Fostamatinib Disodium

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Abstract

The non-receptor tyrosine kinase Syk has a diverse range of biological functions, including a critical role in the intracellular signalling cascade for the surface immunoglobulin receptor on B lymphocytes, and the Fc receptor expressed on numerous immune effector cells. It is therefore seen as a potential therapeutic target in a variety of conditions, including autoimmune, allergic and malignant diseases. Fostamatinib disodium is the orally bioavailable prodrug of R406, a relatively selective small molecule inhibitor of Syk, that has accordingly shown activity in numerous cell types *in vitro*, and efficacy in a remarkable range of animal models *in vivo*, including rodent models of asthma, inflammatory arthritis, lupus, glomerulonephritis, diabetes and lymphoma. Success in these models has translated to phase II clinical trials in autoimmune thrombocytopenia, lymphoma and, most notably, rheumatoid arthritis, in which larger phase III trials are currently in progress. Whilst the diverse biological functions of Syk, coupled to the potential off-target effects of this kinase inhibitor are a source of possible toxicity, the available data thus far augurs well for future clinical use of Fostamatinib in a wide range of human diseases.

Background

Spleen tyrosine kinase (Syk) is a 72kDa cytostolic protein tyrosine kinase that is involved in signal transduction in a variety of cell types. First identified in 1991 [1], it is highly expressed in cells of the haematopoietic system, where it has a clearly established role in intra-cellular signal transduction for classical immunoreceptors that associate with immunoreceptor tyrosine-based activation motifs (ITAMs), including the Fc receptor (FcR) and the B cell receptor (BCR) [2]. It is therefore seen as a possible therapeutic target in antibody and immune-complex mediated diseases, including allergic and autoimmune conditions, due to its role in FcR signalling. Similarly, as Syk has been shown to be critical for B cell growth, development and survival via its role in both tonic and ligand-induced BCR signalling, it is also a putative target in haematological malignancies of B-cell lineage.

In addition, there is accumulating evidence of a role for Syk in other cells types and in other biological functions, including integrin and cytokine receptor signal transduction, innate pathogen recognition, platelet function, and bone resorption [3]. Whilst these diverse functions may also be open to therapeutic manipulation, they have obvious implications for clinical use of Syk directed treatment in terms of toxicity and unwanted adverse effects.

Fostamatinib disodium (R788) is the oral prodrug of the active compound R406, a relatively selective small molecule inhibitor of Syk.

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Pre-clinical Pharmacology

R406 is a competitive inhibitor for ATP binding to the Syk catalytic domain (K_i = 30 nM), and inhibits Syk kinase activity *in vitro* with an IC_{50} of 41 nM [4]. Selectivity assessments using a panel of over 90 *in vitro* kinase assays showed that R406, whilst relatively specific for Syk, did demonstrate inhibitory activity on other kinases, including Flt3, Lyn (IC_{50} 63 nM) and Lck (IC_{50} 37 nM) [5]. When tested in cell-based assays, however, R406 inhibited all other kinases tested at 5- to 100-fold less potency than Syk as judged by phosphorylation of target proteins, despite the similar IC_{50} values on isolated kinase assays.

As expected, R406 inhibits BCR-mediated responses *in vitro*. In primary human B cells, for example, it inhibits CD69 up-regulation in response to anti-IgM with an EC_{50} of 48 nM [4]. BCR-mediated signalling has been implicated as an important survival signal in haematological malignancies of B cell origin, and accordingly R406 has shown anti-proliferative and pro-apoptotic activity in a variety of B cell lymphoma and chronic lymphocytic leukaemia (CLL) cell lines and primary tumour cells *in vitro* [6-8]. These effects are most likely due to the effects of inhibited BCR-induced signalling in these cells, although BCR-independent mechanisms such as disrupted chemokine and integrin signalling have also been implicated [9].

R406 has been shown to inhibit FcR-mediated responses (such as degranulation, cytokine production and FcR-mediated antigen internalisation) in a variety of cell types *in vitro*, including mast cells, macrophages, neutrophils and dendritic cells [4, 10, 11] (EC_{50} for IgE-induced degranulation of primary human mast cells *in vitro* is 56 nM). These effects occur in association with inhibition of intracellular phosphorylation events downstream of Syk. R406 does not demonstrate a significant effect on Syk-independent signalling pathways in these cells; for example, significantly higher levels of R406 are required to inhibit monocyte TNF-alpha production induced by LPS (EC_{50} 2.1 microM). Conditional knock-out of the Syk gene and siRNA knock-down in rodent cells bearing the FcR, have a similar phenotypic effect as treatment with R788/406, further evidence of drug specificity for Syk as its primary target [12, 13].

