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Authors Marijana Virijević*, †, Mirjana Mitrović*, †, Nikola Pantić*, Zlatko Pravdić*, Nikica Sabljić*, Nada Suvajdžić-Vuković*, †, Vojnosanitetski pregled (2021); Online First October, 2021.

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AGONISTI TROMBOPOETINSKIH RECEPTORA U LEČENJU PRIMARNE IMUNOLOŠKE TROMBOCITOPENIJE ODRASLIH - NAŠA ISKUSTVA

Marijana Virijević*,†, Mirjana Mitrović*,†, Nikola Pantić*, Zlatko Pravdić*, Nikica Sabljić*, Nada Suvajdžić-Vuković*†

* Clinic of Hematology, University Clinical Center of Serbia, Belgrade, Serbia
† Faculty of Medicine, University of Belgrade, Belgrade, Serbia

Corresponding author:
Marijana Virijević, MD, PhD;
Clinic of Hematology, Clinical Center of Serbia, 2 Koste Todorovica st., 11000 Belgrade, Serbia;
Telephone: +381113663536; Fax number: +381113065112;
Email address: marijana.virijevic@yahoo.com
Abstract

Background / Aim. The availability of thrombopoietin receptor agonists (TPO-RA) for the treatment of primary immune thrombocytopenia (ITP) over the last decade has transformed its management. The aim of this study was to assess the efficacy of TPO-RA in adults with chronic ITP treated in the University Clinical Centre of Serbia. Methods. A total of 28 adult ITP patients (10 males; 18 females) given eltrombopag and/or romiplostim were enrolled in the study. Data on demographic characteristics, ITP duration, previous therapeutic modalities, comorbidities, concomitant therapy, indications for TPO-RA, bleeding episodes, TPO-RA doses, adverse events and response rates were collected from the patients’ medical records. TPO-RAs were administered: (a) in patients with chronic refractory ITP; (b) when splenectomy was contraindicated/unfeasible; (c) as preparation for splenectomy. A favourable treatment response was defined as a stable platelet count ≥ 50x10⁹/L. Results. Twenty two (78.57%) and 14 (50.0%) subjects were treated with eltrombopag and romiplostim, respectively. A good treatment response (GTR) was achieved in 81.8% of the patients receiving eltrombopag and in 71.4% of those treated with romiplostim. The non-responders to eltrombopag (4 patients) and those who had lost their response to eltrombopag (4 patients) were switched to romiplostim. Six of them achieved a GTR. At the time of TPO-RA initiation, 46.4% of the patients used concomitant ITP therapy which was ceased in all those with a GTR. The following adverse effects of TPO-RA were registered: transaminitis and transient ischemic attack for eltrombopag - one patient each, and pulmonary embolism in one romiplostim treated patient. Conclusion. Our study showed that TPO-RAs are an effective and safe treatment option, since the majority of patients achieved stable remission without bleeding episodes.

Key words: thrombopoietin receptor agonist, eltrombopag, romiplostim, primary immune thrombocytopenia

Abbreviations: AEs – adverse events; GTR – good treatment response; ITP – primary immune thrombocytopenia; PC – platelet count; TPO-RA – thrombopoietin receptor agonists;
Apstrakt

Uvod / Cilj. Lečenje primarne imunološke trombocitopenije (ITP) se značajno izmenilo tokom prethodne decenije zahvaljujući agonistima trombopoetinskih receptorova (TPO-RA). Cilj ove studije je utvrđivanje efikasnosti TPO-RA u lečenju pacijenata sa hroničnom ITP u Univerzitetskom kliničkom centru Srbije. Metode. U studiju je uključeno 28 odraslih pacijenata sa ITP lečenih TPO-RA. Prikupljani su demografski podaci, trajanje ITP, prethodni terapijski modaliteti, komorbiditeti, prateća terapija, kako za komorbiditete tako i za ITP, indikacije za uvođenje TPO-RA, krvarenje pre i tokom primene TPO-RA, prosečne doze TPO-RA, neželjeni događaji i stopa terapijskog odgovora na TPO-RA. Indikacije za primenu TPO-RA bile su: (a) hronična refraktarna ITP; (b) kontraindikovana/neizvodljiva splenektomija; (c) priprema za splenektomiju. Rezultati. Dvadeset dva (78,57%) pacijenta su lečena eltrombopagom, a 14 (50,0%) pacijenata romiplostimom. Dobar terapijski odgovor (DTO) je postignut kod 81,8% pacijenata lečenih eltrombopagom i kod 71,4% pacijenata lečenih romiplostimom. Pacijenti kod kojih nije postignut DTO na eltrombopag (4 pacijenta) i oni koji su izgubili DTO na eltrombopag (4 pacijenta) prevedeni su na romiplostim. Kod njih 6/8 postignut je DTO. U vreme uvođenja TPO-RA, 46,4% pacijenata je koristilo prateću terapiju za ITP koja je kod svih ukinuta po postizanju DTO. U toku primene TPO-RA zabeleženi su sledeći neželjeni događaji: transaminitis i tranzitorni ishemijski atak u po jednog pacijenata lečenog eltrombopagom i plućna embolija kod jednog pacijentova lečenog romiplostimom. Zaključak. Naši rezultati su pokazali da su TPO-RA efikasni bezbedni u lečenju odraslih pacijenata sa ITP s obzirom da je većina pacijenata tokom lečenja postigla stabilnu remisiju bez epizoda krvarenja.

