



## Special article

## JAK inhibitors in 2019, synthetic review in 10 points

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## ABSTRACT

JAK inhibitors are recent treatments. Many publications have appeared in recent years, exposing treatment efficiencies in phases 2 and 3 studies, or their tolerance profile in various rheumatological diseases. We propose here a systematic review of JAK inhibitors, from their mechanism of physiological action up to the estimation of their current risk benefit balance, and their possible future applications.

In order to better synthesize the data, we organized this review into 10 essential points.

- 1- What is the role of JAK/Stat pathway?
- 2- How can a single signaling pathway regulate as many different signals?
- 3- What are the commercialized JAK inhibitors and their validated indications in humans today?
- 4- What is the level of efficiency of JAK inhibitors in inflammatory diseases?
- 5- What is the delay of efficiency of JAK inhibitors?
- 6- Where is the place of JAK inhibitors in the therapeutic strategy today?
- 7- What is the infectious tolerance profile of JAK inhibitors?
- 8- What is the non-infectious safety profile of JAK inhibitors?
- 9- What is the cost of JAK inhibitors compared to other DMARDs?
- 10- What future prospects for JAK inhibitors?

## 1. Introduction

JAK inhibitors are recent treatments. Many publications have appeared in recent years, exposing the efficiency or tolerance profile in various rheumatological diseases [1–4]. The multitude of articles published in recent years and the accumulation of knowledge around JAK inhibitors requires the development of journals synthesizing and clearly collating the current scientific data. We propose here a synthetic systematic review of JAK inhibitors, organized in 10 points.

## 2. What is the role of JAK/Stat pathway?

Kinases of the Jak (janus kinase) family and transcription factors of the STAT (Signal Transducer and Activator of Transcription) constitute a fast intracellular communication pathway between the membrane receptor of an extracellular signal (cytokine) and the cell nucleus [5].

JAK/STAT signaling cascade is initiated by the cytokine binding to its receptor. This triggers its multimerization and thus a modification of its three-dimensional conformation, which results in the activation of associated JAKs. The JAKs phosphorylate themselves, creating a docking site for STAT proteins, which, in turn, are also phosphorylated. This provides the formation of active STAT multimers that can

translocate into the nucleus and regulate gene transcription by promoting permissive or repressive epigenetic marks (Fig. 1). The JAK / STAT pathway induces a negative-feedback signal by increasing production of suppressor of cytokine signaling (SOCS) proteins and protein tyrosine phosphatases (PTPs) that prevents the interaction between JAK and its receptor [6–8].

JAK STAT pathway is known to be activated by > 50 different cytokine receptors [9–11], receiving signals from pro-inflammatory cytokines (IL 6, TNF alpha, IL12, IL23), anti-inflammatory cytokines (IL4, IL10), hematopoietic cell growth factors (G-CSF, EPO, TPO) and metabolic cytokines (leptin, GH).

According to the initially activated membrane receptor, the JAK / STAT pathway will be the intracellular mediator of the transcriptional regulation of a wide variety of genes that regulate cell proliferation, differentiation and activation as well as metabolic homeostatic regulation of the human body [12–14].

JAK/STAT cascade is the intracellular point of convergence of many extracellular regulatory signals, and thus a central communication node for cells.

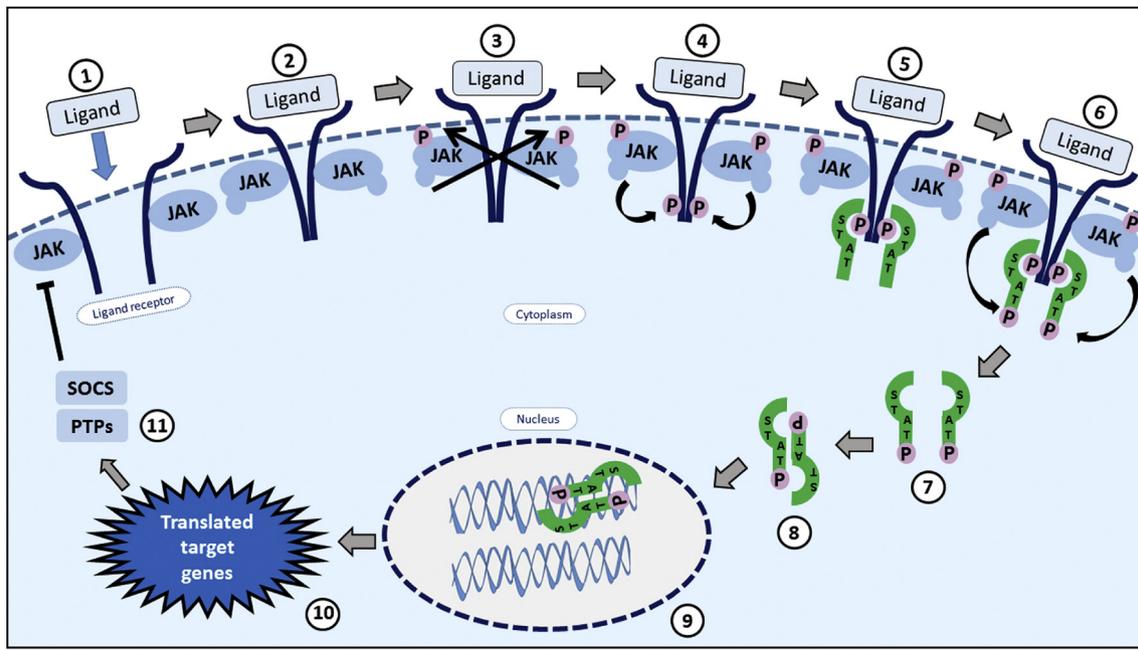
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**Fig. 1.** JAK-Stat signaling.

