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An Indirect Comparison of the Efficacy of Prophylactic Use of rFIXFc and rFIX Products and Simulation of the Effect of Compliance on Effectiveness

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BACKGROUND

- Prophylaxis with replacement factor IX (FIX) for the treatment of hemophilia B generally requires infusions 2 to 3 times weekly.[1] Poor compliance with this regimen may lead to increased bleeding and poor long-term outcomes, such as chronic pain.[2,3]
- With the approval of recombinant factor IX Fc fusion protein (rFIXFc) as a new treatment option, clinicians, payers, and other key decision makers in the treatment of hemophilia will require evidence comparing the efficacy of this new treatment with that of existing treatments. However, no head-to-head clinical studies have been conducted.
- Prophylactic treatment with rFIXFc may require fewer infusions compared with recombinant factor IX (rFIX) products (BeneFIX® and Rixubis®), which has potential implications for compliance. Hence, in addition to comparisons of efficacy based on published clinical studies, there is interest in the potential impact of improved compliance on effectiveness.

OBJECTIVES

- In the absence of head-to-head, direct comparative evidence from clinical trials, this study aimed to indirectly compare the prophylactic efficacy of rFIXFc with that of rFIX products, using published clinical study results.
- A model was developed to assess the potential impact of improved compliance on the real-world effectiveness of prophylactic treatment regimens.

METHODS

Data sources

- Phase 3 B-LONG clinical study,[4] which evaluated treatment with rFIXFc in previously treated subjects, and Biogen Idec data on file[5]
- Published clinical studies of routine prophylactic treatment with rFIX products in previously treated subjects, identified by literature search
  - Sources for the literature search included the PubMed and ClinicalTrials.gov databases (with no restriction on year), and abstracts and posters from the following annual conferences: American Society of Hematology (2004-2012), European Association for Haemophilia and Allied Disorders (2009-2012), and the International Society of Hematology (2012). The search was based on the terms "factor IX and hemophilia and prophylaxis." If a study was presented at both a conference and in a paper, the paper data were utilized.

Study inclusion criteria

- Clinical studies of routine prophylactic use of rFIX in previously treated patients with moderate to severe hemophilia B; studies must have reported mean annualized bleeding rate (ABR) or number of bleeding events.

Screening and data extraction

- Two reviewers independently screened and extracted data from eligible studies using a structured data form. Any discrepancies between reviewers were resolved by consensus.
- The following data were extracted: study design, duration, inclusion and exclusion criteria, treatment intervention (including doses and frequency of administration), characteristics and outcomes of subjects in routine prophylaxis treatment group(s) (ie, number of subjects, mean, and standard deviation [SD] of ABR). In cases where the study did not report characteristics of subjects for the respective prophylaxis treatment group, characteristics of subjects from the overall study were extracted.

