Profilaxis secundaria con rFVIIIFc en adultos jóvenes con hemofilia A severa

Secondary prophylaxis with rFVIIIFc in young adults with severe haemophilia A

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Keywords: prophylaxis, haemophilia, rFVIIIFc, young adults, bleeding rate.

Resumen

Introducción

La profilaxis secundaria en adultos con hemofilia severa no resuelve la artropatía establecida, pero puede reducir el número de hemorragias articulares. Los productos de vida media extendida permiten infusiones menos frecuentes.

Objetivo

En este estudio prospectivo, evaluamos la eficacia de la profilaxis con FVIII recombinante asociado a proteína de fusión (rFVIIIFc) en un grupo de pacientes adultos jóvenes.

Métodos

Pacientes mayores de 18 años de un solo centro fueron tratados con rFVIIIFc 20-40 UI/kg dos veces por semana, durante un período de 6 meses. Analizamos la tasa de hemorragia y la comparamos con el período pre-profilaxis (tratamiento a demanda de eventos hemorrágicos).

Resultados

24 pacientes recibieron una dosis media de rFVIIIFc 32,1 UI/kg dos veces por semana. Hubo 58 hemorragias menores, todas tratadas con 1-2 dosis diaria de rFVIIIFc. La tasa de hemorragia anualizada promedio fue de 15,3 en el período pre-profilaxis frente a 2,4 durante la profilaxis. No se detectaron inhibidores.

Conclusión

rFVIIIFc fue bien tolerado en pacientes adultos jóvenes con hemofilia A severa, y resultó en una tasa de hemorragia anualizada baja cuando se administró 2 veces por semana como tratamiento profiláctico secundario.

Abstract

Introduction

Secondary prophylaxis in adults with severe haemophilia will not resolve the established arthropathy but may reduce the number of joint bleeds. Extend-

ed half-life products permit less frequent infusions.

Aim

In this prospective study, we evaluated the efficacy of prophylaxis with recombinant FVIII Fc fusion protein (rFVIIIFc) in a group of young adult patients.

Methods

Patients older than 18 years old from a single center were treated with rFVIIIFc 20-40 IU kg-1 twice a week, during a period of 6 months. We analyzed the annualized bleeding rate and compared it with the pre-prophylaxis period (on demand treatment).

Results

24 patients received a mean dose of rFVIIIFc 32.1 kg-1 twice a week. There were 58 minor bleedings, all treated with 1-2 daily dose of rFVIIIFc. The mean annualized bleeding rate was 15.3 in the pre-prophylaxis period vs. 2.4 during prophylaxis. No inhibitors were detected.

Conclusion

rFVIIIFc was well-tolerated in young adult patients with severe hemophilia A, and resulted in low bleeding rate when dosed 2 times per week as a secondary prophylactic treatment.

Introduction

Prophylaxis involves regular infusions of coagulation factor concentrates two to three times per week. Primary prophylaxis is most commonly initiated before or soon after the first joint bleeding episode, usually when the patient is at the most 2 years old. Secondary prophylaxis is prophylaxis started after some degree of haemophilic arthropathy has already developed; its objectives are, therefore, more limited than primary prophylaxis, as established arthropathy will not resolve and may continue to deteriorate even in the absence of further joint bleeding. Thus, the objectives of secondary prophylaxis usually are to arrest or reduce the progression of arthropathy, decrease synovitis, permit physiotherapy and increased physical activity, reduce pain, improve quality of life and/or defer the need for surgical intervention[1].

Optimal prophylaxis with conventional FVIII products, which have half-lives of approximately 12 hours, often requires three to four intravenous infusions weekly; more frequent administration may be necessary in children, who generally have a shorter FVIII half-life compared with adults. Recombinant FVIII Fc fusion protein (rFVIIIFc) was developed to prolong the half-life of FVIII[2]. rFVIIIFc consists of a BDD-rFVIII molecule that is genetically fused to the Fc domain of human immunoglobulin G1 with no intervening linker sequence. rFVIIIFc is produced in human embryonic kidney cells (HEK293) to provide human glycosylation patterns and high expression levels, with no added human- or animal-derived materials. The Fc domain provides protection from degradation through an endogenous pathway, mediated by the neonatal Fc receptor, resulting in prolonged half-life of the clotting factor. In a phase 1/2a human clinical study, rFVIIIFc had a 1.5- to 1.7-fold increase in plasma half-life compared with full-length rFVIII.