- 1- Fixation of the ligand (cytokin), to the extracellular domain of his receptor.
- 2- Receptor dimerization (or multimerization) and activation of associated JAK proteins.
- 3- Transphosphorylation of the JAK proteins.
- 4- Phosphorylation of the intracytoplasmic domain cytokine receptor, and creation of a docking site for STAT proteins.
- 5- Fixation of the cytoplasmic quiescent STAT proteins (SH2 domain) to docking phosphorylated site.
- 6- Phosphorylation of STAT C-terminus by JAK.
- 7- STAT dissociation from cytokine receptor.
- 8- STAT dimerization by reciprocal interaction between SH2 and C-terminus phosphorylated domains.
- 9- STAT nuclear importation, and regulation of targeted transcriptional sites.
- 10- Translation of targeted proteins, among which SOCS and PTPs.
- 11- SOCS an PTPs providing negative feedback to the pathway by competitively binding to cytokine receptor and JAK proteins.

### 3. How can a single signaling pathway regulate as many different signals?

The previous flowsheet of JAK/STAT pathway may seem simple, but the reality is much more complex [15,16]. Indeed, there are several types of JAK in humans (JAK1, JAK2, JAK3 and TYK2), as well as several types of STAT (STAT1, STAT2, STAT3, STAT4, STAT5a and b, STAT6). During the activation of the signaling cascade, these JAK and STAT molecules assemble into homo and heterodimers, or even into more complex multimers. The final transcriptional effect induced by the cytokine actually depends on the type of JAK and STAT involved in the multimers.

For example, interferons  $\alpha$  and  $\beta$  activate JAK 1 and TYK 2 then STAT 1, 2 and 4, whereas interferon  $\gamma$  activate JAK1 and JAK 2 before STAT 1 [17]. The effects of hematologic (EPO, TPO, G-SCF) and metabolic (GH, Leptin) cytokines are mainly mediated by JAK2 [18,19]. In the same way that a cytokine will target different JAKs and different STATs, a given JAK will be an intracellular mediator of several different cytokines (Fig. 2). Indeed, JAK 2 may be activated by EPO, IL 6 and IL 11 receptor whereas JAK 1 may be activated by pro-inflammatory cytokines (IL6; IL7; IL10; IL12) such as anti-inflammatory cytokines (IL4 and IL10, which is both an anti and a pro-inflammatory cytokine).

This heterogeneity of activity between JAKs and STATs is also reflected by the wide nosological spectrum of diseases induced by their genetic dysfunctions. For instance, (i) JAK 3 germline loss-of function is associated with SCID (Severe Combined ImmunoDeficiency) [20], (ii) JAK 2 gain of function causes myeloproliferative neoplasm [21], (iii) JAK 1 gain of function may result in lymphoid neoplasm [22–24], and finally (iv) STAT3 is associated with Hyper-IgE syndrome when deficient, and has been associated with obesity in case of chronic activation

[25].

Therapeutically, the various JAK inhibitors developed by the pharmaceutical industry have a selective affinity for some JAKs. This variable selectivity of the anti-JAK for the different JAK is at the origin of the heterogeneity of their action range. Indeed, Ruxolitinib and Baricitinib are JAK 1 and 2 inhibitors [26,27], Tofacitinib inhibits JAK 1 and 3, Oclacitinib, Upadacitinib and Filgotinib are more specific of JAK 1 and Decernotinib of JAK 3. Peficitinib seems to target JAKs more widely, targeting JAK 1, JAK 2, TYK2 and moderately JAK 3 [16,28].

So, the specificity of final effect of this communication cascade used by many different cytokines, is the result of JAK and STAT subtypes recombinations, which constitute an asset for targeted therapeutic inhibitions.

### 4. What are the commercialized JAK inhibitors and their validated indications in humans today?

Three JAK inhibitor are approved by the FDA (Food and Drugs Administration) and the EMA (European Medicines Agency) today:

> Ruxolitinib (Jakavi), targeting JAK1 and JAK 2, for treatment of patients with myelofibrosis and polycythemia vera.

> Tofacitinib (Xeljanz, Jakvins, CP-690550), targeting JAK 1 and 3, for treatment of patients with rheumatoid arthritis and psoriatic arthritis. This treatment is also approved in case of ulcerative colitis in the USA (FDA), but currently not in Europe (EMA).

> Baricitinib, targeting JAK 1 and 2, for treatment of rheumatoid arthritis.

