Efficacy and Safety of Thrombopoietin Receptor Agonists in Modern Treatment of Immune Thrombocytopenia

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Abstract

Immune thrombocytopenia (IT), characterized by isolated platelet decrease and bleeding, could be primary or secondary to infections, autoimmune diseases, drugs. Classical treatments for IT are corticosteroids, immunoglobulins (1st line) and splenectomy, immunosuppression (2nd line), therapies based on decreasing platelets’ destruction. Thrombopoietin receptor agonists (TRA), romiplostim, eltrombopag and avatrombopag, modern drugs used for refractory patients, increase platelets production. The aim of the article is a review of literature based on 59 scientific articles regarding the efficacy and safety of TRA in primary IT. This review is helpful to specialists, given the limited experience with these drugs, approved in 2008 in the United States and in 2009 in Europe. TRA have shown good efficacy, treatment leading to increased platelet counts, decreased hemorrhagic episodes, reduced concomitant medication. TRA were well tolerated, the adverse effects reported were medullary fibrosis, thrombosis, headache, rhinopharyngitis, hepatocitolysis, fatigue.

Keywords: thrombopoietin receptor agonists, immune thrombocytopenia

Introduction

Immune thrombocytopenia (IT) is an autoimmune disease characterized by isolated thrombocytopenia (platelet count under 100.000/µL) in the absence of other causes or disorders that may be associated with thrombocytopenia. The dominant clinical manifestation is bleeding, which generally correlates with the severity of thrombocytopenia [7, 18, 19, 58]. According to the classical pathogenetic theory, immune thrombocytopenia is mediated by autoantibodies, platelet antibodies that accelerate platelet destruction and inhibit their production. New pathogenetic theories are based on multiple immune mechanisms of platelet and their progenitors’ destruction (complement mediated cytotoxicity of T lymphocytes and CD4+ mediated cytotoxicity). Another modern idea is that platelet production is variably impaired, antibodies could contribute to megakaryocyte destruction, induce apoptosis, impede platelet release, or promote intra-medullary phagocytosis [7, 18]. The disease could be primary (idiopathic) or secondary to infections (eg. Helicobacter pylori, B or C hepatitis, HIV), to other autoimmune diseases (systemic erythematous lupus, rheumatoid arthritis or other collagenous pathologies) or to certain drugs. In addition, environmental and genetic factors may impact
Materials and Methods

The objective of this literature review is to perform a systematic review of current evidence on the efficacy and safety of thrombopoietin receptor agonists in primary immune thrombocytopenia. The inclusion criteria of the studies in this review were: primary studies; studies published in English language; the possibility of accessing the entire article for free; studies focused on the safety and efficacy of treatment with TRA in primary immune thrombocytopenia.

The exclusion criteria of the studies were: studies approaching treatment with TRA, but not its efficacy and safety; studies on pediatric patients; studies based on secondary immune thrombocytopenia patients; studies based on other types of thrombocytopenia (non-immune, drug, congenital, etc.)

Study searches were conducted in the Medline and Cochrane Central Register of Controlled Trials (CENTRAL) databases with the “free full text” option enabled.

In the Medline database keywords used were: (thrombopoietin mimetic AND) (thrombopoietin receptor agonists AND) (thrombopoietin receptor thrombocytopenia) OR (eltrombopag AND (thrombocytopenic OR thrombocytopenia) OR thrombocytopenia)) OR (romiplostim AND (thrombocytopenic OR thrombocytopenia)) OR (avatrombopag AND (thrombocytopenic OR thrombocytopenia)).

These searches resulted in 237 articles and an erratum of an article. From the manual search of the key articles in the bibliography, there were no other relevant articles that were not already included in the analysis that met the inclusion criteria.

Following the analysis of the studies, 178 articles were excluded, the ones that did not meet the inclusion criteria or had exclusion criteria. The number of studies included in the analysis was 59 and the erratum.