Ključne reči: agonisti trombopoetinskih receptorova, eltrombopag, romiplostim, primarna imunološka trombocitopenija, ITP
**Introduction**

Primary immune thrombocytopenia (ITP) is an acquired immune-mediated disorder characterized by isolated thrombocytopenia, defined as a platelet count (PC) below 100x10^9/L and the absence of any other cause of thrombocytopenia. The primary manifestation of ITP is an increased bleeding tendency that varies from cutaneous purpura to more severe mucosal bleeding. However, 16–21% of adults diagnosed with ITP are without bleeding symptoms. Nevertheless, patients with ITP have a slightly increased risk of arterial and venous thrombotic events and many of them suffer from fatigue and depression. ITP is classified by disease duration as: newly diagnosed (0-3 months), persistent (>3-12 months), or chronic (>12 months). The estimated incidence of ITP is approximately 2-4 per 100 000 adults/year.

ITP is characterized by both increased platelet destruction as well as inappropriately low platelet production. This is mediated by the proapoptotic action of glycoprotein-specific platelet autoantibodies and cytotoxic lymphocytes on megakaryocytes. The treatment goals aim to prevent severe bleeding episodes and to maintain PC >20-30x10^9/L. Moreover, any medication should have minimal toxicity and should optimize the patients' quality of life.

ITP treatment options are numerous and may be categorized into first line and second line treatment modalities (Table 1). The availability of thrombopoietin receptor agonists (TPO-RA) for the treatment of ITP over the last decade has transformed its management. TPO-RAs activate the same signaling pathways as endogenous TPO, leading to an increase in PC, cessation of bleeding and improved quality of life in 80% of patients with chronic ITP, both splenectomized and nonsplenectomized. This makes them the most effective drugs of the second therapeutic line.

Romiplostim and eltrombopag are licensed by the European Medicines Agency for the treatment of ITP in adults when an insufficient response to corticosteroids or intravenous gammaglobulins has been registered. Eltrombopag is licensed for ITP lasting more than 6 months, while such a restriction does not apply to romiplostim. However, in Serbia both drugs are licensed exclusively for chronic ITP. Romiplostim is a peptibody that binds directly and competitively at the TPO binding site, and is dosed as a weekly subcutaneous injection. In contrast, eltrombopag is a small molecule which binds to a transmembrane site.
on the TPO-R and is given orally. Their effect is manifested after 1-5 weeks from treatment initiation.\textsuperscript{1,3,7,8} Both drugs have been shown to be safe, well tolerated, and equally effective.\textsuperscript{1,3,7-9,14} If one of the two shows ineffectiveness or side effects, the chance of establishing a response to the other one is about 50\% due to the absence of cross-resistance between them.\textsuperscript{15} Rebound thrombocytopenia typically recurs upon abrupt discontinuation of TPO-RA. However, several studies have shown that TPO-RAs induce remission and a stable response in 10-30\% of patients after gradual discontinuation.\textsuperscript{16,17} In addition, successful short-term administration of TPO-RAs as part of the preparation for surgical interventions, including splenectomy, has been described.\textsuperscript{18} The aim of this study was to assess the efficacy and safety of TPO-RAs in chronic ITP patients treated in the University Clinical Centre of Serbia.

