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# Emicizumab Dosing in Children and Adults with Hemophilia A: Simulating a User-Friendly and Cost-Efficient Regimen

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## Abstract

**Background** When emicizumab is dosed according to label, clinicians are obligated to discard or overdose medication due to discrepancies between calculated dose and vial content. The aim of this study was to compose a cost-efficient emicizumab maintenance dosing regimen using Monte Carlo simulation based on vial size, patient-friendly intervals, and patient characteristics, while striving for similar plasma concentrations as observed in clinical trials.

**Methods** Monte Carlo simulations were used to investigate alternative dosing regimens in patients weighing 3 to 150 kg. Simulated regimens were targeted to achieve median emicizumab plasma concentrations at a steady state ($C_{av,ss}$) of 40 to 60 (90% range: 25–95) µg/mL. The cost-efficiency of the alternative dosing regimen was calculated in mg and costs saved per patient per year.

**Results** The developed alternative dosing regimen achieved similar emicizumab $C_{av,ss}$ levels compared with the registered dosing regimen with a median deviation of less than 2 µg/mL in 78% of the body-weight categories. A dose of 60 mg every 3 weeks was advised for children weighing 12 to 16 kg, while adults weighing 76 to 85 kg can receive 120 mg emicizumab every week. Compared with the registered weekly dosing of 1.5 mg/kg, alternative dosing saved €35,434 per year in children weighing between 12 and 16 kg. For patients weighing 76 to 85 kg, the median saving was €29,529 (range: €0–€59,057).

**Conclusion** This alternative maintenance dosing scheme—applicable in patients with hemophilia A receiving emicizumab prophylaxis—reduces financial costs, avoids medication spillage, and is patient-friendly without loss of efficacy.

**Keywords**
- hemophilia A
- emicizumab
- dose
- costs
- pharmacokinetics

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## Introduction

Emicizumab (Hemlibra, Roche, Basel, Switzerland), is a humanized bispecific monoclonal antibody that is used for the prophylactic treatment of patients with hemophilia A with and without factor VIII (FVIII) antibodies. It mimics activated FVIII by connecting activated factor IX and factor X, thereby activating factor X resulting in (partial) restoration of hemostasis in patients with hemophilia A.[1] Emicizumab is administrated subcutaneously and exhibits a terminal half-life of approximately 30 days, which enables less frequent administration than required with factor replacement therapy.[2,3] Therefore, emicizumab may significantly lower the treatment burden for patients with hemophilia A on prophylaxis, especially for those with venous access problems.

According to manufacturer's label, after a loading dose of 3 mg/kg once per week for 4 weeks, three different emicizumab maintenance dosing regimens can be prescribed.[2,4–6] Maintenance doses consist of either 1.5 mg/kg every week, 3 mg/kg every 2 weeks, or 6 mg/kg every 4 weeks. These dosing regimens are based on a study by Yoneyama et al[7] and the clinical HAVEN trials[2,4–6] that demonstrated similar efficacious exposure for these regimens with regard to bleeding reduction. Emicizumab is available in four single-dose vials: 30 mg/1 mL, 60 mg/0.4 mL, 105 mg/0.7 mL, and 150 mg/1 mL. However, in many cases clinicians are unfortunately obligated to discard or overdose medication due to discrepancies between the calculated dose as recommended by the label and the vial content.

Emicizumab exhibits dose-proportional pharmacokinetics (PK) over a dose range of 0.3 to 6 mg/kg.[8,9] During maintenance therapy with whole vials, the dosing interval may therefore be prolonged to achieve steady-state emicizumab concentrations ($C_{av,ss}$) comparable to those observed with the registered dose of 1.5 mg/kg once per week. The necessary dosing interval can then be calculated by multiplying the weekly interval (7 days) with the ratio of a complete vial dose and the registered dose of 1.5 mg/kg once per week. Adaption of the dosing interval reduces spillage and prevents excessive dosing, but may also lead to decreased adherence to treatment as irregular, non-weekly, dosing intervals may be difficult to remember and maintain during long-term treatment. Therefore, a user-friendly emicizumab dosing regimen with minimal waste and practical vial utilization is considered optimal.

