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RESEARCH LETTER

Durability of platelet response after switching to avatrombopag from eltrombopag or romiplostim in immune thrombocytopenia

Immune thrombocytopenia (ITP) is an autoimmune bleeding disorder in which platelet levels are reduced [1]. Currently, 3 thrombopoietin receptor agonists (TPO-RAs) are approved to treat chronic ITP in the United States and the European Union: romiplostim, eltrombopag, and avatrombopag [2–7]. Patients may switch from one TPO-RA to another for different reasons, including lack of effectiveness, adverse events (AEs), insurance coverage, or convenience [8,9]. Variable responses to these TPO-RAs have been observed [8,9], possibly owing to their differing molecular structures, mechanistic characteristics, binding sites, effects on receptors, pharmacology, and downstream effects [10].

The oral TPO-RA avatrombopag was approved more recently than romiplostim and eltrombopag, has no boxed warning for hepatotoxicity, and does not bind polyvalent cations [2–7]. Data describing the durability of platelet response, effectiveness, or loss of response (LOR) characteristics in patients with ITP who have switched to avatrombopag from another TPO-RA are limited. Recently, we reported the results of a multicenter, retrospective observational study of adult patients with primary ITP or secondary ITP who switched from eltrombopag or romiplostim to avatrombopag [9]. After switching, platelet response ($\geq 50 \times 10^9$/L) and complete response ($\geq 100 \times 10^9$/L) were achieved in 93% and 86% of patients, respectively. Here, we report an additional analysis of a retrospective observational study, focusing on the durability of response to avatrombopag following eltrombopag or romiplostim.

This study was a collaboration between 4 tertiary ITP referral clinics in the United States and Sobi, Inc. Adults with ITP who switched TPO-RA treatment from eltrombopag or romiplostim to avatrombopag from July 2019 through December 2020 were retrospectively evaluated. Avatrombopag treatment had to be initiated within 1 month of stopping romiplostim or eltrombopag and had to be continued for at least 2 months to allow for full-dose titration. The manner in which patients were transitioned from romiplostim or eltrombopag was not stipulated but rather left to the investigators' discretion. Response was defined as a platelet count of $\geq 50 \times 10^9$/L at least once without rescue therapy, and LOR was defined as 2 consecutive platelet counts, at least 7 days apart, $< 50 \times 10^9$/L. Platelet counts were disqualified if they were drawn <8 weeks from receipt of rescue corticosteroids or <4 weeks from intravenous immunoglobulin to minimize the impact of rescue therapy on assessment of response. During the observation period, durability of response was evaluated as the total number of days achieving a platelet response compared with the total number of days exposed to avatrombopag. The days between platelet count draws were categorized as response or nonresponse based on the most recent platelet count measurement. Durability and LOR characteristics were summarized for the responding population, and subgroup analyses were performed by reason for switch (convenience, lack of effectiveness, and AE) and disease (primary ITP vs. secondary ITP).

Forty-four patients were included (median [range] age, 61 [21–87] years; men, 48%). At avatrombopag initiation, patients had an ITP diagnosis for a median (range) of 49 (2, 550) months and a median (range) of 4 (2, 10) unique previous ITP therapies. The median (range) duration of avatrombopag exposure was 9.2 (2.8, 17.2) months, and the mean (standard deviation [SD]) weekly avatrombopag dose was 154 (82) mg. For those who switched for convenience (n = 23), lack of effectiveness (n = 14), and AE (n = 7), the mean (SD) average weekly avatrombopag doses were 117 (52) mg, 213 (85) mg, and 157 (85) mg, respectively. In the total population, 52% of patients (23/44) never changed their avatrombopag dose, whereas 25% (11/44) increased and 23% (10/44) decreased their doses. Of the 21 patients who changed their dose, the median (range) frequency of change was 1 (1, 4) time. The median (range) frequency of change was 0 (0, 4) times for the total population and 0 (0, 4), 1 (0, 3), and 0 (0, 3) times for those who switched for convenience, lack of effectiveness, and AE. Patients had a mean of 17.7 platelet count measurements during avatrombopag exposure (median [range], 12 [4, 58]).

Response was achieved by 93% of patients (41/44) at least once while on avatrombopag, including 86% of patients who switched for lack of efficacy (12/14) (Table). Among responders (n = 41), the response was maintained for 84% of their time on treatment (88% of time on avatrombopag for those without the need for rescue therapy [n = 36] and 55% for those who required rescue therapy [n = 5]). Patients who switched for convenience, lack of effectiveness, or AE maintained a response for 93%, 58%, and 87% of their time on avatrombopag.

TABLE Durability of platelet count response[a] (platelet count ≥50 × 10^9/L) to avatrombopag following switch from romiplostim or eltrombopag according to baseline demographic subgroups, reason for switch, ITP disease type, and prior treatment status.