Methods
This retrospective observational study in the Clinic of Hematology included the period from April 2013 to January 2020. A total of 28 adult ITP patients (10 males; 18 females) treated with eltrombopag and/or romiplostim were enrolled. The diagnosis of ITP was made according to the current guidelines.\textsuperscript{3,7,8} The following data were obtained from patients’ medical records: (1) demographics (age and sex); (2) ITP-related data: time from diagnosis, previous therapeutic modalities including splenectomy, PC, bleeding score and concomitant therapy for ITP at the initiation of TPO-RA; (3) each patient’s medical history: comorbidities, concomitant therapy for comorbidities; (4) TPO-RA related data: indication and TPO-RA doses, time to response, adverse events (AEs), response rate and whether TPO-RAs were switched. TPO-RAs were administered: (a) in patients with chronic refractory ITP; (b) when splenectomy was contraindicated/unfeasible; (c) as a preparation for splenectomy. Chronic refractory ITP was defined according to the recommendations of the International Working Group.\textsuperscript{2} A PC \( \geq 50 \times 10^9$/L was considered a good treatment response (GTR). Bleeding was graded according to Khellaf et al.\textsuperscript{19} Eltrombopag was given orally at the starting dosage of 50 mg/day, while romiplostim was initiated at the dose of 1 mcg/kg/week subcutaneously. For both drugs, subsequent doses were adjusted according to the PC, up to the maximum of 75 mg/day for eltrombopag and 10 mcg/kg/week for romiplostim. All data were summarized using descriptive statistical methods.
Results
TPO-RAs were administered to 11 (39.3%) patients with chronic refractory ITP, to 12 (42.9%) patients in whom splenectomy was contraindicated/unfeasible and to 5 (17.9%) patients as a preparation for splenectomy. The characteristics of the patients are shown in Table 2. The median number of previous treatments for ITP was four in the eltrombopag and five in the romiplostim group. Treatment modalities used before TPO-RA initiation are listed in Table 3.
Twenty two (78.6%) patients received eltrombopag and 14 (50%) romiplostim. More than 70% of our patients had experienced some comorbidities (Table 2), mainly cardiovascular conditions (15 patients - 53.6%) often requiring antiplatelet or anticoagulant therapy. At the time of TPO-RA initiation 46.4% of the patients were using concomitant ITP therapy (tranexamic acid, corticosteroids, azathioprine).
An initial GTR was noted in 18 (81.8%) patients receiving eltrombopag and in 12 (71.4%) romiplostim-treated patients (Table 4). The non-responders (4 patients), as well as those who had lost their response (4 patients) while receiving eltrombopag, were switched to romiplostim. Six of them initially achieved a GTR. However, two of them lost their response after 5 and 8 months, respectively (Table 4).
During the observational period the following AEs were noted (in one patient each): pulmonary thromboembolism in the romiplostim group and transaminitis and transitory ischemic attack in the eltrombopag group.
Discussion
In our study, the safety and efficacy of TPO-RA in adults with previously treated chronic ITP were evaluated. Eltrombopag was given almost twice as often as romiplostim since we were guided by patients’ preferences. Our patients were of average age 58.5 years and had numerous comorbidities, mostly of cardiovascular nature (hypertension, ischemic heart disease, atrial fibrillation) often requiring antiplatelet or anticoagulant therapy. The median time from ITP diagnosis to TPO-RA initiation was 71 months [IQR: 29-230.5] for eltrombopag and 97 months [IQR:21-248], for romiplostim, which is significantly longer than reported in other studies.\textsuperscript{20,21} This could be explained by the stringent criteria for TPO-RA initiation dictated by Serbian Public Health Insurance.\textsuperscript{22}
A GTR was achieved in 81.8% of patients treated with eltrombopag and in 71.4% patients treated with romiplostim, which is consistent with previously reported results.\textsuperscript{21,23} All of our patients had been treated with multiple therapeutic modalities before TPO-RA initiation (Table 3). Nevertheless, more than one third of them underwent splenectomy, and more than two thirds achieved a GTR after introducing TPO-RA. Our results are consistent with those in previous publications. Namely, GTR was achieved in 68% of splenectomized patients treated with romiplostim\textsuperscript{23} and 61% of splenectomized patients treated with eltrombopag.\textsuperscript{24}

At the initiation of TPO-RA the majority of our subjects used concomitant ITP therapy, which was discontinued after achievement of a GTR. The median PC was 11.5 \times 10^9/L (IQR:7-19) before eltrombopag and 10 \times 10^9/L (IQR:2-22) before romiplostim initiation. The time to response was 2.2 weeks for eltrombopag and 2.6 weeks for romiplostim, which is in line with previous studies.\textsuperscript{21,25} The median duration of response was 24.5/13.5 months with a follow-up period of 25/23.5 months.

