Farmacia HOSPITALARIA
Órgano oficial de expresión científica de la Sociedad Española de Farmacia Hospitalaria

ORIGINALS
Bilingual edition English/Spanish

Cost-per-responder analysis for eltrombopag and rituximab in the treatment of primary immune thrombocytopenia in Spain

Coste de eltrombopag y rituximab por paciente respondedor al tratamiento de la trombocitopenia inmune primaria en España

José Ramón González-Porras[1], Francisco Javier Parrondo García[2], Eduardo Anguita[3]

[1]Hematology Department, Hospital Universitario de Salamanca-IBSAL, Salamanca. Spain. [2]JParrondoHEALTH. Coslada, Madrid. Spain. [3]Hematology Department, IML, IdISSC; Hospital Clínico San Carlos. Medical School, Department of Medicine, Complutense University (UCM), Madrid, Spain.

Author of correspondence
Eduardo Anguita Mandly
Servicio de Hematología, IML, IdISSC.
Hospital Clínico San Carlos.
Departamento de Medicina, UCM
C/ Profesor Martín Lagos s/n
28040 Madrid, Spain.

Email:
eduardo.anguita@salud.madrid.org

Received 6 June 2020;
Accepted 26 August 2020.
DOI: 10.7399/fh.11525

How to cite this paper
González-Porras JR, Parrondo García FJ, Anguita E. Cost-per-responder analysis for eltrombopag and rituximab in the treatment of primary immune thrombocytopenia in Spain. Farm Hosp. 2020;44(6):279-87.

Abstract

Objective: Splenectomy, thrombopoietin receptor agonists and rituximab are the second-line treatments for steroid-resistant adult primary immune thrombocytopenia. The last two are becoming the most widely used treatments to avoid splenectomy adverse effects and inconveniences. However, the choice between rituximab and thrombopoietin receptor agonists is unclear. Therefore, the treatment cost may be of particular interest to prioritize the therapy option. Our aim is to determine the cost per responding-patient after 6 months of use of rituximab compared to thrombopoietin receptor agonists eltrombopag in the treatment of chronic primary immune thrombocytopenia in the Spanish National Health Service.

Method: A 26-week decision tree model was developed to assess the cost of treatment response of adult patients with chronic-refractory primary immune thrombocytopenia 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.

KEYWORDS

Pharmacoeconomics; Hematologic agents; Hematologic diseases; Cost analysis; Immune thrombocytopenia; Thrombopoietin receptor agonists; Eltrombopag; Rituximab.

Resumen

Objetivo: La esplenectomía, los agonistas del receptor de trombopoyetina y el rituximab son los tratamientos de segunda línea para la trombocitopenia inmune primaria. Los dos últimos se están convirtiendo en los más utilizados para evitar los efectos adversos de la esplenectomía. Sin embargo, la elección entre ambos no está clara. El coste puede ser de interés para priorizar el tratamiento. Nuestro objetivo es determinar el coste por paciente respondedor después de 6 meses de tratamiento de la trombocitopenia inmune primaria crónica con rituximab frente al agonista del receptor de trombopoyetina eltrombopag en el Sistema Nacional de Salud español.

Método: Se desarrolló un modelo de árbol de decisión de 26 semanas para evaluar el coste de la respuesta al tratamiento con eltrombopag y rituximab en pacientes adultos con trombocitopenia inmune primaria crónica refractaria a esteroides. Debido al corto periodo de evaluación, no se aplicó tasa de descuento.

Resultados: El coste medio por paciente tras 6 meses de tratamiento fue ligeramente superior para eltrombopag (13.089,40 €) que para rituxi-

PALABRAS CLAVE

Farmacoeconomía; Fármacos hematológicos; Enfermedades hematológicas; Análisis de costes; Trombocitopenia inmune primaria; Agonistas del receptor de trombopoyetina; Eltrombopag; Rituximab.

Results: The average cost per patient after 6 months of treatment was slightly higher for eltrombopag (€13,089.40) than for rituximab (€11,852.60). However, the greater response rate of eltrombopag decreases the bleeding costs, resulting in a 29% higher cost per responding-patient with rituximab (€18,964.15) than for eltrombopag (€14,732.65). This result is consistent with the results of the 15 sensitivity analyses carried out where eltrombopag always represents a lower cost per responding patient, except in the sensitivity analysis in which treatment with eltrombopag is performed at its maximum dose (75mg). Only in this case, the cost per responder of eltrombopag is €48 more expensive than that of rituximab. Likewise, the greatest difference in favor of eltrombopag occurs in the scenario that uses the minimum dose of this drug —25mg— (eltrombopag €7,622.14 compared to €18,964.15 for rituximab). Thus, the cost per responding patient is lower in eltrombopag even if a second cycle of retreatment with rituximab is not performed (€14,732.65 versus €15,298.61).
Conclusions: The treatment cost of rituximab, including monitoring and bleeding costs, is higher than eltrombopag, favoring the latter over rituximab treatment.

