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Pain while injecting emicizumab predominant in children, a report of Dutch patient experiences

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Dear Editor,

The last couple of years, emicizumab (Hemlibra) has caused a revolution in the treatment of haemophilia A. Besides its obvious useful application in patients with inhibitors, bypassing the inhibitory antibodies, the subcutaneous administration and long half-life, resulting in higher steady-state protection have also made it an attractive treatment for non-inhibitor patients. Since emicizumab became available in the Netherlands as an alternative for Factor VIII prophylaxis in 2020, about 35% of haemophilia A patients on prophylaxis have started using emicizumab according to the national registry.¹

As patient society we have collected real-world patient experiences with emicizumab therapy. One recurring concern, reported by both patients and clinicians, has been the occurrence of injection site pain. Patients indicated a burning or irritating sensation while injecting the liquid. Obviously, pain from an injection is expected and the possibility is identified as frequent side-effect in the summary of product characteristics. Injection-site reactions are reportedly occurring in 20% of patients, although these do not necessarily involve pain.² However, it surprised us to receive this as remark from a population generally used to frequent intravenous injections. Especially since the easy technique and low impact is one of the

advantages of subcutaneous administration. Obviously, when patients do experience painful injections this can cause issues around adherence or change the decisions which therapy fits best (in literature there have been incidental cases of emicizumab users reverting to traditional factor VIII replacement,³ the latest report from the national registry indicates 3 patients stopped emicizumab due to preference for regular FVIII⁴).

To move beyond anecdotal reports, we have conducted a brief survey among the readership of our societies email newsletter and social media channels, asking patients and parents/caregivers for their experiences around injection pain with emicizumab. Of the 72 responses received (Figure 1), 52 (72%) reported pain during injection. Of these, exactly half answered that the pain was problematic. The vast majority (42/49, 86%) experienced this pain during the actual infusion of the emicizumab, while a small part (7/49, 14%) reported pain from the needle injection. When looking at age differences (Figure 2a), the issue is a clear problem in children. Although not always problematic, nearly all of the children (42/43) experienced pain. In some cases (3/43) this was only in the period after starting the subcutaneous therapy. On the other hand, a majority of the adults (18/28, 64%) experienced no pain and if pain was reported they considered it not problematic.

Further, we asked participants that reported pain how they coped with this pain and whether they had recommendations for other patients. Lidocaine-prilocaine cream (EMLA) can be used to reduce injection pain, and 47% (23/49) of our responders reporting pain did so (Figure 2b). An open question for recommendations yielded several responses mentioning distraction of the child, early removal of the emicizumab from the fridge, early application of the EMLA cream, slow or staggered infusion, alternative dosing volumes and frequencies, and experimentation with different injection sites and postures. These responses show that patients and parents are experimenting, trying to find a way to deal with injection site pain with varying success. Nevertheless, most responses suggest that this inconvenience is still

outweighed by the advantages of the therapy with emicizumab, a point of view also reflected by the limited number of patients reverting to traditional FVIII prophylaxis. Additionally, there are some reactions suggesting the injection pain 'is just part of it' and requires 'just dealing with it' or 'growing up'.

This method of a voluntary survey is naturally biased towards persons experiencing pain. But with around 209 patients receiving emicizumab therapy in The Netherlands,¹ and with 52 patients experiencing pain during injection, this survey suggests that the number of patients experiencing pain issues during injection is at least 25%, most of these children. Comparing the age distribution of our respondents, children are also somewhat overrepresented (60%) compared to emicizumab users in The Netherlands in general (40%⁴). All but the very youngest can be expected to have previous experience with intravenous recombinant FVIII prophylaxis, as 94% of severe haemophilia A patients receive prophylactic treatment.¹ Reported pain with administration of other subcutaneous medications show considerable variation, depending on either volume, injection technique, excipients, frequency, injection location.⁵ These experiences provide avenues to explore for mitigation, and with this survey we would like to call attention to this issue. Further investigations to see whether injection pain can be reduced, for example by changes in injection technique or by different dosing strategies might be warranted. Our observations should be a cause for extra alertness with the development of novel subcutaneous treatments. The reported burning sensations of the liquid suggest the chemical composition of the emicizumab solvent could have an influence, while the effects on children are only investigated at a relatively late moment in product development. But also in clinical follow-up and patient information this issue should get more attention, to educate patients what can be done to deal with it, to better inform the choice on type and frequency of the therapy and to make sure patients are not silently coping with an administration issue of their treatment that might be alleviated.