The data was extracted from the articles in a uniform and impartial manner using an electronic data collection file that included: eligibility criteria, year of appearance, study design, population included, number of included patients, intervention, outcome of treatment and treatment safety, including adverse reactions.

The data of the 59 papers included in the systematic analysis were analysed following the intended effects: the efficacy of treatment with analogues of TRA and the short- and long-term safety of the treatment. In these studies, 2 studies approached all three drugs, 16 studies approached eltrombopag and romiplostim, 11 studies approached eltrombopag only, 23 studies approached romiplostim and 7 studies approached avatrombopag.

Results and Discussion

Current guidelines for IT medication

Regarding to IWG, first line of treatment consists in corticosteroids (as immunosuppressors) or high dose immunoglobulins (reticuloendothelial system blockade) and second line treatments are represented by splenectomy (removing the site of platelets’ destruction), rituximab (anti CD 20 monoclonal antibody which targets and destroys CD20+ B lymphocytes which are presumably involved in autoantibody production), thrombopoietin receptor agonists (which increase platelets production), fostamatinib (Syk inhibitor, which inhibits platelet’s phagocytosis by splenic macrophages due to inhibition of cytoskeleton), other immunosuppressors (azathioprine, cyclophosphamide, Vinca alkaloids (spleen macrophage blockade). Immune thrombocytopenia treatment is very well specified in international guidelines based on pharmaceutical good practice [7, 18, 19, 24, 25, 48, 78].

TRA are new and promising second generation drugs. Firstly, there were produced and administrated recombinant human thrombopoietin analogues. These drugs were abandoned because of the development of cross-reactive antibodies against endogenous thrombopoietin which produced sustained thrombocytopenia. This is the reason for producing second-generation thrombopoietin receptor agonists that have no sequence homology to endogenous thrombopoietin. These drugs are romiplostim, eltrombopag and the newest avatrombopag, which proved efficacy even in patients suffering refractory disease [7, 22, 25, 26, 30, 58, 83]. In 2008 romiplostim, and eltrombopag were approved by US Food and Drug Administration (FDA) and in 2009 by European Medicines Agency (EMA) [85]. In 2018 avatrombopag was approved by FDA [25].

Romiplostim (administered as a once-weekly subcutaneous injection) is a synthetic peptide made of four peptides linked to an IgG Fc fragment. This drug binds thrombopoietin receptor on megakaryocytes at the same location as endogenous thrombopoietin and stimulates megakaryocyte proliferation and platelet production through intracellular Janus kinase/signal transducer and activator of transcription (JAK/STAT) and mitogen-activated protein kinase (MAPK) signalling.
In a phase III trial, a durable platelet count response (defined as the achievement of a platelet count of \(50 \times 10^9/L\) or higher for 6 or more of the last 8 weeks of treatment) was achieved in 50% of 83 patients receiving Romiplostim compared with one of 42 patients receiving placebo. Weekly doses of Romiplostim range from 1 to 10 µg/kg. Weekly doses are titrated up or down, depending on the platelet count response, to maintain the platelet count in the appropriate range (30 - 100 \(\times 10^9/L\)) [7, 20, 26, 45, 58, 83].

Eltrombopag (administered as a 50 mg tablet once daily) is a small molecule, nonpeptide TRA that activates thrombopoietin receptor by binding to its transmembrane domain. In contrast to romiplostim, eltrombopag does not compete with circulating thrombopoietin for binding to thrombopoietin receptor. In a phase III trial, the odds of responding to eltrombopag were approximately eight times higher than with placebo throughout the 6-month treatment period. Durable responses were achieved in 60% of 95 patients receiving maintenance eltrombopag compared with 10% of 39 patients receiving placebo. The time to respond similar to Romiplostim, with a minimal need for dose titration. Disadvantage of this drug is that the patient must adhere to dietary restrictions, a four hours restricted window around the dose [7, 22, 23, 58].

