Remissions after long-term use of romiplostim for immune thrombocytopenia

Immune thrombocytopenia (ITP) is an acquired autoimmune condition whereby autoantibodies against platelets lead to increased platelet clearance, suppression of megakaryocytopoiesis, and subsequent thrombocytopenia.[1,2] ITP is associated with increased bleeding risk, and the primary goal of therapy is to prevent clinically significant bleeding. Steroids, and in some cases intravenous immunoglobulin, are recommended first-line therapies.[3] However, many patients relapse and alternative therapies including splenectomy, rituximab, and thrombopoietin (TPO) receptor agonists are available for second-line treatment.

Romiplostim is a TPO receptor agonist that binds to and activates the TPO receptor (c-Mpl) on megakaryocytes and their precursors, resulting in increased platelet production.[4] Romiplostim is approved for the treatment of chronic ITP. Approximately 60-90% of patients respond favorably to romiplostim, but in early studies, few maintained platelet counts >50x10^9/L upon discontinuation.[5-6] Therefore, although romiplostim is clearly effective in durably raising platelet counts in most patients with minimal safety concerns over at least five years,[7,8] there is a perception that indefinite treatment is required.

We sought to explore the real-world use of romiplostim with regard to treatment duration and frequency of treatment-free remission. We extracted patient information from databases of all ITP patients seen by the investigators at Massachusetts General Hospital, Boston, Massachusetts and Princess Alexandra Hospital, Brisbane, Australia. All patients had a diagnosis of chronic ITP as defined by American Society of Hematology criteria[9] and received romiplostim therapy for at least 6 months. Patients were managed according to standard procedures dictating dosing frequency and changes. Platelet counts were measured approximately once a week until a stable dose was achieved, and then measured approximately once monthly. Treatment-free remission was defined as the ability of a patient to discontinue romiplostim without subsequent need for other disease-modifying therapies.

A total of 423 ITP patients were treated; 116 (27%) received a TPO receptor agonist, and 43 (10%) received romiplostim for more than six months and served as the study population. There were no significant differences in patient characteristics or outcomes between the two centers. Patient demographics are presented in Table 1. Most patients were women and median age at romiplostim initiation was 50 years. Most had chronic disease with a median time of 2.6 years between ITP diagnosis and romiplostim initiation. All had previously received multiple ITP treatments; 44% had undergone splenectomy. Patients who had not undergone splenectomy prior to romiplostim had either refused or been recommended to try medical therapy first as per the routine preferences of physicians at both treating institutions.

The median (range) platelet count at romiplostim initiation was 15 (3-55x10^9/L). The median initial dose was 1 (1-10) mcg/kg weekly with subsequent doses determined by the platelet count response. Dose changes were frequent and subsequent doses varied widely. The median minimal weekly dose was 1 (0.4-4) mcg/kg and the median maximal weekly dose was 8 (2-16) mcg/kg. While on therapy, the median minimum platelet count (measured at least four weeks after the start of romiplostim) was 10 (1-173x10^9/L), and median maximum platelet count was 514 (52–1600x10^9/L). Patients experienced broad fluctuations in platelet count during therapy. A few patients had significant elevations in platelet count while on romiplostim and these were acted upon by appropriate romiplostim dose reductions. Many patients required "rescue" therapy while on romiplostim, including steroids [28 patients (65%)], IVIg [15 patients (35%)], and rituximab [3 patients (7%)]. Six patients (14%) ultimately underwent splenectomy.

Of the 43 patients, 12 (28%) were able to discontinue romiplostim successfully (without need for further therapy aside from occasional prednisone in one patient). Characteristics of patients who experienced a treatment-free remission upon romiplostim discontinuation are shown in Table 2. Two of these 12 patients had undergone splenectomy while on romiplostim without durable significant increase in post-operative platelet count; romiplostim was continued after splenectomy and later discontinued successfully. Median (range) duration of romiplostim therapy prior to successful discontinuation was 1.8 (0.5-9.6) years (Figure 1). Patients with a treatment-free remission have now been followed for a median of 2.8 (0.5-9.2) years after romiplostim discontinuation. The

Table 1. Baseline characteristics (N=43).

