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Letter to *Blood*

TO THE EDITOR:

Thrombopoietin receptor agonists as an emergency treatment for severe newly diagnosed immune thrombocytopenia in children

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Immune thrombocytopenia (ITP) is a rare disease that is characterized by autoimmune platelet destruction and, for some patients, by a defect in megakaryocyte proliferation and impaired platelet production.[1,2] Fewer than 10% of ITP patients experience severe bleeding, including 0.1% to 0.9% who experience life-threatening intracranial hemorrhages.[3,4] Two thrombopoietin receptor agonists (TPO-RAs), romiplostim and eltrombopag, are labeled for chronic ITP, to increase platelet production.[5-7] Children with newly diagnosed (ND)-ITP (ie, ITP lasting less than the first 3 months of the course, with absent or mild bleeding) are managed with an expectant "watch and wait" policy, regardless of the platelet count.[8-10] First-line treatments, IV immunoglobulin (IVIg) and/or short-course steroids, are indicated in case of bleeding complications.[11] Second-line treatments are prescribed on a case-by-case basis when first-line treatments are ineffective in children with severe or highly recurrent hemorrhagic syndrome. TPO-RAs are not yet indicated as frontline therapy for children with ND-ITP, but some studies suggest their effectiveness in ND-ITP and persistent ITP.[9,12-14] The French CEREVANCE network conducted a national study to evaluate the efficacy and safety of TPO-RAs as a rescue therapy for patients with severe ND-ITP.

Patients aged 1 to 18 years treated with romiplostim or eltrombopag for primary ND-ITP in an emergency bleeding context were prospectively included in the observational national CEREVANCE database. Written informed consent was obtained from parents and patients. Patients were treated with TPO-RAs according to CEREVANCE guidelines (http://www.cerevance.org). End points were the overall response at day 15 after initiation, the time to response, and the response at 3 and 6 months and at the last follow-up (FU). Bleeding severity was graded on a scale from 0 to 4.[15] Response was assessed according to the International Working Group.[16] Adverse events were recorded. Patients were classified into 2 subgroups: group 1 included patients with severe life-threatening hemorrhage that required urgent therapies, and group 2 included patients with a moderate bleeding tendency, despite first-line treatments. The Fisher's exact test was used to compare response status, and the Mann-Whitney-Wilcoxon test was used to compare durations.

Between 2009 and 2019, 15 patients with ND-ITP from 7 centers were treated with TPO-RAs at a median of 20 days (range, 1-71) from diagnosis. The median age at ITP diagnosis was 4.3 years (range, 1.2-14.2). No patient developed lupus or immune deficiency.

In group 1 (n = 8), romiplostim was used in emergencies soon after diagnosis: all patients had a Buchanan grade ≥4 (epistaxis n = 6 and buccal n = 2), a platelet count $<10 \times 10^9$/L, and transfusion need at a median of 6 days (range, 1-25) from diagnosis; they received a median dose of 5 μg/kg per week (Table 1). The median number of TPO-RA injections was 1 (range, 1-20); 5 patients received only 1 injection. All 8 patients received IVIg and steroids before TPO-RAs. Three patients received concomitant treatment (vinblastine, n = 2; rituximab, n = 1). All patients achieved a response at day 15: 75% achieved complete remission (CR), and 25% achieved partial remission (PR). The median time to response was 4 days (range, 1-7). All patients maintained their response at month 3, month 6, and at last FU (7 CRs and 1 PR). At months 3 and 6, all patients were free of any treatment. The median FU was 18 months (range, 12-87); TPO-RAs were discontinued in all 8 patients because of efficacy.

