

Matched adjusted indirect comparisons and artificial intelligence: complementary or competitors? About a case

Comparaciones indirectas ajustadas emparejadas e inteligencia artificial: ¿complementarios o competidores? A propósito de un caso

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Abstract

We proceeded to compare the efficacy and safety of two prophylactic treatments for severe hemophilia A in patients ≥ 12 years, efanesoctocog alfa and emicizumab, using both traditional adjusted indirect comparison methods (MAIC, matched adjusted indirect comparison) and the artificial intelligence tool ChatGPT4o, highlighting the importance of these studies due to the lack of direct comparisons between treatments in patients with hemophilia, a rare disease. Data from Phase III clinical trials are used: the XTEND-1 study for the efanesoctocog alfa and the HAVEN-3 study for emicizumab. The MAIC analysis concluded that efanesoctocog alfa was more effective than emicizumab in reducing bleeding episodes, with an improvement in joint health score. ChatGPT4o also highlighted the greater efficacy of efanesoctocog alfa, but noted the influence of sample size on the statistical significance and robustness of the results. In terms of cost, we proceeded to estimate what the unit cost of efanesoctocog alfa should be as or more efficient than emicizumab. Both treatments are shown to be safe and effective. In conclusion, MAIC and ChatGPT4o may be complementary assessment strategies and may help in the choice of treatment and can help in the choice of treatment. However, the therapeutic selection process is more complex and must consider additional factors, such as the additional factors, such as treatment convenience, patient preferences and clinical judgment.

Keywords: Adjusted matched indirect comparison. Artificial intelligence. Efanesoctocog alfa. Emicizumab. Annualized bleeding rate. Prophylaxis. Efficacy. Efficiency.

Resumen

Se procede a comparar la eficacia y la seguridad de dos tratamientos profilácticos para la hemofilia A grave en pacientes ≥ 12 años, el efanesoctocog alfa y el emicizumab, utilizando tanto métodos tradicionales de comparación indirecta ajustada emparejada (MAIC, matched adjusted indirect comparison) como la herramienta de inteligencia artificial ChatGPT4o, destacando la importancia de estos estudios debido a la ausencia de comparaciones directas entre tratamientos en pacientes con hemofilia, una enfermedad rara. Se usan datos procedentes de los ensayos clínicos de fase III: el estudio XTEND-1 para el efanesoctocog alfa y el estudio HAVEN-3 para el emicizumab. El análisis MAIC concluyó que el efanesoctocog alfa era más

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eficaz que el emicizumab en la reducción de los episodios de sangrado, con una mejora en la puntuación de salud articular. ChatGPT4o también destacó la mayor eficacia del efanesoctocog alfa, pero señaló la influencia del tamaño de la muestra en la significancia estadística y la robustez de los resultados. En términos de costes, se procedió a estimar cuál debería ser el coste unitario del efanesoctocog alfa para ser tanto o más eficiente que el emicizumab. Ambos tratamientos se muestran seguros y eficaces. En conclusión, MAIC y ChatGPT4o pueden ser estrategias de evaluación complementarias y pueden ayudar a la elección del tratamiento. Con todo, el proceso de selección terapéutica es más complejo y debe considerar factores adicionales, como la comodidad del tratamiento, las preferencias del paciente y el juicio clínico.

Palabras clave: Comparación indirecta ajustada emparejada. Inteligencia artificial. Efanesoctocog alfa. Emicizumab. Tasa anualizada de sangrado. Profilaxis. Eficacia. Eficiencia.

Introduction

One of the current issues in the treatment of hemophilia is the lack of head-to-head comparative studies between different options that compare patient populations with homogeneous characteristics¹. Such studies are often requested by health authorities¹, overlooking the fact that hemophilia is a rare disease, making it very difficult to achieve this homogeneity and comparisons. For some time now, indirect adjusted comparisons² (MAIC, matched adjusted indirect comparison) of treatments from different trials have emerged. These analyses can be biased due to differences in patient populations, sensitivity to modeling assumptions, and varying outcome definitions across trials. In this regard, the incorporation of individual patient data from one treatment trial into these indirect comparisons could address various limitations when these analyses rely exclusively on aggregated data. This could reduce observed differences between trials and provide appropriate comparative evidence to guide, for example, treatment selection. There are numerous examples of MAIC in the field of hemophilia^{3,4}, including in gene therapy⁵. On the other hand, artificial intelligence (AI) is a powerful tool not only for designing new treatments, analyzing outcomes, or developing predictive models, among other uses⁶, but also for performing indirect comparative analyses between different treatments under human supervision. AI has the potential to replace MAIC in certain areas, especially in terms of data analysis, automation, and speed. However, it is most likely that AI will be used to improve and complement existing MAIC methods, creating hybrid systems that leverage the best of both methodologies.

