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Early phase studies of JAK1 selective inhibitors in rheumatoid arthritis

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Abstract

The first approved Janus kinase (JAK) inhibitors for treatment of RA targeted more than one JAK molecule. Although this brings an advantage of simultaneous blocking of more cytokines involved in RA, it may also carry an increased risk of toxicity. Subsequently, more selective JAK inhibitors were developed with the aim of improving the safety–efficacy profile and to further increase drug maintenance. With this proposal, early phase trials of selective JAK1 inhibitors, namely upadacitinib, filgotinib and itacitinib, were initiated in recent years to identify the efficacy and adverse effects of these agents and to define their potential role in treatment of inflammatory and autoimmune diseases. Early phase (Phase I–II) studies of upadacitinib and filgotinib provided evidence for efficacy and safety of the selective JAK1 inhibitors in refractory populations of RA patients and allowed informed selection of the appropriate dose by balancing the optimal benefit–risk profile for further evaluation in the later successfully performed Phase III trials. Although itacitinib also demonstrated a good efficacy and safety in a Phase II trial in RA patients, it is mainly in development for haematologic and oncologic conditions.

Key words: rheumatoid arthritis, treatment, Janus kinase inhibitors, upadacitinib, filgotinib, itacitinib

Rheumatology key messages

- The first JAK inhibitors approved for treatment of RA target more than one JAK molecule and therefore, represent 'pan-JAK' inhibitors. Subsequently, more selective JAK inhibitors were developed with the aim of improving the safety–efficacy profile and to further increase drug maintenance.
- The results of early phase studies provided evidence for efficacy and safety of the selective JAK1 inhibitors in refractory populations of RA patients both as add-on to MTX therapy and as monotherapy.

SUPPLEMENT

Introduction

The first Janus kinase (JAK) inhibitors for treatment of RA target more than one JAK molecule and therefore, represent 'pan-JAK' inhibitors. While this provides simultaneous control of many pathways causing inflammation in inflammatory and autoimmune diseases, it may also carry an increased risk of toxicity. The JAK family comprises JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2) [1]. Theoretically, targeting different components of the JAK family can result in different potential adverse effects (AEs) [2]. JAK3 is specifically expressed on epithelial and haematopoietic cells and is critical for the signalling pathway for interleukins (ILs), which are important for lymphocyte development and survival. Its loss of function results in severe combined immunodeficiency disease [3, 4]. JAK2 inhibition can interfere with the erythropoietin signal and the functions of granulocyte-macrophage colony-stimulating factor (GM-CSF) [5]. Blocking TYK2 also leads to primary immunodeficiency with a hyper-immunoglobulin E syndrome [6, 7]. Accordingly, selective JAK1 inhibition may bring the advantage of minimizing the potential toxicities of pan-JAK blockade. Currently, two JAK inhibitors, tofacitinib and baricitinib, have been approved for clinical use in rheumatology practice. Tofacitinib was initially developed as a JAK3 selective inhibitor, but later studies found the compound to have additional inhibitory action against JAK1 and to a lesser extent against JAK2 [8–10]. In contrast, baricitinib has inhibitory action mainly on JAK1 and JAK2 and little effect upon JAK3 [11]. Subsequently, more selective JAK inhibitors have been developed with the aim of improving the safety–efficacy profile and to further increase drug

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adherence. With this proposal, early phase trials of selective JAK1 inhibitors, namely with upadacitinib, filgotinib and itacitinib, were initiated in recent years to identify the efficacy and adverse effects of these agents and to define their potential role in the treatment of inflammatory and autoimmune diseases. To define selectivity, the concentrations of the individual drugs that produce 50% inhibition (IC_{50}) are generally used. As an example of pan-JAK inhibition, tofacitinib requires 3.2, 4.1, 1.6 nanomolar (nM) IC_{50} for JAK1, JAK2, and JAK3, respectively. Of note, the concentrations for inhibition are very close to each other. However, the IC_{50} concentrations of filgotinib for inhibition of JAK1, JAK2, and JAK3 are 10, 28, 810 nM, respectively, which shows the selectivity for JAK1 compared with JAK2 and JAK3. The respective values are 8, 600, 2300 for upadacitinib and 2, 63, >2000 for itacitinib [12]. This review recapitulates the results from the early development programme of these compounds, since sometimes you can see 'a winner from the start'.

