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ACHIEVING THE LATEST TREATMENTS FOR HEMOPHILIA

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ABSTRACT

These article analysis innovative methods of the treatment of haemophilia A and B is the replacement therapy by preparations obtained from plasma of donors, or by recombinant DNA technology. Among the major shortcomings of unmodified drugs VIII and IX factors should be allocated between the low time circulation of the drug in the body of the patient and the delivery of antibodies (inhibitors) to a protein preparation that significantly reduces their effectiveness. The improvement of the efficiency and safety of recombinant preparations is achieved by removing B-domain of factor VIII molecule, pegylation or development of preparations of fusion proteins (fusion molecules of the preparation to the albumin or Fc-fragment of IgG).

KEYWORDS: *Hemophilia; Recombinant Factor VIII; Recombinant Factor IX; Pegylated Proteins; Monoclonal Antibody Preparations; Preparations Based Fusion Proteins; Aptamer; Antisense Oligonucleotides.*

INTRODUCTION

Hemophilia is a hereditary disease of the blood coagulation system resulting from a deficiency of blood coagulation factor VIII (FVIII) - hemophilia A, or blood coagulation factor IX (FIX) - hemophilia B. Hemophilia is inherited in an X-linked recessive inheritance pattern. Approximately 70% of patients have a positive family history of the disease. Hemophilia is caused by mutations in the gene encoding FVIII (Xq28) or the gene encoding FIX (Xq27). In 30-35% of cases, sporadic mutations are possible without a family history of the disease. The prevalence of hemophilia in the general population is estimated at 1:10,000. Hemophilia A (HA) is more common than hemophilia B (HB) and accounts for 80-85% of the total number of cases.

The vast majority of patients with hemophilia are men. There are isolated cases of hemophilia in women when the gene is inherited simultaneously from the father (with hemophilia) and from the mother (carrier of the gene), or in a woman with a gene mutation on one chromosome, when the gene on the other chromosome is inactive (Shereshevsky-Turner disease, etc.). Some women who carry mutations in the FVIII or FIX genes may also experience clinical manifestations of hemophilia **[1].**

Diagnosis of hemophilia begins with the identification of a history of hemorrhagic syndrome in the patient and family members. When collecting an anamnesis of the disease and a family history of the patient, it is recommended to find out the presence of manifestations of the hemorrhagic syndrome: complaints of easily appearing ecchymosis and hematoma in early childhood; the occurrence of spontaneous bleeding (especially in the joints, muscles and soft tissues); prolonged bleeding after trauma or surgery **[2].** Family history data in approximately 2/3 of patients contain indications of hemorrhagic manifestations in close relatives on the maternal side (in men, less often in women). Personal history data may contain information about the patient's hemorrhagic manifestations. When collecting an anamnesis of the disease, it is necessary to pay attention to the presence of hemorrhagic manifestations in the neonatal period in the form of cephalohematomas, intracranial hemorrhages, bleeding and prolonged healing of the umbilical wound; in infants - ecchymosis not associated with significant trauma, soft tissue hematomas after minor bruises or spontaneous. Some children may not bleed during the first year of life until the child begins to walk **[3].** It is important to pay attention to the discrepancy between the severity of hemorrhagic manifestations of the severity of the previous injury, recurrence of bleeding after the initial stop, not associated with repeated trauma, massive and (or) multiple hematomas, systemic hemorrhagic manifestations (manifestations of different localization), "spontaneous hemorrhagic manifestations". In mild hemophilia, there may be no bleeding until the first injury or surgery. The collection of complaints and anamnesis will determine the scope of the patient's examination. When conducting a physical examination, it is recommended to pay attention to the presence of skin hemorrhagic syndrome of varying severity in the form of multiple ecchymosis and hematomas, which are possible in severe and moderate hemophilia **[4].** It is highly likely to reveal signs of joint damage in the form of deformity, edema and local increase in skin temperature (acute hemarthrosis) and / or signs of impaired mobility, range of motion of the joints, hypotrophy of the muscles of the limb on the side of the affected joint, gait disturbance (deforming arthropathy).