Avatrombopag belongs to the second generation of new oral non peptide TRA and was introduced in USA 2018, for the treatment of ITP and chronic liver disease induced thrombocytopenia. Its mechanism of action is similar to Romiplostim, consists in stimulating megakaryocytes proliferation via JAK/STAT and MAPK signalling. The few studies of avatrombopag showed significantly increased platelet response rate of 67 - 93% and decreased concomitant ITP medication used. Initial dose is 20 mg po/day, with possibility to increase at 40 mg po/day, but not to exceed it. There are no dietary restrictions and this may increase patient’s compliance.

There are some data proving that romiplostim is approximately eight times more potent than eltrombopag at increasing the platelet count and avatrombopag was approximately 3 times more potent than eltrombopag [3, 21, 65, 79].

Lusutrombopag has been developed, its indication being for periprocedural thrombocytopenia in chronic liver diseases. Maybe in the future this drug will also be used in ITP [21, 79].

TRA is generally well tolerated, all three drugs have been statistically associated to development of bone marrow reticulin fibrosis in patients with IT. Myelofibrosis disappeared when the drug was discontinued. TRA has also been associated with thromboembolic events and headache, fatigue and insomnia. Eltrombopag has been associated with serum liver test abnormalities in approximately 10% of patients. Long-term follow-up data for patients treated with these agents are limited [7, 20, 22, 23, 26, 45, 58, 83]. A summary of the number of studies analysed for each effect is shown in Table I.

