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ORIGINAL ARTICLE

The use of thrombopoietin-receptor agonists (TPO-RAs) in immune thrombocytopenia (ITP): a "real life" retrospective multicenter experience of the Rete Ematologica Pugliese (REP)

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Abstract Immune thrombocytopenia (ITP) is a disease which sees one-third of patients failing first and subsequent therapeutic approaches, including splenectomy. Thrombopoietin-receptor agonists (TPO-RAs) are recommended for adults who relapse after splenectomy or who have contraindications for splenectomy. In this multicenter study, a total of 124 patients were retrospectively evaluated: 55 (44.3 %) were treated by romiplostim and 69 (55.6 %) by eltrombopag. Mean age, number of young patients (<60 years), time from primary diagnosis of ITP to TPO-RA treatment, and previous lines of therapy were similar in both groups. The overall response rate was 80 % (44/55) for romiplostim and 94.2 % (65/69) for eltrombopag; the duration of response and the time to response were similar (p=NS). The response rate to both drugs in non-splenectomized patients was higher than that of splenectomized patients (p<0.05). The mean duration of response was 30 months for romiplostim and 15 months for eltrombopag, due to later commercialization of eltrombopag. Failure was the most frequent cause of discontinuation. Thrombotic events were the most consistent adverse events and were recorded in 2 and 3 % of patients treated by romiplostim and eltrombopag, respectively. In conclusion, romiplostim and eltrombopag are effective in the majority of patients with chronic ITP who failed several lines of therapy; whether TPO-RAs could substitute splenectomy is under discussion and studies are warranted.

Keywords Immune thrombocytopenia (ITP) · Thrombopoietin receptor agonists · Splenectomy

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Introduction

Severe immune thrombocytopenia (ITP) is generally a manageable disease and the curative intent of therapy, according to shared guidelines [2], is obtainable in almost half of patients and a stable partial recovery in about 20 % of patients; however, one-third of patients do not respond to the first approach and almost half of them undergo splenectomy [1]. Patients who fail this procedure are considered refractory, and the severity of disease is based on clinically relevant bleeding, regardless of the number of platelets. For these patients, a therapeutic alternative is needed [2]. Rituximab is certainly useful for children as an alternative to splenectomy and for adults at risk of bleeding [3]. Thrombopoietin-receptor agonists (TPO-RAs) have increased the therapeutic chances for ITP patients, and are recommended for adults who relapse after splenectomy or who have contraindications for this procedure and have failed at least one line of therapy. In daily medical practice, physicians have to face an ever-increasing number of refusals for splenectomy by patients who express a preference for treatment with TPO-RAs. Thus, the new scenario of non-splenectomized young patients treated with TPO-RAs leads to the crucial question on the use of these agents as an effective alternative to splenectomy.

We present our multicenter experience on the use of TPO-RAs over the last 5 years, with the aim to analyze "real life" treatment outcome outside of randomized studies, shows differences between the use of romiplostim or eltrombopag, and therefore examine whether TPO-RAs could be an alternative to splenectomy.

Patients and methods

Patients

The study consisted of a collaborative retrospective evaluation of consecutive adult patients with ITP treated by TPO-RAs (romiplostim or eltrombopag) in six of a total of nine hospitals of the Rete Ematologica Pugliese which covers almost four million and half people. The entire population of patients with ITP from which we extrapolated those treated by TPO-RAs consisted of 413 patients treated as first-line therapy with methylprednisolone (MP) 1 mg/kg/day; this therapy produced a remission in 220 patients (53.2 %). Second and third lines of therapies inclusive of MP + intravenous immunoglobulin (IGIV) and/or rituximab produced a response in 102 patients (24.1 %).

One hundred twenty-seven patients resulted relapsed/refractory. Among them, 66 were splenectomized; splenectomy had been proposed to all eligible patients under 60 years of age, after the failure of two or more lines of therapy and following an observational time ranging from 1 to 3 years from the diagnosis, median 18 months (Table 2). The response rate to splenectomy was 77.3 %. Of the relapsed/refractory patients, three died for brain hemorrhage before any further therapy, while 124 were treated with TPO-RAs and were included in this study: 55 were treated by romiplostim and 69 by eltrombopag (Table 1).

