

Steroids versus Eltrombopag for first and second-line treatment of adult immune thrombocytopenia

Esteroides versus Eltrombopag para el tratamiento de primera y segunda línea de la trombocitopenia inmune en adultos

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Abstract

Introduction: Primary thrombocytopenia immune (PTI) is characterized by the progressive destruction of platelets through the formation of antibodies on the different glycoproteins of the platelet membrane. The first-line treatment is steroids. Eltrombopag is an oral thrombopoietin receptor agonist that stimulates Thrombopoietin Receptor Agonists signaling, stimulating the production of functional platelets. It is considered a tolerable drug, but it warrants monitoring of liver function and cell counts due to the risk of fibrosis. **Objective:** To evaluate the response of steroids as a first-line treatment and Eltrombopag as a second-line regimen. **Methods:** Retrospective, observational study based on the clinical records of patients diagnosed with PTI from 2018 to 2023. **Results:** Two hundred and forty-two clinical records of patients were studied; 192 were considered first-line treatment, and 50 received Eltrombopag as second-line therapy. About 69.8% of patients treated with steroids achieved complete remission, compared to 80% of those in the Eltrombopag group. 64% of Eltrombopag patients achieved complete response, 24% had partial response, and 12% had stable disease. **Conclusions:** Eltrombopag is a safe treatment with a high proportion of responses in patients without a splenectomy history and without the combined use of steroids. This suggests that it could be used as a first line of treatment.

Keywords: Corticosteroids. Eltrombopag. Immune thrombocytopenia. Management. Complete response.

Resumen

Introducción: La trombocitopenia inmune primaria (TIP) se caracteriza por la destrucción progresiva de plaquetas mediante la formación de anticuerpos sobre diferentes glicoproteínas de la membrana plaquetaria. El tratamiento de primera línea son los esteroides. Eltrombopag es un agonista del receptor de trombopoyetina oral que estimula la señalización de TPO, induciendo la producción de plaquetas funcionales. Se considera un fármaco tolerable, pero requiere vigilancia de la función hepática y del recuento celular debido al riesgo de fibrosis. **Objetivo:** Evaluar la respuesta de esteroides como tratamiento de primera línea y Eltrombopag como de segunda línea. **Métodos:** Estudio observacional retrospectivo basado en registros clínicos de pacientes diagnosticados con TIP del 2018 al 2023. **Resultados:** Se estudiaron 242 registros clínicos; 192 fueron de primera línea y 50 recibieron Eltrombopag en segunda línea. El 69,8% de pacientes tratados con esteroides alcanzaron remisión completa, comparado con 80% del grupo de Eltrombopag. El 64% de los pacientes con Eltrombopag lograron respuesta completa, 24% tuvieron respuesta parcial y 12% tuvieron enfermedad estable.

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Conclusiones: *Eltrombopag es un tratamiento seguro con alta proporción de respuestas en pacientes sin antecedentes de esplenectomía y sin el uso combinado de esteroides. Esto sugiere que podría utilizarse como primera línea de tratamiento.*

Palabras clave: *Corticoesteroides. Eltrombopag. Trombocitopenia inmune. Manejo. Respuesta completa.*

Introduction

Primary thrombocytopenia immune (PTI) is a disorder characterized by the progressive destruction of platelets through the formation of antibodies on the various glycoproteins (GP IIb/IIIa) of the platelet membrane^{1,2}. According to its evolution, it can be divided into PTI of recent diagnosis (< 3 months), persistent (3-12), and chronic (> 12 months), requiring different strategies of treatment at each stage³. Its diagnostic remains of exclusion, with accurate family history being critical, along with a blood smear analysis and the ruling out of other secondary causes (immunological, neoplastic)⁴. Both the approach and the handling have changed significantly in the past decade, putting more value into the asymptomatic thrombocytopenia, as well as the risk of death from severe thrombocytopenia, going from the steroids and the splenectomy, and up to the inclusion of monoclonal antibodies (rituximab), analogs of the Thrombopoietin Receptor Agonists (TPO) receptor (romiplostim, Eltrombopag), and the inhibitors of splenic tyrosine kinase (Fostamatinib) to the different lines of treatment^{5,6}.

