

## Galician-Asturian experience of avatrombopag use in immune thrombocytopenia

### Experiencia galaico-asturiana de uso del avatrombopag en la trombocitopenia inmunitaria

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#### Abstract

**Introduction:** Avatrombopag, a second-generation thrombopoietin receptor agonist (TPO-RA), has been approved to treat chronic immune thrombocytopenia (ITP) in adults and in patients with chronic liver disease before surgery. Introduced in the pharmacotherapeutic guide of hospitals in Galicia and Asturias (Spain) in 2023, this medication offers an option for patients who do not adequately respond to other treatments. **Objective and method:** This retrospective observational study evaluates the efficacy of avatrombopag in 55 patients with ITP, focusing on those treated in hospitals in Galicia and Asturias over 18 months. Of these, 53 had persistent/chronic ITP, and the majority were middle-aged women with a mean age of 64.7 years. Most patients (85.45%) had primary ITP and used avatrombopag as second or third-line treatment. **Results:** 94.45% of patients achieved a sustained response with a platelet count greater than  $30 \times 10^9/L$ . Additionally, a rapid response to avatrombopag was observed, with a median time to response of only 7 days. Despite some cases of serious adverse effects such as suspected medullary fibrosis and thromboembolism, overall tolerance to the medication was good. **Conclusions:** The study highlights the importance of customizing treatment according to individual patient characteristics and considering factors such as age and comorbidity. With an individualized approach, avatrombopag emerges as an effective and safe option for managing chronic ITP, offering a promising alternative to conventional therapies.

**Keywords:** Immune thrombocytopenia. TPO-RA agonists. Efficacy. Safety. Thrombosis.

#### Resumen

**Introducción:** El avatrombopag, un agonista del receptor de trombopoyetina (TPO-RA) de segunda generación, ha sido aprobado para tratar la trombocitopenia inmunitaria o púrpura trombocitopénica inmunitaria (PTI) crónica en adultos y en pacientes con enfermedad hepática crónica antes de una cirugía. Introducido en la guía farmacoterapéutica de los hospitales de Galicia y Asturias en 2023, este fármaco ofrece una opción para pacientes que no responden adecuadamente a otros tratamientos. **Objetivo y método:** Este estudio observacional retrospectivo evalúa la eficacia del avatrombopag en 55 pacientes con PTI, enfocándose en aquellos tratados en hospitales de Galicia y Asturias durante 18 meses. De estos, 53 tenían PTI

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*persistente o crónica, y la mayoría eran mujeres con una edad media de 64.7 años. La mayoría de los pacientes (85.45%) presentaban PTI primaria y utilizaban avatrombopag como segunda o tercera línea de tratamiento. Resultados: El 94.45% de los pacientes alcanzaron una respuesta sostenida, con un recuento de plaquetas superior a  $30 \times 10^9/L$ . Además, se observó una rápida respuesta al avatrombopag, con una mediana de tiempo hasta la respuesta de solo 7 días. A pesar de algunos casos de efectos adversos graves, como sospecha de fibrosis medular y tromboembolia, la tolerabilidad general fue buena. Conclusiones: El estudio destaca la importancia de personalizar el tratamiento según las características individuales de cada paciente y considerar factores como la edad y la comorbilidad. Con un enfoque individualizado, el avatrombopag se presenta como una opción efectiva y segura para el manejo de la PTI crónica, ofreciendo una alternativa prometedora a las terapias convencionales.*

**Palabras clave:** Trombocitopenia inmunitaria. Agonistas de TPO-RA. Eficacia. Seguridad. Trombosis.

## Introduction

Avatrombopag, a second-generation oral thrombopoietin receptor agonist (TPO-RA), has been approved for the treatment of chronic immune thrombocytopenia or immune thrombocytopenia purpura (ITP) in adults who are refractory or have an inadequate response to other treatments. It is the first TPO-RA approved for adults with chronic liver disease scheduled for surgery<sup>1</sup>. In Galicia and Asturias, Spain it was included in the 2023 hospital pharmacotherapeutic guidelines.

