New molecules for the treatment of rheumatoid arthritis

Inhibition of spleen tyrosine kinase in the treatment of rheumatoid arthritis

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Abstract

The pathogenesis of RA is a complex and ever-changing landscape but amid the chaos of the disease process we have found effective treatment regimes. However, our current therapeutics, although targeting various components of both the innate and adaptive immune response, do not result in disease remission. Protein kinase inhibitors are attractive targets due to their ability to influence downstream signalling and their oral bioavailability. Fostamatinib (R788) inhibits spleen tyrosine kinase (Syk) and has been in clinical trials involving both MTX inadequate responders (MTX-IRs) and biologic inadequate responders. Studies on the MTX-IR population revealed ACR20 responses of 67–72% at higher doses (150 mg bd and 100 mg bd), ACR50 responses of 43–57% and ACR70 responses of 28–40%. The trial in the biologic non-responder population showed no efficacy, however, post hoc analyses of the data suggested that a further trial in this population is warranted. The most common adverse events included gastrointestinal effects, hypertension, neutropenia and transaminitis. Many adverse effects were dose responsive and hypertension was amenable to treatment. Upper respiratory tract infections were more likely at higher doses, but no serious infections with tuberculosis, fungi or opportunistic infections were reported. The oral availability of these agents makes them attractive treatment options for our patients, although the literature from the oncology field suggests that patients will only choose the oral route if efficacy is equivalent. Long-term follow-up studies are ongoing and will be critical for rare side effects. The role of these agents in our current arsenal is unclear and economic analyses are awaited.

Key words: rheumatoid arthritis, fostamatinib, biologic non-responder, spleen tyrosine kinase, R788, R406, DMARD, kinase, methotrexate.

Pathogenesis of RA

RA is a chronic, systemic inflammatory disorder causing significant morbidity and mortality on a global basis. Our concepts of RA pathogenesis are ever evolving and currently comprise malevolent co-operation between the innate and adaptive immune system together with cells of host tissue, including fibroblasts, chondrocytes and osteoclasts. Insights into the disease state at the cellular and molecular level have recently translated into clinical therapeutics. Cytokine inhibitors of TNF-α, IL-6, B cell targeted therapies (rituximab) and T cell co-stimulation inhibition (abatacept) have transformed the options available to clinicians in pursuit of low disease activity states. Similarly the advent of sophisticated therapeutic strategies has significantly improved outcomes. However, current therapies usually achieve an ACR70 response or low disease activity state in only 20–30% of patients, and many who initially respond subsequently lose efficacy and require a change in therapy. Partial and non-responders to therapy usually undergo a sequence of conventional, combination, then biologic therapeutics, based largely on clinical response rather than pathologic rationale. This leads to significant frustration for patient and clinician alike, as well as cost burden to the healthcare system and wider society. Furthermore, current biologics require the patient to either self-inject or attend a hospital or clinic to receive an i.v. infusion. Therefore, despite the major therapeutic advances in RA, there is an ongoing requirement for alternative effective targeted therapies.
Small molecule protein kinase inhibitors are attractive agents in this pursuit because they can be tailored to modulate downstream effects of immune receptor-mediated cell activation and are bioavailable in oral form. Kinase inhibition has been employed with great success in the field of chronic myeloid leukaemia (CML) [1] and many kinases are now under investigation in RA, including agents developed to target Janus kinase (JAK), spleen tyrosine kinase (Syk), mitogen-activated protein kinase (MAPK), Burton’s tyrosine kinase (BTK) and phosphatidylinositol 3-kinases (PI3K). At this stage we do not have a clear hierarchical view of the functional order of importance of signal pathways that are served by these kinases and thus development programmes abound in parallel and in competition.

We present herein an overview of the rationale behind kinase inhibition focusing on the biology of Syk. We will examine the existing preclinical and clinical trial data for the Syk inhibitor R788 or fostamatinib, highlighting both the efficacy of this treatment along with the key side effect signals that have been reported thus far. Finally, we discuss further studies required and the future placement of such agents should they ultimately be approved in the management paradigm of RA.

**Kinase function in immune regulation**

Protein kinases are intracellular enzymes that transmit signals by attaching phosphate groups to target proteins, resulting in their activation and signal transduction. Kinases can be in the form of receptor or non-receptor types and both have potential roles in inflammatory diseases.