At present, steroids persevere as first-line treatment; both prednisone (PDN) (1 mg/kg/day without exceeding 80 mg/day) and dexamethasone (HD-DXM 40 mg for 4 days, three cycles maximum) are the most used steroids with a response between 60% and 80%⁷, while the usage of methylprednisolone pulses has been substituted due to a lack of controlled trials. Matschke et al. compared both strategies Prednisone (PDN) 1-2 mg/kg/day for 2-4 weeks versus dexamethasone 0.6 mg/kg/day for 1-4 days), identifying that the response (counts > 50 × 10³/μL) was registered in a 100% of both groups, but with a more prolonged response in the treatment with dexamethasone (77% vs. 22%)⁸. Wei et al. evaluated the effect of HD-DXM (40 mg/d for 4 days) compared to the effect of prednisone, identifying that the group who received DXM presented a higher early response (82.1%), with a faster response time compared to that of PDN⁹. During a retrospective study of data in the real world (n = 699), Wang et al. carried out the same comparison, obtaining a similar response (88.56% vs. 86.51%, p = 0.462) between both groups but remaining faster with the patients on DXM (3 days vs. 5 days, < p ≤ 0.001), considering this a safer and more tolerable option¹⁰. This suggests that the use of DXM must be

taken into consideration in individuals with very low counts. Still, its superiority above PDN remains controversial, especially with the long-term results¹¹. The second-line treatment has also evolved since the inclusion of anti-CD20 therapies (rituximab) and TPO analogs (Eltrombopag, romiplostim), acting as a bridging strategy toward a splenectomy or as maintenance¹².

Eltrombopag is an oral thrombopoietin receptor agonist that stimulates the TPO signaling by stimulating the production of functional platelets; the effective dosage was determined to be 50 mg; however, when the counts of platelets do not reach values over 50 × 10³/μL, it can be increased to 75 mg¹³. Cheng et al., during the RAISE study (Eltrombopag vs. placebo in chronic immune thrombocytopenia), found a higher response in comparison to the placebo group (79% vs. 28%) and a lower proportion of cases that required a rescue scheme (18% vs. 40%)¹⁴. The response time varies, but in general, the increase of platelets can be observed around the 15th day of treatment with a dose of 50 or 75 mg¹⁵. In contrast to steroids, eltrombopag is considered a tolerable drug. Still, it requires monitoring liver function and cell counts due to the risk of fibrosis or thrombosis¹⁶.

In the cases where first-generation agonists (romiplostim, Eltrombopag) fail, new analogs are available, such as Avatrombopag (93% of responses > 50 × 10³/mcl) or fostamatinib (Syk inhibitor), as sequential treatment in cases of failure^{17,18}. Few trials consider the use of Eltrombopag as a first-line treatment, especially to reduce the adverse events associated with steroids. Zhang et al. evaluated in a small group (n = 50) the combination of Eltrombopag (25-75 mg) plus dexamethasone (40 mg for 4 days, every 4 weeks) as first-line treatment to keep a response above 50 × 10³/μL at 6 months of the treatment: from the 46 cases that could be analyzed, 56.5% (n = 26) sustained the response with only two relapses¹⁹. In Mexico, this protocol (Eltrombopag 50 mg on days 5-32, dexamethasone 40 mg on days 1-4) was analyzed in 12 patients with recently diagnosed PTI. After day 33, a response was obtained in all cases (> 30 × 10³/μL), maintaining this response in 50% of the cases for over 6 months²⁰.

In our country, Mexico, steroids are used as first-line treatment, and Eltrombopag has been incorporated into therapeutic approaches in recent times. The study's

principal objective was to evaluate the response to different types of steroids as first-line treatment and the effectiveness of Eltrombopag as a second-line scheme. Meanwhile, the secondary objective was identifying risk factors associated with the treatment's prognostic response.

Materials and methods

A retrospective, observational study was conducted based on the clinical records of patients diagnosed with PTI between 2018 and 2023 at Hospital General de México, "Dr. Eduardo Liceaga," in Mexico City.

Every case considered to be PTI was included in the study, except those associated with autoimmune diseases (lupus erythematosus, antiphospholipid antibodies syndrome, rheumatoid arthritis), pregnancy, or lymphoproliferative diseases (lymphoma, myeloma, chronic lymphocytic leukemia). Every case within the first-line treatment initiated steroid therapy, excluding the cases that were combined with intravenous immunoglobulin or rituximab.