Other JAK inhibitors currently under study, including Pefacitinib, Filgotinib or Pacritinib, have shown promising results in Phase III clinical trials in rheumatoid arthritis, atopic dermatitis, Crohn's disease

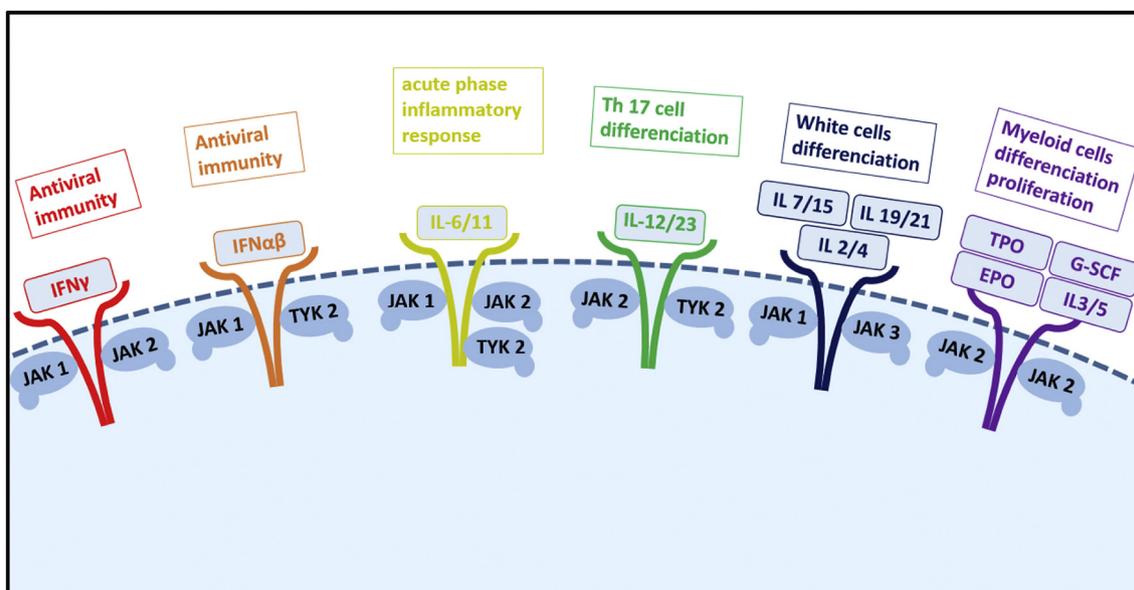


Fig. 2. Relationship between cytokine receptor, JAK recombination and final cell effects of signaling pathway.

or myelofibrosis [29–31].

5. What is the level of efficiency of JAK inhibitors in inflammatory diseases?

5.1. Rheumatoid arthritis: [29,32–40]

Rheumatoid arthritis is the pathology where randomized controlled trials are the most numerous, testing the efficacy of Baricitinib and Tofacitinib in monotherapy or combination therapy versus placebo or standard treatments (Tables 1 and 2).

In monotherapy strategies, Tofacitinib and Baricitinib obviously demonstrated their superiority to placebo. More, they demonstrated their superiority over methotrexate, the standard treatment, both on the ACR 20 score and on the reduction of radiographic lesions. Tofacitinib also demonstrated non inferiority on ACR 20 score compared to adalimumab and methotrexate association.

In bitherapy strategies, associations of Tofacitinib or Baricitinib with methotrexate are of course more efficient than placebo and specially non inferior to the adalimumab / methotrexate combination, at

least on clinical and radiographic criteria.

5.2. Psoriatic arthritis

In the OPAL BROADEN (RCT phase III) study, tofacitinib was studied in patients with inadequate response to chemical background therapy (csDMARD, conventional synthetic disease-modifying anti-rheumatic drugs). At three months, the clinical and functional response of tofacitinib was superior to placebo and comparable to that of adalimumab [41].

5.3. Ulcerative colitis

The efficiency of Tofacitinib for the treatment of moderately to severely active ulcerative colitis was demonstrated in the OCTAVE trials, highlighting significant more frequent remissions than placebo (18.5% of remission at 8 weeks in the 10 mg Tofacitinib group, vs 8.2% in the placebo group) [42]. There is no large-scale randomized trial evaluating the efficiency of Tofacitinib against a reference treatment for the induction of ulcerative colitis. Nevertheless, the efficiency of

Table 1  
Trials testing JAK inhibitors in monotherapy in rheumatoid arthritis.

	JAK Inhibitor	Placebo	Methotrexate	Adalimumab + MTX
Monotherapy	Tofacitinib	ORAL SOLO [32] 611 patients ACR20 response at month (M) 3: : - Placebo: : 26% - Tofacitinib 5 mg: : 60%* - Tofacitinib 10mg: : 66%*	ORAL Start [33] 958 patients Modified total sharp score at M6: - Methotrexate: 0.8 points (pts) - Tofacitinib 5 mg: 0.2pts* - Tofacitinib 10 mg: < 0.1ptsv*	Oral Strategy [34] 1146 patients ACR50 response at M6: - Adalimumab + MTX: 44% - Tofacitinib: 38%
	Baricitinib	RA beacon [35] 527 patients ACR20 response at week 12: - Placebo: 27% - Baricitinib 4 mg: 55%* RA Build [74] 684 patients ACR20 response at week 12: - Placebo: 39% - Baricitinib: 62%*	RA-BEGIN [36] 588 patients ACR20 response at week 24: - methotrexate: 62% - Baricitinib 4 mg: 77%*	

\* JAK inhibitor statistically superior.

