Sustained response off-treatment and thrombotic events in patients with immune thrombocytopenia treated with fostamatinib: a systematic review and meta-analysis

Immune thrombocytopenia (ITP) is an acquired condition characterized by low platelet counts and a paradoxical risk of thrombosis, with a potential for long-term remission following treatment. For this reason, there has been increasing interest in the thrombotic risk and chances of remission associated with ITP-specific treatments. Fostamatinib, an oral Syk inhibitor, has recently become available for the treatment of ITP.[1,2] Although some studies have shown the possibility of obtaining a sustained response off-treatment (SROT) in a subset of patients on fostamatinib,[3-5] the magnitude of this phenomenon is still not well understood. Recent research has detected a very low thrombotic event rate in users of fostamatinib.[6] However, data on this novel drug are still scarce. We have carried out a systematic review to investigate the rates of SROT and thrombosis in fostamatinib users.

We searched Medline and Embase up to September 17, 2025, using a pre-defined research string ["Fostamatinib AND ((Immune Thrombocytopenic Purpura) OR (Autoimmune Thrombocytopenia) OR (Werlhof Disease) OR (Thrombocytopenia) OR (Thrombocytopenic))"] and a snowball strategy. Eligibility assessment was performed independently by two reviewers (SS and CM). Disagreements were solved by consensus or by a third reviewer (BC). We included peer-reviewed published studies in English describing adult ITP patients with known fostamatinib treatment status and available data on at least one of the primary outcomes. We excluded case series describing fewer than five patients. The primary efficacy outcome was the cumulative rate of SROT, extracted as study-defined SROT (fostamatinib discontinuation with sustained safe platelet counts). Study definitions are summarized in *Online Supplementary Table S1*. The primary safety outcome was the cumulative rate of thrombotic events, defined as any fatal or non-fatal thrombosis, in either the arterial or venous district. Secondary outcomes included the rates of arterial and venous thrombotic events analyzed separately. The diagnosis of ITP was based on the authors' judgment. Data extraction was performed independently by two reviewers (SS and CM) using a pre-defined electronic case report form set up on Microsoft Excel. We analyzed data from observational studies and randomized controlled trials (RCT) separately. Categorical data were expressed as counts and percentages, with 95% confidence intervals (95% CI) calculated with the exact binomial method (GraphPad Prism 10). Where necessary, we performed data conversions (e.g., years or days to months). We compared categorical data using the Fisher exact test and χ^2 test, as appropriate. The assessment of the risk of bias was performed independently by BC and CM using the RoB2 tool for RCT and the ROBINS-I version 2 tool for observational studies, with results visualized using the *robvis* tool. We performed meta-analysis of data using the random intercept logistic regression model and logit transformation; heterogeneity was measured using the I^2 statistic and the Wald test (R Core Team software, 2023). We performed a *post-hoc* subgroup analysis, comparing the frequency of SROT between patients with primary and secondary ITP. Two-tailed *P* values <0.05 were considered statistically significant. Institutional review board approval was not required. The study was conducted in accordance with the Declaration of Helsinki.

We retrieved 630 studies, of which 11 (9 observational studies and 2 RCT) were included in the final analysis (Figure 1). Three studies provided data on SROT and ten on thrombosis. Altogether, the eligible studies reported on SROT for 294 patients and thrombosis for 613 patients, for a total of 674 individual adults with ITP treated with fostamatinib (123 in RCT and 551 in observational studies). Additionally, 61 patients received placebo in the context of RCT. Eligible patients' characteristics are detailed in *Online Supplementary Table S2*.

Among 294 patients treated with fostamatinib in observational studies (166 females, 21 patients with secondary ITP and 216 with chronic ITP), SROT was reported in 14 patients (meta-analyzed frequency: 5%, 95% CI: 2-10; I^2 71%, *P*=0.04) over a median follow-up since discontinuation, based on available data, of 263 days (interquartile range, 247-313) (Table 1; see *Online Supplementary Table S1* for SROT definitions). SROT was not reported in any of the eligible RCT. There were no significant differences in the rates of SROT between patients with primary or secondary ITP (primary: 11/183, 6%, 95% CI: 3-11; secondary: 1/15, 7% 95%: CI 0-32; *P*=1). The causes of secondary ITP, as reported by the authors, were lymphoproliferative disorders (N=4), monoclonal gammopathy of undetermined significance (N=3), immune deficiency (N=3), systemic lupus erythematosus (N=2), antiphospholipid antibody syndrome (N=2) and COVID-19 (N=1). The patient with secondary ITP who achieved SROT had ITP secondary to monoclonal gammopathy of undetermined significance.

