RMD Open
Rheumatic & Musculoskeletal Diseases

CLINICAL CASE

Mixed results with baricitinib in biological-resistant adult-onset Still's disease and undifferentiated systemic autoinflammatory disease

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To cite: Kacar M, Fitton J, Gough AK, *et al*. Mixed results with baricitinib in biological-resistant adult-onset Still's disease and undifferentiated systemic autoinflammatory disease. *RMD Open* 2020;**6**: e001246. doi:10.1136/rmdopen-2020-001246

Received 2 April 2020
Revised 14 May 2020
Accepted 1 June 2020

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ABSTRACT

This clinical case series describes our experience with the use of Janus kinase 1/2 inhibitor baricitinib in two patients suffering from refractory adult-onset Still's disease (AOSD) as well as in one case suffering from AOSD-like autoinflammatory disease in the context of myelodysplastic syndrome. All patients suffered from disease non-responsive to conventional Disease-modifying antirheumatic drugs (DMARDs) as well as biological therapies including interleukin (IL)-1 and IL-6 blockade, relying instead on high daily doses of prednisolone. We also report the first case of *Pneumocystis jirovecii* infection following baricitinib use.

Key messages

What is already known about this subject?
- Cytokine inhibition (IL-1 and IL-6) using bilogicals is now established treatment approach in AOSD.

What does this study add?
- JAKi should be tried in patients who fail bilologics 3.

How might this impact on clinical practice?
- Additional studies are needed to determine optimal place for use of JAKi in treatment AOSD.

INTRODUCTION

Adult-onset Still's disease (AOSD) is a rare systemic autoinflammatory disorder characterised by a combination of fever, generalised evanescent salmon-pink rash, pharyngodynia, arthritis/synovitis, lymphadenopathy, serositis and splenomegaly. None of these clinical features are disease-specific, and a wide spectrum of conditions including autoimmune, infectious and malignant diseases need to be considered as part of differential diagnosis. Several classification criteria have been developed for research purposes that can aid the diagnosis of AOSD. The most commonly used are Yamaguchi's[1] and Fautrel's[2] criteria with the latter one not requiring exclusion of other conditions for diagnosis of AOSD to be made. The diagnosis can be particularly difficult in patients with pre-existing conditions such as myelodysplastic syndrome (MDS) or in patients who do not fulfil all classification criteria, but have a condition closely resembling AOSD and who are ultimately treated and respond to therapies used for AOSD. A frequently used diagnostic label in such cases is that of undifferentiated systemic autoinflammatory syndrome (uSAID).[3]

Treatment of AOSD has been revolutionised by the introduction of biologicals DMARD particulary those targeting interleukin (IL)-1 and IL-6.[4–7] The Janus kinase (JAK) inhibitors—tofacitinib, baricitinib and others—are highly effective in refractory inflammatory arthritis, including patients who have failed biological therapy.[8 9] Here, we describe our experience using the JAK-1/JAK-2 inhibitor baricitinib in two patients with biological-resistant AOSD meeting Yamaguchi's diagnostic criteria, as well as in one patient suffering from an AOSD-like disorder in the context of low-grade MDS. Results of relevant investigations are shown in table 1, a summary of medications used (and their doses) are shown in table 2, and clinical characteristics, laboratory results and concomitant medication prebaricitinib and postbaricitinib implementation are shown in table 3.

CASE REPORT

A 43-year-old Sudanese woman (P1) was first treated at in Sudan (at 41 years) for fever and flitting arthralgia. She relapsed in the UK

Table 1 Demographics, clinical characteristics and results

	Patient 1 (P1)	Pateint 2 (P2)	Pateint 3 (P3)
Gender	F	M	F
Age at presentation (years)	41	29	58
Clinical characteristics at presentation			
Fevers >39°Ct*	+	+	+
Joint involvement†	+	+	+
Rash‡	+	+	–
Sore throat	+	–	+
Lymphadenopathy	–	–	–
Splenomegaly	+	–	–
Serositis	+	–	–
Laboratory results			
ANA/RF	–	–	–
WBC >10.000/mL	+	+^	–‘
Elevated LFTs (>1.5X ULN)	+ (ALT, AP, LDH)	+ (ALT)	+ (AP)
Maximum CRP (<10 mg/L)	231mg/L (on 35 mg Pred/day)	94 mg/L (on 40 mg Pred/day)	239 mg/L (on 20 mg Pred/day)
Maximum ESR (1–15 m/hour)	125 mm/hour	16 mm/hour	NA
Maximum ferritin (10–332 ng/mL)	38 940 ng/mL	679 ng/mL	2695 ng/mL’’
Other investigations	PET CT—borderline splenomegaly, traces of pericardial effusion, reactive mediastinal lymphadenopathy	PET CT—no inflammatory arthritis, vasculitis, infection or malignancy	PET CT—no infection, malignancy or vasculitis; USS abdomen—no abnormalities detected

*Lasting 1 week or longer.
†Arthritis/synovitis/arthralgia.
‡Evanescent, salmon-pink maculopapular rash.
‘P3 has been pancytopenic since presentation due to underlying myelodysplasia; however, flares were associated with tripling of neutrophil counts. ‘’The elevation of ferritin does not correspond to disease flares but likely reflects increased transfusion dependence. ^WBC over 13.000 but 77% PBMC.
ALT, alanine aminotransferase; ANA, antinuclear antibody assay; AP, alkaline phosphatase; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; F, female; LDH, lactate dehydrogenase; LFT, liver function test; NA, not available; M, male; PET, positron emission tomography; Pred, prednisolone; RF, rheumatoid factor; ULN, upper limit of normal; USS, ultrasound scan; WBC, white blood cell count.

