JAK Inhibitors in Difficult-to-Treat Adult-Onset Still's Disease and Systemic-Onset Juvenile Idiopathic Arthritis

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Short title: JAK inhibitors in difficult-to-treat Still's disease

Word count: 3343 words

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Competing interest:
L.Gillard, J. Pouchot, F.Cohen-Aubart, I. Koné-Paut, G. Mouterde, M. Michaud, H. Reumaux, L. Savey, A. Belot, B. Fautrel, S. Mitrovic: None relevant to this study

Key Words: Adult-onset Still's disease, systemic juvenile idiopathic arthritis, Janus Kinase inhibitors, targeted synthetic disease-modifying anti-rheumatic drug, corticosteroid-sparing agents, interferon

Contributors: Development of the work–LG, JP, AB, BF, SM. Data collection and descriptive statistics— LG and SM. Preparing the manuscript–LG, BF and SM. Contribution of clinical cases–JP, FCA, IKP, GM, MM, HR, LS, SGL, BF. Manuscript editing and final approval–all authors.

Key messages:
- The therapeutic strategy after inadequate response to IL-1 and/or IL-6 inhibitors is not defined.

- A JAK inhibitor (JAKi) may be a therapeutic option for some patients with difficult-to-treat SJIA/AOSD.

- JAKi agents had a significant corticosteroid-sparing effect in patients who depended on high-dose corticosteroids.

ABSTRACT

Objectives: Excessive and inappropriate production of pro-inflammatory cytokines plays a key role in Still's disease. JAK inhibitor (JAKi) agents mainly block pro-inflammatory cytokine pathways, notably IL-6 and IFN. The objective was to assess the efficacy and safety of JAKi agents in difficult-to-treat systemic juvenile idiopathic arthritis (SJIA) or adult-onset Still's disease (AOSD).

Methods: This retrospective study was based on a national survey conducted in the departments of rheumatology, paediatric rheumatology and internal medicine of French hospitals regarding SJIA and AOSD patients who received JAKi agents. The data were collected with a standardised questionnaire and analysed at different times (treatment initiation, months 1, 3, and 6 and the end of follow-up).

Results: Nine patients (7 adults) were included. All patients showed inadequate response to corticosteroids or conventional synthetic or biologic disease-modifying anti-rheumatic drugs. Baricitinib was used in 5 patients, ruxolitinib in 2, tofacitinib in 2, and upadacitinib in 1. A JAKi was used combined with corticosteroids in all but 2 patients. A JAKi was associated with anakinra and corticosteroids in one patient, and with methotrexate, anakinra and corticosteroids in another. The median follow-up was 16 [1-33] months. Two cases out 9 showed complete remission, 3/9 partial response and 4/9 treatment failure. At the last visit, corticosteroids could be decreased but not stopped. Tolerance of the JAKi was acceptable (no severe adverse events).

Conclusion: JAKi agents may be a therapeutic option for some patients with difficult-to-treat Still's disease, especially those with partial response to medium- or high-dose corticosteroids or biologics.

Introduction

Systemic-onset juvenile idiopathic arthritis (SJIA), and adult-onset Still's disease (AOSD) correspond to the same rare non-familial (sporadic) systemic auto-inflammatory disorder associated with inappropriate activation of the innate immune system occurring at different ages (i.e., before or after age 16) (1).

High-dose corticosteroids are usually the first-line treatment for SJIA/AOSD (1–4). Furthermore, corticosteroids are responsible for multiple side effects. In this context, several studies reported the efficacy of biological disease-modifying anti-rheumatic drugs (bDMARDs) targeting interleukin 1 (IL-1) (anakinra, canakinumab, rilonacept) or IL-6 (tocilizumab) pathways in SJIA/AOSD (1,2,5–12), with striking improvement in prognosis. Despite this success, 20% to 40% of patients show failure to respond to anti-cytokine biologics or experience adverse events during treatment (13,14). Some treatments can also lose efficacy over time. By analogy with other more common rheumatic diseases such as rheumatoid arthritis (RA), difficult-to-treat Still's disease is a heterogenous condition in which, for each patient, different factors may be key to the persistence of signs and symptoms, which is highlighted by the individual drug resistance (15). Therefore, the therapeutic strategy for difficult-to-treat Still's disease is poorly codified, and there is a crucial need for novel therapeutic approaches (1). Although a recombinant human IL-18 binding protein, tadekinig α, has shown promising results in a phase II trial (in patients who had an active disease but with a more rheumatic (arthralgia/arthritis presentation) (16), this drug is not currently available in routine clinical practice. TNF inhibitors can sometimes be prescribed as third-line drugs, preferentially for patients with chronic arthritis, because their efficacy for systemic symptoms is inconsistent (1). Ciclosporin may be indicated for life-threatening complications but is usually not used in non-complicated SJIA/AOSD (1,17).

Janus kinase inhibitor (JAKi) agents are small molecules blocking the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway that have been found efficacious in several inflammatory diseases such as RA, systemic lupus erythematosus, spondyloarthritis and psoriatic arthritis, including in patients with failure of biological therapy (18–22). Moreover, recent studies demonstrated that ruxolitinib or baricitinib improved clinical manifestations and inflammatory biological parameters in patients with interferonopathies, diseases largely involving innate immunity (23,24).