Treatment protocol

The clinical records of patients considered to be first-line based on steroids were reviewed. This included cases treated with prednisone (1-2 mg/kg/day), dexamethasone (40 mg/day, for 4 days, 1-3 cycles), or methylprednisolone pulses (1 g, intravenous, every 24 h, for three doses). In the cases of second-line treatment, the response to a 50 mg dose of Eltrombopag was evaluated, and whether it required an increase in dosage. The response was considered appropriate to the platelet count at 4 weeks of treatment.

The response in both lines of treatment was evaluated with the platelet count achieved during the first 4 weeks of the treatment. A global response for the first and second lines was considered when the platelet count was higher than $50 \times 10^3/\mu\text{L}$. The responses were also categorized as complete response (CR) when the platelet count was over $100 \times 10^3/\mu\text{L}$, partial response (PR) with a platelet count within $30\text{-}100 \times 10^3/\mu\text{L}$, and stable disease when the platelet count was under $30 \times 10^3/\mu\text{L}$ (without hemorrhage) and absence of response when the platelet count was persistently under $10 \times 10^3/\mu\text{L}$.

Statistical analysis

The demographic characteristics of the study were presented using median (range) for quantitative variables and cases (n, %) for categorical variables. Non-parametric

analysis was used for every variable since they did not follow a normal distribution according to the Shapiro-Wilk test. The difference between the groups was calculated using a Mann-Whitney U test for the quantitative variables and Chi-squared tests for the categorical variables. To determine the relationship between the main variables and the main outcomes (relapse and platelet count failure), we calculated the odds ratio. We established a $p < 0.05$ as a statistical difference. We conducted all statistical analyses using the SPSS (SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp) software version 25 and generated figures using GraphPad Prisma version 7.

Ethical considerations

As per the second title of the General Health Law on Health Research, specifically in Chapter I, article 17, the research study poses no risk to the human patient. The researchers involved in the study confirm that all ethical aspects of privacy and confidentiality have been met while dealing with retrospective information. In addition, the information gathered will be solely used for academic and research purposes. It is also important to note that the researchers involved in this study have no economic, pharmaceutical, political, or social interest in said research.

Results

Two hundred and forty-two patients were studied; 192 were considered for first-line treatment, and 50 received Eltrombopag as second-line therapy. Most patients were women ($n = 147$, 60.7%) with an average age of 40 (ranging from 17 to 86 years old). No significant differences were found in age between both groups (39 years vs. 41 years, $p = 0.502$), nor in the distribution by gender ($p = 0.486$, CI of 95%). In terms of clinical features, 54.5% ($n = 132$) of the patients presented some form of hemorrhagic event, with cutaneous purpura (33.1%) and mucous purpura (21.5%) as the most common ones. A higher proportion of hemorrhagic events was observed in patients treated with steroids in comparison with those who received Eltrombopag (65.2% vs. 34.8%, $p = 0.000$, CI of 95%). About 32.6% of the cases presented comorbidities, more frequent in patients over 60 (67.6%). When analyzing general blood cell counts, a hemoglobin average of 12.9g/dL (ranging from 3.4 to 18.4 g/dL) was found, as well as a leukocyte mean of $8.5 \times 10^3/\mu\text{L}$ (ranging from 1.1 to $27 \times 10^3/\mu\text{L}$), $6.0 \times 10^3/\mu\text{L}$ for neutrophils (ranging from 0.8 to $25.2 \times 10^3/\mu\text{L}$), $1.8 \times 10^3/\mu\text{L}$ for lymphocytes (ranging

