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COMMENTARY

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Interpreting data on inhibitor development from previously untreated patient studies, beware of premature conclusions

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As the availability of virally inactivated FVIII concentrates, the development of inhibitory antibodies (inhibitors) to FVIII in previously untreated patients (PUPs) with severe haemophilia A is the most frequent and most serious side effect of modern haemophilia treatment. Inhibitors develop in about one-third of patients, with 98% (176 of 179) developing within the first 50 exposure days (EDs) in the RODIN study.[1] Over the last decades, several genetic and treatment-related risk factors for inhibitor development have been identified.[2] In clinical practice, the efforts regarding the prevention of inhibitors are focused on the modifiable risk factors, including the choice of concentrate. Recently, there have been a number of publications including meta-analyses,[3,4] large cohort studies[5-8] and a RCT[9] which have presented conflicting results on the role of certain concentrates in inhibitor development.

In this context of conflicting publications and the need to compare studies for correct interpretation, it is especially important to consider two sources of bias: patient selection (eg risk factors and/or treatment strategies) and information bias (eg definitions and/or follow-up).

1 | THE NUPROTECT STUDY

In the current issue of Haemophilia journal, Liesner et al[10] present the data from the interim analysis of the NuProtect study, suggesting that Human-cl rhFVIII (Nuwiq®) is associated with a low inhibitor rate in previously untreated patients (PUPs).

After adapting the prespecified analysis plan (ClinicalTrial.gov nr NCT01992549), an interim analysis on inhibitor development was performed in 66 PUPs with a minimum follow-up of 20 EDs on treatment with Nuwiq®.

Median follow-up was 43 EDs (with P25-P75 of 20-100), and during that period, 8 high-titre and 5 low-titre inhibitors were observed after a median of 11.5 and 8.0 EDs, respectively. Using Kaplan-Maier survival analysis, the overall inhibitor incidence was 20.8% (95% confidence interval (CI) 10.7-31.0) and 12.8% (CI 4.5-21.2) for high-titre inhibitors.

Even if the number of patients is still limited and the confidence intervals overlap with published data from larger studies,[5-7] the authors aim to convey the message that inhibitor risk is low on this new recombinant FVIII concentrate. Of course, if this were true, the entire haemophilia community would be pleased: a fourth-generation recombinant FVIII product has the highest standard of safety against transmission of blood-borne pathogens and inhibitor development is the most important treatment complication in PUPs. However, to avoid hasty conclusions and repetition of past mistakes,[11] selection bias and information bias need to be considered.

2 | PATIENT SELECTION

By definition, inhibitor risk is different for participants in PUP studies. To appreciate this, it is important to consider which patients are eligible for a PUP study: first, the diagnosis of severe haemophilia A must be established before any treatment has been given, and the parents must have been allowed sufficient time to consider participation in a study with a new concentrate. Consequently, patients with a negative family history of haemophilia and/or presenting with severe bleeding are unable to enter a PUP study. This group will likely include most or all patients who will need intensive treatment (a "peak treatment") with consecutive days of high-dose FVIII at first exposure, which is associated with increased inhibitor risk.[1] More difficult to establish

TABLE 1 Inhibitor incidence and risk factors for inhibitor development across different studies

Risk factor	NUWIQ®	PedNet[5]	United Kingdom[6]	France[7]
	Number/denominator proportion (95% confidence interval) *or* median (P25-P75)			
Nr of PUPs	66	574	407	303
Age 1st treatment (months)	13.0	9.8 (5.4-13.5)	9.0 (4-13) range 0-95	6-11
Peak treatment at 1st exposure (5 days)	NA[b]	98/574 17.1% (14.1-20.4)	56/394 14.2% (10.9-18.1)	50/303 16.5 (12.5-21.2)
High-risk mutation	44/58 75.9%[a] (62.8-86.1) 47/58 null (81.0%)	331/574 57.7% (53.5-61.8)	244/407 60.0% (55.0-64.8)	214/282 75.9% (70.5-80.8)
Family history of haemophilia	22/66 33.3% (22.2-46.0)	270/574 47% (42.9-51.2)	232/406 57.1% (52.2-62.0)	146/303 48.2% (42.4-54.0)
Family history of inhibitors	4/66 6.1% (1.7-14.8)	83/574 14.5% (11.7-17.6)	41/406 10.1% (7.3-13.5)	36/303 11.9% (8.5-16.1)
Duration of FU non-inhibitors (ED)	67 (range 4-120) 'all ≥ 20'	75	45 months (24.0-61.7)	75
Nr of EDs at inhibitor development	10 (range 6-25)	15 (10-20)	16 (9-30) range 1-442	13 (8-19)
Overall inhibitors (survival analysis)	13/66 20.8% (10.7-31.0)	177/574 32.4% (28.5-36.3)	11 8407 29.0% (24.6-33.7)[a]	114/303 40.2% (34.8-46.2)
High-titre inhibitors (survival analysis)	8/66 12.8% (4.5-21.2)	116/574 22.4% (18.8-26.0)	60/407 14.7% (11.4-18.6)[a]	63/303 23.9% (19.1-29.6)

