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MONOGRAPH

FOSTAMATINIB DISODIUM

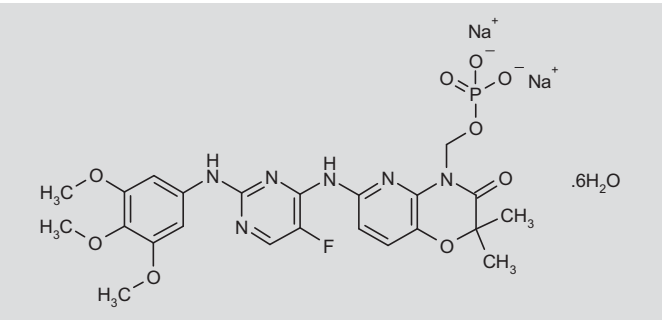
Rec INN

Tyrosine-Protein Kinase SYK/FLT3 Inhibitor
Treatment of Rheumatoid Arthritis
Oncolytic

NSC-745942
R-788
R-935788
Tamatinib fosdium

Phosphoric acid 6-[5-fluoro-2-(3,4,5-trimethoxyphenylamino)pyrimidin-4-ylamino]-2,2-dimethyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-4-ylmethyl monoester disodium salt hexahydrate
6-[5-Fluoro-2-(3,4,5-trimethoxyphenylamino)pyrimidin-4-ylamino]-2,2-dimethyl-4-(phosphonooxymethyl)-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-3-one disodium salt hexahydrate

InChI: 1S/C23H26FN6O9P.2Na.6H2O/c1-23(2)21(31)30(11-38-40(32,33)34)20-14(39-23)6-7-17(28-20)27-19-13(24)10-25-22(29-19)26-12-8-15(35-3)18(37-5)16(9-12)36-4;;;;;;;;/h6-10H,11H2,1-5H3,(H2,32,33,34)(H2,25,26,27,28,29);;;6*1H2/q;2*+1;;;;;;/p-2



$C_{23}H_{36}FN_6Na_2O_{15}P$
Mol wt: 732.5148
CAS: 914295-16-2
CAS: 945745-48-2
CAS: 901119-35-5 (anhydrous, free acid)
EN: 414384

SUMMARY

The non-receptor tyrosine-protein kinase SYK (spleen tyrosine kinase) has a diverse range of biological functions, including a critical role in the intracellular signaling 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 R-406, 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. While the diverse biological functions of SYK coupled with the potential off-target effects of this kinase inhibitor are a source of possible toxicity, the available data thus far augur well for future clinical use of fostamatinib in a wide range of human diseases.

SYNTHESIS*

Chlorination of 5-fluorouracil (I) by means of $POCl_3$ gives 2,4-dichloro-5-fluoropyrimidine (II), which is condensed with the pyrido-[3,2-*b*][1,4]oxazin-3-one derivative (III) to afford the secondary amine (IV). Then, subsequent displacement of the remaining chlorine of pyrimidine (IV) with 3,4,5-trimethoxyaniline (V) yields the substituted pyrimidine-2,4-diamine (VI) (1). Condensation of pyridooxazinone derivative (VI) with di-*tert*-butyl chloromethyl phosphate (VII) –prepared by chlorination of potassium di-*tert*-butylphosphate (VIII) with $ClSO_3CH_2Cl$ by means of Bu_4NHSO_4 in CH_2Cl_2/H_2O (2)– in the presence of Cs_2CO_3 in acetone or DMF gives a mixture of three *N*-substituted regioisomers, which are then subjected to either column chromatography or crystallization on MTBE to provide the major *N*-substituted oxazinone (IX). Hydrolysis of the *t*-butyl ester groups

