Scottish Paediatric & Adolescent Rheumatology Network

SPARN guideline for the use of Janus kinase inhibitors (JAKi): Tofacitinib, Baricitinib, Ruxolinitib

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NOTE

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined based on all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

Contents

Guideline Document Control

Process	Done	N/A	Date	Initials
Literature search and review of available evidence	Y	□		
Review national and international guidance - EMC: tofacitinib - EMC: baricitinib	Y	□		
Review previous guidelines/ask other centres if appropriate - GOSH Baricitinib guideline	Y	□		
Consult key stakeholders: Medical staff Specialist Nurses Physiotherapists Pharmacy Patients and Families Other	 Y Y □ Y □ □	 □ □ Y □ □ □		
Collate information and produce draft guideline	Y	□		
Ensure guideline contains review date (max 3 years hence)	Y	□		
Submit to SPARN steering group for review (see Appendix 1)	Y	□	24/05/2024	MD
Decision made by SPARN steering group	Y	□	07/06/2024	MD
Guideline re-drafted and submitted to SPARN steering group	□	Y		
Final guideline accepted	Y	□	07/06/2024	MD
Guideline posted on SPARN website & review date noted	Y	□	12/02/2025	JN

Guideline Document Control – Appendix 1

Section	Question	Yes	No	N/A	Date	Signature
Scope and Purpose	1) Has the author demonstrated a need for a clinical guideline adequately?	Y	□	□		
	2) Are the overall objectives specifically described?	Y	□	□		
	3) Are the clinical question(s) covered specifically described?	Y	□	□		
	4) Are the patients to whom it is meant to apply specifically described?	Y	□	□		
	5) Does the title accurately reflect the content and scope?	Y	□	□		
Stakeholder Involvement	6) Is there a clearly defined authorship?	Y	□	□		
	7) Did the guideline development group include individuals from all relevant professional groups?	Y	□	□		
	8) Are the target users of the guideline clearly defined?	Y	□	□		
Costs	9) Have the potential cost implications of applying the recommendations been considered?	□	□	□		
Clarity and Presentation	10) Are the recommendations specific and unambiguous?	Y	□	□		
	11) Are the key recommendations easily identifiable?	Y	□	□		
Review	12) Does the guideline contain a review date?	□	□	□		

1. Background

Janus kinase (JAK) inhibitors are orally administered small molecule inhibitors of the Janus Kinase receptor family. The JAKs are involved in signal transducers and activators of transcription (STAT) phosphorylation and activation and affect intra-cellular signalling pathways[1]. There is increasing evidence for their therapeutic benefit in monogenic autoinflammatory disorders of the interferon signalling pathway, with overexpression of type 1 interferons; 'type 1 interferonopathies'.

Their benefit has also been shown in several clinical trials in rheumatoid arthritis and psoriatic arthritis, and is approved for use for these conditions in adults[2–5].

The first clinical trial of tofacitinib, using a withdrawal methodology, in polyarticular JIA has been published, showing efficacy of tofacitinib over placebo[6] and a similar trial showing efficacy of baricitinib in JIA[7]. Tofacitinib has been approved for use in JIA by NICE, and the FDA, if anti-TNF is unsuitable or has inadequate disease control[8,9]. Clinical trials are underway investigating their benefit in JIA-associated uveitis[10], and case reports reporting benefit of JAK inhibitors in systemic JIA (SJIA) and JIA-associated uveitis[11–13]. There is interest in their therapeutic potential in juvenile dermatomyositis (JDM)[14–16], systemic lupus erythematosus and systemic sclerosis[17,18] and clinical trials are awaited.

2. Scope

This guideline aims to provide guidance on the use of JAK inhibitors for rheumatological conditions for use within the SPARN network.

3. Indications for use of JAK inhibitors within the SPARN network

All indications should be assessed on a case-by-case basis.

