Uptake and timing of inhibitor screening in non-severe haemophilia A: results of a pan-London evaluation

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Introduction

The most important complication in the management of non-severe haemophilia A is the occurrence of inhibitory antibodies to factor VIII (FVIII). This complication, although affecting a minority of patients is associated with significant morbidity and a change in bleeding phenotype (1,2). Given the predominance of on-demand treatment in this patient group, timing of inhibitor screening after exposure to FVIII may be crucial in the detection of an immune response. Little data exists to support the optimal timing of inhibitor screening in these patients (3). We hypothesise, that current clinical practice relies on opportunistic, rather than targeted screening within a pre-determined window following FVIII exposure.

Aims

The study aim was to evaluate inhibitor screening practices in patients with non-severe haemophilia A in London. The primary objective was to assess compliance with UKHCDO guidance in inhibitor screening following FVIII exposure for treatments episodes of perceived increased inhibitor risk (3). The secondary objectives were to assess testing of *F8* genotype, frequency of "high risk" *F8* mutations, treatment patterns and inhibitor occurrence.

Materials and Methods

We conducted a pan-London retrospective evaluation of inhibitor screening practices covering a 2 year period (1/1/11 – 31/12/12). Data on *F8* mutation testing, treatment indications and inhibitor screening were collected from all 7 London Haemophilia Treatment and Comprehensive Care Centres. Assessments of uptake of "convalescent" (within 6 weeks) inhibitor testing in patients treated with FVIII for the following indications were made based on UKHCDO guidance (3)

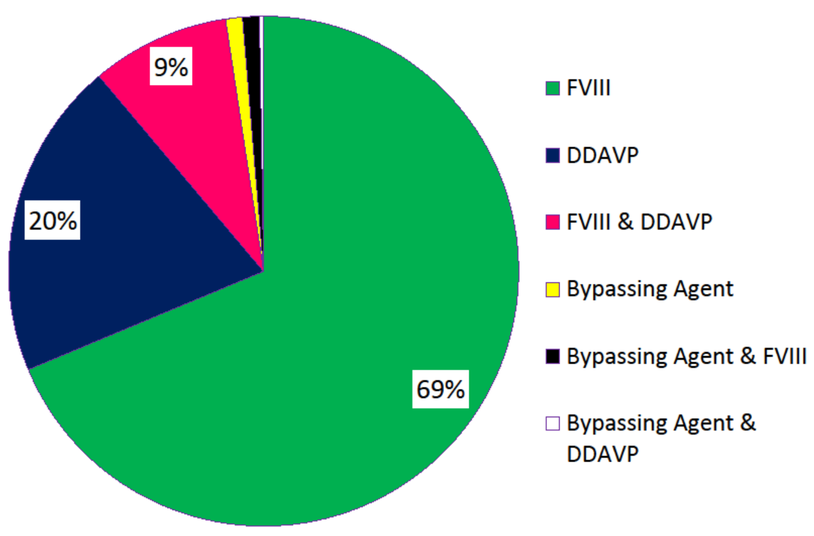
1. High risk *F8* mutation : Any FVIII exposure (bleed or surgery)
2. Standard risk *F8* mutation : Bleed ≥ 5 exposure days
3. Standard risk *F8* mutation : Surgery

Assessment of uptake and timing of annual inhibitor screening was made for all standard risk patients treated with FVIII in 2011 (3).

Demographics

Cohort Demographics	
Registered patients	853
Treatment any (%)	377 (44%)
FVIII treated (%)	296 (79%)
Mean age (years) ± SD	35.7 ± 22.7
Moderate : Mild	102 : 275
Mean FVIII:C (IU/dL) ± SD	12.9 ± 9.9

Treatment



Inhibitor Incidence

Inhibitor Epidemiology	
Inhibitor history	13
FVIII treated (at risk of inhibitor)	290
New inhibitor	3 (1%)
Total inhibitor	16
New Inhibitors	
High : standard risk *F8* mutation	2 : 1
Moderate : Mild	2 : 1
Change in baseline FVIII:C *	2 (67%)
Change in bleeding phenotype	3 (100%)

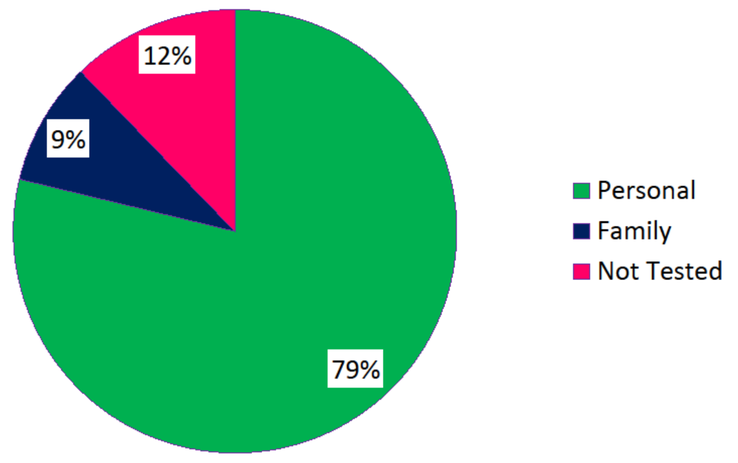
*Change in FVIII:C ≥ 50%. In both cases a fall in baseline FVIII:C to < 1% was observed