Table 2 Treatments used before baricitinib implementation and their efficacy

	P1		P2		P3	
Prednisolone	PR	30–40 mg OD	PR	40 mg OD	PR	20 mg OD
Methotrexate	NR*	7.5 mg 1 weekly	NR	25 mg 1 weekly	/	/
Ciclosporin	PR	100 mg BD	NR	150 mg BD	/	/
Anakinra	PR	300 mg BD	NR	100 mg BD	NR	100 mg OD
Tocilizumab	NR	8 mg/kg 2 weekly	NR	8 mg/kg 2 weekly	CR—vasculitis	162 mg 2 weekly
Sarilumab	/	/	/	/	CR—vasculitis	150 mg 2 weekly
Other medications	/		Rituximab—NR Infliximab—PR		Rituximab for vasculitis—CR	

*In addition to lack of response, P1 experienced a severe generalised toxic drug eruption with MTX.
CR—complete response defined as resolution of all symptoms/absence of flares with normalisation of laboratory parameters.
PR—partial response defined as >50% reduction in frequency/severity of symptoms.
NR—no response.
OD—one time per day.
BD—two times per day.

despite maintenance therapy with prednisolone and hydroxychloroquine, presenting with fever, arthritis/synovitis and evanescent rash in the context of neutrophilia and elevated inflammatory markers. She remained steroid-dependent (multiple unsuccessful tapers below 15 mg prednisolone daily) despite combination therapy with anakinra and

Table 3 Clinical characteristics, lab results and concomitant medication prebaricitinib and postbaricitinib implementation

	P1	P2	P3
Prebaricitinib[X] clinical characteristics	**Inflammatory erosive polyarthritis**	**Polyarthralgia with synovitis, generalised rash**	**Persistent fever >39°C**
Prebaricitinib[X] results			
CRP (<10 mg/L)	231 mg/L	94 mg/L	48 mg/L
ESR (1–15 m/hour)	125 mm/hour	16 mm/hour	NA
Ferritin (10–332 ng/mL)	38 940 ng/mL	679 ng/mL	1812 ng/mL''
Prebaricitinib[X] therapy			
Prednisolone	10 mg OD	40 mg OD	15 mg OD
Methotrexate	/	25 mg 1 weekly	/
Ciclosporin	100 mg OD	150 mg BD	/
Anakinra	300 mg OD	100 mg BD	/
Tocilizumab	8 mg/kg 2 weekly	8 mg/kg 2 weekly	/
Sarilumab	/	/	/
Baricitinib treatment regimen	4 mg OD	4 mg OD	4 mg OD
Postbaricitinib[Y] clinical characteristics	Asymptomatic	Polyarthralgia with synovitis, generalised rash	Asymptomatic
Postbaricitinib[Y] results			
CRP (<10 mg/L)	<5 mg/L	56 mg/L	2 mg/L
ESR (1–15 m/hour)	17 mm/hour	9 mm/hour	NA
Ferritin (10–332 ng/mL)	18 ng/mL	304 ng/mL	1708 ng/mL''
Postbaricitinib[Y] therapy			
Prednisolone	/	30 mg OD	15 mg OD
Methotrexate	/	20 mg 1 weekly	/
Other DMARD	/	/	/

[X] At time of baricitinib implementation. [Y] At first follow-up (8±2 weeks) after implementation of a stable dose of baricitinib. ''The elevation of ferritin does not correspond to disease flares but likely reflects increased transfusion dependence.
BD, two times per day; CRP, C reactive protein; DMARD, disease modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; NA, not available; OD, one time per day.

ciclosporin or methotrexate. Anakinra was briefly replaced with two-weekly intravenous tocilizumab infusions but was restarted due to primary non-response. The disease evolved into a predominantly oligoarthritic phenotype with significant synovial hypertrophy of both 2nd metacarpophalangeal (MCP) joints, multiple proximal interphalangeal joint (PIP) joints and both knee supra-patellar pouches. In addition, there was evidence of bilateral tibialis posterior and extensor carpi ulnaris tenosynovitis with evidence of multiple early bone erosions on ultrasound. Baricitinib was started at this point and the patient has remained in clinical and biochemical remission while on baricitinib monotherapy over the ensuing 15 months.