**Table 2**  
Trials testing JAK Inhibitors in bitherapy in rheumatoid arthritis.

	Control association	Placebo + MTX	Adalimumab + MTX
Bitherapy	Tofacitinib + MTX	ORAL Step [37] 399 patients ACR20 response at M3: - Placebo + MTX: 24.4% - Tofacitinib 5 mg + MTX: 42%* - Tofacitinib 10 mg + MTX: 48%* ORAL Standard [38] 717 patients ACR20 response at M6: - Placebo + MTX: 28% - Tofacitinib 5 mg + MTX: 52%* - Tofacitinib 10 mg + MTX: 53%* ORAL Scan [39] 797 patients ACR20 response at M6: - Placebo + MTX: 25% - Tofacitinib 5 mg + MTX: 52%* - Tofacitinib 10 mg + MTX: 62%* ORAL Sync [75] 795 patients Tofacitinib 5 and 10 mg improved PtGA, Pain, HAQ DI, 7 SF-36 domains, FACIT-F, and MOS Sleep*	ORAL Standard [38] 717 patients ACR20 response at M6: - Adalimumab + MTX: 47% - Tofacitinib 5 mg + MTX: 52%* - Tofacitinib 10 mg + MTX: 53%* Oral Strategy [34] 1146 patients ACR50 response at M6: - Adalimumab + MTX: 44% - Tofacitinib + MTX: 46%**
	Baricitinib + MTX	RA Beam [76] 1307 patients ACR20 response at week 12: - Placebo + MTX: 40% - Baricitinib 4 mg + MTX: 70%*	RA beam [76] 1307 patients ACR20 response at wweek 12: - Adalimumab MTX: 61% - Baricitinib + MTX: 70%*

\* Association with JAK inhibitor statistically superior.

\*\* Association with JAK inhibitor statistically non inferior.

Tofacitinib at a dosage of 10 mg appears to be lower than 5-aminosalicylic acids (5-ASAs), one of the standard treatments, which induction efficiency rate is estimated about 40% in meta-analysis [43,44]. This question will have to be specified by comparative tests over a prolonged period (three months minimum), possibly testing higher doses of Tofacitinib.

In conclusion, in rheumatology (rheumatoid arthritis, psoriatic arthritis), the many data available are in favor of similar to superior efficacy of JAK inhibitors on standard treatments. This hierarchy will have to be established by specific studies in ulcerative colitis.

## 6. What is the delay of efficiency of JAK inhibitors?

In rheumatology, the efficacy of anti-JAK seems to appear relatively early, since measurable from two weeks of treatment. Indeed, in the ORAL Syncn, ORAL Solo or RA BEAM studies, a staggering difference in efficiency of Baricitinib and Tofacitinib compared to placebo is significantly objectified after fourteen days of treatment. The maximum effectiveness of these treatments is effective later on, approximately after three months, like other DMARDS.

Data seem comparable for ulcerative colitis since OCTAVE1 and OCTAVE2 demonstrated that the onset of action of tofacitinib was significantly lower than placebo treated patients from week 2. The maximum of efficiency was reached at two months, when the treatment was then stopped. There is no large-scale trial testing for treatment beyond eight weeks, although this is less than the delay of maximum efficiency found in rheumatoid arthritis studies.

## 7. Where is the place of JAK inhibitors in the therapeutic strategy today?

JAK inhibitors are relatively new treatments, and as such, their position in the therapeutic hierarchy is not yet firmly established.

### 7.1. Rheumatoid arthritis

In the field of rheumatoid arthritis, ACR recommendations of 2015

[45] advise the use of JAK inhibitors in third line, that means in case of failure of a csDMARD in the first line (methotrexate in particular) then a combination of csDMARDs or a TNFi in the second line. The EULAR recommendations are more recent [46], and place JAK inhibitors in the second phase of their algorithm, that means after failure of a first-line csDMARD, and in case of poor prognostic factors (Fig. 3).

Thus, these recommendations place JAK inhibitors behind methotrexate or even bDMARDs (biological DMARDs) on the basis of the lack of data on their long-term tolerance (see questions 7 and 8). Nevertheless, the demonstrated superiority in randomized trials of JAK inhibitors on methotrexate should lead to a gradual increase of JAK inhibitors in the therapeutic hierarchy, as long as the data on their tolerance do not bring worrying information.

### 7.2. Psoriatic arthritis

All recommendations for patients with persistent psoriatic rheumatism despite treatment with DMARD are based on low quality evidence. According to the ACR [47], after failure of csDMARDs, a TNFi biologic is recommended over an IL-17i biologic, which is recommended over IL-12/23i biologic, itself recommended over tofacitinib. But, these recommendations precise that Tofacitinib may be used instead of a TNFi in patients without severe psoriasis preferring oral medication. According to EULAR [48], Tofacitinib is justified only in third line, after (i) failure of non-steroidal anti-inflammatory drugs, (ii) failure of csDMARDs, and (iii) only in case of bDMARDs are not appropriate (Fig. 4).

### 7.3. Ulcerative colitis

It is not possible to rule on the place of anti-JAK in the absence of a randomized study against the treatments usually used in this disease.

In synthesis, anti-JAK are already part of the therapeutic management of rheumatoid arthritis and psoriatic arthritis. Up to now and in spite of strong evidence of their effectiveness and ease of use (oral treatment), the only factor limiting their use is the lack of perspective on long-term tolerance.

