A new drug for rare diseases: pozelimab for CHAPLE disease

Published Online
January 24, 2024
https://doi.org/10.1016/S0140-6736(23)02652-1

See Online/Articles
https://doi.org/10.1016/S0140-6736(23)02358-9

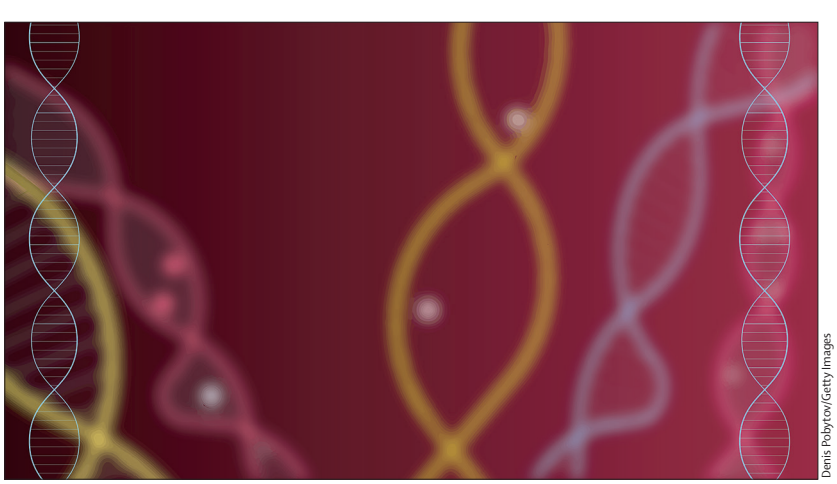
Worldwide, more than 350 million individuals are affected by rare diseases, representing approximately 8000 diseases, with about 80% of these diseases having a genetic basis.[1] Notably, understanding the underlying mechanisms of these prototypic diseases can shed light on common, polyfactorial diseases. Unfortunately, many rare diseases still do not have therapeutic options, making them so-called orphan diseases. Thus, collaboration between the pharmaceutical industry and the academic community is essential to develop new therapies for rare diseases. The low numbers of patients often make randomised controlled trials in rare diseases unfeasible. Therefore, it is imperative for drug regulatory agencies to adopt new evaluation protocols that facilitate access to drugs for patients with rare diseases. These protocols could include real-world studies, incorporating insights from natural history reports, retrospective analyses, and using self-controlled study designs in which patients serve as their own controls. These innovative new approaches are being adopted, and in April, 2022, the US Food and Drug Administration (FDA) approved the repositioning of the phosphoinositide 3 kinase inhibitor alpelisib as a treatment in CLOVES syndrome—a rare disease caused by the somatic gain-of-function mutation of *PIK3CA*—solely on the basis of a retrospective data analysis.[2,3]

Genetic defects in components of the complement pathway can drive various phenotypes such as lupus, haemolytic uremic syndrome, and infectious disease susceptibility.[4] Among them, paroxysmal nocturnal haemoglobinuria is due to the somatic mutations in the *PIGA* gene, which results in the absence of two glycosylphosphatidylinositol anchored proteins regulating the complement activation: CD55 and CD59. Eculizumab, a complement component 5 inhibitor, was the first-in-class FDA-approved treatment targeting the complement system for the treatment of paroxysmal nocturnal haemoglobinuria in 2007. This milestone came after studies reporting the natural history of paroxysmal nocturnal haemoglobinuria[5,6] and a randomised controlled trial.[7] Inherited deficiencies of CD55 were initially identified in patients as the Inab phenotype—a rare blood type characterised by the absence of Cromer blood group system antigens.[8] In 2017, the genetic basis for complement hyperactivation, angiopathic thrombosis, and protein-losing enteropathy (CHAPLE) disease was finally elucidated. Ahmet Ozen and colleagues[9] reported eight families in which affected members carried homozygous loss-of-function variations in *CD55*, causing CD55 deficiency. Kurolap and colleagues[10] also reported an additional family with a loss-of-function mutation. The clinical features of CHAPLE disease are characterised by predominantly gastrointestinal symptoms, including diarrhoea, vomiting, and pain; features of protein-losing enteropathy; and malabsorption, but also include angiopathic thrombosis.

CD55 encodes the DAF protein, which is located on cell surfaces and regulates complement activation by inhibiting the formation of complement component 3 and 5 convertases. Considering the pathophysiology of CHAPLE disease and the proximity to paroxysmal nocturnal haemoglobinuria pathogenesis, complement component 5 inhibitors naturally emerged as the primary choice for targeted therapy in this disease.

In 2021, Ozen and colleagues published a first report on 16 patients with CHAPLE disease who were given eculizumab off-label.[11] This study provided a proof of concept that inhibiting complement component 5 activity in patients with CHAPLE syndrome led to clinical improvement. The findings were limited by the cohort size and the observational nature of the study.

Now in *The Lancet*, Ozen and colleagues[12] present a prospective phase 2 and 3 open-label, single-arm, historically controlled, multicentre clinical trial on ten patients (four male, six female, and with a median age