A population PK model for emicizumab has been published, based on a database of 389 patients from five clinical studies, allowing Monte Carlo simulations to be performed.[9] With Monte Carlo simulations individual concentration curves can be obtained and various dosing regimens and dosing intervals can be evaluated, while striving for efficacious emicizumab concentrations as reported in clinical trials. Importantly, with Monte Carlo simulations the inter-individual variability in achieved emicizumab $C_{av,ss}$ levels is also quantified. Therefore, the aim of this study was to compose a cost-efficient emicizumab maintenance dosing regimen using Monte Carlo simulations based on vial size, patient-friendly intervals, and patient characteristics such as body weight and albumin concentration, while striving for similar plasma concentrations as observed in clinical trials.

## Methods

### Virtual Population

The emicizumab maintenance dosing regimen was evaluated using Monte Carlo simulations in NONMEM (v7.4.1, ICON Development Solutions, Ellicott City, Maryland, United States) using the previously published population PK model.[9] In the published population PK model, increasing body weight was associated with a significant increase in the apparent clearance and volume of distribution; increasing albumin levels were associated with a decreasing apparent clearance; increasing age was associated with a decreasing apparent bioavailability; and black ethnicity was associated with a decreased apparent volume of distribution.

First, a virtual population was simulated in R (v 3.4.1, R-core Team 2017) of which the characteristics largely corresponded to the population used for building of the population PK model.[9] Patients were simulated with a body weight between 3 and 150 kg, as the label advises emicizumab doses within this range.[10] Since the published population PK model is developed based on patients with body weights between 9.5 to 156 kg, the model was extrapolated for infants <9.5 kg. The virtual population was simulated to contain patients with ages between 0 and 77 years, albumin levels ranging between 16.8 and 56.6 g/L, and 8% of patients of black ethnicity, mimicking the patient population used in the population PK model developed by Retout et al.[9] The relationship between age and body weight was implemented using the R package *tmvtnorm* and was based on growth charts utilized in the Netherlands.[11,12] The association between age and serum albumin levels was based on a study by Weaving et al.[13] Since dosing schemes were assessed for every separate body-weight category, increasing with 1 kg, 148 weight categories (from 3 to 150 kg) were created. Furthermore, three albumin level categories were differentiated (<40, 40–50, >50 g/L). For each body weight and albumin category, at least 1,000 patients were simulated.

### Monte Carlo Simulations

Monte Carlo simulations were used to obtain individual concentration–time curves with the examined dosing regimens. The Monte Carlo method takes the inter-individual distribution of PK parameters, such as apparent clearance, volume of distribution, and the absorption rate constant, into account and takes random samples from these distributions in a repeated process, thereby providing individual PK parameters. For our simulations we used parameter values, both the typical (median) and its corresponding interpatient variability, from the published population PK model of Retout et al.[9]

### Dosing Regimen

The alternative dosing regimens were evaluated applying the following requirements: (1) only whole vials were

administered (30, 60, 105, or 150 mg); (2) the preferred dosing interval was once weekly or a multiple of whole weeks; and (3) minimal volumes of injection were favored and did preferably not exceed 2.0 mL.[14] The appropriateness of the dosing regimens was checked by calculating the achieved average steady-state emicizumab plasma concentration ($C_{av,ss}$) and its inter-individual variability. The $C_{av,ss}$ was calculated by dividing the area under the curve during the dosing interval with the dosing interval (Eq. 1).

$$C_{av,ss} = \frac{D \times F}{Cl \times \tau} = \frac{AUC}{\tau} \quad (1)$$

where $D$ is the administrated dose (mg), $F$ the apparent bioavailability, Cl the apparent clearance (L/day), $\tau$ the dosing interval (day), and AUC the area under the curve (mg/day/L).

