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ORIGINAL RESEARCH ARTICLE

Spanish registry of real-world clinical practice in previously untreated or minimally treated patients with severe hemophilia A (RePUM-HA)

Registro español de práctica clínica habitual en pacientes con hemofilia A grave previamente no tratados o mínimamente tratados (RePUM-HA)

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Abstract

Introduction: *The development of inhibitors against factor VIII remains a significant complication in hemophilia A, especially in previously untreated patients. Non-replacement therapies have enabled the initiation of primary prophylaxis at very early stages, although uncertainties persist regarding the risk of inhibitor development after late factor VIII exposure, the choice of concentrate, and tolerization strategies.* **Objective:** *The aim of the RePUM-HA registry is to generate real-world evidence to better understand and reach consensus on the management of these patients in our country.* **Material and method:** *National, multicenter, observational registry running from 2021 to 2028, including previously untreated and minimally treated patients (< 5 exposure days) with severe or moderate hemophilia A, under 3 years of age, without inhibitors, who started prophylaxis after 2020. Clinical, genetic, therapeutic, bleeding, immu-nogenicity, and adverse event data will be collected.* **Results:** *Approximately 50 patients are expected to be enrolled to assess inhibitor risk, clinical outcomes, and prophylactic regimens in real-world practice.* **Conclusions:** *This study will provide evidence to optimize strategies and inform future national recommendations.*

Keywords: *Hemophilia. Previously untreated patient. Prophylaxis. Therapy. Inhibitors.*

Resumen

Introducción: *El desarrollo de inhibidores frente al factor VIII sigue siendo una complicación relevante en la hemofilia A, especialmente en pacientes previamente no tratados. Los tratamientos no sustitutivos han permitido iniciar la profilaxis primaria en etapas muy precoces, aunque persisten dudas sobre el riesgo de inhibidores tras la exposición tardía a factor VIII, la elec-ción del concentrado y las estrategias de tolerización.* **Objetivo:** *El objetivo del registro RePUM-HA es generar evidencia de la vida real que permita conocer y consensuar el manejo de estos pacientes en nuestro país.* **Material y métodos:** *Registro observa-*

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cional, multicéntrico y nacional, entre 2021 y 2028, que incluye pacientes previamente no tratados y mínimamente tratados (< 5 días de exposición) con hemofilia A grave o moderada, menores de 3 años, sin inhibidores, que comenzaron la profilaxis a partir de 2020. Se recogerán datos clínicos, genéticos, terapéuticos, sangrados, inmunogenicidad y eventos adversos. **Resultados:** *Se prevé incluir unos 50 pacientes para evaluar el riesgo de inhibidores, los resultados clínicos y los esquemas profilácticos en la práctica real.* **Conclusiones:** *Este estudio aportará evidencia para optimizar estrategias y futuras recomendaciones nacionales.*

Palabras clave: *Hemofilia. Paciente previamente no tratado. Profilaxis. Tratamiento. Inhibidor.*

Introduction

Hemophilia A is an X-linked congenital disorder characterized by a impairment in the synthesis or function of factor VIII (FVIII) and an associated variable bleeding phenotype, generally related to the severity of the deficiency.[1] The presence of a family history may allow prenatal diagnosis; however, in sporadic cases, the disease is diagnosed after a first bleeding event following birth or during the first months of life.[2] One of the most feared bleeding events within the first year of life is intracranial hemorrhage. Its incidence is 2.1 events per 100 deliveries in patients with hemophilia, and this risk also persists during the first 12 months of life, especially in patients who do not receive prophylactic treatment.[3,4]

Prophylaxis has proven being effective in reducing bleeding events in patients with hemophilia, but the initiation of replacement therapy with FVIII in very young patients entails several challenges.[5,6] On the one hand, periodic IV administration may require placement of a central venous catheter, given the difficulty of accessing peripheral veins in infants, especially those < 3-6 months. On the other hand, exposure to FVIII in previously untreated patients (PUP) with hemophilia A leads to the development of neutralizing antibodies (inhibitors) against FVIII in 25-40% of cases.[7] A total of 79% of inhibitors develop during the first 20 exposures to FVIII, but the risk persists for at least up to 75 exposures.[7] The development of inhibitors is a serious complication, as they neutralize factor activity and reduce its efficacy, increase patient morbidity and mortality, and worsen quality of life.[8,9] It has been described that controlled and regular exposure to FVIII in a prophylactic regimen, especially when initiated early, may reduce the risk of inhibitor development.[7] However, the existence of other risk factors is well known, such as family history of inhibitors, the need for intensive treatment during the first administrations, or the causative mutation of the disease.[2,10] In fact, more than 70% of mutations leading to severe forms of hemophilia A are associated with a high risk of inhibitor development.[7]