Among 490 patients treated with fostamatinib in observational studies (55% females, 21 patients with secondary ITP

and 337 patients with chronic ITP), five patients developed thrombosis over a follow-up ranging from 4 to 60 months (meta-analyzed frequency: 1%, 95% CI: 0-2; I^2=0%, *P*=0.94) (Table 2). In the two eligible RCT, none of the patients treated with fostamatinib or placebo (all with primary ITP) developed thrombosis throughout a study duration of 6 months (meta-analyzed frequency for fostamatinib: 0%, 95% CI: 0-100; I^2=0%; *P*=1) (Table 2). Among the 490 patients treated with fostamatinib in observational studies, the meta-analyzed frequencies of arterial and venous thrombosis were low and comparable (*Online Supplementary Table S3*). None of the RCT patients developed arterial or venous thrombosis (*Online Supplementary Table S3*).

All observational studies eligible for SROT and six of the observational studies eligible for thrombosis analysis were at critical risk of bias due to uncontrolled confounding of treatment selection. The remaining two observational studies, both extension cohorts of previous RCT, were considered at serious risk of bias due to confounding (*Online Supplementary Figure S1*). Results on thrombosis remained consistent considering only studies at lower risk of bias (*Online Supplementary Table S4*). The two RCT eligible for the analysis of thrombosis generated some concerns regarding the presence of bias (*Online Supplementary Figure S1*).

In our systematic review of published studies, we found that the cumulative frequency of thrombosis is low and that a non-negligible proportion of treated patients may achieve a lasting SROT upon discontinuation of fostamatinib. Direct comparisons of our results with data on other ITP treatments are impossible. Moreover, data on SROT are significantly limited by the few eligible studies and heterogeneity in how drug discontinuation was reported and achieved. Nevertheless, spontaneous remission of chronic ITP in adults occurs only sporadically. Splenecto-

