (Sanchez et al. 2018) provided evidence relating to upper respiratory tract infections over a median duration of treatment of 2.8 years. This study mainly included people with CANDLE and SAVI. A prospective case series (Zimmermann et al. 2019) provided evidence relating to upper respiratory tract infections over 3 months in people with FCL. In the cohort study (n=18), 15 people (83%) experienced upper respiratory tract infections. (**VERY LOW**). In the case series (n=3), 2 people experienced repeated mild upper respiratory tract infections. (**VERY LOW**). **These studies provide very low certainty evidence that baricitinib is associated with upper respiratory tract infections in two thirds of people with CANDLE, SAVI, FCL and other interferonopathies.**
Raised liver transaminases **Certainty of evidence: very low**	This outcome is relevant because raised liver transaminases are a marker of liver damage and, if treatment-induced liver injury is suspected, baricitinib may need to be stopped temporarily. One uncontrolled prospective cohort study (Sanchez et al. 2018) provided evidence relating to raised liver transaminases over a median duration of treatment of 2.8 years. In the cohort study (n=18), liver transaminases were raised in 9 people (50%). (**VERY LOW**). **This study provides very low certainty evidence that baricitinib is associated with raised liver transaminases in people with CANDLE, SAVI and other interferonopathies.**

Abbreviations: CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperatures syndrome; CRP, C-reactive protein; DDS, disease-specific daily symptom; ESR, erythrocyte sedimentation rate; FCL, familial chilblain lupus; IFN, interferon; ISG, interferon-stimulated genes; RCLASI, Revised Cutaneous Lupus Area and Severity Index; SAVI, stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy; VAS, visual analogue scale

From the evidence selected, are there any subgroups of patients that may benefit from baricitinib more than the wider population of interest?

Outcome	Evidence statement
Patient Subgroups **Certainty of evidence: Very low**	Neither of the included studies performed statistical analyses in subgroups of people with monogenic interferonopathies. However, the uncontrolled prospective cohort study (Sanchez et al. 2018) reported some outcomes numerically in subgroups of people with CANDLE, SAVI and other interferonopathies. For example, in this study, after a median 2.8 years' treatment with baricitinib, 5/10 (50%) people with CANDLE experienced remission with no disease symptoms (DDS<0.15, no statistical analysis). No people with SAVI (n=4) or other interferonopathies (n=4) experienced remission. Sanchez et al. (2018) reported that half of the patients with CANDLE could permanently discontinue corticosteroid therapy (without return of disease symptoms), their inflammatory markers normalised and they achieved durable inflammatory remission on baricitinib. In patients with SAVI, baricitinib treatment improved flares of vasculitis, and prevented the progression of spontaneous amputations and the development of gangrene. However, inflammatory markers did not normalise in any of the patients with SAVI, and although IFN scores decreased, the absolute levels remained elevated.

Abbreviations: CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperatures syndrome; DDS, disease-specific daily symptom; IFN, interferon; SAVI, stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy

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

Outcome	Evidence statement
Cost-effectiveness	No evidence was found to assess the cost-effectiveness of baricitinib for patients with monogenic interferonopathies.

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

Outcome	Evidence statement
Patient selection criteria	The study by Sanchez et al. (2018), included people with genetically confirmed CANDLE or SAVI, or a suspected undifferentiated interferonopathy who were referred to an expanded access programme. Details of the criteria used to confirm a genetic diagnosis of monogenic interferonopathy (such as CANDLE or SAVI) are not reported. 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. All participants had to have at least 2 of the following systemic signs and symptoms of inflammation: rash, fever, musculoskeletal pain, headache, fatigue, weakness, respiratory or breathing symptoms, and ulcers or ischaemic lesions. It is not reported how FCL was diagnosed in the study by Zimmermann et al. (2019), but the included cases were diagnosed with early onset in childhood.

6. 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 studies included in this evidence review are small uncontrolled observational studies, which are subject to bias and confounding and of low quality. The quality of the evidence for all the outcomes was assessed as very low certainty.

The first study (Sanchez et al. 2018) was an uncontrolled prospective cohort study that assessed the safety and efficacy of baricitinib in people with CANDLE, SAVI and other interferonopathies. Although this study included only 18 people, the duration of treatment with baricitinib was relatively long (mean duration 3.5 years, range 2.3 to 5.6 years). The methods and results 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.

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).

The expanded access programme assessed in the study by Sanchez et al. (2018) enrolled people without other satisfactory treatment options. Most people (78%) had been taking corticosteroids long-term (average 5.7 years) and all included people had found at least 1 conventional or biologic DMARD ineffective. During the study, the dosage of baricitinib was increased if response to treatment was inadequate unless signs of drug toxicity were seen. This 'optimal tolerated treatment dose' was 4−10 mg/day (by mouth, usually in divided doses) and, on average, 1.83-fold higher than the licensed dosage of baricitinib for people

with rheumatoid arthritis (4 mg/day). The mean age of the 18 people was 12.5 years: 6 people were aged at least 18 years.

The second study (Zimmermann et al. 2019) was an uncontrolled prospective case series, which provides limited evidence for using baricitinib to treat another type of monogenic interferonopathy, FCL. This study included only 3 adults (mean age 51 years) and the treatment duration was only 3 months. It was undertaken during the winter when symptoms of FCL are generally more severe. The dosage of baricitinib was 4 mg daily by mouth. The study assessed few relevant outcomes, and these are subject to the same limitations as those assessed by Sanchez et al. (2018).

Observational studies such as those included in this evidence review can only show that baricitinib is associated with improved outcomes in people with monogenic interferonopathies, not that baricitinib caused those improvements. For this reason, observational studies are generally considered hypothesis generating only. However, although better evidence is needed to confirm the results of the studies by Sanchez et al. (2018) and Zimmermann et al. (2019), it is difficult to perform higher quality studies, such as randomised controlled studies, in people with rare conditions because of the limited number of eligible people.

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.

No cost-effectiveness evidence was found to determine whether or not baricitinib is a cost-effective treatment for people with monogenic interferonopathies.

