

Clinical efficacy of new JAK inhibitors under development. Just more of the same?

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Abstract

Janus kinase inhibition is promising in the treatment of RA, with already two oral drugs marketed. New compounds are under investigation that are more selective for Janus kinase 1 or Janus kinase 3. Phase II results for filgotinib, upadacitinib, peficitinib and decernotinib are reviewed showing almost consistently a fast dose-dependent clinical improvement similar to already approved drugs tofacitinib and baricitinib. I will reflect on the most frequently reported dose-dependent adverse events and laboratory changes. Some are similar for all drugs of this class, some are more specific for a certain drug, but all may influence future treatment effectiveness in daily practice. This implies the need for a critical evaluation of phase III trials, and eventually trials specifically powered for conclusions on the safety profile and registries once these drugs become marketed. These innovative drugs also need head-to-head trials *versus* biologics or in-class as well as specific strategy studies to determine their optimal future use.

Key words: Janus kinase inhibitor, RA, filgotinib, upadacitinib, peficitinib, decernotinib

Rheumatology key messages

- Efficacy but also some adverse events of most new Janus kinase inhibitors are dose dependent.
- Target selectivity of new Janus kinase inhibitors is an interplay between selectivity, dosing, drug–drug interaction, pharmacokinetics and pharmacodynamics.
- These new Janus kinase inhibitors might alter treatment paradigms by a rapid dose-dependent action, eventually also in monotherapy.

Introduction

The progress made in treating patients with RA in the past two decades is impressive. It all started in the nineties of the last century with taking the disease more seriously and ended up in the recommendation of early intensive treat-to-target strategies with conventional synthetic DMARDs (csDMARDs) and temporarily glucocorticoids, followed by the use of biologics. In the most recent EULAR recommendations also Janus kinase (JAK) inhibitors were included in the scheme in refractory patients or when response is insufficient [1]. While there is still work needed to support implementation of early intensive treatment strategies to target [2], the use of several classes of biologic drugs has definitely changed the face of rheumatology and more importantly the future of patients with RA

regarding functionality, quality of life and even aspects of participation in daily life. One might even question if there are still patients with a refractory disease in the Western world, although the lack of reliable predictive factors of response is still a major problem for treatment decisions in daily practice. Loss of response (often development of antidrug antibodies to biologics), insufficient stability of response, and side effects such as infections, malignancies and induction of new autoimmunity are still a major concern. Long term drug survival of biologics in the daily practice approach of RA is rather poor [3, 4]. Also the i.v. or s.c. administration of the biologics might be cumbersome for some patients, and certainly also their high costs leads to problems in accessibility for many patients and therefore critical reflection on this issue is warranted [5]. All this—and probably also the issue of patent loss of the first biologics—has stimulated the search for innovative drugs, and more specifically JAK inhibition via oral targeted synthetic (ts) DMARDs has started. The currently marketed drugs, tofacitinib and baricitinib, show fast onset of response and acceptable safety in RA patients and are reviewed elsewhere in this *Rheumatology* supplement [6]. Both drugs show a different JAK inhibition

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profile, tofacitinib having specificity for JAK3 and JAK1 over JAK2 and baricitinib mainly inhibiting JAK1 and JAK2. Although direct comparison is still lacking, fast efficacy has been proven, both with and without MTX, but some safety signals needed additional evaluations. This ultimately led to a rather late approval of tofacitinib in Europe and the questions the FDA has about baricitinib, and is the playing field from where the next generation of JAK inhibitors will come. This paper reviews the current development of new JAK inhibitors, filgotinib (Galapagos/Gilead), upadacitinib (AbbVie), peficitinib (Astellas) and decernotinib (Vertex), summarizing the current peer reviewed literature but also for RA recent abstracts at EULAR and ACR meetings. I will also critically reflect on the future place of these drugs in RA and the research agenda needed and also overview the current development in other inflammatory conditions.