Table 1. Demographic characteristics of the study population

Outcomes	Steroids (n = 192)	Eltrombopag (n = 50)	p-value
Gender (M:F)	76:116	19:31	0.486
Age (years)	39.85 ± 16.47	41.62 ± 16.56	0.502
Age			
< 40 years	103 (53.6%)	25 (50.0%)	0.888
40-60 years	62 (32.3%)	17 (34.0%)	
> 60 years	27 (14.1%)	08 (16.0%)	
Bleeding			
Absence	106 (55.2%)	04 (8.0%)	0.000
Presence	86 (44.8%)	46 (92.0%)	
Purpura			
Absence	106 (55.2%)	04 (8.0%)	0.000
Mucose	28 (14.6%)	24 (48.0%)	
Skin	58 (30.2%)	22 (44.0%)	
Hemoglobin (mg/dL)	12.90 (3.40-18.40)	13.12 (7.00-17.90)	0.070
WBC ($\times 10^3/\mu\text{L}$)	7.50 (1.10-27.00)	8.55 (4.60-24.20)	0.191
Neutrophils ($\times 10^3/\mu\text{L}$)	4.75 (0.80-25.20)	5.75 (2.70-21.80)	0.081
Lymphocytes ($\times 10^3/\mu\text{L}$)	1.70 (0.00-9.70)	1.65 (0.40-3.90)	0.478
NLI	2.56 (0.20-48.50)	3.55 (1.35-18.00)	0.081
Creatinine (mg/dL)	0.70 (0.00-2.70)	0.70 (0.30-1.80)	0.255
Bilirubin (mg/dL)	0.70 (0.00-4.57)	0.70 (0.20-1.50)	0.976
AST (mg/dL)	26.00 (0.00-271.00)	18.00 (7.00-104.00)	0.004
ALT (mg/dL)	24.00 (0.00-499.00)	21.50 (8.00-138.00)	0.293
Steroids			NA
Dexamethasone	52 (27.1%)		
Methylprednisolone	97 (50.5%)		
Prednisone	43 (22.4%)		
Platelets ($\times 10^3/\mu\text{L}$)	5.00 (0.70-75.00)	7.00 (1.00-19.00)	0.229
Platelets response			
< 10 no response	07 (3.6%)	00 (0.0%)	0.004
10-30	24 (12.5%)	06 (12.0%)	
30-100	90 (46.9%)	12 (24.0%)	
>100	71 (37.0%)	32 (64.0%)	

The Mann-Whitney U test was used for non-parametric variables and is expressed in median (range), and the Chi-square test was used for qualitative variables and is expressed in absolute values (%). Statistical significance was considered with a p-value < 0.05. M: male; F: female; WBC: White Blood Cell Count; NLI: Neutrophil/Lymphocyte Index; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

from 0.1 to $9.7 \times 10^3/\mu\text{L}$), and an average neutrophile to lymphocyte ratio of 4.6. No significant differences were found in the counts between the first-line treatment and Eltrombopag. The general characteristics and the laboratory characteristics are detailed in [table 1](#).

Response to the treatment

The average platelet count before starting the treatment was $9.6 \times 10^3/\mu\text{L}$, with most cases (72.3%)

presenting counts below $10 \times 10^3/\mu\text{L}$. No significant differences were observed in terms of severity between both types of treatment. Nevertheless, the proportion of cases with severe thrombocytopenia was slightly higher in the group treated with Eltrombopag (80% vs. 70.3%), while, in terms of higher counts, a higher number of patients in the first-line group were found (27.6% vs. 20% for counts between 11 and $50 \times 10^3/\mu\text{L}$ and 100% vs. 0 in counts above $51 \times 10^3/\mu\text{L}$) ([Fig. 1](#)).

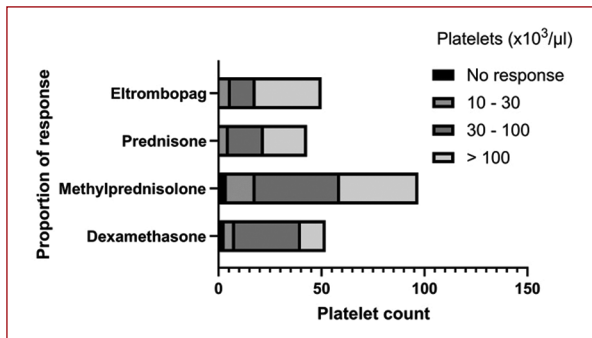


Figure 1. The proportion of response according to first-line (steroids) and second-line (Eltrombopag) treatment.

First-line steroid treatment

From the 192 patients treated as first-line, 27.1% ($n = 52$) received high doses of dexamethasone, 50.5% ($n = 97$) received pulse intravenous methylprednisolone, and 22.4% ($n = 43$) were treated with prednisone. Regarding the response to the treatment (count above $50 \times 10^3/\mu\text{L}$), 69.8% of the patients treated with steroids as first-line reached this goal, compared with the 80% treated with Eltrombopag. A higher proportion of CRs was observed in the cases treated with Eltrombopag (64% vs. 37%), as well as a lesser proportion of cases without a response (3.6% vs. 0%), statistically relevant differences ($p = 0.004$, CI of 95%).