The prevalence of ITP is 9.5 cases per 100,000 adults, with an incidence of 3.3/100,000 adults per year, increasing with age<sup>2</sup>, with no gender differences except between the ages of 30 and 60, when it is more prevalent in women<sup>3</sup>, and in individuals older 70, when it predominantly affects men. Mortality is higher in older ages, and its prevalence is 3 times higher vs younger adults. In adults, primary ITP accounts for 80% of cases, with the remaining 20% being due to other conditions.

In older adults, compared to children and young adults, it tends to be more chronic, with less likelihood of spontaneous remissions and a risk of progressing to other conditions. There is a higher incidence of hematological malignancies, such as lymphomas and leukemias (increased risk by 6 and 20 times, respectively)<sup>4</sup>, and a higher predisposition to autoimmune diseases.

In chronic liver disease<sup>5</sup>, platelet transfusions<sup>6</sup> are the choice for non-elective surgical procedures, especially major ones, and for elective procedures when TPO-RAs are unavailable or inadequate<sup>7</sup>. These transfusions carry various risks. The Subcommittees for Standardization of the International Society on Thrombosis and Hemostasis<sup>7</sup> state that TPO-RAs can be offered to patients with platelet counts of  $30\text{--}50 \times 10^9/L$  without risk factors for venous thromboembolism (VTE) undergoing high-bleeding risk elective surgery.

This study reports the experience of switching to avatrombopag and its use as a first-line therapy in second-line therapy for adults with chronic ITP in hospitals in Galicia and Asturias, Spain over 18 months. Additionally, 2 patients with newly diagnosed ITP on avatrombopag as first-line therapy (6-month follow-up) are included.

## Method

We conducted a retrospective observational study; data were obtained from the patients' electronic health records, with informed consent. Data are expressed as percentages, medians, interquartile ranges (IQR), and means with standard deviation (SD), as appropriate. Patients on avatrombopag as first-line therapy are analyzed separately.

## Results

A total of 55 patients were included, 53 of whom had persistent or chronic ITP. Forty-five (85%) had chronic ITP, with a mean age of 64.7 years (SD, 20.32). A total of 66% of the patients were women, 85.45% (45/55) had primary ITP. A total of 43.4% of all the chronic ITP patients, received avatrombopag as second-line therapy, and the rest (56.6%) as third-line therapy or sometime later (median, 3; IQR, 2-12). A total of 27 patients had previously received a TPO-RA, and 26 had not. The median follow-up was 163.5 days (IQR, 97.5-233.5). In 47 (88.67%) patients, the mean starting dose was 140 mg per week. One patient had received 12 prior lines of treatment.

A total of 94.45% of patients achieved a sustained response ( $> 30 \times 10^9/L$ ), and 90.57% a platelet count  $> 50 \times 10^9/L$ . The median time to response (platelets  $> 30 \times 10^9/L$ ) was 7 days (IQR, 7-11). Eight patients (18.2%) who started on avatrombopag as second-line therapy or sometime later discontinued it due to no

response, adverse effects (suspected bone marrow fibrosis, thrombocytosis, and intolerance), and 1 death unrelated to the drug. Overall tolerability was good, with 1 case of grade 2 bone marrow fibrosis and 1 pulmonary embolism in a patient with a positive lupus anticoagulant. The patient with bone marrow fibrosis was later diagnosed with Tangier syndrome instead of ITP. At the last visit, the median platelet count was  $120.5 \times 10^9/L$  (IQR,  $16-468 \times 10^9/L$ ), with highly variable weekly doses: up to 15 different dosing regimens in 46 patients (mean, 149.13 mg per week; SD, 20-280) (Table 1).

By gender (n = 53), 18 patients were men (33.96%), 6 of whom (30%) were younger than 65, and 7 (38.88%) received avatrombopag as third-line therapy or sometime later; 4 out of these 7 had previously received eltrombopag and 3, romiplostim. Another 11 (61.12%) were on avatrombopag as second-line therapy. There was no discontinuation of avatrombopag in this group. The median dose (n = 18) was 140 mg (IQR, 20-280), with dose titration in 13/18 patients (72.2%). The mean weekly dose of avatrombopag after switching from a previous agonist was similar regardless of the drug: from eltrombopag (n = 3), the mean weekly dose was 166.6 mg, and from romiplostim (n = 4), 160 mg. In the remaining men (n = 12), the mean weekly dose was lower (134.54 mg). Four of the 18 patients required the maximum weekly dose of avatrombopag (280 mg) to maintain platelet counts. Overall, in men, the median platelet count at the last check was  $143 \times 10^9/L$  (IQR,  $16-272 \times 10^9/L$ ) (Tables 2 and 3).