Apart from its anticipated effects on BCR- and FcR-mediated functions, R406 has shown activity in other cells types and signalling pathways. To what extent these effects are due to the biological role of Syk in these pathways, rather than off-target effects of R406, is not definitively established. For example, in T cells from patients with systemic lupus erythematosus (SLE), R406 inhibited T cell receptor (TCR) induced signalling [14]. An altered TCR in which TCR-zeta is replaced by FcR-gamma, allowing it to signal through Syk, has been described in many patients with SLE, and this may be the mechanism of inhibition in this case. R406 has been shown to promote cell death of Flt3-mutant acute myeloid leukaemia (AML) cells *in vivo*, although it has been suggested that this effect may be attributable to its off-target activity on Flt3 rather than Syk inhibition *per se* [15]. Other pathways in which R406 has shown an inhibitory effect include cytokine-induced signalling in fibroblast-like synoviocytes [5], and integrin- and lectin-induced signalling in platelets [16].

Building on the *in vitro* evidence, Fostamatinib (R788) has been shown to be highly active in two animal models of CLL - adoptively transferred T cell leukaemia 1 (TCL1) leukaemias and leukaemias that spontaneously develop in Emu-TCL1 transgenic mice [17]. In addition, it has shown efficacy in murine models of non-Hodgkin's lymphoma (NHL), reducing tumour burden and prolonging survival in treated mice [18]. Notably, this effect was not seen in tumours lacking surface expression on the BCR, in keeping with the drugs proposed mechanism of action.

The effects of Fostamatinib (as either R788 or R406) have been more extensively studied *in vivo* in a diverse range of animal models of allergy, autoimmunity and inflammation, where its inhibitory action on FcR-mediated signalling is thought to be the key mechanism of action. For example, treatment with Fostamatinib effectively prevents the development thrombocytopenia and haemolytic anaemia induced by the passive transfer of anti-platelet and anti-red cell antibodies respectively to mice [19]. In rodent models of asthma, R406 reduced airway hyperresponsiveness (AHR) and markers of airway inflammation following antigen challenge in sensitized mice, in two distinct models [11, 20]. Similarly, in mice passively sensitised with anti-OVA IgE, R406 treatment prevented the development of AHR [20].

Treatment with R406 reduced joint inflammation in two passive transfer models of antibody-induced arthritis (the passive anti-collagen antibody-induced arthritis (passive anti-CAIA) and K/BxN serum transfer models) [4]. In addition, treatment with either R406 or R788 in Louvain and Lewis rats, reduced clinical, histological and radiographic evidence of joint inflammation following active induction of collagen-induced arthritis (CIA) [21]. These improvements were associated with a reduction in pro-inflammatory cytokine and chemokine expression in synovial tissue and fluid.

Fostamatinib has also shown efficacy in animal models of SLE. In the lupus-prone NZB/NZW mouse strain, treatment was effective in both preventing and ameliorating established disease, the treated animals showing reduced proteinuria with improved renal function, improved renal histology, improved platelet counts and prolonged survival [22]. In the MRL/lpr strain, Fostamatinib suppressed both established renal and skin disease, and reduced lymphadenopathy [23]. Notably, this study demonstrated a sustained benefit from Fostamatinib in the period after drug cessation, suggesting a possible immunomodulatory effect of treatment, although this was not investigated further. Treatment with Fostamatinib also prevented lupus-like skin disease and reduced lymphadenopathy in the BAK/BAX knockout mouse [23].

Further evidence of Fostamatinib efficacy in antibody-mediated renal disease was established using the nephrotoxic nephritis (NTN) model in Wistar Kyoto rats. Treatment with Fostamatinib prevented the induction of disease and had a dramatic effect on established glomerulonephritis - reducing proteinuria, histological renal injury and inflammatory cell infiltrates, and renal pro-inflammatory cytokine expression [24]. Remarkably, treatment was effective in reversing the histologic features of established crescentic glomerulonephritis, even when initiated 7 days after the induction of disease.