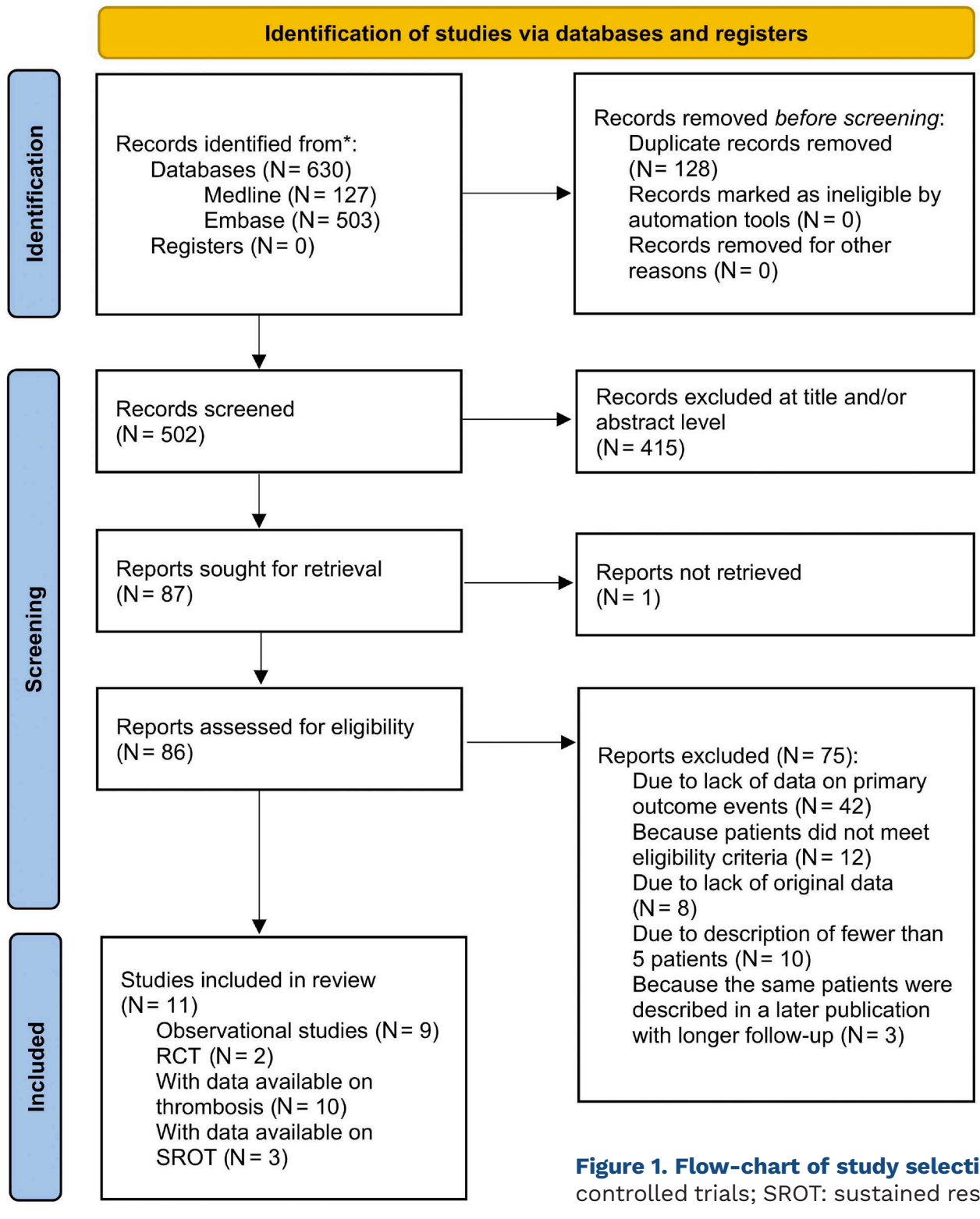

Figure 1. Flow-chart of study selection. RCT: randomized controlled trials; SROT: sustained response off-treatment.

my is a one-time intervention with a modest excess risk of infection and venous thromboembolism and reported durable remissions over 10-12 years.[7] Although thrombotic events have been reported in users of thrombopoietin receptor agonists[8] a meta-analysis from 2021 found no statistically significant increase in thrombosis among ITP patients treated with thrombopoietin receptor agonists.[9] On the other hand, SROT has been reported in 25% to 32% of patients following tapering and discontinuation of thrombopoietin receptor agonists in prospective studies.[10,11] Responses to rituximab generally last 1 year. In an RCT of rituximab *versus* placebo, 4% of patients receiving rituximab experienced thrombosis *versus* none in the placebo group.[12]

The results of our study align with the mechanistic rationale for fostamatinib use, as fostamatinib selectively impairs immune-mediated platelet destruction without promoting prothrombotic pathways. Syk inhibition has been shown to inhibit platelet activation and thrombus formation without significantly impairing primary hemostasis[13] and may reduce the release of neutrophil extracellular traps[14] and contrast atherothrombosis. Moreover, Syk inhibition attenuates autoantibody and proinflammatory cytokine production, underscoring the possibility of obtaining a durable remission.[15] Taken together, our results suggest that fostamatinib may be a suitable option in patients at high risk of thrombosis and support continued efforts to investigate optimal discontinuation strategies.

Our study has limitations. Firstly, the risk of bias of the eligible observational studies was at least serious due to uncontrolled confounding of treatment selection. Moreover, because of the few retrieved results (<10 for each endpoint), we could not formally assess publication bias. Nevertheless, the analyzed studies capture real-world experience with fostamatinib, and we therefore pooled estimates to detect possible safety signals. Moreover, a sensitivity analysis including only observational studies at lower risk of bias yielded comparable results for thrombosis. Secondly, there was considerable heterogeneity in the duration of follow-up and the annualization of thrombosis rates was not possible. Finally, our results regarding SROT are limited by many factors. Firstly, we retrieved only three observational studies suitable for the analysis of SROT, resulting in high heterogeneity of the meta-analyzed data. This reflects the still limited and emerging experience with fostamatinib tapering and discontinuation strategies, based on prior studies on thrombopoietin receptor agonists. Finally, with the available data, we were only able to compute the frequency of SROT among

Table 1. Sustained response off-treatment in patients with immune thrombocytopenia treated with fostamatinib in observational studies.

