Treatment of Immune Thrombocytopenia in the COVID-19 era: Fostamatinib, an Oral Spleen Tyrosine Kinase Inhibitor

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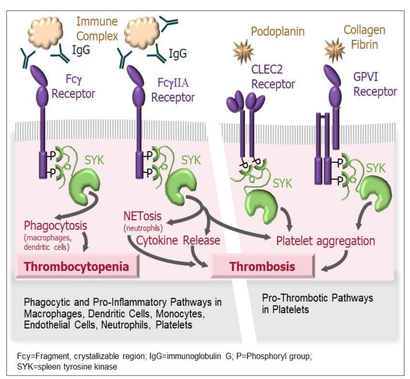
Introduction

- Immune thrombocytopenia (ITP) is an autoimmune disease resulting in both bleeding and, paradoxically, thrombotic events.
- The ongoing COVID-19 pandemic has made ITP management challenging.
- Immunosuppressive treatments may increase susceptibility to viruses.
- Severe COVID-19 patients are at increased risk for thrombosis, and ITP treatments that increase the risk of thrombosis may be unfavorable.
- The need to minimize office visits (potential exposure to virus) renders injectable treatments and difficult-to-titrate treatments less suitable.

Background

- Fostamatinib is an oral ITP treatment taken with or without food.
- Titration is uncomplicated: Dosing is initiated at the low dose (100mg BID) in all patients and increased to the high dose (150mg BID) after 4 weeks if needed.
- Thrombocytosis is rare (1.4% over 5 years), which simplifies monitoring and reduces office visits.
- Long-term safety data on fostamatinib have been collected in >3500 patients, including 146 patients with ITP (up to 5.2 years of treatment) and 3437 patients with rheumatoid arthritis (RA) (up to 6.8 years of treatment).
- Fostamatinib is not an immunosuppressive agent.
- Fostamatinib targets spleen tyrosine kinase (SYK)-mediated destruction of autoantibody-bound platelets by macrophages and may also prevent SYK-mediated events leading to thrombosis (See Figure 1).

Figure 1. Pro-inflammatory, pro-thrombotic and phagocytic pathways mediated by spleen tyrosine kinase (SYK)



Methods

- We reviewed the safety data from:
- The fostamatinib phase 3 studies in ITP (starting dose of 200 mg/day, which was increased to 300 mg/day after 4 weeks.
- The experience of the 58 patients who received fostamatinib for ≥1 year was compared quarterly over the first year to evaluate the cumulative effects of fostamatinib on platelet count, incidence of bleeding events, and use of rescue therapy.
- The fostamatinib phase 2/3 studies in RA (dosing regimen of 100-150 mg/day (n=1232) or 200-300 mg/day (n=2205).

Patient Characteristics

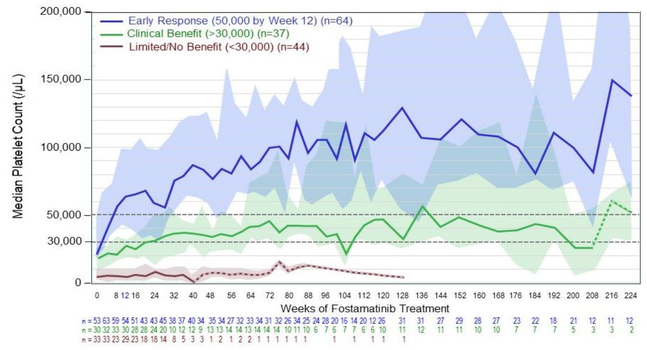
Table 1. Patient Characteristics in the ITP and RA Studies

	ITP Studies Pooled Data	RA studies Pooled data
Total number of Patients	**146**	**3437**
Female Patients	**60%**	**83%**
Median age, years (range)	**53 (20-88)**	**54 (18-87)**
Mean duration of fostamatinib treatment, months (range)	**19 (<1-62)**	**18 (<1-81)**
Number of patient exposure years	**229**	**5134**

Results: Efficacy in ITP Studies

- Fostamatinib increased platelet counts to ≥50,000/μL in 54% of patients, and the response was maintained for 86% of treatment days in the clinical studies.
- In the 32 patients who received fostamatinib as second-line therapy, 78% had platelet counts ≥50,000/μL, and the response was maintained for 83% of their treatment duration.

Figure 3. Median Platelet Counts Over Time in ITP Patients on Fostamatinib



Incidence of TEEs in the ITP Studies

- 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]
- Several studies in animal models have shown that inhibition of SYK in platelets may reduce the incidence of TEEs.[3,4]
- Thrombosis risk factors were identified in 87% of patients in the ITP trials, and 58% had multiple risk factors.
- An SMQ analysis revealed that only 1 of 146 patients (0.7%) had a potential TEE with up to 5.2 years of treatment. The TEE was a mild transient ischemic attack that resolved spontaneously.

Discussion

- Fostamatinib has been evaluated in >3500 patients across different disease populations and 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 6.8 years of continuous treatment in RA patients.
- Fostamatinib demonstrated a low incidence of thrombosis (0.7%) in the ITP trials, which was much lower than observed with ITP trials using thrombopoietin receptor agonists (incidence of TEEs 2.6% to 8.9% in studies of 2-8 years duration).[2]
- The oral administration, easy titration, and infrequency of thrombocytosis reduce the need for office visits.
- Fostamatinib provided increased platelet counts (≥50,000/μL) in 54% of patients overall, and in 78% of second-line therapy patients. Fostamatinib also reduced the frequency of bleeding events and the use of rescue therapy.
- Fostamatinib studies actively enrolling patients include:
  - Three Phase 2/3 studies for the treatment of COVID-19 (NCT04581954, NCT04579393, and NCT04629703)
  - Phase 3 study in patients with warm antibody autoimmune hemolytic anemia (NCT03764618)

Results: Safety in ITP and RA Studies

Table 2. Adverse Events (AE) in fostamatinib clinical studies in ITP and RA

n(%) with AEs	ITP Studies		RA Studies	
	Active	Placebo	Active	Placebo
Number of patients	102	48	2414	1169
Number of Patient Exposure Years	**29.3**	**12.1**	**823**	**367**
Any AE	85 (83%)	36 (75%)	1644 (68%)	634 (54%)
Diarrhea	32 (31%)	7 (15%)	328 (14%)	52 (4%)
Hypertension	29 (28%)	6 (13%)	424 (18%)	78 (7%)
Any Infection	27 (26%)	10 (21%)	388 (16%)	147 (13%)
Upper Respiratory tract infection	6 (6%)	2 (4%)	21 (1%)	16 (1%)
Respiratory tract infection	3 (3%)	1 (2%)	2 (0.1%)	1 (0.1%)
Bronchitis	3 (3%)	0	19 (1%)	7 (1%)
Influenza like illness	3 (3%)	0	0	0
Urinary tract infection	3 (3%)	0	25 (1%)	8 (0.7%)
Nasopharyngitis	2 (2%)	1 (2%)	46 (2%)	11 (1%)
Viral infection	2 (2%)	1 (2%)	4 (0.2%)	1 (0.1%)

- AEs appeared to be somewhat more common in ITP patients than RA patients (Table 2).
- 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).
- The incidence of infections was slightly higher in the fostamatinib groups compared with the placebo groups, which is consistent with the longer duration of treatment in the fostamatinib groups.
- The most common AEs in both studies were diarrhea and hypertension.

References

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2. Altomare I. Blood 2019; **134** (Supp 1): 4889
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4. Andrews, J Blood Med 2014;**5**:59-68

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