Overall, more than 50 cytokines signal via the JAK-STAT pathway, including IL-6 and interferon (IFN) (but not tumour necrosis factor (TNF) and IL-1), to regulate cell homeostasis, proliferation and differentiation as well as control the immune system and inflammatory response (25). The JAK-STAT pathway also plays a central role in mediating the cellular response to the IFN family of cytokines. The type II interferon, IFN-γ, signalling via the JAK-STAT pathway, plays a major role in SJIA/AOSD complications, especially macrophage activation syndrome and lung disease complications (26). Hence, the broad range of activity of JAKi agents, which block the pro-inflammatory effect of a wide range of cytokines and interferons, may be beneficial in Still's disease because excessive and inappropriate production of cytokines is a cornerstone of its pathogenesis (1,27,28). Several recent case reports or small series have suggested that JAKi agents may be effective for some SJIA or AOSD patients who are refractory to or intolerant of treatment with biologics (29–31). However, the data are contradictory because other reports do not show clear evidence of the effectiveness of JAKi treatment in this disease (32,33).

In our study, we aimed to describe the efficacy and safety of different JAKi agents in a series of 9 patients with difficult-to-treat SJIA or AOSD.

Methods

Patient selection

This retrospective study was based on a national survey of the departments of paediatric or adult rheumatology and internal medicine of French hospitals belonging to a clinical research network, the *Club Rhumatismes et Inflammation* (http://www.cri-net.com). To be recruited, SJIA patients had to fulfil the International League Against Rheumatism criteria for SJIA (34), and AOSD patients had to fulfil the Yamaguchi and/or Fautrel criteria for AOSD (35,36). Patients with SJIA or AOSD who received a JAKi in France and had at least one assessment of treatment efficacy and safety after treatment onset were eligible for this study. Concomitant treatment with corticosteroids and/or conventional synthetic or biological DMARDs (cs- or bDMARDs) was allowed.

Data collection

Data were collected retrospectively by using a standardised questionnaire pre-established by 3 authors (LG, SM and BF) and included sex, date of birth, disease duration and age at diagnosis, age at treatment onset, systemic symptoms (fever [defined as body temperature ≥ 39°C for at least 1 week], weight and weight loss, skin rash, myalgia, lymphadenopathy, hepatosplenomegaly, and serositis [i.e., pericarditis and pleuritic]), tender joint count, swollen joint count, and complications (macrophage activation syndrome [MAS], which was confirmed when suspected by the calculation of the HScore, https://saintantoine.aphp.fr/score/ (37), haematological or pulmonary complications, hepatitis). The following laboratory values were collected: haematological profile, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, and serum ferritin level. When available, the percentage of glycosylated ferritin was also recorded. The disease activity was evaluated by the physician global assessment of disease activity and patient assessment of pain for adults and parents' assessment of pain and disease activity for children. The modified Pouchot score was calculated (38). Previous

treatment history (non-steroidal anti-inflammatory drugs, corticosteroids, cs- or bDMARDs) was collected. The analysis timepoint was the time of SJIA or AOSD diagnosis, the time of JAKi initiation, and 3, 6, 9 and 12 months after JAKi initiation or the latest follow-up.

Assessment of JAKi treatment efficacy and tolerability

Response was classified in 4 categories (39): *complete remission*, defined as a complete resolution of all clinical and biological SJIA- or AOSD-related symptoms (i.e., disappearance of fever, arthralgia and arthritis, myalgia, sore throat, skin rash, lymphadenopathy, hepatosplenomegaly, and normalisation of complete blood count, ESR, and CRP and ferritin levels); *partial remission*, defined as some improvement noted by the physician in charge of the patient but with persistence of some systemic, articular or biological manifestations; *primary failure*, defined as absence of clinically relevant improvement within 1 to 3 months after treatment start; and *loss of efficacy*, defined as a deterioration of clinical or biological manifestations within 12 months after initial improvement. We analysed corticosteroids dose reduction. In case of therapy discontinuation, the reason for discontinuation was recorded.

All adverse events (suspected or certain) for each patient were systematically recorded from the onset of JAKi treatment to the last visit.

Ethics

Patients and paediatric patient parents were informed that JAKi treatment was approved in other inflammatory diseases such as RA, systemic lupus erythematosus, and psoriatic arthritis but not Still's disease. Oral informed consent was obtained in all cases before starting treatment and documented in medical charts. According to the rules and regulations of clinical research for descriptive retrospective studies in France, approval of an ethics committee was

not necessary, and consent was indirectly obtained by non-opposition to the use of the data for research purposes from all patients/parents after information was given (40).

Results

Characteristics of SJIA and AOSD patients at disease onset and at JAKi initiation

The survey identified 9 patients (7 adults) from 7 different medical departments (**Table 1, supplementary tables 1 and2**); 6 were female. The median [range] age at diagnosis was 28 [1-50] years (28 [22-50] and 1.5 [1-2] years for AOSD and SJIA patients). The median [range] age at JAKi initiation was 38 [6-59] years (40 [28-59] and 11 [6-16] years for AOSD and SJIA patients) and median disease duration at JAKi onset 5 [1-19] years (4 [1-19] and 10 [5-15] years for AOSD and SJIA patients). The disease was predominantly systemic in 7 patients (mainly fever, arthralgia and rash). Two adults had predominantly chronic articular disease (cases 4 and 9).