For comparison, the emicizumab $C_{av,ss}$ was also calculated for the virtual population using the registered 1.5 mg/kg per week dosing regimen as mentioned in the manufacturer's label. A dosing regimen was considered as appropriate when (1) the median emicizumab $C_{av,ss}$ of the virtual population category was between 40 and 60 µg/mL and (2) the 5th and 95th percentile of emicizumab $C_{av,ss}$ was between 25 and 95 µg/mL (90% range). These requirements were selected based on the results reported by Retout et al[9] and the obtained simulated emicizumab $C_{av,ss}$ after dosing of the currently registered 1.5 mg/kg every week. When multiple simulated dosing schemes showed adequate results, the dosing scheme of which the median emicizumab $C_{av,ss}$ was closest to the median emicizumab $C_{av,ss}$ after administration of 1.5 mg/kg every week was selected. As the registered dose is based on body weight, every body-weight category, differing 1 kg, was first evaluated separately, whereafter body weights with a similar dosing scheme were lumped to form larger body-weight categories.

Additionally, a dosing table based on both body weight and albumin levels was developed. Albumin was chosen to further individualize dosing as it has been demonstrated that emicizumab clearance correlates negatively with serum albumin concentration.[9] More specifically, as both albumin and emicizumab are recycled by the neonatal Fc receptor, albumin can be used as a surrogate for the activity of the neonatal Fc receptor.[15] Therefore, higher albumin levels are associated with lower emicizumab clearance, and thus higher emicizumab levels. These additional dosing schemes were established following the same requirements as set for the dosing scheme based on only body weight.

### Cost Reduction

The consumption of vials using the alternative dosing scheme based on body weight for patients with an average albumin level 40 to 50 g/L is compared with the vial consumption of the registered doses of 1.5 mg/kg once every week, 3 mg/kg once every 2 weeks, and 6 mg/kg once every 4 weeks. The consumption of the registered dose included medication that needs to discarded or administered excessively. The resulting cost reduction per year was calculated based on a price of €2,271.43 per 30 mg emicizumab excluding value added tax.[16] By assigning the corresponding calculated cost reduction per body weight to the virtual simulated patients, the median cost reduction of the virtual population was calculated. This median cost reduction demonstrates the savings that may be achieved in a clinical setting, as the virtual population reflects a real-world hemophilia population.

## Results

In ►**Fig. 1**, the characteristics of the simulated patient population are shown. Every body weight and albumin category contained at least 1,000 patients. The virtual population had a median body weight of 71.3 kg (interquartile range [IQR]: 53.7–88.3 kg), a median age of 33 years (IQR: 21–46 years), and a median albumin level 45.0 g/L (IQR: 41.7–47.8 g/L).

In ►**Table 1**, the proposed alternative maintenance dosing regimens based on body weight are presented. The lumped body-weight categories were created based on the results obtained per body-weight category of 1 kg and independent of albumin. The creation of the lumped body-weight categories masks deviations between emicizumab $C_{av,ss}$ levels achieved with the alternative dosing regimens and the registered dosing regimen. Therefore, in ►**Supplementary Table S1** (available in the online version) the results are presented for the separate 1 kg body-weight categories.

The simulated dosing regimen met the set requirements in all body-weight categories. Specifically, the median achieved emicizumab $C_{av,ss}$ levels achieved with this alternative dosing regimen were largely compatible with levels achieved by the registered dosing regimen of 1.5 mg/kg once every week. In the vast majority (78%) of the body-weight categories, the emicizumab $C_{av,ss}$ level achieved with the alternative dosing regimen deviated less than 2 µg/mL from the emicizumab $C_{av,ss}$ level achieved with the registered maintenance dosing scheme (►**Table 1**). Among the other 22%, the largest difference in median emicizumab $C_{av,ss}$ level between alternative and registered regimens was observed for an individual with a body weight of 3 kg. The alternative and registered dosing schemes produced values of 53.5 and 40.3 µg/mL, respectively. For the