Study	Patients with events/ Patients	Rate, % (95% CI)	I^2; *P*
Gonzàlez-López, 2024	5/138	4 (1-8)	-
Mingot-Castellano, 2024	7/61	12 (5-22)	-
Lucchini, 2025	2/95	2 (0-7)	-
Pooled estimate	14/294	5 (2-10)	71%; 0.04

Treatment duration prior to fostamatinib discontinuation was not available in the study by Gonzàlez-López *et al.*; however, four of the five patients who achieved a sustained response off-treatment had a complete response prior to discontinuation. In the study by Mingot-Castellano *et al.* patients were eligible for tapering and discontinuation of fostamatinib if they had a platelet count greater than $100x10^9$/L (complete response) for at least 6 months OR if they had a platelet count greater than $250x10^9$/L, irrespective of the duration of their complete response. In the study by Lucchini *et al.* two patients discontinued fostamatinib within 6 months of treatment initiation, while in response, without tapering the drug. The median duration of follow-up since discontinuation was 263 days (interquartile range, 247-313) in one study, and unavailable for the other two. The median duration of sustained response off-treatment, based on available data, was 9 months. 95% CI: 95% confidence interval.

Table 2. Thrombosis in patients with immune thrombocytopenia treated with fostamatinib in observational studies and in randomized controlled trials.

Study	Patients with events/ Patients	Rate, % (95% CI)	I^2; *P*
Observational studies			
Lucchini, 2025	0/95	0 (0-4)	-
Kuwana, 2025	0/22	0 (0-15)	-
Gonzàlez-López, 2024	2/138	2 (0-5)	-
Dranitsaris, 2024	2/51	4 (1-14)	-
Mingot-Castellano, 2024	0/18	0 (0-19)	-
Passucci, 2024	0/15	0 (0-22)	-
Mehta, 2022	0/5	0 (0-52)	-
Cooper, 2021	1/146	1 (0-4)	-
Pooled estimate	5/490	1 (0-2)	0%; 0.94
Randomized controlled trials			
Kuwana, 2025	0/22	0 (0-15)	-
Bussel, 2018	0/101	0 (0-4)	-
Pooled estimate	0/123	0 (0-100)	0%; 1

The duration of follow-up ranged from 4 to 60 months in observational studies, whereas treatment duration was 6 months in randomized controlled trials. Regarding observational studies: the temporal association between thrombosis and fostamatinib treatment initiation was not consistently reported. The reported thrombotic events included two deep vein thromboses, one superficial vein thrombosis, one acute myocardial infarction and one transient ischemic attack. Whenever specified, we considered thrombotic events eligible for the analysis only if they occurred while on treatment with fostamatinib. The study by Lucchini *et al.* reported a thrombotic event which occurred 5 months after discontinuation of fostamatinib and, thus, was not included in this analysis. 95% CI: 95% confidence interval.

all treated patients. This is probably the greatest factor limiting the clinical relevance of our findings: computing the rates of SROT over the number of patients who were considered candidates for drug tapering with the goal of discontinuation would have probably led to more clinically meaningful estimates.

The results of our systematic review, although limited by the low quality of eligible studies and by the heterogeneity of follow-up duration, show that treatment with fostamatinib is characterized by a favorable safety profile and by the possibility of obtaining remission in a non-negligible and possibly underestimated proportion of treated patients, supporting the use of fostamatinib as a valuable second-line option for patients with ITP.

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Contributions

BC, SB and GMP conceived the study and were responsible for the methodology. SB and GMP supervised the study. EP was responsible for the software. SS, CM, ET and BC carried out the investigation and curated the data. BC, CM, ET, EP, CP and SS conducted the formal analysis. SS, BC and CM were responsible for visualization. BC wrote the original draft. GMP and CP wrote, reviewed and edited the manuscript.

Data-sharing statement

The raw data supporting the findings of this study will be made available upon reasonable request mailed to the corresponding author.

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