Indian Academy of Pediatrics (IAP)

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Newer **R**esearch and recommendations **I**n **C**hild **H**ealth

Lead Author
Nitin Shah

Co-Author
Sangeeta Mudaliar

UNDER THE AUSPICES OF THE IAP ACTION PLAN 2023

Upendra Kinjawadekar
IAP President 2023

GV Basavaraja
IAP President 2024

Remesh Kumar R
IAP President 2022

Vineet Saxena
IAP HSG 2022-23

Dear fellow IAPans,

nRICH

Newer **R**esearch and recommendations **I**n **C**hild **H**ealth-aims to bring you the abstracts of some of the breakthrough developments in pediatrics, carefully selected from reputed journals published worldwide.

Expert commentaries will evaluate the importance and relevance of the article and discuss its application in Indian settings. nRICH will cover all the different subspecialities of pediatrics from neonatology, gastroenterology, hematology, adolescent medicine, allergy and immunology, to urology, neurology,vaccinology etc. Each issue will begin with a concise abstract and will represent the main points and ideas found in the originals. It will then be followed by the thoughtful and erudite commentary of Indian experts from various subspecialties who will give an insight on way to read and analyze these articles.

I'm sure students, practitioners and all those interested in knowing about the latest research and recommendations in child health will be immensely benefitted by this endeavor which will be published online on every Monday.

Happy reading!

Upendra Kinjawadekar
National President 2023
Indian Academy of Pediatrics

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Upendra Kinjawadekar

Convenor

Vijay Yewale

IAP nRICH team

Arun Bansal

Vaman Khadilkar

Indu Khosla

Srinivas Murki

Nitin K Shah

Tanu Singhal

Rhishikesh Thakre

Prakash Vaidya

SK Yachha

Valoctocogene Roxaparvovec Gene Therapy for Hemophilia A

Nitin Shah[1], Sangeeta Mudaliar[2]

Section Head Pediatrics, PD Hinduja Hospital, Mumbai & Hon. Consultant, Dept of Pediatric Hematology Oncology, BJ Wadia Hospital for Children, Mumbai, India [1],
Head, Dept of Pediatric Hematology Onclogy, BJ Wadia Hospital for Children, Mumbai, India[2]

BASED ON ARTICLE

Ozelo MC, Mahlangu J, Pasi KJ, et al.
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ABSTRACT

Background: Hemophilia A is a lifelong bleeding disorder with incidence of 1:5000 male births. It needs lifelong treatment with factor VIII replacement which is cumbersome, expensive and inconvenient. In developing countries prophylactic treatment is out of reach for most of the affected patients leading to very poor quality and shortened life. Gene therapy for inherited single gene defects are coming in a big way as an alternative therapy. This trial is the first published successful trial on gene therapy in hemophilia A using Valoctocogene Roxaparvovac vector that expresses a B-domain–deleted human factor VIII coding sequence from a hepatocyte-selective promoter.

Methods: GENEEr8-1 is an open-label, single-group, multicenter, phase 3 study conducted between December 2017 to November 2019 using valoctocogene roxaparvovec adeno-associated virus 5 based gene therapy vector. It enrolled men with severe hemophilia A with factor VIII levels of 1 IU per dL or less. Subjects were 18 years or older hemophilia A patients who did not have pre-existing anti-AAV5 antibodies or any history of factor VIII inhibitors in past. Total 132 subjects were enrolled of which 20 subjects were enrolled directly and another 112 were enrolled from the noninterventional 270-902 study which had at least 6 months of data on use of factor VIII and episodes of bleeding. All these subjects were receiving factor VIII concentrate prophylaxis treatment. They all received single infusion of 6×1013 vector genomes of valoctocogene roxaparvovec per Kg body weight. Primary end point was the change in the factor VIII activity from baseline to weeks 49-52 after infusion of gene therapy vector. Secondary end points were change in annual factor VIII concentrate use and episodes of bleeding. Safety end points included clinical and laboratory evaluation.

