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► To cite this version:

Marion Marro, Audrey Françoise Petit, Céline Falaise, Martine Roche, Sophie Gensollen, et al.. Early changes in bleeding perception and quality of life in children and adolescents receiving emicizumab prophylaxis for severe haemophilia A without inhibitor. *Haemophilia*, 2022, 10.1111/hae.14724 . hal-03922555

HAL Id: hal-03922555

<https://amu.hal.science/hal-03922555>

Submitted on 11 Apr 2024

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Early changes in bleeding perception and quality of life in children and adolescents receiving emicizumab prophylaxis for severe haemophilia A without inhibitor

Treatment with emicizumab, a bispecific antibody mimicking activated factor VIII (FVIII) cofactor's function, was first shown to be effective and safe for preventing bleedings in children and adults with haemophilia A (HA), whom replacement therapy with FVIII is impaired by an inhibitor.^{1,2} The benefits of this nonfactor therapy in this subset of patients is unequivocal. After demonstration of efficacy and safety in the HAVEN 3–4 phase 3 studies, emicizumab (Hemlibra®, Roche) was also approved for patients who have severe HA without inhibitor.^{3,4} In France, the drug has been marketed in March, 2020 in this indication without limitation of age. However, these trials included mainly adults and adolescents. Furthermore, the correction of haemostasis under emicizumab is partial, which can limit the benefit of emicizumab treatment in non-inhibitor patients, for whom long-term prophylaxis with FVIII still represents an alternative. The objective of the present study was to evaluate the early effects of emicizumab on bleedings perception and quality of life (QoL).

All patients from the haemophilia treatment centre (HTC) of Marseille, France, who had severe HA (FVIII < 1%) and started on emicizumab prophylaxis before the age of 18 years, without inhibitor at the time of introduction of the drug were eligible for this study. This retrospective, noninterventional study was conducted in accordance with the Declaration of Helsinki principles and was approved by the data protection committee of Assistance Publique - Hôpitaux de Marseille (APHM PADS21-275). Consent was obtained from parents. Clinical and biological data were collected in the patients' haemophilia notebook and medical file. Three questionnaires were administered to monitor early changes in bleeding and treatment burden perception and quality of life. Quantitative variables were expressed using median and interquartile range (IQR) or number and percentage and compared using the Mann-Whitney or Wilcoxon test. Qualitative variables were compared using χ^2 or Fischer's exact test.

At the time of study, the cohort of patients with severe HA (FVIII < 1%) in the HTC of Marseille, France (representing ~7% of all patients included in the FranceCoag registry⁵) comprised 38 male children and adolescents aged ≤ 18 years. Among them, four patients treated with emicizumab prophylaxis were not included in the study due to high responding inhibitor at the time of the study. Fifteen patients remained on standard treatments at the time of the study with no switch to emicizumab prophylaxis and were thus not included in the study. From May, 2020 until January, 2021, all children and adolescents with severe HA without active inhibitor who switched

to emicizumab in the HTC of Marseille, France were included in the study ($n = 19$). The baseline characteristics of the included and non-included patients are presented in the Table 1. The included patients were born between 2002 and 2018. The median age at diagnosis was three months (IQR 0–9 months). Five patients had an inhibitor history, which was diagnosed at a median age of 19 months (IQR 13–24 months). The baseline characteristics of non-included patients were not significantly different from those of included patients. Emicizumab prophylaxis was introduced according to the classical scheme: four weekly high dose administration (3 mg/kg SC), administered within the HTC with close monitoring of the patient, followed by maintenance prophylaxis at home (1.5 mg/kg SC q.wk.). Patients receiving prophylactic FVIII replacement stopped FVIII prophylaxis one week after the switch. At the time of emicizumab switch, one patient was less than two years of age, and 12 patients were less than 12 years of age (median age 9 years, IQR 6–14 years). Four patients experienced transient side effects (injection pain, headaches and leg paraesthesia). No thrombosis or thrombotic microangiopathy were reported. During the first 3 months of emicizumab therapy, 13 (68%) patients had no treated bleeding events. Clotting factor was administered to eight (42%) patients to 1) treat non severe bleeding events or trauma, none of those being joint bleedings in six (32%) patients, 2) prevent the bleeding risk of a surgical procedure (withdrawal of central venous catheter) in one (5%) patient, and 3) continue exposition to FVIII to prevent inhibitor development in one (5%) minimally treated patient (off label).