Age (years)	43 (13 - 83)
Female, N	27 (62%)
Prior Medical Therapies, N	
Steroid	41 (95%)
IVIg	38 (88%)
Rituximab	20 (47%)
Danazol	13 (30%)
Azathioprine	9 (21%)
Splenectomy, N	19 (44%)
Age at romiplostim initiation	50 (18 - 85)
Time between date of ITP diagnosis and romiplostim initiation	2.6 (0 - 30)
Platelet count (x10^9/L at initiation of romiplostim)	15 (3 - 55)

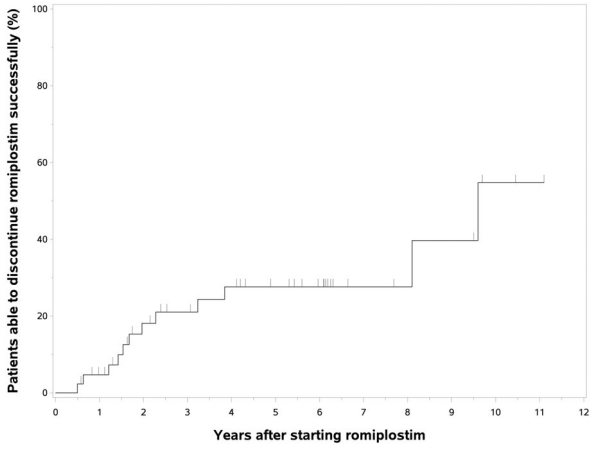

Figure 1. Percentage of patients able to achieve treatment-free remission. Treatment-free remission was defined as the ability of a patient to discontinue romiplostim without subsequent need for future disease-modifying therapies. This does not include patients who died while on romiplostim therapy.

Table 2. Characteristics of patients who achieved a remission after treatment with romiplostim.

#	Sex	Age at ITP diagnosis (years)	Medical treatments prior to romiplostim initiation	Splenectomy prior to romiplostim initiation	Age at romiplostim initiation (years)	Time from diagnosis to start of romiplostim (years)	Platelet count at romiplostim initiation ($x10^9$/L)	Duration of romiplostim therapy (years)	Treatments while on/after romiplostim discontinuation	Follow-up after D/C (years)	Most recent platelet count ($x10^9$/L)
1	M	69.4	Steroid, IVIg, rituximab	Yes	72.5	3.1	42	1.5	Steroids (after discontinuation)	0.5	282
2	F	51.3	Rituximab, azathioprine, eltrombopag (refused steroids)	No	65.4	14.2	25	3.2		2.2	243
3	F	21.1	Steroid, IVIg, rituximab	No	21.9	0.7	45	3.8		1.1	56
4	F	39	Steroid, IVIg, danazol	Yes	53.5	14.5	15	9.6		0.3	57
5	M	34.9	Steroid, IVIg, rituximab	No	37.4	2.6	42	1.4	Splenectomy (while on therapy - no response)	1.5	270
6	F	27.7	Steroid, IVIg, rituximab, azathioprine	Yes	47.3	19.6	32	8.1		0.8	139
7	F	24.4	Steroid	No	29.1	4.8	41	1.2		7.8	285
8	M	61.7	Steroid, IVIg, rituximab	No	62.4	0.7	37	1.7	Steroids	1.8	142
9	M	32.8	Steroid, IVIg	Yes	38.8	6	12	2		3.6	161
10	F	63.5	Steroid, IVIg, rituximab	Yes	70.3	6.8	10	0.6		4.8	366
11	F	44.4	Steroid, IVIg	Yes	45.7	1.2	12	0.5		5.1	185
12	F	18.3	Steroid, IVIg, rituximab	No	18.4	0.1	10	2.3	Steroids, IVIg, splenectomy (while on therapy - no response)	2.3	224

most recent median platelet count of those with treatment-free remission was 205 (56-366 $x10^9$/L); 12 of 12 had a platelet count >$50x10^9$/L; 10 of 12 had a platelet count >$100x10^9$/L (Table 2).

Treatment-free remissions were more likely in patients who had undergone splenectomy prior to romiplostim than in those who failed therapy (P=0.05). Median platelet count at the initiation of romiplostim was slightly higher in patients with treatment-free remissions than in those still on therapy or who those who failed, and there was a higher percentage of females in patients with treatment-free remissions than those who failed treatment; neither difference was significant.