Results: 134 subjects completed 52 weeks follow up after infusion of the vector. In 132 HIV negative subjects the mean factor VIII activity level increased to 41.9 IU per dL (95% CI 34.1-49.7) ($P<0.001$) with a median change of 22.9 IU per dL and interquartile range of 10.9 to 61.3. 81% of the subjects had factor VIII levels of > 5 IU per dL, enough to prevent serios spontaneous bleeding. In the 112 subjects followed up prospectively the mean annualized rates of factor VIII concentrate use decreased by 98.6% and episodes of bleeding needing treatment reduced by 83.8% after 4 weeks ($P<0.001$ for both). At least one adverse event was noted in all the patients. 22 of 134 (16.4%) subjects developed serious adverse events. 85.8% of subjects developed raised alanine aminotransferase levels managed with

immune suppressants. 38.1% of subjects developed headache, 37.3% nausea and 25.1% elevations in aspartate aminotransferase levels. None of the subjects developed factor VIII inhibitors or any episode of thrombosis.

Conclusions: Valoctocogene Roxaparvovec Gene Therapy for Hemophilia A was successful in providing endogenous production of factor VIII that was sustained for at least 52 weeks of follow up and helped reduce use of factor VIII concentrates and episodes of bleeding significantly compared to baseline prophylaxis therapy. It was also found safe with controllable side effects in most.

COMMENTARY

This is a path breaking study in the care of hemophilia A as it gives a glimpse of hope of a 'cure' for hemophilia A patients that otherwise have compromised quantity and quality of life with life-long cumbersome and cost-prohibitive factor replacement therapy. So far, the standard of care for hemophilia A patients in the Western countries is to give bi-weekly factor VIII concentrate as home-based prophylaxis therapy. This needs repeated IV access, training of care takers to give IV therapy at home, availability of adequate quantities of high quality factor VIII concentrates, financial support and psycho-social help. And yet 15-20% of these patients may develop factor VIII inhibitors which complicates the therapy further. Those with inhibitors would need high doses of factor VIII concentrates, immune suppressive therapy or alternative factors like FEIBA or APCC. Prophylaxis therapy is a dream come true for most patients with hemophilia A in developing countries like India as there are very few centres offering this in public health care facilities that too mainly in cities. Cost of factor VIII commercially is almost INR 8-10 per unit that makes is exorbitant for the patients to afford out of pocket even episodic treatment leave aside prophylaxis therapy. At an average of 10 units per Kg of factor VIII concentrate per dose given bi-weekly it translates in to 1000 units per Kg per year that will cost INR 10,000 per Kg per year! And to this cost of frequent hospital visits, cost of testing, cost of routine care, cost of treatment of inhibitors, cost of physiotherapy, cost of management of damaged joints get added! No wonder hemophilia is a 'Royal' disease! Besides this many patients are treated with FFP or Cryo in India exposing them to risk of transmission known and unknown infections. So, an alterative therapy like gene therapy could be a one-time solution for genetic disorders like hemophilia A if it can show sustained benefits after gene therapy.

This novel vector has shown promising 1 year follow up results in form of increased levels of endogenous factor VIII production to level of 40 IU per DL (you need > 5 IU per dL to prevent serious spontaneous bleeding) and reduced use of factor VIII concentrates by 90% and reduced clinical bleeding episodes by 85%. The expression of the transferred gene does decline over time and it will be interesting to see long term efficacy and safety as well as to study need for second or more doses in future. Hope the results are well sustained for years to come and this therapy may soon become the standard of care. In fact, on 24th June 2022, European Medical Agency (EMA) has recommended granting a conditional marketing authorisation in the European Union (EU) to Roctavian (valoctocogene roxaparvovec) for the treatment of severe haemophilia A in adults who do not have factor VIII inhibitors (auto-antibodies produced by the immune system which make factor VIII medicines less effective) and no antibodies to adeno-associated virus serotype 5 (AAV5). There is now a need to have trials in children soon so that it can be used as early as possible in life.