The objective of this study is to evaluate the applicability of generative AI (ChatGPT^{4.0}) in comparing two treatments in patients aged ≥ 12 years with hemophilia A, without inhibitor: efanesoctocog alfa (XTEND-17 study) and emicizumab (HAVEN-3 study)⁸. We will then compare the results obtained with the MAIC results

between these two treatments, conducted by Álvarez Román et al.⁹.

Method

We compared the results of the phase III studies on efanesoctocog alfa⁷ and emicizumab⁸ for prophylaxis in patients with severe hemophilia A ($F8 \leq 1\%$) without inhibitor, aged ≥ 12 years. Data were obtained from the respective studies and compared using ChatGPT4.0. The results obtained were then compared with the MAIC results⁹ between the two treatments published in 2023. Additionally, a simulated efficiency evaluation of both treatments was conducted, considering costs and the reduction of the annualized bleeding rate (ABR), including only patients in both studies who were previously on FVIII prophylaxis (Group A, XTEND-1, for efanesoctocog alfa, and Group D, HAVEN-3, for emicizumab).

Results

Efanesoctocog alfa inaugurates a new class of FVIII with an extended ultra-long half-life. It has been approved by the European Medicines Agency (EMA) for the prophylaxis and treatment of bleeding episodes in patients with hemophilia A, without inhibitor, both adults and children¹⁰. It is currently awaiting reimbursement pricing in Spain. The XTEND-17 study is an open-label, multicenter phase III study evaluating weekly prophylaxis with 50 IU/kg of efanesoctocog alfa in 159 patients aged ≥ 12 years with severe hemophilia A ($F8 \leq 1\%$), without inhibitor. The mean age was 35.4 ± 15.1 years, with 81% of patients aged 18 to 64 years, and 99% of participants were men. Patients were categorized into 2 groups: Group A ($n = 133$), which received weekly prophylaxis with efanesoctocog alfa (50 IU/kg) for 52 weeks, and Group B ($n = 26$), which first received on-demand treatment with efanesoctocog alfa for 26 weeks and then switched to weekly prophylaxis for another 26 weeks. The results (Table 1) show

Table 1. Results of the X-TEND-1 Study (Group A)⁷

	Group A (n = 133)
Median ABR (IQR)	0 (0-1.04)
Estimated Mean ABR (CI)	0.71 (0.52-0.97)
Previous ABR	2.96
Post-treatment ABR	0.69
ABR Reduction	77% (p < 0.001)

CI: confidence interval; IQR: interquartile range; ABR: annualized bleeding rate.

a 77% inpatient reduction in ABR for Group A, while in Group B, 97% of the bleeding episodes were resolved with a single injection. A total of 80% of patients from Group A and 85% from Group B had no spontaneous bleeds, and the percentages without joint bleeds were 96% and 81%, respectively. Additionally, after a 50 IU/kg dose, patients maintained normal or near-normal FVIII levels (> 40%) for 4 days, and 15% on day 7.

Significant improvements were also reported in physical health, reduced pain intensity, and joint health (resolution of target joints, slight improvement in Hemophilia Joint Health Status [HJHS] score). Regarding safety, no development of FVIII inhibitors was reported. The adverse event profile was acceptable, with 77% reporting at least one adverse event, and only 15 patients (9%) reporting serious adverse events. Four patients had transient anti-drug antibodies.

Emicizumab is the first bispecific monoclonal antibody capable of mimicking FVIII function in the prothrombinase complex. It has been approved by the EMA¹¹ for bleeding prophylaxis, but not for treatment, in patients with hemophilia A with inhibitor, severe hemophilia A (F8 ≤ 1%) without inhibitor, and moderate hemophilia A (F8 1% up to 5%) with a severe bleeding phenotype. The HAVEN-3⁸ is an open-label, multicenter phase III trial including 152 patients aged ≥ 12 years with severe hemophilia A (F8 ≤ 1%) without FVIII inhibitor. Patients were categorized into four groups (Table 2). Group D included 48 patients who, after completing 6 months of FVIII prophylaxis, switched to emicizumab at a dose of 1.5 mg subcutaneously once a week.