Updated information on innovative methods of hemophilia a treatment

This phase I/IIa, open-label (non-placebo controlled) clinical trial enrolls 16 previously treated male patients (aged 18 to 65 years) with severe hemophilia A (FVIII activity <1%). Participants received a single intravenous injection of BIVV001 at a dose of 25 IU/kg (lower dose group) or 65 IU/kg (higher dose group). The injection was followed by a washout period (time to clear the drug from the body) of at least 3 days, after which patients again received a single intravenous injection of BIVV001 at the same dose of 25 IU/kg or 65 IU/kg. For up to 28 days after a single dose of BIVV001, no FVIII inhibitors were found and no hypersensitivity or anaphylactic events were reported. The geometric mean half-life of BIVV001 is 3-4 times longer than the half-life of rFVIII (37.6 hours compared to 9.1 hours in the lower dose group; and 42.5 compared to 13.2 hours in the higher dose group). high dose). After administration of BIVV001 in the high dose group, mean FVIII levels were maintained in the normal range (≥51%) for 4 days; and amounted

to 17% on the 7th day. This allows us to talk about a possible break of one week between treatment episodes.

In phase I of this study, a single intravenous injection of BIVV001 provided sustained levels of FVIII activity with a half-life of up to 4 times longer than the half-life of standard rFVIII. Such an increase may indicate replacement therapy with a new class of factor VIII with an interval of one week between injections. Within 28 days after administration, no information was received about any problems with the safety of the drug.

Cross-sectional studies of drugs with an extended half-life The pharmacokinetics (PK) of Jivi® and Elocta® were compared in a crossover study across two treatments. Patients with severe hemophilia aged 18-65 years of age were randomized to receive a single intravenous dose of Jivi® at 60 IU/kg followed by FVIIIFc (Elocta®) 60 IU/kg - or vice versa - with a washout period between doses of ≥7 days. FVIII activity was measured using a one-step assay. The area under the curve (AUC) of Jivi® was significantly greater than that of Elocta®, corresponding to a median time to release of 1 IU/dL approximately 13 hours longer for Jivi® using a population pharmacokinetic (PK) model. A second study with a similar methodology compared Jivi® with Adynovate® at 50 IU/kg. Another additional component in this study was batch-dependent differences in dose. As a result, reported median doses actually administered were 54.3 IU/kg for Jivi® and 61.4 IU/kg for Adynovate®. Based on a population PK model, the median time to reach 1 IU/dL was 16 hours longer for Jivi® than for Adynovate®. Both studies were funded by Bayer.

Ingenza announces progress towards low cost FVIII In a press release, Ingenza announced significant progress in developing a process to produce low-cost rFVIII as a feedstock for ProFactor Pharma Ltd (PFP). Ingenza is now finalizing the manufacturing cycle and is releasing material for preclinical toxicity studies that PFP has scheduled in 2020 ahead of clinical studies in 2021.

Scientists from the University of Colorado (WFH virtual summit (abstract MED-PP-010 (616)) surveyed PsHA who received Hemlibra® at the university's Hemophilia and Thrombosis Center for >1 month. The survey was part of a quality-of-service improvement effort to identify challenges in the provision of treatment and for close monitoring of adverse events or unexpected complications shortly after drug licensure 5-10 minute telephone questionnaires were administered as scripted Questions were asked about adverse events, bleeding, physical activity, pain medication use and travel Questions were answered by adults or legal representatives of pediatric patients There were 69 eligible patients as of September 1, 2019. The study included 47 patients aged 6 months to 79 years (mean age 18.3 years, median age 13.1 years) who were taking " Hemlibru®" for 1.2 - 40.5 months (average duration 9.4 months, median 6.6 months). Patients associated the use of Hemlibra® with improved joint health (23/29, 79%), decreased intake painkillers (13/20, 65%), fewer absences from work/school (23/33, 70%) and increased physical activity (26/47, 55%). Several LsHAs have reported missed Hemlibra® doses, which may be indicative of inaccurate adherence to the treatment regimen.

