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Background: Eradicating inhibitors to restore the effectiveness of Factor VIII (FVIII) is a desirable treatment goal for People with Severe Hemophilia A (PwSHA) and inhibitors, as this enables treatment of bleeding episodes with FVIII concentrates. However, since Immune Tolerance Induction (ITI) is a burdensome and costly treatment, it is important to identify determinants for ITI success to decide if it is worth undertaking ITI. For more effective treatment allocation, there is a need to identify which persons will or will not benefit from ITI. **Aim:** We aimed to identify determinants of successful ITI in PwSHA and to use these determinants in a clinical prediction model. **Methods:** German, Brazilian, Dutch, Canadian, and Italian PwSHA who underwent ITI were included. The primary outcome was clinical ITI success, defined by (1) a negative inhibitor titer, and (2) an adequate clinical response to FVIII concentrates. Clinical determinants included F8 genotype, race, age, cumulative exposure days to FVIII, inhibitor titers, and ITI regimen. Genetic determinants included in the analyses were FCGR gene, IL10 CA short tandem repeat, and gene variants. Crude Relative Risks (RR) were calculated for ITI success with 95% Confidence Intervals (95% CI). **Results:** In total, 224 PwSHA were included (61 German, 51 Brazilian, 45 Dutch, 39 Canadian, and 28 Italian). The median ages at inhibitor development and ITI start were 2-years (Interquartile Range [IQR 1–3]) and 2-years (IQR 1–6). The median interval between inhibitor diagnosis and ITI start was 17-weeks (IQR 2–64). Most ITI trials started with recombinant FVIII (130; 58%) and the median prescribed regimen at ITI start was 43 IU/kg/day (IQR 21–200). The need for adjuvant therapy and central venous access infection were related to failure, while inhibitor titer at detection < 10 BU/mL, inhibitor titer immediately before ITI start < 10 BU/mL, and peak inhibitor titer ever measured < 100 BU/mL were related to success. Inhibitor peak titer below 100 BU/mL showed the highest chance for ITI success (OR = 11.5, 95% CI 5.5–24.3, p < 0.001). **Conclusion:** Historical peak titer below 100 BU/mL was the strongest determinant for ITI success. Genetic analyses will be available by the due date, and we will develop a prediction model to estimate the chance of success.

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GENOMIC DIVERSITY AND ANCESTRY OF ADMIXED PATIENTS WITH HEMOPHILIA A AND INHIBITORS: INSIGHTS FROM WHOLE EXOME SEQUENCING IN THE BRAZILIAN IMMUNE TOLERANCE (BRAZIT) STUDY

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Hemophilia A is an X-linked bleeding disorder caused by mutations in the FVIII gene. BrazIT is a nationwide cohort of 193 patients that, developing neutralizing alloantibodies (inhibitors) against the first line treatment with exogenous FVIII, received Immunotolerance Treatment (ITI). Sixtyseven patients (35%) failed ITI, 62 (32%) achieved partial success, and 64 (33%) had complete success. We performed whole exome sequencing of BrazIT and estimated medians of 64%, 17%, and 13% of European, African, and Native American ancestries, respectively, based on autosome SNVs, underscoring the diversity of this cohort. After controlling for covariates, we did not observe association between these continental ancestries and inhibitor titers or ITI success, but Native American ancestry was negatively associated with large deletions in FVIII gene (β = -0.081, p = 0.011). In Latin American populations, sex-ancestry bias is the rule: during the last five centuries, European admixture has been preferentially mediated by males, while African and Native American admixture preferentially by females. We estimated X-chromosome ancestry to confirm the pervasive sex-ancestry bias in BrazIT. As expected, BrazIT individuals show Native American ancestry bias (Autosome - X-chromosome bias: 0.06, p < 0.001), but exceptionally, no African ancestry bias (-0.005, NS). This result suggests that X-chromosomes of predominant African origins are underrepresented among hemophilia patients high-responding inhibitors, exemplifying the unexplored issue of how sex-ancestry bias in Post-Columbian migrations from Europe and Africa to the Americas have differently shaped the patterns of genetic diversity of X-chromosome and autosomal linked mendelian diseases.