AUTHOR CONTRIBUTIONS

All authors contributed to the study concept and design, participated in reviewing and interpreting the data and the manuscript, and have read and approved the final manuscript before submission.

The authors have no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Ethical review was not required by local regulations, due to the limited size and impact of the one-off survey and no personally identifiable data was collected. Informed consent was in line with the Declaration of Helsinki.

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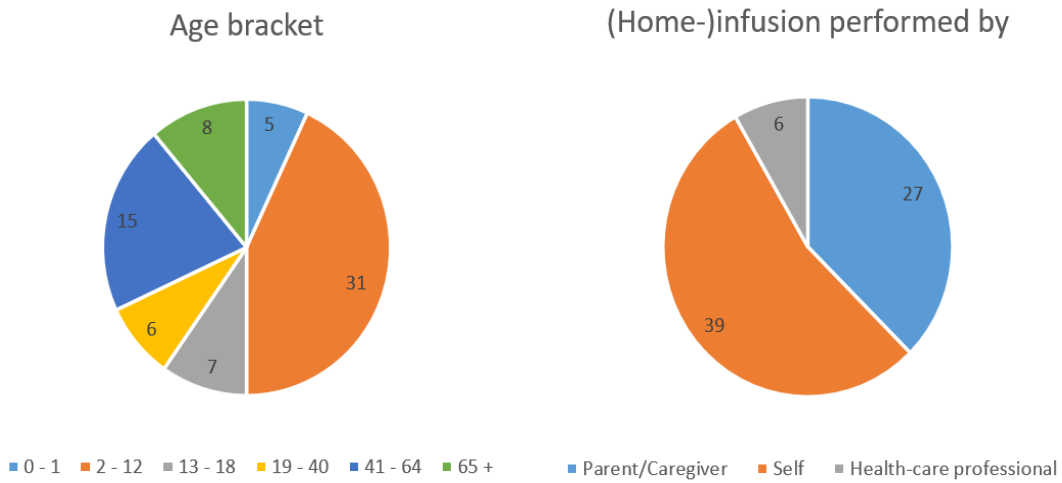
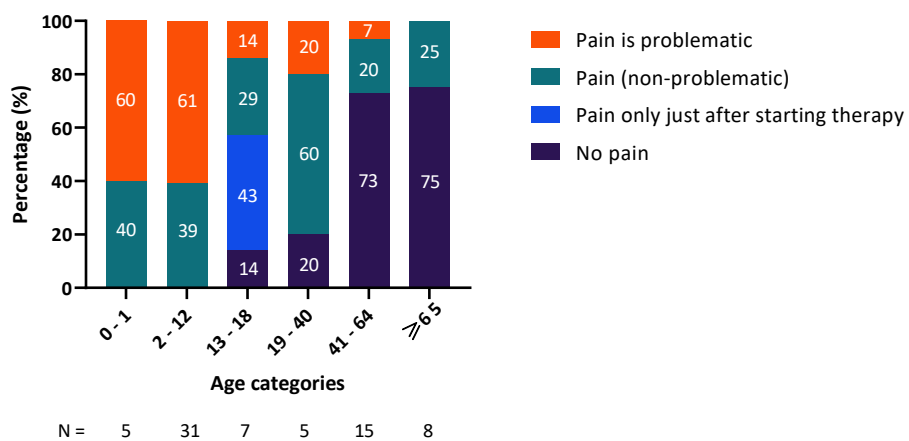


Figure 1: Makeup of the respondents by age and (home-)infusion situation. Numbers in the graph are absolute number of respondents.

a) Experienced pain during administration



b) Use of pain medication during administration

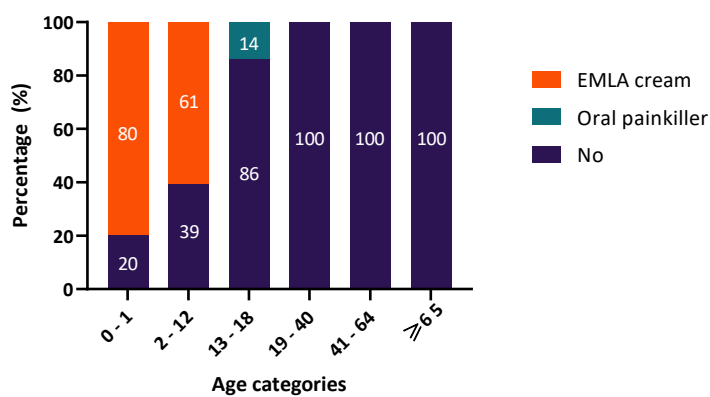


Figure 2: Share of reported pain experiences and use of pain medication during administration by age group.