3.1 Tofacitinib

- JIA
  - Tofacitinib is the preferred JAK inhibitor of choice in patients with JIA
  - It is licenced and approved for polyarticular JIA or psoriatic JIA in patients who have inadequate response to anti-TNF or in whom anti-TNF is intolerable
  - Tofacitinib can be prescribed as monotherapy or alongside methotrexate
- JDM
  - Tofacitinib can be considered in refractory JDM(19); however whilst the BAR-JDM trial is open, we suggest aligning practice BAR-JDM trial and using baricitinib, with the dosing regime as per the BAR-JDM trial.

3.2 Baricitinib

- Type 1 interferonopathies (including Aicardi-Goutières syndrome)
  - Baricitinib is commissioned for use in interferonopathies in NHS England[20].
- JDM
  - Baricitinib can be considered in refractory JDM. Whilst the BAR-JDM trial is open, we suggest aligning practice for JDM patients with the trial and using baricitinib first line with the dosing schedule used in the BAR-JDM trial.
- JIA
  - There is some clinical trial evidence for the use of baricitinib in JIA; however our usual practice would be to use tofacitinib first line for these patients.

3.3 Ruxolitinib

- For GVHD (managed alongside the Bone Marrow Transplant/Immunology/Haematology teams and is out with the scope of this guideline).
- Type 1 interferonopathies: case reports have described efficacy with treatment with ruxolitinib. This is not our first-line JAK inhibitor for this indication. Ruxolitinib can be used for Graft versus host disease in paediatric patients. This is out with the scope of this guideline and we would recommend MDT discussion on a case by case basis with Bone Marrow Transplant/Immunology/Haematology teams.

4. Mechanism of action

Tofacitinib, a first-generation JAKi, is a competitive inhibitor of JAK 1 and JAK 3, with a smaller effect on JAK 2. Metabolism is predominantly hepatic, via the cytochrome P450 system. The half-life is around 3 hours.

Baricitinib, another first-generation JAKi, is a JAK 1 and JAK 2 inhibitor. It is primarily renally excreted. The half-life is around 12 hours[21].

Ruxolitinib is a JAK 1 and JAK 2 inhibitor. It inhibits intracellular signalling of multiple proinflammatory cytokines, including IL-6, IL-12, IL-23 and IFNγ [22]. The half-life is around 3 hours.

TOFACITINIB

5. Tofacitinib

5.1 Contraindications

- Hypersensitivity to a component
- Active tuberculosis, or serious infection
- Severe hepatic impairment
- Pregnancy and lactation
- Should not be started if patient on combination contraceptive pill due to potential thrombotic risk
- Treatment should not be initiated in patients with:
  - Hb ≤ 10.0g/dL **or**
  - absolute neutrophil count ≤ 1.2 x109/L **or**
  - absolute lymphocyte count ≤ 0.75 $x10^9$/L[23]

5.2 Screening prior to starting tofacitinib [23,24]

a. Infection & Vaccines

- Patients should be screened for tuberculosis before starting; JAK inhibitors should not be started in patients with active TB. In patients with untreated latent TB, anti-TB treatment should be considered prior to starting a JAK inhibitor.
- Review vaccination history and consider VZV vaccination prior to initiation of JAK inhibitor if not previously had VZV infection/IgG not detected and consider MMR vaccination if not had previously
- Document previous HSV infection

b. Renal & Liver function

- In patients with severe hepatic or renal impairment: specialist MDT discussion should weight up risks and benefits of initiating a JAK inhibitor
- Tofacitinib should be avoided in patients with severe hepatic impairment
- A reduced dose should be used in severe renal impairment; tofacitinib has been used in some adult patients on dialysis with a reduced dose given following dialysis [23].

TOFACITINIB cont.

5.3 Dosing

Tofacitinib has been approved by NICE for the management of polyarticular and psoriatic JIA for children 2 years and above in whom an anti-tumour necrosis factor (anti-TNF) biologic is not suitable or does not lead to adequate disease control, as monotherapy or along with methotrexate [9].

Tofacitinib is included in the BNFc, for children 2-17 with weight ≥ 10kg [25].

