Feasibility of romiplostim discontinuation in adult thrombopoietin-receptor agonist responsive patients with primary immune thrombocytopenia: an observational retrospective report in real life clinical practice

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Abstract

Thrombopoietin mimetics are new treatment options for patients with immune thrombocytopenia (ITP). Because of their mechanism of action, long-term administration was envisioned in order to maintain effective thrombopoiesis. We report on 30 romiplostim treated patients: 13/27 responders (48%) achieved stable platelet counts on a mean romiplostim dose of 2.43 µg/kg and were able to stop romiplostim after a mean of 44.3 weeks (range 12-122) on therapy with sustained response maintained at a mean of 26 months (range 12-52). No bleeding events occurred during the observational period. No specific patient's features nor pattern of early response seemed to predict for sustained response. However, patients achieving safe platelet counts at lower dosages are probably worth a try of therapy tapering and discontinuation. Our observations support feasibility of romiplostim safe suspension in a relevant proportion of ITP patients.

Introduction

In at least some of immune thrombocytopenia (ITP) patients, thrombocytopenia is worsened by inappropriately low levels of platelet production, unable to compensate for the increased peripheral immune-mediated destruction of platelets. Until recently, management of ITP adult patients with platelet counts $<30\times10^9$/L and/or bleeding signs has relied upon the use of drugs or procedures (*i.e.* splenectomy) aimed at decreasing B-cell and T-cell immune-response to autologous platelets and megakariocytes. The availability of thrombopoietin-receptor agonist (TPO-RA) has offered new opportunities for treating adult ITP patients acting on megakariocyte survival and production of platelets.[1]

Thrombopoietin-receptor agonist increase thrombopoiesis activating the c-Mpl receptor on bone marrow megakariocytes, thus providing an additional stimulus to increase their survival and platelet production.[1]

Response rates up to 90% in long-term follow-up studieshave been reported with both romiplostim and eltrombopag.[2,3] However, platelet counts usually return to pretreatment levels upon discontinuation of treatment and long-term, if not life-long, administration was envisioned in order to maintain effective thrombopoiesis.

In recent years sporadic patients have been reported as being able to discontinue treatment with either romiplostim or eltrombopag without relapsing off-therapy.[4-10] Most studies were not designed to assess feasibility of TPO-RA discontinuation and thus true prevalence of patients able to maintain remission off therapy can not be inferred.

A French observational study confirms that romiplostim can be successfully discontinued:[11] of the 28/54 responding patients, 8 remained in complete remission off therapy at a median follow up of 13,5 months (range 5-27). Data from a recently presented interim analysis of a phase 2 study of platelet response and remission rates in ITP patients receiving romiplostim show that 11 of 38 evaluable patients (29%) were able to maintain remission (*i.e.* 24 weeks of platelet counts $\geq50\times10^9$/L) off any treatment.[12]

We report our experience with the peptibody romiplostim in a small series of patients unresponsive to immunosuppressive therapy who were treated with this TPO-RA for variable lengths of time. Some of these patients were able to discontinue therapy after achieving response, without relapsing at long-term follow-up.

Case Report

Between September 2009 and May 2014 a total of 30 patients (11 M; mean age at romiplostim treatment 50.7 yrs, range 18-82) received romiplostim at two collaborating Centers. Patients with shorter follow-up on treatment with romiplostim or on eltrombopag are not included in the present analysis. Patient characteristics at the time of romiplostim administration are summarized in Table 1. Patients were defined either as non responders or refractory according to the International Working Party (IWP) proposed standardization of terminology for ITP.[13] All patients are enrolled in a local Italian registry (REL-ITP registry), and informed consent to demographic and clinical data use is given at enrollment. The REL registry has received approval by the human subjects research review board of both participating hospitals.

