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ORIGINAL ARTICLE *Musculoskeletal*

Musculoskeletal evaluation in severe haemophilia A patients from Latin America

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Summary. There is a paucity of literature on haemophilia treatment in Latin American countries, a region characterized by rapidly improving systems of care, but with substantial disparities in treatment between countries. The aim of this study was to evaluate the musculoskeletal status of haemophilia patients from Latin America and to examine the relationship between musculoskeletal status and treatment practices across countries. The Committee of Latin America on the Therapeutics of Inhibitor Groups conducted a survey of its member country representatives on key aspects of haemophilia treatment in 10 countries. Musculoskeletal status of patients was obtained during routine comprehensive evaluations between March 2009 and March 2011. Eligible patients had severe haemophilia A (factor VIII <1%) without inhibitors (<0.6 BU mL^{-1}) and were ≥5 years of age. Musculoskeletal status was compared between three groups of countries, based primarily on differences in the availability of long-term prophylaxis. Overall, 143 patients (5–66 years of age) were enrolled from nine countries. In countries where long-term prophylaxis had been available for at least 10 years (Group A), patients aged 5–10 years had significantly better mean World Federation of Hemophilia clinical scores, fewer target joints and fewer affected joints than patients from countries where long-term prophylaxis has been available for about 5 years (Group B) or was not available (Group C). In Latin America, the musculoskeletal status of patients with severe haemophilia without inhibitors has improved significantly in association with the provision of long-term prophylaxis. As more countries in Latin America institute this practice, further improvements are anticipated.

Keywords: haemophilia, haemophilia treatment, haemophilic arthropathy, Latin America, musculoskeletal evaluation

Introduction

According to the World Federation of Hemophilia (WFH) Global Survey, in 2010 there were 25 477 haemophilia patients registered among 18 countries in Latin America, comprising 16% of all patients with haemophilia reported globally in the survey [1]. It is therefore important to assess the current status of haemophilia treatment in Latin America. In this region, some countries have made major efforts to improve the care of haemophilia patients by developing a national programme and acquiring increasing amounts of therapeutic products to meet patients' needs, whereas in other countries, obtaining products for the treatment of haemophilia has not been a priority, resulting in a lack of adequate treatment.

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One way of assessing the impact of improved care in some countries and the treatment disparity among countries in Latin America is via a comprehensive evaluation of musculoskeletal status among haemophilic patients. Such an evaluation is an excellent indicator of treatment effectiveness because 80% of haemorrhages in haemophilia occur in the musculoskeletal system [2,3]. Recurrent haemarthroses and the resulting arthropathy are the most common disabling manifestations of haemophilia [4,5]. The modality and availability of replacement therapy to prevent bleeding episodes, therefore, directly affects musculoskeletal outcomes [3].

The objective of this study was to evaluate the musculoskeletal status of haemophilia patients from 10 countries in Latin America, and to examine the relationship between musculoskeletal status and treatment practices in each country. We sought to determine if early institution of long-term prophylaxis resulted in better musculoskeletal outcomes.

Materials and methods

This study was conducted by members of the Committee of Latin America on the Therapeutics of Inhibitor Groups (CLOTTING) (http://www.clotting.org). The committee comprises 13 physicians specializing in haemophilia from Latin America.

Country information

Information regarding country-specific haemophilia treatment was obtained by surveying members of CLOTTING. The survey requested data on the number of patients diagnosed, whether there was access to safe treatment with factor concentrates, what types of treatment were regularly used, and how much factor VIII (FVIII) was consumed annually. In particular, we investigated if primary or secondary prophylaxis was used and when each was started.

Study cohort

Enrolment took place from March 2009 to March 2011 at each patient's routine comprehensive evaluation. To be eligible for participation in the study, patients had to have severe haemophilia A (FVIII <1%) without inhibitors (<0.6 BU mL^{-1}), be at least 5 years of age, and not experiencing a bleeding episode during the evaluation visit. Patients were placed in one of four prespecified age strata: 5–10, 11–21, 22–35 and >35 years of age.

The study was approved by each local Ethics Committee. Signed informed consent was obtained from patients or their parents or legal guardians before enrolment.