Weight	Dose
10 - <20kg	3.2mg twice daily (3.2ml of 1mg/ml oral solution twice daily)
20 - <40kg	4mg twice daily (4mls of 1mg/ml oral solution twice daily)
≥40kg	5mg twice daily

Patients <40kg need to be prescribed tofacitinib oral solution, for patients ≥ 40kg tablets (5mg) can be prescribed.
For children < 10kg, dosing used in Ruperto et al is suggested(6), as below:

Weight	Dose
5 - <7kg	2mg twice daily (2ml of 1mg/ml oral solution twice daily)
7 - <10kg	2.5mg (2.5ml of 1mg/ml oral solution twice daily) twice daily

5.4 Monitoring & recommendations[40]

FBC, U&Es, LFTs, lipid profile at 6 weeks, at 12 weeks, and if normal, then 3 monthly bloods, along with CRP & ESR.

Blood count		Recommendation
Absolute lymphocyte count ($x10^9$/L)	≥ 0.75 $x10^9$/L	Continue same dose
	≥ 0.5 $x10^9$/L - ≤ 0.75 $x10^9$/L	If persistent reduce or interrupt dosing
	≤ 0.5 $x10^9$/L	If persistent a week later discontinue treatment
Absolute neutrophil count ($x10^9$/L)	≥ 1.0 $x10^9$/L	Continue same dose
	≥ 0.5 $x10^9$/L - ≤ 1.0 $x10^9$/L	If persistent reduce or interrupt dosing
	≤ 0.5 $x10^9$/L	If persistent a week later discontinue treatment
Haemoglobin (g/dL)	≥ 9.0g/dL or ≤ 2g/dL decrease	Continue same dose
	≤ 9.0g/dL or ≥ 2g/dL decrease	Interrupt dosing until values normalised

Skin: the long-term risk of skin cancer in patients treated with JAK inhibitors is currently unclear, although there may be a small increased risk. We recommend safe sun behaviour; with sun protection and avoidance of sunbathing and seeking advice for a new or changing area on the skin.

BARICITINIB

6. Baricitinib

6.1 Contraindications

- Hypersensitivity to a component
- Active tuberculosis, or serious infection
- Severe hepatic impairment
- Pregnancy and lactation
- Should not be started if patient on combination contraceptive pill due to potential thrombotic risk
- EMC: Baricitinib is not recommended in adult patients with creatinine clearance <30ml/min
- Treatment should not be initiated inpatients with Hb ≤ 8.0g/dL, absolute neutrophil count ≤ 1.0 x109/L or absolute lymphocyte count ≤ 0.5 x109/L

6.2 Screening prior to starting baricitinib [20,21,24]

a. Infection & Vaccines

- Patients should be screened for tuberculosis before starting; JAK inhibitors should not be started in patients with active TB. In patients with untreated latent TB, anti-TB treatment should be considered prior to starting a JAK inhibitor.
- Review vaccination history and consider VZV vaccination prior to initiation of JAK inhibitor if not previously had VZV infection/IgG not detected and consider MMR vaccination if not had previously
- Document previous HSV infection

b. Renal & Liver function

i. In patients with severe hepatic or renal impairment: specialist MDT discussion should weight up risks and benefits of initiating a JAK inhibitor

ii. Baricitinib is not recommended in severe renal failure (adult guidance suggests creatinine clearance <10ml/min) (EMC)

iii. Check renal function and calculate eGFR before starting baricitinib as per the calculation below. If eGFR ≦120ml/min/1.73m2 please use dosing schedule as in Appendix 2.

Haycock Schwartz formula

$$eGFR = \frac{36 \times Height(cm)}{Creatinine\ (\mu mol/L)}$$

BARICITINIB cont.

6.3 Dosing: monogenic interferonopathies - eGFR >120mL/min/1.73m^2 [20]

Baricitinib is commissioned for use in interferonopathies in NHS England [20].