In terms of safety, a total of 543 adverse events were reported in 127 of the 150 participants. The most frequent adverse event was injection site reactions (in 38 participants [25%]). No thrombotic events or thrombotic microangiopathy were observed. Co-exposure to FVIII doses ≥ 50 IU/kg for 24 hours or more was not associated with serious adverse events. Due to its higher

affinity for activated FIX and FX, activated FVIII competes with emicizumab at high concentrations, so no synergy occurs between the two products at high FVIII concentrations^{8,12}. No FVIII inhibitors were reported. One controversial aspect is the equivalence in terms of thrombin generation vs FVIII. For example, Kizilcok et al.¹³ estimated that in patients with severe hemophilia A with inhibitor, the thrombin generation potential of emicizumab is equivalent to F8 levels ≥ 10%.

Finally, in 2023, Álvarez Román et al.⁹ reported the results of a MAIC between efanesoctocog alfa and emicizumab at the International Society on Thrombosis and Hemostasis (ISTH) Congress. They used data from the XTEND-1 phase III study (Group A, weekly prophylaxis, n = 133) and results from Group D of the HAVEN-3 study (n = 48). They matched characteristics such as age, race, previous regimen, and target joints before entering the study. They concluded that the reduction in ABR for any bleed, treated bleed, and treated joint bleed was significantly lower with efanesoctocog alfa vs emicizumab, along with a lower incidence of spontaneous bleeds with efanesoctocog alfa, although this was not statistically significant. They concluded that efanesoctocog alfa reduces bleeding episodes more effectively than emicizumab does, with improved HJHS scores, likely associated with higher FVIII levels (> 40%) for most of the week and a larger area under the curve.

Discussion

Both phase III studies demonstrated that both efanesoctocog alfa and emicizumab are safe and effective for the prophylaxis of bleeding in patients with severe hemophilia A, significantly reducing bleeding rates and improving the patients' quality of life. The MAIC results assert that efanesoctocog alfa improves upon the already high efficacy of emicizumab. ChatGPT4.0 concludes, based on the results of Table 3, that the difference in sample size (133 vs 48) may influence statistical significance and the robustness of results. A larger sample size affects statistical precision by providing more accurate estimates and greater statistical power. This, on the one hand, reduces variability, and on the other, increases the power to detect statistically significant differences. Furthermore, the difference in sample size can introduce biases if not properly adjusted, and in this regard, the MAIC is more accurate because it considers various patient characteristics to adjust for differences and improve comparability. Nevertheless, the MAIC also has limitations related to sample size, especially when dealing with adjustments for small sample sizes.

Table 2. Key characteristics of the HAVEN-3 trial⁸

	Median ABR (IQR)	Mean ABR (CI)	Patients without bleeds (%)	Patients without treated joint bleeds (%)	Inpatient bleed reduction (%)
Group A: emicizumab 1.5 mg/kg weekly SC (n = 36)	0 (0.0-2.5)	0.6 (0.0-3.9)	67	69	-
Group B: emicizumab 3.0 mg/kg every 2 weeks SC (n = 35)	0 (0.0-1.9)	1.6 (0.0-4.0)	89	77	-
Group C: no prophylaxis (control) (n = 18)	40.4 (25.3-56.7)	46.9 (26.1-73.9)	22	28	-
Group D: emicizumab 1.5 mg/kg weekly in patients previously on FVIII prophylaxis (n = 48)	0 (previous 1.8)	1.5 (previous 4.8)	54 (previous 40)	-	68 vs. previous FVIII prophylaxis (p < 0.001)

CI: confidence interval; IQR: interquartile range; ABR: annualized bleeding rate.

Table 3. Data considered by ChatGPT4.0 for analysis (taken from phase III clinical trials)^{7,8}

	Efanesoctocog alfa (Group A, n = 133) 50 IU/kg weekly	Emicizumab (Group D, n = 48) 1.5 mg/kg weekly
Pre-treatment ABR	2.96	2.9
Post-treatment ABR	0.69	1.5
ABR reduction	2.27 (77%)	1.4 (48%)

ABR: annualized bleeding rate.

Additionally, although the 2 studies show positive results and are methodologically robust, differences in population, duration, and study design limit a direct and straightforward comparison. Recommending one drug over the other based on these results depends on several clinical and practical factors, including safety, efficacy, patient preferences, ease of use, and other individual considerations. For patients prioritizing the maximum reduction of bleeding events and improvements in physical and joint health, efanesoctocog alfa might be the preferred option due to its greater reduction in the ABR (77% vs 68% with emicizumab vs prior FVIII prophylaxis) and its additional benefits; this reduction is considered significant in the MAIC. For patients prioritizing the convenience of subcutaneous administration (less invasive) and similar efficacy, emicizumab, with weekly or biweekly prophylaxis regimens from the trial, may be the preferred option, although it is essential to remember the importance of personalization and to consider both patient preferences and the clinician's judgment.