Clinical history

Clinical data on haemophilia treatment obtained from the patient's record included the following: age at time of the first replacement treatment; type of product(s) used [cryoprecipitate/transfusion only, FVIII concentrate only (plasma-derived or recombinant products), or both]; type of treatment received (primary prophylaxis, long-term secondary prophylaxis, short-term prophylaxis, on-demand and/or home treatment) from birth up to the evaluation; and the total amount of factor concentrates received per year (IU kg^{-1}) during the 3 years preceding the evaluation. Prophylaxis, whether primary or secondary, was defined as regular factor replacement for at least 46 weeks per year [6].

The musculoskeletal assessment consisted of the following: clinical evaluation of index joints (elbows, knees and ankles) using the WFH Physical Joint Examination instrument [2,6]; radiological evaluation of index joints by a single radiologist blinded to all clinical data and scored using the Pettersson system [7]; determination of the presence of a target joint (≥3 bleeding episodes into the same joint in a consecutive 3-month period [7]) during the 12 months preceding enrolment, regardless of whether it was an index joint; and a lifetime count of invasive joint procedures. The frequency of bleeding episodes over the 3 years preceding enrolment was categorized as: ≥1 bleed/week; 2–3 bleeds/month; 7–12 bleeds/year; 4–6 bleeds/year; 1–3 bleeds/year or <1 bleed/year.

Data analysis

The countries that contributed data to the study were divided into three groups (A, B and C), according to specific characteristics of the haemophilia treatment available in each country (no data were available from Costa Rica) (Table 1). The determining criteria for group assignment were the presence vs. absence of a regular long-term prophylaxis programme and the timing of the initiation of that prophylaxis programme. Group A included Argentina, Chile and Panama; Group B included Colombia, Peru and Venezuela; Group C included Brazil, Mexico and Uruguay. For some countries, such as Peru, the criteria used for classification were not applicable to the country as a whole, but did accurately describe the treatment at the institutions that enrolled patients in this study.

The outcome measures analysed were the total WFH clinical score and Pettersson score for index joints, the number of affected joints, the proportion of patients with at least one target joint, the proportion of patients without joint damage (0 clinical score/0 radiological score), the proportion of patients who had an orthopaedic procedure, the number of patients in long-term prophylaxis and the mean age at which

Table 1. Haemophilia treatment data from each Latin American country participating in the musculoskeletal assessment.*

Country	Haemophilia patients registered	FVIII IU per capita	Estimate of patients with safe treatment access† (%)	Percentage of recombinant FVIII (%)	Primary/secondary prophylaxis (year started)	Short-term prophylaxis	Home treatment
Group A							
Argentina	2264	2.44	100	24	Yes (2000)	Yes	Yes
Chile	1252	2.1‡	100	6‡	Yes (1997/2006)¥	Yes	Yes
Panama	262	1.5‡	100	0‡	Yes (2002)	Yes	Yes
Group B							
Colombia	1915	1.38	100	44	Yes (2007)	Yes	Yes
Peru	743	0.55	46§	15	Yes (2008)§	Yes	Yes
Venezuela	2040	1.51	100	59	Yes (2007)	Yes	Yes
Group C							
Brazil	10 065	1.15	100	0	No	Yes	Yes
Mexico	4527	0.60	70¶	4	No	Yes	Yes
Uruguay	236	2.0‡	100	0‡	No	Yes	Yes
Summary	23 304	1.47	91	17	6/9	All	All

*Data derived from WFH Report on the Annual Global Survey 2010 [1].
†Treatment with factor concentrates.
‡Data from the country survey performed for this study.
§In Peru 46% of patients with haemophilia had access to factor concentrates provided by EsSalud (El Seguro Social de Salud del Perú). The patients affiliated to EsSalud started prophylaxis in 2008 (GC, personal communication).
¶In Mexico 70% of patients with haemophilia had access to factor concentrates provided by IMSS (Instituto Mexicano del Seguro Social) (JG-C, personal communication).
¥In Chile primary prophylaxis was initiated in 1997 only in Hospital Roberto del Rio, Santiago, where most of the patients with haemophilia enrolled in this analysis were treated. In the rest of the country, primary prophylaxis started in 2006.
FVIII, factor VIII.

this was initiated and the annualized FVIII consumption per patient.

Data were analysed for each of the four prespecified age strata: 5–10, 11–21, 22–35 and >35 years of age, as well as for the population as a whole.