Filgotinib

In vitro assays indicated a selective inhibition of JAK1 and JAK2 over JAK3 and TYK2, and specifically in whole blood assays, a selectivity of ~30-fold for JAK1 over JAK2 was revealed. Details of the *in vitro* assays used for determining JAK selectivity are discussed by Van Rompaey *et al.* in their preclinical work on filgotinib [7]. Oral dosing of GLPG0634 (filgotinib) in a therapeutic setup in a collagen-induced arthritis model in rodents resulted in a significant dose-dependent reduction of the disease progression. Paw swelling and inflammatory cell infiltration, and bone and cartilage degradation were reduced in a similar way compared with etanercept [7].

In two 4-week double blind, placebo controlled phase IIa trials [8], RA patients with an insufficient response to MTX received filgotinib daily, at doses ranging from 30 to 300 mg or placebo on top of MTX, to explore safety, efficacy, pharmacokinetics and pharmacodynamics. Early efficacy was noted from a dose of 75 mg daily upwards, and the pharmacokinetics of filgotinib and its JAK1 selective active metabolite was dose-proportional over the 30–300 mg range. Safety issues were not encountered and specifically anaemia, which might be the consequence of JAK2 inhibition, was not seen. Based on additional pharmacokinetics and pharmacokinetics/pharmacodynamics modelling of filgotinib [9], daily doses from 50, 100 and 200 mg were tested in two large phase IIb placebo-controlled studies in combination with MTX [10] and as monotherapy [11]. In DARWIN 1 (filgotinib added to MTX, 594 patients) the three doses tested were administered once daily and twice daily. Rapid onset of action (depending on the outcome studied, statically significant differences for 100 mg once and twice daily and 200 mg once daily doses compared with placebo were shown between week 1 and 2) and dose-dependent responses were observed for most efficacy end points. Interestingly, improvements in inflammatory parameters and in signs and symptoms were associated with a dose-dependent increase in haemoglobin. Interestingly also dose-dependent decreases in mean absolute platelet counts were noted (the latter not observed in for instance

baricitinib trials). Statistically significant differences for most 100 and 200 mg daily dose groups compared with placebo at week 12 for ACR20 (primary outcome), but also ACR50 and other secondary outcomes, were maintained until week 24. No statistically significant differences between once-daily and twice-daily regimens were seen regarding efficacy. While treatment emergent adverse events (AEs) related to study treatment occurred more frequently in the filgotinib groups compared with placebo, few led to discontinuation of therapy. Infections leading to discontinuation were equally spread over all dose groups including placebo, as were the five herpes zoster infections that all resolved without problems. Dose-dependent decreases in leucocyte counts were seen up to week 4 and appeared to plateau afterwards in most patients. Natural killer (NK) cells did not alter. Up to week 4, as with other JAK inhibitors, dose-dependent increases in mean serum creatinine concentrations were observed in filgotinib-treated patients. Up to week 4, dose-dependent increases in both high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol were observed in all filgotinib groups, which stabilized thereafter. The LDL:HDL ratio decreased over this period. In the DARWIN 2 monotherapy study (283 patients) essentially the same efficacy dynamics were seen. Also here we note an increase in haemoglobin, comparable infection rates and also no tuberculosis or opportunistic infections as in DARWIN 1. Most patients from both phase IIb studies are being followed in a long-term extension, with recently reported data up till week 84 [12] with no new safety issues occurring. Filgotinib 100 and 200 mg once daily is currently being evaluated in a large phase III program.

Upadacitinib

In cellular and biochemical assays upadacitinib demonstrated 74- and 58-fold greater selectivity for JAK1 over JAK2 and JAK3, respectively [13] and in an early phase I study this drug was tested as an immediate release formulation in single doses up to 48 mg in healthy persons and multiple doses up to 24 mg twice daily or placebo in healthy volunteers and RA patients [14]. The favourable pharmacokinetics, safety and tolerability results supported further evaluations of this drug in two phase IIb 12-week dose-ranging trials in RA in patients with an inadequate response to MTX (BALANCE 2) [15] as well as in patients with an inadequate response to anti-TNF treatment (BALANCE 1) [16]. In the first study of 300 patients, rapid (from week 2 onwards) and dose-dependent responses in ACR20, the primary outcome, up to week 12 were noted in all doses tested (3, 6, 12 and 18 mg twice daily and 24 mg once daily) with significant differences for the 6, 12 and 24 mg groups. Mean haemoglobin levels remained stable over time at lower doses, but decreases were observed at higher doses. Upadacitinib was associated with elevations in HDL and LDL across all tested doses at week 12 compared with placebo; the LDL:HDL ratio did not change. The incidence of treatment emergent AEs was higher with upadacitinib than with placebo (45% vs 26%), with a trend