A frequently debated aspect is considering drug selection based on efficiency. The MAIC⁹ does not directly address the cost of treatment or efficiency, but it concludes that efanesoctocog alfa provides greater efficacy in terms of ABR reduction. At present, efanesoctocog alfa does not yet have an official retail price (RP) from the Spanish Ministry of Health. Thus, ChatGPT4.0 was asked to estimate the unit cost at which treatment with efanesoctocog would be as efficient or more efficient than emicizumab. For emicizumab, a RP of €32/mg was considered (source: [https://www.farmaceuticos.com/botplus/]). ChatGPT4.0 performed 2 estimates for an average patient of 70 kg. The second scenario assumes that all bleeding events occurring in patients on prophylaxis with either product are treated with efanesoctocog alfa, assuming that 97% of bleeds only require one dose of efanesoctocog alfa at 50 IU/kg for resolution⁸. In the first scenario (Appendix 1), for efanesoctocog alfa to be considered a more cost-efficient option in terms of cost per ABR reduction vs emicizumab, the cost per IU should be < €0.675/IU. If the cost per bleeding event is also considered in the calculation under the stated scenario, the unit cost should be < €0.647 €/IU (Appendix 2). Clearly, these are simulations based on the results of clinical trials that are not directly comparable and based on a simulation for an average patient, but they provide some guidance. An interesting parameter to incorporate would be thrombin generation capacity, as the current discussion focuses on "normalization of hemostasis"¹⁴, a concept intrinsically related to the ability to generate thrombin. The normalization of hemostasis, as a concept, should include the aspiration to enable people to

lead as normal a life as possible, free from the limitations imposed by hemophilia. If it is desired that this item directly influences the efficiency calculation, additional data would be needed on how this capacity translates into a specific reduction in ABR compared to FVIII levels. ChatGPT4.0 logically states that this could require a more detailed pharmacokinetic-pharmacodynamic model, which has not been considered in the simplified calculations provided. Therefore, current calculations focus on costs and ABR reduction, as presented in clinical studies. Finally, ChatGPT4.0 recommends that, to ensure a fair and robust comparison, it would be ideal to increase the sample size in the smaller group (if possible), make sure that patient characteristics are well balanced and adjusted in the analysis, and interpret the MAIC results carefully, considering the limitations of sample size.

Conclusions

Given the current scenario of therapeutic advances in the field of hemophilia and the economic landscape, the MAIC has represented a breakthrough by allowing for the comparison of treatments through the adjustment of baseline differences. These MAICs are already accepted by regulatory and payer agencies. AI could be integrated into MAICs to improve their capabilities by providing faster and more accurate analyses, and even more reliable predictions that could be used in MAICs to optimize processes. The combination of human expertise with AI capabilities could create a safer and more efficient evaluation system. We have used a generative AI (ChatGPT4.0) accessible to any user, more modest than other AI systems, with limitations for this type of analysis. The estimates and simulations presented should therefore be viewed with caution. The use of other generative AI techniques, such as machine learning (ML), capable of processing a larger number of variables and eliminating the preselection stage, is promising. However, designing ML studies requires a multidisciplinary team of clinicians, data scientists, software engineers, and statisticians experienced not only in AI/ML methods but also in the nuances of health research⁶. Therefore, study design and the training and verification of methods can require considerable time and effort. In this case, the 2 approaches (MAIC and ChatGPT4.0) highlight the superior efficacy of efanesoctocog alfa in reducing ABR vs emicizumab. The MAIC offers a more detailed and adjusted analysis of efficacy outcomes, confirming that efanesoctocog alfa more significantly reduces bleeding

episodes, without addressing efficiency. Regarding estimated efficiency, the simulation is based on efficiency measured by ABR reduction per euro spent, considering only the specific groups mentioned in the studies. Beyond economic cost for treatment selection¹⁵, other factors must be considered, such as treatment convenience, patient preferences, overall clinical assessment, joint health, lifestyle, etc. Both drugs have proven to be safe and effective in preventing bleeding in patients with severe hemophilia A ($F8 \leq 1\%$). Ultimately, these analyses should not replace sound clinical judgment, though they can certainly provide additional information for the therapeutic selection process and aid in the personalization of prophylaxis.

