Per-head cost of patients responding to eltrombopag and rituximab in the treatment of primary immune thrombocytopenia in Spain.

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Research article

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Abstract

Background: Splenectomy, thrombopoietin receptor agonists (TPO-RAs) and rituximab are the second-line treatments for steroid-resistant adult primary immune thrombocytopenia (ITP). The last two are becoming the most widely used treatments to avoid splenectomy adverse effects and inconveniences. However, the choice between rituximab and TPO-RAs is unclear. Therefore, the treatment cost may be of particular interest to prioritize the therapy option.

Our aim is to determine the cost per patient after 6 months of treatment of rituximab compared to TPO-RA eltrombopag in a European Health Service.

Methods: A 26-week decision tree model was developed to assess the cost of treatment response of adult patients with chronic-refractory ITP to eltrombopag and rituximab from the perspective of the Spanish National Health System. Effectiveness was obtained from the literature, and cost was obtained from the official rates. Costs were expressed in € (2018). Due to the short period of assessment, no discount rate was applied.

Results: The average cost per patient after 6 months of treatment was similar for eltrombopag and rituximab, although the first cost was slightly higher. However, the greater response rate of eltrombopag decreases the bleeding costs, resulting in a 29% higher cost with rituximab treatment. Eltrombopag cost was always lower, except in the sensitivity analysis in which the patient received a daily dose of 75 mg of eltrombopag, a scenario where eltrombopag cost is 48€ higher than that of rituximab.

Conclusions: The treatment cost of rituximab, including monitoring and bleeding costs, is higher than eltrombopag, favouring the latter over rituximab treatment.

Background

Primary immune thrombocytopenia (ITP) is an acquired autoimmune disease characterized by a platelet count less than 100×10^9 platelets/litre; this is due to platelet destruction and inadequate production [1, 2]. Diagnosis is reached by exclusion of other diseases associated with thrombocytopenia. The annual ITP incidence rate is 3-4/100000 in adults, increasing in older patients [3-5]. This condition is classified as newly diagnosed ITP when the evolution is shorter than 3 months from diagnosis, persistent if the duration of disease is 3-12 months and chronic when it lasts for more than 12 months [1]. Although 1/3 of affected persons are asymptomatic and patients with a platelet count over 50×10^9 platelets/litre do not require treatment, this long-lasting disease may threaten life due to bleeding caused by thrombocytopenia; it negatively impacts quality of life and imparts a high economic burden on the healthcare system [1, 2, 6].

Classical guidelines recommended corticosteroids as first-line treatment for adult ITP followed by splenectomy as second-line treatment and the use of the anti-CD20 chimeric monoclonal antibody rituximab or a thrombopoietin receptor agonist (TPO-RA) in cases of failure or contraindication [2, 7, 8].

Splenectomy achieves a 60% response after 5 years [9]. However, this treatment produces important adverse effects mainly derived from surgery, as well as risk of infection, thrombosis and cancer [10]. In contrast,

rituximab and TPO-RAs cause few toxicities and spare a splenectomy. The first option permits lasting responses after a short treatment, with approximately 60% initial responses and a third of patients in remission after 1 year [11-16]. The second involves long-term treatments, but with high response rates (75-95%), and it has fewer side effects than rituximab and the potential of drug discontinuation [11, 17-22]. Hence, those formerly considered third-line treatments have become extensively used [23]. In fact, the last recommendations indicate that, even if corticoids remain at the first-line treatment, in view of the lack of randomized trials directly comparing splenectomy, rituximab and TPO-RAs, all three can be used as second-line options [11].

TPO-RAs, including eltrombopag and romiplostim, stimulate platelet production, increasing platelet count [18, 24]. Unlike romiplostim subcutaneous administration, eltrombopag oral administration requires no sanitary assistance [25].

The aim of this paper is to provide data for clinical decisions according to their economic implications through the per-head cost of responding patients to oral TPO-RA eltrombopag and rituximab for treating chronic ITP in the context of the Spanish Health Service.

