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A boy with joint pain associated with emicizumab treatment: The importance of plasma level measurement

Dear Editor,

Based on the HAVEN 1 and 2 studies,^{1,2} emicizumab is indicated for patients with haemophilia A and inhibitors. Here, we report on a patient in whom higher emicizumab levels were associated with more episodes of pain in muscles and joints without obvious bleedings. We suggest that emicizumab may result in a local pain syndrome in the absence of significant haemorrhage. Careful monitoring of plasma levels is therefore warranted, and when in doubt, radiological imaging (ultrasound/MRI) should be performed to exclude haemorrhage in order to prevent unnecessary coagulation treatment.

A 10-year-old boy with severe haemophilia A was treated prophylactically with recombinant factor VIII products since the age of 3 years, when he experienced his first joint bleed. He had always been in good health and had an excellent haemophilia joint health status without target joints. After more than 500 previous exposures to factor VIII products, he developed a high titre inhibitor after a switch from Kovaltry® to Refacto AF®, with a maximum inhibitor titre of 32 BU. The patient experienced a high number of bleeds (see Figure 1), which were treated episodically with Novoseven®; therefore, treatment with emicizumab was started. The recommended weekly dose is 3.0 mg/kg for 4 weeks, followed by a weekly dose of 1.5 mg/kg.¹ Our patient (with a weight of 30 kg) initially received 4 weekly injections of 105 mg, followed by injections of 60 mg 4 times once a week, and subsequently every 10 days (see Figure 1). Initially, he showed less bleedings and needed Novoseven® less frequently. After about 2 months, he increasingly complained about pain, initially considered to be caused by bleedings, for which he was again treated with Novoseven® while the emicizumab prophylaxis was intensified (see Figure 1). The pain was mostly located in the muscles of the upper or lower extremities, similar to his clinical picture prior to starting emicizumab. Over time, the duration and intensity of pain increased, mandating opiate treatment for analgesia. Moreover, treatment with Novoseven® did not diminish his pain as before, raising doubts about bleedings as the cause of previous pain episodes. Prior clinical investigations had not shown signs of haematoma or other abnormalities, and only on occasion, swelling was seen. No relationship could be shown between the site of emicizumab injection and the location of the pain episode. In this phase, a number of ultrasound investigations were performed: twice no abnormalities were demonstrated and twice there were signs of a small bleed, which was not considered large enough to explain the level of pain or swelling; no signs of inflammation were seen (see Figure 1). At this point, we decided to measure emicizumab levels using a modified one-stage

FVIII assay with emicizumab calibrators (r² Diagnostics).³ The level of emicizumab was 90 µg/mL (see Figure 1), and subsequently, the administration of emicizumab was halted. After 2 months, emicizumab levels had diminished to 24 µg/mL, and during this period, the episodes of pain gradually disappeared. After subsequently restarting emicizumab prophylaxis at reduced intensity (see Figure 1), the plasma levels were lower and only a few new pain episodes occurred (see Figure 1). During emicizumab treatment, the inhibitor titre gradually declined and immune tolerance treatment with Refacto® was started (see Figure 1).

Pain in joints and muscles in young haemophilia patients is almost always due to bleedings and should be treated with coagulation treatment. In our patient, the pain episodes during emicizumab treatment seemed not to be caused by bleedings; in contrast with the pain episodes before emicizumab treatment, there were less signs of bleeding (clinical or based on ultrasound) and the response to coagulation treatment was insufficient.⁴ Therefore, a relationship with the emicizumab treatment was considered. Pain in joints and muscles are described in 15% of the patients who are treated with emicizumab (www.hemlibra.com). The pain is supposedly caused by haemophilic arthropathy and/or increased physical exercise after long periods of incapacity to move. However, in our patient, these causes are unlikely explanations; he had no arthropathy and had always been physically active. From the Figure 1, one may conclude that in our patient there is a relationship between the level of emicizumab and the occurrence of the pain episodes: a higher level is associated with more pain episodes. It is unclear why emicizumab would cause muscle and joint pain. As emicizumab is a bispecific antibody, it might induce an immune response with subsequent local inflammation, with or without a trauma as a trigger. Additionally, a role for anti-factor VIII antibodies cannot be excluded. In our case, we did not perform laboratory tests or imaging studies other than ultrasound. Therefore, one could consider further investigation by performing MRI during pain episodes to assess for inflammation and/or bleeding not recognized on ultrasound.

The dosing of emicizumab in our patient was only slightly above the recommended regimen; yet, it resulted in a plasma level of 90 µg/mL. Although this is comparable to the levels that were reached in the highest cohort in the dose-finding study,⁵ it was well above the mean steady-state levels in the HAVEN 1¹ and 2 studies.² From these reports, it can be concluded that the individual variation is substantial. Our experience that emicizumab may accumulate and result in high plasma levels associated with (debilitating) pain episodes warrants

FIGURE 1 Pain episodes, emicizumab administrations (105 or 60 mg per dose) and emicizumab plasma levels ($\mu\text{g/mL}$; left Y-axis) by date (dd-mm-yyyy) in our patient. Also are given: the inhibitor titre (BU; right Y-axis) and start immune tolerance induction (ITI). The numbers above the pain episodes indicate that an ultrasound investigation has been performed with as result: 1, normal; 2, <1 cm hematoma intra-articular upper leg/left knee; 3, 1 cm hematoma bursa retrocalcanea left ankle; 4, thickened fascia m masseter left jaw

close monitoring of emicizumab plasma levels. Several ways for monitoring exist; in the HAVEN trials, ELISA-based readouts were used; however, emicizumab specific ELISA tests are not widely available. In our laboratory, we used a recently described modified one-stage FVIII assay with emicizumab specific calibrators and controls.³ This assay is relatively easy to perform and can be adopted by more laboratories allowing for a better monitoring of patients treated with emicizumab.

With a mean through level of 45 $\mu\text{g/mL}$, at least 50% of the patients should experience zero bleeds a year⁶; this level of emicizumab is considered to be comparable to a factor VIII activity of 15%.⁶ In our patient, we think that a maximum emicizumab level of 30 $\mu\text{g/mL}$ should be enough to prevent most bleeds without the risk of pain episodes as side effect.

In conclusion, when pain episodes occur during emicizumab treatment, these may be caused by bleeding but could also be the result of emicizumab itself, accumulated or not. Radiological investigation may help in this differentiation with consequences for the treatment policy. We suggest that plasma levels should be measured when children are treated with emicizumab, in order to correlate plasma levels with symptoms, and detect unexpected emicizumab accumulation in a timely fashion.

KEYWORDS

emicizumab, monitoring, plasma level, side effects

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HLH, KM and RYJT discussed the idea of the manuscript; HLH and RYJT drafted the manuscript; HLH, MSW and RYJT collected the patient data; MVL was responsible for measurement of the emicizumab levels; MVV was responsible for the ultrasound results. All authors contributed to the interpretation of the data, revision of the draft versions and approved the final version.

DISCLOSURES

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

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