7. Conclusion

The results of the study by Sanchez et al. (2018) suggest an association between baricitinib (4−10 mg/day) and improvement in outcomes over a median 2.8 years. However, the results are not reliable and could be due to bias or chance. Statistically significant improvements were seen in symptom scores, physician assessments of global wellbeing, IFN levels, corticosteroid doses, height scores and inflammatory makers. Improvements in quality of life and patient assessments of global wellbeing did not reach statistical significance. These results are of very low certainty.

Generally, the results of this study apply to adults and children 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.

The study by Sanchez et al. (2018) provides very low certainty evidence that serious adverse events and treatment-related adverse events (particularly upper respiratory tract infections) are common in adults and children with CANDLE, SAVI and other interferonopathies taking baricitinib for 2.8 years. However, adverse events caused by baricitinib did not lead to discontinuation of treatment. 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, 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.

Treatment with baricitinib for 3 months was well-tolerated in 3 adults with FCL in the study by Zimmermann et al. (2019). However, the study was likely to have been too small and too short to detect serious and uncommon adverse events.

Appendix A PICO Document

The review questions for this evidence review are:

1. In patients with a monogenic interferonopathy (as described above), what is the clinical effectiveness of baricitinib compared with current standard treatment?
2. In patients with a monogenic interferonopathy, what is the safety of baricitinib compared with current standard treatment?
3. In patients with a monogenic interferonopathy, what is the cost-effectiveness of baricitinib?
4. 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?
5. From the evidence selected, what are the criteria used by the research studies to confirm a diagnosis of monogenic interferonopathy?

PICO Table

P –Population and Indication	People of all ages with clinical and molecular diagnosis of a monogenic interferonopathy. These conditions are exemplified by: ○ Aicardi-Goutières syndrome (AGS) ○ Familial Chilblain Lupus (FCL) ○ Proteasome-associated autoinflammatory syndrome (PRAAS) including chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperatures (CANDLE) ○ Stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI). Subgroups: • Children with developmental delay • Children with evidence of inflammatory skin disease
I – Intervention	Oral baricitinib (with concomitant corticosteroids)
C – Comparator(s)	• Corticosteroids alone • DMARDs or biologics (with concomitant corticosteroids)
O – Outcomes	*Response to treatment for all of the clinical effectiveness outcomes would be expected by 6 months, apart from changes in growth, which would only be seen in the longer term. There are no known standard MCIDs for any of the outcome measures with these conditions.* **Clinical Effectiveness** *Critical to decision making:* • Quality of life: preferred measure is the Childhood Health Assessment Questionnaire (CHAQ) in children or the Health Assessment Questionnaire

	(HAQ) in adults, but other measures could be included as reported in studies. *The CHAQ/HAQ questionnaires assess quality of life by measuring disability, discomfort and pain. These measures of quality of life can impact on the patient's function, activities of daily living and self-perceived wellbeing. Improvement in quality of life is a marker of successful treatment.* • Clinical severity of symptoms: using disease-specific daily symptom score. *This is an interferonopathy-specific measure of symptoms. Improvement in symptoms could help determine treatment choice and impact on patient's function and activities of daily living.* • Physician and patient global assessment on a scale from 0-100mm, with 0mm representing no disease activity and 100mm for maximum disease activity. *The global assessment is an important outcome as it is a holistic measure of treatment effect, subjectively assessed by the patient and clinician, which may not be captured by individual measures.* *These are considered the outcomes most critical to decision making as they include the patient's perspective on the treatment's effect on their condition. They help to determine if the treatment is effective at reducing symptoms, modifying disease activity and improving quality of life.* *<u>Important to decision making:</u>* • Direct measurement of interferon (IFN) or interferon-stimulated genes (ISG). These blood tests are a direct, quantifiable measure of treatment response and with normal levels can indicate remission. • Reduction in corticosteroid use. Long-term steroid use can be harmful and cause side effects unwanted by patients. • Growth improvement in children. Chronic inflammation reduces growth rate, so improved growth is a marker of controlled inflammation in children. • Change in inflammatory markers (ESR, CRP and serum amyloid A). These blood tests are an indirect, quantifiable measure of treatment response, which may be useful in measuring improvement if elevated at baseline. **<u>Safety</u>** • Adverse effects – most important are respiratory infections, clinically relevant derangement in liver function tests (transaminases; AST and ALT) and treatment withdrawal due to adverse effects.

	Cost-effectiveness
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2010-2020
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase and the Cochrane Library were searched on 18 March 2020, limiting the search to papers published in English language in the last 10 years. Conference abstracts, commentaries, letters, editorials and case reports were excluded. Trial registries were also searched. The schedule for the evidence review was affected by COVID-19 and the searches were re-run to identify any additional papers on 8 June 2020.

Database: Medline
Platform: Ovid
Version: Ovid MEDLINE(R) ALL 1946 to March 17, 2020
Search date: 18 March 20
Number of results retrieved: 20
No new results when re-run 8 June 2020
Search strategy:

Database: Medline in-process
Platform: Ovid
Version: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to March 17, 2020
Search date: 18 March 20
Number of results retrieved: 7
No new results when re-run 8 June 2020
Search strategy:
Database: Ovid MEDLINE(R) ALL <1946 to March 17, 2020>
Search Strategy: ES - monogenic interferon baricitinib Medline
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1 exp Hereditary Autoinflammatory Diseases/ (13491)
2 ("hereditary autoinflammatory" or "hereditary auto-inflammatory").ti,ab. (142)
3 (interferonopath* and (auto-inflam* or autoinflam*)).ti,ab. (47)
4 "interferon mediated".ti,ab. (525)
5 (IFN-mediated or "IFN mediated").ti,ab. (645)
6 "monogenic interferonopath*".ti,ab. (10)
7 ("chronic atypical neutrophilic dermatosis" or candle or candle-related).ti,ab. (721)
8 (Nakajo* or "NNS").ti,ab. (1280)
9 "juvenile dermatomyositis".ti,ab. (1094)
10 juvenile dermatomyositis/ (7792)
11 (("stimulator of interferon genes" or sting) and vasculopath*).ti,ab. (44)
12 savi.ti,ab. (250)
13 (Aicardi-Goutieres or "Aicardi Goutieres").ti,ab. (410)
14 Lupus Erythematosus, Systemic/ (53913)
15 ("systemic lupus" or SLE).ti,ab. (55681)
16 ("Familial Chilblain Lupus" or "Chilblain lupus erythematosus").ti,ab. (81)
17 ("Proteasome-associated autoinflammatory syndrome*" or "Proteasome associated autoinflammatory syndrome*" or PRAAS).ti,ab. (25)
18 (mendelian and interferon*).ti,ab. (119)
19 Genetic Diseases, Inborn/ (13629)
20 "Type 1 interferonopathy".ti,ab. (6)
21 or/1-20 (109480)
22 (baricitinib or Olumiant).ti,ab. (233)
23 ("INCB-028050" or "INCB-28050" or "LY-3009104" or "INCB28050" or "INCB028050" or "LY3009104" or "INCB 28050" or "INCB 028050" or "LY 3009104" or "UNII-ISP4442I3Y").ti,ab. (6)
24 or/22-23 (235)
25 21 and 24 (29)
26 limit 25 to yr="2010 -Current" (29)
27 limit 26 to (letter or historical article or comment or editorial or news) (7)
28 26 not 27 (22)
29 Animals/ not (Animals/ and Humans/) (4646711)
30 28 not 29 (21)
31 remove duplicates from 30 (20)

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Database: Embase
Platform: Ovid
Version: Embase 1974 to 2020 March 16
Search date: 18 March 20
Number of results retrieved: 70
9 new results when re-run 8 June 2020, two of which were captured by the original search
Search strategy:

Database: Embase <1974 to 2020 March 16>
Search Strategy: ES - monogenic interferon baricitinib Embase
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1 exp hereditary periodic fever/ (8898)
2 ("hereditary autoinflammatory" or "hereditary auto-inflammatory").ti,ab. (290)
3 (interferonopath* and (auto-inflam* or autoinflam*)).ti,ab. (108)
4 "interferon mediated".ti,ab. (648)
5 (IFN-mediated or "IFN mediated").ti,ab. (851)
6 "monogenic interferonopath*".ti,ab. (26)

7 ("chronic atypical neutrophilic dermatosis" or candle or candle-related).ti,ab. (926)
8 (Nakajo* or "NNS").ti,ab. (1634)
9 "juvenile dermatomyositis".ti,ab. (1939)
10 juvenile dermatomyositis/ (1427)
11 (("stimulator of interferon genes" or sting) and vasculopath*).ti,ab. (107)
12 savi.ti,ab. (504)
13 (Aicardi-Goutieres or "Aicardi Goutieres").ti,ab. (614)
14 Aicardi Goutieres syndrome/ (576)
15 Lupus Erythematosus, Systemic/ (47862)
16 ("systemic lupus" or SLE).ti,ab. (81720)
17 ("Familial Chilblain Lupus" or "Chilblain lupus erythematosus").ti,ab. (117)
18 ("Proteasome-associated autoinflammatory syndrome*" or "Proteasome associated autoinflammatory syndrome*" or PRAAS).ti,ab. (43)
19 (mendelian and interferon*).ti,ab. (193)
20 genetic disorder/ (56508)
21 monogenic disorder/ (2552)
22 "Type 1 interferonopathy".ti,ab. (8)
23 or/1-22 (169136)
24 baricitinib/ (944)
25 (baricitinib or Olumiant).ti,ab. (601)
26 ("INCB-028050" or "INCB-28050" or "LY-3009104" or "INCB28050" or "INCB028050" or "LY3009104" or "INCB 28050" or "INCB 028050" or "LY 3009104" or "UNII-ISP4442I3Y").ti,ab. (27)
27 or/24-26 (969)
28 23 and 27 (103)
29 limit 28 to yr="2010 -Current" (103)
30 limit 29 to english language (103)
31 nonhuman/ not (human/ and nonhuman/) (4589954)
32 30 not 31 (102)
33 (conference abstract or conference paper or conference proceeding or "conference review").pt. (4495060)
34 32 not 33 (70)

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Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL
Platform: Wiley
Version:
CDSR –Issue 3 of 12, March 2020
CENTRAL – Issue 3 of 12, March 2020

Search date: 19 March 20
Number of results retrieved: CDSR – 0; CENTRAL – 7
No new results when re-run 8 June 2020
Search strategy:

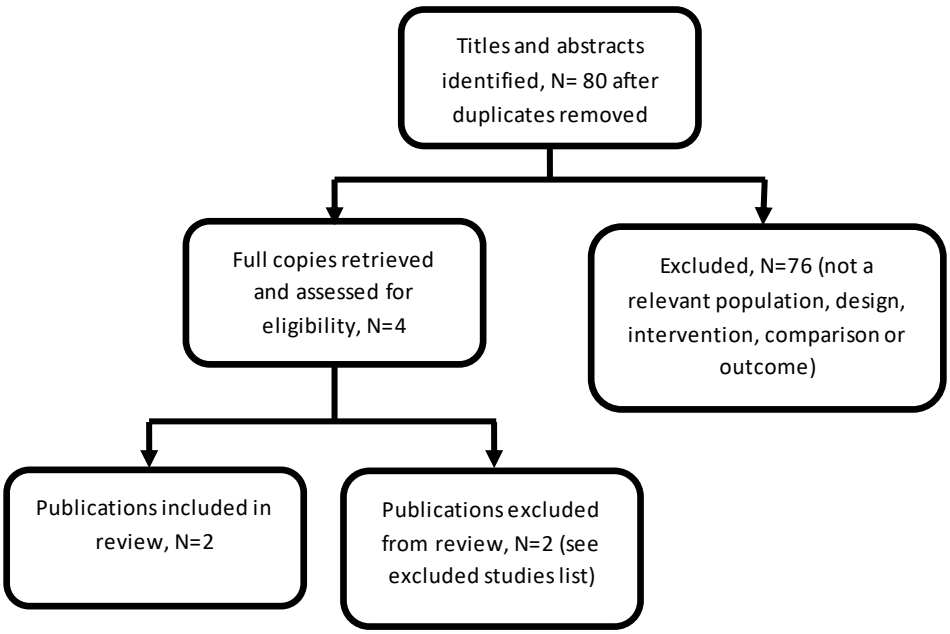
ID	Search	Hits
#1	MeSH descriptor: [Hereditary Autoinflammatory Diseases] explode all trees	185
#2	("hereditary autoinflammatory" or "hereditary auto-inflammatory"):ti,ab	4
#3	(interferonopath* and (auto-inflam* or autoinflam*)):ti,ab	0
#4	"interferon mediated":ti,ab	9
#5	(IFN-mediated or "IFN mediated"):ti,ab	8
#6	"monogenic interferonopath*":ti,ab	0