Initial dosing: eGFR >120mL/min/1.73m^2				
Weight	**Morning**	**Afternoon**	**Evening**	**Total daily dose**
<20kg	2mg	2mg	2mg	6mg in 3 divided doses
20-40kg	4mg	-	2mg	6mg in 2 divided doses
>40kg	4mg	-	4mg	8mg in 2 divided doses

Dose escalation if baseline bloods are normal				
Weight	**Morning**	**Afternoon**	**Evening**	**Total daily dose**
<20kg	2mg	4mg	2mg	8mg in 3 divided doses
20-40kg	4mg	-	4mg	8mg in 2 divided doses
>40kg	6mg	-	4mg	10mg in 2 divided doses (option to maximise evening dose to 6mg if tolerated after discussion with tertiary team to a total daily dose of 12mg)

6.4 Dosing: monogenic interferonopathies - reduced eGFR of ≤120mL/min/1.73m^2

See Appendix 2.

6.5 Dosing: JDM

Baricitinib dosing for JDM is as per the BAR-JDM protocol. Initial dosing is shown in the table below. Dose increases can be considered at 3 or 6 months as per section 6.3 above.

Age	Dosing
<6 years	2mg once a day
≥6 years	4mg once a day

6.6 Dosing: Baricitinib for use in JIA

NOTE: Tofacitinib is first line for this indication.

See Appendix 3.

BARICITINIB cont.

6.7 Monitoring & recommendations based on monitoring bloods

- FBC, U&Es, LFTs (including bilirubin), CRP, ESR fortnightly for the first month, then monthly for 2 months. If normal can do bloods 12 weekly (as per table below). With dose escalation for more frequent blood monitoring
- Check lipid parameters (triglycerides and cholesterol levels) at 6-12 weeks
- If patient is on high dose baricitinib as per section 5.3 on page 7: BK and JC virus quantitative PCR in plasma and BK and JC virus quantitative PCR in urine every 3 months

Table of monitoring requirements:

Time point (weeks)	Investigations
Week 2	FBC, U&Es, LFTs (incl bilirubin), CRP, ESR
Week 4	FBC, U&Es, LFTs (incl bilirubin), CRP, ESR
Week 8	FBC, U&Es, LFTs (incl bilirubin), CRP, ESR, lipid profile
Week 12	FBC, U&Es, LFTs (incl bilirubin), CRP, ESR
3 monthly	FBC, U&Es, LFTs (incl bilirubin), CRP, ESR, BK & JC virus in serum & urine

Consider temporarily stopping or adjusting baricitinib if any of the following:

- Hb <8g/dl
- WCC <2.0x109/L or neutrophils < 1.0 x109/L
- Lymphocytes <0.5 x109/L
- Platelets <75 x109/L
- eGFR <40 mL/min/1.73m2
- ALT or AST >5 x upper limit of normal or ALT or AST >3 x upper limit of normal and total bilirubin >2 x upper limit of normal

SKIN: the long-term risk of skin cancer in patients treated with JAK inhibitors is currently unclear, although there may be a small increased risk. We recommend safe sun behaviour; with sun protection and avoidance of sunbathing and seeking advice for a new or changing area on the skin.

BARICITINIB cont.

6.8 BK virus screening & management

Infectious complications of baricitinib in monogenic interferonopathies includes BK viraemia leading to acute renal injury. This is thought to be unique to patients with type 1 interferonopathies treated with baricitinib compared to those with arthritis. It may however not be solely caused by baricitinib, with the underlying disease or concomitant medications possibly contributing [20].

If patients are on high dose baricitinib (as per the dose escalation section 5.3; they should have BK virus screening in urine and plasma 3 monthly along with their monitoring bloods.

- If the serum logviral load is <3 this should be noted but no further action is required
- If the serum logviral load ≥3 the blood viral load and urinalysis should be monitored 4 weekly. Renal function should also be monitored. A baseline renal ultrasound should be carried out to identify if there is any hydronephrosis, as BK virus can be associated with obstructive nephropathy or nephritis. If there is concern regarding hydronephrosis, deteriorating renal function or evidence of nephritis, consider reducing or stopping treatment.

Management of BK viraemia:

Serum Logviral load	Recommendation
Logviral load ≥3	Consider dose reduction
Logviral load >3 plus signs or symptoms	Reduce dose or stop
Logviral load >4	Reduce dose or stop

7. Generic information re. JAK inhibitors

7.1 Administration

- Taken orally with or without food
- Baricitinib tablets are not licenced to be chewed but can be if necessary. They can be dispersed in 10mL of water for administration and taken immediately. They can also be dispersed in milk or tea.

