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 Inhibitor titers continuously decreased, and ITI was withdrawn after 2.8 of treatment (partial success due to abnormal FVIII pharmacokinetics).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.

https://doi.org/10.1016/j.htct.2024.09.946

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.

https://doi.org/10.1016/j.htct.2024.09.947

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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