Methods

Model

We have developed a cost-consequence model to compare the direct health costs of ITP treatment with eltrombopag and rituximab from the perspective of Spanish public hospitals. As in a similar study comparing romiplostim and rituximab [27], only direct hospital health costs of patients treated with eltrombopag and rituximab were considered. Grade 1 (petechial) bleedings, which are treated by the patients themselves or at the primary care services, were not considered.

To allow the comparison with a similar study that evaluated the cost per response of romiplostim and rituximab [27], a time horizon of 26 weeks (half a year) was set. As shown in Figure 1, it was split into two periods. The first one comprised 8 weeks during which all patients were treated, and the response was evaluated. This was followed by a period of 18 weeks in which a) only patients responding to eltrombopag continued to be treated and b) patients on rituximab were treated according to previously described bases [26]. This structure is coherent with the previously mentioned study carried out in Spain [27], so it may support decision-making.

As the time horizon is less than a year, we did not consider applying discounting to costs or effects.

In this way, over the 26 weeks, the model accumulates treatment costs (drugs plus administration), follow-up costs and the costs produced by bleedings to calculate the final cost per responding patient to both treatment alternatives.

Study population

Considering that eltrombopag is indicated for patients of more than one year of age with chronic ITP who are refractory to other treatments [25] and that although rituximab is not officially approved for this disease, it is indicated for adult patients in the illnesses in which it is approved [28], we have limited our analysis to adults with chronic-refractory ITP.

To determine the effectiveness of these treatments, we carried out a literature review of chronic ITP treatment published in English and Spanish between 2000 and 2017. As a result, we have identified a paper focused on a group of Spanish patients treated with eltrombopag [29]. As no similar paper has been found for rituximab (on Spanish patients with chronic-refractory ITP), we have used the data from the Arnold DM et al systematic review [32].

To estimate rituximab dosage, we used the Dubois & Dubois formula to determine the body surface of patients [30]. Height and weight were determined according to microdata from the Spanish results of the European Health Survey 2014 (basal data shown in Table 1) [31].

Estimate of response

No study or phase 3 clinical trial related to rituximab response was found in Spain; therefore, the more consistent data for this treatment derive from the indicated systematic review [32]. Additionally, we used a retrospective French model to evaluate the need for re-treatment and its effectiveness [26].

Table 2 shows the response rates used in the model, their sources and the criteria employed to evaluate the response. The re-treatment rates and their responses are shown in Table 3.

As Table 2 shows, there are differences in the response criteria. While the eltrombopag study used the full response rate (defined as platelet count $\geq 100 \times 10^9/l$) and the response rate (platelet count ≥ 30 and < 100), the rituximab study used a different response rate (defined as platelet count $\geq 50 \times 10^9/l$). Despite this, a superior efficacy of eltrombopag against rituximab can be established, since its complete response rate is 77.3%, while the rituximab response rate is 62.5%.

Bleeding estimate

As petechial bleeding does not involve hospital attention—it is cared for at primary care services—the model only considers 2-, 3- and 4-grade bleeding (WHO bleeding scale [33], Additional file 1).

There is a relationship between a low platelet count and an increased risk of bleeding. In this way, patients who do not respond to treatment will have a lower count and an increased risk of bleeding than responding patients. To simulate these bleeding risks, we have used the RAISE trial data [19], assuming that non-responding patients behave in the same way as the placebo arm in relation to the risk of bleeding while responding patients present a similar risk decrease to that in the treatment arm of the trial.

This assumption seems to be valid considering the effectiveness of eltrombopag and the duration of this trial, which is equivalent to that of the model (six months). The bleeding rates used in the model are shown

in Table 4. Grade 4 bleedings are potentially life threatening, with a mortality rate of 40%; 80% of patients who survive after such bleeding need rehabilitation [34].

Resources and costs

To make a cost estimation, we used an average of the official lists of prices of the different Spanish regions (Additional file 2. Prices are actualized to 2018 euro (€2018)).

As both alternatives are hospital formulary drugs, prices to wholesalers have been used, thus avoiding the extra costs involved by distribution channels and chemist stores.

Table 5 shows the price to wholesale (PTW) of the different drugs as they appear in BotPlusWeb Portalfarma (online drugs database of the General Council of Official Pharmaceutical Associations, <https://botplusweb.portalfarma.com>, accessed 1 June 2018).