Upadacitinib

The first-in-human evaluation of upadacitinib (ABT-494) was carried out with 56 healthy subjects in a single-site, randomized, double-blind, placebo-controlled study design [13]. Single doses of upadacitinib immediate-release capsules (1, 3, 6, 12, 24, 36 and 48 mg) or placebo were administered in a 3 : 1 ratio, with eight subjects in each dose level (Study 1). Study 2, also with a randomized, double-blind, placebo-controlled study design, consisted of two parts; in Part 1, multiple twice-daily doses of ABT-494 immediate-release capsules were administered to 44 healthy volunteers, and in Part 2, to patients with RA on stable doses of MTX (NCT01741493). The goal of Study 2 was to determine the pharmacokinetics, safety and tolerability of multiple oral doses of upadacitinib immediate-release capsules. In Part 1, four escalating dose regimens consisting of 3, 6, 12 and 24 mg upadacitinib or matching placebo were administered twice daily for 13 consecutive days and once in the morning on day 14. In Part 2, overall 14 patients with RA received 6, 12 and 24 mg upadacitinib or placebo for 26 consecutive days (study days 3 through 28) and a single morning dose of study drug on study day 29, following randomization to one of four parallel twice-daily regimens.

In both studies, upadacitinib was well tolerated even at the highest doses of study drug. Adverse events in study drug and placebo arms were comparable and mild to moderate in nature. No clinically significant laboratory changes were observed in blood cell counts nor in renal and hepatobiliary function tests. The demonstrated pharmacokinetic profile of upadacitinib suggested twice-daily dosing in immediate-release formulation. In patients with RA receiving MTX, no pharmacokinetic interaction was observed between MTX and upadacitinib. Here, upadacitinib did not lead to accumulation after repeated administration.

In a Phase IIb study evaluating the efficacy and safety of upadacitinib in RA patients with an inadequate response to MTX (MTX-IR) until week 12, upadacitinib resulted in higher ACR20 responses (62%, 68%, 80%, 64%, and 76% for the 3, 6, 12, 18 mg twice-daily, and 24 mg once-daily doses, respectively) compared with placebo (46%) [14]. The response rates were statistically significant for the 6, 12 and 24 mg doses. The dose–response relationship was significant over all upadacitinib doses ($P < 0.001$). With an exception for the 12 mg dose for the ACR70 response, significantly higher proportions of patients achieved ACR50 and ACR70 in all upadacitinib arms compared with placebo. Disease Activity Score in 28 joints using the CRP level (DAS28-CRP) improvements were also significantly higher compared with placebo. Improvements could be rapidly seen by significant changes in ACR20 and DAS28-CRP for all doses compared with placebo already at week 2.

Most reported AEs were mild with infections being the most frequent manifestations. Three herpes zoster virus (HZV) infections (all involving single dermatome and considered non-serious by the investigators) were reported in patients receiving upadacitinib (one patient at 3 mg and two at 24 mg). One serious infection (community-acquired pneumonia) occurred under upadacitinib at 12 mg and led to early discontinuation from the study. The low-density lipoprotein (LDL) cholesterol to high-density lipoprotein (HDL) cholesterol ratios remained consistent through week 12, although dose-dependent increases in HDL and LDL cholesterol were observed. Mean haemoglobin values remained stable or increased at lower doses (3 mg and 6 mg), but decreased at higher doses (12 mg, 18 mg and 24 mg). One patient discontinued the study due to decreased haemoglobin in the 18 mg group. Although two patients had grade 4 reductions in lymphocytes (one in the 3 mg group and one in the 18 mg group), there were no statistically significant decreases in mean lymphocyte or neutrophil counts compared with placebo for any upadacitinib dose groups by week 12.