All patients had very active disease at disease onset (median [range] modified Pouchot score 6 [3-8], median CRP level 258.5 [56-424] mg/L, median ferritin level 5915 [155-11468] ng/mL). Three patients had specific organ involvement at onset (2 moderate hepatitis and one acute respiratory distress syndrome with pleuritis and pericarditis). All patients had refractory and active disease at the start of JAKi treatment (median modified Pouchot score 3/12 [1-4], median CRP level 47 [2-168] mg/L, median ferritin level 670 [70-9261] ng/mL). Two patients had complications immediately before JAKi initiation (one MAS with hepatitis and one moderate hepatitis) **(supplementary table 2)**. All patients had shown failure of at least one bDMARD (**Tables 1 and 2, supplementary table 1**). Most patients had received a mean of 3 bDMARDs before starting JAKi treatment **(supplementary table 1)**.

At the time of JAKi initiation, 7 patients concomitantly received oral prednisone and 2 cs- or bDMARDs (one received methotrexate, anakinra and colchicine and one anakinra) **(Table 2)**. Five patients received baricitinib (one later switched to upadactinib), 2 ruxolitinib

and 2 tofacitinib **(Table 2)**.

Efficacy of JAKi treatment in SJIA and AOSD

At the last follow-up after JAKi initiation (median 16 [1-33] months), 2/9 patients achieved complete remission with a median follow-up of 22.5 [12-33] months and 3/9 patients partial remission with a median follow-up of 17 [3-27] months; 4/9 patients showed failure and rapidly discontinued JAKi treatment with a median follow-up of 8.5 [1-16] months **(Tables 2 and 3, supplementary tables, Figure 1 et 2)**. The median treatment duration was 3 [1-17] months for baricitinib, 8.5 [1-16] months for tofacitinib, 23 [13-33] months for ruxolitinib and 10 months for upadacitinib (**Table 3)**.

Two patients achieved complete remission (cases 1 and 2). These were paediatric patients (SJIA), and all clinical and biological manifestations were resolved at last follow-up. However, the JAKi dosage needed to be increased to achieve complete remission in these patients: 30 mg/day of ruxolitinib for case 1 and 8 mg/day of baricitinib for case 2. Furthermore, case 1 had almost stopped prednisone at last follow-up (she had been receiving a stable dosage of 1 mg/day for 22 months), whereas case 2 was receiving 7.5 mg/day prednisone at last follow-up (corticosteroids tapering still in progress).

Three patients achieved partial remission. Two showed initial significant clinical and biological improvement during the first 2 months before experiencing a flare/loss of efficacy at the third month (cases 4 and 6, **Figure 2**). Of note, case 6 experienced MAS (haemophagocytosis features on bone marrow aspirate, HScore 233, probability of having MAS 98%) before the JAKi (ruxolitinib) was introduced **(supplementary table 2)**, which was efficacious for this complication: all clinical and biological manifestations disappeared after 2 weeks of treatment. Case 9 also showed partial remission at 3 months after treatment initiation, but the follow-up period was short (last follow-up at 3 months).

Regarding the 4 patients with treatment failure and discontinuation, 3 showed primary failure to JAKi treatment. Patient 3 still presented intense pharyngitis, active polyarthritis and skin eruption, although fever, neutrophil count and CRP level improved 1 month after baricitinib introduction (**Figure 2**). The patient was switched to sarilumab, which led to significant clinical improvement after 4 months. Patient 5 stopped the drug on his own after only 8 days. Patient 8 still presented fever and elevated CRP level and discontinued baricitinib after 1 month; he remained on high-dose corticosteroids alone. Patient 7 presented an initial good response and showed partial remission during the first months of tofacitinib therapy before a flare at month 6 **(Figure 2)**. After this flare, clinical (polyarthralgia and pharyngitis) and biological (leucocytosis, CRP level) manifestations increased despite the addition of adalimumab at month 14, which led to discontinuation of tofacitinib at month 16 **(Table 2, Figure 2)**.

Corticosteroids-sparing effect

All but 2 patients (cases 5 and 9) were on corticosteroids at the time of JAKi initiation **(Table 2)**. JAKi initiation was accompanied by a decrease in daily dose of corticosteroids: the mean decrease was 80% for patients with complete remission between JAKi onset and the end of follow-up, 76% for patients with partial response and 64% for non-responders **(Figure 2)**. However, no patient who was initially on corticosteroids was able to stop this treatment at the last follow-up (mean 16.4 ± 12 months) **(Table 2, Figure 2)**.

Safety of the JAKi

JAKi tolerance was good in all but 2 patients **(Table 3)**. Case 6 experienced histologically proven organized pneumonia under ruxolitinib, which led to temporary

discontinuation (3 months) of treatment. During the off-ruxolitinib period, the patient did not experience disease flare or MAS recurrence. Case 1 experienced mild Varicella-zoster virus infection under ruxolitinib, with rapid resolution under valaciclovir, which enabled drug reintroduction after a few weeks. No severe adverse event, notably no serious infection, was observed during JAKi treatment, even when used with other cs- or bDMARDs.

Discussion

To the best of our knowledge, we report the second largest case series of Still's disease treated with a JAKi. The originality of our work lies our report paediatric and adult patients, as well as different JAKi molecules (baricitinib, ruxolitinib, tofacitinib and upadacitinib). Still's disease remains a therapeutic challenge due to disease heterogeneity, which makes that not all patients respond to the same therapeutic strategy (41). Our experience with JAKi treatment in biological-resistant SJIA/AOSD (i.e., difficult-to-treat disease) is highly variable, perhaps reflecting the varied clinical presentation and course of this disease. Although 5 of the 9 patients showed partial or complete response to JAKi treatment, 4 did not respond (primary failure).