Resultados: El coste medio por paciente después de 6 meses de tratamiento fue ligeramente superior para eltrombopag (€13,089.40) que para rituximab (€11,852.60). Sin embargo, la mayor tasa de respuesta de eltrombopag disminuye los costes de hemorragia, lo que se traduce en un coste por paciente respondedor un 29% mayor con rituximab (18.964,15 €) que con eltrombopag (14.732,65 €). Este resultado concuerda con los de los 15 análisis de sensibilidad realizados, donde eltrombopag siempre representa un menor coste por paciente respondedor, excepto cuando el tratamiento con eltrombopag se realiza en su dosis máxima (75 mg). Sólo en este caso, el coste por respondedor a eltrombopag es 48 € más caro que el del rituximab. En coherencia con lo anterior, la mayor diferencia a favor de eltrombopag se da en el escenario que utiliza la dosis mínima de éste —25 mg— (eltrombopag 7.622,14 € frente a 18.964,15 € de rituximab). Así, el coste por paciente respondedor es menor en eltrombopag aunque no se realice un segundo ciclo de retratamiento con rituximab (14.732,65 € frente a 15.298,61 €).
Conclusiones: El coste del tratamiento con rituximab, incluidos los costes de monitorización y sangrado, es más alto que el de eltrombopag, lo cual favorece a este último por encima de rituximab.

Introduction

Primary immune thrombocytopenia (ITP) is an acquired autoimmune disease characterized by a platelet count less than 100 x 10^9 platelets/liter; 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 3-4/100,000 in adults, increasing in older patients[3]. 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 x 10^9 platelets/liter 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].

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[2,4].

Splenectomy achieves a 60% response after 5 years[5]. However, this treatment produces important adverse effects mainly derived from surgery, as well as risk of infection, thrombosis and cancer[6]. 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 one year[7]. 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[7-12]. Hence, those formerly considered third-line treatments have become extensively used[13]. 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[7].

TPO-RAs, including eltrombopag and romiplostim, stimulate platelet production, increasing platelet count[9,14]. Unlike romiplostim subcutaneous administration, eltrombopag oral administration requires no sanitary assistance[15].

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 rixutimab from the perspective of Spanish public hospitals. As in a similar study comparing romiplostim and rituximab[16], 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 former study that evaluated the cost per response of romiplostim and rituximab[16], 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[17]. This structure is coherent with the previously mentioned study carried out in Spain[16], so it may support decision-making.

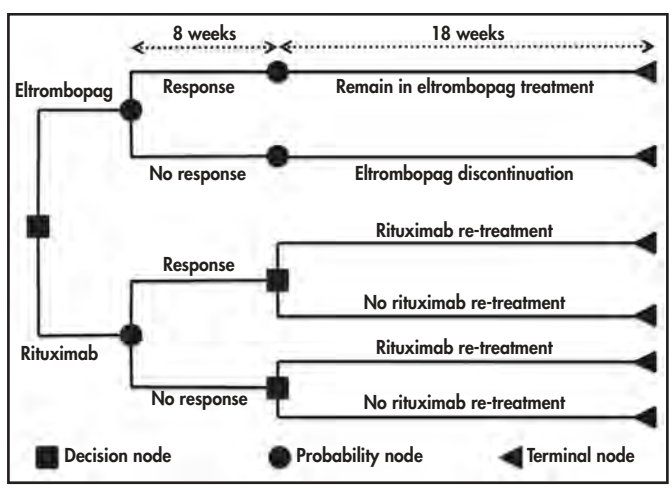
As the time horizon is less than a year, we did not consider applying discounting to costs or effects.

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[15] and that although rituximab is not officially approved for this disease, it is usually restricted to adults with ITP because of the concerns that the effects of rituximab

Figure 1. *Model structure. Decision flow.*



in the childhood immune system may elicit[7,18], 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[19]. 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[20].

To estimate rituximab dosage, we used the Dubois & Dubois formula to determine the body surface of patients[21]. Height and weight were determined according to microdata from the Spanish results of the European Health Survey 2014 (basal data shown in Supplementary Table 1)[22].

Estimate of response

No study or phase III clinical trial related to rituximab response was found in Spain; therefore, the more consistent data for this treatment derive from the indicated systematic review[20]. Additionally, we used a retrospective French model to evaluate the need for re-treatment and its effectiveness[17].

