The Medical Letter®

on Drugs and Therapeutics

Volume 66 January 22, 2024

ISSUE No. 1694

IN THIS ISSUE

***Casgevy* and *Lyfgenia*: Two Gene Therapies for Sickle Cell Disease** ..... p 9

Important Copyright Message

FORWARDING OR COPYING IS A VIOLATION OF U.S. AND INTERNATIONAL COPYRIGHT LAWS

The Medical Letter, Inc. publications are protected by U.S. and international copyright laws. Forwarding, copying, or any distribution of this material without permission to a nonsubscriber is prohibited.

Sharing a password with a nonsubscriber or otherwise making the contents of this site available to third parties is prohibited.

By accessing and reading the attached content I agree to comply with U.S. and international copyright laws and these terms and conditions of The Medical Letter, Inc.

For further information click: Subscriptions, Site Licenses, Reprints
or call customer service at: 800-211-2769

The Medical Letter publications are protected by US and international copyright laws.
Forwarding, copying or any other distribution of this material is strictly prohibited.
For further information call: 800-211-2769

The Medical Letter®
on Drugs and Therapeutics

Volume 66 (Issue 1694) January 22, 2024

Take CME Exams

Casgevy and *Lyfgenia*: Two Gene Therapies for Sickle Cell Disease

Revised 4/26/24: The last sentence in the Standard Treatment paragraph has been revised.

Two cell-based gene therapies – exagamglogene autotemcel (*Casgevy* – Vertex) and lovotibeglogene autotemcel (*Lyfgenia* – Bluebird Bio) – have been approved by the FDA for treatment of sickle cell disease in patients ≥12 years old with recurrent vaso-occlusive crises. They are the first gene therapies to be approved in the US for use in sickle cell disease; *Casgevy* is the first treatment to be approved in the US that uses CRISPR/Cas9 gene-editing technology.

Pronunciation Key

Casgevy: cass jeh' vee ***Lyfgenia***: lif jen' ee uh

THE DISEASE — In sickle cell disease, which affects about 100,000 people in the US, elongated or sickle-shaped red blood cells obstruct small blood vessels, causing inflammation, chronic hemolysis, anemia, ischemic tissue injury, painful vaso-occlusive crises, and multiorgan dysfunction.

STANDARD TREATMENT — The oral antimetabolite hydroxyurea (*Droxia*, and others) is the standard first-line treatment for sickle cell disease; it induces fetal hemoglobin production, reduces inflammation and hemolysis, and decreases the frequency of painful crises and the need for blood transfusions.[1] The amino acid L-glutamine *(Endari)*, the IV P-selectin blocker crizanlizumab *(Adakveo)*, and the oral hemoglobin S (HbS) polymerization inhibitor voxelotor *(Oxbryta)* are used as adjunctive therapy or for second-line treatment.[2,3] L-glutamine is thought to reduce oxidative damage to sickle red blood cells. Crizanlizumab binds to P-selectin on activated endothelial cells and platelets, inhibiting adhesion, reducing vaso-occlusion, and increasing microvascular blood flow. Voxelotor inhibits HbS polymerization, reducing red blood cell sickling, hemolysis, and anemia. Allogeneic stem cell transplantation can be curative.[4]

Key Points: *Casgevy* and *Lyfgenia*

- **Description:** Two cell-based gene therapies for sickle cell disease.
- **Indication:** Treatment of sickle cell disease in patients ≥12 years old with recurrent veno-occlusive crises.
- **Efficacy:** In two small trials, patients who received a single infusion of either gene therapy had marked reductions in the rate of veno-occlusive events.
- **Adverse Effects:** Serious adverse events are related to the pre-treatment myeloablative conditioning regimen.
- **Cost:** $2-3 million.
- **Conclusion:** The efficacy and safety of these gene therapies beyond 1-2 years is unknown.

THE NEW THERAPIES — *Casgevy* and *Lyfgenia* are both prepared from autologous CD34+ hematopoietic stem cells obtained by mobilization and apheresis. In ***Casgevy***, CRISPR/Cas9 gene-editing technology is used to modify the stem cells to reduce BCL11A expression in erythroid lineage cells[5]; the modified stem cells increase production of fetal hemoglobin, preventing sickling of red blood cells. ***Lyfgenia*** is prepared using a lentiviral vector to insert a novel betaglobin gene into the stem cells; the modified stem cells produce a novel hemoglobin (HbA) that inhibits HbS polymerization and sickling of red blood cells.