In another Phase IIb study evaluating the efficacy and safety of upadacitinib in RA patients with an inadequate response to anti–TNF therapy over 12 weeks, upadacitinib showed higher ACR20 responses compared with placebo (53–71% vs 34%) with a dose–response relationship in all upadacitinib doses (3, 6, 12 or 18 mg twice daily) [15]. Also, in patients receiving upadacitinib doses of ≥6 mg, ACR50 and ACR70 response rates were significantly higher (36–42% and 22–26%, respectively). DAS28-CRP improvements were also significantly higher for all doses of upadacitinib than for placebo. The onset of action was rapid and significant differences could be observed at the first post-baseline assessment (week 2) for both ACR20 response rate (for 12 and 18 mg) and DAS28-CRP values (for 6–18 mg).

Most reported AEs were mild to moderate in severity and the most frequent AEs were headache, nausea, upper respiratory tract infection, and urinary tract infection. Seven serious adverse effects (SAEs) were reported in five

patients treated with upadacitinib (one with pancreatitis and one with pulmonary embolism at 3 mg; one with pulmonary embolism and deep vein thrombosis and one with transient ischaemic attack and benign prostate hyperplasia at 6 mg; and one with acute respiratory failure at 18 mg). However, the incidences of SAEs and severe AEs were low and did not demonstrate an apparent dose–response relationship. Infection rates were higher for those treated with 12 mg and 18 mg upadacitinib, but no infection was serious. HZV infections occurred in two patients in the placebo group (4%) and in three patients receiving upadacitinib (2%) (one patient each in the 3, 12 and 18 mg groups; all involving a single dermatome). As in the previously described Phase II study, LDL cholesterol to HDL cholesterol ratios remained unchanged, although dose-dependent increases in HDL and LDL cholesterol were observed. Although decreases in mean haemoglobin levels were observed in a dose-dependent manner with upadacitinib, mean haemoglobin levels remained within the normal range in all dose groups during the study. One patient had to discontinue the study drug due to leukopenia. Two patients receiving 18 mg upadacitinib had a grade 4 lymphocyte reduction, one coinciding with a vaginal yeast infection and the other with HZV infection. Two patients in low-dose groups (3 mg and 6 mg) had a grade 4 lymphocyte reduction without any infection reported during the time of lymphopenia. Grade 4 neutrophil reduction occurred in a patient in the 12 mg upadacitinib group, also without any infection reported during neutropenia. No deaths were reported among those receiving upadacitinib.

In summary, the results of these Phase II studies provided evidence for efficacy and safety of the selective JAK1 inhibitor, upadacitinib, in refractory populations of RA patients with inadequate response or intolerance to MTX or TNF-inhibitors. Furthermore, they allowed informed selection of the appropriate dose by balancing the optimal benefit–risk profile for further evaluation in the later successfully performed Phase III trials. Recently, upadacitinib has been approved at a dosage of 15 mg per day for treatment of RA by the FDA and EMA.

Filgotinib

The pharmacokinetics and pharmacokinetic/pharmacodynamic modelling of filgotinib (GLPG0634) was evaluated in healthy male volunteers in order to support dose selection for Phase IIb [16]. Two Phase I clinical trials (NCT01179581 and NCT01419990) were conducted. In the first study, filgotinib was administered in single doses from 10 mg up to repeated daily doses of 200 mg. In the second study, doses of 300 and 450 mg once daily were evaluated for 10 days. The results showed high exposure to an active metabolite of filgotinib, which contributes to its overall pharmacodynamic effects. The major metabolite has JAK1 selectivity, with higher exposure, but lower potency than filgotinib. After oral administration of filgotinib, dose-dependent pharmacodynamic activity of both filgotinib and its metabolite was demonstrated. Average elimination half-life was 6 h. Although the active metabolite has a lower target selectivity for JAK1 compared with filgotinib, it has an elimination half-life of 23 h, which allows the administration in a single daily dose [17, 18]. Early clinical data suggested that the pharmacokinetics of filgotinib are dose proportional up to 200 mg, and maximum pharmacodynamic response is reached at a daily dose of 200 mg filgotinib.