toward higher incidences of AEs at higher drug doses. Two of the three herpes zoster infections occurred at the 24 mg dose. No statistically significant decline in mean lymphocyte or neutrophil counts relative to placebo was observed, but a dose-dependent decrease in NK cells was observed in patients treated with upadacitinib at ≥ 6 mg daily. At week 12, mean creatinine and creatine kinase (CK) levels were higher in all active dose groups compared with placebo, but these were not considered clinically significant by the authors. No patient discontinued the study due to these CK elevations.

Results in the 276 patients that had an inadequate response to anti-TNF treatment and were treated with the same doses of upadacitinib on top of stable MTX therapy showed essentially the same efficacy dynamics as the patients with inadequate response of MTX. Results of haemoglobin, NK cells, HDL and LDL evolution were also comparable to the other trial and no other new safety signals were observed. Of all patients receiving upadacitinib, 7.5% showed elevated creatinine levels at least twice. A single case of grade 3 creatinine abnormality was observed. Many patients from both phase IIb trials went into long-term follow-up and at the ACR 2017 meeting no new signals of safety were reported after a cumulative exposure of 725.1 patient-years [17]. At the same meeting preliminary data of two successful phase III trials in csDMARD refractory patients as well as in biologic refractory patients were reported and this after administration of an extended release formulation of 15 and 30 mg once daily compared with placebo, results that were published as full papers in June 2018 [18, 19].

Peficitinib

According to early animal studies and data in healthy volunteers [20, 21], peficitinib has moderate selectivity for JAK3 and inhibited JAK1 and JAK3 with 50% inhibitory concentrations of 3.9 and 0.7 nM respectively; it has also shown 7.1-fold selectivity for JAK3 relative to JAK2. In the first studies in healthy volunteers, one noted some dose-dependent neutropenia and reduced NK cell count. After a study in psoriasis [22] discussed later, the first study in RA was a 12-week, double-blind study of 281 Japanese patients with active disease not on concomitant DMARD therapy, randomized (about one-quarter had previously failed a biologic) to once-daily placebo or peficitinib 25, 50, 100 and 150 mg [23]. The primary efficacy variable ACR20 response rates at week 12 were 10.7, 23.6, 31.6, 54.5 and 65.5% in the placebo and peficitinib 25, 50, 100 and 150 mg groups, respectively. This dose response was also seen in the JAK inhibitors previously discussed. ACR50 and 70 responses were statistically significantly different also in the 100 mg QD group compared with placebo at week 12. The total incidence of treatment emergent AEs was similar between the placebo and peficitinib-treated groups. Leucocytes decreased specifically in the two highest dose groups as well as thrombocytes. Increases in serum creatinine, CKs and lipids were similar

compared with the previously discussed JAK inhibitors. Anaemia recovered slightly in the two highest dose groups. Four patients on peficitinib developed herpes zoster in the trial period of 12 weeks. In another double blind placebo-controlled multinational phase IIb trial [24], 378 patients with RA were treated with peficitinib 25, 50, 100 or 150 mg once daily for 12 weeks on top of MTX. ACR20 response rates at week 12 (primary outcome) were only significant different *versus* placebo in the 50 mg group; no clear dose-dependent responses were seen. The placebo response was high in this study, probably explaining this negative result. Another phase IIb trial studied essentially the same doses over a 12-week period in combination with limited csDMARDs [25]. Patients in the peficitinib 100 and 150 mg groups achieved a rapid and statistically significant ACR20 response compared with those in the placebo group, reaching statistical significance by week 2. A dose-dependent decrease in leucocytes and thrombocytes was noted, and mild increase in serum creatinine, some patients with increased CKs and lipid changes comparable to the other JAK inhibitors completed the AE picture. However, there were four incidents of hypertriglyceridaemia higher than grade 3. A dose-dependent increase in haemoglobin was not reported. Astellas completed recently two phase III trials in south-east Asia; results are awaited.