### Table I

Characteristics of the studies included in review

| No. | Design (as author defined it) | Number of patients | Intervention | Follow up | Aim of the study | Reference |
|-----|-------------------------------|--------------------|--------------|-----------|------------------|-----------|
| 1   | Randomised Phase I trial, Placebo controlled | 73 healthy subjects | Eltrombopag treatment | 10 days | Safety, pharmacokinetics | [38] |
| 2   | Retrospective study | 206 subjects | Thrombopoietin levels in several pathologies | Not applicable (NA) | Thrombopoietin level predicts response to TRA | [54] |
| 3   | Prospective study | 142 patients with immune thrombocytopenia (IT) | Romiplostim treatment in chronic IT | 3 years | Efficiency and safety | [14] |
| 4   | Retrospective study | 83 IT patients | Romiplostim treatment | NA | Corelation between thrombopoietin level and TRA response | [47] |
| 5   | Retrospective study | 30 IT patients, refractory after 7 years of treatment | Possibility of stopping romiplostim treatment | 4.5 years | Remission maintenance after stopping romiplostim treatment | [17] |
| 6   | Retrospective study | NA | Romiplostim treatment | NA | Romiplostim safety and efficacy | [84] |
| 7   | Retrospective study | 125 patients | Romiplostim treatment | 24 weeks | Immunoglobulins a therapy after romiplostim treatment | [69] |
| No. | Design (as author defined it) | Number of patients | Intervention | Follow up | Aim of the study | Reference |
|-----|--------------------------------|-------------------|-------------|-----------|-----------------|-----------|
| 8   | Double blind randomised trial, followed up by a prospective study | 23 patients | Eltrombopag treatment, Japanese patients | 26 weeks | Efficacy of TRA in low doses for Asian population | [82] |
| 9   | Retrospective study | 260 patients analysed, 49 TRA treated | Eltrombopag treatment | 6 months | Complete remission maintenance after stopping eltrombopag treatment | [34] |
| 10  | Case series | 9 patients, including 8 splenectomised | TRA treatment | NA | Sustained complete remission after treatment | [32] |
| 11  | Retrospective and prospective study | 11 patients with bone marrow biopsy, selected from 271 patients | Romiplostim treatment | NA | Bone marrow fibrosis | [48] |
| 12  | Case report | 1 patient | Romiplostim treatment | NA | Romiplostim treatment in case of a immunosuppressed patient | [61] |
| 13  | Retrospective study | 494 patients | Eltrombopag treatment | NA | Haemostasis during eltrombopag treatment | [79] |
| 14  | Retrospective study | 115 patients | Romiplostim treatment | 168 weeks | Bleeding and thrombosis | [31] |
| 15  | Prospective study | 17 IT patients, 9 healthy subjects | TRA treatment | NA | Improvement of T lymphocytes activity | [9] |
| 16  | Multicentric randomized trial | 234 patients | IT treatment | 52 weeks | Romiplostim or standard of care | [49] |
| 17  | Case-control study | 24 IT patients, 100 healthy subjects | IT treatment | NA | Nonresponders to eltrombopag | [10] |
| 18  | Observational multicentric retrospective trial | 72 patients | Romiplostim treatment | 2 years | Safety and efficacy | [42] |
| 19  | Case series | 8 patients | IT treatment | NA | Bone marrow fibrosis | [12] |
| 20  | Case-control study | 20 splenectomised patients, 20 healthy volunteers as a control group | Eltrombopag treatment | 28 days | Consequences of eltrombopag on platelets function | [68] |
| 21  | Case series | 4 patients | Eltrombopag treatment | 20 months | Avoiding splenectomy | [40] |
| 22  | Case report | 2 patients | TRA treatment in refractory IT | 2 years | Cross resistance between eltrombopag and romiplostim | [75] |
| 23  | Multicentric randomized trial | 234 patients | Romiplostim treatment | 52 weeks | Romiplostim treatment or standard of care | [46] |
| 24  | Case report | 1 patient | Romiplostim treatment | 1 year | Complete remission of severe thrombocytopenia | [85] |
| 25  | Case report | 1 patient | Romiplostim treatment | NA | Thrombocytopenia evaluation during the treatment | [76] |
| 26  | Cohort study | 18 Korean IT patients | Eltrombopag treatment | 4.5 years | Optimal dose of eltrombopag | [44] |
| 27  | Retrospective study | 18 patients, 5 splenectomised | Romiplostim treatment | NA | Optimal response of patients with platelets > 20 x 10^9/L at the start of the treatment | [8] |
| 28  | Prospective study | 6 patients | TRA treatment | NA | Platelet survival | [55] |
| 29  | Case report | 1 patient | Romiplostim treatment | NA | Bone marrow fibrosis | [36] |
| No. | Design (as author defined it) | Number of patients | Intervention | Follow up | Aim of the study                                                                 | Reference |
|-----|-----------------------------|--------------------|--------------|-----------|----------------------------------------------------------------------------------|-----------|