Thirty-five out of the 53 patients were women (66.04%), and 19 (54.28%) were younger than 65. Twenty (57.1%) were on avatrombopag as a third-line therapy or sometime later: 14 had previously received eltrombopag, and 6, romiplostim. Six (17.14%) were on avatrombopag as a second-line therapy, and 9 (25.7%) had received other previous treatments. Seven discontinuations were reported: 5 in previous agonist recipients and 2 in third-line therapies or later avatrombopag recipients without a previous agonist.

The median avatrombopag dose (n = 28) was 140 mg (IQR, 60-280); dose titration was required in 19/28 (67.8%). The mean weekly dose of avatrombopag in responders from eltrombopag (n = 10) was 184.1 mg, from romiplostim (n = 5) it was 148.1 mg, and in the rest (n = 13) it was slightly lower (115.38 mg). Six patients required the maximum weekly dose of avatrombopag to maintain platelet counts. At the last check, the median platelet count was  $112 \times 10^9/L$  (IQR, 36-468). The mean platelet count in patients with

**Table 1.** General characteristics of the studied population

| Characteristics                                                           | Description                 |
|---------------------------------------------------------------------------|-----------------------------|
| Total patients (n)                                                        | 55                          |
| Patients with de novo ITP (n)                                             | 2                           |
| Patients with chronic ITP (n)                                             | 45 (85%)                    |
| Mean age (years)                                                          | 64.7                        |
| Gender distribution (%)                                                   | Female: 66<br>Male: 34      |
| Primary ITP (n)                                                           | 45 (85.45%)                 |
| Avatrombopag as second-line therapy                                       | 43.4%                       |
| Avatrombopag as third-line or beyond                                      | 56.6%                       |
| Median follow-up                                                          | 163.5 days                  |
| Mean initial dose of avatrombopag                                         | 140 mg (88.67% of patients) |
| Patients achieving partial response (platelets $\geq 30 \times 10^9/L$ )  | 94.45%                      |
| Patients achieving complete response (platelets $\geq 50 \times 10^9/L$ ) | 90.57%                      |
| Patients achieving platelet count $\geq 100 \times 10^9/L$                | 81.13%                      |
| Median time to response (platelets $\geq 30 \times 10^9/L$ )              | 7 days                      |
| Patients discontinuing avatrombopag as second-line therapy or beyond (n)  | 8 (18.2%); 6/8 women (75%)  |
| Median platelet count at last visit                                       | $120.5 \times 10^9/L$       |

previous eltrombopag was  $98.7 \times 10^9/L$  (SD, 62-204  $\times 10^9/L$ ), with previous romiplostim it was  $152.2 \times 10^9/L$  (SD, 39-275), and without previous agonists it was  $144.8 \times 10^9/L$  (SD, 36-468  $\times 10^9/L$ ). Notably, previous eltrombopag recipients had, on average, 4 prior lines of therapy before avatrombopag (SD, 3-7), with no response in those with more than 7 lines of therapy vs the previous romiplostim group (mean, 2.25; SD, 1-4). Better responses were obtained with lower avatrombopag doses in patients without prior a agonist, regardless of gender (Tables 2 and 3).

By age groups, 13/28 patients older than 65 switched from a previous agonist (7 from romiplostim and 6 from eltrombopag), with 10 maintaining the response after the switch, while 15 responded to avatrombopag as a second-line therapy. Three patients discontinued treatment (due to intolerance, suspected myelofibrosis, and death). Dose titration was required in 21/25 patients

