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Comment

Remission-driven discontinuation shapes the observed duration of emicizumab in acquired hemophilia A. Comment on: "Short-term emicizumab in patients with acquired hemophilia A"

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Text

Erard et al. report a retrospective Belgian series of 34 patients with acquired hemophilia A (AHA), 33 of whom received emicizumab.[1] The protocol required stopping the drug once remission was reached. Remission was defined as an inhibitor below 1 BU/mL and endogenous FVIII above 50%. Twenty-three patients stopped for this reason. The authors conclude that prolonged or indefinite treatment is not needed in patients who achieve remission. This is one of the most informative real-world series available on emicizumab, and we agree with its main message. We would like, however, to comment on how the 149-day figure should be interpreted.

The data support the view that emicizumab can be stopped once remission is reached. The observed duration up to that point is a different matter. It is not an independent estimate of how long the drug is needed. It is shaped by the definition of remission and by the discontinuation rule.

What that figure measures also deserves attention. The text links the 149 days to the 23 patients who stopped emicizumab after reaching remission. Figure 1, however, estimates the median by Kaplan-Meier in all 33 treated patients. It counts both discontinuation for remission and death as events, and censors patients still on treatment. The authors do address the competing risk of death in the supplementary material, but it is the curve in Figure 1 that supports the 149 days. We think it is important that the authors clarify this point, because the interpretation of the figure depends on it. As the primary endpoint is defined, the 149 days represent the median time to a composite endpoint, rather than the time to discontinuation after FVIII recovery. The endpoint combines two events with very different clinical meaning.[2]

There is a further point. Among patients who stopped for remission, the timing of discontinuation depends on three factors: the kinetics of inhibitor eradication, the FVIII threshold chosen, and how often FVIII was measured. The duration therefore describes a remission-guided treatment strategy rather than an optimal duration of emicizumab itself.

The authors' own analysis points in the same direction. The only independent predictor of emicizumab duration was the baseline inhibitor titer: 76 days below 20 BU/mL versus 168 days at 20 BU/mL or above (β=0.30; p=0.005). The authors interpret this correctly, citing its established prognostic value for remission.[3] The independent predictor identified for duration is therefore a marker of the probability of remission.

Comparison with earlier studies supports this reading. The authors state that their 149 days agree with GTH-AHA-EMI. In that trial, however, emicizumab was given for 12 weeks fixed by protocol, and not until an FVIII threshold was reached.[4] The contrast with Knoebl et al. is even more informative. Their laboratory-remission threshold for endogenous FVIII matches the >50% threshold used by the authors. In their series, recovery of endogenous FVIII above 50% measured with bovine reagents took a median of 115 days. Emicizumab was stopped much earlier, after a median of 31 days, using a chromogenic FVIII activity of at least 30% with human reagents as the criterion. That measurement is influenced both by endogenous FVIII and by emicizumab activity, and not only by immunological recovery.[5],[6] The two approaches link discontinuation to different phenomena. The first ties it to immunological remission. The second ties it to a chromogenic FVIII activity threshold. The difference in duration is more than three months. Both papers are cited in the article.

Taken together, these data suggest that different discontinuation rules produce very different emicizumab durations, even though immunological recovery follows its own timeline. The 50% threshold comes largely from the convention adopted in AGEHA[7] and

from conventional definitions of remission,[3] rather than from prospective validation. In a scoping review of the literature, FVIII levels at the time emicizumab was stopped ranged from 10% to 86%.[6] A recent review notes that no strict threshold has been established.[8] The US cohort of Poston et al. reported a median of 18 weeks using different criteria.[9]

This has a clinical consequence. The series shows convincingly that emicizumab can be withdrawn after remission and that this is feasible in routine practice. It does not establish how long emicizumab needs to be continued before withdrawal.

One additional piece of information would make that conclusion stronger. The article does not report inhibitor recurrence after emicizumab withdrawal. This is particularly relevant given the median follow-up of 2.1 years. The absence of major bleeding after emicizumab initiation is reassuring, but outcomes are not reported separately for the period after withdrawal. To judge the safety of a remission-guided discontinuation strategy, the period after withdrawal is especially informative. How many of the 23 patients had inhibitor recurrence? How many experienced bleeding after withdrawal? How many needed to restart emicizumab or immunosuppression? An immunological relapse is not necessarily a clinical failure of the discontinuation strategy. Separating the two would be useful. Relapse after remission is not uncommon in AHA.[3] These data may be available from the cohort.

It would also be useful to know the serial course of endogenous FVIII measured with bovine reagents, and how often it was measured. Both would help separate the kinetics of immunological recovery from the effect of the chosen threshold and of the testing schedule.

In our view, the prospective studies the authors call for should separate time to inhibitor eradication from the duration of emicizumab prophylaxis and evaluate prespecified discontinuation criteria.

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