Fostamatinib was effective at reducing local and remote tissue inflammation in a mouse model of mesenteric ischaemia-reperfusion [25]. The precise mechanisms via which these effects occur are not clear, though almost certainly relate to the diverse effects of Syk inhibition on various immune and inflammatory cells.

Finally, Fostamatinib significantly delayed the onset of insulinitis and spontaneous diabetes in NOD mice, and also delayed progression of early established diabetes even when treatment was initiated after the development of glucose intolerance [12]. These findings, in an autoimmune model that is critically T cell-dependent, suggest that Syk inhibition with Fostamatinib may have broader therapeutic potential in autoimmune disease beyond its established role in effector processes mediated by the FcR. The authors suggest that, via its effects on antigen internalisation (and thus antigen presentation) by B cells and dendritic cells, treatment may prevent T cell priming and the development of T cell effector responses, suggesting that Syk inhibition may be a useful target in both antibody-mediated and cellular autoimmune responses. In addition, a window study showed a sustained benefit

up to 11 weeks after withdrawal of treatment in NOD mice (similar to the effects seen in the MRL/lpr lupus-prone strain), again suggesting the possible induction of immunomodulatory or tolerogenic mechanisms. Notably, an increase in the proportion of IL-10 secreting B cells (which have putative regulatory and suppressive function) was seen, and transfer of splenic B cell populations from treated to untreated mice protected from disease. These results suggest that sustained treatment with Fostamatinib may not be necessary in autoimmune disease.

Pharmacokinetics and Metabolism

R788 was developed as the methylene phosphate prodrug of R406, which exhibits low aqueous solubility, to improve its bioavailability and potential for oral dosage development.

Pre-clinical pharmacokinetic studies with Fostamatinib (R788) in Louvain rats confirmed that it is highly bioavailable, rapidly absorbed, and that systemic exposure is proportional to dose, with the following pharmacokinetic parameters for systemic R406 following a single oral dose of R788 10 mg/kg or 20 mg/kg: $AUC_{0-16\ hrs}$ = 10618 ng*h/ml and 30650 ng*h/ml respectively; C_{max} = 2600 ng/ml and 6500 ng/ml respectively (observed at 1 hour); $t_{1/2}$ = 4.2 hours [21]. The prodrug was not detected in plasma suggesting R788 is completely converted to R406.

Phase I clinical studies in patients with NHL yielded the following parameters for R406 exposure following single oral dose of either R788 200 mg or R788 250 mg: C_{max} = 668 ng/ml and 1020 ng/ml respectively; $AUC_{0-4\ hrs}$ = 1800 ng*h/ml and 2590 ng*h/ml respectively [26]. Plasma concentrations increased approximately 2-fold with continued administration, but beyond 29 days' treatment there was no apparent change in concentrations over time.

Pharmacokinetic analysis in a Phase II trial in patients with rheumatoid arthritis (RA) confirmed high bioavailability and dose-dependent increase in R406 exposure, with AUC values of 7766 ng*h/ml, 20166 ng*h/ml and 34916 ng*h/ml at doses of 50 mg, 100 mg 150mg twice daily respectively [27].

A detailed assessment of the pharmacokinetics and metabolic fate of Fostamatinib using a combination *in vitro* intestinal and hepatic microsomes and human mass balance studies has been conducted [28]. This suggests that R788 is rapidly hydrolysed to R406 by intestinal alkaline phosphatases, after which the more hydrophobic R406 is rapidly absorbed. R406 was the major drug-related product observed in plasma, with peak levels observed at 1 hour after dosing, and half-life ranging from 10.8 to 15.7 hours. Small amounts of the parent compound R788 were detected in the plasma at early time-points. Elimination of drug-related material in the urine accounted for 19% of the administered dose (the major urinary metabolite in urine being the lactam *N*-glucuronide of R406) and on average 80% was recovered in faeces. It appears that R406 undergoes both direct glucuronidation and a CYP3A4-mediated *para-O*-demethylation to R529 in the liver. Conjugates of R529 secreted in bile are hydrolysed back to R529 which, the authors suggest, is subsequently *O*-demethylated and dehydroxylated by anaerobic gut bacteria to a unique 3,5-benzene diol metabolite, the major drug-related compound detected in faeces.