7.2 Adverse effects

System Organ Class	Very common	Common	Uncommon	Unknown
Infection	Upper respiratory tract infections	Herpes zoster Herpes simplex Gastroenteritis Urinary tract infections Pneumonia Folliculitis Gastroenteritis	Risk of TB and pneumocystis jiroveci similar to other biologics as shown in adult data; patients with latent TB should be treated with anti-TB treatment prior to initiation of JAK inhibition	BK viraemia & BK virus nephropathy: thought to be unique to baricitinib in interferonopathies; possibly monogenic interferonopathies (please see section 6.8).
Blood & lymphatic system disorders		Thrombocytosis > 600 x 10^9 cells/L	Neutropenia < 1 x 10^9 cells/L	Anaemia
Immune system disorders			Swelling of the face, Urticaria	
Metabolism & nutrition disorders	Hypercholesterolaemia Similar effect on lipid profile to tocilizumab (may be secondary to blocking IL-6)[22]		Hypertriglyceridaemia Weight gain	
Nervous system disorders		Headache		
Vascular disorders			Deep Vein Thrombosis	

System Organ Class	Very common	Common	Uncommon	Unknown
Respiratory, thoracic, mediastinal disorders			Pulmonary embolism	
Gastrointestinal disorders		Nausea Abdominal pain (increased combination JAK inhibitor plus methotrexate)(21)	Diverticulitis	
Hepatobiliary disorders		ALT increased ≥ 3 x ULN (especially if on concomitant hepatotoxic medications)	AST increased ≥ 3 x ULN (especially if on concomitant hepatotoxic medications)	
Renal				Impaired renal function
Skin and subcutaneous tissue disorders		Rash Acne		
Investigations		Creatine phosphokinase increased > 5 x ULN (CK rise to >5 ULN were transient and medication continued); no reports of rhabdomyolysis(21)	Weight increased	

7.3 Additional considerations

- BK & JC viruses: amongst rheumatological indications for JAK inhibitors, BK viraemia and nephropathy is thought to be unique to baricitinib in interferonopathies; possibly monogenic interferonopathies. There is no proven treatment for BK nephropathy; management involves early detection and managing viral load by reducing dose of immunosuppressive medication, as per section 5.6[26]. Additional information re BK viraemia in this cohort of patients is found in Appendix 4.

- Intercurrent infection: JAK inhibition should be interrupted if a patient develops a serious infection whilst febrile or on antibiotics
- Herpes zoster: interrupt JAK inhibition if patient develops herpes zoster infection and follow the SPARN VZV guideline
- Growth: the long-term impact of JAK inhibitors on growth in childhood is unknown[27]
- Venous thrombo-embolism (VTE): in adults, there has been concern about increased risk of venous thromboembolism and interference of lipid metabolism, increasing cholesterol levels and increased cardiovascular events. A dose dependent increased risk in VTE was identified in patients >50 years of age with at least 1 additional cardiovascular risk factor. Retinal venous thrombosis has also been reported. 1 patient treated with baricitinib developed a pulmonary embolism in the JUVE-BASIS trial, however the patient had also had additional risk factors, including thrombocytosis, being overweight, recent immobilisation, high disease activity, pneumonia)[7]. There is no evidence to suggest this risk is applicable to paediatric patients or adult patients without co-morbidities[27]
- GI perforation: Adult studies have shown potential increased gastrointestinal perforation.
- Malignancy: adult studies have also shown a higher incidence of malignancy. In adult practice those with a background of malignancy, smokers or > 65 year old, JAK inhibitors should only be used if no alternatives[23].