[a]Not calculated by survival analysis, therefore representing a proportion without consideration of loss to follow-up.
[b]Fifty percent reported treatment for minimum of 3 consecutive days or prophylactic dose ≥50 IU/kg during the first 100 EDs, but peak treatment at first exposure was not specified.

is the effect of a family history of inhibitors on parents' decision to participate in a study on a new concentrate.

In contrast, the large observational cohort studies such as the performed in the United Kingdom,[6] France[7] and internationally in PedNet[5] aim to include full birth cohorts independent of risk factors or treatment received.

Table 1 compares the endogenous and treatment-related risk factors for inhibitor development between the study on Nuwiq®[10] and the three large cohort studies. Data were extracted from the published data and, if not provided, 95% confidence intervals were calculated by the author using the exact method.

The data in Table 1 appear to support the theory that patients included in the Nuwiq® study are likely to have a more favourable risk profile for inhibitor development. Especially, the first treatment is administrated much later in the two intervention studies (13 and 16 months, respectively), than in the three observational cohort studies, which all show a median age of 9-10 months for the onset of treatment. This observation supports the theory that patients requiring very early treatment, which is often intensive treatments for important bleeds, are not included or under-represented in the Nuwiq® study. Unfortunately, the proportion of patients requiring peak treatment at first exposure, defined as 3 consecutive days of at least 50 IU/kg/d, was not presented in the Nuwiq® study. Instead, they reported 50% of patients ever receiving 3 consecutive days of treatment *or* a prophylactic dose of >50 IU/kg. This does not qualify as peak treatment according to the definitions used for known risk factors for inhibitor development. The inhibitor risk associated with peak treatment of ≥5 EDs at first exposure has been reported at ±50% overall and ±38% for high-titre inhibitors.[1] Cohort studies show that peak treatment at first exposure usually occurs in ±16% of patients. If patients with a peak treatment at first exposure were included in the Nuwiq® study, this could therefore increase overall inhibitor development by 8% (n = 5) and high-titre inhibitor development by 6% (N = 4).

The distribution of high-risk FVIII mutations appeared similar between studies. Patients included in the Nuwiq® study reported a positive family history of haemophilia in only 33.3% compared to 47%-57% in the observational studies. But more importantly, the family history of inhibitors in these participants appeared less frequent at 6.1% vs 10.1%-14.5% in the observational studies.

3 | INHIBITOR DEVELOPMENT AND FOLLOW-UP

Both in clinical practice[12] and according to the official EMA guideline,[13] it is mandatory to perform intensive monitoring for inhibitor development during the first 50 EDs to FVIII in PUPs with severe haemophilia A. The consequences of analysing data without completing follow-up are difficult to establish. However, all the large cohort studies report a median inhibitor development after 13-16 EDs with a 75th percentile of 20-30 EDs, signifying that ±25% of inhibitors develop after 20 EDs. The incomplete follow-up also explains the low median number of ED at inhibitor development reported by the Nuwiq® study at a median of 10 EDs.

Although direct statistical comparisons could not be made, Table 1 shows that the 95% confidence intervals of overall inhibitor development in this study overlap with those from PedNet and the United Kingdom, but not with those from the French data. For high-titre inhibitor development, however, all confidence intervals show some overlap.

In conclusion, a comparison of the Nuwiq® study with large observational studies suggests that both selection bias and information bias due to incomplete follow-up may have resulted in an underestimation of the inhibitor risk in the Nuwiq® study. Although completion of the planned PUP study in Nuwiq will eliminate the information bias by presenting complete follow-up, it will not eliminate the selection bias. These can only be established in large national[5-8] and international registry studies reporting on unselected cohorts of PUPs.

DISCLOSURE

K. Fischer has received speaker's fees from Bayer, Baxter, Biotest, CSL Behring, Biotest Octapharma, Pfizer, NovoNordisk; performed consultancy for Bayer, Baxter, Biogen, CSL-Behring, Freeline, NovoNordisk, Pfizer, Roche and SOBI; and has received research support from Bayer, Pfizer, Baxter, and Novo Nordisk. K Fischer is the epidemiologist for the EUHASS and PedNet registries.

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