Supplementary data

Supplementary data are available at DOI: 10.24875/RHT.M24000015. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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Conflicts of interest

None declared.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. Agencia Española de Medicamentos y Productos Sanitarios. Informe de posicionamiento terapéutico de emicizumab (Hemlibra®) en hemofilia A con inhibidores del factor VIII y en hemofilia A grave sin inhibidores del factor VIII. AEMPS; 4 de mayo de 2020. Fecha de corrección de erratas: 19 de marzo de 2024. Disponible en: <https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/IPT-emicizumab-Hemlibra-hemofilia-A-v2.pdf>.

2. Signorovitch JE, Sikirica V, Erder MH, Xie J, Lu M, Hodgkins PS, et al. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. *Value Health*. 2012;15:940-7.
3. Guillet B, Yan S, Hooper B, Drellich D, Steenkamp J, Tomic R, et al. Matching-adjusted indirect comparison of recombinant factor IX albumin fusion protein versus recombinant factor IX Fc fusion protein for weekly prophylactic treatment of hemophilia B. *Adv Ther*. 2024;41: 649-58.
4. Bonanad S, Núñez RJ, Poveda JL, Kurnik K, Goldmann G, Andreozzi V, et al. Matching-adjusted indirect comparison of efficacy and consumption of rVIII-single chain versus two recombinant FVIII products used for prophylactic treatment of adults/adolescents with severe haemophilia A. *Adv Ther*. 2021;38:4872-84.
5. Klamroth R, Bonner A, Gomez K, Monahan PE, Szafranski K, Zhang X, et al. Indirect treatment comparisons of the gene therapy etranacogene dezaparvovec versus extended half-life factor IX therapies for severe or moderately severe haemophilia B. *Haemophilia*. 2024;30:75-86.
6. Rashidi H, Bowers K, Reyes Gil M. Machine learning in the coagulation and hemostasis arena: an overview and evaluation of methods, review of literature, and future directions. *J Thromb Haemost*. 2023;21: 728-43.
7. von Drygalski A, Chowdary P, Kulkarni R, Susen S, Konkle BA, Oldenburg J, et al. Efanesoctocog alfa prophylaxis for patients with severe hemophilia A. *N Engl J Med*. 2023;388:310-8.
8. Mahlangu J, Oldenburg J, Paz-Priel I, Negrier C, Niggli M, Mancuso ME, et al. Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. *N Engl J Med*. 2018;379:811-22.
9. Álvarez Román MT, Kragh N, Guyot P, Wilson A, Wojciechowski P, Margas W, et al. Efanesoctocog alfa versus emicizumab in the prophylactic treatment of adolescents and adults with severe hemophilia A without inhibitors: a matching-adjusted indirect comparison. *ISTH Congress, Montreal*, 2023; PB0195.
10. Agencia Europea de Medicamentos. Altuvoc (efanesoctocog alfa). Información general sobre Altuvoc y sobre los motivos por los que se autoriza su uso en la UE. EMA; 2024. Disponible en: https://cima.aemps.es/cima/pdfs/ipe/1241824006/IPE_1241824006.pdf.
11. Agencia Española de Medicamentos y Productos Sanitarios. Ficha técnica Hemlibra 150 mg/ml solución inyectable. EMA; 2022. Disponible en: https://cima.aemps.es/cima/dochtml/ft/1181271002/FT_1181271002.html.
12. Bravo MI, Raventós A, Pérez A, Costa M, Willis T. Non-additive effect on thrombin generation when a plasmaderived factor VIII/von Willebrand factor (FVIII/VWF) is combined with emicizumab in vitro. *J Thromb Haemost*. 2020;18:1934-9.
13. Kizilocak H, Marquez-Casas E, Malvar J, Carmona R, Young G. Determining the approximate factor VIII level of patients with severe haemophilia A on emicizumab using in vivo global haemostasis assays. *Haemophilia*. 2021;27:730-5.
14. Holme PA, Blatný J, Chowdary P, Lassila R, O'Connell N, Hermans C, et al. Moving towards normalization of haemostasis and health equity: evolving treatment goals for haemophilia A. *Haemophilia*. 2024 Jul 10. doi: 10.1111/hae.15031. Online ahead of print.
15. Núñez R, Álvarez-Román MT, Bonanad S, González-Porras JR, De La Corte-Rodríguez H, Berrueto R, et al. The limitations and unmet needs of the five cornerstones to guarantee lifelong optimization of prophylaxis in hemophilia patients. *TH Open*. 2022;6:e365-77.