Second-line treatment with eltrombopag

From the 50 patients treated with Eltrombopag, 80% ($n = 40$) presented a platelet count below $10 \times 10^3/\mu\text{L}$ at the beginning of the treatment, and 80% ($n = 40$) reached counts above $50 \times 10^3/\mu\text{L}$ platelets. From the total, 64% ($n = 32$) was considered as having a CR, 24% ($n = 12$) had a PR, and 12% ($n = 6$) presented a stable disease without any patient presenting counts below $10 \times 10^3/\mu\text{L}$ after the treatment. The average time to achieve a response was 18.8 days (3-80 days), which was higher than in first-line treatment (9.7 vs. 18.8 days, $p = 0.000$, CI of 95%).

Treatment response factors

Various factors were analyzed that could have an influence on relapse and platelet count failure, including having age above 40 years, gender, the presence of hemorrhages, the neutrophil/lymphocyte index, $< 10 \times 10^3/\mu\text{L}$ and $< 30 \times 10^3/\mu\text{L}$ platelets, and the type

of steroid administered at first-line treatment. No significant differences were found in the dependent variables for the resolution of relapse. Furthermore, having age above 40 years was found to be a risk factor (OR: 1.77, 1.01 - 3.13 CI95%; $p < 0.05$) for platelet count failure (Fig. 2).

Discussion

The treatment for PTI has evolved since the introduction of more effective, long-lasting strategies with fewer adverse events. Due to its cost and easy access, steroids remain the first-line treatment, with prednisone and dexamethasone as the treatments more frequently used. In our study, the steroids used more frequently were prednisone, dexamethasone, and methylprednisolone; the latter is used more frequently, in particular in the emergency department. When analyzing the first-line response, the speed of response was greater in the DXM group than in the PDN group. Still, when those responses were analyzed, the cases with PDN presented a higher proportion of favorable responses than DXM and Methylprednisolone. Mithoowani et al., during a meta-analysis ($n = 533$), which examined the responses ($> 30 \times 10^3/\mu\text{L}$) based on two therapeutic approaches (PDN vs. DXM), identified that the response to DXM was faster (response at 14 days, 79% vs. 59%, RR 1.22, 95% CI, $p = 0.048$), but the ratio of responses at 6 months was similar (54% vs. 43%, RR 1.16, 95%; $p = 0.44$)²¹. Since a significant proportion of the cases were treated at the emergency department, the use of methylprednisolone was a common practice.

This steroid was selected due mainly to the experience with Evans syndrome, where immune thrombocytopenia combines with hemolytic anemia by warm antibodies²². Finally, most of the responses in the MPD group were PR ($30\text{-}50 \times 10^3/\mu\text{L}$), which does not justify its usage instead of other types of steroids.

Among the aspects of DXM, as opposed to PDN, is that it does not require a dose reduction since the treatment with PDN must not go beyond 8 weeks due to the risk of long-term complications^{23,24}. Still, among the considerations related to DXM usage, one must consider its interactions with other drugs, since DXM is a P-glycoprotein and CYP3A4 substrate, which might produce a heterogeneous response in various populations²⁵.

When analyzing the second-line group of patients, the dose of initial Eltrombopag was 50mg, achieving counts over $50 \times 10^3/\mu\text{L}$ in 80% of cases without presenting

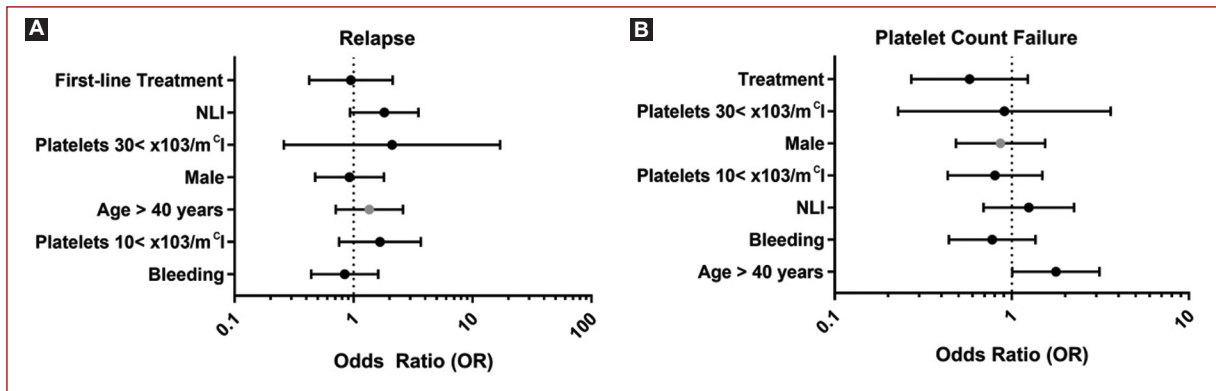


Figure 2. Forest plot on relapse (A) and platelet count failure (B).

treatment failure. These data are similar to the real-world data, where the general response to Eltrombopag was 94% (76% RC, 23% RP), which has recorded thrombosis as one of the adverse events of interest²⁶.

