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POSTER ABSTRACTS

322.DISORDERS OF COAGULATION OR FIBRINOLYSIS: CLINICAL AND EPIDEMIOLOGICAL

Large Deletion in the Factor VIII Gene Is a Predictor of Immune Tolerance Induction Failure in People with Severe and Moderately-Severe Hemophilia a and High-Responding Inhibitors

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Introduction Immune tolerance induction (ITI) is a therapeutic approach to eradicate inhibitors against factor VIII (FVIII) in people with inherited hemophilia A (PwHA). The success of ITI is highly variable, ranging from 60% to 80% across studies. Beyond inhibitor titers, other predictors of ITI outcome are unknown. Deleterious variants in FVIII gene (*F8*) are well established risk factors for alloantibodies development in PwHA, although few studies have investigated the role of *F8* variants on ITI outcome.Therefore we aimed to comprehensively analyze the association of *F8* pathogenic variants on ITI outcome in severe PwHA with high-responding inhibitors.

Methods We included severe (FVIII < 1 international units [IU]/dL) and moderately-severe (FVIII 1-2 IU/dL) unrelated PwHA and high-responding inhibitors who completed ITI from a large, admixed population of two well-characterized cohorts - the HEMFIL and the Brazilian Immune Tolerance (BrazIT) studies. We collected socio-demographic, clinical and laboratory data. ITI outcomes were defined according to previous definitions as failure, partial and total successes. Inversions of intron 1 and 22 (Inv22) were detected by polymerase chain reaction (PCR), and high-throughput sequencing approaches were used to unveil the additional *F8* variants. The association between *F8* pathogenic variants and ITI outcome was adjusted for inhibitor levels. To investigate whether *F8* variants associated with inhibitor development were also related to ITI outcome, variants were categorized as "high-risk", "intermediate-risk", and "low-risk" categories. These categories for inhibitor development were then compared with the outcomes of ITI (total and partial successes and failure) using data from this study.
Results We included158 PwHA, median age 6.6 years at ITI start, 90.5% were severe (Table 1). Inv22 was the most prevalent variant (55.1%) (Table 1). In comparison with Inv22-1, the risk of ITI failure was about 9 times higher (adjusted odds ratio [adjOR] 9.29; 95% confidence interval [95% CI] 1.95-53.70) among carriers of large deletions (Table 2). Conversely, Inv22-2 was associated with favorable ITI outcome in a univariate analysis (OR 0.15; 0.01-0.84), and after adjustment (adjOR 0.32; 95% CI 0.02-1.96) (Table 2). *F8* deleterious variants sorted as high-risk and intermediate-risk according to a previously published classification on inhibitor development were associated with failure and successful outcomes, respectively.
Conclusion Our study showed that *F8* large deletions are independent predictors of ITI failure, and Inv22-2 is likely to be a predictor of successful ITI. We found a correspondence between variants classified as high-risk and intermediate-risk to inhibitor development with ITI failure and success, respectively. We suggest that *F8* genotyping should be considered before indication of ITI, as ITI outcome can vary according to individual variant burden.

Disclosures Camelo: *Takeda:* Consultancy, Other: Scientific event grants, Speakers Bureau; *Hoffman-La Roche:* Consultancy, Other: Scientific event grants, Speakers Bureau; *NovoNordisk:* Other: Scientific event grants, Speakers Bureau; *Bayer:* Other: Scientific event grants, Speakers Bureau. **Oliveira:** *Takeda:* Other: Scientific event grants, Speakers Bureau; *NovoNordisk:* Other: Scientific event grants, Speakers Bureau. **Etto:** *Hoffman-La Roche:* Other: Scientific event grants. **Roberti:** *NovoNordisk:* Other: Scientific event grants, Speakers Bureau; *Hoffman-La Roche:* Other: Scientific event grants; *Brazilian Ministry of Health:* Consultancy; *Takeda:* Other: Scientific event grants. **Callado:** *Hoffman-La Roche:* Other: Scientific event grants; *NovoNordisk:* Other: Scientific event grants. **Cerqueira:** *NovoNordisk:* Other: Scientific event grants; *Hoffman-La Roche:* Other: Scientific event grants. **Pinto:** *Bayer:* Consultancy; *Biomarin:* Consultancy; *Takeda:* Other: Scientific event grants, Research Funding, Speakers Bureau; *NovoNordisk:* Consultancy, Other: Scientific event grants, Speakers Bureau; *Hoffman-La Roche:* Consultancy, Other: Scientific event grants, Speakers Bureau. **Garcia:** *Takeda:* Other: Scientific event grants, Speakers Bureau; *NovoNordisk:* Consultancy, Other: Scientific event grants, Speakers Bureau. **Anegawa:** *Takeda:* Other: Scientific event grants; *Hoffman-La Roche:* Other: Scientific event grants. **Neves:** *Takeda:* Other: Scientific event grants.