**Table 2.** Results by gender (n = 53)

| Characteristics                              | Men                 | Women               |
|----------------------------------------------|---------------------|---------------------|
| Total number                                 | 18 (33.96%)         | 35 (66.04%)         |
| Under 65 years                               | 30%                 | 54.28%              |
| Avatrombopag as third-line therapy or beyond | 7 (38.8%)           | 20 (57.1%)          |
| Median weekly dose of avatrombopag           | 140 mg              | 140 mg              |
| Patients requiring dose titration            | 13 (72.2%)          | 19 (67.8%)          |
| Patients requiring maximum weekly dose       | 4                   | 6                   |
| Median platelet count at last visit          | $143 \times 10^9/L$ | $112 \times 10^9/L$ |

**Table 3.** Results by gender and previous treatment (n = 27)

| Characteristics                          | Men                   | Women                 |
|------------------------------------------|-----------------------|-----------------------|
| Total number                             | (7/18, 33.96%)        | (20/35, 66.04%)       |
| After romiplostim                        | 3/7                   | 6/20                  |
| Responders/Patients needing maximum dose | 3/1                   | 5/1                   |
| Mean weekly dose of avatrombopag         | 160 mg                | 148.1 mg              |
| Mean platelet count                      | $183.2 \times 10^9/L$ | $152.2 \times 10^9/L$ |
| Patients needing maximum weekly dose     | 1                     | 1                     |
| After eltrombopag                        | 4/7                   | 14/20                 |
| Responders/patients needing maximum dose | 4/1                   | 10/5                  |
| Mean weekly dose of avatrombopag         | 166.6 mg              | 184.1 mg              |
| Median platelet count at last visit      | $106 \times 10^9/L$   | $98.7 \times 10^9/L$  |

(84%), and 6/25 (24%) required the maximum weekly dose to maintain platelet counts  $\geq 50 \times 10^9/L$ . The median last platelet count was  $137 \times 10^9/L$  (IQR,  $16-334 \times 10^9/L$ ), with a median weekly dose of avatrombopag of 140 mg (IQR,  $40-280 \times 10^9/L$ ).

There are 25 patients younger than 65, 14 of whom (56%) started on avatrombopag after another previous agonist (11 on eltrombopag and 3 on romiplostim). Of these, 11 maintained the platelet response after the switch, and 3 from the eltrombopag group discontinued treatment (thrombocytosis, 2 due to relapse or lack of response). Ten of the 11 patients on avatrombopag as

**Table 4.** Results by age (n = 53)

| Characteristics                                            | < 65 years          | $\geq 65$ years     |
|------------------------------------------------------------|---------------------|---------------------|
| Total number                                               | 25 (47.16%)         | 28 (52.83%)         |
| Patients from another TPO-RA                               | 14/25 (56%)         | 13/28 (46.42%)      |
| Patients responding after previous agonist                 | 11/14 (78.57%)      | 10/13 (76.92%)      |
| Patients responding to avatrombopag as second-line therapy | 10/11 (90.9%)       | 15/15 (100%)        |
| Median weekly dose of avatrombopag                         | 140 mg              | 140 mg              |
| Patients requiring dose adjustment                         | 19/25 (76%)         | 21/25 (84%)         |
| Patients requiring maximum weekly dose (280 mg)            | 4 (16%)             | 6/25 (24%)          |
| Median platelet count at last visit                        | $112 \times 10^9/L$ | $137 \times 10^9/L$ |

the first-line agonist in second-line therapy achieved a response, with 1 discontinuing treatment due to loss of response. The median last platelet count (n = 21) was  $112 \times 10^9/L$  (IQR,  $36-468 \times 10^9/L$ ), lower than in the older group, with a median weekly dose of 140 mg (IQR, 20-280), which is similar to the older-than-65 group. A total of 19 out of the 25 patients (76%) required dose titration. Four patients maintaining platelet response with the maximum weekly dose switched from eltrombopag (Table 4).

By previous lines of therapy, 26 received avatrombopag as a second-line therapy, 57.69% of whom were women. Of these 26 patients, 12 (46.15%) required dose titration, and only 2 required the maximum weekly dose to maintain platelet counts. The median last platelet count was  $138.5 \times 10^9/L$  (IQR,  $29-468 \times 10^9/L$ ), with a median weekly dose of avatrombopag of 130 mg (IQR, 20-280) (n = 24). Two patients discontinued treatment (due to loss of response and death).

