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LETTER TO THE EDITOR

Making treatment decisions in hemophilia based on available safety data

The availability of emicizumab (Hemlibra) for the treatment of hemophilia A has been the most disruptive therapy to treat the condition since factor VIII (FVIII) concentrate was introduced. While for patients with antibodies to FVIII (inhibitors) this treatment has been life changing in dramatically reducing the annual bleed rate, for non-inhibitor patients on good FVIII prophylaxis the benefits are less clear. For non-inhibitor patients the benefit of emicizumab is largely that of convenience because it can be given subcutaneously every 1, 2, or 4 weeks rather than intravenously two to three times weekly.

As hemophilia clinicians, we have embraced emicizumab treatment and have seen its benefits. All of our hemophilia A patients with FVIII inhibitors are now on emicizumab, as are 25% to 30% of our non-inhibitor patients. Patient-level decisions to change hemophilia treatment are based on discussion of many issues including efficacy and available safety data.

At the time of approval of a drug by the regulatory authorities, the clinical studies performed during its development are likely to have shown good efficacy and reasonable safety. It should be appreciated, however, that much of the safety data come after the drug has been released onto the market. The primary adverse events that concern treaters and patients in relation to emicizumab are thrombosis and death. Following the launch of emicizumab the manufacturer provided a website that showed three-monthly data on the number of thrombosis, thrombotic microangiopathies, and deaths occurring in patients taking emicizumab. Following the update of events to 30 June 2020 this service was discontinued, and we were informed that these data will in the future be presented in publications and at scientific meetings. The mortality issue was recently addressed by three papers in this journal.[1-3]

The first paper largely analyzes publications reporting on mortality in hemophilia since 2010.[1] As the authors identify, the cited literature shows significant heterogeneity and pooling the data can be problematic. The ideal situation in which prospective data are collected from complete populations of patients of all severities, where the primary as well as contributing causes of death are included and the data are audited, is rarely achieved. In the second paper the authors provide a framework to categorize causes of death enabling a separation into those which are related or unrelated to hemophilia.[2] This is rather artificial, and we have some issues such as the assignment of thrombosis as a hemophilia-related cause and malignancy as unrelated to hemophilia when one of the commonest malignancies in hemophilia is hepatitis C--related hepatocellular carcinoma. To us it would seem simpler to ignore the relatedness to hemophilia and simply compare the individual groups of causes between studies. The third paper describes the application of the framework algorithm[2] to the deaths of patients on emicizumab up to 15 May 2020, which are recorded on the Roche Emicizumab Global Safety Database.[3] We believe the way the data are presented, and the information provided, raise a number of questions.

a. In 11 (44%) of the 25 cases in which the cause of death was specified, it was reported as hemorrhage and in 5 of these (20%) cases the location was intracranial. Patients on emicizumab behave clinically (in terms of bleeding) like patients with mild hemophilia who have FVIII levels of 10% to 20% (0.10–0.20 iu/ml). To us, this is a cause of concern as intracranial hemorrhage (ICH) is rare in patients with mild hemophilia. It must be borne in mind that these are the fatal cases, and we have no information on non-fatal ICH in emicizumab-treated patients.
b. Despite the number of non-fatal thromboses including myocardial infarctions reported in patients on emicizumab, it is remarkable that none of the deaths were attributed to thrombosis. We believe this is likely due to under-reporting because the two cases of cardiac arrest could have been due to coronary thrombosis.
c. Another remarkable observation concerns relatedness. Emicizumab is a new drug for which the full safety profile remains to be established and most deaths likely occurred in patients taking the medication for less than 2 years. Despite this, the reporting clinicians felt sufficiently confident to report that in 22 (92%) of the cases in which relatedness was reported, there was no relation to emicizumab. Even in the other 2 (8%) cases, the reporting clinicians indicated unknown relatedness or identified multiple causes. In the circumstances, we feel that more doubt in relatedness could have been expressed.
d. These three papers discuss congenital hemophilia only. We are concerned about the use of emicizumab in acquired hemophilia, a condition for which the drug is not approved. The manufacturer website contained data on the number of deaths in patients with acquired hemophilia taking emicizumab, but this information is no longer available or updated. As clinicians are starting to use emicizumab for acquired hemophilia off-license, it is important

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that they are aware of the latest data on adverse events in this population.

The discontinuation of the three-monthly update service on thrombosis and deaths on emicizumab after June 2020 means that the next update will likely be at the ISTH meeting in July 2021, more than 1 year after the last data report. We feel that reporting data on thrombosis and death at scientific meetings should be in addition to, rather than instead of, providing the information every 3 months online as was the case until recently. We do accept that when drugs are well established, periodic presentation of data by publication or at scientific meetings is acceptable. Given the drug was launched relatively recently and large numbers of patients are considering changing to this medication, they deserve to make their decision on the most up-to-date information.

CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Both authors contributed equally to the writing of this letter to the editor.

Mike Makris[1,2]
Cedric Hermans[3]

[1]*Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, UK*
[2]*Sheffield Haemophilia and Thrombosis Centre, Royal Hallamshire Hospital, Sheffield, UK*
[3]*Hemostasis and Thrombosis Unit, Division of Hematology, Cliniques Universitaires Saint-Luc, Université catholique de Louvain (UCLouvain, Brussels, Belgium*

Correspondence
Mike Makris, Sheffield Haemophilia and Thrombosis Centre, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF, UK.
Email: m.makris@sheffield.ac.uk

ORCID

Mike Makris https://orcid.org/0000-0001-7622-7939
Cedric Hermans https://orcid.org/0000-0001-5429-8437

TWITTER

Mike Makris @ProfMakris

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