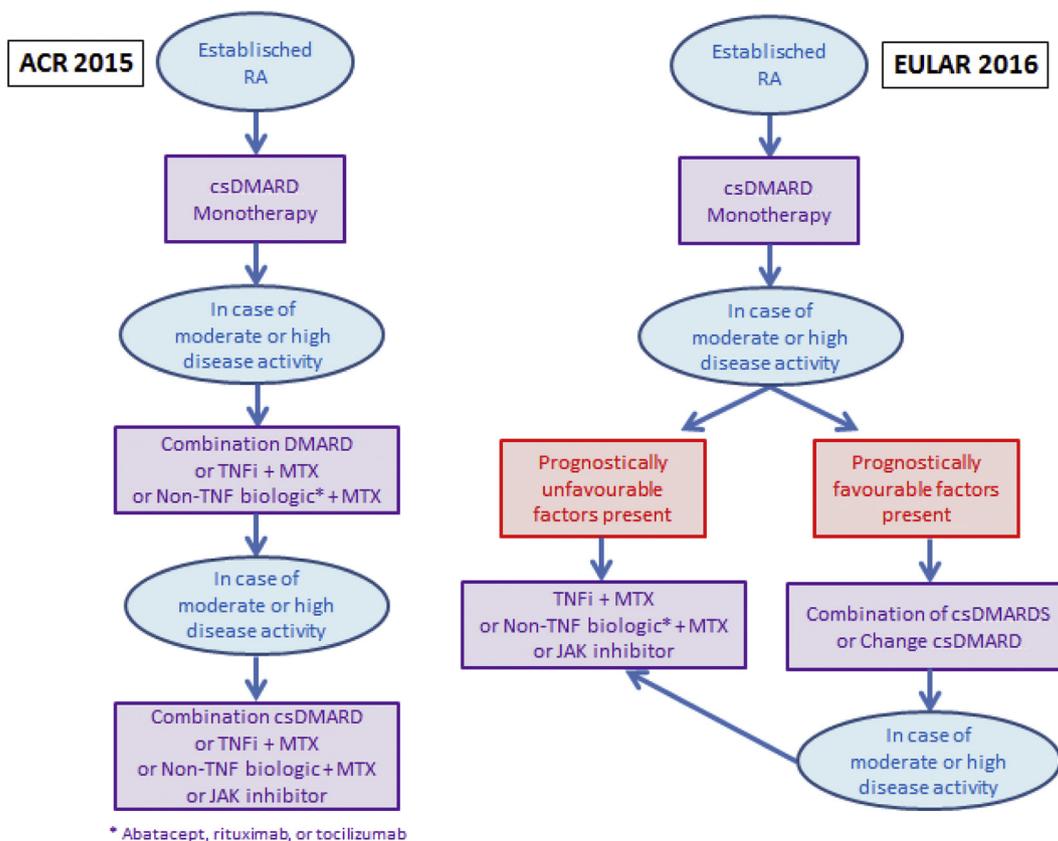


Fig. 3. Therapeutic recommendations of ACR and EULAR in rheumatoid arthritis.

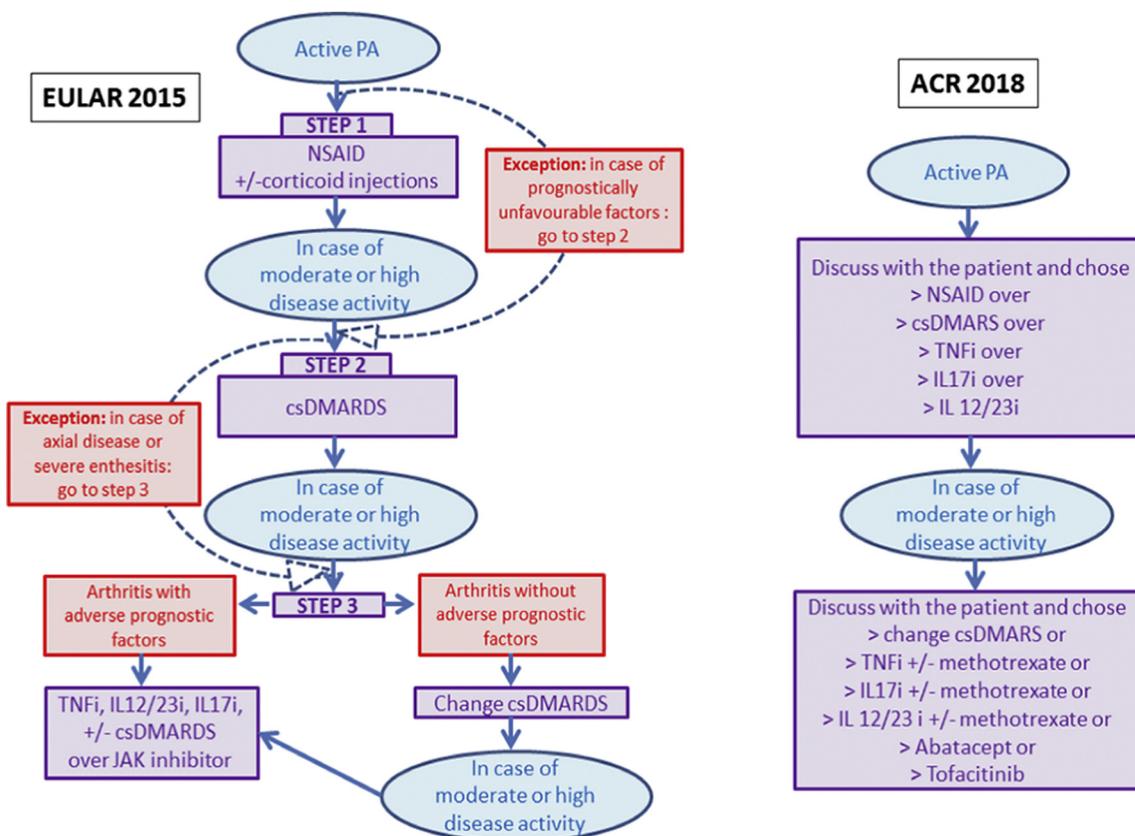


Fig. 4. Therapeutic recommendations of ACR and EULAR in psoriatic arthritis.