| 30  | Retrospective study         | 200 patients, 361 (control) | TI treatment | NA        | Correlations between polymorphism of beta 1 tubulin R307H and efficacy of treatment | [11]      |
| 31  | Prospective study          | 299 patients, 33% with concomitant medication, 38% splenectomised | Eltrombopag treatment | 3 years | Safety and efficacy                                                              | [72]      |
| 32  | Prospective study          | Cord culture cells  | High dose Romiplostim treatment | NA        | Effect on megakaryocytes                                                          | [27]      |
| 33  | Case series                | 2 patients         | TRA treatment | NA        | Cross resistance of TRA                                                            | [28]      |
| 34  | Retrospective analyse      | 46 patients, 23 splenectomised | TRA treatment | NA        | Changing between TRA                                                               | [43]      |
| 35  | Case study                 | 1 patient           | Romiplostim, rituximab and Vincristine combination treatment | 74 days   | Acute severe IT with bleeding                                                      | [59]      |
| 36  | Case study                 | 1 patient           | TRA treatment | NA        | Cross efficacy of romiplostim and eltrombopag                                     | [63]      |
| 37  | Cohort retrospective study | 900 patients, 50% with splenectomies | TRA treatment | NA        | Cost - efficiency report of rimpilostim and eltrombopag                           | [50, 51]  |
| 38  | Case study                 | 1 patient           | Pregnancy Romiplostim treatment | 10 months | Romiplostim efficiency during pregnancy                                           | [62]      |
| 39  | Case-control study         | 62 TI and acute leukaemia patients (case group), 4759 IT patients (control group) | TRA treatment | NA        | Association between Romiplostim and acute leukaemia                              | [60]      |
| 40  | Case study                 | 1 patient           | TRA treatment | 50 months | Cross resistance of TRA                                                            | [74]      |
| 41  | Case study                 | 1 patient           | Romiplostim treatment | NA        | Bone marrow fibrosis                                                              | [70]      |
| 42  | Retrospective study followed by prospective study | 66 IT patients, 50 lymphoma patients | TRA treatment | NA        | Bone marrow fibrosis                                                              | [33]      |
| 43  | Case-control study         | 13 IT patients TRA treated, 2 IT splenectomised, 17 IT patients treated with immunoglobulins | TRA treatment | NA        | Effect of TRA on plasma APRIL (proliferation – inducing ligand) levels on IT patients | [4]       |
| 44  | Prospective study          | 12 patients         | Eltrombopag and dexamethasone treatment | 12.5 months | Treatment of new diagnosed IT                                                     | [35]      |
| 45  | Case-control study         | 13 IT patients, 13 healthy individuals | TRA treatment | 2 weeks   | Effect of TRA on platelet survival                                                 | [57]      |
| 46  | Case series                | 2 patients           | Romiplostim and corticosteroids treatment |          | Efficacy of combination                                                           | [52]      |
| 47  | Case report                | 1 patient           | Eltrombopag and cyclophosphamide in refractory IT | 12 months | Efficacy and safety                                                               | [5]       |
| 48  | Retrospective analyse      | 41 patients         | Romiplostim treatment | NA        | Efficacy and safety                                                               | [15]      |
| 49  | Multicentric retrospective study | 15 patients         | Romiplostim treatment | 10 months | Efficacy and safety                                                               | [71]      |
| 50  | Multicentric retrospective study | 14 refractory patients | TRA treatment | 15 months | Efficacy                                                                       | [45]      |
According to our literature search, the efficacy of treatment is the subject of 52 studies, being evaluated by obtaining and maintaining remission (high platelet counts) after treatment completion [2, 3, 16, 17, 29, 32, 39, 41, 55, 57, 71, 77, 79, 84], decrease in the number of haemorrhagic episodes [16, 31, 39, 59, 60, 68, 77], immunomodulatory activity [4, 9], avoidance of splenectomy [40, 49], reduction or withdrawal of concomitant medication [16, 56]. It was also intended to correlate certain factors with the efficacy of the treatment: thrombopoietin level [2, 3, 21, 54], tuberculin R307H nucleotide polymorphism [11], thrombocyte count above 200000/µL at the initiation of treatment [8].