Of the 53 patients, 27 received 3 or more previous lines of therapy, 19 of whom (70.37%) were women. Of these 27 patients, 5 discontinued therapy (due to intolerance, relapse, lack of response, suspected bone marrow fibrosis, and thrombocytosis). Dose titration was required in 20/23 patients, and 8/23 patients maintained the response with the maximum weekly dose of avatrombopag. The median platelet count (n = 23) was  $104 \times 10^9/L$  (IQR,  $16-275 \times 10^9/L$ ), with a median weekly

**Table 5.** Results by therapy line (n = 53)

| Characteristics                                 | Second-line therapy        | Third-line therapy or beyond |
|-------------------------------------------------|----------------------------|------------------------------|
| Total number                                    | 26                         | 27                           |
| Female patients                                 | 57.69%                     | 70.37%                       |
| Median weekly dose of avatrombopag              | 130 mg                     | 155 mg                       |
| Patients responding                             | 24/26 (92.3%)              | 23/27 (85.18%)               |
| Patients requiring dose adjustment              | 12/26 (46.15%)             | 20/23 (86.95%)               |
| Patients requiring maximum weekly dose (280 mg) | 2/24 (8.33%)               | 8/23 (34.78%)                |
| Median platelet count at last visit             | 138.5 × 10 <sup>9</sup> /L | 104 × 10 <sup>9</sup> /L     |

dose of 155 mg (IQR, 60-280). Seventeen out of 27 patients had previously received eltrombopag, with 13/17 maintaining the response after the switch (4 discontinued due to thrombocytosis, suspected myelofibrosis, relapse, and lack of response). The mean platelet count (n = 13) was 100.3 × 10<sup>9</sup>/L (SD, 62-204 × 10<sup>9</sup>/L), with a mean weekly dose of 193.84 mg (SD, 100-280). Up titration was required in 12/13 patients, with 6 maintaining the response with the maximum weekly dose of avatrombopag (mean platelet count: 96.8 × 10<sup>9</sup>/L; SD, 71-108 × 10<sup>9</sup>/L). Ten out of 17 patients switched from romiplostim, with 9 maintaining the response with a mean weekly dose of 151.11 mg (SD, 60-280); 1 discontinued due to intolerance. The mean platelet count was 166 × 10<sup>9</sup>/L (SD, 16-275 × 10<sup>9</sup>/L). Nine patients required dose titration, and 2 maintained the response with the maximum weekly dose (Table 5).

Two patients (7.7%) had newly diagnosed ITP (< 3 months), with a mean age of 81.5 years (range, 66-97), both women. The mean platelet count before starting avatrombopag was 16.5 × 10<sup>9</sup>/L, and they had comorbidities, some associated with increased bleeding risk (female gender, hypertension, diabetes mellitus). The initial avatrombopag dose was 280 mg per week in both cases, with subsequent dose adjustment in one. The mean time to response was 7 days (mean platelet count: 136 × 10<sup>9</sup>/L; range, 52-220 × 10<sup>9</sup>/L). At the 6-month follow-up, they maintained a mean platelet count of 104 × 10<sup>9</sup>/L (range, 51-157 × 10<sup>9</sup>/L) with a mean weekly dose of avatrombopag of 170 mg (range, 60-280). Tolerability was good; one case of headache with the maximum dose resolved with dose reduction.

## Discussion

The goal of ITP treatment is to achieve a safe platelet count to prevent or stop bleeding (> 20-30 × 10<sup>9</sup>/L), at least, in symptomatic patients. Consideration should be given to lifestyle, age, comorbidities, and patient expectations, and therapeutic goals should be individualized according to the patient's disease phase<sup>4,7,8</sup>. Treatment-related aspects should also be considered, avoiding unnecessary drugs and being alert to toxicities and side effects. First-line therapy is corticosteroids<sup>4,7,8</sup>, highly effective but no stranger to side effects. As second-line therapy, the Spanish ITP Group recommends TPO-RAs, including avatrombopag, although fostamatinib is suggested as an option for patients with high thrombotic risk<sup>7</sup>.