Nonetheless, the key message of our work is that JAKi treatment seems to be helpful for some patients with incomplete remission and who depend on medium- to high-dose corticosteroids. Indeed, although not all patients in our series achieved complete remission, JAKi treatment significantly decreased corticosteroids use, from 64% to 80% depending on the response group considered. This potential corticosteroids-sparing effect has also been reported in other isolated cases or case series (29–31), including a recent report from China of 14 patients receiving tofacitinib (33). This work also found heterogeneity in the response to JAKi treatment. However, partial responders exhibited the corticosteroids-sparing effect. Given the potential iatrogenicity of corticosteroids and although the number of patients in our series is

low and corticosteroids were tapered but not discontinued, this potential corticosteroids-sparing effect seems particularly interesting.

JAKi agents are small-molecule inhibitors that use a novel mechanism of action by affecting the intracellular signalling pathway instead of targeting a specific cytokine or its receptor (26). JAKi agents target both type I (13 subtypes of IFN-α and one IFN-β) and type II (also called IFN-γ) IFN pathways as well as other cytokines, notably IL-6 (42) by interfering with the JAK-STAT pathway (26). JAKi agents provide high biological plausibility as efficacious targets in diseases in which IFNs or other cytokines, or both, are driving the disease. Although data are contradictory, non-complicated SJIA/AOSD is not generally associated with a robust type I or type II IFN signature (26). The starting point of the pro-inflammatory cascade in this subset is related more to an activation of specific inflammasomes, leading to caspase activation and overproduction of active IL-1β, intense innate immune cell activation and overproduction of several pro-inflammatory cytokines including IL-6, IL-8, IL-17, IL-18 and TNF, called the "cytokine storm". In contrast to non-complicated SJIA/AOSD, with SJIA/AOSD complications, especially with MAS or lung disease, substantial evidence supports a key role for type II IFNs (26,43,44). One of our patients (case 6) exhibited MAS immediately before starting ruxolitinib; the JAKi was efficacious for this complication because all clinical and biological manifestations of MAS resolved in less than 2 weeks. This finding is consistent with another report of significant clinical improvement of SJIA-MAS within 3 months of tofacitinib treatment (45). Interestingly, several papers reported the use of JAKi in other causes (mainly genetic) of haemophagocytosic lymphohystiocytosis (MAS not related to SJIA/AOSD) and showed interesting/promising results (46,47).

Apart from this potential effect on MAS, the best patient profile for JAKi remains to be defined. According to the theoretical considerations described above, in particular that JAKi agents block the IL-6 and IFN pathways but not the IL-1 pathway, we can raise the issue of

combining a JAKi with an anti-IL-1 agent. However, in our case series, this combination was somewhat disappointing: the 2 patients who received an anti-IL-1 agent in addition to the JAKi (cases 4 and 6) achieved only partial and not complete remission. The 2 patients who achieved complete remission (cases 1 and 2) received a JAKi without a concomitant bDMARD but rather corticosteroids. They achieved complete remission after having previously shown failure to respond to anakinra, canakinumab or tocilizumab. The success of a JAKi in patients with failure of IL-1– 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 IFN-γ (32). However, the optimal therapeutic dose of JAKi used for SJIA/AOSD might differ from what is used for licenced indications. This point was illustrated by a recent report of baricitinib use for treating interferonopathies with larger treat-to-effect dosages used, which raises the possibility of underdosing in our cases that did not respond (23). Increased doses of the JAKi were required in the 2 patients who did show response. Despite a possible difference in efficacy for SJIA/AOSD between the different JAKi molecules (because the various JAKi agents have different selectivity toward JAK1, JAK2, JAK3 and TYK2) (48), our small number of patients does not allow for drawing conclusions. Similarly, we cannot exclude that children may show a different response to JAKi agents than adults: the 2 fully responding patients were paediatric cases.

Besides the small sample size, our study has several other limitations. First, there is a loss of some clinical and paraclinical information, which is inherent to all retrospective observational studies. Also, our study focused on a particular subtype of patients with difficult-to-treat disease who had shown failure of at least one biological treatment. There is no negative prognostic factor of difficult-to-treat disease clearly established so far. Several polymorphisms in the IL1RN gene that may be at risk of non-response to anakinra have been reported in children (49,50), but not confirmed in adults. We have not performed genetic research in our

patients. We did not measure serum cytokine levels in our patients either, which does not allow for drawing robust conclusions about our hypothesis of an IFN signature and cytokine profile in this particular subset. Additionally, it does not inform the above-raised question of the JAKi dose to administer to Still's patients in whom cytokine levels are often quite high. Whether it would have been useful to have the response data to JAKi in first-line therapy or at least at an earlier stage (because most of our patients showed failure of several [on average 4] cs- or bDMARDs) is debated. Anti-IL1 and anti-IL6 are the established first-line treatments in corticosteroid-refractory AOSD (1). Furthermore, given the current controversy about the safety of JAKi agents, it would not have been reasonable to propose these small molecules as first-line therapy. Indeed, the European Medicines Agency safety committee has started a review of the safety of JAKi agents used to treat several chronic inflammatory disorders, especially regarding the cardiovascular, infectious and cancer risks (48). This risk was most apparent in patients older than the population preferentially affected by SJIA and AOSD. JAKi tolerance was good in our patients: only 2 experienced non-severe infectious complications, with favourable outcome and reintroduction of the drug after resolution.