Overall, 27/30 patients (90%) responded to romiplostim according to IWP criteria.[13] Of the 27 responders: 1 patient (#4) was lost to follow-up; 1 patient (#5) discontinued romiplostim due to acute myocardial infarction, at the time of SAE, romiplostim dose was 10 µg/kg/week and platelet counts were 84×10^9/L; in 5/27 patients (#6-10) romiplostim was used as bridge to splenectomy; 5/27 patients (#11-15) lost response at 11, 6, 11, 12 and 11 months respectively; neutralizing anti-romiplostim antibodies could be searched for in 3/5 patients; in three (#13, 14 and 15) the test yielded a positive result; the remaining two patients could not be tested; in 2/27 patients (#16 and 17) romiplostim administration is ongoing (56 and 12 months respectively); 13/27 patients (#18-30) achieved stable, safe platelet counts and were able to stop romi-

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plostim after a mean of 43.3 weeks (range 12-122) on therapy with sustained response maintained at a mean of 28.8 months (range 15-55).

Data on patients who achieved stable response off therapy are summarized in Table 2. Strict platelet monitoring was maintained during follow up off therapy. In 7/13 patients a decreased platelet count compared to a previous control was found weeks from discontinuation of weekly romiplostim administration. These patients were re-exposed to a limited number of *one shot* low (1 or 2 mcg/kg) dose of romiplostim and regained a stable response, as shown for four patients in Figure 1.

No bleeding events occurred during the observational period. Patient #29 developed lower limb superficial phlebitis while on romiplostim 1 µg/kg on alternate weeks and warfarin was started; platelets were 135×10^9/L at the time of the event; screening for lupus anticoagulant, anti-phospholipids antibodies, anti-

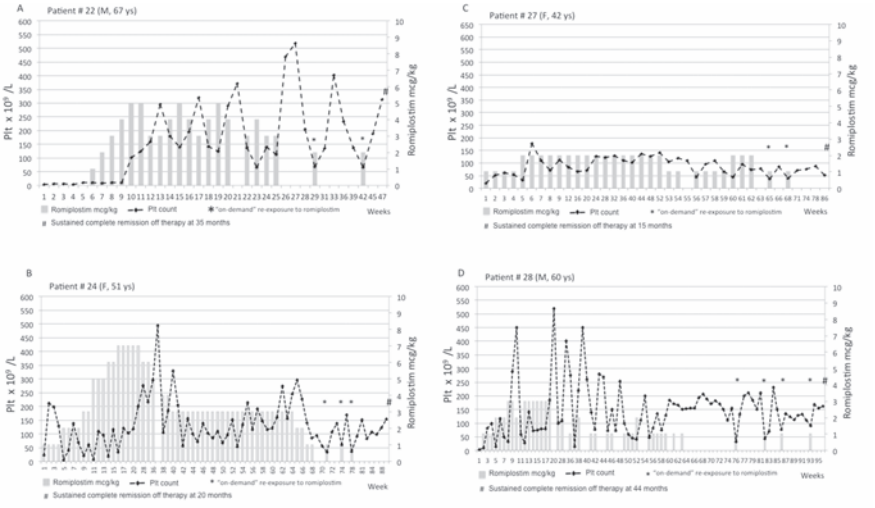

Figure 1. Platelet count in 4 patients who achieved a sustained response after romiplostim discontinuation and a limited number of *on-demand* re-exposure to the drug.

Table 1. Main characteristics of enrolled patients.

Patient (sex, age)	Age at diagnosis	Age at start of first line	N, P, C at romipl start	N. of previous treatment*	Time from any treatment to romiplostim**
1 (F, 47)	37	37	C	4	120
2 (F, 71)	69	69	C	4	24
3 (F, 33)	11	15	C	4	264
4 (M, 66)	48	66	C	2	5
5 (M, 56)	34	34	C	4	264
6 (F, 22)	20	20	P	3	7
7 (M, 68)	61	61	C	2	89
8 (F, 58)	57	57	C	2	12
9 (F, 24)	24	24	N	2	1
10 (F, 50)	50	50	N	2	3
11 (M, 59)	42	42	C	4	204
12 (F, 55)	55	55	N	2	2
13 (F, 37)	37	37	P	2	2
14 (F, 38)	38	28	P	2	6
15 (M, 18)	18	18	N	2	2
16 (F, 65)	56	56	C	4	108
17 (M, 28)	28	28	P	2	7
18 (F, 60)	60	60	P	2	3
19 (M, 66)	64	64	C	3	24
20 (F, 69)	69	69	N	3	3
21 (M, 20)	11	11	C	2	2
22 (M, 67)	67	67	N	2	3
23 (M 42)	41	41	N	2	2
24 (F, 51)	51	51	P	2	6
25 (F, 55)	47	47	C	3	96
26 (F, 42)	20	20	C	5	252
27 (F, 42)	42	42	P	2	5
28 (M, 60)	57	57	C	4	26
29 (F, 82)	79	80	C	4	32
30 (F,72)	72	72	P	4	9