Decernotinib

Decernotinib in first evaluations was demonstrated to be a selective and potent inhibitor of JAK3 *in vitro* and modulated proinflammatory responses in models of immune-mediated diseases, such as collagen-induced arthritis and delayed-type hypersensitivity [26]. In the first, 204-patient, placebo-controlled monotherapy study, decernotinib was efficacious in improving clinical signs and symptoms of RA at week 12 at doses of 50–150 mg twice daily [27]. Infections and increases in liver transaminase and lipid levels were noted as potential safety signals especially in the 100 and 150 mg groups. There were more frequent infections on decernotinib, two herpes zoster infections and one case of tuberculosis. Mild increase in creatinine, and HDL and LDL increases as seen in this class of drugs were also noted. In a next phase IIb study [28], at week 12, the ACR20 response rates were 46.5, 66.7, 56.9 and 68.1% in the groups receiving decernotinib on top of MTX at doses of 100, 150 and 200 mg daily, and 100 mg twice daily, respectively, compared with 18.3% in the placebo group (all statistically significant compared with placebo), responses that were retained till week 24. But the safety profile was also comparable to the previous monotherapy study with negative signals for sometimes severe infections and with patients with an increase in transaminases. Haemoglobin essentially did not change over time in the study. A separate small study confirmed the fast responses of this JAK inhibitor on MRI findings [29]. Vertex discontinued to develop this drug in RA.

Relative potential of the new jakinibs and the research agenda needed

The JAK inhibitors discussed above, as well as the already marketed compounds in this class of tsDMARDs, in general show a very fast and profound dose-dependent efficacy. Data of the next generation JAK inhibitors are currently available with up to about 2 years' follow-up at this moment. Only one study with peficitinib failed, mainly due to a very high placebo response [24]. The decernotinib results were also very positive regarding efficacy in all doses tested, but the higher doses were clearly associated with a higher rate of infections and increase in liver enzymes, besides the other AEs that were also observed with the other compounds. Decernotinib showed no clear dose-response curves for efficacy, and specific trial issues such as an unbalanced randomization scheme and an early escape arm might have been partly responsible [28]. Also with filgotinib and upadacitinib there are some dose-dependent safety signals related to, for instance, leucocyte count, platelets, creatinine and lipids, while their clinical relevance is not yet fully clear although currently judged reassuring.

Even monotherapy of some of these new JAK inhibitors might work, although definite conclusions about this are not yet feasible. With regard to this, there will certainly also need to be a critical appraisal of the price of these drugs, specifically in early disease, if they are to be considered for use in that indication in monotherapy. At least the discomfort of intake (nausea, vomiting, and so on) of these new drugs seems minimal and at least better than MTX according to the data reported and also according to the trial experience of this author so far. A relatively high price limiting the use of these innovative drugs would be a missed opportunity.

All this shows the great opportunities and at the same time challenges with this class of drugs, which become even more relevant with the data of the new compounds discussed above in comparison with tofacitinib and baricitinib. A complex interplay between JAK specificity, dose, pharmacokinetics and pharmacodynamics and also drug-drug interactions is probably determining the target specificity of these drugs and their efficacy/safety balance. One has to realize that the different biologics originally presented as targeted therapies had many aspecific and sometimes unexpected effects: so how targeted are these tsDMARDs really? Target specificity of JAK inhibitors depends on both the assay used and the concentration/dose studied *in vitro* or *in vivo* [30]. As with any small-molecule drug, target specificity is not absolute and will depend on the dose ultimately delivered to the respective tissues and on the characteristics of eventual metabolites. In the first place with oral compounds drug-drug interactions should be evaluated. *In vivo* as well as *in vitro* research on drug-metabolizing enzymes and on key drug transporters supports co-administration of filgotinib with commonly used RA drugs such as MTX to patients without the need for dose adjustments [31]. *In vitro*, filgotinib and its active metabolite at clinically relevant

concentrations did not interact with cytochrome P450 enzymes and uridine 5'-diphospho-glucuronosyltransferases, and did not inhibit key drug transporters. In the clinic, a lack of relevant pharmacokinetic drug interactions with substrates of CYP3A4, as well as with organic anion transporters involved in MTX elimination, were found. Upadacitinib was well tolerated when co-administered with ketoconazole (a strong CYP3A inhibitor), rifampin or after a high-fat meal [32]. With regard to this topic, one has to note that the data for peficitinib is mainly from an Asian population and cannot automatically be transferred to other populations.