The second objective of the study was to identify some of the factors that could predict the response, both to the steroids as well as the use of Eltrombopag as second-line treatment (gender, age, blood cell counts); the results indicated that at an older age (over 40 years old), a lower ratio of patients achieves a response.

As recorded in our series, Yu et al. identified that age is a constant factor for the failure of response, along with high levels of ferritin or the presence of HbsAg²⁷. Other series have used the morphology of megakaryocytes (granularity, core distribution, and number) to predict sensitivity to steroids in patients of first-line treatment, and increased levels of TPO can also be associated with an early therapeutic failure^{28,29}. Regarding second-line treatment, a proportion of patients may still be resistant to the use of analogs of the TPO receptor. Still, it remains to be challenging to identify some of the factors which might predict this response. Still, when metabolized by isoenzymes belonging to the P450 cytochrome (CYP1A, CYP2C8), it can be subject to different interactions, which may affect its concentration³⁰. Despite this, the benefit is evident when analyzing the response in various clinical trials on using these analogs compared to monoclonal antibodies or placebos, making this the established election for patients with refractory immune thrombocytopenia³¹. To identify predictive factors for early response to steroids, the association of some accessible factors, such as the combination of different indices like the neutrophil-to-lymphocyte ratio, was analyzed without finding any significant association. This lack of

significant findings suggests that NLR, at least in isolation, may not be a reliable predictor of early steroid response. It highlights the complexity of inflammatory and immune-mediated processes and suggests that other factors, potentially in combination with NLR, need to be considered.

Finally, despite reaching a favorable response, the mortality rate in general is between 2 and 3 times higher than in the general population, mainly due to cardiovascular diseases (RR 1.5), infections (RR 2.4), or the association with different types of hematologic neoplasia (RR 5.4)³². Cardiovascular complications are of particular interest since they present between 1 and 2% during the first year of the treatment, especially with the chronic use of steroids, and it is independent of the platelet count³³. Paradoxically, the risk of venous thrombosis is also higher, especially in those who received high doses of steroids or who underwent splenectomy³⁴. In terms of arterial territory, Patel et al. described the characteristics of the patients with immune thrombocytopenia who had a myocardial infarction, where, similar to the general population, the male gender was the most affected; some factors like female gender, having an age above 80 years, the need for transfusion support, or a higher number of comorbidities were associated with a higher mortality rate³⁵.

These complications have made it necessary to reconsider the order of the treatment, as well as the use of a lower dose of the steroid with a lesser exposure time, due to the high proportion of complications.

We can conclude that steroids remain an efficient first-line treatment, especially when using PDN or DEX; in terms of second-line treatment, Eltrombopag is a safe treatment with a higher proportion of responses in patients without a history of splenectomy, and without

the joint use of the steroid, which suggests that it might also be an option for first-line treatment.

Institutional review board statement

The study was conducted following the Helsinki Declaration and approved by the Biosecurity, Ethics and Research Committee of "Hospital General de México "Dr. Eduardo Liceaga," under protocol number (DECS/JPO-CT-1986-2023).

Authors' contribution

Conceptualization, M.S.C., and J.A.E.; methodology, A.G.G.R., M.S.C., and C.R.P.; software, M.S.C., and J.A.E.; validation, C.R.P., C.M.M., and A.G.G.R.; formal analysis, A.G.G.R., and C.R.P.; investigation, A.G.G.R., and C.R.P.; resources, C.R.P. and C.M.M.; data curation, A.G.G.R., M.S.C., and J.A.E.; writing-original draft preparation, A.G.G.R., and M.S.C.; writing-review and editing, C.R.P., and C.M.M.; visualization, C.R.P., and C.M.M.; supervision, C.R.P.; project administration, C.R.P., and C.M.M.; funding acquisition, C.R.P., and C.M.M. All authors have read and agreed to the published version of the manuscript.

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Conflicts of interest

The authors declare no conflicts of interest.

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 no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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 or for the creation of images, graphics, tables, or their corresponding captions.

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