In all the studies included in this review, the administered dosages were the standard ones for all three drugs [2, 7, 16, 20, 22, 23, 26, 29, 39, 45, 58, 82, 83]. A study [42] and a series of case presentations [28, 63, 74, 75] focusing on the lack of cross-resistance between eltrombopag and romiplostim, showed that a drug is effective despite the inefficiency of the other. Khellaf et al. reported that 80% of patients who did not respond to eltrombopag, responded to romiplostim, respectively 46% who did not respond to romiplostim, responded to eltrombopag [43]. Patients refractory to multiple previous treatments and then to a TRA were responsive to treatment with the other agent [28, 63, 74, 75].

Obtaining and maintaining remission after treatment are an important criterion for evaluating the effectiveness of the treatment. Most of studies reported the increase in platelet counts, obtaining the remission of the disease [2, 4, 5, 14-17, 32, 37-39, 46, 49, 53, 71, 72, 76, 84]. In some cases, thrombocytopenia reoccurred when a medication was interrupted. Several studies reported maintaining remission for 29% - 60% of patients treated with TRA, refractory to multiple treatment lines. Data reporting was performed over 4.5 to 6 years after discontinuation. The recommendation of most authors is that once the therapeutic goal is reached at an effective minimum dose, to stop the therapy aiming to maintain remission in the absence of treatment [8, 14, 17, 32, 37, 42, 84].

The primary objective of the treatment of immune thrombocytopenia is to decrease the number and intensity of haemorrhagic episodes, for this reason this parameter is the strongest evidence of TRA treatment efficacy. A large study of 299 patients diagnosed with primary IT, at least 6 months refractory to 2 - 3 treatment lines, treated with eltrombopag, demonstrated a decrease in haemorrhagic events after treatment. 38% of patients experienced severe bleeding events (3 - 4 degree) before starting the treatment. After TRA, half of the patients had no bleeding and 13% had only moderate bleeding (1 - 2 degree). The treatment lasted for an average of 25 weeks and the follow-up period was 3 years [71]. These results are also confirmed by other studies with eltrombopag [5, 44, 68].

Similar results in the reduction of haemorrhagic episodes are also reported with romiplostim [15, 31, 53, 59, 71, 84]. One study evaluated 125 patients treated with romiplostim, compared to placebo. After 6 months of follow-up, in the placebo group, 24.4% had 4 or more severe haemorrhagic events than in the romiplostim group. 15.5% of the patients treated with romiplostim experienced a small number of mild haemorrhagic episodes [31]. Bussel et al. in a trial based on 64 avatrombopag treated patients proved a decrease in the proportion of subjects with bleeding by week 14 of treatment [16].

| No. | Design (as author defined it) | Number of patients | Intervention | Follow up | Aim of the study | Reference |
|-----|-------------------------------|-------------------|-------------|-----------|------------------|-----------|
| 51  | Multicentric retrospective study | 743               | Avatrombopag | 6 months  | Efficacy and safety | [83]      |
| 52  | Prospective multicentric study | 64               | Avatrombopag | 1 month   | Efficacy and safety | [16]      |
| 53  | Prospective multicentric study | 49               | Avatrombopag | 6 months  | Efficacy and safety | [39]      |
| 54  | Prospective multicentric study | 296              | Avatrombopag | 3 weeks   | Efficacy          | [69]      |
| 55  | Prospective multicentric study | 204              | Avatrombopag | 1 week    | Efficacy          | [80]      |
| 56  | Retrospective analysis         | 615              | Avatrombopag, eltrombopag, romiplostim | 6 months | Efficacy and safety | [21]      |
| 57  | Theoretical analysis           | Not applicable    | Avatrombopag, eltrombopag, romiplostim | Not applicable | Efficacy and safety | [3]       |
| 58  | Theoretical analysis           | Not applicable    | Avatrombopag | Not applicable | Efficacy and safety | [52]      |
| 59  | Prospective randomized study   | 49               | Avatrombopag | 6 months  | Efficacy and safety | [8]       |
Many studies have tracked the effectiveness of TRA administered together with concomitant medication. The results were positive, treatment efficacy has been shown in addition to increase platelet counts, decreased bleeding episodes and dose reduction or interruption of concomitant medication that was represented by corticotherapy [6, 35, 56, 72], cyclophosphamide, danazol [5], intravenous immunoglobulin [68], rituximab and vincristine [59]. A randomised trial based on 64 patients treated with avatrombopag, included a subgroup of 23 subjects treated with steroids as concomitant medication. Thirteen of them had a ≥ 50% reduction in steroid dose and 8 permanently discontinued concomitant steroid medication after four weeks avatrombopag treatment [16].