Kinases are activated by various ligands such as cytokines or growth factors and can also be activated by cellular stress. They then transmit this extracellular signal to an intracellular signal transduction mechanism, which often results in activation of transcription factors. In general this results in cell growth, differentiation, cytokine production and therefore inflammation. The complete arsenal of human kinases has been mapped into a dendrogram allowing visualization of the selectivity and magnitude of inhibition of the various kinase inhibitors [2]. Various kinase families and specific kinases have been implicated in human diseases.

**Lessons from kinase inhibition in other human diseases**

The structural identity of kinases allows for targeting specific kinases involved in distinct pathogenic disease processes, with a potentially favourable balance of therapeutic benefit vs side effects. Kinase inhibition was one of the first major wins for translational medicine with the use of imatinib mesylate (gleevac, glivec), a selective tyrosine kinase inhibitor, in the treatment of CML [3]. This remains the archetypal model driving the rational drug design approach for developing new cancer therapies. While the association of the Philadelphia chromosome (reciprocal translocation between chromosome 9 and 22) with CML had long been known, understanding the functional mechanism resulting from the genetic defect allowed novel therapeutic development. The reciprocal translocation results in the creation of the BCR-ABL oncogene, which puts the ABL tyrosine kinase under the control of the B cell receptor promoter, resulting in a constitutively activated tyrosine kinase in these patients [4]. Imatinib mesylate binds in a semi-competitive fashion to the ATP binding site of BCR-ABL, resulting in inhibition of target phosphorylation [5, 6]. However, after 5 years of treatment approximately 17% of patients treated with imatinib had developed secondary resistance or relapse, while 7% had progressed to a terminal blast phase [7]. The mechanisms underlying imatinib resistance are multifactorial and include BCR-ABL point mutations (altering kinase inhibitor binding), gene amplification, as well as BCR-ABL independent factors (reviewed by [8]). Second-generation BCR-ABL inhibitors, nilotinib and dasatinib, have subsequently been licensed for CML. Both these agents have a higher affinity and selectivity for BCR-ABL than imatinib, resulting in increased inhibition of BCR-ABL kinase and superior clinical efficacy [9, 10].

Kinase inhibitors are being developed and investigated in multiple clinical areas, including other malignancies and macular degeneration. While some of these inhibit specific kinases affected by known mutations (as is the case for imatinib in CML and crizotinib in non-small cell lung cancer patients with the ALK mutation), others target kinases involved in signal transduction pathways believed to be central in disease pathogenesis. Improved understanding and stratification of common diseases by their molecular disturbance will facilitate reappropriation of agents and more personalized therapy.

Inhibition of kinases was a logical evolution in the therapeutic armamentarium of rheumatologists due to their ability to act on multiple downstream pathological pathways. Studies are most advanced for JAK inhibition [11, 12].

**Biology of Syk relevant to RA**

Syk is a non-receptor tyrosine kinase involved in a number of diverse biological functions, including adaptive and innate immune receptor signalling, cellular adhesion, pathogen recognition, signalling tissue damage, inflammation, bone metabolism and vascular development (reviewed in [13]). Syk therefore has effects on multiple pathways that have been implicated in RA.

Syk is expressed in rheumatoid synovium, with activated phosphorylated Syk being differentially expressed between RA and OA synovium [14]. It is likely that it is widely expressed in a range of haemopoietic cell lineages therein. Syk activation plays an essential role in TNF-α-induced cytokine production in fibroblast-like synovocytes through suppression of the JNK pathway [14]. Syk has been shown to be necessary for emerging pathology in several animal models of arthritis [15–17]. Thus the Syk inhibitor R788 and its active metabolite R406 exhibit potent anti-inflammatory effects in the CIA model [15]. Importantly, inhibition of Syk suppressed both inflammation and bone erosion in such studies [15], consistent with
its reported effector function in both immune cells and osteoclasts that together mediate articular damage [13]. Taken together, these studies provide a clear rationale for targeting this pathway in the treatment of RA.

Clinical trials of fostamatinib

Fostamatinib (R788) is a pro-drug that, following oral administration, is rapidly converted to the active Syk inhibitor R406. Three clinical trials have been performed to determine the appropriate dosage, effectiveness and safety of fostamatinib in the treatment of RA. The initial two studies were in MTX inadequate responders (MTX-IRs) [18, 19] and the third was in biologic inadequate responders [20]. It should be noted that both the former studies also included subsets of patients who had previously failed to respond to biologic agents (20% and 15%, respectively).