Two Phase IIa trials (NCT01384422 and NCT01668641) were conducted in a double-blind, placebo-controlled 4-week exploratory design, evaluating the safety, efficacy, pharmacokinetics and pharmacodynamics of filgotinib in 127 MTX-IR RA patients on a stable regimen of MTX [17]. The primary efficacy end point was the ACR20 response at week 4. Study 1 enrolled 36 patients and evaluated the daily doses of 200 mg of filgotinib (GLPG0634, GS-6034), given at 200 mg once daily or 100 mg twice daily, vs placebo, in a single centre. Study 2 was a multi-centre study and enrolled 91 patients receiving filgotinib once daily at 30 mg, 75 mg, 150 mg, or 300 mg vs placebo. At the end of 4 weeks, in study 1, the ACR20 response rate was $>$83% in filgotinib-treated patients with statistical significance. However, in study 2, the differences from the placebo group were not statistically significant in all filgotinib treatment groups, although there was a high percentage of ACR20 response rate (65%) in the 300 mg group. Of note, in both studies and all treatment arms, ACR20 response rates tended to increase progressively from week 1 to week 4, with the exception of the 300 mg group in which the peak response was already reached at week 2 and maintained at week 4. Perhaps the short-term trial period was not enough to show the exact response rates especially for the doses lower than 300 mg. Filgotinib and its major metabolite demonstrated dose-proportional pharmacokinetics over the 30–300 mg range. Filgotinib was generally well tolerated with all reported treatment-emergent adverse effects (TEAEs) being mild or moderate in nature. All TEAEs were transient with no permanent discontinuations reported due to TEAEs. During this 4-week trial, there were no infections, no worsening of anaemia (instead a modest Hb increase), and no effect on liver transaminases or LDL cholesterol. Nausea was the most reported event (in 7% of patients). A limited decrease was observed in neutrophils ($\sim$14–24% decrease from baseline for doses of $\geq$75 mg) without causing neutropenia. The results of the early 4-week trial led to the Phase IIb step with a longer efficacy evaluation period.

In the first Phase IIb study over 24 weeks, 594 moderately to severely active RA patients with an inadequate response to MTX were randomized to receive placebo or 50, 100 or 200 mg of filgotinib with a primary end point of ACR20 response rates at week 12 [19]. Filgotinib was administered once daily or twice daily in addition to a stable dose of MTX. After 12 weeks, patients on placebo without a 20% improvement in swollen and tender joint counts based on 66 joints were reassigned to receive filgotinib 100 mg once daily or 50 mg twice daily; patients on filgotinib 50 mg once daily who had not achieved the

same target were reassigned to receive filgotinib 100 mg once daily, and patients on filgotinib 25 mg twice daily received filgotinib 50 mg twice daily, continuing treatment until week 24. The primary end point was evaluated at week 12, with significantly higher ACR20 response rates for 100 mg once-daily, 200 mg once-daily, and 100 mg twice-daily doses compared with placebo (64%, 69%, 79%, and 44%, respectively). At week 12, response rates were also in favour of filgotinib 100 mg and 200 mg groups regarding other end points including ACR50, ACR-N, DAS28-CRP, Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI) and Health Assessment Questionnaire-Disability Index (HAQ-DI), which was maintained through week 24. Onset of action was rapid, and responses were dose-dependent for most of the efficacy end points. Once-daily and twice-daily regimens had similar efficacy outcomes. Filgotinib was generally well tolerated at all doses and TEAEs were similar in all filgotinib dose groups and placebo. Serious AEs were infrequent, and few AEs led to discontinuation. Serious treatment-emergent infections occurred in one patient receiving placebo and five patients receiving filgotinib. The only death in the study was in the filgotinib 100 mg twice-daily group due to pneumonia and septic shock. Five HZV infections resolved without complications (one in placebo, four in filgotinib groups). There were no reported cases of tuberculosis, opportunistic infections, lymphoma or cancer throughout the study. Dose-dependent increases were observed in mean haemoglobin concentrations in all filgotinib groups possibly related to anti-inflammatory effects of filgotinib without interfering with erythropoietin signalling through JAK2 inhibition. There were no reductions in absolute lymphocyte counts. Some decreases in mean neutrophil counts did not have any clinical consequence. Filgotinib co-administered with MTX had only a minimal effect on liver enzymes. The LDL : HDL ratio decreased although dose-dependent increases were seen in both.