To calculate the cost of the drugs, we considered the cost per mg and applied it to doses as described in the trials. Each rituximab treatment comprises 4 cycles of 375 mg for each square metre of body surface [32], implying a daily dose of 25 mg for 17.13% of the patients, a dose of 50 mg for 40.89% and a dose of 75 mg for 41.98% [19]. In the case of rituximab, an extra administration cost must be added; as the drug is administered in the hospital, we have assumed it is equivalent to day-hospital costs.

Table 6 shows the costs and their use in the model. Eltrombopag response is monitored weekly during the first 8 weeks and then once a month after week 8. For rituximab, monitoring is carried out weekly for the first 4 weeks and once a month after that. We assumed that a grade 2 bleeding cost is 0.6 times the cost of a specialist consultation plus 0.3 times the cost of an urgency consultation. For grade 3 bleedings, we assumed a diagnosis-related group (DRG) 174 (gastrointestinal bleeding) cost; for grade 4 bleedings, we assumed a cost of 0.2 times DRG 810 (medical intracranial haemorrhage) plus 0.8 times the cost of DRG 833 (surgical intracranial haemorrhage) and the cost of rehabilitation when applying. This rehabilitation process after grade 4 bleeding, when needed, was assumed to last 6 months and to include a monthly visit to the physiotherapy consultant, five physiotherapy and speech therapy sessions every week and three weekly occupational therapy sessions [35].

Sensitivity analysis

To analyse the effect of the different variables on the model results, we carried out 15 sensitivity analyses, described in Table 7.

Results

The average cost per patient after a 6-month treatment was 13089.40€ for eltrombopag and 11852.60€ for rituximab. Itemised costs show that the greater response rate of the first involves a decrease in bleeding costs (811.27€ with rituximab, 499.97€ with eltrombopag). Due to the lower efficacy of rituximab, the average cost of response is 14732.65€ with eltrombopag and 18964.15€ with rituximab (29% higher with the latter).

Tables 8, 9 and 10 show the base case and sensitivity analysis results. The cost of eltrombopag is always lower, excluding the sensitivity analysis in which the patient received a daily dose of 75 mg of eltrombopag – a scenario where eltrombopag global cost is 5039.58€ over rituximab, but when response cost is considered, the difference is reduced to only 48€ higher than that of rituximab.

Discussion

Patient refusal and hazards derived from surgery plus lifelong increased risk of infection, thromboembolic events and malignancy after splenectomy have increased the use of TPO-RAs and rituximab [36, 37]. The last American Hematology Association guideline for ITP treatment update recommends rituximab over splenectomy and places splenectomy and TPO-RAs at the same level. The preference between rituximab and TPO-RAs is under discussion in unresponsive to steroids or persistent ITP [11]. Hence, the cost and effectiveness of both types of treatment must be carefully evaluated to make appropriate medical decisions. We selected TPO-RA eltrombopag for this study over romiplostim due to its oral, out-of-hospital administration, in contrast to the subcutaneous administration of romiplostim, which needs sanitary assistance.

Here, we show that the cost of a 6-month treatment is similar using rituximab and eltrombopag, 13089.40€ and 11852.60€, respectively. Both treatments accomplish responses and have low side effects, but lower beneficial effects have been observed with rituximab [23]. Therefore, as the response to treatment with eltrombopag is greater, the cost per-responding patient is smaller, even though the treatment cost itself is higher, turning the budget to 14732.65€ for eltrombopag and 18964.15€ for rituximab in that period of time. These results are indirectly consistent with those from other economic evaluations in Spain showing that eltrombopag was cost-effective against romiplostim and romiplostim was cost-effective against rituximab [27, 35]. Additionally, a recent meta-analysis indirectly comparing rituximab and TPO-RAs eltrombopag and romiplostim treatment for persistent or chronic ITP suggests that the second type of treatment is superior to the former when considering response (platelet $\geq 50 \times 10^9/L$), clinically significant and severe bleeding [38]. Additionally, although treatment with eltrombopag is considered chronic, there is evidence that suggests that it is possible to discontinue the treatment [29].