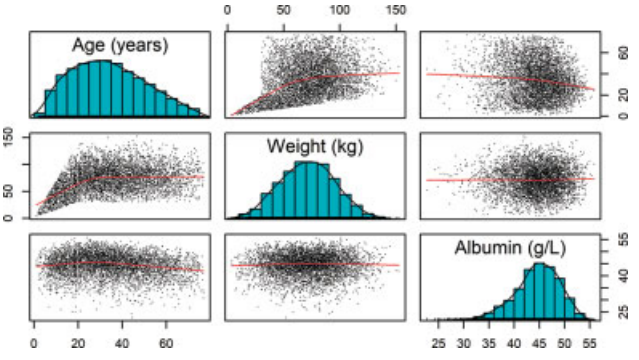


**Fig. 1** Relationships between the simulated patient characteristics for emicizumab based on data from Retout et al.[9] The total population included at least 1,000 patients per body weight and albumin category. For readability, this figure only shows 5,000 virtual patients that were randomly sampled from the total population. The plot shows bivariate scatter plots below and above the diagonal, and histograms with density plots of the patient characteristics on the diagonal. The bivariate scatter plots show the relation between the simulated patient characteristics.

 

**Table 1** Alternative emicizumab maintenance dosing regimen and resulting average steady state emicizumab levels per body weight category based on simulations when striving for plasma concentration as tested in HAVEN trials

| Body weight | Alternative maintenance dose | Injection volume (mL) | No. of vials per dose | Median average emicizumab level–alternative dose (μg/mL) (90% range) | Median average emicizumab level–1.5 mg/kg every week (μg/mL) (90% range) |
|---|---|---|---|---|---|
| 3 kg | 30 mg every 5 weeks<br>*30 mg every 4 weeks*[a] | 1.0<br>1.0 | 1<br>1 | 53.5 (34.2–88.1)<br>66.9 (42.5–107.4) | 40.3 (25.1–66.3)<br>40.3 (25.1–66.3) |
| 4–5 kg | 30 mg every 4 weeks | 1.0 | 1 | 46.0 (27.9–76.8) | 42.0 (26.3–69.0) |
| 6–7 kg | 30 mg every 3 weeks | 1.0 | 1 | 44.3 (27.3–71.9) | 43.3 (27.2–69.9) |
| 8–11 kg | 60 mg every 4 weeks | 0.4 | 1 | 46.8 (28.2–77.6) | 45.3 (28.2–72.9) |
| 12–16 kg | 60 mg every 3 weeks | 0.4 | 1 | 44.2 (26.8–72.8) | 46.9 (29.0–75.9) |
| 17–25 kg | 60 mg every 2 weeks | 0.4 | 1 | 45.9 (27.6–76.5) | 49.0 (30.4–78.9) |
| 26–35 kg | 90 mg every 2 weeks | 1.4 | 2 | 48.1 (28.7–79.7) | 50.0 (30.6–81.0) |
| 36–45 kg | 120 mg every 2 weeks | 0.8 | 2 | 49.5 (29.5–81.6) | 50.3 (30.3–82.1) |
| 46–55 kg | 150 mg every 2 weeks | 1.0 | 1 | 50.0 (29.8–82.6) | 50.6 (30.4–83.1) |
| 56–65 kg | 90 mg every week | 1.4 | 2 | 50.5 (30.0–83.5) | 51.0 (30.5–83.8) |
| 66–75 kg | 105 mg every week | 0.7 | 1 | 50.9 (30.3–84.3) | 51.3 (30.6–84.5) |
| 76–85 kg | 120 mg every week | 0.8 | 2 | 51.4 (30.6–85.1) | 51.6 (30.8–85.2) |
| 86–95 kg | 135 mg every week | 1.7 | 2 | 51.8 (30.8–85.7) | 51.9 (30.9–85.7) |
| 96–105 kg | 150 mg every week | 1.0 | 1 | 52.1 (31.0–86.4) | 52.1 (31.1–86.2) |
| 106–115 kg | 315 mg every 2 weeks | 2.1 | 3 | 50.0 (29.8–82.9) | 52.4 (31.2–86.8) |
| 116–125 kg | 180 mg every week | 1.2 | 3 | 52.7 (31.3–87.4) | 52.6 (31.2–87.2) |
| 126–135 kg | 195 mg every week | 2.1 | 3 | 52.8 (31.3–88.0) | 52.7 (31.5–87.5) |
| 136–150 kg | 210 mg every week | 1.4 | 2 | 52.8 (31.4–87.5) | 53.1 (31.4–87.9) |