8. Concomitant disease modifying or biologic medications

- Tofacitinib can be given as monotherapy or along with methotrexate
- In most cases avoid combination with other biologics due to risk of increased immunosuppression and increased infection risk
- Caution with leflunomide and JAK inhibitors as this may lead to increased baricitinib exposure[21]
- Some adult RA studies showed increased infections in tofacitinib in combination with methotrexate group over tofacitinib monotherapy[23], although not consistently in all studies[3]

9. Peri-operative management

- There is no clear guidance for peri-operative use of JAK inhibitors currently
- Consideration re balance risk of infection and disease flare

- JAK inhibitors have a short half-life
- Generally we would recommend continuing JAK inhibition throughout the operative period and recovery, interrupting if develops a significant post-operative infection
- Consider stopping if operation itself carries a high risk of infection
- If stopping, the German Society of Rheumatology suggest stopping 3-4 days prior to surgery and re-starting 3-5 days following surgery[28]; the adult QUEH guidelines suggest stopping JAK inhibitor (tofacitinib or baricitinib) 3 days prior to surgery for a low risk procedure and 2 weeks prior to surgery for a moderate or high risk procedure[29]
- One retrospective orthopaedic RA adult study has suggested JAKi are safe in the peri-operative period and not associated with increased infection risk[30]

10. Pregnancy & contraception

- JAK inhibitors are contraindicated during pregnancy and women of child-bearing age have to use effective contraception during and for at least 1 week after treatment with baricitinib[21], for tofacitinib this is for at least 4 weeks
- Tofacitinib does not affect the efficacy of oral contraceptives, however due to increased thrombotic risk, we suggest the oral contraceptive pill should not be prescribed alongside JAK inhibitors.

11. Vaccinations

- Avoid live vaccinations whilst on JAK inhibitors

12. JAK inhibition withdrawal syndrome

- In some patients with monogenic interferonopathies, JAK inhibition withdrawal syndrome has been reported which describes a severe relapse of disease symptoms. It may depend on the underlying condition, but when JAK inhibition is interrupted, they may be a need for careful tapering of the drug[24]. This has been more commonly reported in haematology patients with myelofibrosis.

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Appendix 1: Summary of the evidence-base for the use of JAK inhibitors

Janus kinase (JAK) inhibitors are orally administered small molecule inhibitors of the Janus Kinase receptor family. The JAKs are involved in signal transducers and activators of transcription (STAT) phosphorylation and activation and affect intra-cellular signalling pathways[1].

The tyrosine kinase (TYK) family of protein kinases is comprised of the four known JAKs; JAK 1, 2, 3 and TYK2. JAK inhibitors work by competitive inhibition of ATP binding of the JH1 kinase domain. JAK-STAT signalling is involved in several cytokine pathways; cytokines bind to their receptors, which induces JAK activation and, consequently, STAT phosphorylation. Activated STATs form homo or heterodimers, which translocate to the nucleus and regulate gene transcription of target genes. Distinct receptors pair differing JAK subtypes, receptor subunits have variable specificity for specific JAK subtypes[27,31,32].

There is increasing evidence for their therapeutic benefit in monogenic autoinflammatory disorders of the interferon signalling pathway, with overexpression of type 1 interferons; 'type 1 interferonopathies'. These include proteasome-associated inflammatory syndromes (PRAAS), STING-associated vasculopathy of infancy (SAVI) and Aicardi-Goutières syndrome (AGS)[26,33–35], as well as other autoinflammatory diseases, such as A20 haploinsufficiency[36,37].

There is no clinical trial data for the use of JAK inhibitors in monogenic interferonopathies. A series of 18 patients with autoinflammatory conditions, with CANDLE, SAVI and other interferonopathies showed some improvement in the majority of patients; with improved symptoms and reduced corticosteroid use[38]. A further open-label study treated 35 patients with Aicardi-Goutières syndrome with baricitinib, reporting improvement in symptoms, including skin involvement, and neurological development. 2 patients died during the study; including 1 from an opportunistic infection (they had also been on long term corticosteroids) and another with AGS-related pulmonary hypertension with thrombotic microangiopathy[35]. The dosing schedule below is based on pharmacokinetic and pharmacodynamic data studied on patients treated with baricitinib with monogenic interferonopathies[39].

Their benefit has also been shown in several clinical trials in rheumatoid arthritis and psoriatic arthritis, and is approved for use for these conditions in adults[2–5]. A randomised control trial in adult RA showed non-inferiority of tofacitinib plus methotrexate compared with methotrexate plus adalimumab. Tofacitinib monotherapy was not non-inferior to either combination. There were no unexpected safety signals[3].

