

Estimative of costs of two therapeutic schemes for aplastic anemia among young individuals

Estimativa de custo de dois esquemas terapêuticos para aplasia de medula óssea em indivíduos jovens

Estimación del coste de dos esquemas terapéuticos para la aplasia de la médula ósea en jóvenes

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Abstract

Introduction: Aplastic anemia (AA) is the deficiency of the production of blood cells, with pancytopenia and hypocellular marrow as a result. Eltrombopag® (EPAG), a synthetic thrombopoietin mimic, showed improvement in bone marrow, CD34 and blood precursor cell counts. Today, it is indicated as first-line therapy, in addition to Immunosuppressive Therapy (IST) with cyclosporine and horse Antithymocyte Globulin (ATG). The aim of this study is to compare costs and results of the main current therapeutic schemes for AA among young individuals. **Method:** This is a study to estimate costs and results of a therapeutic scheme using EPAG associated with IST and the management of complications in comparison with standard therapy. The protocols used were those of the Ministry of Health and the scheme indicated in the literature for the EPAG. As a basis for calculation, a typical patient was simulated, who would be followed up by a pediatric hematology service in Sergipe, which works as part of the Unified Health System. **Result:** The cost of Cyclosporine + rabbit ATG treatment for 6 months, based on patient weight, was US\$4500. The cost of Cyclosporine + rabbit GAT + EPAG treatment for 6 months was US\$182,000. **Conclusion:** It is concluded, therefore, that drug therapy with EPAG increases the cost of treatment by 40 times. Several studies, however, point to clinical and laboratory gains and increased response rates to the proposed therapy, thus contributing to a better quality of life for a pediatric patient with AA.

Keywords: Anemia, aplastic; Economic evaluation; Pancytopenia; Adolescent; Child.

Resumo

Introdução: A Aplasia de Medula (AM) consiste em deficiência na produção de células sanguíneas, com pancitopenia e medula hipo celular como resultado. O Eltrombopag® (EPAG), mimetizador sintético da trombopoietina, mostrou melhora nas contagens de células medulares, CD34 e precursoras sanguíneas. Hoje, é indicado como primeira linha, em adição à Terapia Imunossupressora (TIS) com ciclosporina mais Globulina Antitímocítica (GAT) de cavalo. O objetivo deste estudo é comparar custos e resultados das principais propostas terapêuticas atuais para a AM em indivíduos jovens. **Método:** Trata-se de estudo para estimar custos e resultados de uma proposta terapêutica utilizando o EPAG associado à TIS e o manejo das complicações em relação à terapia padrão. Os protocolos utilizados foram o do Ministério da Saúde e o esquema indicado na literatura para o EPAG. Como base para cálculo, foi simulado um paciente típico, que seria acompanhado por um serviço de hematologia pediátrica em Sergipe, que funciona como parte do Sistema Único de Saúde. **Resultado:** O valor do tratamento com Ciclosporina + GAT de coelho durante 6 meses, com base no peso do paciente, foi de 4500 dólares americanos. O valor do tratamento com Ciclosporina + GAT de coelho + EPAG durante 6 meses foi de 182000 dólares americanos. **Conclusão:** Conclui-se, portanto, que a terapia medicamentosa com o EPAG eleva em 40 vezes o custo do tratamento. Diversos estudos, entretanto, apontam o ganho clínico, laboratorial e o aumento das taxas de resposta à terapia proposta, concorrendo, assim, para melhor qualidade de vida de um paciente pediátrico com AM.

Palavras-chave: Anemia aplástica; Avaliação econômica; Pancitopenia; Adolescente; Criança.

Resumen

Introducción: La aplasia medular (AM) consiste en una deficiencia en la producción de células sanguíneas, resultante en pancitopenia y médula hipocelular. Eltrombopag® (EPAG), un imitador sintético de la trombopoyetina, mostró una mejora en los recuentos de células precursoras sanguíneas, CD34 y de la médula ósea. Hoy, está indicado como primera línea, además de la Terapia Inmunosupresora (TIS) con ciclosporina más Globulina Antitimocitaria de caballo (GAT). **Objetivo:** comparar costes y resultados de las principales propuestas terapéuticas actuales para la AM en jóvenes. **Método:** Este es un estudio para estimar costos y resultados de una propuesta terapéutica utilizando EPAG asociado a TIS y el manejo de complicaciones en relación a la terapia estándar. Los protocolos utilizados fueron los del Ministerio de Salud y el esquema indicado en la literatura para la EPAG. Como base de cálculo, se simuló un paciente tipo, que sería acompañado por un servicio de hematología pediátrica de Sergipe, que funciona como parte del Sistema Único de Salud. **Resultado:** El valor de Ciclosporina + GAT de conejo durante 6 meses, basado en el peso del paciente, fue de US\$4500. El valor de Ciclosporina + GAT de conejo + EPAG durante 6 meses fue de US\$182.000. **Conclusión:** Se concluye que la terapia farmacológica con EPAG aumenta en 40 veces el coste del tratamiento. Varios estudios apuntan a ganancias clínicas y de laboratorio y mayores tasas de respuesta a la terapia propuesta, contribuyendo así a una mejor calidad de vida para un paciente pediátrico con AM.