## 8. What is the infectious tolerance profile of JAK inhibitors?

JAK kinases inhibitors being immunosuppressive treatments, infectious side effects are obviously feared. These effects are therefore monitored and collated.

### 8.1. Infectious safety of Tofacitinib [49–51]

The infectious tolerability profile of tofacitinib in patients with active rheumatoid arthritis is based on pooled data from pivotal studies. The latter pooled analysis included data from a total of 6194 patients who had received tofacitinib for a total of 19,406 patient-years (median exposure of 3.4 patient-years). The most common infections occurred in the upper airways. Herpes zoster infections occurred in patients at a rate of 3.9 per 100 patient years, most often affecting a single dermatome (92%). The frequency of these infections seemed particularly high in Asia, and the occurrence of a severe form seemed exceptional (2 per 1000 patient years). The occurrence of tuberculosis in a patient undergoing treatment is a rare event since < 2 cases per 1000 patient years have been reported. More generally, a serious infection, defined by the need for hospitalization, intravenous antibiotic therapy or death, occurred at a frequency of 2.7 per 100 patient years.

### 8.2. Infectious safety of Baricitinib [52,53]

The assessment of the safety profile of baricitinib is also based on the integrated data from the pivotal studies. A recently published study unveiled the safety profile of Baricitinib in 3492 patients, for a total of 6637 patient years. The trend is the same as for Tofacitinib, with a good tolerance on the infectious plane. Herpes zoster cutaneous infections are again in the foreground, at a frequency roughly similar to that of Tofacitinib (3.2 per 100 patient years). The frequency of severe infections was measured at 2.9 per 100 patient years, and that of tuberculosis at 1.5 per 1000.

By way of comparison, the meta-analysis [54] show a severe infection rate between 3 and 5 per 100 patient years for bDMARDs (TNFi, Rituximab, Tocilizumab). These results suggest a slightly lower rate of severe infection with JAK inhibitors. In contrast, herpes zoster infections are clearly more common with JAK inhibitors than with other DMARDs since in the corona register the Herpes zoster infections occurred at a rate of 1.9 to 1.3 per 100 patient years [55,56].

Overall, the tolerance of JAK inhibitors at the infectious level is very good, the main notable element is the occurrence of benign herpes zoster virus infection, which does not call into question the risk/benefit balance of this treatment.

## 9. What is the non-infectious safety profile of JAK inhibitors?

JAK kinases are associated with a large number of cytokine receptors, regulating the general homeostasis and not just the immune system. As such, side effects can be feared, as for corticosteroid.

### 9.1. Malignancy [49,52,57,58]

No over-risk of cancer was observed in pivotal study meta-analysis, nor for Tofacitinib nor baricitinib. Nevertheless, the duration of patient follow-up (5.5 years maximum) does not allow to formally rule out long-term neoplastic over-risk. Patients who have received, or are receiving, JAK inhibitors should be followed in the long term to formally estimate this risk.

### 9.2. Gastrointestinal perforations [49,52,57,58]

Gastrointestinal perforations have been reported for approximately 1 in 100 patients years for both Baricitinib and Tofacitinib. In developmental studies, all patients with gastrointestinal perforation

concomitantly received treatment with non-steroidal anti-inflammatory drugs or corticosteroids, known to give this type of side effect. Note that, overall, in the comparative studies, gastrointestinal disorders were less important in patients on JAK inhibitors than in placebo. This is certainly in connection with a lower consumption of non-steroidal anti-inflammatory drugs and corticosteroids. It is therefore likely that the JAK inhibitors do not present any digestive toxicity by themselves, a fact that will have to be specified in other studies, with in particular an alleviation of digestive side effects on the concomitant consumption of pro-ulcerative treatments.

### 9.3. Cardiovascular events [59,60]

Pooled studies focused on cardiovascular risk have not been found to be over-risk in patients treated with Baricitinib or Tofacitinib versus placebo. These studies being based on a large number of patients reasonably allow avoiding an over-risk of short-term arterial thromboses under treatment. But patients will need to be followed in the long-term to ensure the absence of long-term vascular toxicity, as can be observed with corticosteroids.

### 9.4. Lipid levels [49,52,59,60]

Pooled studies focused on lipid levels revealed that Tofacitinib and baricitinib increase LDL cholesterol in patients with rheumatoid arthritis. This increasing appears to be not only attributable to correction of the low levels caused by inflammation associated with the disease since it is more frequent than with DMARD or adalimumab. The LDL/HDL ratio remained stable, suggesting small impact on long-term cardiovascular risk. Similar findings have been reported with tofacitinib in patients with psoriasis.