The first clinical trial of tofacitinib, using a withdrawal methodology, in polyarticular JIA has been published, showing efficacy of tofacitinib over placebo. The first clinical trial of JAKi in JIA compared tofacitinib to placebo in a withdrawal design and showed reduced flare rate in the tofacitinib group compared to the placebo group[6]. 65% of patients were on concomitant methotrexate in this study.
(6) and a similar trial showing efficacy of baricitinib in JIA[7]. Tofacitinib has been approved for use in JIA by NICE, and the FDA, if anti-TNF is unsuitable or has

inadequate disease control[8,9]. One double-blinded, placebo-controlled clinical trial (JUVE-BASIS) has shown efficacy of baricitinib in children from 2 up to 18 years with polyarticular JIA, extended oligoarticular JIA, enthesitis-related arthritis or juvenile psoriatic arthritis[7]. Findings showed a 74% JIA-ACR30 response and time to flare was significantly shorter with placebo compared to baricitinib. Of note, 1 patient on baricitinib developed a pulmonary embolism, thought to be related to the study drug. (Note- this patient had additional risk factors including thrombocytosis, being overweight, recent immobilisation, high disease activity, pneumonia)[7]
Clinical trials are underway investigating their benefit in JIA-associated uveitis[10]. Case reports have reported benefit of JAK inhibitors in children with refractory JIA, in some patients with systemic JIA (SJIA) and JIA-associated uveitis[11–13]. There is interest in their therapeutic potential in juvenile dermatomyositis (JDM); retrospective case series have shown benefit of JAK inhibition in rash and muscle strength in JDM patients[14–16], and clinical trials are awaited. There is also interest in their potential in systemic lupus erythematosus and systemic sclerosis[17,18]. There is also increasing evidence for their use in inborn errors of immunodeficiency and immune dysregulation syndromes[40]. Ruxolitinib has been used in graft-versus-host-disease (GVHD) in paediatrics and for sclerodermatous GVHD[31,41].

Appendix 2: Baricitinib: Dosing: monogenic interferonopathies with eGFR ≤120mL/min/1.73m^2

Initial dosing: eGFR ≤120mL/min/1.73m^2				
Weight	**Morning**	**Afternoon**	**Evening**	**Total daily dose**
<20kg	2mg		2mg	4mg in 2 divided doses
20-40kg	2mg	-	2mg	4mg in 2 divided doses
>40kg	2mg	-	2mg	4mg in 2 divided doses
Dose escalation				
Weight	**Morning**	**Afternoon**	**Evening**	**Total daily dose**
<20kg	2mg	2mg	2mg	6mg in 3 divided doses
20-40kg	4mg	-	2mg	6mg in 2 divided doses
>40kg	4mg	-	2mg	6mg in 2 divided doses

Appendix 3: Baricitinib dosing for use in JIA

If Baricitinib is used in the management of JIA, a lower dose is recommended as per the table below, which is the dosing used from the JUVE-BASIS, in children from 2 up to 18 years with polyarticular JIA, extended oligoarticular JIA, enthesitis-related arthritis or juvenile psoriatic arthritis[7].

Age	Dosing
2-8 years	2mg once a day
9-17 years	4mg once a day

Appendix 4: BK viraemia in patients with monogenic interfernopathies on baricitinib

BK viraemia, azotemia and acute kidney injury was reported in 1 patient, who was also on corticosteroids, with CANDLE in study of 18 patients treated with baricitinib. It resulted in cessation of baricitinib, after just over 2 years of treatment. They sadly died 4 months after from complications of their disease. 8 additional patients developed intermittent BK viraemia during baricitinib treatment, with stable low copy number and stable renal function[38]. This has been reported in renal transplant patients treated with high dose tofacitinib and mycophenolate mofetil[42]. The 2021 EULAR/ACR guidance for management of autoinflammatory type 1 interferonopathies recommends monitoring for BK viral loads in blood and urine with patients with PRAAS, SAVI and AGS who are on JAK inhibitors[26].