It is notable that in a trial of Fostamatinib in patients with idiopathic thrombocytopenic purpura (ITP), similar levels of Syk inhibition (as assessed by basophil activation assay) at peak and trough times (2 and 12 hours post-dose respectively) were associated with better platelet responses, although the numbers in this study were small and no other pharmacokinetic parameters were reported [19]. In RA, total exposure (as determined by AUC) was related to adverse outcomes and study withdrawal [27]. Conversely, in the Phase I NHL study, there was no correlation between clinical outcomes and measured

pharmacokinetic parameters [26]. Ideally, future studies will assess more precisely the relationship between pharmacokinetics and clinical outcomes in order to establish the most effective and tolerable dosing regimes.

Safety

The results of detailed toxicity and immunotoxicology assessments in rats have been reported [29]. Animals were treated with R406 at doses up to 100 mg/kg/day for 28 days, achieving peak plasma concentrations up to approximately 5600 ng/ml and AUCs of up to approximately 54000 ng*h/ml, well in excess of those needed to achieve inhibition of Syk-mediated signalling in clinical studies. Consistent with the reported observations of the cited studies using animal disease models, there were no R406-related changes in appearance, behaviour, food consumption, ophthalmoscopy, coagulation or urinalysis seen in normal animals. At high doses (100 mg/kg/day) there was a reduction in circulating lymphocyte count, thymic and spleen weight and bone marrow cellularity. These effects generally resolved during a 14 day recovery period. In host-resistance mouse models of viral and both intracellular and capsulated bacterial infection, treatment with Fostamatinib at doses up to 80 mg/kg/day did not impair the ability to clear influenza, listeria or streptococcal infection, consistent with previous *in vitro* observations that R406 had negligible effects on phagocytosis, oxidative burst, chemotaxis, or microbicidal activity of human leucocytes [4], suggesting that Fostamatinib does not adversely affect innate immune responses. The effects (both desirable and adverse) of Fostamatinib on humoral immunity are less clear. R406 did not affect IgG or IgM antibody production following immunisation with a T-cell dependent antigen (KLH) in the immunotoxicity assessments. Conversely, in the NTN model, there was a significant reduction in autologous rat anti-rabbit antibody titre in animals pre-treated with Fostamatinib [24]. Similarly, treatment of pre-disease lupus prone mice resulted in a trend (albeit not statistically significant) towards a reduction in circulating anti-dsDNA antibodies [22]. As such, the effect of treatment on the induction of allo- and autoantibodies is undefined. Similarly, the long-term effects of Fostamatinib on antibody production by established plasma cells are uncertain. In the CIA and AHR models, animals were treated after sensitization, and no effect on antigen-specific antibody titres was seen, although the half-life of circulating antibody probably exceeds the short follow-up period of these studies [11, 21]. In NOD mice, followed up for a longer period of 2 months, treatment with Fostamatinib resulted in a modest but significant reduction in total IgG and IgM antibodies, and a reduction in anti-GAD anti-islet antibodies [12]. There is no available pre-clinical data on the effects of treatment on humoral immunity beyond 2 months, and the published clinical studies do not comment in detail on B cell or immunoglobulin parameters. The long-term effects of Syk inhibition on plasma cell and B cell function will need careful assessment in future trials.

Neutropenia (as opposed to lymphopenia) was a common adverse event in the Phase II clinical studies to date, occurring in up to 30% of patients receiving highest doses in the RA and NHL trials [26, 27]. Co-administration of methotrexate, previous immunosuppressant therapy and underlying bone marrow disease may have been contributing to these rates. Neutrophil counts recovered with temporary withdrawal or dose reduction of Fostamatinib. In a second Phase II study in RA [30], there was increase in the incidence of upper respiratory tract infection (14.5% in 100 mg bd group versus 7.1% in placebo group; p <0.05), however none of the infections seen were associated with neutropenia. To date, there are no reports of opportunitistic or atypical infection in clinical studies.

The most common adverse event seen in clinical studies with Fostamatinib was gastro-intestinal toxicity. Diarrhoea was reported at rates of up 45% in some groups [27]. This is a common side effect of other kinase inhibitors, and symptoms appeared to be dose-related

and responsive to temporary withdrawal or dose reduction. Nausea and diarrhoea were, however, the most common reasons for patient withdrawal from the treatment groups in larger RA studies [30, 31].

