CLINICAL NOTE

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Challenges for Hemophilia Patient Care Across the Middle East and North Africa

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Hemophilia A and B are inherited bleeding disorders characterized by deficiencies in blood coagulation factors VIII (FVIII) or IX (FIX), respectively. The estimated prevalence of hemophilia in selected countries from the Middle East and North Africa (MENA) —Iraq, Iran, Turkey, Egypt, Jordan, Syria, and Saudi Arabia—ranges between 1.4 and 8.1 per 100 000 of the general population.[1] The current standard of care for patients with hemophilia comprises regular prophylaxis with intravenously administered recombinant or plasma-derived factor concentrates.[2] Adherence to a prophylactic regimen allows patients to maintain adequate factor levels to prevent hemarthrosis and other spontaneous bleeding episodes.[2]

In recent years, the increased availability of extended half-life (EHL) factor concentrates that require less frequent intravenous dosing has reduced the treatment burden for many patients.[3] Emicizumab has recently emerged as a subcutaneous treatment for hemophilia. Other subcutaneous non-factor therapies are undergoing clinical trials.[4] Together, these novel treatments are helping many individuals with hemophilia across the world to improve their quality of life (QoL).

Recently, Novo Nordisk hosted two expert meetings to discuss challenges to the management of people with hemophilia A and B across the MENA region. Experts from Azerbaijan, Egypt, Iraq, Kuwait, Lebanon, Morocco, Oman, South Africa, and UAE provided feedback on key issues relating to hemophilia care. The challenges highlighted in the meeting could be classified into three major topics:

1. Clinical monitoring

- *Pharmacokinetic (PK) analysis.* To achieve optimal protection from bleeds, an individualized PK-based approach to prophylaxis is recommended by the World Federation of Hemophilia (WFH) treatment guidelines.[2] However, assessment of PK parameters is challenging for physicians in some countries due to cost factors (e.g., Jordan, Iraq, Lebanon, and Morocco), and treatment decisions are made based purely on clinical signs such as annualized bleeding rate and joint health. A tailored treatment approach is important to help such patients reach and maintain normalized hemostasis.

- *Chromogenic assays.* The use of chromogenic factor activity assays is necessary to monitor factor activity with EHL products due to known issues with certain one-stage clotting assays.[5] While chromogenic assays are available in some countries such as the UAE and Oman, access is limited in Iraq, Kuwait, and Lebanon (Egypt will be introducing these assays soon). If factor activity analysis with chromogenic assays is required in these countries, samples can be sent abroad to Germany, France, or the UK.

2. Current treatments

- *Treatment availability and reimbursement.* Most health authorities in the region use tender systems to procure factor products, and price is the most important factor influencing product

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availability. This can result in limited availability of some products, including EHL factor concentrates. Reimbursement for non-residents and refugees is also problematic, particularly in Lebanon where Syrian and Palestinian refugees count on donations from the WFH to the Lebanese Association of Hemophilia. The ongoing economic crisis in Lebanon has also contributed to the shortages of some drugs.

- *Use of prophylaxis versus on-demand therapy.* Prophylaxis is currently recommended to prevent spontaneous bleeds and maintain joint health.[2] In some resource-constrained countries, prophylaxis is often unaffordable at the higher dosing levels used in more affluent countries. On-demand therapy is predominantly used in countries such as Azerbaijan and Egypt. However, the option of low-dose prophylaxis, recommended by the WFH over episodic therapy,[2] has been shown to be a cost-effective solution that could have a major impact on the bleeding frequency and QoL.[6] In Lebanon, children receive prophylaxis treatment while adults are given on-demand therapy. All UAE nationals and most non-nationals receive prophylaxis, while non-national residents without medical insurance are covered under the Activity-Based Mandate plan.

- *Safety of PEGylated products.* The use of PEGylation—the process of attaching a polyethylene glycol (PEG) molecule to a biopharmaceutical molecule—has enabled the extension of circulation half-life for several recombinant FVIII and FIX products. Despite extensive clinical use of PEGylated therapeutics in patients with other indications, hypothetical concerns have been expressed that long-term prophylactic treatment could lead to accumulation of PEG molecules in plasma and certain tissues .[7] PEGylated EHL factor products are approved in Europe for patients ≥ 12 years of age until long-term safety data in children are available, and the USA has approved three PEGylated factor products for patients of all ages. Recent studies have shown that PEG levels reach steady state in children, adolescents, and adults receiving long-term treatment with PEGylated factor concentrates and no unexpected safety issues have been identified so far.[8,9]

3. Patient QoL

- *Recreational activities.* Hemophilia patients should avoid contact sports such as football and rugby. They should be encouraged to engage in milder activities such as walking, swimming, and cycling. While having swimming pools at hemophilia treatment centers would be ideal, this may not be practical in regions prone to water shortages and economic constraints. Meanwhile, hot climate and uneven terrain in some regions may make walking and cycling unattractive and even risky for some patients. This calls for recommending safe indoor physical activities for hemophilic individuals to enhance their QoL.

- *Shelf-life and temperature stability of factor concentrates.* Many patients mistakenly believe that their factor products must be refrigerated at all times. In a survey, 85% of 200 patients with hemophilia A from the UK, France, Italy, Mexico, Brazil, Argentina, and Japan revealed they kept their FVIII products refrigerated.[10] This false belief is important to correct because many patients across the affected regions do not have refrigerators at home, or certain parts of the product transport chain may be non-refrigerated. Frequent power cuts in some areas can also interrupt refrigeration. Awareness of proper storage requirements for factor products may also enable patients to carry their medications with them while traveling, again improving their QoL. Physicians should therefore educate their hemophilia patients on this aspect when discussing treatment.

CONCLUSION

Despite significant advances in the management of hemophilia, challenges persist in certain countries in the MENA region such as limited access to laboratory assays and novel treatments. Increased use of tailored PK-based prophylaxis, better access to chromogenic assays, adoption of low-dose prophylaxis in resource-strained countries, improved access to swimming pools, and increased awareness

of storage conditions for factor concentrates may improve health outcomes and QoL of patients with hemophilia in this region.

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