In order to exclude clonal disease or dysplasia, a bone marrow evaluation (immunophenotypic evaluation for all patients, 45 bone marrow biopsies) was performed to all relapsed/refractory patients before starting TPO-RAs. Patients unable to maintain a stable platelets count over 30×10^9/L were considered resistant or relapsed, eligible for TPO-RA, and included in the evaluation, independently from the time of diagnosis of ITP. The choice of this subset of patients is due to shared guidelines considering the number of platelets under 30×10^9/L as mandatory for treatment for real risk of bleeding. We collected data on the previous lines of therapy, including splenectomy, baseline patient characteristics, TPO-RA treatment, adverse events (AEs) to TPO-RAs, and clinical outcome. A line of therapy was defined as each treatment received by the patient from the time of first diagnosis, then in case of resistance or relapse, up to the start of TPO-RAs. Corticosteroids alone or combined with IGIV, splenectomy, rituximab, and each of the two TPO-RAs (when a patient switched from one to the other) were considered different lines of therapy. The therapy with TPO-RA was started when a failure to maintain a sustained number of platelets over 30×10^9/L was documented following at least two lines of therapy when splenectomy was not performed or following splenectomy whenever it was performed. The median number of platelets before the treatment by TPO-RAs was similar in both groups of patients, 17×10^9/L in the romiplostim group and 16×10^9/L in the eltrombopag group. A total of 72 patients had been considered ineligible for splenectomy; 70 because older then 60 years and 2 due to severe diabetes and dilatative cardiomyopathy. Of the 54 eligible patients for splenectomy, 18 (33.3 %) did it and 36 (66.7 %) refused the procedure, being aware of the therapeutic alternative with a TPO-RA.

All patients signed informed consent according to the regulations of each investigational site.

Therapy with TPO-RAs

Romiplostim was made available for prescription in Italy in the middle of 2010, and eltrombopag 2 years later; so the first patients were treated with romiplostim and had a longer observation period. Then the assignation to one of the two drugs was at discretion of the hematologist. The starting dose of romiplostim was 1 μg/kg a week subcutaneously, then the

Table 1 Patient characteristics of enrolled to TPO-RAs

	Romiplostim		Eltrombopag	
n (%)	55	(44.3 %)	69	(55.6 %)
Age, mean (range)	64	(30–88)	67	(30–92)
Sex, M/F	26/29		33/36	
<60 years, # (%)	23	(41.8 %)	31	(44.5 %)
Time of diagnosis	1989–2014		1988–2014	
<2 years from diagnosis	26	(47.2 %)	45	(65.2 %)
Major bleedings	4	(7.3 %)	7	(7 %)
Minor bleedings	12	(21.8 %)	18	(26.1 %)
Median plts before TPO-RAs (range)	17×10×9/L	(1–30)	16×10×9/L	(1–30)

dosage was up modulated on the basis of the platelet count or tolerance to a maximum of 10 μg/kg/week and administered over three times a week when the dose exceeded 750 μg in order to avoid platelets rebound in responding patients. Eltrombopag was given orally with a starting dose of 50 mg/day and up or down modulated to 75 or 25 mg/day according to the platelet count and tolerance.

Evaluation of response

The patients underwent clinical and laboratory evaluation before the start of TPO-RA, weekly when under romiplostim and monthly when under eltrombopag. The laboratory tests consisted of complete blood count, hepatic and renal function and coagulation; the clinical evaluation consisted on the detection of bleedings and side effects. As major bleedings, conferring a risk of life or impact on the morbidity of patients, were considered: gastrointestinal, cerebral, and deep hemorrhages (abdominal, thoracic, retinic, or gross hematuria) and as minor: cutaneous or mucosal bleeding or mild hematuria. No specific tests for occult hemorrhages were applied routinely, but only when clinically indicated.

Response was assessed according to the standardized criteria by IWG [4]. Complete response (CR) was defined as any platelet count of at least $100\times10\times9$/L. Partial response (PR) was defined as any platelet count between 30 and $100\times10\times9$/L and at least doubling of the baseline count, and no response (NR) when the target of $30\times10\times$/L platelets was not reached or there was less than doubling of the baseline count. Out of the number of platelets, we evaluated also the clinical benefit in patients with hemorrhages. The duration of response was calculated from the first time of achievement of CR or PR to its loss.

Toxicity profile

AEs occurring during TPO-RA treatment and discontinuation due to toxicity were registered. Thrombotic events, including arterial and venous thrombosis, and grade III–IV elevation of transaminases were considered major events for discontinuation of TPO-RAs. Grade I–II AEs were considered for temporary discontinuation. Reductions of dose were applied according to the European prescribing information. In case of events including deep vein thrombosis, a heparin-based therapy was immediately started.