Both JAK1 and JAK3 inhibition apparently are effective and one needs to explore the mechanistic pathways leading to efficacy. Just labelling for a certain specificity is not appropriate when one looks to the differences in *ex vivo* results and *in vitro* cellular pharmacology from baricitinib to upadacitinib, filgotinib and tofacitinib [33]. JAK inhibitors display different *in vitro* pharmacological profiles which, coupled to their *in vivo* pharmacokinetics, suggests that they modulate distinct cytokine pathways to differing degrees and durations over 24 h. Baricitinib and filgotinib inhibited JAK1/3 signalling to a lesser extent than upadacitinib and tofacitinib.

The speed of response is certainly a plus for the complete class of JAK inhibitors and could result in less use of glucocorticoid bridging. The dose-dependent responses make treat-to-target approaches with these drugs possible, but success will be determined by eventual increased AEs with higher dose. Probably tapering of dose will be a workable strategy with these drugs but needs formal testing.

Differences between the drugs are certainly there and the differential clinical relevance needs specific study. Platelet increase is not seen in filgotinib- and upadacitinib- as seen in some baricitinib-treated patients. If we need to conclude formally about eventual thrombosis risk, properly powered studies seem inevitable. That NK cells decrease dose dependently with upadacitinib while staying unaltered in filgotinib is a point of attention that needs critical follow-up.

A dose-dependent increase of haemoglobin with filgotinib is not seen in the other compounds. Restoring anaemia related to inflammation is what is preferred in RA, as anaemia is one of the independent factors associated with decreased physical function, as shown in the past with infliximab [34]. CK increase, mild creatinine increase and lipid changes are seen as class effects, although minor differences might exist between the compounds discussed and clinical relevance needs further attention in future trial and registry data. To date CK increases do not seem to be associated with clinically overt myopathy, and an eventual association of the changing lipid profile with hard cardiovascular outcomes would only become clear with a longer and specific follow-up. The importance of creatinine increase is also seen in the new generation of JAK inhibitors (i.e. a mean increase of 11.5% from baseline value with up till now no clear influence of the decreased glomerular filtration on the occurrence of side

TABLE 1 Overview of efficacy in phase II and III RA studies (full papers)

	Phase and reference	Type of patients	n	Combi or mono R/	ACR20 response ^a	
Filgotinib	Phase IIa [8]	MTX refr.	36+91	+MTX		
	Phase IIb [10]	MTX refr.	594	+MTX	+19/+18%at 6 m 100 mg/d ^b	+31/+38%at 6 m 200 mg/d ^b
	Phase IIb [11]	MTX refr.	283	Mono R/	+37% at 3 m 100 mg QD	+44% at 3 m 200 mg QD
Upadacitinib	Phase IIb [15]	MTX refr.	300	+MTX	+18% at 3 m 18 mg BID (NS)	+30% at 3 m 24 mg QD
	Phase IIb [16]	TNF refr.	276	+MTX	+38% at 3 m 12 mg BID	+36% at 3 m 18 mg BID
	Phase III [18]	DMARD refr.	661	+StablecsDMARD	+28% at 3 m 15 mg QD	+30% at 3 m 30 mg QD
	Phase III [19]	Biologic refr.	499	+Stable csDMARD	+37% at 3 m 15 mg QD	+28% at 3 m 30 mg QD
Peficitinib	Phase IIb [23]	Prior MTX or anti-TNF	281	Mono R/	+43.8% at 3 m 100 mg QD	+54.8% at 3 m 150 mg QD
	Phase IIb [24]	MTX refr.	378	+MTX	+2% at 3 m 100 mg QD (NS)	+13.3% at 3 m 150 mg QD (NS)
	Phase IIb [25]	Prior DMARD or biologic	289	+LimitedDMARD	+18.9% at 3 m 100 mg QD	+26.9% at 3 m 150 mg QD
Decernotinib	Phase IIb [27]	Prior DMARD or biologic	204	Mono R/	+35.7% at 3 m 100 mg BID	+36.6% at 3 m 150 mg BID
	Phase IIb [28]	MTX refr.	358	+MTX	+48.4% at 3 m 150 mg QD	+38.6/+49.8% at 3 m 200 mg/d ^c
	Phase IIb [29]	DMARD refr.	43	+DMARD		