N, newly; P, persistent; C, chronic. *Any type of steroid is considered as a single line of therapy. IVIG given as isolated drug is considered as a single line of therapy. IVIG + steroid if given associated, is considered as a single line of therapy. Other possible therapies: Rituximab, Cyclosporin, Azathioprine, Vincristine. **Time elapsed (months) from any treatment required for ITP and romiplostim.

beta2glycoprotein1 was negative. Romiplostim was discontinued a month later because platelet counts remained stable at around 100×10^9/L. Three patients (#18,20,28) had received the last rituximab course 4, 6 and 33 weeks before starting romiplostim; one patient (#19) received a first course of romiplostim as bridge to splenectomy having failed steroids and cyclosporine; a week after surgery he relapsed with severe thrombocytopenia and was re-treated with romiplostim. He received a total of 7 romiplostim doses administered over a 22 week period of time; romiplostim was discontinued at 22 weeks from splenectomy since stable, $\geq100\times10^9$/L platelet counts were achieved.

Bone marrow biopsies for detection of fibrous changes during romiplostim use were not performed since most of our patients received treatment for less than 18 months.

Discussion

Overall, our experience with romiplostim in real life practice is in line with reported findings from controlled studies with 90% of patients (27/30) responding. However, in our experience the percentage of patients able to discontinue romiplostim without relapsing is noteworthy: 48%, if we consider the whole number of romiplostim responders (13 of 27 responders) and 65% if we consider only patients who received long-term treatment (13 of 20 patients) *i.e.* not considering patients receiving romiplostim as bridge to splenectomy, lost to follow-up, or who discontinued the drug because of SAE.

In 5 chronic ITP patients out of 13 long term responders, romiplostim seemed to be the only treatment responsible for sustained response. Indeed, it has been proposed that TPO-RA therapy may result in improved immune regulation by regulatory T cells (Tregs) possibly restoring immune tolerance.[14]

Similar immune-modulating effects have also been described for other treatment modalities (*e.g.* rituximab, high-dose dexamethasone, intravenous immunoglobulin) which result in sustained responses in a fraction of ITP patients.[15,16]

In the remaining 8 patients, response might have been either spontaneous (2 newly diagnosed and 3 persistent disease patients) or secondary to rituximab (2 patients) or splenectomy (1 patient). Nevertheless, use of romiplostim may be a treatment option for patients with persistently low platelet counts awaiting for platelet recovery, either it be spontaneous or secondary to disease-modifying treatments for which a possible late-response can be anticipated.

No specific patient's features (*e.g.* age, ITP

Table 2. Characteristics of patients who achieved a sustained response after romiplostim discontinuation.