As reported previously, TPO-RA are generally well tolerated.\textsuperscript{21,25,26} The prevalence of adverse events was 9.1% in our eltrombopag- and 7.1% in our romiplostim-treated patients. Thus, transaminitis and transient ischemic attack were registered in single eltrombopag-treated patients, while pulmonary embolism occurred in one romiplostim-treated individual.

The occurrence of thrombotic events in romiplostim-treated patients has been described earlier with an incidence of 6.5%.\textsuperscript{27} However, it should be underlined that our subject was obese (38 kg/m\textsuperscript{2}), splenectomized and experienced transient thrombocytosis of 800 \times 10^9/L at the time of pulmonary embolism. On the other hand, adverse events were noted in two individuals treated with eltrombopag. One patient had transaminitis and the other a transient ischemic attack, which had been previously described as well.\textsuperscript{3,28}

To avoid PC oscillation in our romiplostim-treated patients, we administered the same dose regardless of the PC. As a result, we observed stable disease remission with PC \geq 50 \times 10^9/L. This was maintained with romiplostim at a mean level of 6.41 \mu g/kg and eltrombopag (mean 54.9 mg). Our romiplostim dose was higher than that recorded by others (2.8-5.1 \mu g/kg).\textsuperscript{25,26} In those studies romiplostim was introduced earlier in the disease course, sometimes as a second line just after corticosteroids, while in our case it was given to highly refractory patients, including those who failed with eltrombopag.
Long-term remission despite TPO-RA discontinuation has been reported.\textsuperscript{25} Two of our patients (7\%) achieved a sustained response after gradual discontinuation of TPO-RA (one on romiplostim and the other on eltrombopag therapy), which is less than observed by others (10-30\%) but early introduction of TPO-RA has been shown to be associated with a higher frequency of treatment-free response.\textsuperscript{17} Many studies have confirmed that switching TPO-RA could be beneficial.\textsuperscript{15,28,29} In our study eight patients were changed from eltrombopag to romiplostim; a GTR was achieved in 50\% of them which supports earlier data.\textsuperscript{15,28} However, all of the patients who were initially treated with romiplostim achieved a GTR, and we registered no cases of romiplostim to eltrombopag switch. Additionally, four patients treated with eltrombopag lost their response after an initial GTR but two of them achieved a GTR after switching to romiplostim. Among the patients who lost their response or remained refractory to both TPO-RAs, TPO-RAs were discontinued and tranexamic acid was introduced. Moreover, corticosteroids and/or intravenous gammaglobulins were administered in cases of bleeding.

**Conclusion**

On balance, our study showed that the patients treated with TPO-RA achieved stable remission with minimal incidence of AEs and no serious bleeding events during the therapy. Moreover, we have confirmed the efficacy of a TPO-RA switch, since the response to the second TPO-RA was long lasting in our group. Bearing in mind the aforementioned characteristics, wider use of TPO-RAs during the earlier course of the disease should be considered.
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Table 1. Primary immune thrombocytopenia treatment modalities\textsuperscript{7}

| First line (initial) treatment | Corticosteroids |
|-------------------------------|-----------------|
|                               | IVIg            |
|                               | IV anti-D       |

| Second line (subsequent) treatment | Medical therapies | Surgical therapies |
|-----------------------------------|-------------------|--------------------|
|                                   | TPO-RA – eltrombopag | splenectomy       |
|                                   | – romiplostim     |
|                                   | Rituximab         |
|                                   | Fostamatinib      |
|                                   | Medical therapies with less robust evidence: azathioprine, cyclophosphamide, cyclosporin A, danazol, dapsone, mycophenolate mofetil, vinca alkaloids |