Efficacy in MTX-IR subjects

The first study in MTX-IR patients was a 3-month phase II randomized, placebo-controlled trial of 189 patients with active RA despite therapy with MTX (15-25 mg/week). Patients were randomized (3:1 ratio) to receive fostamatinib in an ascending dose manner (50, 100 and 150 mg bd) or placebo on a background of stable MTX [18]. The doses were based on previous phase I studies in healthy volunteers and RA patients [21]. Patients were recruited from 40 centres in the USA and Mexico. Treatment and placebo populations were similar in terms of their baseline characteristics, including the use of concomitant DMARDs within the study protocol. The primary endpoint was the ACR20 response rate at week 12.

The rates of ACR20 response were similar in the 50 mg compared with the placebo group (32% vs 38%). However, both the 100 mg and 150 mg bd dose groups exhibited significantly superior ACR20 response rates to placebo (65% vs 38%, \( P = 0.008 \) and 72% vs 38%, \( P < 0.001 \), respectively). These levels of statistical superiority also extended to rates of ACR50 and ACR70, and these are included in Table 1. These results suggest a dose-dependent effect, as well as a rapid clinical response, with ACR20 at 1 week being achieved in 43% of patients in the 100 mg group and 51% in the 150 mg group. In comparison, the placebo response rate was 15%. Congruous with the superior clinical response, significant decreases in the levels of IL-6 and MMP-3 levels were observed in the 100 and 150 mg active treatment groups as early as 1 week following commencement of treatment. This response persisted in these groups throughout the study. While the 100 mg bd and 150 mg bd doses were both effective, adverse events were dose-related (described later), suggesting the 100 mg bd dose was the suitable maximum dose for further study.

The efficacy and safety profile of fostamatinib in MTX-IR RA was further evaluated in a larger 6-month multicentre randomized, double-blind, placebo-controlled phase II study [19]. A total of 457 patients with active RA despite MTX (between 7.5 and 25 mg/week) for a minimum of 3 months were recruited at 64 sites in six countries. Participants were randomized to receive fostamatinib at a dose of 100 mg bd, 150 mg/day or placebo, with stratification according to geographic region and previous biologic therapy exposure (limited to a maximum 30% of the total study population). Patients who completed the trial or withdrew early due to a lack of efficacy were eligible for open-label follow-up in which they received one of the fostamatinib regimens.

The primary outcome (ACR20 response at 6 months) was met in 67% of the 100 mg bd group and 57% of the 150 mg/day group, compared with 35% of the placebo group (both \( P < 0.001 \)). Again, the response to fostamatinib could be seen as early as 1 week and most of the patients in whom there was a response at 6 months already had a response at 2 months. The treatment groups were also superior with respect to ACR50 (43% for the 100 mg bd and 32% for the 150 mg/day groups compared with 19% for the placebo group, \( P < 0.001 \) and \( P = 0.007 \), respectively) and ACR70 (28% for the 100 mg bd and 14% for the 150 mg/day groups vs 10%

### Table 1 Clinical response rates for the three fostamatinib studies

<table>
<thead>
<tr>
<th>Study population</th>
<th>Study A (Weinblatt et al. [18])</th>
<th>Study B (Weinblatt et al. [19])</th>
<th>Study A (Genovese et al. [20])</th>
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<tbody>
<tr>
<td>Size, n</td>
<td>MTX inadequate responders</td>
<td>MTX inadequate responders</td>
<td>Biologic non-responders</td>
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<tr>
<td>Previous biologic, %</td>
<td>Placebo</td>
<td>50 mg bd</td>
<td>100 mg bd</td>
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<tr>
<td>Duration, months</td>
<td>3</td>
<td>Placebo</td>
<td>38</td>
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<tr>
<td>Interventions</td>
<td>Placebo</td>
<td>50 mg bd</td>
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<tr>
<td>ACR20, %</td>
<td>19</td>
<td>17</td>
<td>49*</td>
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<tr>
<td>ACR50, %</td>
<td>4</td>
<td>2</td>
<td>33*</td>
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<tr>
<td>ACR70, %</td>
<td>8</td>
<td>16</td>
<td>26*</td>
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<tr>
<td>DAS28 &lt; 2.6</td>
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*P < 0.05 in comparison with placebo for that study. DAS28: DAS in 28 joints.
for the placebo group; \( P < 0.001 \) and \( P = 0.34 \), respectively) response rates (Table 1). The 100 mg bd group consistently had better outcomes across all measures than the 150 mg/day group, including DAS28 remission and individual components of the ACR20 score. Interestingly, and perhaps informing interpretation of the final of the trial of studies thus far reported (see below), a subset of patients (15%, similarly distributed across the three groups) who had previously failed to respond to a biologic agent exhibited rather less robust response rates. While the ACR20 response was significantly greater for the two treatment arms (43% for the 100 mg bd and 46% for the 150 mg/day group) than the placebo group (14%; \( P = 0.04 \) and \( P = 0.02 \), respectively), these response rates were lower than those seen in the overall study population for these treatment groups. Adverse events were similar to the previous trial and are described below.