Another issue to consider is that the rituximab administration route is intravenous or subcutaneous after the first dose, and it has to be monitored at the hospital for undesired side effects versus oral administration at home in the case of eltrombopag. Therefore, treatment with eltrombopag lessens the workload at day hospitals, allowing resources to be focused on other patients who need day-hospital facilities for the administration of their treatments (such as chemotherapy). A limitation of this study is that the model does not take into account the adverse effects caused by treatments, which may potentially be more severe in the first perfusions of the monoclonal antibody than in the case of the receptor agonist thrombopoietin.

As data for rituximab do not inform of splenectomised patients, our model considers the Spanish average of 22% splenectomised patients, but it cannot itemise the splenectomised group of patients. Clinical studies have shown that eltrombopag is more effective in non-splenectomised patients [19, 39, 40], so an increase in the number of splenectomised patients could mean a decrease in the response rate.

A final limitation is related to the use of rituximab at a lower dose (100 mg). In the absence of efficacy data at this dose, this option has not been considered for the present analysis (it should be noted that the use of data that are not sufficiently comprehensible would in turn imply another limitation). Additionally, using a standard dose of rituximab of 375 mg is consistent with a similar article in which rituximab was evaluated against romiplostim [27] and may allow comparison between both.

Conclusions

The treatment budget of rituximab, considering monitoring and bleeding costs, is higher than that of eltrombopag. This, together with long response rates and the reduced undesirable effects, supports the recommendation of the latter treatment over rituximab. This type of analysis should be required to guide healthcare policies and treatment decision-making.

List Of Abbreviations

CI: Confidence interval

CR: Complete response

DRG: Diagnosis-related group

EHIS: European Health Interview Survey

IC: Intracranial

ITP: Primary immune thrombocytopenia

GI: Gastrointestinal

Ref: Reference

SA: Sensitivity analysis

TPO-RAs: Thrombopoietin receptor agonists

WHO: World Health Organization

Declarations

Ethics approval and consent to participate

Not applicable

Consent to publish

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article, its supplementary information files and references.

Competing interests

JRG-P has received fees for consulting services by Amgen, Novartis, SOBI, Grifols and CSL Behring and speaking honoraria from Novonordisk, Shire, SOBI, Roche, Daiichi Sankyo, Pfizer, Rovi, Amgen, and Novartis. EA has received speaking honoraria and support for attending conferences from Amgen and Novartis.

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Authors' contributions

FJP-G performed the data analysis. EA, JRG-P, and FJP-G designed the study, wrote the paper and participated in the interpretation of data as well as in the critical revision of the manuscript.

All authors have read and approved the manuscript.

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Tables

Table 1. Basal characteristics of the population used in the model.

Variable	Value	Reference
Sex (women %)	63	Gonzalez-Lopez TJ, et al. 2015 [29].
Average age (years)	60	Gonzalez-Lopez TJ, et al. 2015 [29].
Average women weight (kg)	65.75	European Survey of Health in Spain. INE 2014; 2015 Oct 21 [31].
Average men weight (kg)	79.90	European Survey of Health in Spain. INE 2014; 2015 Oct 21 [31].
Average women height (cm)	161	European Survey of Health in Spain. INE 2014; 2015 Oct 21 [31].
Average men height (cm)	173	European Survey of Health in Spain. INE 2014; 2015 Oct 21 [31].

Table 2. Response rates according to treatment.

Treatment/kind of response	Response rate	Response criteria (platelets $\times 10^9/l$)	Ref.
Eltrombopag/Full response	77.31%	≥ 100	Gonzalez-Lopez TJ, et al. 2015 [29].
Eltrombopag/Partial response	11.54%	<100 & ≥ 30	Gonzalez-Lopez TJ, et al. 2015 [29].
Eltrombopag/No response	11.15%	<30	Gonzalez-Lopez TJ, et al. 2015 [29].
Rituximab/Response	62.50%	≥ 50	Arnold DM, et al. 2007 [32].
Rituximab/No response	37.50%	<50	Arnold DM, et al. 2007 [32].

Ref, reference.

Table 3. Re-treatment rates.