TABLE 1 Characteristics of the study population according to immune tolerance induction outcome.

Patient and hemophilia A characteristics	ITI outcome (n = 158)		p-value
	Success* (n = 108)	Failure (n = 50)	
Ethnicity, n (%)			
Black	11 (10.1)	1 (2.0)	0.062
Pardo	37 (34.3)	25 (50.0)	
White	60 (55.6)	24 (48.0)	
Hemophilia A diagnosis			
Age, in years, median (IQR)	0.79 (0.44-1.25)	0.9 (0.6-1.1)	0.400
FVIII activity, in IU/dL, n (%)			
< 1	96 (88.8)	47 (94.0)	0.315
1-2	12 (11.2)	3 (6.0)	
F8 variant type, n (%)			
Intron 22 inversion	69 (63.9)	18 (36.0)	0.001
Inv22-1	50 (72.5)	17 (94.4)	0.147
Inv22-2	19 (27.5)	1 (5.6)	0.024
Nonsense	13 (12.0)	9 (18.0)	0.316
Small insertion/deletion	10 (9.3)	9 (18.0)	0.122
Poly-A run†	3 (30.0)	3 (33.3)	0.189
Large deletion	3 (2.8)	10 (20.0)	0.002
Multiple exons/UTR	1 (33.3)	10 (100.0)	0.002
Missense	5 (4.6)	2 (4.0)	0.858
Splice site	5 (4.6)	1 (2.0)	0.434
Conserved nucleotide‡	5 (100.0)	1 (100.0)	0.434
Intron 1 inversion	3 (2.8)	1 (2.0)	0.760
Inhibitor characteristics	**Success**	**Failure**	**p-value**
Age at inhibitor diagnosis, in years, median (IQR)	2 (1-7)	4 (2-8)	0.130
Age at ITI start, in years, median (IQR)	6 (2-18)	7 (2-19)	0.600
Interval between diagnosis of hemophilia A and inhibitor development, in years, median (IQR)	1.2 (0.6-4.8)	2.8 (0.5-6.1)	0.700
Historic inhibitor peak, in BU/mL, median (IQR)	30 (12.0-60.0)	81.0 (37.0-442.0)	<0.001
Inhibitor titer immediately before ITI, in BU/mL, median (IQR)	4.0 (2.0-9.0)	13.2 (5.7-57.0)	<0.001
Inhibitor peak during ITI, in BU/mL, median (IQR)	12.0 (4.0-46.0)	170.0 (58.0-666.0)	<0.001
ITI duration, in years, median (IQR)	2.3 (1.6-3.0)	3.1 (2.6-3.6)	<0.001

* Success represents the sum of total and partial successes.
† Poly-A run was defined as at least 6 adenines in a row.
‡ Conserved splice site was defined as those affecting the +1, +2, −1, or −2 nucleotide position at a splice site.
BU, Bethesda Units; *F8*, factor VIII gene; FVIII, factor VIII; IQR, interquartile range; ITI, immune tolerance induction; IU, International Units; UTR, untranslated region.

TABLE 2 *Odds ratios* for the association of *F8* variants and immune tolerance induction outcome.

F8 variant, n (%)	ITI outcome (n = 158)		OR (95% CI)	
	Success* (n = 108)	Failure (n = 50)	Crude	Adjusted†
Intron 22 inversion	69 (63.9)	18 (36.0)		
Inv22-1	50 (72.5)	17 (94.4)	1.00 (Reference)	1.00 (Reference)
Inv22-2	19 (27.5)	1 (5.6)	0.15 (0.01-0.84)	0.32 (0.02-1.96)
Large deletion	3 (2.8)	10 (20.0)	9.80 (2.65-47.7)	9.29 (1.95-53.7)

* Success represents the sum of total and partial successes.
† Adjusted for inhibitor pre-ITI titre, historic inhibitor peak titre, and inhibitor titre peak during ITI.
CI, confidence interval; *F8*, factor VIII gene; ITI, immune tolerance induction; OR, *odds ratio*.

Figure 1

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