In conclusion, JAKi therapy may be an option for some patients with difficult-to-treat Still's disease, especially for those otherwise depending on medium- to high-dose corticosteroids because JAKi treatment had a significant corticosteroid-sparing effect. Additional studies are required to better define the subset of patients who may benefit from this strategy as well as the optimal JAKi dose and molecule to administer, and to establish negative prognostic factors of more difficult-to-treat disease. Points to address in the future are summarised in **Table 4**. In addition, there is an urgent need for unravelling the origin of the pathogenesis of SJIA/AOSD, particularly the distinct roles of inflammasome, cytokines, and type I and II IFNs in the different subsets and clinical phenotypes of the disease, to guide future decisions for novel alternative treatments. Although the JAKi tofacitinib has been recently

approved by the US Food and Drug Administration for treating the polyarticular course of JIA, a clinical trial for SJIA with systemic features is ongoing (ClinicalTrials.gov: NCT03000439) and should provide additional data on the efficacy and tolerance of this molecule in this disease.

Table 1. Main demographic, clinical and biological characteristics of patients with systemic juvenile idiopathic arthritis (SJIA) or adult-onset Still's disease (AOSD) at disease onset and at Janus kinase inhibitor (JAKi) initiation

	At disease onset			At start of JAKi treatment		
	SJIA (n=2)	AOSD (n=7)	Total (n=9)	SJIA (n=2)	AOSD (n=7)	Total (n=9)
General characteristics						
• Age, median (range) years	1.5 (1-2)	28 (22-50)	28 (1-50)	11 (6-16)	40 (28-59)	38 (6-59)
• Sex, M:F	0:2	3:4	3:6	0:2	3:4	3:6
Clinical characteristics						
• Fever > 39°C, X/n patients	2/2	6/7	8/9	1/2	4/7	5/9
• Rash, X/n patients	2/2	6/7	8/9	0	2/7	2/9
• Pharyngitis, X/n patients	0	6/7	6/9	0	3/7	3/9
• Arthritis/arthralgia, X/n patients	2/2	7/7	9/9	2/2	4/7	6/9
• TJC, median (range) °	NA	NA	NA	28	4 [0-6]	4 [0-28]
• SJC, median (range) °	NA	NA	NA	23.5 [21-26]	0 [0-1]	0 [1-26]
• Lymphadenopathy, X/n patients	1/2	2/7	3/9	0	1/7	1/9

	At disease onset			At start of JAKi treatment		
	SJIA (n=2)	AOSD (n=7)	Total (n=9)	SJIA (n=2)	AOSD (n=7)	Total (n=9)
• Serositis (pericarditis, pleuritis), X/n patients	0	1/7	1/9	0	0	0
• Complications °°, X/n patients	0	3/7 [a]	3/9 [a]	½ [b]	1/7 [c]	2/9 [b, c]
Laboratory characteristics						
• Leukocytes (/mm^3), median (range)	13470 [¶]	19950 (12400-47740)	19900 (12400-47740)	9185 (7470-10900)	11110 (1540-30010)	10900 (1540-30010)
• Neutrophil count (/mm^3), median (range)	9833 [¶]	18610 (10040-42580)	14905 (9833-42580)	5315 (5130-550)	9110 (20-29120)	5590 (20-29120)
• CRP level, median (range) , mg/L	117 [¶]	284 (56-424)	258.5 (56-424)	62 (28-96)	47 (2-168)	47 (2-168)
• Ferritin, median (range) , ng/mL	155 [¶]	6541.5 (1966-11468) [$]	5915 (155-11468)	410 (150-670)	738 (70-9261) [¥]	670 (70-9261)
• Elevated liver transaminase levels, X/n patients	0 [¶]	2/7	2/9	1/2	1/7	2/9
Disease activity scores						
• Modified Pouchot score, median,	4 (3–5)		6 (3–8)		4 (1–4)	3 (1–4)

	At disease onset			At start of JAKi treatment		
	SJIA (n=2)	AOSD (n=7)	Total (n=9)	SJIA (n=2)	AOSD (n=7)	Total (n=9)
(range)		6 (3–8)		2 (1–3)		
Previous treatments						
• MTX, X/n patients				2/2	4/7	6/9
• TNF inhibitors, X/n patients *				2/2	3/7	5/9
• IL-1 inhibitors, X/n patients **				2/2	7/7	9/9
• IL-6 inhibitors, X/n patients ***				2/2	5/7	7/9
• Other DMARDs, X/n patients ****				2/2	3/7	5/9

° Evaluated on 28 joints according to DAS28 score

°° Macrophage activation syndrome, hepatitis, pulmonary and/or haematological complications

[a] Two patients had moderate hepatitis and one acute respiratory distress syndrome with pleuritis and pericarditis. [b] One patient had moderate hepatitis immediately before the JAKi was started

[c] One patient had developed macrophage activation syndrome with hepatitis immediately before JAKi therapy was started

¶ Data available only for one patient

¥Data available for 5 patients

*TNF inhibitors used: infliximab (n=2), etanercept (n=3), adalimumab (n=2)

** IL-1-inhibitors used: anakinra (n=9), canakinumab (n=5), rilonacept (n=0)

***IL-6 inhibitors used: tocilizumab (n=7), sarilumab (n=2)

****Other DMARDs used: ciclosporine (n=3), imurel (n=2), IgIV (n=2), thalidomide (n=2)

CRP, C-reactive protein; DMARDs, disease modifying anti-rheumatic drugs; IL-1, interleukin 1; IL-6, interleukin 6; JAKi, Janus Kinase inhibitor; MTX, methotrexate; SJC, swollen joint count; TJC, tender joint count; TNF, tumour necrosis factor