Emicizumab is a recombinant, humanized, bispecific monoclonal antibody approved for prophylaxis in patients with hemophilia A, with or without inhibitors, of all ages. It exerts its action by mimicking the function of FVIII, acting as a bridge between activated factor IX and factor X to activate the latter, and is administered subcutaneously on a weekly regimen or every 2 or 4 weeks.[11] Initial registration studies demonstrated that emicizumab is safe and effective in preventing bleeding in patients with hemophilia A > 1 year;[12] however, there were concerns regarding its efficacy in very young children, as factors XI and X have physiologically lower levels compared to adults.[13] The HAVEN-7 study demonstrated the safety and efficacy profile of emicizumab as prophylactic treatment in 55 patients with hemophilia A younger than 1 year. In fact, no patient experienced intracranial hemorrhage after initiating treatment at a mean age of 5 months (compared with the previously reported 13.1 months).[14] These results have made it possible to consider initiation of primary prophylaxis at an earlier age, immediately after diagnosis.[12]

However, this therapy also presents several limitations. Prophylaxis with emicizumab reduces spontaneous and severe bleeding, but the risk of bleeding does not completely disappear, as described in all HAVEN registration studies and in other real-world studies.[11,15-17] These bleeding episodes may require administration of FVIII concentrates which, in PUP and minimally treated patients (MTP), could result in the development of inhibitors.[12] Nevertheless, prophylaxis with emicizumab may alter the "natural" course of inhibitor development associated with conventional replacement therapy. Prophylaxis with replacement therapy implies that newborns and infants with severe hemophilia A require a mean of 1.2 years to reach 75 exposures. However, patients on emicizumab may require much longer, even years, to reach those 50-75 exposures.[12,18] Although age does not appear to be a key factor in the risk of inhibitor development, the financial impact of inducing immune tolerance in older children is considerably higher. Therefore, there are many

uncertainties regarding several issues, such as whether regular exposure to FVIII is necessary in patients with hemophilia A initiating prophylaxis with emicizumab. The lack of consensus in the scientific community was highlighted in a survey conducted in 32 centers belonging to PedNet.[8] In 20 of 25 centers, emicizumab was the preferred option to initiate prophylaxis in PUP and MTP, and in most cases (80%), FVIII was not administered concomitantly. Another controversy concerns the type of FVIII that should be used, especially with the emergence of new extended and ultra-extended half-life products not included in the SIPPET study.[19] There are also no recommendations regarding which treatment to continue once those first 20-50 exposures have been reached.[5] The objective of the RePUM-HA registry is to generate real-world evidence to better understand and standardize the management of these patients in Spain.

Method

Study design

We conducted an observational, multicenter study with retrospective data collection (from January 2021 through October 2025) and prospective data collection (from October 2025 through December 2028) in PUP and MTP patients with severe and moderate hemophilia A without inhibitors who initiate prophylactic treatment during the study period in Spain. This registry is part of the initiatives of the Sociedad Española de Trombosis y Hemostasia.

Endpoints

- Primary endpoint**:** to investigate the safety and efficacy of replacement and non-replacement therapies used as prophylaxis in PUP or MTP patients with severe hemophilia A (FVIII: C ≤ 1%) or moderate hemophilia A (FVIII: C > 1 to ≤ 5%) without inhibitors during routine clinical practice in a single country.
- Secondary endpoints: to evaluate the rate of inhibitor development during the study period in a series of PUP and MTP patients on prophylactic treatment.
  - To evaluate the annual bleeding rate in a series of PUP and MTP patients on prophylaxis during the study period, analyzing episodes requiring treatment administration.
  - To evaluate different therapeutic and follow-up approaches in relation to the initial FVIII tolerization regimen, bleeding management, and surgical management, with the aim of designing and implementing uniform and consensus-based treatment strategies across different centers in Spain.