IVIg – intravenous gammaglobulin; IV anti-D – intravenous anti-D; TPO-RA – thrombopoietin receptor agonist
**Table 2. Characteristics of the study population**

|                                | Eltrombopag* (N = 22) | Romiplostim (N = 14) |
|--------------------------------|------------------------|----------------------|
| **Age at TPO-RA initiation**   |                        |                      |
| **Median (IQR)**               | 58.5 (IQR: 53-69)      | 52.5 (IQR:24-66.5)   |
| **Females/males**              | 13 / 9 (59.1% / 40.9%) | 12 / 2 (85.7% / 14.3%) |
| **ITP duration (months)**      | 71 (IQR:29-230.5)      | 97 (IQR:21-248)      |
| **Splenectomized patients**    | 9 (40.9%)              | 6 (42.9%)            |
|                          | N (%)   |   |
|--------------------------|---------|---|
| Patients with comorbidities | 19 (86.4%) | 10 (71.4%) |
| Patients who used therapy for comorbidities | 17 (77.3%) | 7 (63.6%) |
| Platelet counts at TPO-RA initiation |   |   |
| Median (IQR) (x10⁹/L) | 11.5 (IQR:7-19) | 10 (IQR:2-22) |
| Bleeding score |   |   |
| Median (IQR) | 0 (IQR:0-2.25) | 3.5 (IQR:0-13) |
| ITP treatment modalities prior to TPO-RA (N) |   |   |
| Median (IQR) | 4 (IQR: 3-4) | 5 (IQR: 4-5) |
| Concomitant ITP medications at TPO-RA |   |   |
| 14 (63.6%) | 10 (71.4%) |
Eight patients were initially treated with eltrombopag and afterwards switched to romiplostim
Table 3. ITP treatment modalities administered before the initiation of TPO-RAs

| Type of ITP treatment       | Eltrombopag (N = 22) | Romiplostim (N = 14) |
|-----------------------------|----------------------|---------------------|
| Corticosteroids             | 22 (100.0%)          | 14 (100.0%)         |
| Intravenous gammaglobulins  | 8 (36.4%)            | 10 (71.4%)          |
| Splenectomy                 | 9 (40.9%)            | 6 (42.9%)           |
| Rituximab                   | 0 (0.0%)             | 1 (7.1%)            |
| Azathioprine                | 19 (86.4%)           | 11 (78.6%)          |
| Mycophenolate-mofetil       | 2 (9.1%)             | 3 (21.4%)           |
| Cyclosporine A              | 0 (0.0)              | 2 (14.3%)           |
| Vinca alkaloids             | 12 (54.5%)           | 8 (57.1%)           |
| Danazol/dapsone             | 4 (18.2%)            | 3 (21.4%)           |
| Cyclophosphamide            | 5 (22.7%)            | 4 (28.6%)           |

ITP – primary immune thrombocytopenia; TPO-RAs – thrombopoietin receptor agonists; N - number
Table 4. Treatment response characteristics

|                                | Eltrombopag (N = 22) | Romiplostim (N = 14) |
|--------------------------------|-----------------------|----------------------|
| GTR N (%)                      | 18 (81.8%)            | 12 (71.4%)           |
| GTR in splenectomised patients | 7/9 (77.8%)           | 4/6 (66.7%)<sup>*</sup> |
| Time to response (weeks)       | 2.2±1.2               | 2.6±1.2              |
| Average TPO-RA dose Mean±SD    | 54.19±16.59 mg        | 6.41 ± 2.63 μg      |
|                                    | Duration of response (months) Median (IQR) | Follow-up (months) Median (IQR) |
|------------------------------------|------------------------------------------|---------------------------------|
| Duration of response               | 24.5 (IQR: 5.5-36)                      | 13.5 (IQR: 8-37.5)             |
| Median (IQR)                       |                                          |                                 |
| Median (IQR)                       | 25 (IQR: 6-36.5)                        | 23.5 (IQR: 8-37.5)             |
| Loss of response                   | 4/18 (22.2%)                            | 2/12 (16.7%)                   |
| N (%)                              |                                          |                                 |
| Switch to other TPO-RA             | 8 (36.4%)                               | 0 (0%)                         |
| N (%)                              |                                          |                                 |
| Sustained response after TPO-RA    | 1 (4.5%)                                | 1 (7.1%)                       |
| discontinuation                    |                                          |                                 |
| N (%)                              |                                          |                                 |
| Adverse events | 2 (9.1%) | 1 (7.1%) |
|---------------|----------|----------|
| N (%)         |          |          |

N – number; GTR – good treatment response; SD – standard deviation; TPO-RA – thrombopoietin receptor agonist; IQR – interquartile range

* 2 of 3 splenectomised patients who were switched to romiplostim, achieved good treatment response

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