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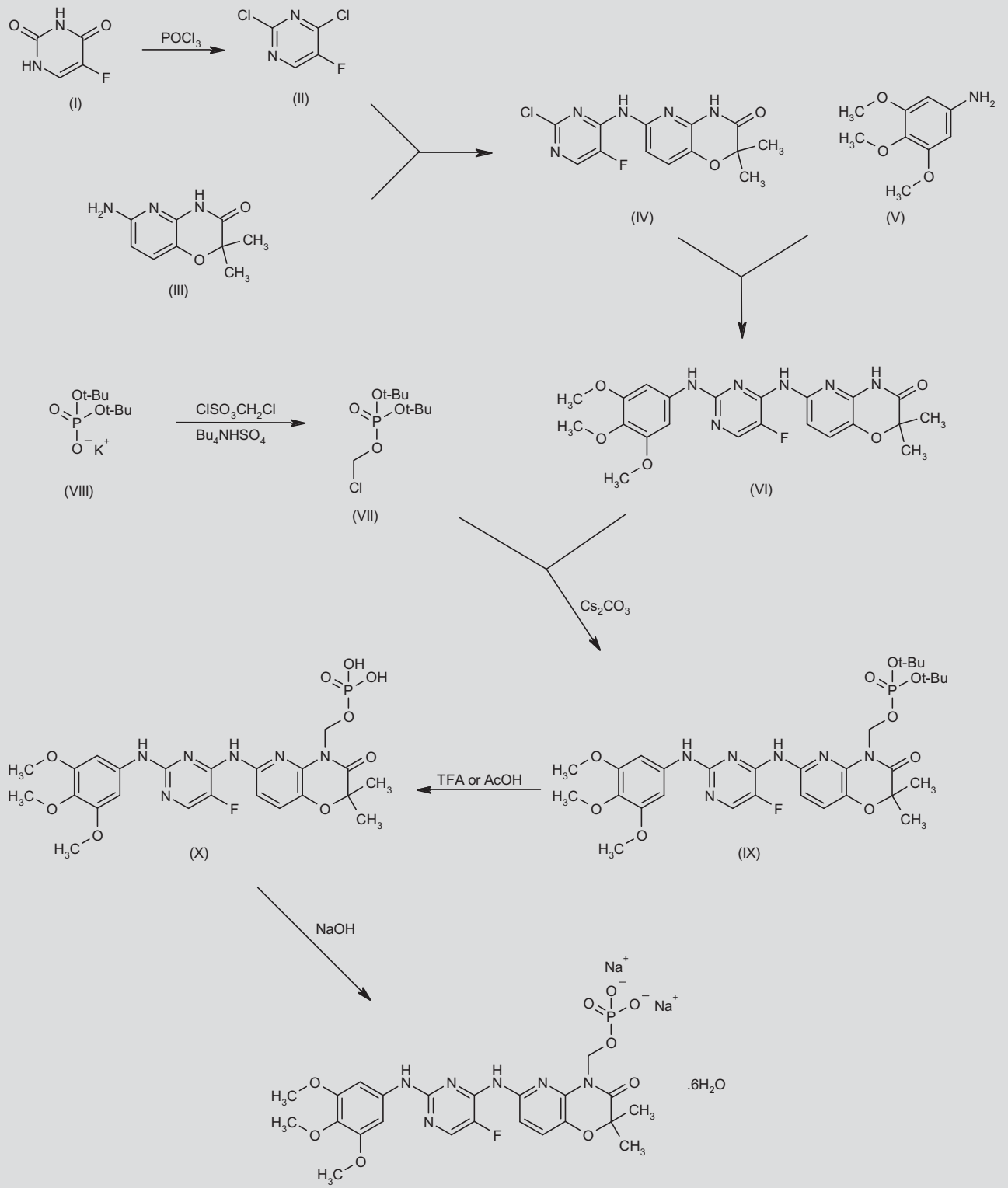
*Synthesis prepared by R. Pandian, J. Bolos, R. Castañer. Thomson Reuters, Provença 398, 08028 Barcelona, Spain.

Scheme 1. Synthesis of Fostamatinib Disodium



of (IX) by means of AcOH in H_2O or TFA in CH_2Cl_2 affords free acid (X) (3-5), which is finally treated with aqueous (3) or IPA/H_2O (2) NaOH (2, 3). Scheme 1.

Alternatively, condensation of pyridooxazinone (VI) and chloromethyl phosphate (VII) with Cs_2CO_3 in DMAC at 40 °C affords the *N*-substituted oxazinone (IX), which is directly hydrolyzed by means of AcOH in H_2O, and the phosphoric acid (X) is submitted to purification by crystallization on DMF (2).

BACKGROUND

The tyrosine-protein kinase SYK (spleen tyrosine kinase) is a 72-kDa cytostolic protein tyrosine kinase that is involved in signal transduction in a variety of cell types. First identified in 1991 (6), it is highly expressed in cells of the hematopoietic system, where it has a clearly established role in intracellular signal transduction for classic immunoreceptors that associate with immunoreceptor tyrosine-based activation motifs (ITAMs), including the Fc receptor (FcR) and the B-cell receptor (BCR) (7). 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 signaling. 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 signaling, it is also a putative target in hematological malignancies of B-cell lineage.

In addition, there is accumulating evidence of a role for SYK in other cell types and in other biological functions, including integrin and cytokine receptor signal transduction, innate pathogen recognition, platelet function and bone resorption (8). While these diverse functions may also be open to therapeutic manipulation, they have obvious implications for the clinical use of SYK-directed treatment in terms of toxicity and unwanted adverse effects.