Statistical analyses

Differences between groups were analysed using Kruskal–Wallis test for nonparametric data. Whenever significant differences were detected between the three groups, Mann–Whitney test was applied between pairs of groups (Groups A vs. B, A vs. C, and B vs. C). All pairwise results were corrected for multiplicity using the Bonferroni correction. We also compared Group A vs. Groups B and C combined to provide greater statistical power to detect a difference between the countries with the longest history of providing long-term prophylaxis (Group A) and the remaining countries (Groups B + C).

Results

Participants

A total of 143 severe haemophilia A patients without inhibitors from nine countries in Latin America, ranging in age from 5 to 66 years, were enrolled in this study. The mean age of study participants was similar across groups in each age stratum (Tables 2 and 3).

Treatment characteristics by country

In countries from Group A, long-term prophylaxis was made available between 1997 and 2002; in Group B countries since 2007 or 2008; and not at all in countries from Group C (Table 1). In the 5- to 10-year-old age stratum, all 12 patients from Group A received long-term prophylaxis, beginning at a mean age of 1.7 years. In Group B, 6 of 8 patients received primary prophylaxis, with a mean age at initiation of 3.4 years (Table 2). The most commonly used prophylaxis regimen was a flexible protocol of 20–30 IU kg^{-1} 3x/week. In Panama, a fixed protocol of 25 IU kg^{-1} 3x/week was used. Venezuela was the only country to offer tailored prophylaxis based on the Canadian protocol (50 IU kg^{-1} 1x/week or 30 IU kg^{-1} 2x/week or 25–30 IU kg^{-1} 3x/week) [8].

Per capita factor usage was highest in Argentina and Chile, where long-term prophylaxis has been available for the longest period of time (Table 1). Uruguay had similarly high usage despite not offering long-term prophylaxis. Mexico and Peru had the lowest usage of factor per capita, and were also the only countries without 100% access to safe treatment. The use of recombinant factor was highest in Venezuela and Colombia (about 50%) [1].

In contrast, all countries provided home treatment and short-term prophylaxis for all patients (Table 1).

Musculoskeletal outcomes by country group

The most striking difference between country groups was with respect to the proportion of patients with no joint damage in the two younger age strata. In Group A, 12 patients (50% of the total) aged 5–21 years had no joint damage, compared with 3 (19%) in Group B and just 1 (4%) in Group C (Fig. 1a). In addition, only 2 of 24 patients had orthopaedic procedures

Table 2. Musculoskeletal evaluation of patients aged 5–21 years with severe haemophilia A in Latin America.

	Group A (Argentina, Chile, Panama)		Group B (Colombia, Peru, Venezuela)		Group C (Brazil, Mexico, Uruguay)	
Age group (years)	5–10 (*N* = 12)	11–21 (*N* = 12)	5–10 (*N* = 8)	11–21 (*N* = 8)	5–10 (*N* = 12)	11–21 (*N* = 16)
Mean age, years (range)	7.3 (5–10)	15.2 (11–19)	7.2 (5–10)	14.5 (11–20)	8.1 (6–10)	15.4 (11–20)
N of patients without joint damage (0/0)* (%)	6 (50)	6 (50)	2 (25)	1 (13)	1 (8)	0 (0)
Mean *N* of affected joints per patient (range)	1.2 (0–3)	1.8 (0–6)	1.6 (0–4)	1.8 (0–4)	2.3 (0–4)	3.6 (1–6)
N of patients with target joints (%)	1 (8)	2 (17)	3 (38)	4 (50)	6 (50)	10 (63)
N of patients with joint procedure (*N* of joints treated)	1 (1)	1 (1)	1 (1)	4 (6)	2 (3)	7 (11)
Clinical score, mean [SD] (range 0–90)	1.2 [1.4] (0–4)	9.1 [16.7] (0–49)	3.0 [2.2] (0–10)	5.1 [3.6] (0–17)	4.4 [2.9] (0–10)	11.5 [6.4] (1–26)
Pettersson score, mean [SD] (range 0–78)	1.4 [3.1] (0–6)	7.9 [6.1] (0–34)	6.1 [3.5] (0–14)	8.8 [6.6] (0–25)	3.0 [2.3] (0–11)	13.1 [9.4] (0–35)
Frequency of bleeding episodes, last 3 years (categorical estimate)†	1–3/year	1–3/year	4–6/year	2–3/month	7–12/year	2–3/month
Mean FVIII consumption IU kg^{-1} per year, last 3 years (SD)	2207 (497)	2162 (968)	2337 (481)	2360 (683)	1607 (946)	1733 (1119)
N of patients on long-term prophylaxis (%)	12 (100)	6 (50)	6 (75)	7 (88)	0 (0)	0 (0)
Mean age at start of prophylaxis, years (range)	1.7 (0.8–5)	5.7 (1.1–13)	3.4 (1–7)	14 (10–18)	NA	NA