Re-treatment/kind of response	Brah S, et al. 2012 [26].
<i>Patients responding to first treatment: eltrombopag</i>	
No re-treatment	75%
Re-treatment/Partial response	21.43%
No response	3.57%
<i>Patients responding to first treatment: rituximab</i>	
No re-treatment	63.64%
Response	27.27%%
No response	9.09%

Table 4. Bleeding rates on the basis of response.

Kind of bleeding	Responding patients	Non-responding patients
Grade 2	13.19%	22.95%
Grade 3	4.40%	14.75%
Grade 4	0.55%	3.28%

Table 5. Price of drugs used for the model.

Drug	Price (€)
Eltrombopag 25 mg x 28 pills	843.62
Eltrombopag 50 mg x 28 pills	1687.24
Mabthera 100 mg solution x 2 vials	495.18
Mabthera 500 mg solution x 1 vial	1234.53
Truxima 100 mg solution x 2 vials	420.90
Truxima 500 mg solution x 1 vial	1049.35

Table 6. Costs included in the model.

Concept	Cost (€)
Specialist consultation	96.95
Urgency consultation	234.80
DRG 174 (GI bleeding)	5015.89
DRG 810 (medical IC haemorrhage)	7305.87
DRG 833 (surgical IC haemorrhage)	25515.31
Physiotherapy consultation	21.46
Speech therapy consultation	20.65
Occupational therapy consultation	19.58
Day-hospital consultation	306.36
6-month rehabilitation	4004.46
<i>Costs for calculated event</i>	
Bleeding grade 2	128.61
Bleeding grade 3	5015.89
Bleeding grade 4	23795.57

DRG, diagnosis-related group; GI, gastrointestinal; IC, intracranial.

Table 7. List of carried out sensitivity analyses.

Analysis	Description
Base case	<ul style="list-style-type: none"> · Body surface after EHIS 2014 data · Eltrombopag dose after RAISE trial (56.21 mg/day) · Re-treatment with rituximab after retrospective study. · Both full and partial responses to eltrombopag are considered as response · Average value of rituximab efficacy · Rituximab administration cost (=1 day-hospital consultation) · Monthly monitoring of rituximab after the first 4 weeks of response evaluation · Rituximab, mabthera price
SA 1	<ul style="list-style-type: none"> · Body surface 1.70 m²
SA 2	<ul style="list-style-type: none"> · Eltrombopag dose 50 mg/day
SA 3	<ul style="list-style-type: none"> · Eltrombopag dose 25 mg/day
SA 4	<ul style="list-style-type: none"> · Eltrombopag dose 75 mg/day
SA 5	<ul style="list-style-type: none"> · No re-treatment with rituximab
SA 6	<ul style="list-style-type: none"> · Re-treatment with rituximab only for the responding group.
SA 7	<ul style="list-style-type: none"> · Re-treatment with rituximab only for the non-responding group.
SA 8	<ul style="list-style-type: none"> · Only full responses to eltrombopag were considered.
SA 9	<ul style="list-style-type: none"> · Decrease in rituximab efficacy to the lower threshold of the confidence interval
SA 10	<ul style="list-style-type: none"> · Increase in rituximab efficacy to the upper threshold of the confidence interval
SA 11	<ul style="list-style-type: none"> · Rituximab administration cost (=specialist consultation)
SA 12	<ul style="list-style-type: none"> · Twice-a-month rituximab monitoring after the first 4 weeks of response evaluation
SA 13	<ul style="list-style-type: none"> · 10% decrease in bleeding costs
SA 14	<ul style="list-style-type: none"> · 10% increase in bleeding costs
SA 15	<ul style="list-style-type: none"> · Rituximab, truxima price

EHIS, European Health Interview Survey; SA, sensitivity analysis.

Table 8. Base case and sensitivity analysis results. Per-patient global cost of treatment with eltrombopag and rituximab.

