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SCIENTIFIC LETTER

Thrombopoietin receptor agonists and thrombotic risk in immune thrombocytopenia

Agonistas del receptor de la trombopoyetina y riesgo trombótico en trombocitopenia inmune

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Abstract

The thrombopoietin receptor agonists are undoubtedly the first choice as a second-line treatment in primary immune thrombocytopenia, due to their effectiveness and good safety profile. Although debatable, some authors consider them inappropriate as a therapeutic option in patients at high thrombotic risk, perhaps overlooking the thrombogenic nature of the disease, which may restrict their use and limit therapeutic benefit in some patients. We reviewed the literature and explored thrombotic risk not only associated with thrombopoietin receptor agonists, but also with other therapeutic options and the disease itself.

Keywords: *Immune thrombopenia. Thrombopoietin agonists. Thrombosis.*

Resumen

Los agonistas del receptor de la trombopoyetina son, indiscutiblemente, la primera opción como segunda línea de tratamiento en la trombocitopenia inmunitaria primaria, por su eficacia y buen perfil de seguridad. Aunque es discutible, algunos autores los consideran inapropiados como opción terapéutica en pacientes de alto riesgo trombótico, quizás obviando el propio carácter trombogénico de la enfermedad, que puede restringir su uso y limitar el beneficio terapéutico en algunos casos. Revisamos la literatura y exploramos el riesgo trombótico asociado tanto a los agonistas del receptor de la trombopoyetina como a otras opciones terapéuticas y a la propia enfermedad.

Palabras clave: *Trombopenia inmune. Agonistas de trombopoyetina. Trombosis.*

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Introduction

Primary immune thrombocytopenia (PIT) or idiopathic thrombocytopenic purpura (ITP) is a disease characterized by isolated thrombocytopenia (platelets < 100 × 10^9/L) in the absence of other diseases or conditions, whether infectious, central, autoimmune, or hematological, that could explain it, making its diagnosis one of exclusion. The incidence of ITP is estimated to be between 2 and 5 per 100,000 people in the general population. It is frequently diagnosed in the elderly, with a chronic course (60% up to 80%), an insidious onset, or different patterns of clinical expression, and has proven to be resistant to various treatments (80%)[1-4]. In fact, the incidence of ITP increases from 1.94 up to 4.62 per 100,000 in patients aged 60 to 75 years up to 9 per 100,000 in those older than 75 years[2,5]. In adults, primary ITP, which has no recognizable cause, accounts for approximately 80% of cases, while the remaining 20% are due to other conditions, including autoimmune diseases, lymphoproliferative syndromes, etc.

Overall, patients are asymptomatic at diagnosis or exhibit minimal hemorrhagic symptoms, usually mucocutaneous. Severe hemorrhagic symptoms, such as GI bleeding, extensive mucocutaneous bleeding, or intracranial hemorrhage, are rare, and this symptomatic variability, without a consistent correlation with platelet count, suggests that compensatory mechanisms in hemostasis may be involved[6]. In fact, they exhibit less intensity and frequency of hemorrhagic signs for any platelet count vs other clinical situations with similar platelet counts, and factors such as the presence of less dysfunctional platelets, increased thrombin generation by microparticles, increased resistance to activated protein C, or elevated plasma concentrations of E-selectin and plasminogen activator inhibitor 1 appear to reduce hemorrhagic risk[7,8].

Discussion

Various publications indicate a higher thrombotic risk in patients diagnosed with ITP[6]. The vascular risk in subjects with ITP, for example, regarding venous thromboembolic disease (VTE), is estimated to be at least twice as high, especially elevated within the first year after diagnosis and overall similar to other autoimmune diseases regardless of platelet counts[9]. Venous thromboembolic risk is reported to increase in more than 8% of patients[10]. Acute myocardial infarction, stroke, and VTE occur even with platelet counts < 30 × 10^9/L, but the reasons for this increased are still to be elucidated. One review concludes that the thrombosis risk in this context is multifactorial[11]. In fact, Lambert et al.[12] categorize thrombotic risk factors as related to the disease *per se* (increased circulating procoagulant microparticles, pro-inflammatory state, more immature and apoptotic platelets), those related to the patient and their comorbidities (presence of 3 or more cardiovascular risk factors, age > 60 years, positive antiphospholipid antibodies, or increased neutrophil extracellular traps[13,14]), and those related to treatment, due to the side effects associated with, for example, IV immunoglobulins and corticosteroids – documented prothrombotic agents – the splenectomy *per se* which carries a relatively high risk of VTE, or thrombopoietin receptor agonists (TPO-RAs), which also seem to increase the risk of vascular events, though less so when administered for non-ITP indications[15].

