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Case Report

Twelve months of emicizumab prophylaxis in a severe hemophilia A man with inhibitor who failed immune tolerance induction: effectiveness, economic, and safety outcomes

Ricardo Mesquita Camelo [a,*], *Tenille Capuxú de Medeiros* [b], *Daniela Gonçalves Braz de Albuquerque* [b], *Juliana Álvares-Teodoro* [c]

[a] *Faculdade de Medicina da Universidade Federal de Minas Gerais, 1020/101 Padre Eustáquio, Belo Horizonte, MG, Brazil*
[b] *Centro de Hematologia e Hemoterapia do Rio Grande do Norte (HEMONORTE), Natal, RN, Brazil*
[c] *Faculdade de Farmácia da Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil*

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Introduction

Hemophilia A (HA) is a rare inherited bleeding disorder characterized by reduced/absent activity of the clotting factor VIII (FVIII).[1] Until recently, treatment consisted mainly of FVIII concentrate intravenous infusions exclusively during hemorrhages (on demand) or regularly to avoid bleedings (prophylaxis).[1] Unfortunately, about 30% of previously untreated PwHA may develop antibodies which inactivate FVIII, called inhibitors.[1] PwHA and inhibitors (PwHAi) have worse outcome, higher frequencies of bleeding episodes, with lower quality of life and enhanced mortality risk.[1] Moreover, since FVIII is ineffective for hemostasis in inhibitor individuals, intravenous bypassing agents (activated prothrombin complex concentrate [aPCC] or recombinant activated factor VII [rFVIIa]) used to be recommended for both on demand and prophylaxis treatments, and treatment cost can be considerably increased.[1] Therefore, the best treatment for PwHAi is eradicating the antibodies by regular intravenous infusions of FVIII, called immune tolerance induction (ITI).[2] The success rate of ITI is about 70%–80% worldwide, after which FVIII replacement as episodic treatment or prophylaxis can be resumed.[2] PwHAi who fail treatment had only the option to receive bypassing agents.[1,2]

In 2017, the first phase III trial with the humanized bispecific antibody emicizumab was published,[3] adding renewed options for treatment of PwHAi. Emicizumab binds to factors IX-activated and X, speeding up the activation of factor X.[4] It solved some unmet needs of HA treatment, such as regimen (once weekly up to once monthly infusion) and route of administration (subcutaneous). Most importantly, emicizumab reduced bleeding episodes, and improved the quality of life of PwHAi.[3] Although it is an effective non-replacement alternative in the prophylaxis of PwHA with or without inhibitors, its

* Corresponding author at:
E-mail address: cameloric@gmail.com (R.M. Camelo).
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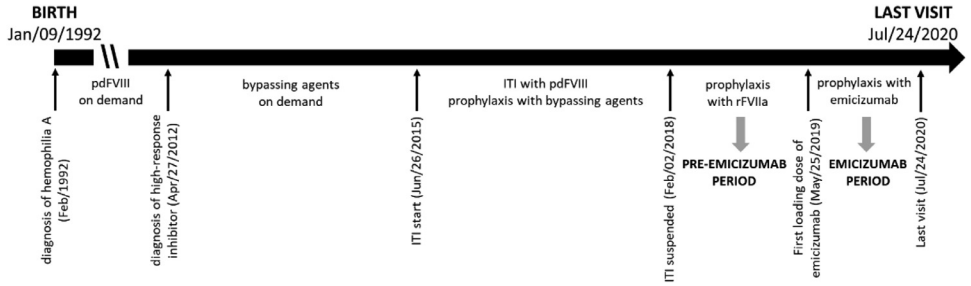

Figure 1 – Patient history and the periods which were evaluated in this case report. pdFVIII, plasma-derived factor VIII; ITI, immune tolerance induction; rFVIIa, recombinant activated factor VII.

safety has not been clarified yet, and a few – although unprecedent – cases of thrombosis have been described.[5,6]

The "Brazilian registry of persons with hemophilia A receiving emicizumab" (EMCase Study) is a multicenter observational study and any PwHA receiving emicizumab can be included (e.g., sex, age, inhibitor status etc. are not inclusion nor exclusion criteria). It was approved centrally by the Committee on Ethics in Research of the Universidade Federal de Minas Gerais (CAAE 10,664,919.6.0000.5149), locally by each Hemophilia Treatment Center's Committee on Ethics in Research, and registered in the Brazilian Registry of Clinical Trials (RBR-57rnpz). All the included patients signed the Informed Consent Form, according to the Helsink Declaration. The treatment will be decided among the patient, the physician, and the interdisciplinary team of the hemophilia treatment center. Outcome data, laboratory tests and therapeutic progression will be compiled yearly over a maximum of 10 years. Economic analyses and pharmacovigilance will also be evaluated. Herein we described the one-year experience of emicizumab treatment in the first patient included in the EMCase Study.