Inclusion and exclusion criteria

- Inclusion criteria:
  - Patients diagnosed with severe (FVIII < 1%) or moderate (FVIII 1-5%) hemophilia A without inhibitors at study initiation.
  - PUP patients (1-2 exposures) or MTP patients (3-5 exposures) who initiated primary prophylaxis after January 1, 2020.
  - Age < 3 years at the time of prophylaxis initiation.
  - Complete records of treatment administration, bleeding episodes, administration of coagulation factor for bleeding management, and periodic inhibitor assessment.
  - Signed informed consent from parents, caregivers, or legal guardians.
- Exclusion criteria:
  - Patients who do not meet inclusion criteria at the time of prophylaxis initiation.
  - Patients who developed inhibitors prior to starting prophylaxis.
  - Patients for whom informed consent cannot be obtained.
  - Patients participating in a clinical trial involving replacement or non-replacement therapy.

Sample size calculation

The annual number of male newborns in Spain has been approximately 320,000 in recent years, of whom around 170,000 are male. The incidence rate of hemophilia A is 1 per 5,000 live male births, and that of severe hemophilia A is approximately 1 per 16,000; it is estimated that 15% of patients with hemophilia A have a moderate form. Based on these data, we estimate approximately 10 patients with severe hemophilia A per year and 5 patients with moderate hemophilia A per year.

Considering that this registry includes a geographically representative sample of centers across Spain (Table 1 of the Supplementary Data), including the main referral units and the four CSUR centers, as well as the fact that not all patients with moderate hemophilia A will receive prophylaxis, we estimate a total of 12 patients per year, resulting in a minimum of 50-60 patients by the end of the study.

Recruitment and ethical aspects

Recruitment and the consent process will be carried out during routine follow-up visits at the referral hemophilia unit. Due to the age of the patients, their parents or legal guardians will be informed about the study. After signing the informed consent, clinical data will be collected from the medical records. Patients and their caregivers will not undergo any tests or questionnaires beyond those used in routine clinical practice.

Results

The expected results of this study will address the primary endpoint of evaluating safety (development of inhibitors) and efficacy (annual bleeding rate) of replacement and non-replacement prophylactic treatment in PUP or MTP patients with severe (FVIII ≤ 1%) or moderate (FVIII > 1 to ≤ 5%) hemophilia A without inhibitors. Secondary objectives include bleeding and surgical management, as well as the effects of tolerization strategies.

Variables

Clinical data will be collected by the investigator in a specific study data collection form, which will be pseudo-anonymized to protect patient identity. The following will be recorded:

- Demographic data: age (calculated in months) and sex.
- Medical history:
  - Severity level of hemophilia: moderate or severe.
  - Genetic diagnosis: information related to the detected mutation.
  - Family history of FVIII inhibitors.
- Treatment history:
  - Number of prior FVIII exposures: this value must not exceed 5.
  - Reason for prior administration of each FVIII dose received.
  - Type of FVIII administered.
- Prophylactic treatment:
  - Age at initiation of prophylactic treatment.
  - Dose and regimen of the administered treatment.
  - Main reason for treatment choice: patient or caregiver preference, treating team preference, prevention of inhibitor development in high-risk patients, bleeding prevention, or others.
- Follow-up and evaluation (minimum data collection every 12 months, preferably every 6 months):
  - Age at follow-up.
  - Weight and height.
  - Dose and treatment regimen.
- Treatment efficacy:
  - Patient age at the time of bleeding episode.
  - Bleeding episodes and information regarding spontaneous or traumatic bleeding, location, severity, administered treatment, hospital admission, and additional follow-up visits.
- Safety and tolerability:
  - Treatment-related adverse events: adverse events and serious adverse events will be reported according to protocol.
  - Development of inhibitors: age at diagnosis and number of prior FVIII exposures; inhibitor titer at diagnosis.
  - Treatment adherence.
- Medical interventions:
  - Surgeries or other invasive procedures performed during follow-up.
  - Patient age at the time of surgery or invasive procedure.
  - FVIII administration (if required), number of administrations, and dose.
- Joint health (if available):
  - Clinical assessment scale (Hemophilia Joint Health Score [HJHS]).
  - Ultrasound joint assessment scale (Hemophilia Early Arthropathy Detection with Ultrasound [HEAD-US]).