A subsequent Phase IIb study aimed to evaluate efficacy and safety of different doses of filgotinib, as monotherapy in 283 MTX-IR RA patients [20]. In this 24-week trial, after a $\geq$4-week washout from MTX, moderately to severely active RA patients received 50, 100 or 200 mg filgotinib once daily, or placebo with a primary end point of ACR20 response rates at week 12. After 12 weeks, all patients in the placebo group, and patients in the filgotinib 50 mg group without at least 20% improvement in swollen and tender joint counts based on 66 joints were reassigned to receive filgotinib 100 mg, and continued on this dose until week 24. Significantly more patients in the filgotinib groups achieved ACR20 responses vs placebo at week 12 (67, 66, 73, and 29%, respectively, for 50, 100, 200 mg doses, and placebo; $P < 0.001$). Also other key end points, ACR50, ACR70, ACR-N, DAS28-CRP, CDAI, SDAI, HAQ-DI and DAS28 (CRP) EULAR 'good' response rates, showed significant differences from baseline in filgotinib 100 and 200 mg groups vs placebo at week 12, which were maintained or improved through week 24. Onset of action was rapid for most efficacy end points, changes in ACR20 in filgotinib 200 mg group and DAS28-CRP and CDAI in all filgotinib dose groups were evident even at week 1. Also, in the filgotinib 200 mg group, ACR50 responses significantly differed from placebo already at week 2, and for ACR70 responses at week 4. Dose-dependent increases were observed in mean haemoglobin concentrations. TEAEs were reported at similar frequencies in the placebo and filgotinib groups from baseline to week 12. Serious TEAEs were observed in eight patients in the filgotinib groups and one in the placebo group. Four patients under filgotinib developed a serious infection. Discontinuations due to TEAEs were rare in all groups with a greater proportion in the placebo group.

Throughout the study, one case of HZV was reported in a patient receiving 50 mg filgotinib, which resolved after 10 days. There were no reported cases of tuberculosis, opportunistic infections, lymphoma, or cancer. As in other filgotinib studies, reductions in neutrophil counts were observed; however, did not cause a clinical consequence or discontinuation. Also, as in line with previous studies, lymphocyte and natural killer cell counts did not decrease. Increases in HDL/LDL ratio was in favour of HDL, leading to a lower LDL : HDL ratio. As in previous studies, slight increases in creatinine were observed with filgotinib, although ALT and AST levels remained stable during the study.

Patient-reported outcomes (PROs) were evaluated in patients with RA treated with filgotinib, as MTX add-on therapy or as monotherapy, during these two Phase IIb, 24-week, randomized, placebo-controlled studies [21]. With the exception of the 36-item Short Form health survey (SF-36) mental component in the add-on study, all PROs significantly improved compared with placebo at week 12, and some improvements could even be observed in first assessment point (week 1 or 4). Filgotinib improved HAQ-DI by 0.58–0.84 points, the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) scale by 6.9–11.4 points, Patient Global by 25.2–35.6 mm, and Pain by 24.2–37.9 mm and these were sustained throughout the 24-week period. More patients in the filgotinib 200 mg group reported minimal clinically important differences and normative values compared with placebo. Improvements in PROs were demonstrated also in patients reassigned to filgotinib 100 mg at week 12.

In summary, the results of these Phase II studies also demonstrated efficacy and safety for filgotinib in MTX-IR RA patients in monotherapy as well as in MTX add-on therapy and informed about the optimal dose selection for further evaluation in Phase III trials. Recently, EMA has adopted a positive opinion, recommending the granting of a marketing authorization for filgotinib intended for the treatment of RA (https://www.ema.europa.eu/en/medicines/human/summaries-opinion/jyseleca). For final consideration by the FDA, results of the MANTA and MANTA-RAy studies are awaited to provide requested data on spermatogenesis.