Case report

The patient history was depicted in Figure 1. A 28-year-old white man was diagnosed as severe HA (FVIII activity 0.9%) when he was born. He had been treated exclusively on demand, even after developing a high response inhibitor at the age of 20 years. Three years later, ITI was prescribed for 32 months with plasma-derived FVIII 50 IU/kg 3x/week and prophylaxis with bypassing agent. ITI regimen was not increased due to a difficult peripheral venous access and a central line was not implanted due to social barriers about caring of the device. He had 11 bleeding episodes requiring treatment (annualized treated-bleeding rate [ABR] 4.1 episodes/y). ITI failure was reported on Feb/27/2018.

Prophylaxis with rFVIIa 70 μg/kg intravenously 3x/week was prescribed from Feb/27/2018 to Jul/24/2019 (pre-emicizumab period). The ABR was 2.1 episodes/y during this period. Mean consumption of rFVIIa was 55,420 ± 15,440 μg/month. After withholding rFVIIa prophylaxis, emicizumab was loaded with 3.0 mg/kg subcutaneously once weekly for 4 weeks, starting on Jul/25/2019, and 1.5 mg/kg weekly thereafter. Mean consumption of emicizumab from Jul/25/2019 to Jul/24/2020 (emicizumab period) was 366.92 ± 93.40 mg/month, with no bleeding episode requiring factor concentrate replacement. The mean monthly cost of the treatment reduced from US$ 34,590.00 ± 8903.00/month (US$ 0.57/μg, in 2018), in the pre-emicizumab period, to US$ 25,736.25 ± 6677.04/month (US$ 71.50/mg, in 2020), during the emicizumab period. The rFVIIa price was cost of the product purchased by the Brazilian Ministry of Health. The emicizumab price was the cost of the product purchased by the Health Secretariat of Rio Grande do Norte, according to the converted R$/mg of the last bill (Jul/06/2020) into US$/mg.[a] ABR and monthly treatment costs of both periods were depicted in Figure 2.

The patient self-infused both rFVIIa and emicizumab at home. While he had one bleeding episode in the puncture site secondary rFVIIa infusion requiring replacement treatment in the pre-emicizumab period, he denied puncture site complications after emicizumab treatment. No thrombotic event has been reported during both evaluated periods.

Discussion and comments

We described the successful one-year prophylactic treatment with emicizumab of a Brazilian PwHAi who failed ITI. After starting the antibody, he self-infused less than previously, always subcutaneously. He experienced no bleeding episodes and no thrombotic event was reported. Finally, treatment costs reduced considerably.

HA treatment consists in frequent intravenous infusions of coagulation concentrates,[1] which can be time-consuming and stressful for many patients and caregivers. Besides that, PwHAi are prone to worse outcomes, such as more frequent and difficult-to-control bleedings, higher prevalence of joint damage, lower quality of life, and higher mortality, than their non-inhibitor counterparts.[1] HA treatment is expensive, even more if inhibitor is clinically significant. Unfortunately, ITI failure is common and the only treatment option for PwHAi with a bleeding phenotype who failed ITI was bypassing agent prophylaxis.[1]

The first clinical trial of once-weekly subcutaneous emicizumab as prophylaxis for PwHAi showed that ABRs were reduced by 79% in a follow-up of 24 weeks, compared to previous bypassing agent prophylaxis ($n = 49$).[3] During the same trial, three patients developed thrombotic microangiopathy and two patients developed venous thrombosis.[3] These

