same day as infusion, and second, given 4 weeks after valoctocogene roxaparvovec. **Results:** Discontinuation of emicizumab the day of valoctocogene roxaparvovec infusion compared with continued dosing for 4 weeks offered similar levels of hemostatic control. The time course for bleeding risk was comparable across the emicizumab dosing regimens for both scenarios. An algorithm to provide guidance for discontinuing emicizumab was developed based on these results. To guide how treatment decisions for emicizumab discontinuation may vary among individuals, theoretical case examples were developed based on participants of GENEr8-1. **Conclusions:** Regardless of the emicizumab dose or dosing regimen, pharmacokinetic simulations showed no meaningful difference in the risk of bleeding related to FVIII and FVIII equivalent activity determined by the dynamic balance of decaying emicizumab levels and increasing gene therapy –derived endogenous FVIII. These original data suggest individuals on emicizumab prophylaxis can safely transition to valoctocogene roxaparvovec. COIs for presenting author. Suresh Agarwal is an employee and stockholder of BioMarin Pharmaceutical Inc.

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QUANTITATIVE PHARMACOKINETIC MODEL TO CHARACTERIZE AND EXTRAPOLATE LONG-TERM FVIII ACTIVITY LEVELS IN PATIENTS WITH SEVERE HEMOPHILIA A TREATED WITH VALACTOCOGENE ROXAPARVOVEC

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Aim: Valoctocogene roxaparvovec delivers a B-domain deleted factor VIII (FVIII) coding sequence with an adeno-associated virus vector to reduce bleeding and FVIII concentrate use in people with severe hemophilia A. This study aimed to characterize the long-term trajectory of transgene-derived FVIII activity using a linear mixed effects (LME) model to estimate mean and median FVIII activity levels 5 years post-infusion. **Methods:** In GENEr8-1, an open-label, single-arm, multicenter phase 3 trial, 134 participants with severe hemophilia A received a single 6 x 10^{13} vg/kg dose of valoctocogene roxaparvovec. FVIII activity was assessed using the chromogenic substrate assay and one-stage assay. A previously published quantitative pharmacokinetic (PK) modelwas updated to extrapolate FVIII activity levels to 5 years post-infusion. Ln-transformed FVIII activity values from week 76 to 104 were fit to the LME model with random effects for participants on slope and intercept using a restricted maximum likelihood method with the lmer package in the R statistical computing software (R Foundation for Statistical Computing, Vienna, Austria). The precision of parameter estimates and model diagnostics were evaluated to confirm goodness-of-fit. The model and extrapolation approach was further qualified by comparing to observed FVIII activity at week 156. **Results:** The final LME model dataset included 928 observations from 120 participants. The long-term trajectory of FVIII activity was consistent with first-order elimination kinetics starting at week 76. Model parameter estimates were consistent with the previously published model; diagnostic plots showed no major deficiencies. FVIII activity was extrapolated to 5 years post-gene transfer. Mean and median FVIII activity extrapolations at week 156 were consistent with observed values, confirming adequacy of the model. **Conclusions:** Pharmacokinetic modeling indicates valoctocogene roxaparvovec-derived FVIII activity levels will remain in the mild hemophilia range for ≥5 years post-gene transfer for the majority of patients treated. **COIs for presenting author: Suresh Agarwal** is a paid employee of BioMarin Pharmaceutical Inc. and holds stock ownership with BioMarin Pharmaceutical Inc.

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BLEEDING, FVIII ACTIVITY, AND SAFETY 3 YEARS AFTER GENE TRANSFER WITH VALOCTOCOGENE ROXAPARVOVEC: RESULTS FROM GENER8-1