Table 2. Patient outcomes under JAKi therapy

Nb.	Sex	Main clinical expression	SJIA or AOSD duration at JAKi start (years)	Age at JAKi start (years)	Treatments tried before JAKi†	Last treatment before JAKi start	Main symptoms at JAKi start	JAKi (name and posology)	Concomitant cs- or bDMARD	Response at last follow-up	Last follow-up	Modified Pouchot score at last follow-up	CRP level at last follow-up (mg/l)	Prednisone at onset (mg/day)	Prednisone at end of follow-up (mg/day)	Remaining symptoms
1	F	Systemic	5	6	csDMARDs IL-1i IL6i TNFi Other	**IFX**	Polyarthritis	Ruxolitinib 5mg x 2/day => 15 mg x2/day	None	Complete remission	33 months. JAKi ongoing	0	3 mg/l	5 mg/day	1 mg/day	None
2	F	Systemic	15	16	csDMARD IL-1i IL6i TNFi Other	**TCZ**	Fever, polyarthritis, **hepatitis**	Baricitinib 4mg / day => 8mg/day	None	Complete remission*	12 months. JAKi ongoing	0	2 mg/l	40 mg/ day	7.5 mg/day*	None
3	M	Systemic	< 1	28	IL-1i	**ANA**	Fever, polyarthralgia, pharyngitis,	Baricitinib 4 mg / day	None	**Primary failure**	30 months. JAKi stopped after 1 month**	4	31 mg/l	80 mg/day	10 mg/ day	Polyarthralgia, rash, pharyngitis, elevated CRP
4	M	Articular	4	32	csDMARD IL-1i IL-6i TNFi Other	**CYCLO**	Polyarthritis, pharyngitis	Baricitinib 4 mg / day	MTX 20 mg/week, ANAKINRA 100mg/day, Colchicine 1.5 mg/day	Partial remission	17 months. JAKi stopped			40 mg/ day	15 mg/ day	Arthritis, elevated CRP
								Switch to Upadacitinib 15 mg / day	CANAKI 300 mg/month at M24 Colchicine 2 mg/day	Partial remission	10 months. JAKi ongoing	1	23 mg/l	15 mg/day	14 mg/day	Arthritis, elevated CRP
5	M	Systemic	10	38	IL-1i IL-6i	**SARI**	Fever	Tofacitinib LP 11 mg /day	None	**Primary failure*** **	One month JAKi stopped	0	54 mg/l	0	0	Asthenia, elevated CRP

											after 8 days ***					
6	F	Systemic	18	40	csDMARD IL-1i IL-6i TNFi Other	**MTX**	Fever, **MAS, hepatitis**	Ruxolitinib 15 mg x 2/day => 30 mg x 2/day	ANAKINRA 200mg/day	Partial remission	17 months. JAKi ongoing	2	23 mg/l	60 mg/day	7.5 mg/day	Elevated CRP level
7	F	Systemic	4	48	csDMARD IL-1i IL-6i Other	**IMU**	Polyarthritis, rash, pharyngitis	Tofacitinib 5 mg x 2/day => LP 11 mg/day	None Adalimumab 40 mg / week at M14	**Loss of efficacy**	16 months. JAKi stopped ****	1	14 mg/l	60 mg/day	15 mg/day	Polyarthralgia, pharyngitis, elevated CRP level
8	F	Systemic	< 1	50	IL-1i	**ANA**	Fever, rash	Baricitinib 4 mg / day	None	**Primary Failure**	1 months. JAKi stopped after 1 month *****	1	71 mg/l	60 mg/ day	40 mg/ day	Fever, elevated CRP level
9	F	Articular	19	59	csDMARD IL-1i IL-6i TNFi	**SARI**	Polyarthritis	Baricitinib 4 mg /jour	None	Partial remission	3 months. JAKi ongoing	1	2 mg/l	0	0	Arthritis

Cases 1 and 2 correspond to SJIA, other cases to AOSD. The terms complete remission, partial response, primary failure and loss of efficacy are defined in the Methods.

†The details of treatments tried before JAKi are summed in supplementary Table 1. JAKi was thus started because of inadequate response to one or more of these treatments: csDMARDs, including methotrexate and/or imurel; IL-1i, including anakinra and/or canakinumab; IL-6i, including tocilizumab and/or sarilumab; TNFi, including infliximab and/or adalimumab and/or etanercept; other, including intravenous immunoglobulins, thalidomide and/or cyclosporine.

*The patient was in complete remission although the corticosteroids taper was still in progress at last follow-up. Corticosteroids were being tapered.

** Primary failure (primary lack of efficacy). Switch to sarilumab: remission after 3 months of treatment

*** Treatment stopped at a very early stage according to the patient's wish.

**** Loss of efficacy. Switch to adalimumab

***** Lack of efficacy then lost to follow-up

ADA, adalimumab; ANA, anakinra; CANAKI, canakinumab; CRP, C-reactive protein; csDMARDs, conventional synthetic disease modifying anti-rheumatic drugs; CYCLO, cyclosporine; IFX, infliximab; IL-1i, IL-1 inhibitors; IL-6, IL-6 inhibitors; IMU, imurel; JAKi, Janus Kinase inhibitor; MAS, macrophage activation syndrome; MTX, methotrexate; SARI, sarilumab; TCZ, tocilizumab

Table 3. Treatment response and tolerance

	All treatment (n=9)	**Baricitinib (n=5)**	**Ruxolitinib (n=2)**	**Tofacitinib (n=2)**	**Upadacitinib (n=1)***
Treatment duration (months)					
Median (range)	12 (1-33)	3 (1-17)	23 (13-33)	8.5 (1-16)	10
Response to therapy*					
Complete remission	2	1	1	0	0
Partial response	3	2	1	0	1
Primary failure	3	2	0	1	0
Loss of efficacy	1	0	0	1	0
Adverse events	2***	0	2***	0	0

* Upadicitinib was prescribed in one patient (case 4) after previous 17 months' therapy with baricitinib, which had led to partial response (see **Table 2** and **Figure 1**).