The specific activity of rFVIIIFc is equivalent to that of native FVIII (on a molar basis) and the clotting and chromogenic substrate assays demonstrated similar results. Despite the methodological variables that have been observed in laboratory assays, post infusion plasma rFVIIIFc levels can be monitored in patients by either the one-stage or chromogenic substrate assays routinely performed in clinical coagulation laboratories[3]. Mahlangu et al. reported in a trial with males aged ≥12 years with severe haemophilia A treated with rFVIIIFc, that the annualized bleeding rate was significantly reduced with prophylaxis (25-65 IU kg-1 every 3-5 days) by 92% compared with episodic treatment[4]. The lower clearance as compared to conventional rFVIII gives rFVIIIFc the potential for improved efficacy with regard to bleed prevention, without increasing the overall factor consumption[5].

The primary objective of this study was to evaluate the efficacy of prophylaxis in a group of young adult patients treated with an extended half-life FVIII (rFVIIIFc) to prevent bleeding episodes, as assessed by an intraindividual comparison of the annualized bleeding rate (ABR) during prophylaxis with the ABR during the previous on-demand treatment period. The second objective of the study was to evaluate the safety of rFVIIIFc, as assessed by the occurrence of inhibitors against FVIII in all patients.

Materials and methods

Patients older than 18 years old with severe haemophilia A (FVIII <1 IU dL^{-1}) followed in our center, who were on demand treatment, with at least 150 exposure days (ED) with previous FVIII replacement products, and no detectable inhibitor to FVIII, were invited to participate in this prospective trial. All the patients were treated with rFVIIIFc 20-40 IU kg-1 twice a week, during a period of 6 months. The first infusion had to be administered in our center and then they continued with self-administration at home. While on prophylaxis in the study, they had to be involved in an intensive physical rehabilitation program that included swimming activities. Pharmacokinetic studies were performed to measure the plasma FVIII levels (one stage method) at 10 minutes, 24, 72 and 96 hours of post infusion samples. Inhibitor test (Nijmegen-modified Bethesda assay) was performed at 0, 3 and 6 months, in all patients. All bleeding episodes were treated with rFVIIIFc at doses between 20-40 IU kg^{-1}. Any patient requiring surgery during the course of the study could use rFVIIIFc. Patients were encouraged to contact our Haemotological Service if there was any concern. Detailed data on all patients and treatment history were collected from medical records.

The institutional review board approved the protocol, and the study was conducted in accordance with the Guidelines for Good Clinical Practice and the ethical principles outlined in the Declaration of Helsinki. All patients signed a written informed consent.

Results

Twenty five patients with severe haemophilia A were enrolled in the study, with a mean age of 24.7 years old (range 19-33). One patient reported a mild chest pain after the infusion of the eighth dose of rFVIIIFc. There were no changes in the clinical, laboratory or imaging parameters evaluated. This patient decided to withdraw from the study. As the same symptom was reported in later opportunities (after stopping rFVIIIFc), it was finally considered an adverse event not related to the study drug.

The assessable population was 24 patients who completed the six-month prophylaxis period. All patients had a history of haemophilic arthropathy. Seven patients had ≤ 3 target joints and seventeen (70%) had more than 3. Only 11 patients had been on a late secondary prophylaxis before 18 years old. The mean patient´s weight was 72.8 kg and the mean prophylactic dose of rFVIIIFc was 32.1 IU kg^{-1} (range 25-39), twice a week.

The mean in vivo recovery of FVIII level (after 10 min post infusion) was 57 IU dL^{-1} (1.7). At 24 hours post infusion, mean FVIII level was 15.6 IU dL^{-1}, in 20 patients evaluated. 17/19 (89.4%) and 14/24 (58.3%) patients had trough levels of FVIII ≥ 1 IU dL^{-1} at 72 and 96 hours respectively. The mean ABR and annualized joint bleeding rate (AJBR) was 2.4 and 1.6 during prophylaxis versus 15.3 and 14 respectively (P<0.0001), in the pre-prophylaxis period (Figure 1). There were 369 bleedings in the pre-prophylaxis period vs 58 minor bleedings (40 were haemarthrosis and the rest were mouth and nose bleeding episodes), all treated with 1-2 daily dose of rFVIIIFc, in the prophylaxis period. Seven patients had zero joint bleeding during prophylaxis. Twelve patients underwent minor programmed surgeries: 5 dental extractions and in 7 patients, autologous platelet rich plasma was injected in one affected joint (with chronic synovitis). In all procedures, a previous bolus dose of rFVIIIFc to reach FVIII levels over 50 IU dL^{-1} was administered, followed by a daily dose of rFVIIIFc to reach FVIII levels over 30 IU dL^{-1}, for one or two days. There were no bleeding complications associated with these procedures. No major bleedings were reported during the study period. All patients achieved ≥50 ED with the study drug. No inhibitors were detected at 0, 3 or 6 month-evaluations. The adherence was evaluated as excellent in 23 patients. The patients performed regular physical activity and they reported a marked improvement in chronic joint pain, and an increase in muscle strength and self-confidence.