#7 ("chronic atypical neutrophilic dermatosis" or candle or candle-related):ti,ab 32
#8 (Nakajo* or "NNS"):ti,ab 160
#9 "juvenile dermatomyositis":ti,ab 49
#10 MeSH descriptor: [Dermatomyositis] explode all trees 84
#11 (("stimulator of interferon genes" or sting) and vasculopath*):ti,ab 0
#12 savi:ti,ab 12
#13 (Aicardi-Goutieres or "Aicardi Goutieres"):ti,ab 1
#14 MeSH descriptor: [Lupus Erythematosus, Systemic] explode all trees 997
#15 ("systemic lupus" or SLE):ti,ab 2107
#16 ("Familial Chilblain Lupus" or "Chilblain lupus erythematosus"):ti,ab 0
#17 ("Proteasome-associated autoinflammatory syndrome*" or "Proteasome associated autoinflammatory syndrome*" or PRAAS):ti,ab 2
#18 (mendelian and interferon*):ti,ab 2
#19 MeSH descriptor: [Genetic Diseases, Inborn] this term only 54
#20 "Type 1 interferonopathy":ti,ab 0
#21 {or #1-#20} 2915
#22 (baricitinib or Olumiant):ti,ab 336
#23 ("INCB-028050" or "INCB-28050" or "LY-3009104" or "INCB28050" or "INCB028050" or " LY3009104" or "INCB 28050" or "INCB 028050" or "LY 3009104" or "UNII-ISP4442I3Y"):ti,ab 70
#24 #22 or #23 345
#25 #21 and #23 with Cochrane Library publication date Between Jan 2010 and Mar 2020 7

Appendix C Evidence selection

The literature searches identified 80 references. These were screened using their titles and abstracts and 4 references were obtained and assessed for relevance. Of these, 2 references are included in the evidence summary. The remaining 2 references were excluded and are listed in Appendix D.

Figure 1 – Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection decision and rationale if excluded
Sanchez GAM, Reinhardt A, Ramsey S et al. (2018) JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies. J Clin Invest 128(7): 3041–52	Included. Also identified in literature search
Wallace DJ, Furie RA, Tanaka Y et al. (2018) Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet 392(10143): 222–31	Excluded. Not a relevant population
Briand C, Frémond ML, Bessis D et al. (2019) Efficacy of JAK1/2 inhibition in the treatment of chilblain lupus due to TREX1 deficiency. Ann Rheum Dis 78(3): 431–33	Excluded. Not a relevant study design (case report)

Appendix D Excluded studies table

Study reference	Reason for exclusion
Montealegre G, Reinhardt A, Brogan P et al. (2015) Preliminary response to Janus kinase inhibition with baricitinib in chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperatures (CANDLE). Pediatric Rheumatology 13(1): o31	Not a relevant publication type (conference abstract)
Kim H, Brooks KM, Tang CC et al. (2018) Pharmacokinetics, Pharmacodynamics, and Proposed Dosing of the Oral JAK1 and JAK2 Inhibitor Baricitinib in Pediatric and Young Adult CANDLE and SAVI Patients. Clinical pharmacology and therapeutics, 104(2): 364–73	Duplicate study (outlines dosing in early stages of cohort in Sanchez study)

Appendix E Evidence Table

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Sanchez GAM, Reinhardt A, Ramsey S et al. (2018) JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies. J Clin Invest 128(7): 3041–52 United States, Canada, Germany, Israel, Spain, Turkey, United Kingdom Uncontrolled prospective cohort study	Inclusion criteria included systemic signs and symptoms of inflammation; average daily diary score of ≥0.5 (CANDLE diary) or ≥1.0 (SAVI diary); ≥17.5 months of age; body weight ≥8.5 kg; treatment with oral corticosteroids; and treatment with at least 1 biologic therapy with limited or no response (if a diagnosis of monogenic interferonopathy had not previously been established)	Open label treatment with baricitinib The dose was escalated until the 'optimal tolerated treatment dose' was reached.[1] This was 4−10 mg/day, usually in divided doses (twice daily in 15 people, 3 times daily in 2 people and 4 times daily in 1 person) The median duration of treatment was 2.8 years, during which people took	**Critical outcomes** ***Quality of life***[2] Quality of life measurements improved numerically from baseline in people with CANDLE, SAVI and other interferonopathies. However, the improvements were not statistically significant (p value not reported) ***Clinical severity of symptoms: using disease-specific daily symptom (DDS) scores***[3] During treatment with baricitinib, DDS scores improved from baseline by an amount considered to be clinically meaningful in 12/18 (67%) people (8/10 [80%] with CANDLE, 3/4 [75%] with SAVI and 1/4 [25%] with other interferonopathies, no statistical analyses)	This study was assessed using the CASP cohort study checklist 1. YES 2. YES 3. YES 4. YES 5. UNCLEAR 6. UNCLEAR 7. YES 8. YES 9. The results are reported well and appear to show an association between baricitinib and improvement in some outcomes 10. It is unclear how precise the results are 11. YES 12. YES 13. UNCLEAR