A questionnaire provided by the French national haemophilia care network was used to measure the parent-perceived symptoms and bleeding events. It was administered before and three months after emicizumab start. This questionnaire evaluates six items (bleeding frequency, bleeding duration, spontaneous nature of bleeding, acute pain associated with bleeding, identification of bleeding and chronic pain) using a visual analog scale ('Lowest' = 1 to 'Highest' = 9; arbitrary units). After 3 months, emicizumab prophylaxis was significantly associated with perception of decreased bleeding frequency/duration and decreased chronic pain. Bleedings were perceived as significantly less spontaneous and less painful but more difficult to identify (Supplementary Figure 1). The perceived reduction of bleeding events was mainly related to minor bleeding events such as ecchymosis. Difficulty to recognize bleedings may be partly due to less frequent and more subtle bleeding episodes. Patient education will be

TABLE 1 Baseline characteristics of the patients

Patients' characteristics	Median (interquartile range) or n (%)
Median (interquartile range) or n (%) n = 19	
Year of birth	
2002–2006	6 (32%)
2007–2012	5 (26%)
2013–2018	8 (42%)
Factor leading to diagnosis and age at diagnosis	
Family history	7 (37%)
Bleeding	12 (63%)
Age at diagnosis (months)	3 (0–9)
Factor	VIII replacement
Age at first factor replacement (months)	9 (2–11)
Long-term prophylaxis	18 (95%)
Age at long-term prophylaxis start (months)	25 (13–53)
Annualized joint bleeding rate	
0	11 (58%)
1–2	4 (21%)
≥3	4 (21%)
Inhibitors	
Inhibitor history	5 (26%)
Age at inhibitor diagnosis (months)	19 (13–24)
High responding ^a	1 (20%)
Transient ^a	2 (40%)
Other complications	
Target joint	5 (26%)
Intracranial haemorrhage	2 (11%)
Thrombosis	0 (0%)

The data are expressed as the median (interquartile range) or number and percentage. Target joints were defined according to the World Federation of Haemophilia 2012 guidelines as a joint in which three or more spontaneous bleeding events occurred within a consecutive six-month period.

^aAmong patients with inhibitor history. No patient had active inhibitor at the time of emicizumab start.

required to avoid the risk of occurrence of severe bleedings without recognition.

The QoL was measured using a specific questionnaire developed in Marseille HTC and using the Kidscreen-27 tool. These are the first data regarding the effect of emicizumab prophylaxis on QoL in children and adolescents treated for severe HA without inhibitor. The first questionnaire measured the parent-perceived change in experience of haemophilia treatment three months after emicizumab start (Table S1). We showed a parents-perceived improvement in health status, autonomy in everyday life, treatment constraints, schooling, social life, relationship and family life and emotional status, though

no change was reported for fatigue. The parent version of Kidscreen-27 was administered 3 months after emicizumab start. This tool is a cross-cultural survey developed in 13 European countries to evaluate parents' perception of their child's health-related quality of life.⁶ This instrument measures physical well-being (five items), psychosocial well-being (seven items), autonomy and parent relations (seven items), peer relations and social support (four items), and school environment (four items). Each item is scored on a five-point scale ('Not at all' = 1 to 'Very much' = 5; arbitrary units). Rasch scores are computed from the sum of items' raw score for each dimension. Higher scores indicate greater QoL. Patients' QoL scores for 'psychosocial well-being', 'autonomy and parent relations', 'peer relations and social support' and 'school environment' dimensions were not significantly different from those observed in age and-sex-matched controls from the general population: 75 (IQR 63–86) vs. 77 (IQR 75–79), $p = .3$, 68 (IQR 50–84) vs. 59 (59–60), $p = .2$, 71 (IQR 44–88) vs. 55 (IQR 53–57), $p = .1$, 66 (IQR 55–88) vs. 64 (IQR 59–69), $p = .9$, respectively (Figure 1). All individual patients' QoL scores for 'physical well-being' remained in the 10–90 percentile range of the general population. However, the patients' median score for this dimension was lower than that of age- and sex- matched control in the general population: 55 (IQR 50–66) vs. 67 (IQR 62–71), $p = .02$ (Figure 1). This may be partly explained by the facts that no improvement in fatigue was perceived under emicizumab prophylaxis. In our centre, children were still restricted in daily activities such as sport practice in the early period after switching. These QoL data suggest that emicizumab prophylaxis may be associated with improvements in QoL among children without inhibitor, as previously shown in children with inhibitor by Mancuso et al.^{2,7} These investigators used another QoL measure instrument, hampering direct comparisons.