*WFH clinical score 0/Pettersson score 0.
†Categories (in order of decreasing frequency): ≥1 bleed/week; 2–3 bleeds/month; 7–12 bleeds/year; 4–6 bleeds/year; 1–3 bleeds/year; <1 bleed/year.
NA, not applicable; SD, standard deviation.

Table 3. Musculoskeletal evaluation of patients >21 years of age with severe haemophilia A in Latin America.

	Group A (Argentina, Chile, Panama)		Group B (Colombia, Peru, Venezuela)		Group C (Brazil, Mexico, Uruguay)	
Age group (years)	22–35 (*N* = 10)	>35 (*N* = 10)	22–35 (*N* = 11)	>35 (*N* = 11)	22–35 (*N* = 18)	>35 (*N* = 15)
Mean age, years (range)	27.0 (22–33)	45.6 (38–57)	26.6 (22–32)	44.2 (36–66)	27.7 (22–34)	44.3 (36–61)
N of patients without joint damage (0/0)*	0	0	0	0	0	0
Mean *N* of affected joints per patient (range)	4.4 (3–7)	5.6 (3–6)	4 (2–6)	4.5 (2–6)	4.7 (2–7)	5.1 (4–6)
N of patients with target joints (%)	7 (70)	8 (80)	7 (64)	7 (64)	12 (67)	9 (60)
N of patients with joint procedure (*N* of joints treated)	7 (11)	3 (4)	8 (15)	8 (27)	9 (17)	7 (9)
Clinical score, mean [SD] (range 0–90)	31.2 [18.4] (6–82)	43.7 [25.1] (6–82)	18.6 [8.5] (4–43)	24.3 [11.5] (2–48)	17.1 [6.7] (3–36)	22.9 [8.1] (8–37)
Pettersson score, mean [SD] (range 0–78)	38.9 [7.5] (23–54)	40.4 [9.2] (16–53)	28.7 [8.2] (9–26)	45.8 [9.4] (20–62)	25.9 [8.3] (4–47)	28.7 [10.5] (6–48)
Frequency of bleeding episodes, last 3 years (categorical estimate)†	2–3/month	4–6/year	7–12/year	7–12/year	7–12/year	7–12/year
Mean FVIII consumption IU kg^{-1} per year, last 3 years (SD)	2200 (1,245)	1817 (1,118)	1931 (561)	1576 (607)	719 (390)	562 (339)
N of patients on long-term prophylaxis (%)	2 (20)	0 (0)	5 (45)	4 (36)	0 (0)	0 (0)
Mean age at start of prophylaxis, years (range)	21.5 (16–27)	NA	21.4 (19–26)	45 (36–62)	NA	NA

*WFH clinical score 0/Pettersson score 0.
†Categories (in order of decreasing frequency): ≥1 bleed/week; 2–3 bleeds/month; 7–12 bleeds/year; 4–6 bleeds/year; 1–3 bleeds/year; <1 bleed/year.
NA, not applicable; SD, standard deviation.

(8%), compared with 5 of 16 (31%) from Group B and 9 of 28 (32%) from Group C (Fig. 1b).

Clinical score was significantly better in Group A vs. Group C in the 5- to 10-year-old stratum ($P = 0.04$) (Fig. 1c). In contrast, in the >35-year-old stratum, Group C had a nonsignificantly lower score than Group A ($P = 0.051$) (Fig. 1c). As expected, the younger age strata showed significantly better scores for Group A compared with Groups B + C (5–10 years old, $P = 0.02$; 11–21 years old, $P = 0.04$; data not shown). Group A patients had significantly worse scores than Groups B + C in the >35-year-old stratum ($P = 0.01$; data not shown).