^aACR20 response = ACR20 response on top of placebo response. ^bIn the study with Ref. [10] all doses were tested in one and two gifts ^cIn the study with Ref. [28] the 200 mg dose was tested in one and two gifts. PubMed accessed 1 July 2018. BID: twice daily; d: day; DQ: once daily; m: month; n: number of patients in study; NS: non-significant; refr.: refractory.

effects of MTX). This issue today is more extensively studied in tofacitinib [35] without apparently major influence on pharmacokinetics of other drugs. The position of these new drugs will also depend of the strategy wherein they are going to be used. Head-to-head trials will become mandatory and will hopefully be organized in an earlier stage than we witnessed in the biologic era—within this drug class probably not so much for efficacy comparison but for safety issues. Nevertheless, more daily practice pragmatic trials comparing JAK inhibitors with biologics would also be interesting.

At the same time this new class of drugs with some intraclass differences as well as differences with the different biologics are widening the scientific scope on RA as well as on other inflammatory diseases, which might lead to a better understanding of these diseases as was recently extensively reviewed by Baker and Isaacs [36]. The new JAK inhibitors have already been explored or are currently recruiting in several inflammatory and autoimmune diseases. Peficitinib, as noted earlier, showed some efficacy in psoriasis in an early small phase IIa trial [22]. Filgotinib has been shown active in Crohn's disease [37]. One hundred and seventy-four patients were enrolled, and in the intention-to-treat population 47% of patients treated with filgotinib 200mg achieved clinical remission at week 10 *versus* 23% of patients treated

with placebo, which was statically significant. Trials with filgotinib in ulcerative colitis (phase III), psoriatic arthritis, ankylosing spondylitis, uveitis, cutaneous lupus erythematosus, lupus nephritis and Sjögren's syndrome (all phase II) are underway. Upadacitinib is being tested also in atopic dermatitis, giant cell arteritis, ankylosing spondylitis (phase II) and psoriatic arthritis, Crohn's disease and ulcerative colitis (phase IIb/III) [38]. In a recently published peficitinib trial in ulcerative colitis, the primary outcome of a dose-response at week 8 assessed by a Mayo score change was not met [39].

To conclude

From the new generation JAK inhibitors (see Table 1 for a summary of currently published trials in RA patients), filgotinib and upadacitinib seem to be very promising for treating RA. Fast and profound efficacy is demonstrated as with tofacitinib and baricitinib and long-term efficacy is looked for in currently running long-term follow-up of phase II trials. Both drugs are currently being tested in an extensive phase III program as well in MTX (as biologic)-insufficient responders but also in DMARD-naïve patients. These phase III trials have a classical design, and an active biologic comparator is also included. Peficitinib phase III is running in south-east Asia only.

Despite both upadacitinib and filgotinib being proposed as JAK1 selective, some differences in laboratory parameters are noted, such as haemoglobin levels and evolution of NK cells. The clinical relevance of these and other changes in lab parameters, such as serum creatinine, CK, leucocytes and lipids, should be carefully regarded in future registries when the drugs become marketed, and why not in specifically powered trials as was also done for the first biologic infliximab [40]. The ultimate proof of the pudding—the *in vivo* importance of JAK selectivity for side effects—will be in the eating.

Fast and dose-dependent responses as well as efficacy as monotherapy are all appealing for proper future strategy trials, but also AE findings seem dose dependent. Such properly powered trials should study optimal effectiveness [41] in different disease phases and also in comparison with biologics. Specifically in early disease, one needs to focus on optimal combination therapy and tapering possibilities, but of course drug pricing and cost-effective treatment is key in this phase. One may also hope that adequately designed head-to-head trials will be performed earlier than was the case in the biologic era. The responsibility is with the pharmaceutical companies, but also health authorities, regulatory boards and the rheumatological scientific community have a major task here.

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