A 32-year-old Caucasian male (P2) presented at 29 years with a flitting inflammatory polyarthritis (affecting hands, wrists, elbows, shoulders and knees) associated with a non-pruritic, evanescent rash, fevers, rigours and sweating. The condition was responsive to high-dose prednisolone. A diagnosis of AOSD was made and steroid-sparing immunomodulatory therapy was initiated with ciclosporin, with methotrexate added subsequently. Anakinra was added as prednisolone requirement remained at least 15 mg/day, with marked initial improvement but subsequent relapses despite doubling and then tripling the dose. Two-weekly intravenous tocilizumab was commenced in combination with methotrexate, resulting in complete biochemical and partial clinical response. After 6 months, he developed a persistent urticaria-like rash, which improved only transiently with the anti-IgE therapeutic, omalizumab. The patient developed severe synovitis and baricitinib was added without improvement. After 9 months, both drugs were discontinued. Since then, the patient has received one cycle of rituximab (to no effect) and more recently infliximab with modest improvement in symptoms.

A 63-year-old Caucasian woman (P3) was diagnosed with AOSD-like condition (uSAID) after presenting at 58 years with pharyngitis, fever and arthralgias. The patient had pre-existing myelodysplasia diagnosed 2 years previously. Haematologist input deemed that her symptoms were not due to MDS, which was low grade and according to the MDS International Prognostic Scoring System had low scores and therefore minimal possibility of malignant transformation. Her MDS has remained clinically unchanged to this date. The initial flare was treated with high-dose corticosteroids. DMARDs were omitted due to the patient's MDS. She was established

on two-weekly intravenous tocilizumab monotherapy, successfully resulting in complete symptomatic control for 4 years. Subsequently, the patient developed chilblain vasculitis, deemed to have been caused by IL-6 blockade itself (and replicated after receiving subcutaneous sarilumab). The vasculitis, although seronegative, responded to rituximab, but AOSD symptoms remained problematic. A trial of anakinra failed due to intolerance; therefore, baricitinib was gradually introduced with careful monitoring. The patient has remained in biochemical and clinical remission for 9 months. At 7 months, she developed *Pneumocystis jirovecii* pneumonia, which responded to trimethoprim-sulfamethoxazole and she remains on it prophylactically.

DISCUSSION

AOSD remains a diagnostic and therapeutic challenge due to its myriad clinical manifestations and the confounding effects of comorbidities, partially effective therapies and continually evolving phenotypes. Our experience with baricitinib in biological-resistant AOSD is highly variable, perhaps reflecting the varied clinical presentation of this disease. One patient had pre-existing MDS and subsequently developed a clinical syndrome, which clinically resembled AOSD. Considering that there was significant time interval (2 years) between diagnosis of MDS and eventual emergence of AOSD-like condition, it could be argued that this was simply coincidence, particularly since it is often considered that AOSD tends to precede an eventual diagnosis of malignancy.[10] However, a number of studies have already reported that autoimmune/autoinflammatory conditions are more common in MDS than in the general population, although with no clear classification of these inflammatory disorders. The range of autoimmune/autoinflammatory disorders in patients with MDS is highly variable with a prevalence rate ranging from 7% to 30% according to the different studies.[11 12] Therefore, it is also reasonable to assume that AOSD-like condition in P3 is possibly a complication of underlying MDS. Considering that a JAK1/2 inhibitor (ruxolitinib) is already used in haematology to treat myelofibrosis, P3 response to baricitinib might not be surprising. However, ruxolitinib is typically approved for the treatment of intermediate-risk and high-risk myelofibrosis and associated symptoms.[13] Interestingly, P3 also developed an opportunistic infection with pneumocystis while on baricitinib, a complication previously described only once in the context of myelofibrosis therapy with ruxolitinib.

The response to baricitinib in two other patients with AOSD was mixed. Nonetheless, JAKi remains a promising therapeutic option for patients otherwise dependent on high-dose corticosteroids. A recent report from China describes the successful use of tofacitinib in 14 patients with AOSD; however, not all patients had a complete response and some were still needing to take steroids on a long-term basis.[14] The success of JAKi in patients who have failed IL-1-directed and IL-6-directed therapies might be explained by the ability of these medications to block other likely relevant cytokines such as IL-12/IL-23 and interferon-γ. However, the optimal therapeutic dose of JAKi used for AOSD might be different from what is used for licenced indication. This point was illustrated by a recent report of baricitinb use in the treatment of interferonopathies by Sanchez *et al* where larger, treat-to-effect, dosages were used, raising the possibility of underdosing in our cases.[15]

Contributors Data collection—MK, JF. Preparing the manuscript—MK, SS. Contribution of clinical cases—MHB, AKG, DGM and SS. Manuscript editing and final approval—MK, JF, AKG MHB, DGM.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests Yes, there are competing interests for one or more authors and I have provided a Competing Interests statement in my manuscript.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement For further queries related to the cases presented here please contact the corresponding author.

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