TABLE 1 Phase 2 studies of most advanced selective JAK1 inhibitors for treatment of RA [14–15, 17, 19–20, 24]

Drug	Key objective(s)	Patients enrolled	Study design
Upadacitinib	Efficacy (ACR20 at week 12), safety, dose ranging, add-on MTX	Patients with active RA despite MTX therapy	Phase IIb, 12-week, randomized, double-blind, parallel-group, placebo-controlled, multi-centre study
Upadacitinib	Efficacy (ACR20 at week 12), safety, dose ranging, add-on MTX	Active RA patients with an inadequate response or intolerance to at least 1 anti-TNF agent.	Phase IIb, 12-week, randomized, double-blind, parallel-group, placebo-controlled, multi-centre study
Filgotinib	Proof-of-concept, preliminary safety, efficacy (ACR20 at week 4), PK and PD, add-on MTX	Patients with active RA despite MTX therapy	Phase IIa, 4-week exploratory, randomized, double-blind, parallel-group, placebo-controlled study
Filgotinib	Dose ranging, preliminary safety, efficacy (ACR20 at week 4), PK and PD, add-on MTX	Patients with active RA despite MTX therapy	Phase IIa, 4-week exploratory, randomized, double-blind, parallel-group, placebo-controlled, multi-centre study
Filgotinib	Dose finding, efficacy (ACR20 at week 12), safety, add-on MTX	Patients with active RA despite MTX therapy	Phase IIb, 24-week, randomized, double-blind, parallel-group, placebo-controlled, multi-centre study
Filgotinib	Dose finding, efficacy (ACR20 at week 12), safety, monotherapy	Patients with active RA despite MTX therapy	Phase IIb, 24-week, randomized, double-blind, parallel-group, placebo-controlled, multi-centre study
Itacitinib	Dose finding, efficacy, safety	Patients with active RA	Phase II, 12-week, randomized, parallel-group, placebo-controlled, multi-centre study

PD: pharmacodynamics; PK: pharmacokinetics.

Itacitinib

Itacitinib (INCB039110) is another JAK1-selective inhibitor with a >20-fold selectivity over JAK2 and >100-fold selectivity over JAK3 and TYK2 and non-JAKs [22, 23]. Safety and efficacy of itacitinib was evaluated in patients with active RA in a two-part, multi-centre Phase II study [24]. Part 1 was performed over an initial 28-day treatment period in an independent group of active RA patients to identify the dosing ranges to be evaluated in Part 2. Part 2 was a 12-week trial, where active RA patients (≥6 tender/≥4 swollen joints based on 28 joint count) with a CRP level of ≥6 mg/l were randomized to receive placebo or itacitinib at daily oral doses of 100 mg twice a day, 200 mg twice a day or 300 and 600 mg once daily. RA patients were allowed to stay on stable doses of MTX, hydroxychloroquine, corticosteroids (<10 mg/day) and/or sulfasalazine. Other disease-modifying anti-rheumatic drugs (DMARDs) or biologics were not permitted as co-medication. Approximately 90% of RA patients were on background DMARDs and ~33% had been previously treated with biologics. Forty patients completed the day 84 visit and were included in the analysis. Onset of action was rapid, and responses could be observed even at the first assessment (14 days). Similar ACR responses were achieved with itacitinib regardless of background therapy or previous biologic experience. Better clinical improvements were observed with a 600 mg once-daily dose compared with other arms. There were no reported cases of serious or opportunistic infections and no grade 3 or 4 AEs. No dose relationship was observed for TEAEs. A dose-dependent increase was observed in LDL levels without any change in LDL : HDL ratio. Currently, itacitinib is mainly in development for haematologic and oncologic conditions.

Conclusion

In summary, the early studies using upadacitinib and filgotinib were important in characterizing the efficacy and safety profile of these selective JAK1 inhibitors and paved the way for the subsequent Phase III development programme, also regarding dose finding. In the meantime, upadacitinib has been approved by the EMA and the FDA and by many other regulatory authorities. Recently, filgotinib was also approved by the EMA and will be available in European countries. However, further extensive clinical and experimental research is required to fully understand the similarities as well as the differences of the available compounds in the clinical setting. This includes their potentially different features such as of metabolism and excretion, of immunosuppression with respect to the risk of opportunistic infections as well as herpes zoster, and most importantly, of disputable contribution to the overall increased thrombophilic risk in rheumatic diseases. In this context, the new, more selective JAK inhibitors could be advantageous and represent important additions to our therapeutic armamentarium in RA where in many patients additional therapeutic options are necessary.

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InSight: The related InSight paper for this supplement can be accessed at https://academic.oup.com/rheumatology/article-lookup/doi/10.1093/rheumatology/keab341.

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