### 9.5. Cytopenias [49,52,61]

Because of their more or less specific inhibition of JAK2, JAK inhibitors are likely to induce cytopenias. This cytopenic effect is the mode of action of Ruxolitinib, used in myeloproliferative disorders. Although both Tofacitinib and Baricitinib have a lower JAK2 tropism, decreased neutrophil counts, thrombocytopenia, decreased hemoglobin, and anemia were observed with these treatments.

### 9.6. Weight increasing [49,52,62,63]

Since JAK2 is an element of intracellular IGF-1 / GH axis signaling, weight gain is expected under JAK inhibitor. This effect is clearly demonstrated for Ruxolitinib, and has been observed also with Baricitinib and Tofacitinib. The degree of weight gain under treatment and its impact on long-term cardiovascular risk should be evaluated in long-term prospective studies.

### 9.7. Thromboembolism [64–66]

In 2017, the US FDA expressed concern about deep venous thrombosis and pulmonary embolism observed in placebo-controlled clinical trials of baricitinib. Specific warnings have thus been inserted in RCPs. Since the publication of these concerns, a few studies have been conducted to determine precisely this risk. To date, there is no evidence that JAK inhibitors are responsible for more venous thromboses than TNF inhibitors [66], and there is no evidence that Baricitinib induces more thromboses than tofacitinib or ruxolitinib [65].

### 9.8. Others

Abnormal liver function tests and cutaneous or allergic reactions have also rarely been described.

In conclusion, side effects such as elevated cholesterol, weight gain

and cytopenias were observed with JAK inhibitors. The cardiovascular and oncological risks will need to be clarified in the long term, but the current data are reassuring. These effects seem in most cases well tolerated: thus in rheumatoid arthritis, the meta-analysis do not find more stop treatment in patients treated with JAK inhibitors than in patients treated with DMARDS or adalimumab.28.

## 10. What is the cost of JAK inhibitors compared to other DMARDS?

### 10.1. Cost of the drug

The answer to this question is not simple since health economics policies differ across countries. The price is fixed by state institutions in a few countries, as in France, whereas it is free in the United States for instance. As a result, drug prices differ from country to country. The equation is even more complex because of price fluctuations over time within each country (lower prices due to placing biosimilars on the market or renegotiations in case of fixed prices; price increasing because of significant demand in open-tariff countries).

In France for instance (fixed prices), according to the data of the website “legifrance”, the price of four weeks of Tofacitinib 5 mg and Baricitinib 4 mg is set at 729.66 €. For comparison, methotrexate (imeth 20 mg injection) is set at 313.12 €, and adalimumab at 715 € for four weeks of treatment.

In UK (free prices then negotiated), according to data from the NICE website, 28 days of Tofacitinib cost £ 690.3, versus £ 805.56 for Baricitinib and £ 715 for adalimumab.

In the US (free prices), according to the RED BOOK ONLINE website, prices are \$ 3797.1 for adalimumab, \$ 1479.8 for Tofacitinib and about \$ 200 for methotrexate.

The overall trend is therefore that JAK inhibitors are more expensive than csDMARDS, but at prices comparable to those of bDMARDS.

### 10.2. Overall cost of treatment [67]

The overall cost of a treatment is not limited to the price of the concerned molecules. Other parameters need to be taken into account, such as the price of the method of administration of treatment, and the cost of taking care of any side effects.

For instance, some bDMARDS are administered only intravenously, requiring administration in a care facility, whereas this is not the case for JAK inhibitors, whose oral administration allows daily administration at home at a lower cost. To our best knowledge, only one cost study of JAK inhibitors has been managed (carried out in the USA by the Pfizer laboratory in rheumatoid arthritis) and has shown that Tofacitinib was the cheapest treatment after failure of methotrexate. Nevertheless, these calculations have been based on the prices of drugs and cares in the United States.

## 11. What future prospects for JAK inhibitors?

Inhibitors of JAK are in full swing. On one hand, many JAK inhibitors are currently being studied and in the process of being marketed. On the other hand, the list of pathologies testing the efficacy of these treatments continues to grow (<https://clinicaltrials.gov>).

### 11.1. New JAK inhibitors (Table 3)

- Upacitinib (ABT 494) is a JAK 1 inhibitor. This treatment demonstrated superiority to placebo in rheumatoid arthritis (phase IIb), and is actually tested in moderate to severe atopic dermatitis, ulcerative colitis, Crohn's disease, psoriatic arthritis, giant cell arteritis, juvenile idiopathic arthritis, and ankylosing spondylitis

**Table 3**  
New JAK inhibitors.

New JAK inhibitors	JAK targeted	Tested diseases
Upacitinib ABT 494	JAK1	Rheumatoid arthritis phase IIb Moderate to severe atopic dermatitis Ulcerative colitis, Crohn's disease Giant cell arteritis, juvenile idiopathic arthritis Psoriatic arthritis, ankylosing spondylitis [68–70]
Decernotinib VX-509	JAK3	Rheumatoid arthritis phase IIb [71]
Peficitinib (ASP015K)	JAK1, 2, 3 TYK2	Rheumatoid arthritis phase III Ulcerative colitis Moderate to severe psoriasis [29,72]
Filgotinib (GLPG0634)	JAK1	Rheumatoid arthritis phase III Psoriatic arthritis III Moderate to severe Crohn's disease [73]
Itacitinib (INCB039110)	JAK1	Rheumatoid arthritis Myelofibrosis Psoriasis
Momelitinib (CYT387)	JAK1, 2	Primary myelofibrosis Post-polycythemia vera Post-essential thrombocytemia
Pacritinib (SB1518)	JAK2 FLT3	Myelofibrosis phase III, Graft versus host disease prevention phase II [31]
Gandotinib (LY-2784544) Lestaurtinib (CEP-701)	JAK 2 JAK2	Myeloproliferative neoplasm Myeloproliferative neoplasm Severe/moderate psoriasis

[68–70].