Note: The simulated results are compared with the registered maintenance dosing scheme (1.5 mg/kg per week in steady state). Doubling of both the amount and dosing interval of the alternative dosing regimen will result in similar emicizumab Cav,ss levels. Values are based on data of at least 1,000 virtual patients per weight category. Vials available are 30 mg in 1 mL; 60 mg in 0.4 mL; 105 mg in 0.7 mL; 150 mg in 1 mL.
[a]The dosing interval every 5 weeks has not been tested in clinical trials.

virtual patients with a body weight of 25 kg, the median emicizumab $C_{av,ss}$ level was lowest when the alternative dosing regimen was applied (40.0 μg/mL), compared with the level produced by the registered regimes (49.8 μg/mL) (►**Supplementary Table S1** [available in the online version]). For all body weights, the 5th and 95th percentiles, reflecting the inter-individual variability in emicizumab $C_{av,ss}$ levels, ranged between 24.9 and 90.7 μg/mL (►**Supplementary Table S1**, available in the online version).

In ►**Supplementary Table S2** (available in the online version), a dosing regimen based on both individual body weight and albumin level is presented. Patients with an albumin level between 40 and 50 g/L can receive the same dose as recommended in the dosing regimen based on body weight (►**Table 1**). For patients with a body weight >35 kg, the following adaptations apply based on albumin level: patients with an albumin >50 g/L require a lower emicizumab dose, while patients with an albumin level <40 g/L require a higher dose to achieve the specified emicizumab $C_{av,ss}$ levels.

The alternative dosing regimen based on body weight generates a significant cost saving. The magnitude of the cost reduction is dependent on the body-weight category and on which of the three registered maintenance dosing regimen the alternative dosing regimen is compared with (►**Table 2**). For children weighing 3 to 25 kg, alternative dosing saved a median of 780, 468, and 78 mg emicizumab per patient per year compared with respective dosing of 1.5 mg/kg once every week, 3 mg/kg once every 2 weeks, and 6 mg/kg once every 4 weeks, respectively. The corresponding savings were €59,057, €35,434, and €5,906, respectively, per patient per year. For adult patients weighing 66 to 85 kg, the respective median savings were 390, 195, and 97.5 mg corresponding to €29,529, €14,764, €7,382 per patient per year (►**Table 2**).

When the alternative dosing regimen is applied, costs are saved in 53 to 60% of the patients in the virtual population (►**Fig. 2**). For 28 to 47% of the patients in the virtual population, the cost of treatment is similar to the costs spent when the registered dosing regimen is applied, as for certain body weights no or little medication needs to be discarded or administered excessively when the registered dosing regimen is applied. For example, for a patient of 20 kg body weight, a whole vial of 30 mg is used when the registered dose of 1.5 mg/kg once every week is administrated. When a hemophilia treatment center applies the 6 mg/kg once every

 