Modest but significant elevations in blood pressure (BP) were noted in all the large clinical studies. In the largest RA trial, for example, the incidence of hypertension (systolic BP >140 or diastolic BP >90) was 29% in treatment groups versus 17% in the control group (P = 0.006) at 1 month follow-up. Increases in blood pressure were seen most frequently in those with pre-existing hypertension or who were already on treatment at enrolment. It has been suggested that off-target effects of R406 on vascular endothelial growth factor receptor 2 may account for this phenomenon. In general, hypertension responded to conventional antihypertensive therapy or dose-reduction of Fostamatinib. Nonetheless, the long-term implications of even small increases in blood pressure in populations with renal or autoimmune rheumatic diseases, who have significantly increased cardiovascular risk, must be considered and carefully monitored in clinical use.

Moderate elevation in transaminase enzymes were reported in all the clinical studies. Transaminitis was also reported in the pre-clinical toxicity studies, where it was not associated with any histopathological changes in the liver. In both pre-clinical and clinical studies, liver function normalised with dose-reduction or withdrawal of Fostamatinib.

Clinical studies with Fostamatinib have not, to date, identified any effect of treatment on lipid metabolism, renal function or other biochemical parameters. There was one episode of unexplained acute-on-chronic renal injury in a patient receiving Fostamatinib in the NHL study; the role of the drug in this case is unclear.

As previously discussed, Syk has been implicated in collagen and integrin induced signalling in platelets. Systemic exposures of R406 at concentrations up to 25 microM did not extend bleeding time in mice [4]. Similarly, R406 did not appear to affect aggregation responses in platelets from human volunteers, suggesting redundancy of Syk-dependent pathways *in vivo*. Bleeding episodes have not been reported in the Phase II clinical studies to date.

Developmental toxicity studies in gravid rabbits and rats showed a dose-dependent increase in fetal malformations, including renal and ureteric agenesis and a specific major vessel anomaly - retro-oesophageal right subclavian artery - a phenotype similar to that seen in c-Ret knockout mice [32]. The c-Ret gene encodes a receptor tyrosine kinase that has a critical role in renal and ureteric development and, strikingly, R406 has been shown to inhibit Ret kinase in *in vitro* and cell-based assays (IC_{50} 5 nM and 80 nM respectively). Off target effects on this protein may account for some of the developmental anomalies seen. In addition, Syk knockout mice show perinatal lethality with petechial haemorrhage, a consequence of the failure to separate developing lymphatic and blood vessels, and so disruption of Syk signalling *in utero* may account for the vascular anomalies seen.

Clinical Studies

Early phase studies in over 100 normal human volunteers in single and multiple dose (7-21 days) pharmacokinetic-safety-pharmacodynamic studies showed that R788/R406 was well tolerated, with an effective concentration for Syk inhibition of approximately 0.5-1.0 microM [4, 33]. For example, R406 administered orally to human volunteers inhibited human basophil activation in response to anti-IgE *ex vivo*, with an IC_{50} of 1.06 microM (corresponding plasma concentration 496 +/− 42 ng/ml). These concentrations were achievable within the dose range (75-150 mg bd) that was well tolerated by volunteers. The

disparity between the cell-based and *in vivo* IC_{50} values is attributed to the high protein binding of R406 in human plasma (>98%).

To date there have been 5 phase II clinical studies, recruiting almost 1000 patients, using Fostamatinib. A small open-label, single-arm cohort dose escalation trial in 16 patients with ITP, with an average follow-up time of 36 weeks, showed that Fostamatinib 75-175mg bd induced a sustained improvement in platelet count in 50% of patients [19]. Those who had a sustained response tended to have early response, with improvements seen in the first few weeks of treatment. Four patients (25%) had transient responses and improved in other clinical parameters such as fewer bleeding episodes, avoidance of rescue mediations and tapering of steroids. Although 4 patients did not respond, it should be noted that the majority of patients in the study had refractory disease, with a mean number of previous ITP treatments of 5. Over two thirds of patients had been treated previously with steroids, intravenous immunoglobulin, rituximab, and splenectomy. As such, the results of this study are encouraging and larger randomised trials in ITP are planned.