Denis Pobytov/Getty Images

of 8·5 years) at three study sites in Thailand, Türkiye, and the USA. Although the proof of concept of complement component 5 inhibition in CHAPLE disease was already shown, the prospective design of this study enabled the approval of pozelimab (marketed as Veopoz) by the FDA as the first treatment of this devastating, ultra-rare disease. In this study, a single intravenous loading dose of pozelimab 30 mg/kg, followed by subcutaneous dosing once per week for 144 weeks, showed improvement in gut symptoms and haematological anomalies, a rapid disappearance of oedema associated with a sharp increase in albumin and protein into the normal range, and an improvement in quality of life. These findings are consistent with what was already shown in the prospective, observational case series with eculizumab.[11] Of note, patient 9 in the phase 2 and 3 *Lancet* study[12] was part of the first case series[11] and relapsed at day 125 after eculizumab withdrawal, suggesting that sustained complement component 5 blocker therapy is required at least in some patients, and that the long-term evaluation of the safety of pozelimab is required. An advantage of pozelimab over eculizumab is the subcutaneous administration, providing an important benefit for quality of life compared with intravenous administration in hospital. Additionally, pozelimab appears to be well tolerated, with no severe adverse events associated with the treatment. Similar to other complement component 5 inhibitors, the risk of infection requires ongoing vigilance. The prevention strategy in the study included antibacterials and vaccination for *Neisseria meningitidis*. Notably, no severe infections were recorded in this small cohort. However, it is essential to conduct a real-life evaluation over an extended period of drug exposure to assess potential risks related to encapsulated pathogens. One patient had mild treatment-related adverse events, including three episodes of metabolic acidosis. Finally, on the basis of the doses recommended in these studies, pozelimab appears, according to our calculation,[13,14] to be up to more than three times more expensive than eculizumab.

High-throughput sequencing has transformed current understanding of many genetic diseases, and genomic medicine is now being integrated into everyday clinical care. Progress in this field is on the threshold of a profound transformation, particularly in rare monogenic disorders of the immune system. Two substantial challenges persist as major barriers: the limited access to genetic diagnosis and the unaffordability of targeted therapy. These techniques and treatments can be prohibitively expensive, rendering them inaccessible in low-income countries. This problem underscores the need for a collaborative effort to reduce costs and develop a system that fosters innovation, facilitates diagnosis, and ensures the delivery of personalised medicine to all individuals affected by rare diseases worldwide.

AB reports consulting fees from Kabi, Roche Chugai, GlaxoSmithKline, AbbVie, Novartis, and Boehringer Ingelheim; research grants from Boehringer Ingelheim, ANR, and Horizon Europe outside the scope of this Comment; and is an unpaid co-chair of the French National Network on Rare Autoimmune and Autoinflammatory Diseases. All other authors declare no competing interests.

**Alexandre Belot, Sarah Benezech, Maud Tusseau*
alexandre.belot@chu-lyon.fr

Centre International de Recherche en Infectiologie, Inserm U1111, Université Claude Bernard Lyon 1, CNRS UMR5308, ENS de Lyon, Lyon, France (AB, SB, MT); Pediatric Nephrology, Rheumatology, Dermatology, Hôpital Femme Mère Enfant, Hospices Civils de Lyon, Bron 69677, France (AB); Pediatric Immunology, Haematology, Oncology, Hospices Civils de Lyon, Lyon, France (SB); Genetic Department, Hôpital Femme Mère Enfant, Hospices Civils de Lyon, Bron, France (MT)

1 Faviez C, Chen X, Garcelon N, et al. Diagnosis support systems for rare diseases: a scoping review. *Orphanet J Rare Dis* 2020; **15:** 94.
2 Canaud G, Gutierrez JCL, Irvine AD, et al. Alpelisib for treatment of patients with PIK3CA-related overgrowth spectrum (PROS). *Genet Med* 2023; **25**: 100969.
3 FDA. FDA approves alpelisib for PIK3CA-related overgrowth spectrum. June 4, 2022. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-alpelisib-pik3ca-related-overgrowth-spectrum (accessed Oct 28, 2023).
4 Holers VM. Complement and its receptors: new insights into human disease. *Annu Rev Immunol* 2014; **32:** 433–59.
5 Socié G, Mary JY, de Gramont A, et al. Paroxysmal nocturnal haemoglobinuria: long-term follow-up and prognostic factors. French Society of Haematology. *Lancet* 1996; **348:** 573–77.
6 Hillmen P, Lewis SM, Bessler M, Luzzatto L, Dacie JV. Natural history of paroxysmal nocturnal hemoglobinuria. *N Engl J Med* 1995; **333:** 1253–58.
7 Hillmen P, Young NS, Schubert J, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med* 2006; **355:** 1233–43.
8 Telen MJ, Green AM. The Inab phenotype: characterization of the membrane protein and complement regulatory defect. *Blood* 1989; **74:** 437–41.
9 Ozen A, Comrie WA, Ardy RC, et al. CD55 deficiency, early-onset protein-losing enteropathy, and thrombosis. *N Engl J Med* 2017; **377:** 52–61.
10 Kurolap A, Eshach-Adiv O, Hershkovitz T, et al. Loss of CD55 in eculizumab-responsive protein-losing enteropathy. *N Engl J Med* 2017; **377:** 87–89.
11 Ozen A, Kasap N, Vujkovic-Cvijin I, et al. Broadly effective metabolic and immune recovery with C5 inhibition in CHAPLE disease. *Nat Immunol* 2021; **22:** 128–39.
12 Ozen A, Chongsrisawat V, Sefer AP, et al. Evaluating the efficacy and safety of pozelimab in patients with CD55 deficiency with hyperactivation of complement, angiopathic thrombosis, and protein-losing enteropathy disease: an open-label phase 2 and 3 study. *Lancet* 2024; published online Jan 23. https://doi.org/10.1016/S0140-6736(23)02358-9.
13 Jain P. US FDA approves Regeneron's ultra-rare blood disease drug. Reuters. Aug 18, 2023. https://www.reuters.com/business/healthcare-pharmaceuticals/us-fda-approves-regenerons-ultra-rare-blood-disease-drug-2023-08-18/ (accessed Nov 22, 2023).
14 Drugs.com. Soliris prices, coupons and patient assistance programs. 2023. https://www.drugs.com/price-guide/soliris (accessed Nov 22, 2023).