Nineteen patients (44.2%) remained on romiplostim at the end of the study with a median duration of therapy of 6.1 (1.1-10.4) years, and a median platelet count of 10^7 (7-$915x10^9$)/L. Thirteen of 19 had a platelet count >$50x10^9$/L; 10 of 19 had a platelet count >$100x10^9$/L. Whether some of these patients could have discontinued therapy could not be determined from the data collected. Six patients (14%) discontinued romiplostim for treatment failure (inability to maintain platelet counts >$50x10^9$/L and/or bleeding). None had undergone splenectomy prior to romiplostim; all six eventually underwent splenectomy while still on romiplostim or soon after discontinuation.

Six patients (14%) died while on romiplostim: two of myocardial infarction, one of pneumonia, one of progressive multifocal leukoencephalopathy, one from a pulmonary embolism, and one from an unknown cause. All had pre-existing medical comorbidities. Platelet counts at or near the time of death were available for 5 of the 6 patients including: $526x10^9$ (2 weeks before death, at which point romiplostim was held), $154x10^9$ 2-3 days prior to death, <$5x10^9$ the day prior to death, $314x10^9$ 2-3 days prior to death, and $102x10^9$ at the time of death.

Three patients (7.0%) had a WHO grade three or four bleeding event while on romiplostim [one pulmonary hemorrhage (platelet count $3x10^9$/L), one retinal hemorrhage (23 $x10^9$/L), and one upper gastrointestinal tract bleed ($22x10^9$/L]. Six patients (14%) had venous thromboembolism: two isolated deep venous thromboses (platelet counts $18x10^9$/L and $143x10^9$/L), three isolated pulmonary emboli ($255x10^9$/L, $102x10^9$/L and $28x10^9$/L), and one concomitant deep venous thrombosis and pulmonary embolism ($812x10^9$/L). This last patient developed VTE three weeks after splenectomy; splenectomy was felt to be a major risk factor for both thrombocytosis and VTE.

The TPO receptor agonists are of significant benefit in the symptomatic treatment of ITP, but as there is no defined treatment "course" for these agents, treatment is often continued indefinitely. This presents a challenge in terms of patient quality of life, decision to undergo splenectomy, potential risk of bone marrow fibrosis,[10] risk of arterial and venous thromboembolism, and health care costs. We investigated the concept and, frequency of a "remission" after TPO receptor agonist therapy, and delineate the term "treatment-free remission" to indicate that the patient no longer requires active ITP therapy and is considered at low risk for subsequent bleeding. Of those patients treated with romiplostim for over six

months, 12/43 (28%) were able to obtain a treatment-free remission after a median of 1.8 years.

Our data in no way suggests an absence of ITP disease activity in all patients with treatment-free remission. When assessed by the international consensus criteria,[11] all subjects had a response (platelets >30x10^9/L) and 10/12 had a complete response (platelets >100x10^9/L), but only 6/12 had platelet counts that would be considered normal especially after splenectomy. These data also challenge more optimistic reports of sustained remission rates of 53% after discontinuation of eltrombopag and 48-57% after discontinuation of romiplostim.[12-14] While these studies had similar patient populations including percent of patients undergoing splenectomy prior to TPO, and receptor agonist treatment, treatment duration varied, and in some cases was much shorter than in our study. Our data are similar to findings from a recent study of 75 patients with newly diagnosed ITP treated with romiplostim, where 32% of patients achieved a remission (defined as a platelet count >50x10^9/L for 24 consecutive weeks with no ITP treatments).[15] In these studies, some patients experienced remission after very brief exposure to TPO receptor agonist, in some cases less than one month. Spontaneous remissions occur commonly in ITP patients, and their association with brief exposure to TPO receptor agonists is unclear, and may simply be a coincidence.

As with all retrospective studies, our data must be interpreted in the context of potential biases, including our choice to focus on romiplostim (rather than all TPO receptor agonists). There were no uniform rules regarding when to discontinue romiplostim. We cannot know the final treatment response in patients who died of non-ITP related causes while still on romiplostim.

Our data reflects the nature of "real-life" treatment of a large number of ITP patients at two major centers. These data suggest that TPO receptor agonist treatment may not be indefinite in ~30% of patients and helps guide the timing of other therapies, including splenectomy, in those who continue treatment. More rigorous studies with drug discontinuation should be considered to assess remission rates and cost-effectiveness analyses as well as established standardized treatment guidelines for the use of these agents in the management of ITP.

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