Three clinical studies investigating the use of Fostamatinib in RA have been published. The first enrolled 189 patients with active RA despite methotrexate therapy who were randomised (3:1 ratio) to receive Fostamatinib in an ascending-dose manner or placebo in a double-blind trial [27]. The study included a significant proportion of patients who had received multiple previous therapies: more than 50% of the patients were receiving concomitant steroid therapy, approximately one third were receiving other disease-modifying anti-rheumatic drugs (DMARDS) in addition to methotrexate, and 28% had received biologic response modifiers in the past. The primary end-point was the American College of Rheumatology 20% improvement criteria (ACR20) response rate at 12 weeks. This was achieved in 72% and 65% of patients receiving Fostamatinib 150mg bd and 100mg bd respectively, significantly greater response rates than seen with 50mg bd (32%) or placebo (38%) (p <0.01). Improvements in a number of secondary end-points (including ACR50, ACR70 and DAS-28 scores) were noted. These clinical responses were rapid, with effects noted within 1 week of treatment, and were associated with reduced levels of circulating pro-inflammatory cytokines such as interleukin-6. A second double-blind, placebo-controlled study enrolled 457 patients with active RA despite long-term (i.e. greater than 3 months) methotrexate therapy, who were randomised (1:1:1) to receive Fostamatinib 100mg bd, Fostamatinib 150mg od, or placebo [30]. 67% and 57% of the patients in the respective treatment groups achieved the primary end-point of an ACR20 response after 6 months, versus 35% of patients receiving placebo (p<0.001). In keeping with the findings of the earlier study, treatment with both dosing schedules also had a significant impact on ACR50, ACR70, and DAS-28 remission. Again, clinical responses were seen as early as one week and the majority of patients in whom there was a response at 6 months had already demonstrated a response at 2 months, suggesting that an early response may identify those patients who are likely to benefit from ongoing therapy. Fewer patients in this study (15%) had failed previous biologic therapy than in the first RA trial. Although overall response rates in this subgroup were lower than for the whole study population, the ACR20 response was achieved in 43% and 46% of patients receiving Fostamatinib 100mg bd or 150mg od respectively, versus 14% in the placebo group (p=0.04 and p=0.02 respectively). These encouraging results, however, must be tempered with the findings of the latest study in RA, which aimed to look specifically at this population - 229 patients with RA who had failed at least one prior biologic therapy were enrolled to receive Fostamatinib 100mg bd or placebo (2:1 ratio) [31]. There was no difference between groups in the rate of ACR 20/50/70 or DAS-28 response (38% vs 37% for primary endpoint of ACR20 at 3 months, p = 0.84). There were, however, statistically significant improvements in synovitis scores as judged by MRI, and inflammatory markers (ESR and CRP), in the treatment group. Despite randomization, there were baseline differences in steroid use, prior biologic use, and

synovitis scores that the investigators suggest may account in part for the lack of efficacy seen in this trial. Three Phase III trials in RA are now in progress (NCT01197521, NCT01197534, NCT01197755) and are due to complete between June 2012 and January 2013.

Sixty-eight patients were enrolled to a phase II study investigating the effect of Fostamatinib in a heterogeneous group of non-Hodgkin lymphomas (NHL) and chronic lymphocytic leukemia (CLL) [26]. This cohort included many patients with heavily pre-treated and relapsed disease (median number of prior treatments = 4). Previous treatments included rituximab (65%), multi-agent chemotherapy (64%) and prior autologous stem cell transplantation (27.9%). Patients received Fostamatinib 200mg bd and were assessed for initial response at 8 weeks. Remission rates varied from 10-55% depending on tumour subtype and the median progression free survival for all patients was 4.2 months, suggesting significant clinical activity. Further trials should identify those lymphomas and leukaemias that are most susceptible to Syk inhibition as a therapeutic target.

Drug Interactions

Hepatic microsome studies show that R406 is extensively metabolised by expressed human CYP3A4 *in vitro*, and that this is inhibited by cytochrome P450 inhibitors, such as ketoconazole, by up to 90% [28]. These interactions have not been explored *in vivo* or in clinical studies.

The effects of Fostamatinib on the metabolism of methotrexate, the most commonly used disease modifying drug used in RA, have been examined in a small phase I study, where no significant pharmacokinetic interaction between the two drugs was reported [34]. Notwithstanding, neutropenia was observed more frequently in the RA trials, where it was co-adminstered with methotrexate, than in the ITP trial, suggesting a possible synergistic effect on the bone marrow beyond their individual pharmacokinetic parameters.

A potential and important, though as yet unexplored, interaction is that of Fostamatinib with monoclonal therapies such as rituximab, which may rely on FcR-mediated processes such as antibody-dependent cell-mediated cytotoxicity, for their effects.

Acknowledgments

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