UKPK trial interim analysis: Use of Pharmacokinetic intervention to optimise Factor VIII prophylaxis in severe haemophilia A

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Introduction

Prophylaxis with Factor VIII (FVIII) infusion is the standard of care for management of severe haemophilia A

There is variation in patients bleeding phenotype and further some patients bleed despite satisfactory prophylaxis by the current standard of maintaining FVIII trough > 1 IU/ dL

There is a need to personalise prophylaxis to suit patient phenotype and lifestyle

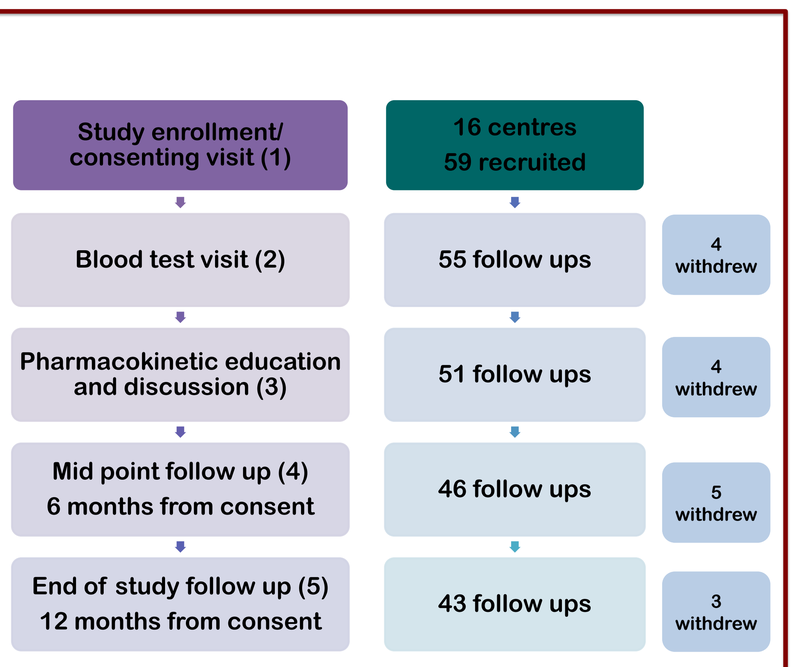
The UK-PK trial

Prospective multicentre study in adults with severe haemophilia A on regular Advate® prophylaxis

First national study to use the population pharmacokinetic (PK) tool myPKFiT®

Intervention: Standardised PK focussed educational animation, followed by PK guided prophylaxis dosing discussion

Figure 1: Study protocol and Progression



Methods

Clinical and joint status, patient recollected bleed data, Haemtrack recorded bleed and prophylaxis data, blood test data, PK discussion and outcome obtained from UKPK trial

PK profiles were individually modelled using myPKFiT: Predicted troughs achieved on old and new prophylaxis regimens (where there were changes in treatment) were estimated

Troughs and bleed rates at study start, midpoint and end of study were used to group patients (fig. 2)

Definition of Optimal treatment:
Patients with trough >1 IU/ dL, Bleed rate 0 to 1- Quadrant 1 (Q1)

Definition of Sub-optimal treatment:
Patients with trough < 1 IU/ dL, Bleed rate 0 to 1- Quadrant 2 (Q2) or
trough < 1 IU/ dL, Bleed rate > 1- Quadrant 3 (Q3) or trough > 1 IU/ dL, bleed rate > 1- Qudarant 4 (Q4)

Pragmatic study design, not powered to demonstrate statistical significance

Hypothesis

Use of pharmacokinetic education and dosing to guide prophylaxis in severe haemophilia A will have an effect on bleed rates, FVIII consumption, and adherence

Trial Findings

59 patients were recruited from 16 participating centres, 16 patients withdrew through the study, 8 patients did not go through PK discussion (fig.1)

51 (85%) patients went through PK education, 43 (73%) followed up to 12 months, 36 patients with complete data-set are considered for the following analysis

13 (36%) patients were on irregular treatment (which left them with trough < 1 for at least a part of the week) at start of study, 8 patients opted to move to regular treatment after PK discussion; at end of study 5 (14%) patients were on irregular treatment, and 31 (86%) on regular treatment

23 (64%) patients reported bleeds at study entry, 47% reported bleed rates on > 1 every 6 months

The intervention increased the number of bleed free patients from 36% to 50% however 44% reported bleeds despite a trough > 1 IU/ dL

Overall reduction in median bleed rate at 12 months (1 to 0.5; p= 0.044; Wilcoxon Signed Rank test); median estimated weekly factor usage remained similar 86 units/ kg and 82 units/ kg

20 patients (56%) did not change treatment after PK discussion, 9 (39%) of patients reporting bleeds opted to change regime

In those who changed regime- 13 (81%) benefited from higher troughs (median >2 IU/ dL) and reduction of bleed rate (median 2 to 1)

15 (94%) of patients who opted to change agreed to increase frequency, 5 patients agreed to daily treatment for least for part of the week

PK discussion and dose modification increased number of patients on optimal prophylaxis from 33% to 44 % (i.e. trough >1, bleeds 0-1) at 12 months, decreased number with trough <1: 34% to 23%, increased number with trough > 1: 66% to 77% (fig. 2)

Patient reported treatment data

Patients record treatments and bleeds through the online Haemtrack system in the UK, this may be a surrogate marker for adherence to treatment