High Risk *F8* Mutations

Domain	Legacy	HGVS
A2	Arg593Cys	Arg612Cys
C1	Tyr2105Cys	Tyr2124Cys
C1	Arg2150His	Arg2169His
C1	Arg2163His	Arg2182His
C2	Trp2229Cys	Trp2248Cys
C2	Asn2286Lys	Asn2305Lys
C2	Pro2300Leu	Pro2319Leu

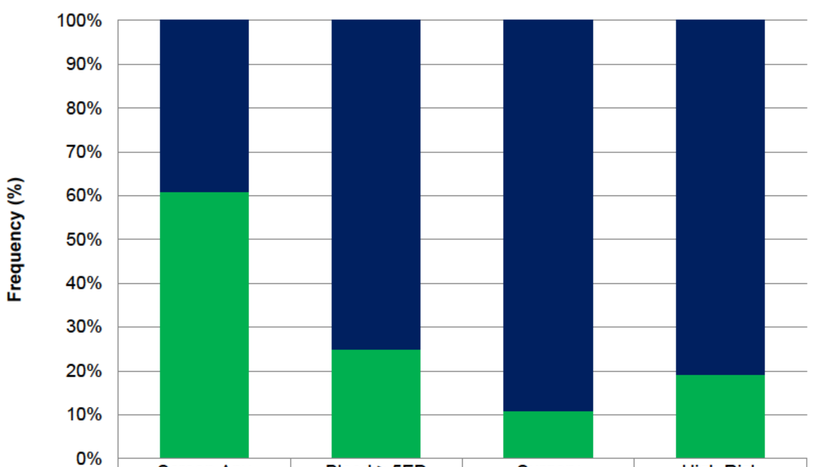
* High risk mutations were selected based on *F8* non-synonymous single nucleotide polymorphisms previously associated with an increased incidence of inhibitor formation (4). *F8* mutations are stated in both "legacy" and Human Genome Variation Society (HGVS) formats, with numbering excluding and including the signal region (19 amino acids) respectively.

F8 Genotype Testing



Pan-London Cohort *F8* Mutations	
F8 mutation known (n)	88% (331)
High risk *F8* mutation (n)	18% (58)

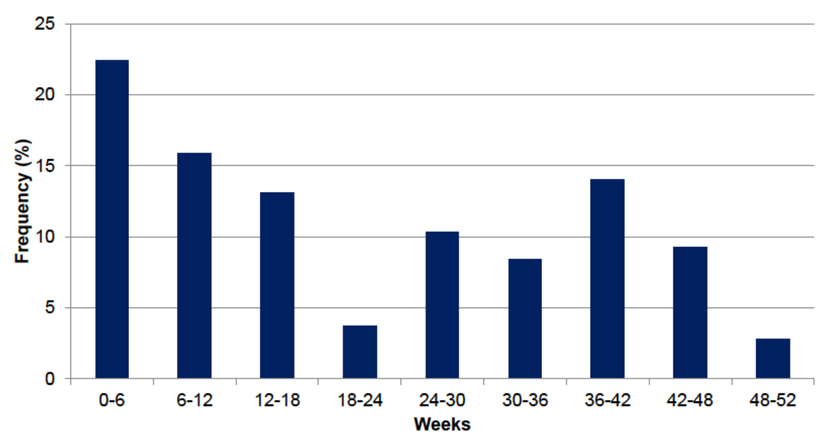
Convalescent Inhibitor Screening



	Screen Any	Bleed ≥ 5ED	Surgery	High Risk
Not Tested	116	39	156	71
Tested	180	13	19	17

Screen any = number of patients treated with FVIII concentrate who had ≥ 1 inhibitor screen in the study period. High Risk = "high risk" *F8* mutation.

Annual Inhibitor Screening



Standard Risk *F8* Mutation Treatment Episodes (2011)	
Annual inhibitor screen (episodes)	47% (107/229)
Mean days from FVIII exposure to inhibitor screen ± SD	149 ± 111.3

Conclusions

Our data suggests that current inhibitor screening timing in non-severe haemophilia A is opportunistic with a proportion of these tests sent immediate prior to further treatment. Our key findings are as follows:

1. A substantial proportion of patients (44%, n=377) received treatment in the study period, with a large proportion (79%) receiving exposure to FVIII.
2. Good compliance with *F8* genotype testing was observed, with this information known in 88% of patients treated.
3. Convalescent inhibitor screening was performed within 6 weeks in only 11 – 25% of treatment episodes of perceived increased inhibitor risk.

We believe patients with non-severe haemophilia A require more focussed (convalescent) timing of inhibitor screening to optimise inhibitor detection. The relevance of this will need to be determined in a prospective multi-centre clinical trial.

References

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