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Aims: Valoctocogene roxaparvovec (AAV5-hFVIII-SQ) provides endogenous factor VIII (FVIII) production to prevent bleeding in people with severe hemophilia A. This study evaluated bleeding, FVIII activity and safety outcomes 3 years after receiving valoctocogene roxaparvovec. **Methods:** The open-label, multicenter phase 3 GENEr8-1 trial (NCT03370913) evaluated 6 x 10^{13} vg/kg valoctocogene roxaparvovec in 134 adult men with severe hemophilia A (FVIII ≤1 IU/dL) without inhibitors. Bleeds and FVIII use were self-reported after regular prophylaxis ended (scheduled for week [W] 4) through data cutoff. Comparisons to baseline on FVIII prophylaxis were performed in a subset of 112 HIV-negative participants enrolling from a non-interventional study (rollover population). FVIII activity per chromogenic assay and quality of life (QOL) per Haemo-QOL-A were assessed in 132 HIV-negative participants (modified intent-to-treat [mITT] population). Safety was assessed in all participants. **Results:** Median follow-up was 162 weeks (n = 134); 131 participants completed W156. The mean annualized treated bleeding rate in 112 rollover participants over 3 years was 0.8 bleeds/year, mean annualized rate of all bleeds was 1.3 bleeds/year, and mean FVIII utilization was 125 IU/kg/year. During year 3, 73.2% of 110 rollover participants had zero treated bleeds and 61.6% had no bleeds (excluding surgeries/procedures). At W156, mean and median FVIII were 18.8 and 8.4 IU/dL (mITT, N = 132); 11.4%, 56.1%, and 32.6% of mITT participants had FVIII activity ≥40 IU/dL, ≥5 and <40 IU/dL, and <5 IU/dL, respectively. Overall, 10/132 (7.6%) participants resumed prophylaxis. Mean Haemo-QOL-A Total Score improvement from baseline to W156 was 6.6 (n = 122; $p < 0.0001$), exceeding the anchor-based clinically important difference (5.5). No new safety signals emerged. Since the previous data cut, 34/134 participants (25.4%) had alanine aminotransferase (ALT) elevation, mostly Grade 1, but none initiated immunosuppressants. Overall, 106/134 (79.1%) used corticosteroids for ALT elevation for median 33 weeks. **Conclusions:** Valoctocogene roxaparvovec provided robust hemostatic efficacy relative to FVIII prophylaxis for 3 years, with QOL improvement and stable safety.

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PORTADORES DE HEMOFILIA LEVE: O DESAFIO DA CONSCIENTIZAÇÃO AO AUTOCUIDADO

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Introdução: As hemofilias são as coagulopatias hereditárias com maior prevalência e tem tratamento embasado em protocolos bem definidos que melhoraram a qualidade de vida dos pacientes e aumentaram a longevidade. No entanto, os pacientes com hemofilia leve (PHL) raramente apresentam sintomas, o que os leva a descuidar do acompanhamento da condição. **Objetivo:** Descrever um caso de PHL que abandonou o seguimento ambulatorial e as consequências clínicas advindas. **Material e métodos:** Os dados apresentados foram retirados do prontuário eletrônico de um paciente em seguimento ambulatorial irregular no serviço de Hemofilia do Hospital São Paulo (HSP) durante internação no mês de julho/2023. **Relato de caso:** S. T. C., 58 anos, diagnosticado com Hemofilia A leve em 2003 (dosagem de Fator VIII = 7,6%), quando iniciou acompanhamento em nosso serviço de maneira irregular, com reposição sob demanda. Em 2005, foi solicitado retorno ambulatorial para consulta anual em 2006, no entanto, paciente não compareceu mais ao ambulatório da especialidade. Em 2016, durante consulta com Gastroenterologia, foi diagnosticado com infecção pelo vírus da hepatite C (HCV), porém também abandonou acompanhamento antes de avaliação para o tratamento. Em setembro de 2022, após receber diagnóstico de colelitíase em hospital externo, com indicação de abordagem cirúrgica, comparece ao pronto atendimento do nosso serviço para orientação do preparo pré-operatório. Foram solicitados exames para avaliação e o paciente foi orientado que o planejamento para colecistectomia pela equipe da Hemofilia só poderia ser realizado após avaliação destes. Paralelamente, foi encaminhado para avaliação com Infectologia devido hepatopatia crônica pelo HCV, o que resultou no diagnóstico de cirrose hepática. Iniciou tratamento já em 2023, sendo concluído em maio deste ano com último PCR negativo. Em 08/07/23, o paciente apresenta primeiro episódio de hemorragia digestiva alta, exteriorizada como melena. Procurou serviço de pronto-socorro do HSP, sendo internado para estabilização clínica e investigação da origem do sangramento. Houve queda significativa da hemoglobina (entrada: 13.1 g/dL e 72 horas após: 10 g/dL). Realizou endoscopia digestiva alta onde foram achadas varizes esofágicas de fino calibre, sem sinais de sangramento ativo/recente, bem como colonoscopia com alguns pólipos (realizada polipectomia - aguarda resultado de biópsia), também sem sangramento ativo. Evoluiu com melhora clínica e recuperação laboratorial após reposição de concentrado de fator VIII plasmático por 7 dias consecutivos. Após estabilização, teve alta hospitalar em 19/07/23 com encaminhamentos para retorno com equipes da Hematologia e Gastroenterologia. **Discussão e conclusões:** Preocupa o diagnóstico do comprometimento hepático em estágio avançado já que, caso houvesse conscientização da importância da regularidade das avaliações clínicas e laboratoriais, este paciente poderia ter sido tratado previamente e, talvez, a evolução pudesse ter sido mais favorável. PHL precisam estar conscientes da importância do autocuidado pois podem evitar o aparecimento de comorbidades que põem em risco a continuidade de suas vidas. O desenvolvimento de ferramentas que auxiliem o indivíduo a entender sua condição clínica poderia ser útil para melhorar este cenário.

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