Other studies that have demonstrated the efficacy of TRA, highlighted the following issues: efficacy of eltrombopag use before invasive non-dental procedures associated with bleeding risk in patients with chronic immune thrombocytopenia [77], treatment efficacy in a case of immune thrombocytopenia in a patient with immunodeficiency and infections, the optimal cost-effectiveness ratio of Romiplostim compared to other drugs [50, 51], TRA-regulating effect on T lymphocytes (possibly mediated via platelet/megakaryocyte-mediated TGF-β1), pathogenetic cells in immune thrombocytopenia [4, 9, 10]. Elevated levels of endogenous thrombopoietin were correlated with the absence of response to TRA (p < 0.002) [54]. This data was infringed by Kuter et al., who demonstrated that correlation between endogenous thrombopoietin and absence of response to TRA was not statistically significant in a study based on Romiplostim [47]. The impact of endogenous thrombopoietin level and platelet response to avatrombopag has not been studied [21].

As in the case of other drugs [66], TRA have differences in pharmacokinetics for different ethnicities. Because of that, treatment of Asian patients starts at lower doses. Two studies evaluated the efficacy of eltrombopag on groups of Japanese and Korean patients [44, 81]. The response rate for the Japanese population was between 47.8% and 69.6% and the Korean population was 67%, with patients with refractory primary thrombocytopenia treated on multiple lines [81, 44]. At the end of treatment all Japanese patients fall back within two weeks [81] and 83.3% of Korean patients [44].

The safety of treatment was the main subject of 22 studies. Most studies reported the development of bone marrow fibrosis after TRA [12, 14, 33, 44, 48, 60, 70], but the most severe adverse effects were thrombosis [14, 16, 31, 72, 82] or thrombocytopenia that occurred after discontinuation [49, 69, 81]. The incidence of adverse reactions reported in a study of eltrombopag (299 patients) was 43% of which only 11% had severe adverse effects [72]. Two important trials centred on avatrombopag showed no significant difference in severe adverse effects in patients treated with avatrombopag versus placebo. These studies have demonstrated a slight difference for adverse effects after the administration of avatrombopag compared to placebo [16, 39].

It’s difficult to demonstrate the occurrence of bone marrow fibrosis after TRA treatment because in immune thrombocytopenia a bone marrow biopsy is not routinely performed. This is an examination of choice for evidence of fibrosis. However, the fibrosis after Romiplostim treatment is low degree (2 degree of 4). Medullary fibrosis has no clinical consequence and decreases when the treatment is stopped [12, 33]. A prospective study on a group of 142 patients reported 8 cases of bone fibrosis, but bone marrow biopsy was not routinely performed [14]. In another study of 217 patients suffering IT, TRA treated, for 11 there were performed bone marrow biopsies and 10 cases were positive for bone marrow fibrosis, which decreased after stopping the treatment [48]. Bone marrow fibrosis was not reported in the case of avatrombopag.

Thrombocytopenia was considered by most authors as the most severe adverse effect of TRA treatment and occurred approximately 2 weeks after discontinuation of the treatment. Thrombocytopenia correlated with a severe haemorrhagic syndrome. The incidence of thrombocytopenia was 1.4% in one study done based on a group of 291 patients [15, 21, 39, 49, 81]. The appearance of deep vein thrombosis was analysed on a group of 299 patients and occurred in 2% of the patients that had other thrombogenic risk factor [72]. Another study in a group of 142 patients with chronic immune thrombocytopenia treated with Romiplostim, reported 5% post-treatment thrombosis [14], while other studies [4, 31, 49] did not report thrombosis differences between TRA treatment and placebo, or did not record the appearance of thrombosis. Avatrombopag was incriminated in 5 thrombotic events occurred in a group of 64 patients, but there were not severe adverse events [16].

The only study that demonstrated a statistically significant association between TRA and the occurrence of acute myeloblastic leukemia (AML) was conducted by Oshima in Japan [59]. Of the 4821 patients with primary immune thrombocytopenia, 594 patients were treated with eltrombopag and 62 developed AML, respectively 3102 were treated with Romiplostim and 54 developed AML. TRA use, male gender and age between 60 to 69 years were associated with AML.

