

CORRESPONDENCE

The prophylaxis of hereditary angioedema attacks with recombinant human C1 inhibitor: who will take advantage of the individualized treatment approach?

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Replacement therapy, given intravenously, has been used for many years in the treatment of acute hereditary angioedema (HAE) attacks. Recently, the indications for long-term prophylaxis with plasma derived (pd) or recombinant human (rh) C1INH concentrate in HAE have been debated (1). Clearly, there is a need for more data on the benefit and safety of this therapy. The study by Reshef et al. (2) investigating rhC1INH in the prevention of HAE attacks is a welcome contribution to this evidence base. The authors have demonstrated that a weekly administration of 50 U/kg rhC1INH reduced the frequency of HAE attacks from a mean of 0.9 attacks/week in the past to the rate of 0.4 attacks/week during the treatment period, which corresponds to the avoidance of one attack per every 2 weeks, on average. There are some issues arising from this study that may be considered in more detail.

Firstly, despite the fact that the overall average effect of intervention was positive, the response to rhC1INH differed one from another in individual cases. Four (16%) of the patients were symptom free during the treatment period, another two had a considerable decrease in the frequency of HAE attacks, but the others experienced only a moderate reduction in the occurrence of attacks. Similar observations were made in another study on replacement prophylactic therapy in HAE (3). This differentiation in patients' response to treatment brings up questions (i) whether there is a possibility for an *a priori* identification of the best responders to investigated therapy (based on clinical features or the other biomarkers) and (ii) whether it would be helpful to use additional secondary end points, which would allow us to measure more precisely the clinical benefit from therapy for those patients who did not have a substantial decrease in the frequency of attacks (e.g., the severity and duration of attacks, the total number of days without swelling, the time to the onset of an unequivocal relief of the symptoms, or the need for hospitalization and rescue treatment due to life-threatening symptoms).

Secondly, the available data on a patient's clinical course after there has been a discontinuation of the long-term prophylactic treatment with C1INH are limited and are usually not discussed widely in clinical trials. Here, the authors reported a serious adverse event (a fatal laryngeal edema, 25 days after the last administration of rhC1INH in the study). In another study, a tendency to develop more attacks

during long-term prophylaxis with pdC1INH was observed (4). It would be of interest to practitioners and patients to know how, and to what extent, a discontinuation of prophylactic replacement therapy influences the severity and frequency of HAE attacks. It is certain that the safety of this treatment still requires further studies.

Thirdly, the authors are absolutely right when they notice that inpatient variation in a disease course over time can be significant (5, 6). If there is seen to be a great variance of the clinical expression of HAE in the same patient, this factor can obviously cause a potential bias in the assessment of the efficacy of the prophylactic treatment. Moreover, it seems that even an accurate recording of symptoms cannot overcome this limitation, especially in studies with a long-term observation period.

Finally, efforts should also be made, in the future, to collect comprehensive information on a head-to-head comparison between the various existing prophylactic regimens, and on determination of what the most effective dose of prophylactic C1INH is required to optimize clinical response.

As long as pointed questions remain unanswered, it is reasonable to limit the prophylaxis with rhC1INH only to highly selected patients with the most severe clinical course of HAE. A further extension of the number of patients for whom this treatment may be indicated needs to be based on convincing pieces of evidence that a considerable percentage of patients profit from this treatment. We should also take into account what prospect this treatment gives the patient of avoiding serious HAE attacks, how much effort is required of the patient, and, finally, how cost-effective the treatment is.

Conflict of interest

Dr Porebski has served as an investigator for clinical trials sponsored by CSL Behring, Jerini/Shire, and Pharming.