Definitions

- Severe hemophilia A: FVIII deficiency < 1%.[20]
- Moderate hemophilia A: FVIII deficiency 1-5%.[20]
- Previously untreated patient (PUP): patient who has not received FVIII or has received only 1 or 2 doses.
- Minimally treated patient (MTP): patient who has received 3 to 5 doses of FVIII.
- Inhibitors: presence of neutralizing antibodies against FVIII determined according to the modified Bethesda method, with a value > 0.6 Bethesda units.
- Assessment of treatment adherence: good (80-100%), moderate (65-80%), or poor (< 65%), determined based on patient-reported information or indirect pharmacy records.

Analysis of results

A descriptive analysis of the entire series and of the results in relation to the primary and secondary

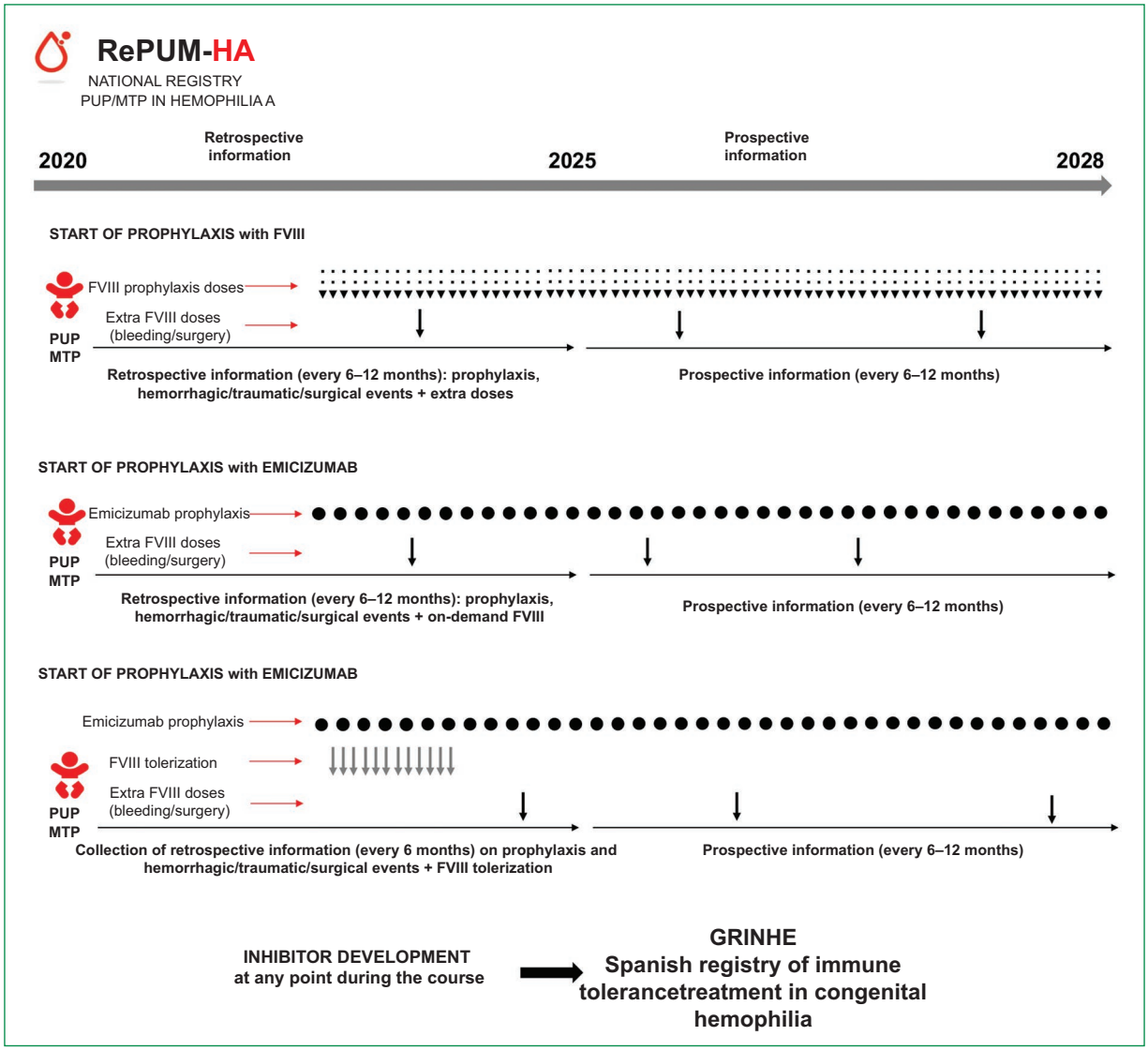

Figure 1. Scheme of retrospective and prospective data collection in the study according to the type of treatment with which prophylaxis was initiated, the use of FVIII doses for tolerization, or the use of FVIII as additional doses.

endpoints will be conducted. Subsequently, results will be analyzed by classifying patients into different subgroups. The following assumptions are proposed: 1) type of prophylaxis received; 2) severity of hemophilia; 3) PUP or MTP patients; 4) causative mutation of the disease; and 5) patients receiving emicizumab who have (or have not) undergone FVIII tolerization.

