Commentary

Pros and Cons of the ISTH Treatment Guidelines for Hemophilia

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The readership of this journal is cognizant of the striking therapeutic advances that, particularly in the last two decades, materialized for both hemophilia A and B [1]. With this background, the main scientific and learned society in the field (ISTH) chose to summon in 2021 and 2022 a panel of expert clinicians, epidemiologists and patients in order to produce treatment guidelines published in the official journal [2]. The guidelines come on the heels of those released in 2020 by the World Federation of Hemophilia (WFH), a non-profit organization of patients and healthcare providers dedicated to worldwide improving and sustaining the care of people with inherited bleeding disorders [3]. There is a substantial difference in methodology between the two texts, that share the feature of being authored by panels of distinguished experts and patient representatives. The WFH guidelines were a consensus-based clinical guidance document, whereas ISTH chose the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to evaluate and rank the strength of the recommendations based upon a comprehensive array of questions related to therapeutic strategies for patients with hemophilia [2]. GRADE emphasizes higher quality evidence such as obtained in randomized trials [4]. In rare diseases such as hemophilia A and B randomized studies are seldom performed. It is therefore not surprising that the only recommendation released with strong evidence by the ISTH guidelines pertains to prophylaxis for both severe and moderately severe hemophilia A and B. This choice is unequivocal for hemophilia A, because at least two randomized clinical trials established the superiority of prophylactic replacement therapy [5,6], but is not fully justified for hemophilia B, because no randomized trial compared prophylaxis with episodic treatment. On my opinion, however, this recommendation is justified by analogy with hemophilia A, and because of
the availability of recombinant FIX medicines that attain and maintain high trough levels of plasma FIX with much reduced treatment frequencies [7].

With this nuance, it must be emphasized upfront that of the 13 therapeutic questions addressed by the ISHT panel (11 for hemophilia A and 2 for hemophilia B) a strong recommendation, albeit with moderate certainty, was released only for prophylaxis, and that only conditional therapeutic recommendations, in practice equivalent to suggestions, were issued by the panelists for the remaining questions. When conditional recommendations were further split according to the level of certainty, it was very low for most of them. The only exception is low certainty for recommendation 7, that suggests prophylaxis of bleeding over episodic treatment in patients with severe hemophilia A with inhibitors.

With these overall results, the first issue is whether it was appropriate for the ISTH and its panel to tackle guidelines and related recommendations employing the GRADE methodology instead of expert consensus as WFH did. Incidentally, I asked myself the same question when ISTH with other scientific societies chose to produce therapeutic guidelines for another rare bleeding disorder, i.e., von Willebrand disease [8], because it was predictable that no strong recommendation could be released for the treatment of a disease lacking randomized clinical trials. On the other hand, it is understandable that such a scholarly organization as ISTH chose to employ a methodology considered the gold standard for therapeutic guidelines. I am also cognizant that in the recent past other GRADE-based recommendations raised turmoil, for instance those on use of antithrombotic drugs for cardiovascular disease, notwithstanding the fact that randomized clinical trials are much more numerous for thrombosis than bleeding disorders. The most common scenario is that clinicians complain that epidemiologists do not sufficiently value
the weight of clinical experience and observational studies and blame the stiffness of the GRADE methodology, in turn worshipped by epidemiologists/methodologists.

On the whole, the critiques generated by the ISTH guidelines in the community of hemophilia treaters, patients and other stakeholders seem to me a storm in a teacup, because nobody would object on the strength of the recommendation for prophylaxis. In addition and regarding the remaining conditional only recommendations, the panelists were astute enough to accompany each of them with cogent and comprehensive remarks that fully discuss the pros and cons of each recommendation/suggestion, thereby providing stakeholders with ample room for alternative therapeutic choices [2].

For sake of an example, recommendation 5 suggests, albeit with very low certainty, for initial prophylaxis of previously untreated patients with severe HA, the choice of plasma-derived FVIII over recombinant products, considering that the findings of the randomized SIPPET study [9] were confirmed by two very large registry-based observational studies [10,11]. The current viral safety of plasma-derived products has been established by more than 30 years of real-life experience. On the other hand, it is understandable that countries that can afford prophylaxis with recombinant products with extended half-life prefer this option for the advantages of patient feasibility and adherence, notwithstanding the higher early inhibitor risk.

Another comment is on recommendation 4, that conditionally, but again with very low level of certainty, suggests low-dose prophylaxis with FVIII or IX concentrate for resource-limited settings, where full dose prophylaxis is not a feasible scenario. In most low- but also in a number of middle-income countries this approach is not truly feasible: not only for the scarce availability of replacement products but mainly because this therapeutic regimen warrants frequent monitoring of patients, of their through plasma levels and
inhibitor development in settings characterized by few specialized treatment centers often at long distances from where patients live. Thus, factor products with standard or extended plasma half-life are often an unfeasible option for low-dose prophylaxis. On the other hand, the potential advantages offered by lower dosages of a subcutaneously and monthly administered medication such as emicizumab are too preliminary to be recommended and a face-to-face comparison of low and regular dosage regimens is warranted [12].

I suspect that one of the main causes of critique to the ISTH guidelines stems from recommendations 7 and 8, which deal with prophylaxis in patients with severe hemophilia A with inhibitors and suggest with low certainty prophylaxis over episodic treatment and also, but with very low certainty, the use of emicizumab over traditional bypassing agents. I cannot help by recalling the mayhem raised in 2005 when a Cochrane report stated that there was no evidence on the superior efficacy of prophylaxis in hemophilia versus episodic treatment [13]. The mayhem was stopped by the publication of randomized trials, but it seems to me unrealistic to envisage at this time a randomized study comparing emicizumab with bypassing agents, considering the blatant advantages of prophylaxis with subcutaneous emicizumab as well as the poor feasibility of using bypassing agents for prophylaxis in real life.

A final comment is that these recommendations were prepared in 2021 and 2022, at a time when gene therapy for both the hemophilias and the ultraextended half-life FVIII product efanesoctocog alfa were still in infancy of clinical development and approval. However, even now it would be difficult to offer recommendations with a high level of certainty!

All in all, I believe that the guidelines released by the ISTH panel are temporarily useful even if of low or very low certainty of evidence. The conditional suggestions by definition
give space to other options owing to the deed of being conditional. The detailed discussion of the pros and cons contained in the remarks accompanying each recommendation is comprehensive and offers to stakeholders (clinicians, patients and payers) options for therapeutic choices that anyway must be personalized and shared with patients on a case by case basis.

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