Patient	Sex, age at R start	Plt count at R start ($\times10^9$/L)	Max dose R (mcg/kg)	Mean dose R (mcg/kg)	Last dose R (mcg/kg) before suspension	Re exposure: n. of *on-demand* R doses	Time interval at re exposure after R stop (weeks)	Plt at time of re-exposure ($\times10^9$/L)	Min-max Plt after R definitive stop ($\times10^9$/L)	Duration of R treatment (weeks)	Plt at last follow up ($\times10^9$//L)	Time (months) of therapy
18	F, 60	2	1	1	1	0	n.a	n.a	210-320	12	250	55
19*	M, 66	13	7	3,5	2	2	4, +7	12, 25	94-324	22	287	31
20	F, 69	4	3	1,5	1	10	4 (10 wkly doses)	63	96-120	37	145	19
21	M, 20	1	6	3,3	5	0	n.a	n.a	194-334	15	243	43
22	M, 67	11	5	3,09	2	2	4, +11	67, 64	67-314	25	118	35
23	M, 42	1	7	3,3	3	0	n.a	n.a	207-355	14	134	15
24	F, 51	22	7	3,3	1	3	3, +4, +4	35, 60, 37	84-153	68	128	20
25	F, 55	20	6	3,8	6	0	n.a	n.a	67-298	122	115	19
26*	F, 42	22	5	2,7	2	0	n.a	n.a	243-411	16	210	19
27	F, 42	21	2	1,8	1	2	3, + 3	38, 40	52-120	62	87	15
28*	M, 60	5	3	1,71	1	4	12, +7, +4, +7	31, 42, 76, 91	155-313	63	113	44
29*	F, 82	21	1	0,5	1	1	10	75	63-289	94	107	32
30*	F, 72	10	3	2,09	2	0	n.a	n.a	138-281	27	121	28
Mean (range)	56 (42-82)	11.7 (1-22)	4.3 (1-7)	2.43 (0.5-3.8)	2.1 (1-6)	–	–	–	min 128 (52-243)	44.3 (12-122)	158.3 (87-287)	28.8 (15-55)

R, Romiplostim; Plt, platelet; n.a, not applicable. Mean dose of Romiplostim: it is calculated as the mean of all administered doses during all period of treatment. *Splenectomized patients.

duration, lines of previous treatment) nor pattern of early response (*e.g.* dose requirements, time to response) seemed to consistently predict for sustained response off therapy. However, it seems that patients achieving safe platelet counts at lower dosages are probably worth a try of therapy tapering and discontinuation. Manufacturer dose adjustment rules allow romiplostim to be discontinued when appropriate and clinical judgment was used to manage patients.

Moreover, it appears that TPO-RA do not cause tachyphylaxis. This has been specifically tested and demonstrated for eltrombopag and it is conceivable also for romiplostim:[17] one of the patients presented by Newland[5] received a single romiplostim dose after 11 weeks off therapy and regained high platelet counts; thereafter, hemostatic platelet counts were maintained without any therapy for 2 years. Similar results were observed in a fraction of our patients. All 7 patients who were re-exposed to romiplostim weeks after weekly administration was stopped (Table 2 and Figure 1), regained a platelet response. Knowledge that TPO-RA can be safely administered on a *on-demand* basis without loss of effectiveness offers the possibility of re-exposing relapsed patients without the threat of these patients not being able to regain a response. Moreover, need of *on demand* therapy doesn't seem to predict for lost of long-term response to romiplostim. This new finding is probably worth being taken into account in planning prospective studies of feasibility of romiplostim discontinuation.

The finding that at least 3 of 5 patients who abruptly lost response to romiplostim tested positive for neutralizing antibodies suggests that development of these antibodies may be a more frequent event than expected.

Being a retrospective observational study, our results should be interpreted with caution, but still they suggest that in a significant fraction of patients, in *real world* practice, sustained remission without disease recurrence may be obtained after a relatively short-term administration of romiplostim.

Conclusions

To date, because of their known mechanism of action, TPO-RA are thought to be effective only while the treatment is ongoing and the proper dose is being administered. However increasing reported evidence exists on the occurrence of sustained responses after TPO-RA discontinuation. Our observations support the proposal of using romiplostim as *bridge to recovery*, either it be spontaneous (*e.g.* in newly diagnosed or persistent ITP), TPO-RA induced or representing a late-response to previously administered treatments, rather than long-term treatment. This approach would have relevant clinical implications. First of all, concern about TPO-RA long-term sides effects (marrow fibrosis, increased risk of thrombotic events), especially in younger patients, would be greatly reduced. Moreover, treatment costs, which currently also limit their use[18] would be less of an issue. If results on persistent remissions after short-term romiplostim use were to be confirmed in larger patient population, this approach could be used to defer or avoid splenectomy and to spare patients the untoward effects of prolonged immunosuppressive treatments. This would be especially beneficial in newly diagnosed severe ITP failing first line therapy with steroids. Future biological and intervention studies are needed in order to identify predictive factors of long term sustained response, allowing clinicians to tailor the best treatment for each ITP patient.