[1] At the start of the programme, baricitinib was initiated at a dosage of 100 mg daily but this was amended as more data around dosing requirements became available. The dosage was increased if response to treatment was inadequate (defined as elevated average diary scores and active clinical disease) unless signs of drug toxicity were seen (such as drop in haemoglobin levels). A suggested dosing table has been published based on weight and renal function in another paper relating to this study (Kim et al. 2018). Dosages used in the study were generally higher than those licensed for treating adults with rheumatoid arthritis (usually 4 mg once daily)

[2] Quality of life (Pediatric Quality of Life Inventory [PedsQL]) was measured using a standardised age matched test that ranges from 0% to 100% with higher percentages indicating improvement

[3] Disease-specific patient diaries were used for collecting daily information on participants' signs and symptoms. People with CANDLE and other interferonopathies recorded daily symptoms of fever, rash, musculoskeletal pain, headaches and fatigue; and people with SAVI recorded, fever, rash, musculoskeletal pain, fatigue, respiratory symptoms and severity of ulcers/ischemic lesions. Each symptom was rated on a scale of 0 to 4, where 0=no symptoms and 4=severe symptoms. At each visit, median diary scores were calculated across all symptoms. 'Primary benefit' was defined as a decrease in the disease-specific daily symptom score to <0.5 for people with CANDLE and other interferonopathies and to <1.0 for people with SAVI. The authors state that 'these cutoffs corresponded with clinically meaningful responses to treatment'

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Expanded access programme looking at the safety and efficacy of baricitinib for treating people with CANDLE, SAVI and other presumed interferonopathies with no other treatment options October 2011 to October 2016	Exclusion criteria included treatment with an immunosuppressive biologic agent or monoclonal antibody within 4 half-lives of study entry; active or recent infection with, for example, herpes zoster, hepatitis B or C, or HIV; serious risk of participating because of being, for example, immunocompromised or seriously ill; and eGFR <40 ml/min/1.73 m^2 or abnormalities on certain other screening tests 18 people: 10 with CANDLE, 4 with SAVI, and 4 with other interferonopathies. 1 person was later found to have Aicardi-Goutières syndrome 5 (AGS5), and 1 had a novel disease-causing mutation Mean age was 12.5 years (6 were ≥18 years); 72% of	optimal doses for a median of 2.5 years At the time of safety analysis (June 2017), mean baricitinib exposure was 3.5 years There was no comparator	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 The median diary score statistically significantly decreased by 1.05 (from 1.3 [IQR[4] 0.93 to 1.78] at baseline to 0.25 [IQR 0.10 to 0.63], p<0.0001). It is not known if this improvement is clinically meaningful ***Physician and patient global assessment[5]*** During treatment with baricitinib, the median score for physicians' global assessment statistically significantly improved by 87.5 mm (from 90 mm [IQR 55.50 to 96.25 mm] at baseline to 2.5 mm [IQR 0.75 to 5.50 mm], p<0.001). This improvement is likely to be clinically meaningful The median score for patient or carers' global assessment improved by 22 mm (from 48 mm [IQR 18 to 55 mm] at baseline to 26 mm [IQR 1 to 36 mm]). However, the improvement was not statistically significant	14. UNCLEAR Other comments: although the evidence is of poor quality, the results suggest an association between baricitinib and improvement in some outcomes. However, the results are not reliable and could be due to bias or chance. Generally, the results apply to people with CANDLE and SAVI, rather than people with 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. Source of funding: This research was supported by the Intramural Research Program of the NIH, NIAID and NIAMS. Baricitinib was provided by Eli Lilly, the sponsor of the compassionate use programme.

[4] Interquartile range
[5] Parent or patient and physician assessments of global wellbeing were assessed using a visual analogue scale in which a value of 100 mm indicates the worst possible measure for the condition assessed by the test. Data for 2 people who dropped out of the study are not included

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
	people were below the 3rd percentile for height; 50% were below the 3rd percentile for weight; and 78% were on chronic corticosteroid treatment (average 5.7 years). Corticosteroid treatment was ineffective and had been stopped in 3 people with SAVI and 1 with CANDLE. 1 to 6 conventional and/or biologic DMARDs were ineffective in all people		**Important outcomes** ***Direct measurement of interferon (IFN) or interferon-stimulated genes (ISG)[6]*** IFN biomarker responses decreased by a statistically significant amount during treatment with baricitinib Median 25-gene IFN reduced from 417.5 (IQR 216.8 to 735.1) at baseline to 113.3 (IQR 18.5 to 288.8), p<0.01 Median serum IP-10 reduced from 9196.7 (IQR 2814.7 to 13299.4) at baseline to 1857.6 (IQR 868.7 to 4587.2), p<0.005 The IFN score normalised in the 5 people with CANDLE who experienced remission The clinical significance of these results in people with SAVI and interferonopathies is unclear ***Reduction in corticosteroid use[7]*** Of the 14 people on corticosteroids at baseline, 10/14 (71%) successfully reduced their dose and fulfilled the corticosteroid improvement criteria while taking baricitinib (no statistical analysis)	

[6] IFN signalling was assessed in several ways including quantification of a 25-IFN-gene score in whole blood, and measurement of serum IP-10
[7] 'Secondary benefit' was assessed for participants treated with corticosteroids at enrolment (n=14). 'Successful reduction' was defined as a reduction in corticosteroids to <0.15mg/kg/day of prednisone equivalent or a decrease of at least 50% of the person's daily dose at baseline

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			Median corticosteroid dose statistically significantly reduced by 0.33 mg/kg/day (from a prednisone equivalent dose of 0.44 mg/kg/day [IQR 0.31 to 1.09 mg/kg/day] at baseline to 0.11 mg/kg/day [IQR 0.02 to 0.24 mg/kg/day], p<0.005) ***Growth improvement in children***[8] Before baricitinib treatment, growth and physical maturation were delayed in all patients, with mean bone age 3.49 (±3.99) years lower relative to chronological age During baricitinib treatment, in 13 children with growth potential, mean height Z-scores improved from −4.03 (±2.64) to −3.19 (±2.33; statistically significant, p=0.015). The authors report 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. Mean height percentile increased from the 1.4th percentile to the 7.2nd percentile ***Change in inflammatory markers***[9] CRP continuously decreased on treatment. However, no significant difference was seen from baseline. Median CRP reduced from 15.9 mg/L	