**Table 2** Milligram emicizumab and costs saved per patient per year when using the alternative body weight dosing scheme for emicizumab

| | Alternative dose compared with 1.5 mg/kg every week | | Alternative dose compared with 3 mg/kg every 2 weeks | | Alternative dose compared with 6 mg/kg every 4 weeks | |
|---|---|---|---|---|---|---|
| | Median (range) | | Median (range) | | Median (range) | |
| | Amount (mg) | Price (€) | Amount (mg) | Price (€) | Amount (mg) | Price (€) |
| 3–25 kg | 780 (0–1,560) | 59,057 (0–118,114) | 468 (0–780) | 35,434 (0–59,057) | 78 (−195 to 390) | 5,906 (−14,764 to 29,529) |
| 26–45 kg | 780 (0–1,560) | 59,057 (0–118,114) | 195 (0–390) | 14,764 (0–29,523) | 97.5 (−195 to 390) | 7,382 (−14,764 to 29,529) |
| 46–65 kg | 780 (0–780) | 59,057 (0–59,057) | 195 (0–390) | 14,764 (0–29,523) | 97.5 (−195 to 390) | 7,382 (−14,764 to 29,529) |
| 66–85 kg | 390 (0–780) | 29,529 (0–59,057) | 195 (0–390) | 14,764 (0–29,523) | 97.5 (−195 to 390) | 7,382 (−14,764 to 29,529) |
| 86–105 kg | 390 (0–780) | 29,529 (0–59,057) | 195 (0–390) | 14,764 (0–29,523) | 97.5 (−195 to 390) | 7,382 (−14,764 to 29,529) |
| 106–125 kg | 585 (0–1,170) | 44,293 (0–88,586) | 390 (0–780) | 29,529 (0–59,057) | 390 (−195 to 780) | 29,529 (−14,764 to 59,057) |
| 126–150 kg | 780 (0–780) | 59,057 (0–59,057) | 390 (0–780) | 29,529 (0–59,057) | 195 (−195 to 780) | 14,764 (−14,764 to 59,057) |
| Overall | 780 (0–1,560) | 59,057 (0–118,114) | 390 (0–780) | 29,529 (0–59,507) | 195 (−195 to 780) | 14,764 (−14,764 to 59,057) |

Note: The alternative dosing scheme is compared with the three registered dosing regimens. A full overview is presented in ►**Supplementary Table S2** (available in the online version). The cost reduction was calculated based on a price of €2,271.43 per 30 mg emicizumab.[16]

4 weeks regimen, 19% of the patients will receive a more expensive dose with the alternative dosing scheme. This is caused by the fact that doses in the alternative dosing scheme are based on dosing every 1 or 2 weeks (to keep the injection volume as much as possible $\leq$2 mL), while more costs could be saved when higher doses are administrated at once as discrepancies between calculated dose and vial size are then smallest. Therefore, among the registered maintenance dosing schemes, dosing with 6 mg/kg once every 4 weeks is associated with the lowest costs. A more extensive overview of the vial and cost reduction per body weight and dosing interval category is presented in ►**Supplementary Table S3** (available in the online version).

## Discussion

In this study, Monte Carlo simulations were used to generate user-friendly and cost-efficient alternative emicizumab maintenance dosing regimens. These alternative dosing regimens achieve similar emicizumab $C_{av,ss}$ levels as the registered dosing regimens, though at much lower costs. A median cost reduction of emicizumab prophylaxis of €59,057 (range: €0–€118,114) per patient per year is achieved due to more economic application of vials and dosing intervals. Furthermore, this alternative dosing regimen is more patient-friendly and could increase compliance as the scheme is based on dosing intervals of whole weeks and low volumes that reduce pain at injection sites, which is especially important for children.