In group 2 (n = 7), TPO-RAs (eltrombopag, n = 4; romiplostim, n = 3) were introduced for persistent Buchanan grades 1 to 3 and platelet count $<20 \times 10^9$/L, at a median of 37 days from diagnosis (range, 20-71). The median duration of TPO-RA exposure was 99 days (range, 43-407). All patients received IVIg and steroids, and 2 patients also failed previous second-line treatments (vinblastine, n = 1; azathioprine, n = 1). Four patients received concomitant second-line treatment (vinblastine, n = 3; azathioprine, n = 1). The response rates at day 15 were 1 in 3 for romiplostim and 0 in 4 for eltrombopag, the response rates at month 3 were 1 in 3 for romiplostim and 3 in 4 for eltrombopag, and the response rates at last FU were 3 in 3 for romiplostim

Table 1. Patient characteristics and therapeutic responses

UPN	Sex	Age at diagnosis, y	Buchanan score	Platelet transfusion*	Treatments before TPO-RA	Time from diagnosis to TPO-RA initiation, d	TPO-RA	Treatment duration*	Concomitant therapy	Response delay, d	Day 15	Month 3	Month 6	FU, mo	Current status	Ongoing treatment at last FU
1	F	5.6	4	Yes	IVIg (day 1), Cs (days 1-4)	1	R	1 × 5 μg/kg	Cs (days 1-4)	3	CR	PR	CR	30	CR	No
2	F	12.6	4	Yes	IVIg (days 1, 3), Cs (days 3-6)	7	R	1 × 5 μg/kg	Vb (day 7)	1	CR	CR	CR	18	CR	No
3	F	1.2	4	Yes	IVIg (days 1, 3), Cs (days 2-5)	7	R	1 × 5 μg/kg	—	3	CR	CR	CR	14	CR	No
4	F	4.3	4	Yes	IVIg (day 1), Cs (days 2-5)	3	R	1 × 5 μg/kg	Cs (days 3-5)	3	CR	PR	CR	12	CR	No
5	F	2.8	4	Yes	IVIg (days 1, 3, 12, 16), Cs (days 7-10, days 16-19)	18	R	2 × 3 μg/kg to 18 × 4 μg/kg	IVIg (day 18), Cs (days 18-19)	7	CR	PR	CR	26.7	CR	No
6	M	5	4	Yes	IVIg (days 1, 3), Cs (days 2-9)	3	R	1 × 5 μg/kg	Cs (days 3-9), Vb (day 3)	7	PR	PR	CR	19.5	CR	No
7	M	3.1	4	Yes	IVIg (days 1, 3), Cs (days 5-8)	6	R	2 × 5 μg/kg	Cs (days 6-8)	4	CR	CR	CR	11.5	CR	No
8	M	2.3	4	Yes	IVIg (days 1, 7), Cs (days 10-13, days 15-18)	25	R	12 doses (1-10 μg/kg)	RTX (days 25, 32, 39, 46)	7	PR	PR	PR	87	PR	No
9	M	1.7	3	No	IVIg (×3), Cs (×1), AZA (day 67)	71	R	1 dose per wk for 40 wk	AZA (days 67-157)	7	CR	PR	CR	29.8	CR	No
10	M	1.3	3	No	IVIg, Cs	20	R	Initial 5 μg/kg dose followed by 1 10 μg/kg dose per wk for 68 wk	IVIg, Cs, Vb (day 23)	N/A	NR	NR	PR	17	CR	R ongoing
11	M	6.6	3	No	IVIg (day 1), Cs and Vb (day 9)	30	R	1 × 2 μg/kg to 13 × 6 μg/kg	IVIg, Cs, Vb (day 9)	N/A	NR	NR	NR	38	PR	No
12	F	13.5	3	No	IVIg (days 1, 14), Cs (days 14-17)	26	E	43 d (50 mg/d)	—	33	NR	CR	CR	12	CR	No
13	M	13.4	3	No	IVIg (×3), Cs (×2)	53	E	96 d (50 mg/d)	IVIg (day 82)	28	NR	CR	NR	13	NR	HCQ, Cs, IVIg

AZA, azathioprine; Cs, steroid; E, eltrombopag; F, female; HCQ, hydroxychloroquine; M, male; N/A, not applicable; NR, no response; R, romiplostim; RTX, rituximab; UPN, unique patient number; Vb, vinblastine.

*Once a day for eltrombopag and once a week for romiplostim.