Supplementary 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 Supplementary Table 3.

As Supplementary Table 2 shows, there are differences in the response criteria. While the eltrombopag study used the full response rate (defined as platelet count ≥ 100 x 10^9/L) and the response rate (platelet count ≥ 30 and < 100), the rituximab study used a different response rate (defined as platelet count ≥50 x 10^9L). 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[23], Supplementary Table 4).

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[12], 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 Supplementary Table 5. Grade 4 bleedings are potentially life threatening, with a mortality rate of 40%; 80% of patients who survive after such bleeding need rehabilitation[24].

Resources and costs

To make a cost estimation, we used an average of the official lists of prices of the different Spanish regions (Supplementary Table 6). 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.

Supplementary Table 7 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 meter of body surface[20], 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%[12]. 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.

Supplementary Table 7 also indicates 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 hemorrhage) plus 0.8 times the cost of DRG 833 (surgical intracranial hemorrhage) 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[25].

Sensitivity analysis

To analyze the effect of the different variables on the model results, we carried out 15 sensitivity analyses, described in Supplementary Table 8.

Results

The average cost per patient after a 6-month treatment was €13,089.40 for eltrombopag and €11,852.60 for rituximab. Itemized 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 €14,732.65 with eltrombopag and €18,964.15 with rituximab (29% higher with the latter).

Tables 1, 2 and 3 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 €5,039.58 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[26,27]. The last American Hematology Association guideline for ITP treatment update recommends rituximab over splenectomy and places splenectomy and TPO-RAs at the same level[7]. The preference between rituximab and TPO-RAs is under discussion in patients unresponsive to steroids or suffering from persistent ITP[7]. 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, €11,852.60 and €13,089.40, respectively. Both treatments accomplish responses and have low side effects, but lower beneficial effects have been observed with rituximab[13]. 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 €14,732.65 for eltrombopag and €18,964.15 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[16,25]. 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 ≥ 50 × 10^9/L), clinically significant and severe bleeding[28]. Additionally, although treatment with eltrombopag is considered chronic, there is evidence that suggests that it is possible to discontinue the treatment[19].

Table 1. Base case and sensitivity analysis results. Per-patient global cost of treatment with eltrombopag and rituximab

		Cost per patient (€)	
		Eltrombopag	Rituximab
BASE CASE		13,089.40	11,852.60
SA 1	Body surface	13,089.40	11,454.77
SA 2	Eltrombopag dose 25 mg/day	6,771.98	11,852.60
SA 3	Eltrombopag dose 50 mg/day	11,832.08	11,852.60
SA 4	Eltrombopag dose 75 mg/day	16,892.18	11,852.60
SA 5	No re-treatment with rituximab	13,089.40	9,561.63
SA 6	Re-treatment with rituximab only for responding patients	13,089.40	10,784.96
SA 7	Re-treatment with rituximab only for non-responding patients	13,089.40	10,629.27
SA 8	Decrease in eltrombopag efficacy (CR patients)	12,240.82	11,852.60
SA 9	Rituximab efficacy lower CI threshold	13,089.40	12,057.65
SA 10	Rituximab efficacy higher CI threshold	13,089.40	11,645.47
SA 11	Rituximab administration = specialist consultation cost	13,089.40	10,769.87
SA 12	Monitoring decrease in rituximab	13,089.40	11,537.50
SA 13	Decrease bleeding costs (–10%)	13,039.40	11,771.47
SA 14	Increase bleeding costs (+10%)	13,139.39	11,933.72
SA 15	Rituximab, Truxima® price	13,089.40	10,572.16

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

Table 2. Base case and sensitivity analysis results. Itemized costs of per-patient treatment with eltrombopag and rituximab