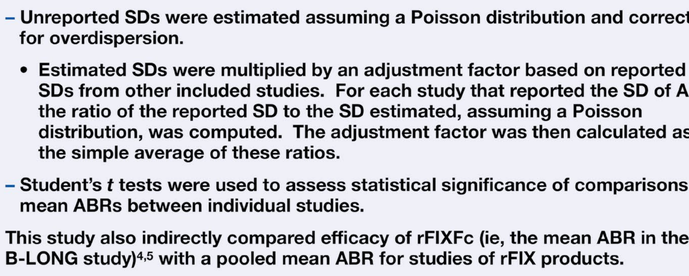
Statistical analysis

- This study conducted unadjusted indirect comparisons of the efficacy of rFIXFc and rFIX, as measured by mean ABR reported in the weekly prophylaxis arm (Arm 1) of the B-LONG study,[4,5] and individual studies of rFIX products identified through the literature search. This study focused on the once-weekly prophylaxis arm of B-LONG, as it was comparable in design to the fixed interval treatment regimens of most other comparison studies identified.
  - Simple difference in mean rFIXFc ABRs and rFIX ABRs reported by individual studies was calculated.
  - Unreported SDs were estimated assuming a Poisson distribution and corrected for overdispersion.
    - Estimated SDs were multiplied by an adjustment factor based on reported SDs from other included studies. For each study that reported the SD of ABR, the ratio of the reported SD to the SD estimated, assuming a Poisson distribution, was computed. The adjustment factor was then calculated as the simple average of these ratios.
  - Student's *t* tests were used to assess statistical significance of comparisons of mean ABRs between individual studies.
- This study also indirectly compared efficacy of rFIXFc (ie, the mean ABR in the B-LONG study)[4,5] with a pooled mean ABR for studies of rFIX products.
  - Heterogeneity across studies was assessed via the I^2 statistic, which quantifies the degree of heterogeneity and describes the percentage of total variation across studies due to heterogeneity rather than chance.
  - Based on the moderate heterogeneity and expected variability of effect across the studies, a meta-analysis with random-effects models, using the DerSimonian and Laird method,[6] was used to compute the weighted pooled summary ABR estimates from individual studies of prophylaxis treatment with rFIX products.
  - Simple difference in reported mean ABR of rFIXFc and pooled rFIX ABR was calculated.
  - For all pooled ABR estimates, 95% confidence intervals (CI) were computed.
  - *Z* test statistics were used to assess statistical significance of the comparison between rFIXFc ABR and the pooled ABR of rFIX products.
- Given the small number of published rFIX studies, the differences in design across studies, and the limited data on subject characteristics reported, an adjusted comparison was not feasible.

Compliance simulation

- A model was developed to explore the impact of simulated changes in real-world compliance on ABR (Figure 1). The compliance-adjusted ABR for a given product at each level of compliance with prophylaxis was calculated as the weighted average of the compliant and noncompliant ABRs.
- Noncompliant was defined as being 0% compliant with prophylaxis, therefore exhibiting a bleed rate on par with an on-demand patient.

Figure 1. Methodology to adjust ABR for compliance[a]



ABR, annualized bleeding rate; rFIXFc, recombinant factor IX Fc fusion protein; OD, on-demand; P, prophylaxis; rFIX, recombinant factor IX.
[a]Adapted from *Mickisch et al*.[7]

- Base case estimates of compliance were based on data reported in the literature. The following 2 prophylaxis compliance estimates were used in the simulation:
  - The percentage of hemophilia A or B patients, or their caregivers, who administer 76% to 100% of prescribed infusions was reported by *Hacker et al* as 58.8%.[8]
  - The median adherence to prescribed frequency for severe hemophilia A patients, based on infusion logs, was reported by *Ho et al* as 75.7%.[9]

RESULTS

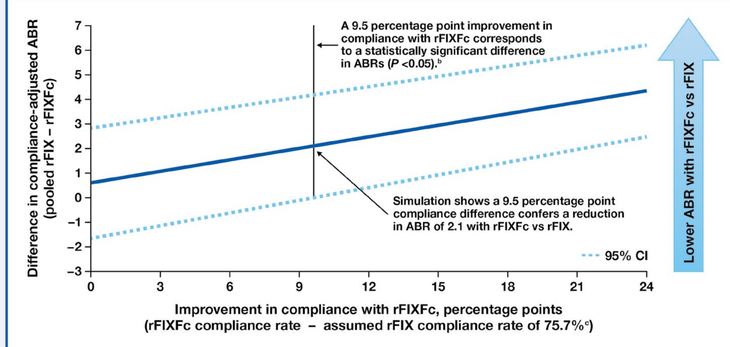
Relevant studies identified

- The literature search identified 4 published studies of rFIX in subjects with moderate/severe hemophilia.[10-13] Key study design and subject characteristics for the B-LONG study and rFIX studies are described in Table 1.
- Infusion frequencies in studies by *Roth et al*[10] and *Lambert et al*[11] were 1 to >3 times/week (dose and frequency were determined by the study investigator). *Valentino et al*[12] examined 2 different prophylaxis regimens: 100 IU/kg once weekly and 50 IU/kg twice weekly. *Windyga et al*[13] examined a prophylaxis regimen of 50 IU/kg twice weekly.
- All studies specified maximum baseline FIX levels allowable as part of their inclusion criteria (≤2%-≤5%).
- Overall study duration ranged from 26 to 104 weeks.