References

1. Kuter DJ. Thrombopoietin and thrombopoietin mimetics in the treatment of thrombocytopenia. Ann Rev Med 2009;60:193-206.
2. Kuter DJ, Bussel JB, Newland A, et al. Long-term treatment with romiplostim in patients with chronic immune thrombocytopenia: safety and efficacy. Br J Hematol 2013;161:411-23.
3. Saleh MN, Bussel JB, Cheng G, et al. Safety and efficacy of eltrombopag for treatment of chronic immune thrombocytopenia: results of the long-term, open-label EXTEND study. Blood 2013;121:537-45.
4. Bussel JB, Rodeghiero F, Lyons R, et al. Sustained hemostatic platelet counts in adults with immune thrombocytopenia (ITP) following cessation of treatment with the TPO receptor agonist romiplostim: report of 9 cases. Blood 2011;118:3281.
5. Newland A, Cervinek L, Eggermann J, et al. Sustained hemostatic platelet counts in adult patients with primary immune thrombocytopenia (ITP) following cessation of romiplostim – four European case studies. Haematologica 2011;96:ABS237.
6. Ghadaki B, Nazi I, Kelton JG, Arnold DM. Sustained remissions of immune thrombocytopenia associated with the use of thrombopoietin receptor agonists. Transfusion 2013;53:2807-12.
7. Thachil J, Salter I, George JN. Complete remission of refractory immune thrombocytopenia (ITP) with a short course of Romiplostim. Eur J Hematol 2013;91:376-7.
8. Bussel JB, Wang X, Eisen M. Case studies of remission in adults with immune thrombocytopenia (ITP) following cessation of treatment with the TPO receptor agonist romiplostim. Blood 2013;122:ABS328.
9. Bussel JB, Saleh MN, Wong RSM, et al. Update on the safety and efficacy of EXTENDed treatment with eltrombopag (EPAG) in adults with chronic immune thrombocytopenia (ITP). Blood 2013;122:ABS2315.
10. González-López TJ, González-Porras JR, Arefi M, et al. Sustained response after short-medium-term treatment with eltrombopag in patients with ITP. Blood 2013;122:ABS2323.
11. Mahévas, M, Fain, O, Ebbo, M, et al. The temporary use of thrombopoietin-receptor agonists may induce a prolonged remission in adult chronic immune thrombocytopenia. Results of a French observational study. Br J Hematol 2014;165:865-9.
12. Stasi R, Newland A, Godeau B, et al. An interim analysis of a phase 2, single-arm study of platelet responses and remission rates in patients with immune thrombocytopenia (ITP) receiving romiplostim. Blood 2013;122:ABS1074.
13. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood 2009;113:2386-93.
14. Bao W, Bussel JB, Heck S, et al. Improved regulatory T-cell activity in patients with chronic immune thrombocytopenia treated with thrombopoietic agents. Blood 2010;116:4639-45.
15. Stasi R, Cooper N, Del Poeta G, et al. Analysis of regulatory T-cell changes in patients with idiopathic thrombocytopenic purpura receiving B cell-depleting therapy with rituximab. Blood 2008;112:1147-50.
16. Ling Y, Cao X, Yu Z, Ruan C. Circulating dendritic cells subsets and CD4+ Foxp3+ regulatory T cells in adult patients with chronic ITP before and after treatment with high-dose dexamethasome. Eur J Hematol 2007; 79:310-6.
17. Bussel JB, Psaila B, Saleh MN, et al. Efficacy and safety of repeated intermittent treatment with eltrombopag in patients with chronic idiopathic thrombocytopenic purpura. Blood 2008;112: ABS3431.
18 Zeng Y, Duan X, Xu J, Ni X. TPO receptor agonist for chronic idiopathic thrombocytopenic purpura. Cochrane Database Syst Rev 2011;CD008235