Rodeghiero's review[6] found that the annual risk of thromboembolic events in the context of ITP was 0.41-0.67 vs 0.2-0.42 in the general population, concluding that there seems to be an increased thrombotic risk in ITP patients, especially influenced by age and other predisposing factors for thrombosis, with this risk being up to 3-4 times higher in splenectomized patients. Another retrospective study estimated the annual risk of venous thrombosis at 0.39 vs 0.71 for arterial thrombosis; the 5-year cumulative incidence was 1.4% for venous thrombosis and 3.2% for arterial thrombosis[16]. Greater thrombotic risk was noted in patients > 60 years, with more than 2 thrombotic risk factors at diagnosis, or using corticosteroids. Special attention should be paid to splenectomized and elderly patients. Another publication from 2018 reported an increased rate of VTE (4.05-5.32 per 1000 patient-years) vs the general population, though the rates of acute myocardial infarction (1.13% vs 1.30%) and ischemic stroke (2.09% vs 2.56%) were similar in the 2 groups[17]. Moreover, some first-line therapies such as corticosteroids and IV immunoglobulins, are no stranger to thrombotic risk. For example, low-dose corticosteroids (prednisolone equivalent < 5 mg/day) are associated with a 2-fold increased risk of pulmonary embolism (odds ratio [OR], 1.8; 95% confidence interval [CI], 1.3-2.4), while high-dose (prednisolone > 30 mg) carries an estimated 10-fold risk (OR, 9.6; 95% CI, 4.2-20.5)[18].

Currently, TPO-RAs are the treatment of choice as a second-line therapy for patients with chronic refractory ITP to previous treatments[19]. While fostamatinib is considered an option for patients with high thrombotic risk, other authors[20] suggest the possibility of associating anticoagulation or antiplatelet therapy once platelet counts reach ≥ 50 × 10^9/L, which is similar to other

treatments such as luspatercept in transfusion-dependent beta-thalassemia[21]. In patients requiring second-line therapy, Provan et al.[22] confirm the need to regularly assess thrombotic risk, both clinically and with laboratory tests, and indicate that in elderly patients, those with comorbidities or a history of thrombosis, or with positive lupus anticoagulant, an alternative to TPO-RAs should be taken into consideration, with fostamatinib being a valid option in this context. Interestingly, in this publication, the case of a refractory patient is presented in whom the use of fostamatinib allowed spacing out concomitant IV immunoglobulin administration every 3-6 weeks. For these, the thrombotic risk reported in the literature ranges from 0.6% up to 3% per patient and from 0.15% up to 1.2% per treatment cycle[18], with arterial thrombosis being up to 4 times more frequent than venous thrombosis.