[8] Z-scores for height, weight, body mass index (BMI), bone age, and bone mineral density were calculated. Only results for height are presented here
[9] Immunological evaluations included inflammatory markers, including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			[IQR 4.25 to 51.8 mg/L] at baseline to 2.9 mg/L [IQR 1.2 to 16.4 mg/L]) Median ESR reduced from 53 mm/hour [IQR 16.25 to 71.75 mm/hour] at baseline to 37 mm/hour [IQR 10.5 to 74 mm/hour]) but the reduction was not statistically significant ***Adverse effects***[10] No deaths were reported during the expanded access programme 1 person without a genetic diagnosis stopped baricitinib because of osteonecrosis and an unsatisfactory treatment response. 1 person with CANDLE developed BK viremia and azotemia and stopped treatment because of acute kidney injury. These people later died due to worsening disease 15 people (83%) had at least 1 serious adverse event. In most instances, these resolved without interrupting baricitinib treatment 16 people (89%) experienced treatment-related infections (most commonly upper respiratory tract infections, n=15). 2 people developed herpes zoster. Transient cytopenias developed in the context of infections and intermittent	

[10] The development of comorbidities and hospitalisations were documented. Vital signs including weight and height, clinical labo ratory tests, complete blood cell count with differential, renal and liver function, lipid profile, urinalysis, and other safety assessments were assessed

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			disease exacerbations. Viral reactivation with BK virus (BK viremia and viruria, n=9 and n=15 respectively) was also seen and considered unique to the study population compared with people with rheumatoid arthritis (the licensed indication) Other non-infection treatment-related adverse events included blood and lymphatic system disorders (n=9), gastro-intestinal disorders (n=12), injury, poisoning and procedural complications (n=12), metabolism and nutrition disorders (n=16), musculoskeletal and connective tissue disorders (n=13), renal and urinary disorders (n=10), Respiratory, thoracic and mediastinal disorders (n=13) and skin and subcutaneous tissue disorders (n=12) Liver transaminases were raised in 9 people (50%)	
Zimmermann N, Wolf C, Schwenke R et al. (2019) Assessment of clinical response to Janus kinase inhibition in patients with familial chilblain lupus (FCL) and TREX1 mutation.	3 adults (2 women and 1 man; mean age, 51 years [standard deviation 24 years]) with FCL with painful and mutilating erythematous ulcerative skin infiltrates	Open label treatment with baricitinib 4 mg daily for 3 months (during the winter season) There was no comparator	**Critical outcomes** ***Clinical severity of symptoms***[11] After 3 months' treatment, a statistically significant improvement was seen in the area and severity of cutaneous lesions (mean RCLASI score reported graphically, p=0.01)	This study was assessed using the Joanna Briggs Institute checklist for case series 1. NO 2. UNCLEAR 3. UNCLEAR 4. UNCLEAR 5. UNCLEAR

[11] Cutaneous lesions were assessed using the Revised Cutaneous Lupus Area and Severity Index (RCLASI) and pain was assessed using a visual analogue scale score (where 0 indicates no pain and 10 indicates most severe pain)

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
JAMA Dermatology 155(3) 342–6 Germany Case series Investigated the efficacy and safety of baricitinib in people with FCL Study dates not reported	on acral locations as well as arthritis All patients had previously been treated with topical corticosteroids and hydroxychloroquine, with unsatisfactory results. These treatments had been stopped at least 6 weeks before the baricitinib was started		At 3 months, 1 patient had complete remission of skin and joint pain. In the other 2 patients, pain was partially reduced (individual VAS scores reported graphically, all p<0.001) The clinical importance of these improvements is unclear ***Quality of life*** Not assessed ***Physician and patient global assessment*** Not assessed **Important outcomes** ***Reduction in corticosteroid use*** Not applicable because corticosteroid treatment had ceased ***Direct measurement of IFN or ISG[12]*** After 3 months' treatment with baricitinib, a statistically significant reduction was seen in the ISG score (mean reported graphically, p=0.01) ***Growth improvement in children*** Not applicable because patients were adults ***Change in inflammatory markers (ESR, CRP and serum amyloid A)***	6. UNCLEAR 7. UNCLEAR 8. YES 9. UNCLEAR 10. UNCLEAR Other comments: this study included only 3 people. The results are not reliable and could be due to bias or chance. Source of funding: This study was supported by grants from the Deutsche Forschungsgemeinschaft and the Technical University Dresden and a Roche research award.

[12] This was calculated from the messenger RNA expression levels of the IFN-stimulated genes IFI27, IFI44, IFI44L, IFIT1, ISG15, RSAD2, and SIGLEC1

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			Not reported ***Adverse effects*** Baricitinib was reportedly well-tolerated and no severe adverse effects occurred. 2 patients experienced repeated mild upper respiratory tract infections during the winter season.	

Appendix F Quality appraisal checklists

CASP cohort study checklist

Section A: Are the results of the study valid?

1. Did the study address a clearly focused issue?
2. Was the cohort recruited in an acceptable way?
3. Was the exposure accurately measured to minimise bias?
4. Was the outcome accurately measured to minimise bias?
5. Have the authors identified all important confounding factors?
6. Have they taken account of the confounding factors in the design and/or analysis?
7. Was the follow up of subjects complete enough?
8. Was the follow up of subjects long enough?

Section B: What are the results?

9. What are the results of this study?
10. How precise are the results?
11. Do you believe the results?

Section C: Will the results help locally?

12. Can the results be applied to the local population?
13. Do the results of this study fit with other available evidence?
14. What are the implications of this study for practice?

Joanna Briggs Institute checklist for case series

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series?
3. Were valid methods used for identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was statistical analysis appropriate?