- Decernotinib (VX-509) is a JAK inhibitor demonstrating particular affinity of JAK3. Phase II and IIb trials demonstrated efficiency compared to placebo in rheumatoid arthritis [71]
- Peficitinib (ASP015K) inhibiting JAK1, 2, 3 and TYK2, is currently being tested in phase III trials in rheumatoid arthritis, ulcerative colitis or moderate to severe psoriasis [29,72].
- Filgotinib (GLPG0634) rather inhibits JAK1, and demonstrated its superiority to placebo in rheumatoid arthritis (phase IIb) and psoriatic arthritis, and is actually tested in phase III trials, and moderate to severe Crohn's disease [73].
- Itacitinib (INCB039110) inhibits JAK1, and is actually tested in rheumatoid arthritis, myelofibrosis and psoriasis.
- Momelitinib (CYT387) inhibiting JAK 1 and 2, is actually tested in primary myelofibrosis, or post-polycythemia vera or post-essential thrombocytemia.
- Pacritinib (SB1518) a dual JAK2 and FLT3 inhibitor, demonstrated efficiency in phase III trials in myelofibrosis, and is actually tested in graft versus host disease prevention (phase II) [31].
- Gandotinib (LY-2784544) inhibits JAK 2, and is actually tested in myeloproliferative neoplasm.
- Lestaurtinib (CEP-701) inhibiting many kinases, including JAK 2, is tested in myeloproliferative neoplasm and severe/moderate psoriasis.

Other JAK inhibitors are under development, at early stages (Solcitinib (GLPG0778), BMS-911543...).

### 11.2. Pathologies in which JAK inhibitors are currently being tested

JAK inhibitors acting at the crossroads of cellular signaling pathways enable a deep modulation of cellular activity. This simultaneous multi-cytokine action allows to hope for an effectiveness in various autoimmune pathologies, independently of their precise pathophysiology.

Indeed, in addition to currently validated indications (rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, myelofibrosis and

**Table 4**  
JAK inhibitors, synthetic review in 10 points.

1- What is the role of JAK/Stat pathway?	JAK/STAT cascade is the intracellular point of convergence of many extracellular regulatory signals
2- How can a single signaling pathway regulate as many different signals?	The specificity of final effect is the result of JAK and STAT subtypes recombinations
3- What are the commercialized JAK inhibitors and their validated indications in humans today?	Ruxolitinib (Jakavi): myelofibrosis and polycythemia vera. Tofacitinib (Xeljanz): rheumatoid arthritis and psoriatic arthritis (and ulcerative colitis in the USA) Baricitinib: rheumatoid arthritis
4- What is the level of efficiency of JAK inhibitors in inflammatory diseases?	Superior to reference treatment (methotrexate) in rheumatoid arthritis Equivalent to Adalimumab in psoriatic arthritis Superior to placebo in ulcerative colitis
5- What is the delay of efficiency of JAK inhibitors?	Measurable efficacy from 2 weeks Maximum efficacy after 3 months
6- Where is the place of JAK inhibitors in the therapeutic strategy today?	To be considered only if more conventional treatments failed
7- What is the infectious safety profile of JAK inhibitors?	Maybe slightly lower rate of severe infection than others DMARDs. Frequent herpes zoster infections (4% par an)
8- What is the non-infectious safety profile of JAK inhibitors?	Overall reassuring security profile to date Possible cytopenias, changes in lipid balance, weight gain and digestive perforations Long-term cardiovascular and neoplastic effects not known
9- What is the cost of JAK inhibitors compared to other DMARDs?	Close to other DMARDs, with fluctuations depending on the country
10- What future prospects for JAK inhibitors?	Actually > 150 registered clinical trials in > 20 diseases Maybe the mainstay of the management of autoimmune diseases in the coming years.

polycythemia vera), trials are currently underway in Lupus, Crohn's disease, dermatomyositis, uveitis, graft versus host disease, atopic dermatitis, psoriasis, x, vitiligo, Sjogren's disease, giant cell arteritis, systemic sclerosis, juvenile idiopathic arthritis, and ankylosing spondylitis

Thus, to date, there are > 150 registered clinical trials testing JAK inhibitors, in > 20 different diseases. These treatments may be the mainstay of the management of many autoimmune diseases in the coming years (Table 4).

## 12. Conclusion

JAK inhibitors are an emerging treatment for autoimmune diseases. The evaluation of their risk/benefit balance is favorable to date, subject to possible long-term adverse effects. Their therapeutic field, currently restricted to four diseases, is in full swing. These treatments, acting at the heart of intracellular signaling, will undoubtedly be tomorrow at the heart of the management of autoimmune diseases.

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