		Cost per patient (€)	
		Eltrombopag	Rituximab
BASE CASE		13089.40	11852.60
SA 1	Body surface	13089.40	11454.77
SA 2	Eltrombopag dose 25 mg/day	6771.98	11852.60
SA 3	Eltrombopag dose 50 mg/day	11832.08	11852.60
SA 4	Eltrombopag dose 75 mg/day	16892.18	11852.60
SA 5	No re-treatment with rituximab	13089.40	9561.63
SA 6	Re-treatment with rituximab only for responding patients	13089.40	10784.96
SA 7	Re-treatment with rituximab only for non-responding patients	13089.40	10629.27
SA 8	Decrease in eltrombopag efficacy (CR patients)	12240.82	11852.60
SA 9	Rituximab efficacy lower CI threshold	13089.40	12057.65
SA 10	Rituximab efficacy higher CI threshold	13089.40	11645.47
SA 11	Rituximab administration = specialist consultation cost	13089.40	10769.87
SA 12	Monitoring decrease in rituximab	13089.40	11537.50
SA 13	Decrease bleeding costs (-10%)	13039.40	11771.47
SA 14	Increase bleeding costs (+10%)	13139.39	11933.72
SA 15	Rituximab, truxima price	13089.40	10572.16

CI, confidence interval; SA, sensitivity analysis; CR, complete response.

Table 9. Base case and sensitivity analysis results. Itemised costs of per-patient treatment with eltrombopag and rituximab.

	Treatment costs (€)		Monitoring costs (€)		Bleeding costs (€)	
	Eltrombopag	Rituximab	Eltrombopag	Rituximab	Eltrombopag	Rituximab
BASE CASE	11377.51	10120.27	1211.91	921.05	499.97	811.27
SA 1	11377.51	9722.45	1211.91	921.05	499.97	811.27
SA 2	10120.20	10120.27	1211.91	921.05	499.97	811.27
SA 3	5060.10	10120.27	1211.91	921.05	499.97	811.27
SA 4	15180.29	10120.27	1211.91	921.05	499.97	811.27
SA 5	11377.51	7829.31	1211.91	921.05	499.97	811.27
SA 6	11377.51	9052.64	1211.91	921.05	499.97	811.27
SA 7	11377.51	8896.94	1211.91	921.05	499.97	811.27
SA 8	10392.60	10120.27	1211.91	921.05	636.31	811.27
SA 9	11377.51	10208.35	1211.91	921.05	499.97	928.25
SA 10	11377.51	10031.30	1211.91	921.05	499.97	693.11
SA 11	11377.51	9037.54	1211.91	921.05	499.97	811.27
SA 12	11377.51	10120.27	1211.91	605.96	499.97	811.27
SA 13	11377.51	10120.27	1211.91	921.05	449.98	730.14
SA 14	11377.51	10120.27	1211.91	921.05	549.97	892.40
SA 15	11377.51	8839.83	1211.91	921.05	499.97	811.27

SA, sensitivity analysis.

Table 10. Base case and sensitivity analysis results. Per-response cost of treatment with eltrombopag and rituximab.

		Cost per response (€)	
		Eltrombopag	Rituximab
BASE CASE		14732.65	18964.15
SA 1	Body surface	14732.65	18327.63
SA 2	Eltrombopag dose 25 mg/day	7622.14	18964.15
SA 3	Eltrombopag dose 50 mg/day	13317.49	18964.15
SA 4	Eltrombopag dose 75 mg/day	19012.84	18964.15
SA 5	No re-treatment with rituximab	14732.65	15298.61
SA 6	Re-treatment with rituximab only for responding patients	14732.65	17255.94
SA 7	Re-treatment with rituximab only for non-responding patients	14732.65	17006.83
SA 8	Decrease in eltrombopag efficacy (CR patients)	13777.55	18964.15
SA 9	Rituximab efficacy lower CI threshold	14732.65	19292.24
SA 10	Rituximab efficacy higher CI threshold	14732.65	18632.75
SA 11	Rituximab administration = specialist consultation cost	14732.65	17231.79
SA 12	Monitoring decrease in rituximab	14732.65	18460.00
SA 13	Decrease bleeding costs (-10%)	14676.38	18834.35
SA 14	Increase bleeding costs (+10%)	14788.93	19093.96
SA 15	Rituximab, truxima price	14732.65	16915.45

CR, complete response. CI, confidence interval; SA, sensitivity analysis.

Figures

Figure 1

Figure 1

Model structure. Decision flow.

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