Age can influence the efficacy and treatment-related toxicities. It is important to provide care that allows patients to reintegrate into their daily lives as quickly as possible, with safe platelet counts and minimal iatrogenesis<sup>7,8</sup>. Although corticosteroids are the treatment of choice, other first-line options, such as TPO-RAs<sup>9</sup>, are being explored, which due to their safety and efficacy profile, even considering their slightly higher thrombotic risk could be the second-line option in patients unresponsive to first-line therapy, or even be first-line options when corticosteroids are contraindicated or expected to have undesirable side effects. This first-line use is not approved outside the clinical trial setting<sup>7</sup>. In our registry, patient age and gender do not seem to influence the response to avatrombopag.

In a controlled trial<sup>10</sup>, patients with chronic ITP (≥ 12 months) and low baseline platelet counts (mean of 2 platelet counts < 30 × 10<sup>9</sup>/L) were randomized to a 6-month regimen of placebo (n = 17) or avatrombopag (n = 32). The initial dose was 20 mg/day, titrated to minimum and maximum doses of 5 and 40 mg/day based on response (n = 32). After 26 weeks, those not participating in the subsequent open-label extension phase entered a down titration phase (4 weeks), with another 4 weeks of follow-up. Concomitant use of other standard treatments for chronic ITP and bailout therapy was allowed. A total of 47% of avatrombopag recipients and 41% of placebo recipients received concomitant medication for ITP at the beginning of the study, while 34% and 29%, respectively, were splenectomized. Avatrombopag showed rapid response and sustained efficacy: 65.6% had platelet counts ≥ 50 × 10<sup>9</sup>/L by day 8, compared to 0% from the placebo group. Additionally, they maintained platelet counts ≥ 50 × 10<sup>9</sup>/L longer without bailout therapy (median: 12.4 vs. 0 weeks in the placebo group). The median platelet count after the visit day was higher in the avatrombopag group (80.5 × 10<sup>9</sup>/L

vs  $8 \times 10^9/L$  in the placebo group) from day 8 onwards. Efficacy was maintained in an extension phase of this trial. After completing the placebo-controlled phase, patients could continue avatrombopag treatment (maximum exposure duration in both phases: 76 weeks)<sup>11</sup>. In our registry, the median time to response, defined as a platelet count  $\geq 30 \times 10^9/L$ , was 7 days.

In a post hoc analysis during the extension phase, the adverse event profile was similar to that reported with other TPO-RAs. The efficacy of avatrombopag was studied in a trial comparing it with eltrombopag, but it was stopped early without conclusions<sup>12</sup>. The authors emphasize the rapid response to avatrombopag vs other agonists, which is important when choosing treatment<sup>10</sup>. In our registry, chronic ITP shows this rapid response (median of 7 days), though limited by the small sample size ( $n = 53$ ) and short follow-up time (median of 165 days), but in line with the findings reported by other groups. The AVAMAD<sup>13</sup> trial reports the experience of switching to avatrombopag in 10 centers in Madrid, with 66 patients, from July 2022 through May 2023. Patients are similar to those from our series: median age 52 years (IQR, 34-71), 55% younger than 65 (vs. 43.39%) and 53% women (vs. 66%). At avatrombopag initiation, 73% had chronic ITP, and 83% primary, with a median platelet count of  $36 \times 10^9/L$ . A total of 88% started with 20 mg/day, and  $> 70\%$  needed dose titration. Regarding previous treatment lines before the switch, 40% received avatrombopag as second-line therapy, 23% as third-line therapy, and 36% as a different line of therapy. One patient received avatrombopag as first-line therapy. A total of 70% of patients switched due to loss of response to previous treatment or refractoriness or corticosteroid dependence (60% had previous corticosteroids). The median follow-up was 212 days, with 86% responses, 73% complete (platelets  $> 100 \times 10^9/L$ ); in our registry, responses were 90.57% and 81.13%, respectively. More complete responses are seen with fewer prior therapy lines (1 vs. 3.5;  $p < 0.001$ ). The median time to response was 2.1 weeks. The drug was safe; the most common side effect (15%) was headache. A total of 6 out of 66 patients had no response and discontinued treatment (in our registry, 8 of 53 patients). The switch experience reported by Al-Samkari et al.<sup>14</sup> shows similar results in 44 patients. The main reason for switching was convenience (52%), while 32% switched due to previous treatment inefficacy. The switch effectively rescued patients with previous agonist failure (93% platelet response [ $> 50 \times 10^9/L$ ] and 86% complete [ $> 100 \times 10^9/L$ ]), reducing the need for concomitant treatment (63% stopped corticosteroids after switching). In our initial results<sup>15</sup>, we reported