Regarding the thrombotic risk of TPO-RAs, for romiplostim, the incidence of thrombotic or thromboembolic events observed in clinical trials was 6.0% vs 3.6% in patients on placebo[23]. For eltrombopag, 27 thromboembolic events were observed in patients with ITP with low and normal platelet counts. With avatrombopag, thromboembolic episodes (arterial or venous) occurred in 7% of patients[24], and in a recent publication[25] involving 75 patients aged 37 to 77 years with ITP at different treatment phases, no thromboembolic events were reported, even in those with platelet counts ≥ 400×10^9/L. For fostamatinib, a lower incidence of thromboembolic events of 0.7% is reported[26], supporting its recommendation. However, although studies are subject to interpretation, in vitro tests do not consistently show increased platelet activity to explain this apparent association between ITP and TPO-RAs[11]. In fact, the results of Dong et al.'s review and meta-analysis[27] suggest that patients with ITP on TPO-RAs have no significantly higher risk of overall thrombotic, arterial, and venous events vs a control group (relative risk, 1.73, 1.98, and 1.06, respectively), with an overall rate of 2.2% in the analyzed patients (2109, in 17 randomized clinical trials). However, like other authors, they confirm a higher risk in elderly patients, those with a history of thrombosis, or those on TPO-RAs for a long time. In the context of ITP, this risk is logical considering the epidemiological aspects mentioned earlier and that VTE risk increases with age, especially due to greater comorbidity and other thrombotic risk factors in this population[28,29]. Recently, the RIETE (Computerized Registry of Patients with Thromboembolic Disease)[30] reported that of the 100,000 confirmed thromboembolic disease patients included in the registry between 2001 and 2021, 47.9% were elderly (> 70 years), and of these, 58.2% were women. Moreover, as recognized in the literature, the main recurrence risk factor for VTE is a history of thromboembolic disease, especially in patients who experience an unprovoked thromboembolic event or with permanent or inherited risk factors[31], regardless of age. According to other authors[32], as the overall population's aging is accelerating rapidly (from 461 million people older than 65 years in 2004 up to about 2 billion by 2050), ITP is likely to increasingly become a disease of the elderly, like VTE *per se*. In this study, although no control group is included, in 451 elderly patients, including 134 treated with TPO-RAs, the thrombosis rate was 1.7 per 100 patient-years which significantly increased with the presence of cardiovascular risk factors – highlighting diabetes – and previous thrombosis, but not by TPO-RA use. An extensive review by Moulis et al.[33] to assess thrombotic risk factors, both venous and arterial, in adults with primary ITP, including ITP treatments, followed 7225 adult patients from 2009 to 2015 and found that risk factors for arterial thrombosis are the same as those described in the general population, while the most important ones for venous thrombosis are age (≥ 60 vs < 40 years, hazard ratio [HR], 2.22; 95% CI, 1.39-3.53), history of VTE (HR, 4.38; 95% CI, 1.07-18.02), splenectomy (HR, 3.22; 95% CI, 2.06-3.03), exposure to IV immunoglobulins (HR, 2.30; 95% CI, 1.41-3.75), and corticosteroid use (HR, 3.29; 95% CI, 2.39-4.53). Regarding TPO-RAs, a HR of 3.16 (95% CI, 2.04-4.88) is described, but of all the 25 patients who experienced a venous thrombotic episode, only 3 had no additional risk factors (3 women younger than 50 years), highlighting the coexistence of associated risk factors. The review by Tjepkema et al.[34] concludes that there is no statistically significant relationship between thrombosis and TPO-RA use, implying that no higher risk of incident thromboembolic events can be demonstrated in patients on TPO-RA vs untreated ITP patients. Another meta-analysis by Catalá-López et al.[15] including 8 randomized controlled trials with TPO-RAs (n = 1180 patients) to identify potential VTE risk factors estimated a VTE incidence rate of 3.1% (95% CI, 1.8-4.4) for patients on TPO-RAs vs 1.7% (95% CI, 0.3-3.1) for controls. Patients on TPO-RAs – vs controls – showed an absolute risk increase of 1.8% (95% CI, –0.1 to 3.6) and a 49.3% increase in thromboembolic risk, concluding that TPO-RAs showed a statistically nonsignificant numerical trend towards increased thromboembolic events vs control patients.

The experience of our center, since the availability of TPO-RAs in 2018, is that among about 75 patients followed for ITP in the last 6 years, we diagnosed a total of 3 cases of VTE. Two in women older than 65 years, 1 with newly diagnosed ITP and marked peripheral venous insufficiency who had a deep femoral vein thrombosis and was on dexamethasone with a platelet count of 8×10^9/L, and the other with a nearly 20-year history of chronic, multi-refractory ITP on a third TPO-RA, who experienced a pulmonary embolism, presenting at diagnosis with a platelet count of 142×10^9/L; the study found a strongly positive lupus anticoagulant (1.62), later confirmed. The third case, a 53-year-old hypertensive, smoking, overweight man with primary refractory ITP, splenectomized 20 years ago and on a 4-year regimen of TPO-RA after a late relapse in 2018, who after receiving 3 new dexamethasone cycles experienced a new relapse and needed treatment 2 years later, developing a pulmonary embolism approximately 2 weeks after a non-consolidative lower respiratory tract infection. Therefore, we can see that in all cases, there were associated VTE risk factors unrelated to TPO-RAs, and ITP *per se* might confer a high basal risk.