	Treatment costs (€)		Monitoring costs (€)		Bleeding costs (€)	
	Eltrombopag	Rituximab	Eltrombopag	Rituximab	Eltrombopag	Rituximab
BASE CASE	11,377.51	10,120.27	1,211.91	921.05	499.97	811.27
SA 1	11,377.51	9,722.45	1,211.91	921.05	499.97	811.27
SA 2	10,120.20	10,120.27	1,211.91	921.05	499.97	811.27
SA 3	5,060.10	10,120.27	1,211.91	921.05	499.97	811.27
SA 4	15,180.29	10,120.27	1,211.91	921.05	499.97	811.27
SA 5	11,377.51	7,829.31	1,211.91	921.05	499.97	811.27
SA 6	11,377.51	9,052.64	1,211.91	921.05	499.97	811.27
SA 7	11,377.51	8,896.94	1,211.91	921.05	499.97	811.27
SA 8	10,392.60	10,120.27	1,211.91	921.05	636.31	811.27
SA 9	11,377.51	10,208.35	1,211.91	921.05	499.97	928.25
SA 10	11,377.51	10,031.30	1,211.91	921.05	499.97	693.11
SA 11	11,377.51	9,037.54	1,211.91	921.05	499.97	811.27
SA 12	11,377.51	10,120.27	1,211.91	605.96	499.97	811.27
SA 13	11,377.51	10,120.27	1,211.91	921.05	449.98	730.14
SA 14	11,377.51	10,120.27	1,211.91	921.05	549.97	892.40
SA 15	11,377.51	8,839.83	1,211.91	921.05	499.97	811.27

SA: sensitivity analysis.

Table 3. Base case and sensitivity analysis results. Per-response cost of treatment with eltrombopag and rituximab

		Cost per response (€)	
		Eltrombopag	Rituximab
BASE CASE		14,732.65	18,964.15
SA 1	Body surface	14,732.65	18,327.63
SA 2	Eltrombopag dose 25 mg/day	7,622.14	18,964.15
SA 3	Eltrombopag dose 50 mg/day	13,317.49	18,964.15
SA 4	Eltrombopag dose 75 mg/day	19,012.84	18,964.15
SA 5	No re-treatment with rituximab	14,732.65	15,298.61
SA 6	Re-treatment with rituximab only for responding patients	14,732.65	17,255.94
SA 7	Re-treatment with rituximab only for non-responding patients	14,732.65	17,006.83
SA 8	Decrease in eltrombopag efficacy (CR patients)	13,777.55	18,964.15
SA 9	Rituximab efficacy lower CI threshold	14,732.65	19,292.24
SA 10	Rituximab efficacy higher CI threshold	14,732.65	18,632.75
SA 11	Rituximab administration = specialist consultation cost	14,732.65	17,231.79
SA 12	Monitoring decrease in rituximab	14,732.65	18,460.00
SA 13	Decrease bleeding costs (10%)	14,676.38	18,834.35
SA 14	Increase bleeding costs (+10%)	14,788.93	19,093.96
SA 15	Rituximab, Truxima® price	14,732.65	16,915.45

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

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 thrombopoietin receptor agonist.

As data for rituximab do not inform of splenectomized patients, our model considers the Spanish average of 22% splenectomized patients, but it cannot itemize the splenectomized group of patients. Clinical studies have shown that eltrombopag is more effective in non-splenectomized patients[12,29,30], so an increase in the number of splenectomized 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[16], and may allow comparison between both.

In conclusion, 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.

Funding

No funding.

Conflict of interests

No conflicts of interest.

Financial activities outside the submitted work: José Ramón González-Porras 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. Francisco Javier Parrondo-García has received consultancy fees from Takeda Farmacéutica España, Tesaro España, Pierre Fabre España, Servier España, Bristol-Myers Squibb S.L., Lilly S.A., Biogen Spain S.L., ViiV Healthcare Spain and Pfizer SLU. Eduardo Anguita has received speaking honoraria and support for attending conferences from Amgen and Novartis.

Presentation at congress

This work was an oral presentation at the LXI National Conference of SEHH and XXXV Congress of SETH, Valencia, October 24-26, 2019.

Contribution to the scientific literature

The cost for responding primary immune thrombocytopenia patient in the Spanish Health Service.

Our data favor eltrombopag over rituximab for primary immune thrombocytopenia treatment in Spain.

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

Variable	Value	Reference
Sex (women %)	63	González-López TJ, *et al.* 2015[19]
Average age (years)	60	González-López TJ, *et al.* 2015[19]
Average women weight (kg)	65.75	European Survey of Health in Spain. INE 2014; 2015 Oct 21[22]
Average men weight (kg)	79.90	European Survey of Health in Spain. INE 2014; 2015 Oct 21[22]
Average women height (cm)	161	European Survey of Health in Spain. INE 2014; 2015 Oct 21[22]
Average men height (cm)	173	European Survey of Health in Spain. INE 2014; 2015 Oct 21[22]

Supplementary Table 2. Response rates according to treatment

Treatment/kind of response	Response rate	Response criteria (platelets x 10^9/l)	Reference
Eltrombopag/Full response	77.31%	≥ 100	González-López TJ, *et al.* 2015[19]
Eltrombopag/Partial response	11.54%	< 100 & ≥ 30	González-López TJ, *et al.* 2015[19]
Eltrombopag/No response	11.15%	< 30	González-López TJ, *et al.* 2015[19]
Rituximab/Response	62.50%	≥ 50	Arnold DM, *et al.* 2007[20]
Rituximab/No response	37.50%	< 50	Arnold DM, *et al.* 2007[20]