In the two younger age strata, the mean number of affected joints in patients from Group C was approximately double that of patients from Group A (Table 2). The mean number of affected joints was significantly fewer in Group A vs. Groups B + C in these age strata ($P = 0.04$ for both comparisons; data not shown). No differences were noted in the two older age strata across the three groups (Table 2) or between Group A and Groups B + C.

Similarly, Group A patients also had a lower mean number of target joints than Group C patients in the 11- to 21-year-old stratum ($P = 0.02$) (Fig. 1d) and

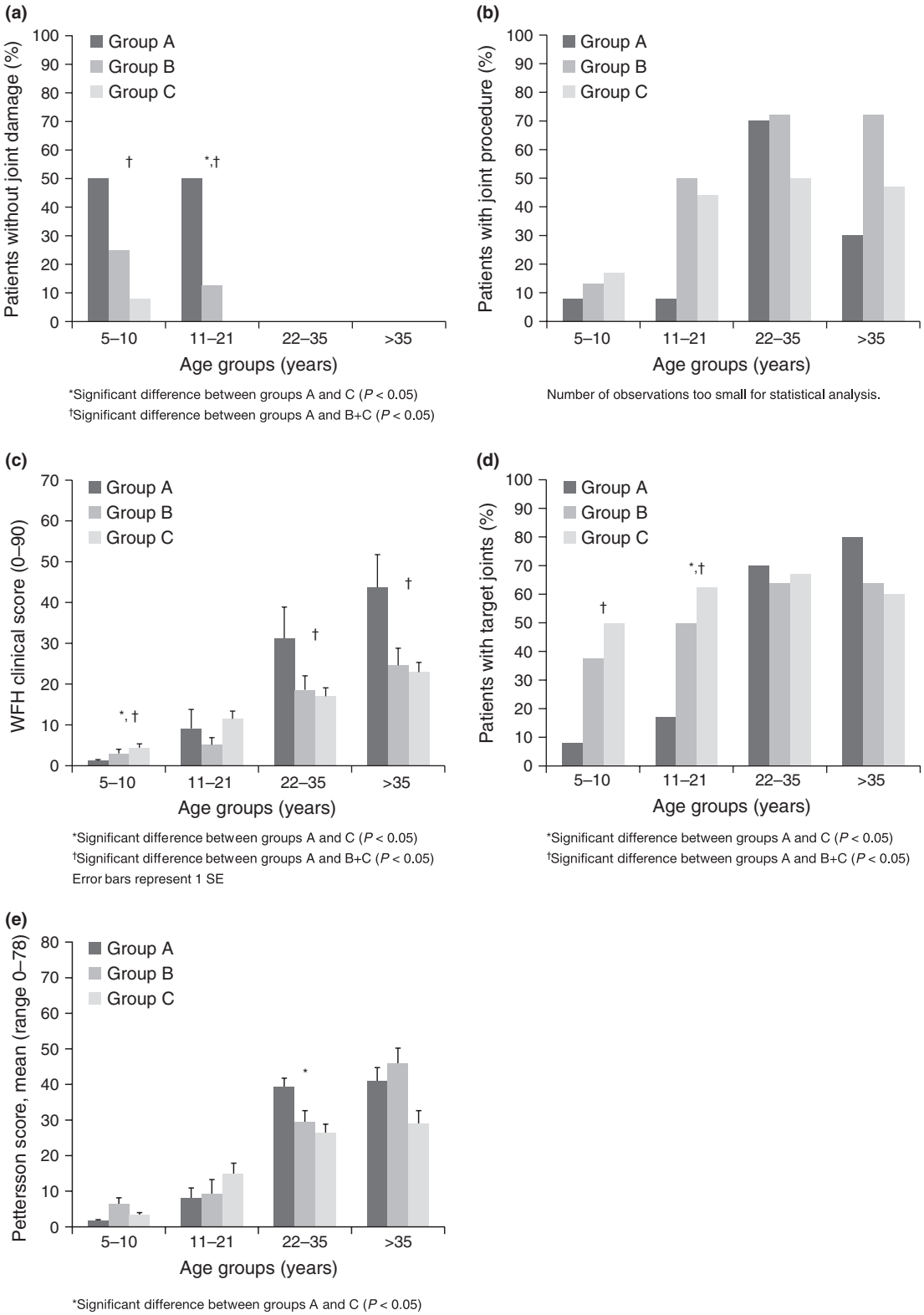

Fig. 1. Outcomes by country groups stratified by age.

the mean number of target joints was significantly fewer in Group A compared with Groups B + C in both younger age strata ($P = 0.048$, 0.02 for the 5- to 10- and 11- to 21-year-old strata respectively). The three groups did not differ significantly with respect to Pettersson scores (Fig. 1e).