Fostamatinib disodium (R-788) is the oral prodrug of the active compound R-406, a relatively selective small-molecule inhibitor of SYK.

PRECLINICAL PHARMACOLOGY

R-406 is a competitive inhibitor of 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 (9). Selectivity assessments using a panel of over 90 in vitro kinase assays showed that R-406, while relatively specific for SYK, did demonstrate inhibitory activity against other kinases, including tyrosine-protein kinase receptor FLT3, tyrosine-protein kinase Lyn (IC_{50} = 63 nM) and tyrosine-protein kinase Lck (IC_{50} = 37 nM) (10). When tested in cell-based assays, however, R-406 inhibited all other kinases tested with 5- to 100-fold lower potency than for SYK, as judged by phosphorylation of target proteins, despite the similar IC_{50} values in isolated kinase assays.

As expected, R-406 inhibits BCR-mediated responses in vitro. In primary human B cells, for example, it inhibits CD69 upregulation in response to anti-IgM with an EC_{50} of 48 nM (9). BCR-mediated signaling has been implicated as an important survival signal in hematological malignancies of B-cell origin, and R-406 has shown antiproliferative and proapoptotic activity in a variety of B-cell lymphoma and chronic lymphocytic leukemia (CLL) cell lines and primary tumor cells in vitro (11-13). These effects are most likely due to its inhibitory effects on BCR-induced signaling in these cells, although BCR-independent mechanisms such as disrupted chemokine and integrin signaling have also been implicated (14).

R-406 has been shown to inhibit FcR-mediated responses (such as degranulation, cytokine production and FcR-mediated antigen internalization) in a variety of cell types in vitro, including mast cells, macrophages, neutrophils and dendritic cells (EC_{50} = 56 nM for IgE-induced degranulation of primary human mast cells in vitro) (9, 15, 16). These effects occur in association with inhibition of intracellular phosphorylation events downstream of SYK. R-406 does not demonstrate a significant effect on SYK-independent signaling pathways in these cells; for example, significantly higher levels of R-406 are required to inhibit monocyte TNF-α production induced by lipopolysaccharide (EC_{50} = 2.1 μM). Conditional knockout of the *Syk* gene and siRNA knockdown in rodent cells bearing the FcR, have a similar phenotypic effect as treatment with R-788/406, providing further evidence of drug specificity for SYK as the primary target (17, 18).

Apart from its anticipated effects on BCR- and FcR-mediated functions, R-406 has shown activity in other cell types and signaling pathways. To what extent these effects are due to the biological role of SYK in these pathways, rather than off-target effects of R-406, has not been definitively established. For example, in T cells from patients with systemic lupus erythematosus (SLE), R-406 inhibited T-cell receptor (TCR)-induced signaling (19). An altered TCR in which TCR-α is replaced by FcR-γ, 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. R-406 has been shown to promote cell death of FLT3-mutant acute myeloid leukemia (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 (20). Other pathways in which R-406 has shown an inhibitory effect include cytokine-induced signaling in fibroblast-like synoviocytes (10), and integrin- and lectin-induced signaling in platelets (21).

Building on the in vitro evidence, fostamatinib disodium (R-788) has been shown to be highly active in two animal models of CLL: adoptively transferred T-cell leukemia 1 (TCL1) and leukemias that spontaneously develop in Emu-TCL1 transgenic mice (22). In addition, it has shown efficacy in murine models of non-Hodgkin's lymphoma (NHL), reducing tumor burden and prolonging survival in treated mice (23). Notably, this effect was not seen in tumors lacking surface expression of the BCR, in keeping with the drug's proposed mechanism of action.

The effects of fostamatinib (as either R-788 or R-406) 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 signaling is thought to be the key mechanism of action. For example, treatment with fostamatinib effectively prevents the development of thrombocytopenia and hemolytic anemia induced by the passive transfer of anti-platelet and anti-red cell antibodies, respectively, to mice (24). In rodent models of asthma, R-406 reduced airways hyperresponsiveness (AHR) and markers of airways inflammation following antigen challenge in sensitized mice in two distinct models (16, 25). Similarly, in mice passively sensitized with anti-ovalbumin IgE, R-406 treatment prevented the development of AHR (25).

Treatment with R-406 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) (9). In addition, treatment with either R-406 or R-788 of Louvain and Lewis rats reduced clinical, histological and radiographic evidence of joint inflammation following active induction of collagen-induced arthritis (CIA) (26). These improvements were associated with a reduction in proinflammatory 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 (27). In the MRL/lpr strain, fostamatinib suppressed both established renal and skin disease, and reduced lymphadenopathy (28). Notably, this study demonstrated a sustained benefit for 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 (28).