Palabras clave: Anemia aplásica; Evaluación económica; Pancitopenia; Adolescente; Niño.

1. Introduction

Marrow Aplasia or Aplastic Anemia (AA) is the deficiency of the production of blood cells by the bone marrow and can be clinically classified as two levels: moderate and severe. Even though it has a low incidence, consequences can be catastrophic. Literature evidence point to an immunologic physiopathology to the AA, in which effector cells and cytokines destroy the youngest elements of the bone marrow, leading to pancitopenia and an “empty marrow” appearance. (Miguel et al., 2016; Usuki, 2016; Verghese, 2011)

For a long time, the therapeutic proposals for AA were Hematopoietic Stem Cell Transplantation (HSCT) or immunosuppressive therapies (IST), in addition to the treatment of infections, when they occur, and also blood transfusions. However, most cases are treated with options other than transplantation, whether due to low availability of compatible donors, older age, comorbidities, patient choice or lack of access. About the IST, what has been more effective is horse Antithymocyte Globulin (ATG) combined with cyclosporine, with good hematological response in 2/3 of patients. (Darrigo et al., 2019; Kako et al., 2020; Scheinberg, 2011; Usuki, 2016)

With scientific advancement, Eltrombopag® (EPAG), a synthetic mimic of thrombopoietin, has brought increased cell counts. EPAG is a pan-stimulating agent of the bone marrow, of the thrombopoietin receptor agonist class, that was developed for an immunity to thrombocytopenia. It promotes the increase of marrow cellularity, of CD34 cells and blood precursors. Due to the demonstrated success, EPAG is now indicated as a first line therapy, added to TIS with cyclosporine and horse ATG. (Huan Ng et al., 2021; Kuter, 2021; Scheinberg, 2021; Usuki, 2016)

Thus, the objective of this study was to compare costs and results of the main current therapeutic schemes for AA among young individuals.

2. Methodology

This is a study to estimate cost and results of a therapeutic proposal using a thrombopoietin receptor agonist associated with immunosuppressants and the management of complications in comparison to standard therapy. The treatment protocol used was that the one preconized at the Ministry of Health. It stipulates the use of 5 to 6 mg/kg/day of Cyclosporine for 1 year and rabbit ATG 2.5 mg/kg/day in 5-day cycles, with repetition allowed every 3 months, if there is no complete response to the initial cycle. Complete response (CR) is defined as the return to normal hemoglobin levels for the age group, neutrophils above 1,500/mm³ and platelets above 150,000/mm³; the partial response (PR) is the suspension of the transfusion need, duplication of initial counts or normalization of at least one cell line. The lowest market price found for the products,

researched with the same presentation was included (Table 1). To calculate the EPAG incrementation cost, the regimen indicated in the literature was used: dose of 150 mg/day for 6 months. Non-medical and indirect costs and the fees of the professionals involved, were not evaluated. (Imada et al., 2021; Jie et al., 2021; Saúde, 2010)

A theoretical simulation of a typical patient was used as a basis for cost calculation, which would be followed up by a pediatric hematology service in the state of Sergipe, which is as part of Brazil's Unified Health System. Based on the literature, the typical patient is male, 14 years old, weighing 49 kg, without previous immunosuppressive therapy use, with a history of more than 20 blood transfusions, without family history of hematological disease. (Arcuri et al., 2020; Iftikhar et al., 2021; Organization, 2007)

Table 1 - Drugs, schemes and costs.

Drug	Dose	Treatment duration	Cost per dose (\$)
Cyclosporine	5-6 mg/kg/day	1 year with full dose	7.2
Rabbit ATG	2,5 mg/kg/day	5 days	647.74
Eltrombopag	150 mg/day	6 months	990.6

Source: Authors (2022).