Statistical analysis

Time to response was calculated from the start of therapy with TPO-RA to the platelets increase over 30×10^9/L. The duration of response was calculated from the time of a response to the drop of platelets under 30×10^9/L. Differences between the romiplostim and eltrombopag groups were estimated by Kaplan-Meier method. Response was further evaluated according to age (over 60 years), previous splenectomy, lines of therapy (two or more) and type of TPO-RA; the multivariate analysis was performed by Cox regression model to assess the predictive power of each variable with a level of significance of $p<0.05$.

Results

Patients

A total of 124 consecutive patients were enrolled from 2010. Patient characteristics are reported in Table 1. Fifty-five (44.3 %) patients received treatment with romiplostim and sixty-nine (55.6 %) with eltrombopag. Mean age, sex distribution, number of young patients (<60 years), and time from primary diagnosis of ITP to the start of TPO-RAs were similar in both groups. A substantial difference was recorded in the assignation to the type of TPO-RA in the last 2 years, with 65 % of patients treated with eltrombopag and 47 % with romiplostim. Major bleedings were recorded before treatment by TPO-RA in 4 (7.3 %) and 7 (7 %) in the group of treated by romiplostim and eltrombopag, respectively; minor bleedings were recorded in 12 (21.8 %) and 18 (26.1 %) in the group treated by romiplostim and eltrombopag, respectively. The mean number of lines of therapy were 2.5 before romiplostim and 2.4 before eltrombopag (Table 2). For all patients, the first-line therapy included glucocorticoids, except for one patient with severe diabetes who received romiplostim frontline. The combination of intravenous immunoglobulin (IVIG) and repetition of glucocorticoids was applied similarly in both groups in 67 % of patients. Rituximab was administered either before or after splenectomy in 31 % of patients of the romiplostim group and in 20 % of the eltrombopag group.

In the group treated by romiplostim, 11/55 (20 %) of the whole group and 11/23 (47.8 %) of those under 60 years were splenectomized. Differently, a small number of patients treated by eltrombopag were splenectomized: 7/69 (10.1 %) of the whole group and 7/31 (22.5 %) under 60 years. A subset of patients switched from one TPO-RA to the other: 2/55 (3.6 %) of the romiplostim group had received eltrombopag as previous therapy, while 7/69 (10.1 %) of the eltrombopag group had received romiplostim.

Response to TPO-RAs and impact of splenectomy

The overall response rate (ORR) (CR + R) was (Table 3): 80 % (44/55) for patients treated with romiplostim, while 94.2 % (65/69) for patients in the eltrombopag group. However, if we consider only CR, this was similar in the two groups: 43.6 % (24/55) for romiplostim and 47.8 % (33/69) for eltrombopag. The increase of platelets count from baseline

Table 2 Lines of therapy before TPO-RAs

	Romiplostim		Eltrombopag	
Lines of therapy, mean (range)	2.5	(0–4[a])	2.4	(1–5)
Glucocorticoids, *n* (%)	54	(98.1 %)	69	(100 %)
IGIV +/− glucocorticoids, *n* (%)	37	(67.2 %)	46	(66.6 %)
Rituximab, *n* (%)	17	(30.9 %)	14	(20.2 %)
Splenectomy, *n* (%)	11	(20 %)	7	(10.1 %)
Splenectomy pts <60 years, *n* (%)	11/23	(47.8 %)	7	(22.5 %)
TPO-RA switch	2/55	(3.6 %)	7	(10.1 %)

[a] One patient with severe diabetes started romiplostim as first-line therapy

was obtained for 51/55 patients (92.7 %) in the romiplostim group and 67/69 (97.1 %) in eltrombopag group. The median number of platelets reached by the two TPO-RAs was comparable (Table 3).

The resolution of clinical bleedings was obtained similarly in 15/16 (93.7 %) of patients treated by romiplostim and in 23/25 (92 %) of those treated by eltrombopag.

There were no differences in the response rate according to age over or under 60 years. Median time to response was 4 weeks for romiplostim and 4 week and half for eltrombopag, with no statistical differences according to Kaplan-Meier analysis. Duration of response was apparently different between the romiplostim group and eltrombopag group but this is due to different time of onset of the two therapies due to later commercialization of eltrombopag than romiplostim. The mean duration of response was 30 months for romiplostim and 15 months for eltrombopag. A loss of response was recorded in 9 % (4/44) of patients treated by romiplostim and 4.6 % (3/64) of those treated by eltrombopag.