Further evidence of fostamatinib's 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 proinflammatory cytokine expression (29). Remarkably, treatment was effective in reversing the histological 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 ischemia–reperfusion (30). The precise mechanisms via which these effects occur are not clear, although 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 (17). 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 internalization (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

R-788 was developed as the methylene phosphate prodrug of R-406, which exhibits low aqueous solubility, to improve its bioavailability and potential for oral dosage development.

Preclinical pharmacokinetic studies with fostamatinib (R-788) 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 R-406 following a single oral dose of R-788 10 or 20 mg/kg: $AUC_{0\text{-}16h}$ = 10,618 and 30,650 ng*h/mL, respectively, C_{max} = 2600 and 6500 ng/mL, respectively (observed at 1 hour), and $t_{½}$ = 4.2 hours (26). The prodrug was not detected in plasma, suggesting that R-788 is completely converted to R-406.

Phase I clinical studies in patients with non-Hodgkin's lymphoma (NHL) yielded the following parameters for R-406 exposure following single oral doses of R-788 of 200 or 250 mg: C_{max} = 668 and 1020 ng/mL, respectively, and $AUC_{0\text{-}4h}$ = 1800 and 2590 ng*h/mL, respectively (31). Plasma concentrations increased approximately twofold 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 R-406 exposure, with AUC values of 7766, 20,166 and 34,916 ng*h/mL, respectively, at doses of 50, 100 and 150 mg twice daily (32).

A detailed assessment of the pharmacokinetics and metabolic fate of fostamatinib using a combination of in vitro intestinal and hepatic microsomes and human mass balance studies has been conducted (33). This suggests that R-788 is rapidly hydrolyzed to R-406 by intestinal alkaline phosphatases, after which the more hydrophobic R-406 is rapidly absorbed. R-406 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 R-788 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 R-406) and on average 80% was recovered in feces. It appears that R-406 undergoes both direct glucuronidation and a cytochrome P450 CYP3A4-mediated *para*-*O*-demethylation to R-529 in the liver. Conjugates of R-529 secreted in bile are hydrolyzed back to R-529, 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 feces.

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 (24). In RA, total exposure (as determined by AUC) was related to adverse outcomes and study withdrawal (32). Conversely, in the phase I NHL study, there was no correlation between clinical outcomes and measured pharmacokinetic parameters (31). Ideally, future studies will assess more precisely the relationship between pharmacokinetics and clinical outcomes in order to establish the most effective and tolerable dosing regimens.

SAFETY

The results of detailed toxicity and immunotoxicology assessments in rats have been reported (29). Animals were treated with R-406 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 54,000 ng*h/mL, well in excess of those needed to achieve inhibition of SYK-mediated signaling in clinical studies. Consistent with the reported observations of the cited studies using animal disease models, there were no R-406-related changes in appearance, behavior, 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 indicating that R-406 had negligible effects on phagocytosis, oxidative burst, chemotaxis, or microbicidal activity of human leukocytes (9), suggesting that fostamatinib does not adversely affect innate immune responses.

The effects (both desirable and adverse) of fostamatinib on humoral immunity are less clear. R-406 did not affect IgG or IgM antibody production following immunization 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 titer in animals pretreated with fostamatinib (29). Similarly, treatment of pre-disease lupus-prone mice resulted in a trend (albeit not statistically significant) towards a reduction in circulating anti-dsDNA antibodies (27). 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 titers was seen, although the half-life of circulating antibody probably exceeds the short follow-up period of these studies (16, 26). 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 (17). There are no available preclinical 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 the highest doses in the RA and NHL trials (31, 32). Coadministration of methotrexate, previous immunosuppressant therapy and underlying bone marrow disease may have contributed to these rates. Neutrophil counts recovered with temporary withdrawal or dose reduction of fostamatinib. In a second phase II study in RA (35), there was an increase in the incidence of upper respiratory tract infection (14.5% in the 100 mg b.i.d. group versus 7.1% in the placebo group; $P < 0.05$), although none of the infections seen were associated with neutropenia. To date, there are no reports of opportunistic or atypical infection in clinical studies.

The most common adverse event seen in clinical studies with fostamatinib was gastrointestinal toxicity. Diarrhea was reported at rates of up 45% in some groups (32). 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 diarrhea were, however, the most common reasons for patient withdrawal from the treatment groups in larger RA studies (35, 36).

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 mmHg or diastolic BP > 90 mmHg) 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 preexisting hypertension or who were already on treatment at enrollment. It has been suggested that off-target effects of R-406 on vascular endothelial growth factor receptor 2 (VEGFR-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 a significantly increased cardiovascular risk must be considered and carefully monitored in clinical use.

