Long-Term Safety Profile of the Oral Spleen Tyrosine Kinase Inhibitor Fostamatinib in Immune Thrombocytopenia (ITP) and Other Diseases

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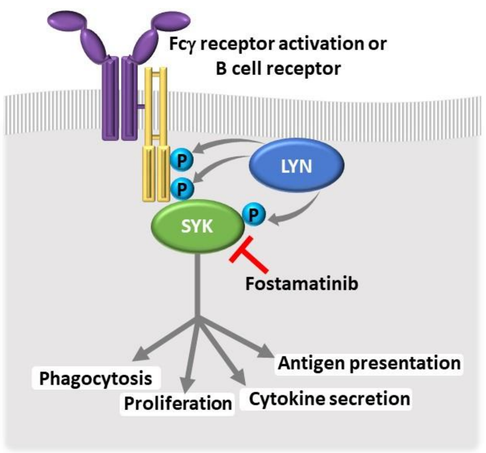
Introduction

- Fostamatinib is an oral, potent inhibitor of spleen tyrosine kinase (SYK) with proven efficacy and a manageable safety profile for the treatment of immune thrombocytopenia (ITP).
- SYK inhibition prevents platelet phagocytosis by Fcγ receptors on macrophages.

Figure 1. SYK Signaling Pathway



- SYK may also prevent antibody production by B cells.
- SYK is situated in an intracellular signaling pathway upstream of Bruton's tyrosine kinase (BTK) (see Fig 1).

Purpose and Methods

- Long-term safety data on fostamatinib at various dosing regimens (up to 300 mg/day) has been collected in >3500 patients with ITP or rheumatoid arthritis (RA).
- We present a summary analysis of the fostamatinib safety data from the ITP and RA studies.
- Fostamatinib safety data from 2 randomized, double-blind, placebo-controlled, phase 3 studies and the long-term, open-label, extension (OLE) study in ITP were pooled. These data are based on a starting dose of 200 mg/day (100 mg BID), which was increased to 300 mg/day (150 BID) after 4 weeks in 88% of patients.
- Fostamatinib safety data from 13 phase 2/3 studies in RA were pooled and are based on a dosing regimen of 100-150 mg/day (n=1232) or 200-300 mg/day (n=2205).

Results: Adverse events

- In the placebo-controlled RA studies, 2414 patients received fostamatinib with 823 patient exposure years and 1169 received placebo with 367 patient exposure years.
- Despite a two-fold (125%) increase in exposure with fostamatinib vs placebo (823 vs 367 patient exposure years), there was only a 26% increase in AEs (68% vs 54%, respectively).
- Some AEs may be dose-related, and one-third of the RA patients were on lower dosages (100-150 mg/day) than were generally given in the ITP trials (200-300 mg/day).

Table 1. Comparison of Data From ITP and RA Studies

Pooled Data	ITP Studies	RA studies
Total number of Patients	146	3437
Female Patients	60%	83%
Median age, years (range)	53 (20-88)	54 (18-87)
Mean duration of treatment with fostamatinib, months (range)	19 (<1-62)	18 (<1-81)
Number of patient exposure years	229	5134
Percentage of patients with AEs	87%	86%
Percentage of patients with mild/moderate AEs	63%	73%
Percentage of patients with serious AEs	31%	14%

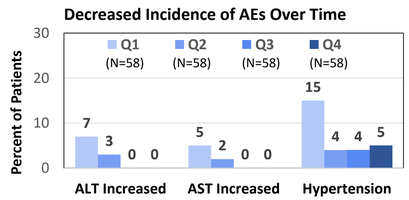
Table 2. Common Adverse Events in ITP and RA Studies

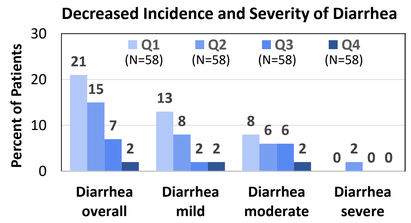
Common AEs	ITP Studies	RA Studies
Diarrhea	36%	24%
Hypertension	22%	19%
Nausea	19%	8%

Results: Time Course of AEs in ITP Studies

- 58 patients with ITP received fostamatinib for ≥1 year. Their experience was compared in 3-month increments over the first year to evaluate the cumulative effects of fostamatinib (figure 2).
- Diarrhea, hypertension, and increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) decreased in frequency during the second, third, and fourth quarters of the initial year of fostamatinib compared with the first quarter of treatment.
- The severity of diarrhea also decreased with ongoing treatment.

Figure 2. Incidence of Adverse Events by Quartile in the First Year

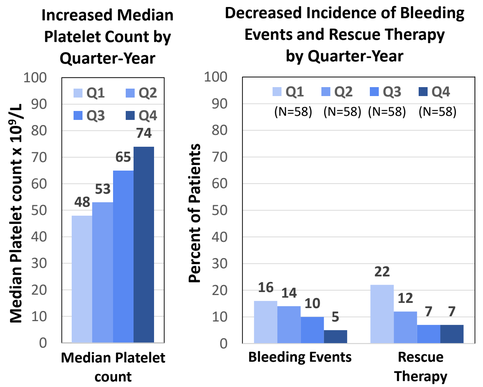




Results: Time Course of Response in ITP Studies

- The cumulative effect of fostamatinib on platelet counts was also apparent: median platelet counts increased each quarter over the first year of treatment in the 58 patients with ITP who received fostamatinib for ≥1 year (figure 3).
- Similarly, the incidence of bleeding events and the need for rescue therapy decreased each quarter over the first year of continued fostamatinib treatment.

Figure 3. Time Course of Response, Bleeding Events, and use of Rescue Medication by Quartile in the first Year



Results: Incidence of Thrombosis

- Patients with ITP have a higher risk of developing arterial and venous thromboembolic events (TEEs) than the general population. [1]
- The incidence of TEEs may be 3-4 times higher in ITP patients than in control subjects.[1]
- Studies in ITP patients treated with thrombopoietin receptor agonists have shown an incidence of TEEs of 2.6% to 8.9% in studies of 2-8 years duration.[2]
- In the fostamatinib phase 3 studies in ITP, an SMQ analysis revealed that only 1 of 146 patients (0.7%) had potential TEEs with up to 5 years of fostamatinib exposure.
- Several studies in animal models have shown that inhibition of SYK in platelets may reduce the incidence of TEEs.[3,4]

Summary

- Fostamatinib has been evaluated in >3500 patients with ITP or RA.
- Fostamatinib has a consistent and manageable safety profile.
- No new safety signals and no cumulative toxicity were observed with up to 62 months (5.2 years) of continuous treatment in ITP patients and up to 81 months (6.8 years) of continuous treatment in RA patients.
- Fostamatinib may reduce the risk of thromboembolic events.
- Ongoing studies of fostamatinib include:
  - Phase 3 study in patients with warm antibody autoimmune hemolytic anemia (NCT03764618)
  - Three phase 2/3 studies in hospitalized patients with COVID-19 (NCT04581954, NCT04579393, and NCT04629703).
  - All studies are actively enrolling patients.

References

1. Rodgehiero F. Blood Advances **2017;1(24)**:2280
2. Altomare I. Blood 2019; **134** (Supp 1): 4889
3. Spalton J. Thromb Haemost 2009;**7**:1192-9
4. Andrews, J Blood Med 2014;**5**:59-68

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