Patients from the two younger age strata from Group A had the lowest frequency of bleeding. The next lowest frequency of bleeding was observed in the 5- to 10-year age group from Group B, whereas the 11- to 21-year-old age group from Group B had a much higher frequency (Table 2). The frequency of bleeding in the older age strata was at least 7–12 bleeds/year, except in the >35-year-old stratum from Group A (Table 3).

Although mean annualized factor consumption per patient during the 3 years preceding enrolment was greater in Group A than in Group C ($P < 0.0001$) and greater in Group B than in Group C ($P < 0.0001$) when all age strata were combined, analysis by age stratum showed no significant difference in this metric for either of the two younger age strata. However, in the two older age strata, factor consumption in Group C was significantly less compared with either Group A or B (22- to 35-year-old stratum, $P \leq 0.001$; >35-year-old stratum, $P \leq 0.01$) (Fig. 2).

Discussion

To our knowledge, this is the first publication providing comprehensive data on the musculoskeletal status of haemophilic patients in Latin America, as well as a representative cross-sectional assessment of haemophilia treatment across Latin America. To best understand the effects of treatment on musculoskeletal outcome, we included only haemophilia A patients with severe disease and without inhibitors. We then compared the musculoskeletal status of patients between groups of countries according to their different access to long-term prophylaxis.

As anticipated, these data provide confirmatory evidence of the benefits of primary prophylaxis in preserving musculoskeletal health in patients with severe haemophilia without inhibitors, extending the evidence derived from studies conducted in North America and Europe [8–10]. The cardinal finding of this study was that in countries (centres) where long-term prophylaxis was available for at least 10 years (Group A), the musculoskeletal status of patients with haemophilia 5–10 years of age was superior to that of patients 5–10 years of age from countries where long-term prophylaxis was not available to this extent (Groups B + C). This benefit was particularly evident with respect to the greater number of joints without damage and the lower clinical scores; it was also evident in fewer target joints and a lower frequency of bleeding. Similar results were obtained in the 10- to 21-year-old stratum, though the differences were of lesser magnitude.

The mean per patient factor consumption among severe haemophilia A patients without inhibitors up to 21 years of age was similar between groups whether long-term prophylaxis was available or not. This is likely a result of the greater need for on-demand treatment in patients not receiving prophylaxis, and suggests that prophylaxis may not entail as great an increase in factor consumption and associated cost as may have been anticipated. Taken together, these data suggest that primary prophylaxis is associated with better outcomes and with similar factor usage, consistent with data reported from Europe [11].

However, these data do not provide empirical evidence confirming the benefit of secondary prophylaxis, which has been documented in clinical studies [12,13]. In fact, clinical scores were significantly worse in Group A vs. Groups B + C in patients older than 35 years, though there were no significant differences in pairwise comparisons between Group A and Group B or between Group A and Group C. We investigated this issue further by comparing individual countries within Group A and found that clinical scores from Chile were markedly worse than scores from Argentina and Panama (data not shown). In Chile, patients in the oldest age group were referred to a haemophilia reference centre for orthopaedic procedures, possibly resulting in biased enrolment. Other factors that may have contributed to the lack of demonstrated benefit of secondary prophylaxis include delayed initiation and/or too short a period of prophylaxis administration.

In the oldest age group, increased factor consumption did not appear to be associated with superior musculoskeletal outcomes. In fact, patients in Groups A and B aged >21 years showed a trend for higher factor consumption and worse clinical scores than patients in the same age strata in Group C. In these patients, increased factor usage may have been related to more frequent bleeding episodes requiring more on-demand therapy, more orthopaedic procedures, more frequent use of secondary prophylaxis (e.g. in Chile,