** The terms complete remission, partial response, primary failure and loss of efficacy are defined in the Methods.

***Histologically proven organized pneumonia developed in one patient (case 6) under ruxolitinib, which led to temporary (3 months) discontinuation of the treatment temporarily (3 months). One patient (case 1) presented a Varicella-zoster virus infection under ruxolitinib, with no signs of gravity and favourable outcome. The drug was reintroduced after resolution of the infection.

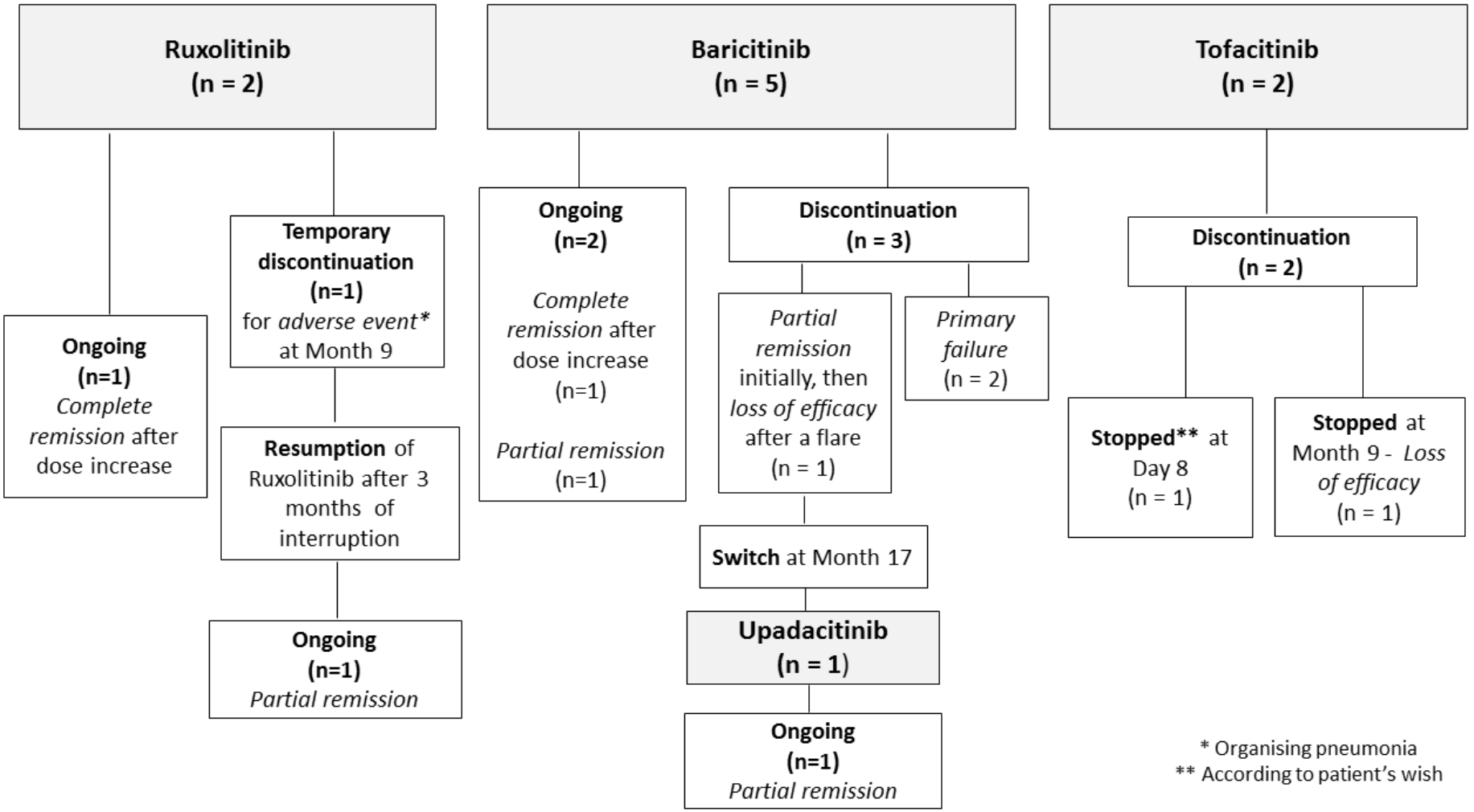
Table 4. Points to address in the future regarding the place of JAKi agents in the treatment strategy for SJIA and AOSD

Patient profile
• In case of difficult-to-treat disease*, especially in case of dependence on medium- to high-dose corticosteroids despite IL-1 or IL-6 inhibitors concomitant therapy
• In case of complications, especially MAS or lung disease?
• Guided by biomarkers predictive of difficult-to-treat disease, to be defined: genetic polymorphisms? IFN-γ plasmatic levels? IFN signature? Elevated CRP level?
• Better efficacy in children than in adults?
JAK inhibitor
• Type of JAKi?
• Dose of JAKi to administer?
• Monotherapy or combination therapy with anti-IL-1 agent?