Population	All responders (*n* = 41)	Responders with no LOR (*n* = 28)	Responders with LOR (*n* = 13)	Nonresponders (*n* = 3)
Median platelet count × 10^9/L (all measurements during the study)				
All	108	118	83	14
Switch for convenience	129 (*n* = 23)	133 (*n* = 18)	109 (*n* = 5)	-
Switch for lack of effectiveness	64 (*n* = 12)	71 (*n* = 6)	65 (*n* = 6)	18 (*n* = 2)
Switch for AEs	93 (*n* = 6)	93 (*n* = 4)	92 (*n* = 2)	14 (*n* = 1)
Proportion of time response (platelet count ≥50 × 10^9/L) to avatrombopag was maintained, %				
All	84	93	69	0
Sex				
Female	88 (*n* = 22)	95 (*n* = 16)	74 (*n* = 6)	0 (*n* = 1)
Male	79 (*n* = 19)	90 (*n* = 12)	65 (*n* = 7)	0 (*n* = 2)
Age (y)				
≥61	86 (*n* = 21)	91 (*n* = 13)	79 (*n* = 8)	0 (*n* = 1)
≤60	82 (*n* = 20)	94 (*n* = 15)	56 (*n* = 5)	0 (*n* = 2)
Reason for switch				
Convenience	93 (*n* = 23)	95 (*n* = 18)	87 (*n* = 5)	-
Lack of effectiveness	58 (*n* = 12)	81 (*n* = 6)	49 (*n* = 6)	0 (*n* = 2)
Adverse event	87 (*n* = 6)	95 (*n* = 4)	75 (*n* = 2)	0 (*n* = 1)
ITP disease type				
Primary ITP	87 (*n* = 22)	94 (*n* = 17)	68 (*n* = 5)	0 (*n* = 3)
Secondary ITP	79 (*n* = 19)	90 (*n* = 11)	70 (*n* = 8)	-
No. of previous ITP treatments				
≤4 treatments	89 (*n* = 25)	92 (*n* = 20)	82 (*n* = 5)	0 (*n* = 1)
≥5 treatments	76 (*n* = 16)	94 (*n* = 8)	62 (*n* = 8)	0 (*n* = 2)
Duration of ITP				
≤50 mo	84 (*n* = 22)	93 (*n* = 13)	74 (*n* = 8)	0 (*n* = 1)
≥51 mo	84 (*n* = 19)	92 (*n* = 15)	61 (*n* = 5)	0 (*n* = 2)
Most recent TPO-RA				
Romiplostim	84 (*n* = 31)	94 (*n* = 20)	70 (*n* = 11)	0 (*n* = 2)
Eltrombopag	81 (*n* = 9)	87 (*n* = 7)	67 (*n* = 2)	0 (*n* = 1)
Both	100 (*n* = 1)	100 (*n* = 1)	-	-
Splenectomy status				
Splenectomized	88 (*n* = 8)	95 (*n* = 5)	73 (*n* = 3)	0 (*n* = 1)
Nonsplenectomized	83 (*n* = 33)	92 (*n* = 23)	68 (*n* = 10)	0 (*n* = 2)

AE, adverse event; ITP, immune thrombocytopenia; LOR, loss of response; TPO-RA, thrombopoietin receptor agonist.
[a]Patients in the study had a mean of 17.7 platelet count measurements during avatrombopag exposure (median [range], 12 [4, 58]).

A durable response was achieved by patients switching from romiplostim (*n* = 31) or eltrombopag (*n* = 9) for 84% and 81%, respectively, of their time on avatrombopag (Table). Previously splenectomized patients (*n* = 8) maintained a durable response for 88% of their time exposed to avatrombopag. Patients treated with ≥5 (*n* = 16) and ≤4 (*n* = 25) before ITP therapies experienced a durable response for 76% and 89%, respectively, of their time on avatrombopag. Twenty-two of 25 patients (88%) with primary ITP and 19 of 19 patients (100%) with secondary ITP achieved a response that was maintained for a respective 87% and 79% of their time on treatment (Table).