[a] http://www.ipeadata.gov.br/ExibeSerie.aspx?serid=38590&module=M

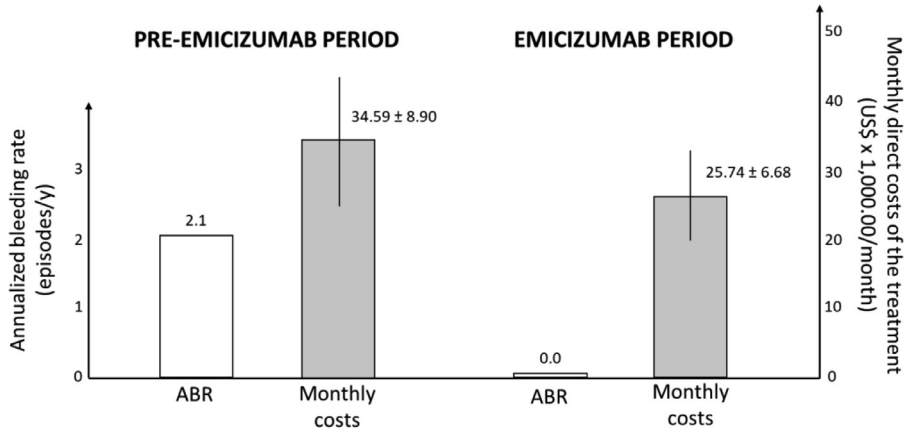

Figure 2 – Annualized treated-bleeding rates (ABR) and monthly direct treatment costs before (pre-emicizumab period, from Feb/27/2018 to Jul/24/2019) and during prophylaxis with emicizumab (emicizumabe period, from Jul/25/2019 to Jul/24/2020). Annualized treated-bleeding rates (bars in white; left-sided y-axis) were calculated as a proxy annual number of bleeding episodes requiring replacement treatment for hemostasis during the evaluated periods. The monthly direct treatment costs (bars in gray; right-sided y-axis) were calculated according to the prices of the respective products in United States dollar currency of the day of purchase. They were expressed by mean ± standard deviations.

events were associated with a concomitant infusion of aPCC in a high frequency and/or reaching high daily doses.[7] Although the guidance for treatment of bleedings while on emicizumab prophylaxis was modified,[8] few cases of thrombotic events have been reported worldwide.[5] Moreover, thrombosis related to concomitant use of emicizumab and rFVIIa has also been reported.[6] Nevertheless, it should be noticed that few thrombotic events associated both with rFVIIa or aPCC without emicizumab have also been reported, but no thrombotic microangiopathy events associated with any bypassing agents without emicizumab have been reported yet.[9] Finally, a recent study about the cost-effectiveness and the budget impact showed that, compared with bypassing agents prophylaxis, emicizumab prophylaxis was more effective and cost-saving in PwHAi who failed ITI, associated to an overall budget reduction following years.[10] Furthermore, emicizumab treatment was also associated to a significant reduction of the healthcare budget.[10]

When emicizumab was prescribed for this patient, it had been registered by the National Health Surveillance Agency (in Portuguese, ANVISA),[b] but the selling price on the Brazilian market had not yet been established. So the medicine was imported by the Health Secretariat of the state of Rio Grande do Norte to comply with the judicial decision to provide access for this patient, and its purchase cost was US$ 71.50/mg. Later, Brazilian Ministry of Health incorporated it into the national guides for the prophylaxis of PwHAi who failed ITI.[c] The proposed price for incorporation was US$ 32.15/mg, which represents a 43.2% of the import price and 59.1% of the maximum sale price to the government (U$ 54.44/mg). Considering that there were 268 PwHAi on ITI in 2016, and the failure rate of ITI is about 25%,[2] we expect that at least 67 PwHAi may be treated with emicizumab in the following years. More evidence on its effectiveness, safety and economic aspects may be elucidated with the reports of phase IV studies (e.g., EMCase Study [RBR-57rnpz]).

Conclusion

Prophylaxis with emicizumab for this PwHAi who failed ITI has been considered safe and effective. The annualized direct costs reduced about 25% after switching from prophylaxis with rFVIIa to emicizumab. This is a promising result, considering that PwHAi have few therapeutic alternatives. However, these results need to be confirmed by more robust studies, which will provide better levels of scientific evidence, such as prospective cohorts.

Conflicts of interest

RMC reports personal fees from Takeda, personal fees from Hoffman-La Roche, non-financial support from Takeda, non-financial support from Hoffman-La Roche, outside the submitted work. TCdM reports personal fees from Takeda, non-financial support from Takeda, outside the submitted work. DGBdA reports non-financial support from Takeda, non-financial support from Hoffman-La Roche, non-financial support from Novo Nordisk, outside the submitted work. JAT has nothing to disclose.

Authorship contributions

RMC planned the study, collected and analyzed the data, wrote the paper, and approved the final version. TCdM and DGBdA collected the data and approved the final version. JAT planned the study, analyzed the data, and approved the final version.

[b] https://www.in.gov.br/materia/-/asset_publisher/Kujrw0TZC2Mb/content/id/65900108/do1a-2019-03-06-resolucao-re-n-537-de-28-de-fevereiro-de-2019-65899875

[c] http://conitec.gov.br/images/Relatorios/2019/Relatorio_Emicizumabe_HemofiliaA_Inibidores.pdf

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