* Given the current state of knowledge that positions anti-IL1 and anti-IL6 as the first line of treatment in corticosteroid-refractory SJIA and AOSD, and the safety issues regarding JAKi (especially in older patients), the issue of JAKi as first line therapy doesn't seem reasonable.

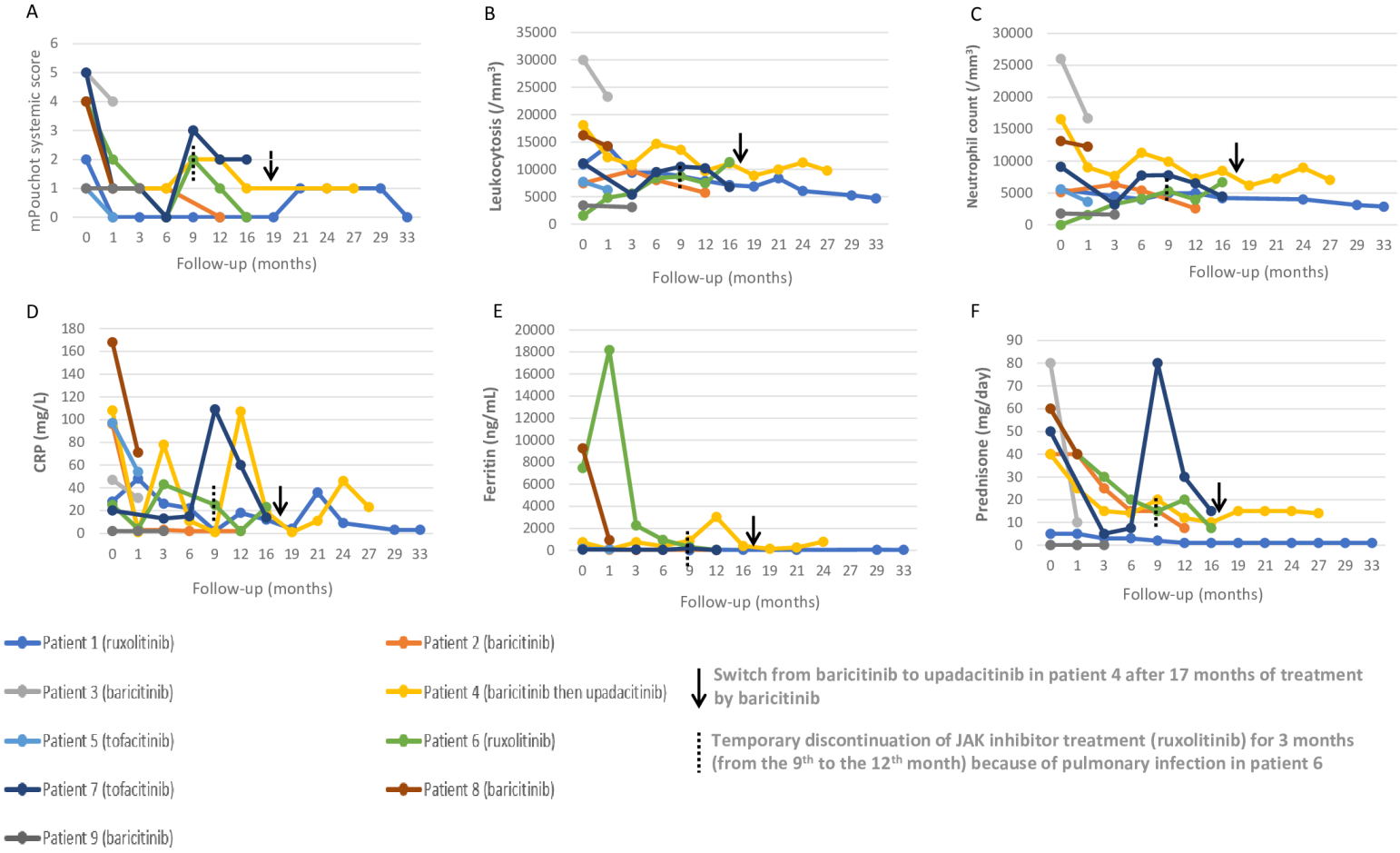
IL, interleukin; MAS, macrophage activation syndrome; IFN, interferon; CRP, C-reactive protein

Figure 1. Janus kinase inhibitor (JAKi) treatment for the 9 patients and switch of molecule



The terms complete remission, partial response, primary failure and loss of efficacy are defined in the Methods.

Figure 2. Evolution of the modified Pouchot systemic score, laboratory findings and prednisone medication over time during follow-up.


A
mPouchot systemic score
Follow-up (months)
B
Leukocytosis (/mm³)
Follow-up (months)
C
Neutrophil count (/mm³)
Follow-up (months)
D
CRP (mg/L)
Follow-up (months)
E
Ferritin (ng/mL)
Follow-up (months)
F
Prednisone (mg/day)
Follow-up (months)
Patient 1 (ruxolitinib)
Patient 2 (baricitinib)
Patient 3 (baricitinib)
Patient 4 (baricitinib then upadacitinib)
Patient 5 (tofacitinib)
Patient 6 (ruxolitinib)
Patient 7 (tofacitinib)
Patient 8 (baricitinib)
Patient 9 (baricitinib)
Switch from baricitinib to upadacitinib in patient 4 after 17 months of treatment by baricitinib
Temporary discontinuation of JAK inhibitor treatment (ruxolitinib) for 3 months (from the 9th to the 12th month) because of pulmonary infection in patient 6

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