Twenty-eight of the 41 responders never experienced a LOR while on avatrombopag (Figure). Importantly, 6 of 12 responders

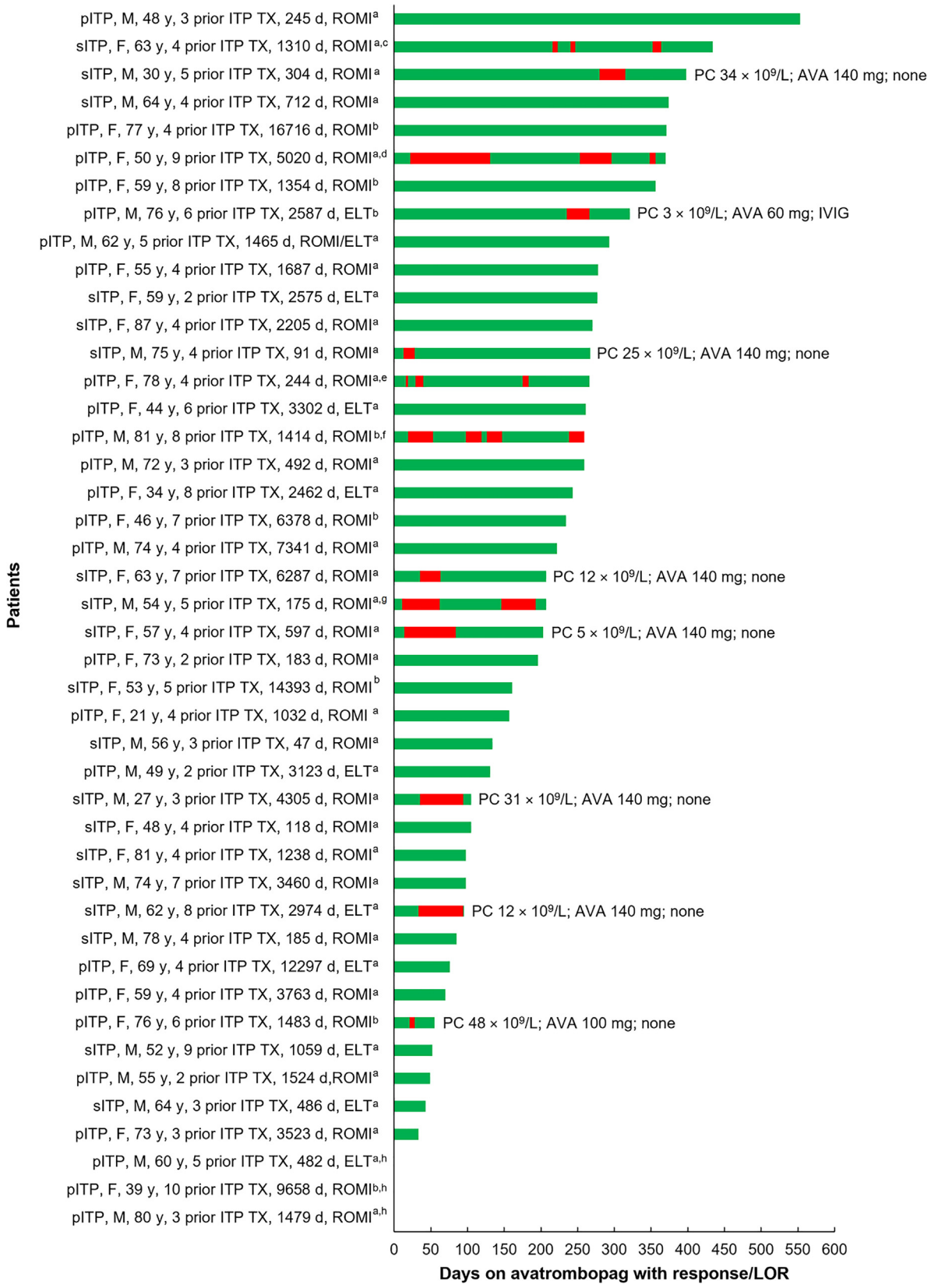

FIGURE Days on avatrombopag with platelet response (platelet count ≥50 × 10^9/L) and LOR (2 consecutive platelet counts, at least 7 days apart, <50 × 10^9/L). Y-axis labels the current type of disease, sex, age, number of previous ITP treatments, ITP disease duration, and most recent TPO-RA for each individual patient. Green bars represent the time on avatrombopag with a response (platelet count ≥50 × 10^9/L); red bars represent the time on avatrombopag with LOR (2 consecutive platelet counts, at least 7 days apart, <50 × 10^9/L). Labels are next to the

(50%) who switched for lack of efficacy never experienced a LOR. As previously reported, the mean (SD) and median (range) times on avatrombopag for all 44 patients were 9.2 (4.0) months and 9.2 (2.8, 17.2) months, respectively [9]. All but 1 patient regained a platelet count response after experiencing a LOR, and 7 of 12 patients who regained a response did not experience another LOR during avatrombopag treatment (Figure). The median platelet count at LOR was 25 $\times$ 10^9/L. The average percentage of time experiencing a LOR episode was 13%. Among those who had LOR, the nadir platelet count was $\leq$10 $\times$ 10^9/L in 3 patients and 11–20 $\times$ 10^9/L in 4 patients, and 3 required rescue therapy (one patient with 2 LOR episodes required rescue therapy both times). One patient reduced their concomitant steroid dose 13 days before a LOR. As previously reported, 6 of 44 patients (14%) discontinued avatrombopag; one patient (2%) discontinued avatrombopag for each of the following reasons: remission attempt, formulary limitations, lack of response, AEs (headache and portal vein thrombosis), patient preference, and the initiation of rituximab for autoimmune hemolytic anemia [9].