One of the known models in cost-effectiveness studies is the Markov model, which considers both the use of resources and the outcomes and has been disseminated as a model of economic decision at the health sector. This study brings the initial step of using the complex Markov model. (Zhang et al., 2021)

3. Results and Discussion

The results were calculated using the dose for weight for the typical patient and are exposed at Table 2.

Table 2 - Total cost per scheme for a 6 months-duration treatment.

Standard therapy	Standard therapy + Eltrombopag
180 days x 7.2 \$	180 days x 7.2 \$
5 days x 647.74	5 days x 647.74
	180 days x 990.6 \$
Total: 4,534.7\$	Total: 182,842.7\$

Source: Authors (2022).

The calculated cost for treatment with the standard regimen (Cyclosporin + rabbit ATG), recommended by the Ministry of Health, based on the weight of the typical patient in question, was 4500 US dollars. The cost obtained for the typical patient was about 182 thousand US dollars for 6 months of treatment with Cyclosporine + rabbit ATG + Eltrombopag. The dose of EPAG used can be reduced every two months or more frequently, according to the hematological responses to the treatment, reducing the cost of the second regimen. If there is no response to the initial cycle of rabbit ATG, there is an additional cost of \$3238 per new cycle, which can be repeated up to twice in 6 months.

The present study simulated the costs and possible evolution of a pediatric patient with AA with the simulated characteristics described above. It was observed that the inclusion of EPAG multiplied the cost of treatment by 40, when considering only the cost of medications in the standard IST regimen.

A patient who does not go into remission remains dependent on transfusion, a greater number of hospitalizations and complications, a higher risk of death and a lower disease-free survival, with an impact on the entire health system and on the patient's quality of life.

The inclusion of EPAG in IST is associated with a significant increase of complete hematologic response in patients with severe AA. When compared to IST with ATG + cyclosporine only, Groarke et al observed a 7% higher CR; Fang et al, 10% higher; Jie et al, 30% higher. In a study carried out in Greece, among pediatric patients, the complete response reached 72.7% (almost 35% higher than the median response in previous studies with IST in children). Tremblay et al found a CR rate of 58.06% versus a 10% rate among the groups with and without EPAG, respectively. (Fang et al., 2021; Groarke et al., 2021; Jie et al., 2021; Tremblay et al., 2019)

As for disease remission, Fang et al described only one patient in the entire study who relapsed within 6 months, compared with none in the IST group; in the work by Jie et al, no relapse was observed within 2 years of observation, in addition to demonstrating an event-free survival in 78.6% of the cases using the EPAG. The difference in mean survival has not been shown to be statistically significant between the different studies. (Fang et al., 2021; Jie et al., 2021)

Despite there are known adverse effects after using EPAG, most are shown to be reversible and tolerable. In an American study, the most frequent effect was the elevation of liver enzymes. In China, jaundice with indirect bilirubin elevation was the most seen. In Japan, the most common adverse event was myalgia, followed by hyperbilirubinemia, which is resolved with EPAG dose reduction or brief interruption of the regimen. (Imada et al., 2021; Jie et al., 2021; Tremblay et al., 2019)

The adverse effects of EPAG bring additional cost to the system, as they are absent in the GAT + Cyclosporine group, but when compared to the adverse effects of this second group, the EPAG does not add a statistically significant cost. (Tremblay et al., 2019)

The costs for the IST with the addition of the EPAG are still an important obstacle to its acquisition by health services financed by the Unified Health System of Brazil. However, considering that the current regimen brings increased survival, reduced hospitalizations, transfusion independence and complete response rates faster and more frequently, it is evident that the application of EPAG brings much more than just economic costs. According to a study by Tremblay et al, the highest response rates with the EPAG reduce the costs of secondary therapies, hospital care and mortality. (Moraz et al., 2015; Tremblay et al., 2019)

This study has limitations due to: individual variations, such as infections, treatment tolerability and other interferences during hospitalization; and the fact that it is a study based on a controlled scenario, not being able, therefore, to cover all the real variables. This is an estimative of the costs of the two regimens, as it would be economically unfeasible to afford the medication in question for studies in our patients.

4. Conclusion

It is concluded that drug therapy that includes the thrombopoietin receptor agonist increases the cost of treatment by 40 times. Several studies, however, point to clinical and laboratory gains and increased response rates to the proposed therapy. Therefore, it is possible to consider that, despite the high costs, the EPAG would bring benefits such as reducing the number and duration of hospitalizations and increasing the rate of partial and complete remissions, thus contributing to a better quality of life for a pediatric patient with AA. Future studies may include the cost of other variables such as hospitalizations, transfusions and infections, so the total cost of the treatment is even closer to what happens daily with real patients.

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