We therefore analyzed the responses distinguishing between splenectomized and non-splenectomized patients, recording substantial differences. Non-splenectomized patients treated with TPO-RAs showed a higher ORR than patients treated after splenectomy. In detail, among non-splenectomized patients, the ORR was 81.8 % (36/44) for romiplostim and 95.1 % (59/62) for eltrombopag, while among splenectomized patients the ORR was of 72.7 % (8/11) for romiplostim and 71.4 % (5/7) for eltrombopag. In fact, the multivariate analysis showed that only splenectomy is a negative independent prognostic factor for response ($p<0.05$).

Causes of discontinuation and AEs

Table 4 shows data on temporary or permanent discontinuation of therapy. Treatment failure was the most frequent cause

Table 3 Data on response according to age and splenectomy; duration and loss of response

	Romiplostim		Eltrombopag	
ORR, *n* (%)	44	(80 %)	65	(94.2 %)
Median plts after TPO-RAs $\times 10^9$/L (range)	98	(37–432)	89	(38–344)
CR, *n* (%)	24	(43.6 %)	33	(47.8 %)
PR, *n* (%)	20	(36.3 %)	32	(46.3 %)
Increase of platelets (>than baseline)	51	(92.7 %)	67	(97.1 %)
Resolution of bleedings	15	(93.7 %)	23	(92 %)
NR, *n* (%)	11	(20 %)	5	(7.2 %)
>60 years: CR, *n* (%)	12	(37.5 %)	17	(44.7 %)
PR, *n* (%)	14	(43.7 %)	19	(50 %)
NR, *n* (%)	6	(18.7 %)	2	(5.2 %)
<60 years: CR, *n* (%)	12	(52.7 %)	15	(48.3 %)
PR, *n* (%)	6	(26 %)	13	(41.9 %)
NR, *n* (%)	5	(21.7 %)	3	(9.6 %)
Splenectomy: CR, *n* (%)	4	(36.3 %)	3	(42.8 %)
PR, *n* (%)	4	(36.3 %)	2	(28.5 %)
NR, *n* (%)	3	(27.2 %)	2	(28.5 %)
No splenectomy: CR, *n* (%)	20	(45.4 %)	29	(46.7 %)
PR, *n* (%)	16	(36.3 %)	30	(48.3 %)
NR, *n* (%)	8	(18.1 %)	3	(4.8 %)
Duration of response in months:	30	(2–57)	15	(2–41)
CR, mean months (range)	45	(8–57)	25	(9–41)
PR, mean, months (range)	18	(7–48)	10	(2–19)
Loss of response, *n* (%)	4	(9 %)	3	(4.6 %)

ORR overall remission rate, *Plts* platelets, *CR* complete remission, *PR* partial remission, *NR* no response

Table 4 Causes of permanent and temporary discontinuation of TPO-Ras

	Romiplostim		Eltrombopag	
Permanent discontinuation				
Failure	11	(20 %)	5	(7.2 %)
Thrombotic events	1	(1.8 %)[a]	2	(2.8 %)[b]
Grade III–IV increase of transaminases	–		2	(2.8 %)
Temporary discontinuation				
Platelets >400×10^3/μL	7	(12.7 %)	9	(13 %)
Arthralgia	1	(1.8 %)	–	
Gastritis	–		1	(1.4 %)
Headache	–		1	(1.4 %)

[a] Vein thrombosis

[b] Myocardial infarction

of permanent discontinuation and accounted for 20 % in the romiplostim group and 7 % in the eltrombopag group. Among patients who failed to romiplostim, seven switched to eltrombopag and four responded, four underwent splenectomy and three responded, one patient, not responding to splenectomy died for brain hemorrhage. Among patients who failed to eltrombopag, two switched to romiplostim and both responded and four were addressed to splenectomy with an appreciable response. Thrombotic events were recorded in 2 and 3 % of patients treated by romiplostim and eltrombopag, respectively, and determined permanent drug interruption. Two patients of the eltrombopag group stopped treatment due to an elevation of transaminases more than five times the normal value.

Temporary drug interruptions were recorded for several causes such as platelet count over 400×10^9/L, arthralgia, gastritis, and headache, and together accounted for 17 % of patients treated with romiplostim and 18 % of patients treated with eltrombopag.

Discussion

This evaluation on the use of TPO-RAs for ITP treatment in real life, based on patients observed in the last 5 years in six hospitals of the Rete Ematologica Pugliese, leads to some considerations with possible implications for the future clinical practice.