Discussion

Patients who begin secondary prophylaxis in adulthood may derive some benefit despite haemophilic arthropathy having established at that stage. Fischer et al. described patients who started prophylaxis after age 17 that were examined on the basis of the duration of prophylaxis: short (median 2.5 years) or long (median 20.3 years). The median number of bleeds after starting prophylaxis decreased by more than 50% in both groups. Long-term secondary prophylaxis does not prevent the progression of haemophilic arthropathy, but may modestly slow the rate of progression[6].

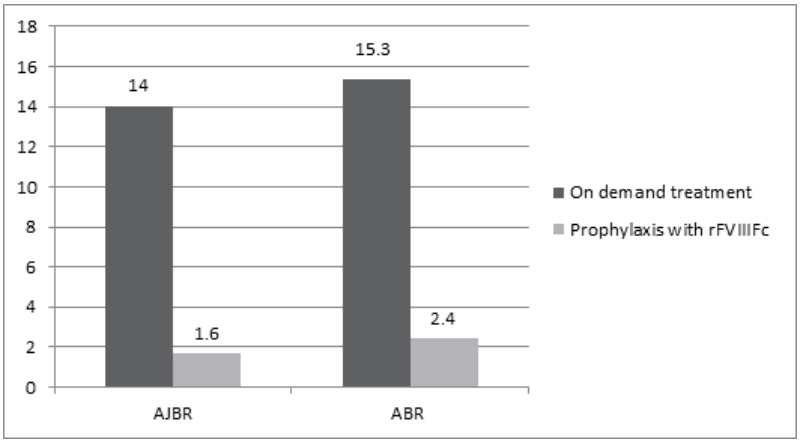

Figure 1. Mean AJBR and ABR in the pre-prophylaxis period vs. during prophylaxis with rFVIIIFc.

A survey organized by patients' groups in Europe examined the use of prophylaxis in people aged 20–35 with severe haemophilia and found an inverse correlation between time on prophylaxis and occurrence of major bleeds, presence of target joints and time off work. As expected, patients from Sweden who had spent the longest period on prophylaxis had the best preserved joints and best quality of life[7]. Berntorp et al reported that more than 60% of patients between 20 and 40 years old were on regular prophylaxis in many European centers[8].

In our study, a significantly low ABR and AJBR during prophylaxis was achieved with an intermediate dose of rFVIIIFc in a fixed twice-weekly scheme. Although all the patients had several target joints and only 58.3% had FVIII levels $\geq$ 1 IU dL^{-1} at all times, all patients had a marked decrease in bleeding. Björkman et al. had reported that some patients did not bleed in spite of a trough level of <1 IU dL^{-1} and others did in spite of trough levels >3 IU dL^{-1}[9]. No inhibitor development was detected in our study population of previously treated patients with the use of rFVIIIFc. Prophylaxis also allowed the patients to perform physical activities on a regular basis, avoiding the fear of bleeding and favoring the indisputable benefits of exercising.

The limitation of this study is that it does not compare different doses/frequency of prophylaxis nor the results of rFVIIIFc vs. conventional FVIII products. We can conclude that rFVIIIFc was well tolerated, safe and efficacious in the prevention and treatment of bleeding in young adults with severe haemophilia A. Patients with twice weekly prophylaxis experienced clinically meaningful reductions in bleeding compared with episodic treatment.

Even when the cost was not analyzed in this study, Fischer et al. suggested that conservative prophylaxis yields significant benefits over intensive on-demand treatment, even when annual factor consumption rates are similar, in adult patients[10]. Coppola et al. also reported that late prophylaxis vs. on-demand therapy results in a cost-effective approach in adolescents and adults with severe haemophilia A[11]. Iorio et al. in a literature review concluded that prophylaxis with rFVIIIFc may be associated with improved bleeding rates and lower weekly factor consumption than more frequently injected rFVIII products[12].

Finally, as Makris stated[13], we also consider that for the majority of patients with severe haemophilia, prophylactic treatment for life should be the standard of care.

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Disclosures

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

Authorship contributions

ND and EL designed the study, collected and analyzed the data, and wrote the manuscript. ND, EL and CA performed the performed the follow up of the patients. PL was in charge of all the laboratory tests. All the authors read and approved the manuscript for submission/publication.

Conflictos de interés: Los autores declaran no poseer conflictos de interés.

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