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REPLY

We are indebted to Dr. Porebski for his helpful remarks on our paper (1). Indeed, the dilemma of whom to treat prophylactically has been debated for many years and was already incorporated in a few recently published clinical guidelines (2–4). Most experts agree that the purpose of prophylaxis in HAE is to diminish the frequency, intensity, and humanistic and economic burden of the disease. Unfortunately, despite the long history of human plasma-derived C1 inhibitor (pdC1INH) concentrates in Europe, and in contrast to the valuable data gained by studies on acute HAE treatments, very few prospective studies have been designed to answer the important issues and concerns addressed by Dr. Porebski.

Realistically, the proposed *a priori* identification of a subset of patients who will mostly benefit from prophylaxis is unlikely. Patient attacks are unpredictable and differ in intensity and location, as well as in their inciting triggers. There are no biomarkers available to predict oncoming attacks, and no clinical phenotypes of patients prone to frequent attacks have yet been identified.

In regard to Dr. Porebski's concern about a potential acceleration of attacks following discontinuation of prophylactic treatment, we disagree with the notion that the unfortunate death of one patient in our prophylactic study could be related to the treatment. This patient had not experienced a sharp increase in the frequency of her attacks after the last per-protocol dose of rhC1INH. She had an acute severe laryngeal attack (one of many) while residing in a remote area of the country, and efforts by a local medical team failed to save her. Actually, this case represents an additional rationale for implementing a long-term prophylaxis in patients who live far away from modern medical facilities.

There are a few reports of increasing rate of attacks in pdC1INH-treated patients. However, it should be noted that such cases are rare and definitely not due to discontinuation

of treatment. They were reported in patients who were frequently treated on-demand and not as part of a prophylactic regimen (5). There is reason to believe that this infrequent phenomenon is not associated with the development of resistance or tachyphylaxis, as none of the rhC1INH studies has demonstrated neutralizing antibodies against the recombinant agent (6).

Finally, we concur with Dr. Porebski's third point about the high variability among individual patients in the location of swellings and frequency of attacks. Evidently, current knowledge limits our capacity to define an 'HAE recidivists' and prescribe a long-term prophylaxis to such patient populations. Furthermore, an individualized approach is already practiced, since in view of the soaring price of new HAE medications and high variability within health systems worldwide, even expert consensus guidelines fail to convince insurers and health maintenance organizations to apply the recommended prophylactic regimens.

Despite all these limitations, we believe that future research will show that prophylactic treatment is effective and safe and can be offered to many patients whose disease course is prolonged and for whom frequent attacks have a detrimental bearing on their quality of life (7).

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Increased mortality in AR patients?

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In their contribution to the April issue of *Allergy* titled ‘Allergic rhinitis and risk of erectile dysfunction – a nationwide population-based study’, Su et al. (1) described a case–control study which they have conducted in allergic rhinitis (AR) patients and matched controls not suffering from this disease.

It is one of the largest, well-designed clinical observation trials in the history of epidemiologic research dealing with allergic disorders, and the authors come up with the surprising finding that AR is a predisposing factor for erectile dysfunction (ED). The hazard ratio (HR) for the development of ED was 1.37 which is higher than, for example, the HR for asthma or COPD.

The most surprising finding, however, can be found in Fig. 1 of their publication:

In 60 421 AR patients followed up for a mean time of 5.79 years, 1621 deaths occurred compared with only 548 deaths in 61 828 controls without AR. The authors do not explain this finding nor do they mention this fact at all.

It appears more than astonishing that in this population with a mean age of 34.25 years, there are 1073 more deaths in AR patients than in completely matched controls. These data therefore seem to suggest a 197% increase (relative risk 2.97, 95% confidence interval 2.70–3.27) in mortality in AR

patients compared with matched controls (though we were not able to account for the matching in our analysis). One may only speculate about the reasons for this surplus mortality in young to mid-age allergic subjects: Could it be the adverse result of taking anti-ED medication? Did these patients die in accidents caused by sedative antiallergic medication or somnolence due to the disease as described before (2)? The authors should reanalyze their data in this light.

Author contributions

RM has written the manuscript; MH has conducted the analysis.

Conflict of interest

There is no conflict of interest with this topic.

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