Appendix G GRADE Profiles

Table 1: Question: In people with a monogenic interferonopathy, what is the clinical effectiveness and safety of baricitinib compared with current standard treatment?

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study type and number of studies	Risk of bias	Indirectness	Inconsistency	Imprecision	Baricitinib	Comparator	Result		
Quality of life (1 uncontrolled prospective cohort study)									
Change from baseline in median quality of life scores measured using PedsQL (median duration of treatment 2.8 years)									
1 cohort study Sanchez et al. (2018)	No serious limitations[1]	No serious indirectness	Not applicable	Serious limitations[2]	n=18	None	Reported graphically No statistically significant improvement (p value not reported)	Critical	Very low
Clinical severity of symptoms (1 uncontrolled prospective cohort study and 1 prospective case series)									
Change from baseline in median DDS scores by an amount considered to be clinically meaningful[3] (%, median duration of treatment 2.8 years)									
1 cohort study Sanchez et al. (2018)	No serious limitations	No serious indirectness	Not applicable	Serious limitations[4]	n=18	None	Overall, scores improved in 67% (12/18) of patients CANDLE 80% (8/10) SAVI 75% (3/4) Other 25% (1/4) No statistical analyses reported	Critical	Very low
Change from baseline in median DDS score (median duration of treatment 2.8 years)									
1 cohort study	No serious limitations	No serious indirectness	Not applicable	Serious limitations[5]	n=18	None	Statistically significantly improvement of 1.05, p<0.0001	Critical	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study type and number of studies	Risk of bias	Indirectness	Inconsistency	Imprecision	Baricitinib	Comparator	Result		
Sanchez et al. (2018)									
Change from baseline in mean area and severity of cutaneous lesions measured using RCLASI scores (duration of treatment 3 months)									
1 case series Zimmermann et al. (2019)	Serious limitations	No serious indirectness	Not applicable	Serious limitations[5]	n=3	None	Statistically significant improvement reported graphically, p=0.01	Critical	Very low
Change from baseline in mean severity of skin and joint pain measured using VAS scores (duration of treatment 3 months)									
1 case series Zimmermann et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Serious limitations[5]	n=3	None	Statistically significant improvement reported graphically, all p<0.001	Critical	Very low
Physician and patient global assessment of wellbeing (1 uncontrolled prospective cohort study)									
Change from baseline in median physician global assessment measured using a VAS (median duration of treatment 2.8 years)									
1 cohort study Sanchez et al. (2018)	No serious limitations	No serious indirectness	Not applicable	Serious limitations[5]	n=18	None	Statistically significant improvement of 87.5 mm, p<0.001	Critical	Very low
Change from baseline in median patient global assessment measured using a VAS (median duration of treatment 2.8 years)									
1 cohort study Sanchez et al. (2018)	No serious limitations	No serious indirectness	Not applicable	Serious limitations[5]	n=18	None	Improvement of 22 mm, not statistically significant	Critical	Very low
Direct measurement of IFN or ISG (1 uncontrolled prospective cohort study and 1 prospective case series)									
Change from baseline in median chemokine IP-10 serum levels (median duration of treatment 2.8 years)									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study type and number of studies	Risk of bias	Indirectness	Inconsistency	Imprecision	Baricitinib	Comparator	Result		
1 cohort study Sanchez et al. (2018)	No serious limitations	No serious indirectness	Not applicable	Serious limitations[5]	n=18	None	Statistically significant improvement of 7339.1, p<0.005	Important	Very low
Change from baseline in median 25-gene IFN response gene scores (median duration of treatment 2.8 years)									
1 cohort study Sanchez et al. (2018)	No serious limitations	No serious indirectness	Not applicable	Serious limitations[5]	n=18	None	Statistically significant improvement of 304.2, p<0.01	Important	Very low
Change from baseline in mean ISG scores (duration of treatment 3 months)									
1 case series Zimmerman et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Serious limitations[5]	n=3	None	Statistically significant improvement reported graphically, p=0.01	Important	Very low
Corticosteroid use (1 uncontrolled prospective cohort study)									
Change from baseline in median corticosteroid dosage (median duration of treatment 2.8 years)									
1 cohort study Sanchez et al. (2018)	No serious limitations	No serious indirectness	Not applicable	Serious limitations[5]	n=14	None	Statistically significant reduction of 0.33 mg/kg/day, p<0.005 71% (10/14) of people taking corticosteroids at baseline reduced their dose (no statistical analysis)	Important	Very low
Growth improvement in children (1 uncontrolled prospective cohort study)									
Change from baseline in mean height Z-scores (median duration of treatment 2.8 years)									
1 cohort study	No serious limitations	No serious indirectness	Not applicable	Serious limitations[5]	n=13	None	Statistically significant improvement in height Z-scores	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study type and number of studies	Risk of bias	Indirectness	Inconsistency	Imprecision	Baricitinib	Comparator	Result		
Sanchez et al. (2018)							of 0.84 in 13 children with growth potential, p=0.015		
Inflammatory markers (1 uncontrolled prospective cohort study)									
Change from baseline in CRP (median duration of treatment 2.8 years)									
1 cohort study Sanchez et al. (2018)	No serious limitations	No serious indirectness	Not applicable	Serious limitations[5]	n=18	None	Improvement of 13.0 mg/L, not statistically significant	Important	Very low
Change from baseline in ESR (median duration of treatment 2.8 years)									
1 cohort study Sanchez et al. (2018)	No serious limitations	No serious indirectness	Not applicable	Serious limitations[5]	n=18	None	Improvement of 16.0 mm/hour, not statistically significant	Important	Very low
Adverse events (1 uncontrolled prospective cohort study and 1 prospective case series)									
Number of people who withdrew from treatment due to adverse events (median duration of treatment 2.8 years)									
1 cohort study Sanchez et al. (2018)	No serious limitations	No serious indirectness	Not applicable	Serious limitations[4]	n=18	None	2/15 (13.3%), no statistical analysis	Important	Very low
Number of people with serious adverse events (median duration of treatment 2.8 years and 3 months respectively)									
1 cohort study Sanchez et al. (2018)	No serious limitations	No serious indirectness	Not applicable	Serious limitations[4]	n=18	None	15/18 (83.3%), no statistical analysis	Important	Very low
1 case series	Serious limitations[1]	No serious indirectness	Not applicable	Serious limitations[4]	n=3	None	0/3 (0%), no statistical analysis	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study type and number of studies	Risk of bias	Indirectness	Inconsistency	Imprecision	Baricitinib	Comparator	Result		
Zimmerman et al. (2019)									
Number of people with treatment-related adverse events (median duration of treatment 2.8 years)									
1 cohort study Sanchez et al. (2018)	No serious limitations	No serious indirectness	Not applicable	Serious limitations[4]	n=18	None	16/18 (88.9%), no statistical analysis	Important	Very low
Number of people with upper respiratory tract infections (median duration of treatment 2.8 years and 3 months respectively)									
1 cohort study Sanchez et al. (2018)	No serious limitations	No serious indirectness	Not applicable	Serious limitations[4]	n=18	None	15/18 (83.3%), no statistical analysis	Important	Very low
1 case series Zimmerman et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Serious limitations[4]	n=3	None	2/3 (66.7%), no statistical analysis	Important	Very low
Number of people with raised liver transaminases									
1 cohort study Sanchez et al. (2018)	No serious limitations	No serious indirectness	Not applicable	Serious limitations[4]	n=18	None	9/18 (50.0%), no statistical analysis	Important	Very low
Number of people with viral reactivation with BK viremia									
1 cohort study Sanchez et al. (2018)	No serious limitations	No serious indirectness	Not applicable	Serious limitations[4]	n=18	None	9/18 (50.0%), no statistical analysis	Important	Very low
Number of people with viral reactivation with BK viruria)									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study type and number of studies	Risk of bias	Indirectness	Inconsistency	Imprecision	Baricitinib	Comparator	Result		
1 cohort study Sanchez et al. (2018)	No serious limitations	No serious indirectness	Not applicable	Serious limitations[4]	n=18	None	15/18 (83.3%), no statistical analysis	Important	Very low
Number of people with blood and lymphatic system disorders									
1 cohort study Sanchez et al. (2018)	No serious limitations	No serious indirectness	Not applicable	Serious limitations[4]	n=18	None	9/18 (50.0%), no statistical analysis	Important	Very low
Number of people with gastro-intestinal disorders									
1 cohort study Sanchez et al. (2018)	No serious limitations	No serious indirectness	Not applicable	Serious limitations[4]	n=18	None	12/18 (66.7%), no statistical analysis	Important	Very low
Number of people with injury, poisoning and procedural complications									
1 cohort study Sanchez et al. (2018)	No serious limitations	No serious indirectness	Not applicable	Serious limitations[4]	n=18	None	12/18 (66.7%), no statistical analysis	Important	Very low
Number of people with metabolism and nutrition disorders									
1 cohort study Sanchez et al. (2018)	No serious limitations	No serious indirectness	Not applicable	Serious limitations[4]	n=18	None	16/18 (88.9%), no statistical analysis	Important	Very low
Number of people with musculoskeletal and connective tissue disorders									
1 cohort study Sanchez et al. (2018)	No serious limitations	No serious indirectness	Not applicable	Serious limitations[4]	n=18	None	13/18 (72.2%), no statistical analysis	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study type and number of studies	Risk of bias	Indirectness	Inconsistency	Imprecision	Baricitinib	Comparator	Result		
Number of people with renal and urinary disorders									
1 cohort study Sanchez et al. (2018)	No serious limitations	No serious indirectness	Not applicable	Serious limitations[4]	n=18	None	10/18 (55.6%), no statistical analysis	Important	Very low
Number of people with respiratory, thoracic and mediastinal disorders									
1 cohort study Sanchez et al. (2018)	No serious limitations	No serious indirectness	Not applicable	Serious limitations[4]	n=18	None	13/18 (72.2%), no statistical analysis	Important	Very low
Number of people with skin and subcutaneous tissue disorders									
1 cohort study Sanchez et al. (2018)	No serious limitations	No serious indirectness	Not applicable	Serious limitations[4]	n=18	None	12/18 (66.7%), no statistical analysis	Important	Very low