Other key aspects in treatment selection are efficacy and infectious risk. Regarding the latter, it is known that with age, the propensity for infections increases, conditioning higher mortality and morbidity due to decreased immune system capacity to fight infections once functional defects occur, such as decreased phagocytosis, chemotaxis, cytokine production, or defective antibody production, among other changes[35]. A study conducted in 2001 evaluated a total of 134 patients with 20-year follow-up: 9% (12/134), all with severe thrombocytopenia, had refractory disease and a death risk of 4.2 (95% CI, 1.7-10.0), with hemorrhage and infection equally contributing to mortality[36]. The mortality rate of 8 patients (6%) with platelet counts $> 30 \times 10^9$/L while on maintenance treatment was only slightly higher than the general population. Infections were identified as a risk factor due to corticosteroid or other immunosuppressive treatments in the refractory patient group. Notably, treatment options like TPO-RAs were not available at that time, which may reduce not only bleeding risk but also infection risk in the elderly[32], unlike other new treatments such as fostamatinib, where mild infections were slightly more frequent in patients on fostamatinib than placebo during clinical development, though moderate or severe infection rates were similar in the 2 groups (8% vs 6%). However, since the infection-related mortality rate determined in fostamatinib clinical trials for rheumatoid arthritis was 0.20 per 100 person-years (95% CI, 0.09-0.38), monitoring for opportunistic and severe infections is recommended[37]. This infectious risk also relates to another reported side effect, neutropenia – reported in 7% of treated patients, with febrile neutropenia in 1% – which may require down-titration and even temporary or permanent treatment discontinuation[38]. On the other hand, efficacy is comparatively lower with fostamatinib vs TPO-RAs, with an expected response rate of 18% up to 43%, contrasting with the 70%-80% reported with romiplostim and eltrombopag, and 65% response after 8 days on avatrombopag[19], not to mention the possibility of treatment discontinuation, yet to be explored in controlled studies or real life, although clinical trial populations were mostly multi-refractory patients. All in all, the authors' personal experience with fostamatinib monotherapy differs, even in combination with TPO-RAs, although literature reports successful combined use experiences, such as fostamatinib and avatrombopag in primarily TPO-RA-refractory patients[39], though more studies with larger patient numbers are needed to establish recommendations in this regard. A Spanish consensus on ITP management reported disagreement among panelists regarding this recommendation to prioritize fostamatinib over TPO-RAs in high thrombotic risk patients[40].

Conclusions

In light of the above, it is clear that thrombotic risk in the context of ITP is multifactorial, that ITP *per se* carries a basal risk of thromboembolic disease, and that the effect of TPO-RA use may not be definitive enough to avoid them in some patients. What is likely mandatory is distinguishing between patients with high risk of bleeding requiring treatment and those without, in whom treatment might increase the incidence of thrombotic events, yet this can be particularly complicated given most patients' profiles and the disease *per se*. In fact, RIETE highlights higher incidence with age, female sex, and other commonly present risk factors in ITP patients of certain age. Although, worldwide, studies indicate that any thromboembolic disease risk increase is not significant and related to specific patient characteristics, being observant and gathering more long-term data is required. Therefore, evaluating individual patient risk profiles before considering TPO-RA use seems like the reasonable thing to do, rather than conclusively avoiding their use and limiting therapeutic benefits, especially as higher chronicity rates in ITP,

and hence greater potential treatment need, occur in older patients who, basally, have higher thromboembolic risk regardless of ITP diagnosis, and for whom other therapeutic alternatives are ill-advised (like splenectomy), or present lower efficacy, at least, in clinical trials (like fostamatinib), and carry other risks, such as infections, and a lower risk with TPO-RA use. When using these drugs, the lowest dose to maintain a safe platelet count (≥ 30-50 × 10^9/L) is always recommended, especially in patients with a history of thromboembolic episodes, due to the lack of studies including this population in their analyses. This recommendation is already included in the technical data sheets of different agonists. Finally, of note the absence of data in Spain, which is why it would be imperative to know the cardiovascular health of ITP patients in follow-up at centers across our region to estimate associated thromboembolic risk and contribute to greater treatment individualization.

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Conflicts of interest

None declared.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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