Table 1. (continued)

UPN	Sex	Age at diagnosis, y	Buchanan score	Platelet transfusion*	Treatments before TPO-RA	Time from diagnosis to TPO-RA initiation, d	TPO-RA	Treatment duration*	Concomitant therapy	Response delay, d	Day 15	Month 3	Month 6	FU, mo	Current status	Ongoing treatment at last FU
14	F	4.2	3	No	IVIg (days 1, 7, 30, 37), Cs (day 20)	37	E	660 d (75 mg/d)	—	90	NR	PR	PR	21.2	PR	E ongoing
15	M	14.2	4	No	IVIg (days 1, 20, 30), Cs (days 20-23)	48	E	407 d (50 mg/d)	Vb (day 60)	N/A	NR	NR	NR	17.6	NR	IVIg, Cs

AZA, azathioprine; Cs, steroid; E, eltrombopag; F, female; HCQ, hydroxychloroquine; M, male; N/A, not applicable; NR, no response; R, romiplostim; RTX, rituximab; UPN, unique patient number; Vb, vinblastine.
*Once a day for eltrombopag and once a week for romiplostim.

and 2 in 4 for eltrombopag. The median FU was 16 months (range, 12-30). TPO-RAs, although efficient, were discontinued in 3 patients to avoid long-term side effects. In 2 patients, they were discontinued for inefficacy. Two patients were on TPO-RAs at last FU (>17 months, >21 months).

No severe adverse events were reported. Patient 14 presented with mild urticarial rash of unclear etiology. No patient stopped treatment because of adverse effects or experienced thrombosis. Cytological marrow findings in 14 of 15 patients were consistent with ITP diagnosis. Bone marrow biopsies were not performed during FU, considering the limited time of exposure and normal blood cell counts and smear analysis.

Despite the heterogeneity of the cohort, we report a safe and rapid overall response facilitated by the combination of TPO-RAs and standard treatments warranted by the severity of the clinical presentation.

Very few studies detail the role of TPO-RAs in the early course of ITP, especially in children.[17] Fourteen children treated with TPO-RAs for ND-ITP showed an initial overall response of 89% without significant differences between romiplostim and eltrombopag ($P = .26$).[18] However, the lack of well-defined time points and the combination of several concomitant therapies prevented the investigators from providing an accurate picture of time responsiveness. Twelve adults with ND-ITP were given first-line treatment with eltrombopag and dexamethasone, with a median CR rate of 83%, achieved at a median of 33 days.[19] Among 8 adult patients with ND and persistent ITP refractory to first-line treatment who were treated with romiplostim, 7 patients responded within a median of 10 days, in line with our pediatric study.[20]

Seven of our 15 patients actually received a combination of TPO-RAs and other second-line therapies, which was warranted by the severity of the clinical presentation. This might influence response and induce bias. However, the role of azathioprine in early response is unlikely, given its known response delay, usually within 3 months.[21] In rare studies, vinblastine did not prove to be of rapid or constant efficacy.[22] Three of our 5 patients concomitantly treated with vinblastine still did not have a response. Overall, the early response rate in our study appears high, as warranted in children with severe hemorrhage who are known to be at risk for initial refractoriness.[23]

Our main result, from group 1, is that romiplostim given as a frontline therapy, even as a single dose, safely and quickly controlled severe clinical bleeding at day 15 in 100% of cases. In addition, all patients in this group were free of any treatment after month 3, with a sustained response at last FU. This raises the interesting question of the induction of long-term apparent immunomodulation by TPO-RAs in children as well, as already described in 8 of 20 refractory ITP adult patients after discontinuation of TPO-RAs[24] and as suggested in a preclinical study.[25] In group 2, the response rate is more difficult to establish, but some patients did benefit from TPO-RAs, and 2 patients were treated for >6 months.

In summary, our study reported the rapid clinical efficacy of TPO-RAs in children with ND-ITP and severe bleeding issues. Romiplostim appears to be durably efficient and safe in this

indication. Prolonged remission rates suggest possible immunomodulation that deserves further study. In addition to chronic ITP cases, limited courses of TPO-RAs could be considered as frontline therapy in children with refractory ND or persistent ITP, to avoid recurrent or catastrophic bleeding and to enhance the efficacy of first-line therapies.

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Authorship

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Footnotes

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