The present study has some limitations. In order to describe the results of all patients in our cohorts, we used parent-perceived tools for evaluating changes in bleeding symptoms, treatment burden and QoL. The questionnaires used to assess the parents-perceived bleeding phenotype and pain (Supplementary Figure 1) and the perceived change in experience of treatment (Table S1) were not previously validated. Our study cohort included a limited number of patients recruited in a single HTC. The results from this study should thus be confirmed in a multicentre setting. QoL was only assessed after three months of emicizumab prophylaxis without baseline evaluation. However, bleeding symptoms and experience of treatment improved compared to baseline and the QoL scores after three months of emicizumab prophylaxis was in the normal range of the general population. Finally, a longer follow-up is required to evaluate the long-term effect of emicizumab on QoL.

In conclusion, our study reports original data on QoL of children and adolescents receiving emicizumab prophylaxis for HA without inhibitor. Our results suggest a benefit of emicizumab in terms of treatment burden and QoL even in patients without inhibitor. These data may help inform future studies in this population. Further data are needed to evaluate emicizumab prophylaxis long-term effects on QoL.

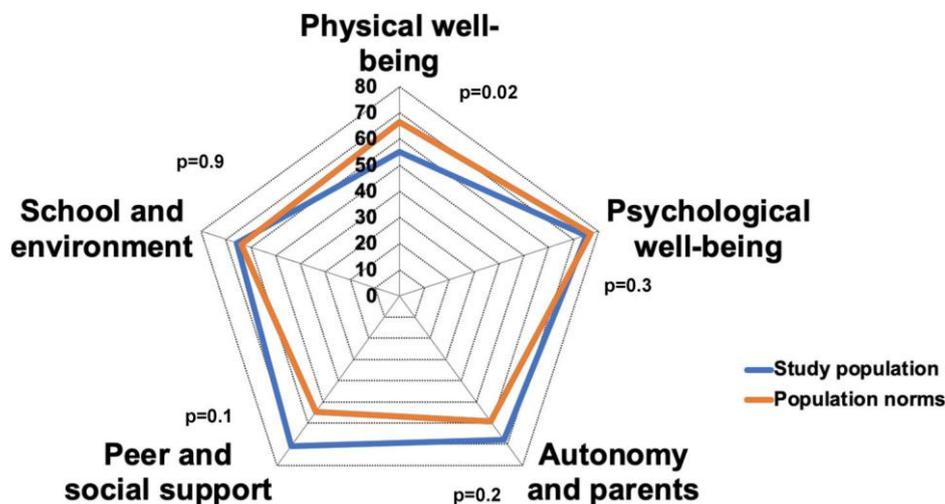


FIGURE 1 Quality of life assessment after three months of emicizumab prophylaxis. The figure represents the scores of the Kidscreen-27 parent-version. The scores (arbitrary unit) of the five dimensions (physical well-being, psychosocial well-being, autonomy and parent relations, peer relations and social support, and school environment) are represented for the study population (blue) and age- and sex-matched controls (red). Higher scores indicate greater QoL

AUTHOR CONTRIBUTIONS

Marion Marro and Paul Saultier analysed the data and wrote the manuscript; Audrey Françoise Petit, Céline Falaise, Martine Roche, Sophie Gensollen, Nathalie Hezard provided clinical or biological data, Mohamed Boucekine performed the statistical analysis, Pascal Auquier and Hervé Chambost designed and supervised the study.

ACKNOWLEDGEMENTS

The authors thank Vanessa Milien for help in data collection and the patients and their families for participation in the study.

CONFLICT OF INTEREST

CF: Investigator of clinical trials (Biomarin, Bioverativ, CSL Behring, LFB, Sanofi, SOBI, Takeda), has received support for attending scientific meetings and educational events (Baxalta-Shire, Novo Nordisk, Pfizer, Octapharma, Roche, and Sobi) and has received honoraria (consultant/advisory boards) from Novonordisk, Roche, CSL Behring; SG: has received honoraria for advisory boards and/or speaker from LFB, NovoNordisk, Octapharma and Sobi; NH: Consultant Roche Chugai; HC: Consultant and/or Speaker bureau (BioMarin, CSL Behring, NovoNordisk, Pfizer, Roche Chugai, SOBI), Investigator of clinical trials (BioMarin, Bioverativ, CSL Behring, LFB, Sanofi, SOBI, Takeda); PS: PS has been an investigator in studies sponsored by Biomarin, Celgene, Gilead, Sanofi, and Takeda, has received support for attending scientific meetings and educational events from Baxalta-Shire, Novo Nordisk, Pfizer, Octapharma, Roche, Servier and Sobi and has received honoraria (consultant/advisory boards) from Octapharma.

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KEYWORDS

bleeding disorders, emicizumab, haemophilia, quality of life

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SUPPORTING INFORMATION

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