that 37.5% of patients were in previous response with another TPO-RA and maintained it after the switch, sometimes reducing the need for treatment to maintain the same platelet count; data pending confirmation. In this update, 81.13% of patients achieve and maintain platelet counts  $> 100 \times 10^9/L$ , which is similar to AVAMAD data (73%), with higher response rates when used as second-line therapy, regardless of age and gender, influenced by the number of previous therapy lines. In second-line therapy, although the rate of response is similar (92.3% vs 85.18%), lower doses are needed (20% less), fewer dose titrations (50% less), and fewer patients require the maximum weekly dose of avatrombopag to maintain a platelet count  $\geq 50 \times 10^9/L$ .

As first-line therapy, an American group<sup>16</sup> hypothesized that avatrombopag is safe and effective at any disease phase. In an observational, multicenter cohort trial of adults with ITP on avatrombopag, the outcomes of 75 patients were compared: 23 with newly diagnosed or persistent ITP and 52 with chronic ITP. With avatrombopag, 91% of patients with newly diagnosed or persistent ITP, vs. 96% of chronic patients, achieved a platelet response ( $\geq 50 \times 10^9/L/mL$ ), and 86%, vs. 81% ( $p = 0.78$ ), had a complete response ( $\geq 100 \times 10^9/L$ ), with a similar median platelet count ( $165 \times 10^9/L$  vs  $129 \times 10^9/L$ ;  $p = 0.57$ ). Long response duration was reported, similar in both groups, without severe bleeding, VTE, or avatrombopag discontinuation. No other drug-related adverse events were reported. In our case, 2 patients received avatrombopag as first-line therapy and achieved a platelet response ( $> 50 \times 10^9/L$ ) quickly (mean, 7 days); only 1 patient achieved a complete response ( $> 100 \times 10^9/L$ ). The AVAMAD<sup>13</sup> trial included 1 patient on avatrombopag as first-line therapy, but we have no follow-up data, and our small sample size prevents drawing conclusions or comparisons with Virk et al.<sup>16</sup>.

When patients can choose any of the 3 available TPO-RAs, our practice, in line with the literature<sup>7</sup>, is to let them decide after presenting the options with their pros and cons. One reason for switching to avatrombopag is convenience or patient preference; in the AVAMAD trial, this accounted for 8%, and in our initial registry data<sup>15</sup>, it accounted 37.5% of the changes, due to oral administration, no food interferences, and no need to respect fasting periods.

The thrombotic risk of TPO-RAs is also associated with corticosteroid and immunoglobulin use<sup>17</sup>. In our registry, 1 case of VTE (1 patient with risk factors) was treated initially with low molecular weight heparin and later with vitamin K antagonists, maintaining avatrombopag. Various reports indicate an increased thrombotic risk in

ITP patients<sup>18</sup>. The estimated VTE risk increase is, at least, 2-fold, particularly high within the first year after diagnosis, comparable to other autoimmune diseases and regardless of platelet count<sup>2</sup>. Additionally, although it occurs even with platelet counts  $< 30 \times 10^9/L$ , the reasons for this increased risk in ITP remain unclear. Factors include increased circulating procoagulant microparticles, a proinflammatory state, the presence of immature and apoptotic platelets, a high prevalence of clinical thrombotic predisposition factors, antifosfolipid antibodies, or increased neutrophil extracellular traps<sup>19,20</sup>. Additional risk factors include side effects of therapies such as TPO-RAs, which seem to increase the risk of vascular episodes, although less so when administered for non-ITP indications<sup>21</sup> and generally in patients who, like ours, are susceptible to these disorders due to age ( $> 60$  years) or conditions such as hypertension, diabetes mellitus, or overweight<sup>8</sup>. Regarding VTE risk, TPO-RAs seem to increase it 2- to 3-fold, with no differences between them, being the risk higher within the first year after therapy initiation<sup>3</sup>. Compared directly with placebo, no agonist increased the VTE rate<sup>21</sup>, and the risk is also recognized to increase in untreated ITP patients. Some authors<sup>22</sup> and guidelines<sup>7</sup> recommend fostamatinib as first choice in second-line therapy for patients with high thrombotic risk; in our opinion, this is debatable because RIETE<sup>23</sup> reported risk factors are the same as in ITP and are compounded by the ITP *per se*<sup>24</sup>. In a Spanish consensus on ITP treatment, panelists disagreed on this option<sup>25</sup>. A possible strategy suggested by Ghanima et al.<sup>26</sup> is to consider anticoagulation or antiplatelet therapy when the platelet count is  $\geq 50 \times 10^9/L$ .