Abbreviations: CRP, C-reactive protein; DDS, disease-specific daily symptom; ESR, erythrocyte sedimentation rate; IFN, interferon; ISG, interferon-stimulated genes; MCID, minimal clinically important differences; PedsQL, Pediatric Quality of Life Inventory; RCLASI, Revised Cutaneous Lupus Area and Severity Index; VAS, visual analogue scale

[1] The study is a small uncontrolled observational study and assessment using the Joanna Briggs Institute checklist for case series found many criteria were unknown or unclear

[2] This outcome was illustrated graphically and the numerical data, confidence intervals and p values are not reported. There is no known standard MCID for this outcome measure

[3] Diary score reduction criteria are a mean daily diary score of <0.5 for CANDLE and other interferonopathy, or <1 for SAVI

[4] No p values or confidence intervals were reported. In a small study, confidence intervals are generally wide and the result imprecise. There is no known standard MCID for this the outcome measure

[5] No confidence intervals were reported. In a small study, confidence intervals are generally wide and the result imprecise. There is no known standard MCID for this outcome measure

Glossary

Azotemia	An abnormally high level of nitrogen waste products in the blood
BK viremia and viruria	BK is a type of virus, also called also called polyomavirus. Viremia means the virus is in the blood and viruria means it is in the urine
Interferon	A type of protein produced by cells as part of the body's inflammatory and immune response to infections
Interferonopathy	A type of autoinflammatory disorder associated with interferon, in which the immune system behaves abnormally causing inflammation and other symptoms
Janus kinase	Enzymes involved in the immune pathway
Liver transaminases	Enyzmes in the liver, which can indicate liver damage if levels are raised
Monogenic	Involving or controlled by a single gene

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