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 Inhibitor titers continuously decreased, and ITI was withdrawn after 2.8 of treatment (partial success due to abnormal FVIII pharmacokinetics).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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Background: Fitusiran, a Subcutaneous (SC) investigational siRNA therapeutic, lowers Antithrombin (AT) to increase thrombin generation and rebalance haemostasis in people with Haemophilia (PwH) A or B, regardless of inhibitor status. We report interim safety and efficacy of the fitusiran Antithrombin-based Dose Regimen (AT-DR) in a Phase 3 Open-Label Extension (OLE) study (ATLAS-OLE; NCT03754790). **Materials and Methods:** Males aged ≥12-years with severe haemophilia A or B, with or without inhibitors, who completed a fitusiran Phase 3 study were enrolled. The original 80 mg SC monthly (QM) dose regimen [ODR] was adjusted to the AT-DR, targeting AT activity levels 15%–35% to mitigate adverse events. Participants received fitusiran prophylaxis 50 mg or 20 mg every other month (Q2M) or QM. Doses were individually adjusted to achieve target AT activity. Safety was compared with the ODR across all fitusiran studies, and efficacy was compared with control groups in the parental studies. **Results and discussion:** Overall, 227 participants were enrolled. Mean (SD) AT level was 23.5 (4.6) on AT-DR. 78% of participants were on Q2M regimes; 38% required zero and 56% required one dose adjustment to achieve AT 15%–35%. Safety analyzes included all participants exposed to fitusiran (n = 270 ODR, n = 286 AT-DR). For ODR, total patient (pt)-years of exposure was 306.8 (≥ 12-months exposure n = 101). For AT-DR, total patient (pt)-years of exposure was 486.0 (≥ 12-months exposure n = 238). The exposure-adjusted incidence rate of adverse events was substantially reduced on AT-DR: Thrombotic Events (TE) (ODR 2.28 vs. AT-DR 0.82/100 pt-years), ALT/AST > 3×ULN (ODR 16.62 vs. AT-DR 2.26/100 pt-years), and cholecystitis/cholelithiasis (ODR 14.67 vs. 2.26/100 pt-years). All TE had significant contributing risk factors. Median ABR (IQR) was 3.7 (0.0; 7.5); 1.9 (0.0; 5.6) in PwH with inhibitors and 3.8 (0.0; 11.2) in PwH without inhibitors. Superior bleed control was demonstrated vs on-demand Clotting Factor Concentrations (CFC)/By Passing Agents (BPA) in PwH with or without inhibitors (73% and 71% reductions, $p < 0.0006$, 0.0001, respectively). Bleed rate was reduced by 70% vs. BPA prophylaxis ($p = 0.0002$) and was comparable with CFC prophylaxis ($p = 0.6$). **Conclusions:** In this study, the fitusiran AT-DR targeting AT levels of 15%–35% improved the safety profile substantially versus the ODR and maintained bleed protection in PwH A or B, with or without inhibitors, with most on a Q2M regimen.

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SURGICAL EXPERIENCE IN PEOPLE WITH HEMOPHILIA A OR B WITH AND WITHOUT INHIBITORS RECEIVING FITUSIRAN

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Background: Fitusiran, a subcutaneous, investigational siRNA therapeutic lowers antithrombin to rebalance hemostasis and enhance thrombin generation in People with Hemophilia (PwH) A or B, regardless of inhibitor status. For the management of perioperative hemostasis, Bleed Management Guidelines (BMG) with reduced dose and/or frequency of Clotting Factor Concentrates (CFC), or Bypassing Agents (BPA) were implemented. **Aims:** To describe hemostatic outcomes of major surgeries conducted while on fitusiran prophylaxis in PwHA/B aged ≥12-years, regardless of inhibitor status. **Methods:** All major surgeries in the fitusiran clinical development program until June 2023 were evaluated, including participants on the 80 mg QM and revised antithrombin-based dose regimen. Informed consent and ethics committee approval were obtained for all studies. Procedures conducted during fitusiran prophylaxis and AT activity < 60% were included. Major surgeries included: opening into a major body cavity, operation on a joint, removal of an organ, operative alteration of normal anatomy, crossing of a mesenchymal barrier, dental extraction of molar teeth or ≥3 nonmolar teeth, or tooth implantation. Investigators/surgeon assessed peri-operative hemostatic control based on the ISTH 4-point response scale (excellent/good/moderate/poor). **Results and discussion:** Sixty major surgeries (24 in inhibitor patients) were performed. In 47 (78.3%) major surgeries, BMG were followed, and reduced doses were used as perioperative prophylaxis. Four major surgeries were conducted without additional CFC/BPA. Hemostatic control on the day of the surgery was rated excellent/good in 30/31 (97%) cases following BMG and 9/10 (90%) cases