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SWITCHING PROPHYLAXIS DURING AN IMMUNE TOLERANCE INDUCTION EVOLVING WITH FAILURE: A CASE REPORT FROM A BRAZILIAN HEMOPHILIA TREATMENT CENTER

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Factor VIII (FVIII) prophylaxis is recommended to prevent bleeds in people with hemophilia A (PwHA). However, up to 30% of severe PwHA (residual plasmatic FVIII activity < 1%) develop anti-FVIII (FVIII) neutralizing antibodies (i.e., inhibitors), leading to ineffectiveness of FVIII replacement and worse outcomes. Immune Tolerance Induction (ITI) is the treatment of choice to eradicate inhibitors, but it demands frequent intravenous infusions and a higher risk of bleeding. Bypassing Agent (BpA) prophylaxis was recommended to avoid bleeding during ITI. Emicizumab is currently available as a prophylactic agent for PwHA and inhibitors, although its impact during ITI is not well described. We reported the effect

of changing the prophylactic agent during ITI in a child treated at a Brazilian Hemophilia Treatment Center. The male child was diagnosed with severe hemophilia A (non-identified mutation) at 1.3-year, starting primary prophylaxis with standard half-life recombinant FVIII soon after. A high-titer inhibitor was detected at 1.5-year and ITI was started within 0.2-year (50 IU/kg, 3×/week) after 1 treated bleed. Both historic inhibitor peak and inhibitor titer immediately before ITI start were 4.9 BU/mL. During ITI, inhibitor titers continuously rose to 104 BU/mL, associated with 6 treated bleeds, despite regimen increment to 100 IU/kg daily and BpA prophylaxis. BpA prophylaxis was switched to emicizumab prophylaxis at 0.9-year of ITI. Two bleeds were treated during emicizumab loading. No treated bleeds were reported after that. Inhibitor titers continuously decreased, and ITI was withdrawn after 2.8 of treatment (partial success due to abnormal FVIII pharmacokinetics). Emicizumab prophylaxis was maintained, and no treated bleeds were reported after 6-months of ITI withdrawal. Switching to emicizumab prophylaxis was associated with ITI partial success in a predefined good-outcome risk child with hemophilia A and inhibitor evolving with ITI failure.

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LARGE DELETIONS IN THE F8 GENE PREDICT IMMUNE TOLERANCE INDUCTION FAILURE IN PEOPLE WITH SEVERE HEMOPHILIA A

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Immune Tolerance Induction (ITI) is the only treatment to eradicate inhibitors in people with Severe Hemophilia A (SHA). Successful ITI restores Factor VIII (FVIII) tolerance. ITI is demanding and successful in approximately 70% of people. Therefore, identifying predictors of ITI outcome is essential to guide clinical decision-making. We aimed to identify genetic predictors of ITI success in people with SHA and inhibitors who underwent ITI. This observational multicenter study included people with SHA who underwent ITI, between 2015 and 2023. Clinical and patient data including factor VIII gene (F8) mutation type and DNA samples were collected. Successful ITI was defined by a negative inhibitor titer and an adequate response to FVIII concentrates. The associations between ITI success and F8 genotype and 216 candidate predictors including single nucleotide polymorphisms (SNPs) and human leukocyte antigen (HLA)-variants employing a global screening array (GSA), CA dinucleotide Short Tandem Repeat (STR) polymorphisms in the Interleukin (IL)-10 promoter region, and FCGR2/3 gene locus variations were analyzed. Of 204 participants, 147 (72.1%) achieved ITI success. The majority (52.0%) of participants had F8 intron 22 inversion. None of the candidate SNPs/HLA-variants, IL-10 CA dinucleotide STR, or FCGR2/3 gene locus variations were associated with ITI success. F8 large deletions were negatively associated with ITI success (OR = 0.15, 95% CI 0.04–0.51, p = 0.002). Our study including 204 people with SHA identified F8 large deletions as a predictor of ITI failure. Pooling cohorts may allow the identification of additional genetic predictors of ITI success in the future.

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SAFETY AND EFFICACY OF THE FITUSIRAN REVISED ANTITHROMBIN-BASED DOSE REGIMEN IN PEOPLE WITH HAEMOPHILIA A OR B, WITH OR WITHOUT INHIBITORS (ATLAS-OLE)

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