Statistical analysis

A descriptive analysis of the main study variables will be performed. For qualitative variables, results will be expressed as frequency, percentage, and confidence interval. For quantitative variables, mean and SD, and median with IQR, will be reported. Statistical analyses will include comparison of frequencies of categorical variables between groups using the chi-square or Fisher's exact test. For comparison of quantitative variables between groups, Student's t test will be used in case of normal distribution, and the nonparametric Mann-Whitney U test if the distribution is not normal. To compare quantitative variables within the same subjects at different time points, paired Student's t test will be used in case of normal distribution, and the nonparametric Wilcoxon test in case of non-normal distribution. Results will be considered statistically significant when $p < 0.05$. Statistical analyses will be performed using SPSS v23.0 (IBM Corp, Armonk, NY, USA).

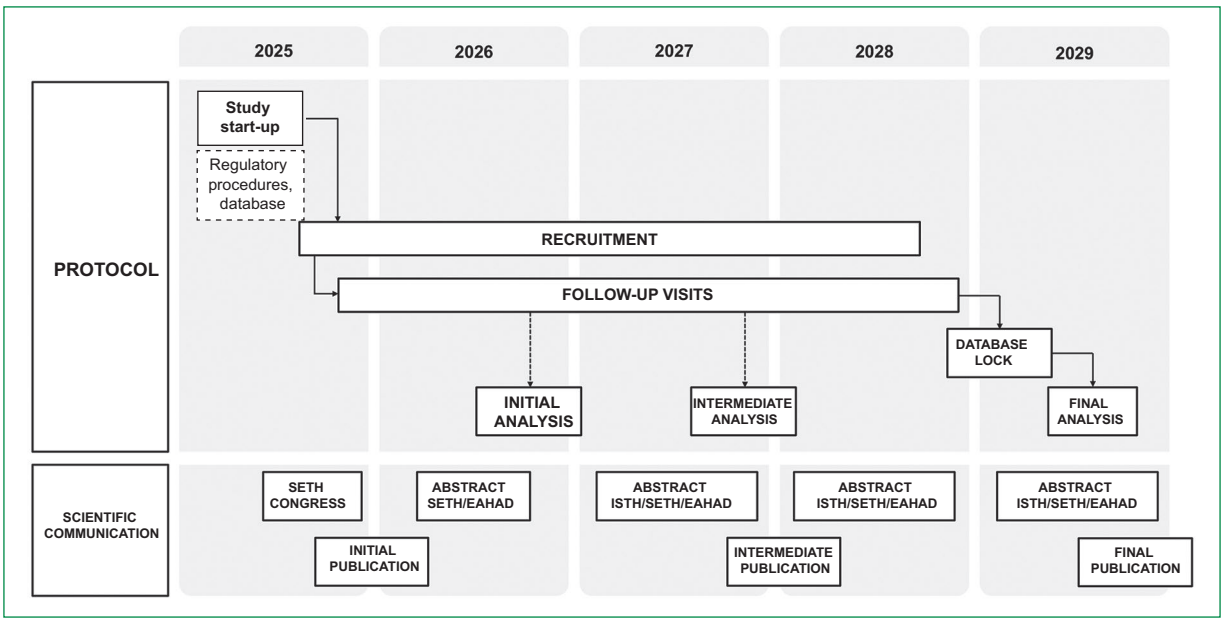

Figure 2. Work timeline.