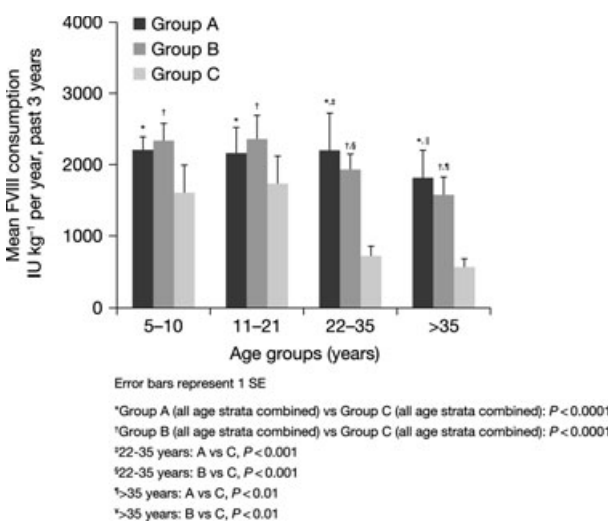

Fig. 2. Factor VIII consumption by country groups stratified by age.

Venezuela and Columbia), or a combination of these reasons.

Overall, we found that haemophilia care in Latin America is heterogeneous, particularly with respect to the availability of primary prophylaxis, safe treatment and recombinant factor. During the past 10 years, treatment has improved in many countries, as evidenced by the introduction of long-term prophylaxis in Colombia (www.pos.gov.co), Venezuela and in several centres in Peru. More recently, in Brazil (www.saude.gov.br), Uruguay (www.msp.gub.uy) and at some centres in Mexico (www.salud.gob.mx), long-term prophylaxis has been made available.

However, further optimization is needed in many countries. For the majority of countries/centres in Latin America, including those countries not involved in this study, treatment is still given exclusively on demand. In addition, access to orthopaedic procedures remains limited in many countries and some do not have a national programme. Moreover, there is lack of patient registries, which provide an extremely valuable tool for evaluating treatment effectiveness over time.

In addition to the differences in musculoskeletal outcomes between groups of countries, our survey found important differences between certain countries with respect to haemophilia treatment policies and practices. For example, the prophylaxis protocols adopted differed by country, with Venezuela, and more recently Brazil, being the only countries to institute tailored prophylaxis based on the Canadian protocol. Another example is that although treatment protocols are standardized in most countries, in Mexico, Peru and Colombia the practices followed by the centres represented in this study may not reflect prevailing practice in other parts of those countries.

There are several notable strengths of this study. First, it includes nine countries, large and small, located throughout Latin America. Second, we stratified patients by age, enabling us to detect differences among the youngest patients, who have experienced the largest impact from changes in the availability of primary prophylaxis. Third, standardized instruments were used for assessment, thereby helping to harmonize the data obtained from disparate clinical settings. In addition, the CLOTTING group is a well-established entity that brings together Latin American leaders in the field of haemophilia care, which facilitated the development of the study protocols, the collection and analysis of data and the writing of this manuscript.

One important limitation of the study is that data were gathered only from reference centres and may not be entirely generalizable to each country as a whole. In Chile, for example, the musculoskeletal status of patients managed at the reference centre was reportedly worse than that of patients seen elsewhere in the country. Another limitation is that although the evaluations were standardized, inter-rater reliability was not formally established. Lastly, we were not able to determine the exact number of bleeding episodes for all patients.

Conclusions

This is the first report on the musculoskeletal status of patients with severe haemophilia A residing in Latin America. We documented that severe musculoskeletal complications are a major problem among haemophilia patients from this region. Although haemophilia treatment remains heterogeneous among Latin American countries, there has been considerable improvement in most countries. Most importantly, our data show that in countries that have had established programmes for long-term prophylaxis for at least 10 years, the musculoskeletal status of patients in the early age groups was similar to haemophilia patients from developed countries. In countries that only started long-term prophylaxis programmes more recently, it is too soon for significant benefits to be observed.

In addition, we observed in patients up to 21 years of age that factor consumption among countries providing prophylaxis was similar to that observed in countries with treatment based on demand, while musculoskeletal status was significantly better. It therefore appears that providing primary prophylaxis treatment in developing countries, such as those we studied in Latin America, results in better musculoskeletal status outcomes than on-demand therapy, with similar factor consumption.

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Author contributions

MCO, PRV and AR-S designed the study, collected and analysed the data and wrote the paper, MBR performed the Pettersson score analysis, RP-B, MC, GC, JG-C, BM-R, IR-G, MBR, MHS and MMM-G, collected data and wrote the paper. All authors approved the final and submitted versions.

Disclosures

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