Moderate elevations in transaminase enzymes were reported in all the clinical studies. Transaminitis was also reported in the preclinical toxicity studies, where it was not associated with any histopathological changes in the liver. In both preclinical and clinical studies, liver function normalized 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 or 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 signaling in platelets. Systemic exposures of R-406 at concentrations up to 25 μM did not extend bleeding time in mice (9). Similarly, R-406 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 –retroesophageal right subclavian artery– a phenotype similar to that seen in c-Ret knockout mice (37). The *RET* gene encodes a receptor tyrosine kinase that has a critical role in renal and ureteric development, and strikingly, R-406 has been shown to inhibit c-Ret kinase in in vitro and cell-based assays (IC_{50} = 5 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 hemorrhage, a consequence of the failure to separate developing lymphatic and blood vessels, and so disruption of SYK signaling 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 and pharmacodynamic studies showed that R-788/R-406 was well tolerated, with an effective concentration for SYK inhibition of approximately 0.5-1.0 μM (9, 38). For example, R-406 administered orally to human volunteers inhibited human basophil activation in response to anti-IgE ex vivo with an IC_{50} of 1.06 μM (corresponding plasma concentration of 496 ± 42 ng/mL). These concentrations were achievable within the dose range (75-150 mg b.i.d.) 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 R-406 in human plasma (> 98%).

To date, there have been 5 phase II clinical studies recruiting almost 1,000 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 75-175 mg b.i.d. induced a sustained improvement in platelet count in 50% of patients (24). 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 improvement in other clinical parameters, such as fewer bleeding episodes, avoidance of rescue medications and tapering of steroids. Although four 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 five. 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 randomized 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 randomized (3:1 ratio) to receive fostamatinib in an ascending-dose manner or placebo in a double-blind trial (32). 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 antirheumatic drugs (DMARDs) in addition to methotrexate, and 28% had received biological response modifiers in the past. The primary endpoint was the American College of Rheumatology 20% improvement criteria (ACR20) response rate at 12 weeks. This was achieved in 72% and 65% of patients, respectively, receiving fostamatinib 150 and 100 mg b.i.d., significantly greater response rates than seen with 50 mg b.i.d. (32%) or placebo (38%) ($P < 0.01$). Improvements in a number of secondary endpoints (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 proinflammatory cytokines such as interleukin-6.

A second double-blind, placebo-controlled study enrolled 457 patients with active RA despite long-term (i.e., > 3 months) methotrexate therapy, who were randomized (1:1:1) to receive fostamatinib 100 or 150 mg b.i.d. or placebo (35). A total of 67% and 57% of the patients in the respective treatment groups achieved the primary endpoint of an ACR20 response after 6 months, compared to 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 1 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 biological 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, respectively, receiving fostamatinib 100 and 150 mg once daily 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 1 prior biological therapy were enrolled to receive fostamatinib 100 mg b.i.d. or placebo (2:1 ratio) (36). There was no difference between groups in the rate of ACR 20/50/70 or DAS-28 response (38% vs. 37% for the primary endpoint of ACR20 at 3 months; $P = 0.84$). There were, however, statistically significant improvements in synovitis scores, as judged by magnetic resonance imaging (MRI), and inflammatory markers (ESR and CRP) in the treatment group. Despite randomization, there were baseline differences in steroid use, prior biological 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 be completed between June 2012 and January 2013.

Sixty-eight patients were enrolled in a phase II study investigating the effect of fostamatinib in a heterogeneous group of NHL and CLL (31). This cohort included many patients with heavily pretreated and relapsed disease (median number of prior treatments = 4). Previous treatments included rituximab (65%), multiagent chemotherapy (64%) and prior autologous stem cell transplantation (27.9%). Patients received fostamatinib 200 mg b.i.d. and were assessed for initial response at 8 weeks. Remission rates varied from 10% to 55%, depending on tumor 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 leukemias that are most susceptible to SYK inhibition as a therapeutic target.

DRUG INTERACTIONS

Hepatic microsome studies show that R-406 is extensively metabolized by expressed human CYP3A4 in vitro, and that this is inhibited by cytochrome P450 inhibitors such as ketoconazole by up to 90% (33). 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 (39). Notwithstanding, neutropenia was observed more frequently in the RA trials, where it was coadministered with methotrexate, than in the ITP trial, suggesting a possible synergistic effect on the bone marrow beyond the individual pharmacokinetic parameters.

A potential and important, although 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.

SOURCES

AstraZeneca (GB); discovered and developed by Rigel Pharmaceuticals (US).

DISCLOSURES

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