Ethical aspects

The study will be conducted in accordance with the Declaration of Helsinki (2024) on ethical principles for medical research involving human subjects, Royal Decree 1090/2015 of December 24 on clinical trials, specifically the provisions of Article 38 on good clinical practice, and the Convention on Human Rights and Biomedicine, signed in Oviedo on April 4th, 1997, and its subsequent updates.

Patients, parents, or legal representatives will sign informed consent for inclusion in the registry. The study has been evaluated by the CEIm of the Fundación Sant Joan de Déu (EOM-02-25).

Safety reporting

Local investigators will report, in accordance with applicable legal obligations, and study data will be collected on all adverse events, including inhibitors, allergic reactions, thromboembolic complications, thrombotic microangiopathic complications, and deaths suspected to be related to hemophilia treatment. Reports on non-replacement therapies will include data on any other adverse events, as appropriate. Non-serious adverse events will be recorded according to the appropriate MedDRA classification level. Annual reports of all reported inhibitors will be prepared, correlated with the products used. Data reports will be sent to all participating centers and sponsors in relation to their products. Safety reporting for registered products will be carried out by participating centers in accordance with national regulations established by competent authorities.

Timeline and current status

The first patient was recruited in September 2025. Data collection is expected to continue for the next 3 years (until study completion) (Fig. 1). Results, analyzed annually, will be presented at scientific meetings and published in indexed journals. All publications and presentations related to the study will be authorized and reviewed by all investigators. The project timeline is shown in figure 2.

Conclusions

RePUM-HA represents a unique opportunity to understand the impact of new prophylactic strategies in PUP and MTP patients in routine clinical practice in our country. The collected information will help address still unanswered questions, such as the timing and type of FVIII exposure, the need to design tolerization protocols, and the economic and clinical impact of new therapies. This registry aims to lay the groundwork for future national recommendations and to promote

collaboration among centers and, subsequently, with other international groups.

Funding

The study sponsor is the Fundación Española de Trombosis y Hemostasia, and the registry is funded by Roche.

Conflicts of interest

R. Berrueco has received contract support from Roche, reimbursement for conference attendance, honoraria for lectures and consultancy, and research funding from Takeda, Roche, Bayer, CSL-Behring, Novo Nordisk, Sobi, Octapharma, Amgen, Werfen, Stago, Boehringer Ingelheim, and Pfizer. M.T. Álvarez-Román has participated as a speaker, in advisory boards, and in symposia sponsored by Novo Nordisk, Takeda, Roche, Pfizer, Octapharma, Amgen, Novartis, CSL Behring, and Sobi. M. Rodríguez-López has received reimbursement for conference attendance and honoraria for lectures and consultancy from Octapharma, Sobi, Roche, CSL Behring, Amgen, Takeda, Novo Nordisk, Pfizer, Grifols, and LFB. V. Jiménez-Yuste has received support and contracts from F. Hoffmann-La Roche Ltd, Novo Nordisk, Sobi, Takeda, Grifols, Bayer, Pfizer, Octapharma, and CSL Behring, as well as honoraria for lectures, presentations, manuscript writing, and educational events from F. Hoffmann-La Roche Ltd, Novo Nordisk, Sanofi, Sobi, Takeda, Grifols, Bayer, Pfizer, Spark Therapeutics, BioMarin, Octapharma, and CSL Behring. R.J. Núñez-Vázquez has received honoraria for lectures and advisory board participation from Roche, CSL Behring, Sobi, Octapharma, Novo Nordisk, Takeda, and Pfizer, as well as support for meeting attendance from Octapharma, Roche, and Sobi.

Ethical considerations

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

Confidentiality, informed consent, and ethical approval. The authors have followed their healthcare institution's protocols for accessing clinical record data. Informed consent has been obtained from patients, and approval from the Ethics Committee has been secured. SAGER guidelines have been followed.

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

Supplementary data

Supplementary data is available at 10.24875/RHT.25000022. This material is provided by the corresponding author and published online for the benefit of the reader. The content of the supplementary material is the sole responsibility of the authors.

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