The findings of this study should be confirmed in a larger patient population. A phase 4 trial evaluating the safety, platelet count, and treatment satisfaction of adults with chronic ITP after switching to avatrombopag from eltrombopag or romiplostim is currently underway (NCT04638829).

In a heavily pretreated, chronic ITP population switched from eltrombopag or romiplostim to avatrombopag, the platelet response was both durable and stable, with just over two-thirds of patients never experiencing an LOR. To our knowledge, this is the first study to examine the durability of avatrombopag over time in patients who have switched from another TPO-RA. The data reported herein support the durability of response with avatrombopag after switching from a different TPO-RA and underscore the potential value of switching between TPO-RAs when a previous TPO-RA is inconvenient, not effective, or associated with tolerability issues and regardless of whether the patient presents with primary ITP or secondary ITP.

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AUTHOR CONTRIBUTIONS

H.A.-S. and A.C. contributed to concept and design, data collection, data analysis, writing of the manuscript, critical revisions of the intellectual content, and final approval. D.J., T.G., H.L., and S.L. contributed to data collection, critical revisions of the intellectual content, and final approval. C.B., M.V., and M.W. contributed to concept and design, data analysis, critical revisions of the intellectual content, and final approval.

RELATIONSHIP DISCLOSURE

H.A.-S. has served as a consultant for Agios, Dova/Sobi, argent, Rigel, Novartis, Forma, and Moderna, and his institution has received research support on his behalf from Agios, Dova/Sobi, Novartis, Vaderis, and Amgen. T.G. has received honoraria from Amgen, Dova/Sobi, and Novartis; has acted as a consultant for the Platelet Disorder Support Association, Amgen, Dova Pharmaceuticals, Biogen, Momenta, Sanofi, Vertex, Cellphire, Fujifilm, Rigel, Shionogi, and Principia; and has received research support from the National Heart, Lung, and Blood Institute, Principia, Rigel, and Cellphire. H.L. has served as a consultant for Amgen, argenx, Dova/Sobi, Genzyme, Novartis, and Sanofi and has received research funding from argenx, Momenta/Janssen, and Principia/Sanofi. C.B., M.W., and M.V. are employees of Sobi, Inc., Durham, North Carolina. A.C. has served as a consultant for Synergy; he has received royalties from UpToDate; and his institution has received research support on his behalf from Alexion, Bayer, Novartis, Novo Nordisk, Pfizer, Sanofi, Spark, and Takeda. D.J. declares no conflicts of interest. S.L. declares no conflicts of interest.

KEYWORDS

avatrombopag, eltrombopag, immune thrombocytopenia, romiplostim, thrombopoietin receptor

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horizontal bars, and the information in footnotes [c, d, e, f] and [g] represent PC at LOR, weekly avatrombopag dose at LOR, and rescue therapy required for each LOR (separated by /). AVA, avatrombopag; ELT, eltrombopag; IVIG, intravenous immunoglobulin; LOR, loss of response; PC, platelet count; pITP, primary immune thrombocytopenia; ROMI, romiplostim; sITP, secondary immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonists; TX, treatment. [a]Patient not splenectomized. [b]Patient splenectomized. [c]PC 37 $\times$ 10^9/L; AVA 140 mg; none / PC 31 $\times$ 10^9/L; AVA 280 mg; none / PC 30 $\times$ 10^9/L; AVA 280 mg; none. [d]PC 29 $\times$ 10^9/L; AVA 140 mg; none / PC 33 $\times$ 10^9/L; AVA 280 mg; none / PC 37 $\times$ 10^9/L; AVA 280 mg; none. [e]PC 5 $\times$ 10^9/L; AVA 140 mg; none / PC 35 $\times$ 10^9/L; AVA 140 mg; none / PC 35 $\times$ 10^9/L; AVA 280 mg; none. [f]PC 15 $\times$ 10^9/L; AVA 140 mg; IVIG / PC 31 $\times$ 10^9/L; AVA 280 mg; none / PC 34 $\times$ 10^9/L; AVA 280 mg; none / PC 21 $\times$ 10^9/L; AVA 280 mg; none. [g]PC 18 $\times$ 10^9/L; AVA 280 mg; IVIG / PC 21 $\times$ 10^9/L; AVA 280 mg; IVIG. [h]Patient did not achieve PC $\geq$ 50 $\times$ 10^9/L.

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