Gene therapy

FDA Delays Licensing of ROCTAVIAN® (valoctocogene roxaparvovec = valoctocogene roxaparvovec) until complete data on the cohort of patients in the 3rd phase of the clinical trial

The FDA (USA) on August 18 issued a full response letter (CRL) to the company BioMarin, requesting additional information for a thorough evaluation of BioMarin's ROCTAVIAN® gene therapy for hemophilia A. In this letter, the FDA requested that BioMarin provide 2 years of safety and efficacy data for all 134 patients in a phase III study (GENER8-1, NCT03370913). Having received a request from the EMA (by the end of November 2020 to provide full data for 12 months on all participants in the III phase of the study), BioMarin announced on October 5th that it was withdrawing its application to the EMA for the issuance of state registration. BioMarin plans to submit a new marketing authorization application in the second quarter of 2021. The aforementioned request for additional data is most likely related to the duration of FVIII expression. During the Phase I/II studies, FVIII activity levels dropped from a mean of 64.3 IU/dl (one year after high-dose treatment) to a mean of 24.2 IU/dl (four years after treatment): i.e. the fall was 63%.

Updates at 4 years (6e13 vg/kg cohort) and 3 years (4e13 vg/kg cohort) indicate that all patients are still not on FVIII prophylaxis after receiving a single dose of valoctocogen roxaparvovec. The pooled mean HCH remains <1 in both cohorts and below baseline levels prior to treatment. In year 4, the mean HCH in the 6e13 vg/kg cohort was 1.3, and the mean HCH in year 3 in the 4e13 vg/kg cohort was 0.5. Over the past year, 6 (out of 7) patients in the 6e13 vg/kg cohort and 5 (out of 6) patients in the 4e13 vg/kg cohort had no spontaneous bleeding. At the end of year 4 after infusion of valoctocogen roxaparvovec, the mean FVIII activity in all patients in the 6e13 vg/kg cohort was 24.2 IU/dL by chromogenic substrate testing and 35.4 IU/dL by the one-step clotting method. **[5]**

Treatment

The main principle of hemophilia treatment is specific replacement therapy with clotting factor concentrates. Purified, virus-inactivated preparations made from human donated plasma (FVIII concentrate, FIX concentrate, FVIII concentrate + von Willebrand factor, anti-inhibitor coagulant complex [AICC]) or recombinant clotting factor concentrates (Octocog alfa, Moroctocog alfa, Nonacog alfa, Eptacog alfa) should be used. (activated), Simoctocog alfa, Turoctocog alfa). At present, there is no reason to prefer plasma (von Willebrand factor or not) or recombinant coagulation factors to each other. Since frequent changes in the trade names of FVIII and FIX preparations can lead to an increased risk of the appearance of an inhibitor, it is desirable to create conditions for long-term (for many years) use of one type of INN preparation by a patient. It is recommended to give preference to the drug that, with equal effectiveness, is best tolerated by the patient, has the best pharmacokinetic individual indicators and is most convenient to use, based on specific conditions **[6, 7, 8].** A change in INN in a particular patient in the absence of registered adverse effects on the administration of the drug used and a satisfactory clinical response to therapy is possible after 100 exposure days of administration of blood clotting factor concentrates. Coagulation factor concentrates are administered intravenously. Most often, a bolus infusion is used at the rate recommended by the manufacturer. In rare cases, it is possible to use continuous infusion if the attending physician has similar experience. Modern therapy for hemophilia is based on the principle of "home treatment". Mandatory conditions for conducting "home treatment" are: the patient has hemostatic drugs (the drug is located in the same place as the patient), the decision to use the hemostatic drug is made by the patient or his relatives in accordance with the recommendations of the hematologist, the patient and / or his relatives are trained in the rules of storage and drug use. The use of crude

preparations - blood components (fresh frozen plasma or cryoprecipitate) - is recommended only in exceptional cases and should not be a permanent practice. There are two types of specific therapy - treatment upon the occurrence of bleeding (on demand) and prophylactic therapy.

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