Patients undergo myeloablative conditioning therapy between 2 and 7 days before infusion of a single dose of *Casgevy* or *Lyfgenia* as part of a hematopoietic stem cell transplant.

CLINICAL STUDIES — FDA approval of ***Casgevy*** was based on the results of an ongoing single-arm trial (unpublished; summarized in the package insert) in 31 patients ≥12 years old with sickle cell disease who had experienced ≥2 severe vaso-occlusive events within the previous 2 years. Patients were treated with myeloablative conditioning therapy and then with a single dose of *Casgevy*. The primary endpoint, an absence of severe vaso-occlusive events for at least 12 consecutive months within the first 24 months after treatment, was achieved in 93.5% of patients. All treated patients achieved successful engraftment and none had graft failure or graft rejection. A trial

evaluating the effects of *Casgevy* for up to 15 years post-infusion is ongoing.

FDA approval of ***Lyfgenia*** was based on the results of a single-arm trial in 36 patients with sickle cell disease who had experienced ≥4 vaso-occlusive events within the previous 2 years. Patients were treated with myeloablative conditioning therapy and then with a single dose of *Lyfgenia*. A complete absence of vaso-occlusive events 6 to 18 months post-infusion was achieved in 90.9% of patients. All treated patients achieved successful engraftment and none had graft failure or graft rejection.[6] A trial evaluating the effects of *Lyfgenia* for up to 15 years post-infusion is ongoing.

ADVERSE EFFECTS — In the clinical trials of *Casgevy* and *Lyfgenia*, mucositis, stomatitis, febrile neutropenia, decreased appetite, neutropenia, anemia, leukopenia, and lymphopenia were related to the myeloablative conditioning regimen. The label of *Lyfgenia* has a boxed warning about an increased risk of hematologic malignancy in patients treated with the gene therapy.

DRUG INTERACTIONS — Hydroxyurea, voxelotor, and crizanlizumab should be stopped at least 2 months before mobilization and until all cycles of apheresis are completed. Iron chelation therapy should be stopped at least 7 days prior to myeloablative conditioning therapy. Granulocyte-colony stimulating factor (G-CSF) products should not be used with either gene therapy. In patients receiving *Lyfgenia*, antiretroviral drugs should be stopped at least one month before apheresis and until all cycles of apheresis are completed.

PREGANCY AND LACTATION — *Casgevy* and *Lyfgenia* have not been studied in pregnant or lactating women and neither is recommended for use during pregnancy or while breastfeeding. Females with childbearing potential and their male partners should use effective contraception during stem cell mobilization and apheresis and for at least 6 months after receiving either gene therapy.

The myeloablative conditioning regimen for both of these therapies will likely cause infertility; fertility preservation should be offered before starting treatment.

DOSAGE, ADMINISTRATION, AND COST — A single weight-based (3 x 10^6 CD34+ cells/kg) dose of *Casgevy* or *Lyfgenia* is infused at least 48 hours after myeloablative conditioning therapy. Absolute neutrophil counts should be monitored after infusion of either gene therapy and platelet counts should be monitored until platelet engraftment and recovery are achieved. The list price of one dose is expected to be $2.2 million for *Casgevy* and $3.1 million for *Lyfgenia*.

CONCLUSION — In two small trials, about 90% of patients who received myeloablative conditioning therapy followed by a single IV infusion of either exagamglogene autotemcel (*Casgevy*) or lovotibeglogene autotemcel (*Lyfgenia)*, gene therapies prepared from autologous CD34+ hematopoietic stem cells, achieved marked reductions in the rates of vaso-occlusive events. The durability of the response beyond 1-2 years is unknown. Whether these very expensive gene therapies prevent the multiorgan dysfunction or neurologic complications of sickle cell disease remains to be established. ■

1. PL Kavanagh et al. Sickle cell disease: a review. JAMA 2022; 328:57.
2. L-glutamine (Endari) for sickle cell disease. Med Lett Drugs Ther 2018; 60:21.
3. Two drugs for sickle cell disease: crizanlizumab (Adakveo) and voxelotor (Oxbryta). Med Lett Drugs Ther 2020; 62:51.
4. M Eapen et al. Effect of donor type and conditioning regimen intensity on allogeneic transplantation outcomes in patients with sickle cell disease: a retrospective multicentre, cohort study. Lancet Haematol 2019; 6:e585.
5. H Frangoul et al. CRISPR–Cas9 gene editing for sickle cell disease and β-thalassemia. N Engl J Med 2021; 384:252.
6. J Kanter et al. Efficacy, safety, and health-related quality of life (HRQOL) in patients with sickle-cell disease (SCD) who have received lovotibeglogene autotemcel (lovo-cell) gene therapy: up to 60 months of follow-up. Blood 2023; 142(Supplement 1):1051.