Efficacy in RA subjects with inadequate response to biologic agents

A separate, concurrent trial of fostamatinib was undertaken in patients with active RA who had not responded to biologic therapies [20]. This 3-month multicentre randomized, double-blind, placebo-controlled study recruited 219 patients at 49 sites in seven countries. Patients were randomized 2:1 to either fostamatinib 100 mg bd or placebo. In contrast to the previous two studies in MTX-IR patients, at 3 months there were no significant differences in the primary endpoint (ACR20) or clinical secondary endpoints of ACR50 and ACR70 and change in DAS28 score between the two groups (Table 1). The ACR20 response in the fostamatinib group was 38%, compared with 37% in the placebo group at 3 months. There were significant changes from baseline in CRP and ESR values in the fostamatinib group compared with placebo. Fostamatinib also significantly improved synovitis and oesteitis scores on MRI compared with placebo at 3 months. However, both groups showed progression of bone erosions, with no significant differences between the groups in terms of mean change in erosion scores from baseline.

The lack of clinical response in this trial was unexpected. One explanation is clearly that in a population of biologic-resistant patients, Syk inhibition with fostamatinib 100 mg bd offers no benefit. However, the authors performed post hoc analyses in which they tested the possibility that issues in trial design could have affected the observed outcomes. This is also addressed in the related editorial [23]. Despite randomization and similar levels of disease activity at baseline, patients in the fostamatinib treatment group had disease that had failed to respond to a greater number of biologic agents, took a higher dose of prednisolone and had more synovitis, oesteitis and erosions on MRI than patients in the placebo group. Patients in the active treatment group may therefore have had disease that is more therapy resistant [23]. The authors also found that >30% of the participants qualified on the basis of raised ESR (measured locally) with normal CRP and that these participants were recruited from two sites, raising questions about eligibility [20, 23], particularly with respect to intercurrent active inflammation. This subgroup of patients had a high placebo response rate, with 64% achieving an ACR20 response compared with 38% in the active treatment arm. When the results were reanalysed in only those patients qualifying for the study with an elevated CRP, it was found that there were statistically significant improvements in the ACR20, ACR50 and DAS criteria when active agent was compared with placebo. It should be noted, however, that the trial was not designed for this subgroup analysis or powered to detect differences with this number of patients. The lack of improvement in MRI erosion scores may be due to the short duration of the study, lack of effect of the medication on bone erosions or due to the above differences in baseline between study groups. A longer-term follow-up study will be necessary to enhance our understanding of this area, especially given the in vitro effect of osteoclast inhibition [15].

Adverse events noted upon Syk inhibition in RA subjects

The most common adverse events reported in the trials were gastrointestinal symptoms (mainly nausea and diarrhoea), hypertension, dizziness, headaches, neutropenia, upper respiratory tract infections and increased serum alanine transaminase (ALT) levels. Table 2 compares reported adverse events in the studies recruiting MTX-IRs. It should be noted that hypertension was measured at different time points in each trial and also that the third trial in biologic inadequate responders had very little safety information. The majority of side effects were dose dependent and were most often reported with the 150 mg bd dose of fostamatinib [18, 19]. This dose was most often associated with patient withdrawal due to adverse effects or blood monitoring abnormalities. In trials with a dose reduction strategy, these abnormalities generally resolved with a drug hiatus and were less prevalent when the dose was lowered.