54/ 59 patients on study were identified on Haemtrack

52/ 54 patients had data entries for the period of 6 months before trial entry and the 12 month trial period

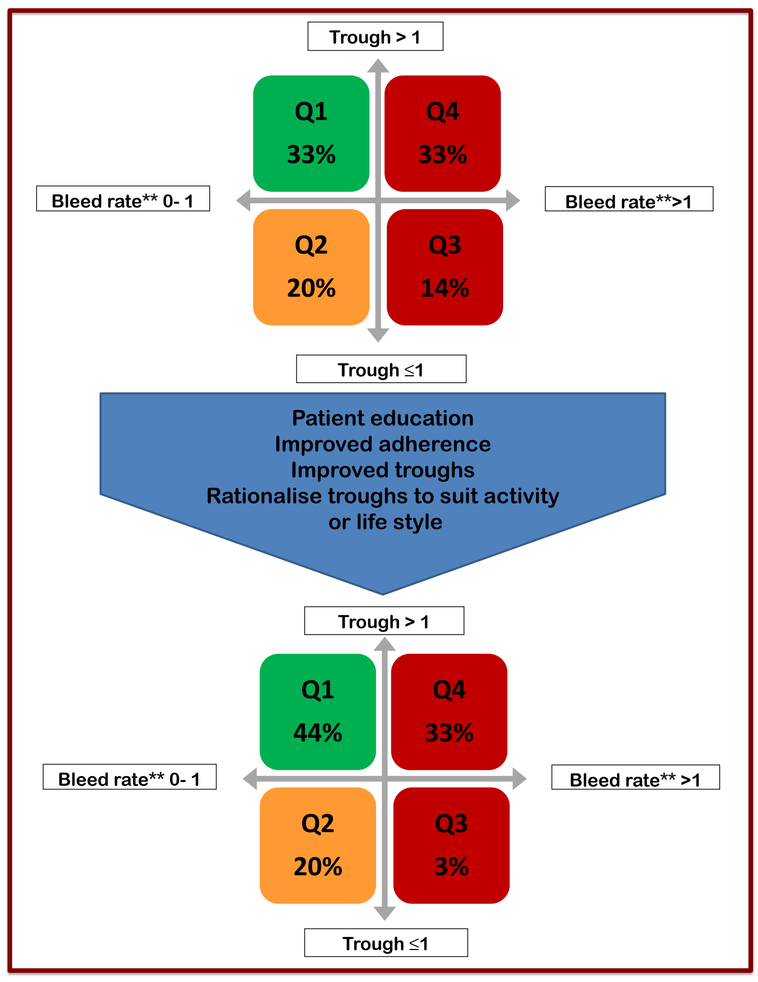
At study start 21 (40%) patients were compliant* with Haemtrack returns, at midpoint and end of study 40 (76%) and 35 (67%) patients were compliant respectively

Median factor usage for compliant patients through trial remained the same; patient recorded bleeds on haemtrack were reduced (median 4 to median 2 at 6 months), this was higher than patient recollected bleed rate (Table 1)

Median factor usage and patient recorded bleeds at start and end of trial, for patients who changed treatment (and had haemtrack records, n= 17) is shown in Table 2. Patients who changed regimen used more factor. The patients who achieved higher trough (median > 2) also needed more factor concentrate, however continued to report bleeds (median 1) at end of study

*Compliant by Haemtrack standards is when patient records 75% of product issued

Figure 2: Optimising prophylaxis for 36 patients from consent to end of trial; patient movement between prophylaxis quadrants (** patient recollected bleed rate at study visit)



Conclusions

Population-PK guided prophylaxis is more easily available and an important step toward personalisation of care

PK education allows discussion of prophylaxis regime bespoke to individual patient

PK-Optimisation and education increased the number of patients with a measurable predicted trough and reported bleed free

Improved adherence to Haemtrack returns was demonstrated through the period of trial

50% of patients continue to report bleeds (bleeds >= 1), 56% of bleeding patients declined change in regime despite the PK-optimisation opportunity

Familiarity to older regimen may be a limiting factor to uptake of PK guided dose change

>30% of patients consistently report bleeds despite predicted trough levels >1 IU/ dL

Table 1. Prophylaxis and bleeds for Haemtrack compliant patients through trial (median (25^{th} – 75^{th} centile))

	No. of prophylaxis treatment episodes over 6 months	Number of prophylaxis units used over 6 months (IU)	No. of patient recorded bleed on Haemtrack over 6 months
Patients compliant at consent	80 (72- 110)	150000 (128125- 198000)	4 (1- 9)
Patients compliant at 6 months	80 (66- 96)	152500 (126938- 179625)	2 (0- 4)
Patients compliant at 12 months	82 (65- 99)	145000 (125000- 175000)	2 (0- 4)

Table 2. Prophylaxis and bleeds for patients who changed treatment at PK discussion (median(25^{th}- 75^{th} centile))

	No. of prophylaxis treatment episodes over 6 months	Number of prophylaxis units used over 6 months (IU)	No of patient recorded bleed on Haemtrack over 6 months
Consent	74 (63- 78)	143000 (116000- 166500)	1 (0- 5)
12 months follow-up	86 (75- 106)	148500 (128375- 174250)	0.5 (0- 5)
Patients with higher troughs at 12 months (n= 14)	91 (78- 128)	152000 (125000- 172000)	1 (0- 6)

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