PRESIDENT: **Mark Abramowicz, M.D.**; *VICE PRESIDENT, EDITOR IN CHIEF:* **Jean-Marie Pflomm, Pharm.D.**; *ASSOCIATE EDITORS:* **Susan M. Daron, Pharm.D.**, **Amy Faucard, MLS**, **Michael P. Viscusi, Pharm.D.** *CONSULTING EDITORS:* **Joanna Esterow, PA-C**, **Mordechai Sacks, DMSc, PA-C**, **Brinda M. Shah, Pharm.D.**, **F. Peter Swanson, M.D.**

CONTRIBUTING EDITORS: **Carl W. Bazil, M.D., Ph.D.**, Columbia University College of Physicians and Surgeons; **Ericka L. Crouse, Pharm.D., B.C.P.P., C.G.P., F.A.S.H.P., F.A.S.C.P.**, Virginia Commonwealth University; **Vanessa K. Dalton, M.D., M.P.H.**, University of Michigan Medical School; **Eric J. Epstein, M.D.**, Albert Einstein College of Medicine; **David N. Juurlink, BPhm, M.D., Ph.D.**, Sunnybrook Health Sciences Centre; **Richard B. Kim, M.D.**, University of Western Ontario; **Sandip K. Mukherjee, M.D., F.A.C.C.**, Yale School of Medicine; **Dan M. Roden, M.D.**, Vanderbilt University School of Medicine; **Esperance A.K. Schaefer, M.D., M.P.H.**, Harvard Medical School; **Neal H. Steigbigel, M.D.**, New York University School of Medicine; **Arthur M. F. Yee, M.D., Ph.D., F.A.C.R.**, Weill Medical College of Cornell University

MANAGING EDITOR AND DIRECTOR OF CONTENT OPERATIONS: **Susie Wong**; *EDITORIAL ASSISTANT:* **Karrie Ferrara**

FULFILLMENT AND SYSTEMS MANAGER: **Cristine Romatowski**; *EXECUTIVE DIRECTOR OF SALES:* **Elaine Reaney-Tomaselli**
EXECUTIVE DIRECTOR OF MARKETING AND COMMUNICATIONS: **Joanne F. Valentino**; *INTERIM PUBLISHER:* **Jean-Marie Pflomm, Pharm.D.**

Founded in 1959 by Arthur Kallet and Harold Aaron, M.D.

Copyright and Disclaimer. The Medical Letter, Inc. is an independent nonprofit organization that provides healthcare professionals with unbiased drug prescribing recommendations. The editorial process used for its publications relies on a review of published and unpublished literature, with an emphasis on controlled clinical trials, and on the opinions of its consultants. The Medical Letter, Inc. does not sell advertising or receive any commercial support. No part of the material may be reproduced or transmitted by any process in whole or in part without prior permission in writing. The Medical Letter, Inc. does not warrant that all the material in this publication is accurate and complete in every respect. The Medical Letter, Inc. and its editors shall not be held responsible for any damage resulting from any error, inaccuracy, or omission.

Subscription Services

Address:
The Medical Letter, Inc.
145 Huguenot St. Ste. 312
New Rochelle, NY 10801-7537
www.medicalletter.org

Customer Service:
Call: 800-211-2769 or 914-235-0500
Fax: 914-632-1733
E-mail: custserv@medicalletter.org

Permissions:
To reproduce any portion of this issue, please e-mail your request to:
permissions@medicalletter.org

Subscriptions (US):
1 year - $159; 2 years - $298;
3 years - $398. $65 per year
for students, interns, residents,
and fellows in the US and Canada.
Reprints - $45 per issue or article

Site License Inquiries:
E-mail: SubQuote@medicalletter.org
Call: 800-211-2769
Special rates available for bulk subscriptions.

Get Connected:

Copyright 2024. ISSN 1523-2859