Serious adverse event (SAE) rates at 3 months were 6% for the fostamatinib group vs 1% for the placebo group in the biologic inadequate responder study [20], but were not reported according to treatment group in the other studies. The bulk of the safety data comes from the larger MTX-IR study [19], with only limited safety data reported in the biologic inadequate responder study [20]. Overall, one death (in the placebo group) [20] was reported in the formal phase II studies, with a further three deaths in the 6-month open-label extension (one cerebrovascular event in a patient on heparin, one septicemia and one unknown cause) [19]. Two additional deaths (two cardio- or cerebrovascular events) are reported in the fostamatinib groups in the longer-term follow-up abstract report [24].

Infections

Upper respiratory tract infections were significantly more common in the 100 mg bd dose (14.5%) compared with the lower dose of 150 mg/day (7.2%) and placebo (7.1%, \( P < 0.05 \)) groups [19]. Analysis of 2-year follow-up data of
the three trials, presented in abstract form, revealed similar levels of infections in both the placebo and treated arms [24]. No cases of tuberculosis, fungal or opportunistic infections were reported.

### Neutropenia

Neutropenia (absolute neutrophil count <1500/mm³) is the most common laboratory abnormality associated with kinase inhibitors. The neutropenia was dose dependent and rapidly reversed when the drug was stopped. Neutropenia was reported in 6% of the 100 mg bd and 7% of the 150 mg/day fostamatinib groups, compared with 1% in patients receiving placebo (P < 0.05 for both) [19]. The neutrophil dose returned to ≥1500/mm³ in all patients within 3–7 days after interruption or reduction of the fostamatinib dose. In the biologic inadequate responder study, the reported rate of neutropenia in the 100 mg bd fostamatinib group was 2% compared with 0% in the placebo group and returned to ≥1500/mm³ in 3–21 days [20]. No infections were associated with neutropenia in either study. It has been suggested that this effect could be due to the involvement of Syk in haematopoiesis [25]. However, the study authors propose that the kinetics of the observed neutropenia make inhibition of haematopoiesis unlikely and hypothesize that the likely mechanism may be margination or impaired bone marrow neutrophil release; concurrent MTX use may also play a role [25].

### Elevation of liver transaminases

All three trials reported increases in ALT levels, with all cases resolving on reducing the dose or stopping fostamatinib. In the two larger trials, ALT values >3 times the upper limit of normal (ULN) were reported in 3–4% of the patients treated with fostamatinib compared with 0–2% of the patients receiving placebo [19, 20]. ALT levels >1.5 times ULN were reported in 20% of the 100 mg bd and 18% of the 150 mg/day fostamatinib groups vs 10% in the placebo group [20]. Of the 12 patients in the fostamatinib groups with ALT values >3 times ULN, 1 withdrew and the other 11 patients completed the study on a reduced dose of fostamatinib without recurrence of an elevated ALT level. The mechanism of transaminis is unknown, but could be exacerbated by concomitant MTX use.

### Hypertension

All three trials reported an increase in hypertension in the fostamatinib groups. The increase in blood pressure was seen at month 1 in 29% of the patients in the fostamatinib groups vs 17% of the placebo group [19]. Increases in blood pressure were more pronounced in those with existing hypertension at screening or baseline, with a mean increase in systolic blood pressure of 3 mmHg in those without pre-existing hypertension and 5 mmHg for the total fostamatinib-treated population. All cases responded to conventional antihypertensive medication or reduction in fostamatinib dose. It has been postulated that an

<table>
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<th>TABLE 2 Adverse events reported in fostamatinib studies</th>
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<tr>
<td>Diarrhoea</td>
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<td>Dyspepsia</td>
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<td>Rash/urticaria</td>
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<td>Cough</td>
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<td>Hypertension</td>
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<td>Neutropenia (&lt;1500/mm³)</td>
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<td>Increased ALT (&gt;3 × ULN)</td>
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<td>Increased alkaline phosphatase</td>
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<td>Anaemia</td>
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<td>Hypothyroidism</td>
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Values are the percentage of patients experiencing adverse events in fostamatinib clinical trials. There was insufficient adverse event data in the biologic non-responder study [20] to include in this table. Figures have been rounded to the nearest percentage. a12 weeks. b6 months. cHypertension reported at 1 month only.
off-target effect on vascular endothelial growth factor receptor 2 (VEGFR2) may be responsible for the elevation in blood pressure [26]. This will require careful monitoring in the context of patients who are already at an increased risk of cardiovascular events due to a combination of their underlying inflammatory condition, non-steroidal anti-inflammatory medication and relative sedentary lifestyle.