Given the multifactorial determinism of AML, there can be no clear conclusion that the treatment with TRA causes AML [59]. One avatrombopag treated patient developed leucocytosis and after a short period of time was diagnosed with myelodysplastic syndrome which transformed in acute myeloid leukaemia. It’s difficult to prove a causality between avatrombopag and leukaemia development [16].
Other side effects reported by different studies for all the three drugs were low-grade reactions such as rhinopharyngitis [72], hepatocytolysis, cholestasis [44, 81], headache [15, 16, 39, 42, 49, 52], fatigue [16, 42, 49] or severe side effects like cataract in 5% of patients which were also treated with corticosteroids and the exact cause of cataract was not established [72]. Other severe side effects reported for avatrombopag were vomiting and headache [21, 39]. We compared the results of our systematic review with those of other published systematic reviews that were not included in our study [20, 22, 26, 73, 83, 67]. Most conclusions were comparable. Discordance may appear regarding the used parameters for monitoring the efficacy of the treatment, these parameters being different from one study to another (increased post-treatment platelet counts, reduction of bleeding episodes, avoidance of splenectomy, reduction or discontinuation of concomitant medication, etc.).

Bleeding events are a common complication of the disease and their evaluation is the best method to assess the efficacy of immune thrombocytopenia treatment as recommended by the European Medicines Agency [64]. In our review, we found a reduction in haemorrhagic events, on average about 50% of patients had not experienced haemorrhages following TRA administration, and in case of 10 - 20% of patients, severity of bleeding decreased, from 3 - 4 degree to 1 - 2 degree of bleeding [31, 59, 60, 68, 77]. These results are concordant to the other reviews published on the same topic [20, 22, 26, 67, 73, 83]. The efficacy and safety of romiplostim, eltrombopag and avatrombopag were comparable in all studies analysed. We have not identified primary studies to compare the efficacy of the three drugs across different groups of patients. Boyers et al. demonstrated greater efficacy of romiplostim over eltrombopag through an indirect study analysing other publications. After that, they noted an error in the previous analysis, the primary effect being different in studies with romiplostim (probability of achieving a durable platelet response) versus eltrombopag (the probability of achieving a platelet count of 50 - 400 × 10⁹/L). There were also differences between the design of the studies and the definitions of the response to treatment. The authors reanalysed the data by correcting the errors of the research methodology by applying other statistical methods. The new results did not show a statistically significant difference between the efficacies of the two treatments [13].

The limits of this review of literature are mainly represented by the small groups of patients in most studies. We have also included trials of hundreds of patients [11, 14, 31, 37, 46, 49, 54, 56, 69, 72, 77]. TRA treatment is a new approved one, it is not a 1st line treatment, it is reserved for refractory cases, so the number of patients undergoing therapy with these agents is not large. Last but not least, treatment has not been studied for long enough, evidence of long-term safety is still limited.

Conclusions
Thrombopoietin receptor analogues (romiplostim, eltrombopag and avatrombopag) are a new line therapy recommended for the second line for immune thrombocytopenic purpura. These drugs have proven a good efficacy and tolerance; the safety results so far are promising.

The efficacy of the treatment was evaluated in the 59 studies reviewed by obtaining and maintaining post-treatment remission, decreasing the number and intensity of bleeding episodes and avoiding splenectomy. The main adverse events reported were the appearance of low degree and reversible post-treatment bone marrow fibrosis, the most severe adverse effects being thrombosis or thrombocytopenia occurred after discontinuation of treatment. Studies still need to be made to assess the safety of long-term treatment as well as to find factors associated with sustained remission after discontinuation of treatment. Perhaps in the future new molecules could correct the downs of the current medication.

Conflict of interest
The authors declare no conflict of interest.

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