Routine prophylaxis ABRs

- Mean ABRs for prophylaxis treatment with rFIXFc and rFIX products are described in Table 2.

Figure 2. An example of simulated differences in ABR between rFIXFc and rFIX products resulting from improved compliance with rFIXFc[a]



ABR, annualized bleeding rate; rFIXFc, recombinant factor IX Fc fusion protein; rFIX, recombinant factor IX; CI, confidence interval.
[a]Pooled estimates of ABRs on prophylaxis based on random-effects meta-analysis of all rFIX comparator studies. Standard deviations for the *Roth et al*,[10] *Lambert et al*,[11] and *Valentino et al*[12] studies were estimated assuming Poisson distributions and adjusted for overdispersion; other studies are as reported.
[b]When assumed rFIX compliance rate is 75.7%. Note that lower 95% confidence limit is >0.
[c]Based on estimates of current levels of prophylaxis compliance reported in *Ho et al*.[9]

Table 1. Study characteristics

Study	Product	Design	Subjects, N	Baseline FIX, % of normal	Duration,[b] wk
Powell et al[4,a]	rFIXFc	Open-label, nonrandomized	119	≤2%	52
Roth et al[10]	rFIX (BeneFIX)	Open-label, nonrandomized	56	≤5%	104
Lambert et al[11]	rFIX (BeneFIX)	Double-blind, randomized, crossover design for establishing equivalency of PK profiles between original and reformulated rFIX; open-label, nonrandomized prophylaxis	34	≤2%	32
Valentino et al[12]	rFIX (BeneFIX)	Open-label, randomized, crossover	50	≤2%	56
Windyga et al[13]	rFIX (Rixubis)	Randomized crossover design for establishing equivalency of PK profiles between Rixubis and commercial rFIX on subset of patients; open-label, nonrandomized prophylaxis	86	≤2%	26

rFIXFc, recombinant factor IX Fc fusion protein; rFIX, recombinant factor IX; n/r, not reported; PK, pharmacokinetics.
[a]And data on file (Biogen Idec).[5]
[b]Actual duration was dependent on each study's "end of study" criteria, and may have been less than the specified number of weeks.

Table 2. Prophylaxis ABRs reported in included studies

Study	Routine prophylaxis regimen	Subjects, N	Age, y[a]	Mean prophylaxis duration, wk	Median ABR	Mean ABR ± SD[b]
Powell et al[4,c]	Once weekly, 50 IU/kg	63	28	48.4	2.96	3.07 ± 2.87
Roth et al[10,d]	2-3 times weekly, 40.3 IU/kg	19	23	n/r	n/r	5.49 ± 5.00
Lambert et al[11,e]	1 to >3 times weekly, 51.7 IU/kg	17	28.3	25.6	n/r	3.11 ± 3.76
Valentino et al[12]	Once weekly, 100 IU/kg Twice weekly, 50 IU/kg	44	27.7	16	n/r	4.60 ± n/r 2.60 ± n/r
Windyga et al[13]	Twice weekly, 50 IU/kg	56	34.5	24.8	1.99	4.26 ± 5.80

ABR, annualized bleeding rate; SD, standard deviation; n/r, not reported.
[a]Median reported for *Powell et al* and *Roth et al*; mean reported for all other studies.
[b]SD of ABR for *Windyga et al* was reported in the published study; SDs of ABRs for *Roth et al*, *Lambert et al*, and *Valentino et al* were not reported, and were estimated assuming Poisson distributions and adjusted for overdispersion, as described in the Methods section. The adjustment factor used was 2.13.
[c]And data on file (Biogen Idec).[5]
[d]Dose reported is the mean of actual infusions. Mean ABR was not reported and was estimated based on the reported number of bleeds, the number of patients in the study, and the mean follow up.
[e]Dose reported is the median of actual infusions.

Meta-analysis

- Based on the relevant clinical studies identified for this analysis, the pooled mean ABR estimate for rFIX was 3.84; I^2 = 57.5%.