Withdrawals and dose reductions

In all three trials, withdrawal rates in the fostamatinib groups (14–16%) were similar to or lower than the rate in the placebo group (14–23%). The withdrawals in the placebo group were mainly due to lack of response, while in the fostamatinib groups this was due to a lack of response and adverse events (nausea, diarrhoea and laboratory abnormalities). Fourteen per cent of patients receiving fostamatinib required dose reductions due to adverse events (mainly gastrointestinal symptoms, hypertension, elevations of ALT or transient neutropenia) compared with 3–4% in the placebo group [19, 20]. In the longer-term follow-up report, around 60% of patients remained on the drug after 2 years, with most of the withdrawals occurring within the first 6 months [24].

Future therapeutic potential

New therapeutic agents for RA need to offer alternative strategies for treating RA, with at least equivalent effect on improving disease activity and reducing damage as currently available therapies, while being well tolerated and convenient to ensure compliance. Furthermore, cost-effectiveness is an important issue given the development of generic biologic agents and biosimilars.

While Syk inhibition appears efficacious in MTX-IR patients, the balance of benefit and harm remains uncertain and therefore the role for this agent in our armamentarium requires clarification. In particular, further dose optimization and combination therapy strategies need exploration. Novel therapeutics are disadvantaged by the relative scarcity of safety data compared with existing therapies, and the same will be true if fostamatinib comes to the clinic as a licensed agent. It is currently unclear how well tolerated this approach will be when used in an established dose regimen, in that the optimal risk–benefit window has been established. Phase IV follow-up will be crucial in identifying rare signatures and delayed effects.

The debate around the acceptability of oral, s.c. and i.v. routes as methods of administration of a medication for a chronic disease is already under way. In the oncology field, studies have shown that patient preference is an important reason for shifting from i.v. to oral therapy [27]. Patients preferred the convenience of treatment at home and avoiding the need for further procedures such as the placement of long-term i.v. catheters. Personal economic factors such as workdays lost to treatment for both patients and relatives also influenced the decision. However, patients expect oral therapy to be as efficacious as the i.v. treatment and up to three quarters would not tolerate poorer efficacy or duration of effect [27]. Our current experience suggests that after a brief initial training period, our RA patients are able to successfully use ergonomically designed devices at home, while avoiding the inconvenience associated with i.v. treatments.

Fewer studies have evaluated patients’ views on s.c. vs oral routes of administration. Most of the published studies exploring this issue have compared different formulations of triptan therapies for the treatment of acute migraine, where speed of onset of action is a major determining factor in patient preference and are therefore not directly transferable to chronic diseases. It is likely that patient preference will be determined largely by individual factors and beliefs. However, it should be considered that long-term adherence and compliance with weekly–monthly s.c. injections may be better than additional multiple daily oral therapies in patients already taking numerous oral medications. These considerations around adherence and compliance are likely to be as important as issues surrounding efficacy and tolerability and will be important determinants as to where these agents are placed in our current treatment practice. Finally, the issue of treatment cost is likely to be significant—robust economic analysis will be essential in the development programmes around all new oral DMARDs and inevitably it is likely that uptake will vary depending on national and health care funding models.

Conclusion

Syk is implicated in several pathways linked to the pathogenesis of RA and therefore Syk inhibition is a plausible strategy for oral therapeutic intervention in RA. However, based on the available evidence, the balance of benefit and harm with the Syk inhibitor fostamatinib in RA is currently uncertain. While fostamatinib was rapidly effective in MTX-IR patients, there was toxicity that requires clarification in terms of its impact on longer-term use. In treatment-resistant patients failing biologic therapies, where unmet need is the highest, fostamatinib did not achieve its efficacy endpoints. However, previous subgroup data and confounding issues in the trial suggest this area is worthy of further study. As with our current biologic agents, long-term safety data and economic analyses are awaited and will determine clinical utility.

Rheumatology key messages

- In patients with RA who are MTX intolerant, fostamatinib is an effective treatment.
- In RA patients unresponsive to biologic treatments, the efficacy of fostamatinib requires further clarification.
- The safety signature of fostamatinib in RA relates to neutropenia, elevated liver transaminases and hypertension.

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References