Firstly, in the last 2 years, we registered that a greater number of patients have been treated by eltrombopag instead of romiplostim. Although these patients should have been addressed to splenectomy before the treatment with TPO-RAs, according to the international guidelines [2]; in our series, most patients were older than 60 years and the decision to do splenectomy was questionable. Further, many patients refused splenectomy for being aware of alternatives and our health system forecasts the possibility to prescribe TPO-RAs even in these situations. Certainly, the significantly better result with TPO-RAs in non-splenectomized patients warrants a specific point of discussion on which the possible explanation could be. We consider that patients resistant to splenectomy are negatively selected for response, also because they had already been treated by several lines of therapy. In our population, the two drugs demonstrated comparable effectiveness, leading to an increased platelet level in the majority of patients. The explanation of the major use of eltrombopag may be found in the advantages of oral administration. It might be a preferable choice of patients; however, the results showing a non-superiority of romiplostim imply also an easy choice for physicians. As the costs of such therapy, almost 14,000 dollars over 6 months at 50 mg/day of eltrombopag, are sustainable, we have to consider all economical aspects, the number of saved splenectomies at 12,000 dollars each, the morbidity and mortality saved; it is a difficult question if it is economically convenient to treat patients before or after splenectomy, when the procedure is feasible.

A second important observation is that splenectomy was mainly delayed after the eventual failure of TPO-RAs. In fact, the majority of patients did not undergo splenectomy even if they were eligible for the procedure, mainly due to patient refusal. Therefore, as a consequence of the arrival of TPO-RAs, a minority of patients are directed towards splenectomy in daily practice.

A third point of discussion is that the results, in terms of quality and duration of response, were similar in both groups of patients, even if the observation time was longer for romiplostim due to its approval in Italy approximately 2 years before eltrombopag. Interesting differences were recorded between splenectomized and non-splenectomized patients, with better responses to both TPO-RAs in the latter group. No substantial differences were found regarding the age of patients.

Finally, we recognized some possible causes of the discontinuation of TPO-RAs, principally the unmaintained response. In patients who had reached a CR, a close modulation of the dose was needed in order to maintain response and avoid thrombocytosis. Side effects were acceptable, except for deep thrombosis which were fortunately rare.

Certainly, the principal open question is whether TPO-RAs could represent an alternative to splenectomy. It is known that TPO-RAs cause the stimulation of platelet production by megakaryocytes, leading to an increase of circulating platelets, while their action as immunomodulatory agents is under investigation and they are not considered curative. The abrupt discontinuation of TPO-RA may

give a rebound of thrombocytopenia [5]. However, the possibility to maintain the response after discontinuation has recently been reported, [6, 7] leading to the rationale that TPO-RAs may restore immune tolerance via Treg function principally by an indirect effect due to the increased platelet number and exposure to platelet antigens [8, 9]. We observed sustained responses in three patients who stopped therapy 2 or more years after remission, while those with shorter duration of remission lost the response after discontinuation. Perhaps immune tolerance could be obtained with long lasting remission and this aspect may help to plan treatment approach in the future. The lacking use of splenectomy, especially in young patients, implies the possibility to stop the therapy and we hope that prospective studies could focus on this particular aspect. Our experience shows that non-splenectomized patients respond better to TPO-RAs than splenectomized ones; the same result is reported by other authors [10] and splenectomy has therefore been avoided in several patients [11]. These data support the idea that splenectomy could be avoided in some selected patients who completely respond to TPO-RAs with a lasting duration of response and are then candidate to discontinue the therapy. Studies finalized to discover the proportion of the population who could benefit from drug discontinuation instead of splenectomy are warranted. The idea is strengthened by the possibility to use both available TPO-RAs that are not cross-resistant [12, 13], supported by their action in different sites of the thrombopoietin receptor [14]. We also reported that some patients switched from one TPO-RA to the other, obtaining response.

In conclusion, the rapid change in the therapeutic scenario of ITP leaves some open questions that need to be addressed by clinical trials: the role of splenectomy, the sequence of lines of treatment according to age and comorbidity, the switch between the two TPO-RAs, their safe discontinuation, and the eventual combination with other drugs with different mechanisms of action such as rituximab.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest. The authors received no financial support for the study.

Ethical standards The study was conducted in accordance with the Declaration of Helsinki. All patients signed informed consent according to the regulations of each investigational site.

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