Supplementary Table 3. Re-treatment rates

Re-treatment/ kind of response	Brah S, *et al.* 2012[17]
Patients responding to first treatment: eltrombopag	
No re-treatment	75%
Re-treatment/Partial response	21.43%
No response	3.57%
Patients responding to first treatment: rituximab	
No re-treatment	63.64%
Response	27.27%
No response	9.09%

Supplementary Table 4. Types of bleeding after the WHO scale

Degree	Description
0	Absence of bleeding
1	Petechial bleeding
2	Moderate hemorrhage
3	Severe hemorrhage
4	Severe hemorrhage with life danger

Adapted from Fogarty *et al.* 2012[23].

Supplementary Table 5. 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%

Supplementary Table 6. List of official prices in the Spanish regions

Price/region	Source
Andalusia	Boletín Oficial Junta Andalucía num. 210 27/10/2005
Aragon	Boletín Oficial de Aragón num. 156 10/08/2012
Asturias	Boletín Oficial Principado de Asturias num. 77 04/04/2013
Balearic Islands	Boletín Oficial Islas Baleares num.89 01/07/2014
Canary Islands	Boletín Oficial de Canarias num. 70 14/04/2015
Cantabria	Boletín Oficial de Cantabria num. 85 05/05/2011
Castile-La Mancha	Diario Oficial Castilla La Mancha num. 226 21/11/2014
Castile-Leon	Boletín Oficial de Castilla y León num. 249 30/12/2013
Catalonia	Diario Oficial Generalidad Cataluña num. 6387 31/05/2013
Extremadura	Boletín Oficial de Extremadura 19/02/2009
Galicia	Diario Oficial de Galicia num. 96 21/05/2014
La Rioja	Boletín Oficial de La Rioja num. 156 19/12/2014
Madrid	Boletín Oficial Comunidad Madrid num. 215 10/09/2013
Murcia	Boletín Oficial Región de Murcia num. 129 06/06/2007
Navarre	Boletín de Navarra num. 45 14/04/2006
Basque Country	http://www.osakidetza.euskadi.eus/contenidos/informacion/libro_tarifas/es_libro/adjuntos/Libro_de_tarifas2017.pdf
Valencia	Decreto Legislativo 1/2005 25/02/2005 Con modificaciones hasta Ley de Tasas Ejercicio 2015

Num: number.

Supplementary Table 7. Costs included in the model

Concept	Cost (€)
Eltrombopag 25 mg x 28 pills	843.62
Eltrombopag 50 mg x 28 pills	1,687.24
MabThera® 100 mg solution x 2 vials	495.18
MabThera® 500 mg solution x 1 vial	1,234.53
Truxima® 100 mg solution x 2 vials	420.90
Truxima® 500 mg solution x 1 vial	1,049.35
Specialist consultation	96.95
Urgency consultation	234.80
DRG 174 (GI bleeding)	5,015.89
DRG 810 (medical IC hemorrhage)	7,305.87
DRG 833 (surgical IC hemorrhage)	25,515.31
Physiotherapy consultation	21.46
Speech therapy consultation	20.65
Occupational therapy consultation	19.58
Day-hospital consultation	306.36
6-month rehabilitation	4,004.46
Costs for calculated event	
Bleeding grade 2	128.61
Bleeding grade 3	5,015.89
Bleeding grade 4	23,795.57

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

Supplementary Table 8. List of carried out sensitivity analyses

Analysis	Description
Base case	• 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	• Body surface 1.70 m^2
SA 2	• Eltrombopag dose 50 mg/day
SA 3	• Eltrombopag dose 25 mg/day
SA 4	• Eltrombopag dose 75 mg/day
SA 5	• No re-treatment with rituximab
SA 6	• Re-treatment with rituximab only for the responding group
SA 7	• Re-treatment with rituximab only for the non-responding group
SA 8	• Only full responses to eltrombopag were considered
SA 9	• Decrease in rituximab efficacy to the lower threshold of the confidence interval
SA 10	• Increase in rituximab efficacy to the upper threshold of the confidence interval
SA 11	• Rituximab administration cost (= specialist consultation)
SA 12	• Twice-a-month rituximab monitoring after the first 4 weeks of response evaluation
SA 13	• 10% decrease in bleeding costs
SA 14	• 10% increase in bleeding costs
SA 15	• Rituximab, Truxima® price

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

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