In our series, 1 case of bone marrow fibrosis was reported, leading to treatment discontinuation and subsequent recovery. Bone marrow fibrosis is reported with other TPO-RAs at low frequency ( $\geq 1/1,000$  to  $< 1/100$ ), and to date, it has always been reversible upon discontinuation of the agonist. Some authors<sup>27</sup> recommend avoiding starting treatment with agonists if the patient develops reticulín deposits in the bone marrow (European Consensus MF-2 to MF-3), and any TPO-RA should be avoided until these deposits and associated clinical symptoms resolve.

The possibility of discontinuing avatrombopag was not possible in our case, unlike what has been reported with other agonists. A priori, same as other agonists<sup>28</sup>, avatrombopag may have an immunomodulatory effect associated with fewer helper T cell effector functions. It is known that other agonists are associated with continuous activation of the JAK/STAT signaling pathway, which could cause prolonged response; this activation is also

observed with avatrombopag<sup>29</sup>. Therefore, after achieving hemostatic platelet counts, some patients may show a sustained response after discontinuing avatrombopag. In our registry, 7/53 patients maintain a platelet count  $\geq 100 \times 10^9/L$  with a weekly dose  $\leq 60$  mg (mean, 42.85 mg) and are in the process of tapering to discontinuation.

## Conclusions

Avatrombopag has proven effective and safe in our patients with chronic ITP and newly diagnosed ITP. We highlight:

- Efficacy and rapid response.
- Convenience of oral administration, avoiding the disadvantages of subcutaneous administration and the need (in many cases) to visit the hospital for treatment administration.
- No dietary restrictions, especially in elderly patients with frequent dietary restrictions, as food or divalent cations do not affect absorption, avoiding the need for fasting, leading to greater patient independence.
- No need for liver function monitoring.

All these aspects make avatrombopag very attractive. The drug tolerability is very good, with generally mild and easily manageable side effects and a low incidence of VTE; only 1 case in our registry and 0 in the AVAMAD trial, figures that do not seem to justify special measures in these patients. It will probably be necessary to emphasize controlling cardiovascular risk factors to minimize this risk, and even consider antiplatelet or prophylactic anticoagulation because the benefit-risk ratio of avatrombopag use is very high. Of note that it is the only TPO-RA indicated for ITP and chronic liver disease. Although the success of avatrombopag in this indication in chronic liver disease is highly dependent on adequate surgical scheduling and good inter-service coordination, it can offer a significant advantage over platelet transfusions in terms of transfusion safety, expenses, and managing a resource highly dependent on a fluctuating donor population.

The financial aspect is also interesting. Although highly variable by hospital, switching to avatrombopag can save treatment costs in some patients and centers, as fewer doses are often required to maintain a safe platelet count than would proportionally be needed from other agonists. In line with Virk et al.<sup>16</sup>, the potential use of TPO-RAs, in this case, avatrombopag, as first-line therapy is very promising. However, there are gaps, such as whether we will be able to induce remissions in newly diagnosed ITP similarly to what is observed with corticosteroids, and other questions, but our experience encourages us to think so.

Controlled clinical trials should be conducted to establish an indication for TPO-RAs as first-line therapy in newly diagnosed ITP in the future. Although our sample size does not allow us to draw definitive conclusions, avatrombopag seems to be the optimal second-line therapy for adult ITP, which is consistent with what other authors have expressed<sup>30,31</sup>, achieving the highest efficacy with the most favorable balance of benefits and acceptability<sup>31</sup>.

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## Conflicts of interest

None declared.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

**Use of artificial intelligence for generating text.** The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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