Unadjusted indirect comparisons

- Results of the unadjusted indirect comparisons are described in Table 3.
- The rFIXFc once-weekly mean ABR was statistically indistinguishable from the ABRs of the individual comparator studies.
- The rFIXFc once-weekly mean ABR was statistically indistinguishable from the pooled mean ABR estimate for rFIX based on meta-analysis.

Table 3. Unadjusted indirect comparisons of prophylaxis ABRs

rFIX comparator	Once-weekly rFIXFc prophylaxis: Δ in ABR[a]	Once-weekly rFIXFc prophylaxis: *P* value[b]
Individual rFIX studies		
Roth et al[10]	–2.42	0.11
Lambert et al[11]	–0.04	0.79
Valentino et al (100 IU/kg)[12]	–1.53	0.12
Valentino et al (50 IU/kg)[12]	0.47	0.60
Windyga et al[13]	–1.13	0.33
All rFIX studies pooled (I^2 = 57.5%)[c]	–0.77	0.23

ABR, annualized bleeding rate; rFIXFc, recombinant factor IX Fc fusion protein; rFIX, recombinant factor IX.
[a]Negative value indicates fewer bleeds with rFIXFc compared with rFIX.
[b]Student's *t* test used for comparisons of individual studies; *Z* test used for comparison of pooled estimate.
[c]Pooled estimates are based on meta-analysis with random effects, as described in the Methods sections.

Compliance simulation

- In compliance simulations, the mean ABR (SD) of 18.7 (10.0) for patients receiving on-demand treatment in the B-LONG study[4,5] was used to describe a 0% compliant patient (noncompliant) on both rFIXFc and rFIX prophylaxis.
- Simulations showed that statistically significant reductions in mean ABR could result from improved prophylaxis compliance.
  - Based on literature-reported compliance levels of 75.7%[9] and 58.8%,[8] improvements in prophylaxis compliance with rFIXFc of ≥9.5 and ≥14.1 percentage points, respectively, would result in a significant decrease in mean ABR (simulation based on 75.7% compliance level depicted in Figure 2).

DISCUSSION AND LIMITATIONS

- This indirect comparison used a random-effects meta-analysis approach to account for between-study variance. Due to the small number of comparison studies evaluated, a meta-regression could not be performed; however, this approach may begin to shed light on a question of importance to key decision makers.
- Meta-analysis is a commonly used method in the literature, and has been conducted previously in studies of the hemophilia population.[14,15]
  - Although there were few relevant studies of rFIX products for inclusion in the meta-analysis, this approach is consistent with that taken in a Cochrane review to assess the relationship between adherence to prophylaxis therapy and number of bleeds in hemophilia patients, in which 2 studies were included in a meta-analysis.[14]
- Standard errors for some studies were estimated due to missing data. The potential bias was mitigated by adjusting estimates for possible overdispersion.
- The real-world impact of rFIXFc on compliance is unknown. However, rFIXFc has the potential for improved compliance due to less frequent dosing, and has also been associated with improved factor trough levels.[4] Separately, achieving target factor trough levels above 1% has been associated with a reduction in the number of bleeding episodes.[2,16]
- Compliance simulations were based on the assumption that patients today exhibit bleed rates between those typically observed for patients treated with on-demand and full prophylaxis regimens (as reported in clinical trials).
  - In interpreting these findings for patients with intermediate levels of compliance with prophylaxis treatment in the real world, an assumption of a linear relationship between compliance and ABR was used. Real-world studies on compliance and outcomes are needed to refine the nature of this relationship.

CONCLUSIONS

- Based on unadjusted indirect comparison of rFIXFc and rFIX products, the efficacy of prophylaxis treatment with once-weekly rFIXFc and other more frequently infused rFIX products is comparable.
- Modeling based on simulated differences in real-world compliance suggests that less burdensome dosing with rFIXFc has the potential to lead to improved real-world effectiveness.
  - Simulations suggest that improvement in prophylaxis compliance levels of ≥9 to 14 percentage points with rFIXFc would result in statistically significant reductions in mean ABR.
  - These findings are consistent with those of studies in other chronic diseases.[17]
- Additional studies are necessary to fully validate these findings and understand the true impact of rFIXFc on real-world effectiveness versus rFIX products.

DISCLOSURES

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