Importantly, when doubling both the amount and dosing interval of the alternative dosing regimen, similar emicizumab $C_{av,ss}$ levels are obtained in patients.[8,9] At the moment, a maximum of 2.0 mL is recommended per subcutaneous emicizumab injection by the product insert. Therefore, higher doses that are necessary with longer dosing intervals could be impractical for some patients, as multiple subcutaneous injections are needed. If it becomes possible to inject larger volumes or when vials contain higher concentrations, higher doses could be more easily administrated and dosing may even become more economical.[17] A more economical dosing scheme could also be reached when the manufacturer could supply dosing vials of 15 mg, which would be especially valuable for young children. Importantly, the product insert advises not to combine vials with different emicizumab concentrations (30 and 150 mg/mL) in one syringe. In particular, when exact volumes of two vials with different concentrations are mixed in one syringe, the end concentration cannot be guaranteed. However, when only whole vials are administered, thereby accepting possible administration of excess volume, this problem will be absent. Furthermore, an adapter can be used that safeguards the combination of two exactly measured volumes with different concentrations in one syringe. In addition, another solution would be to administrate two separate injections to the patient, but this is of course not patient-friendly and not preferred. Therefore, we believe that there are multiple safe solutions enabling administration of doses which are composed of different concentrations.

 

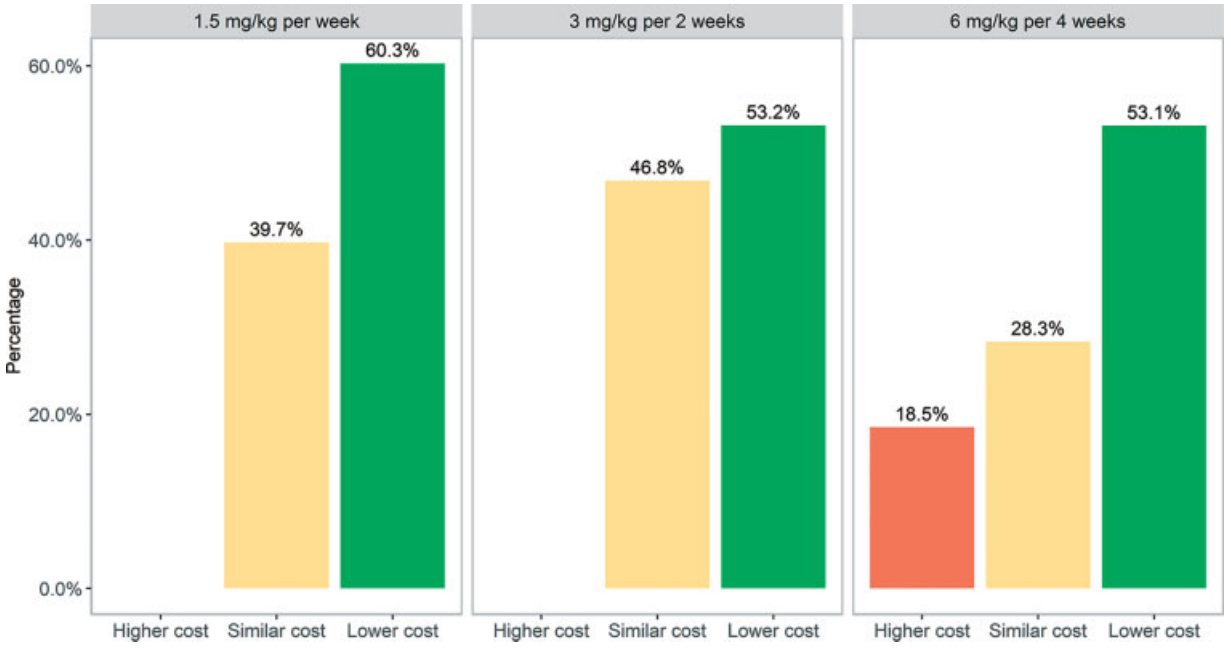


**Fig. 2** Percentage of patients in the virtual population (3–150 kg) in which the alternative dose dosing scheme will result in lower, similar, or higher costs compared with the registered dosing schemes (1.5 mg/kg per week, 3 mg/kg per 2 weeks, or 6 mg/kg per 4 weeks). The cost savings depend on the body weight of the patient and registered dosing scheme to which the alternative dosing scheme is compared.

Dosing regimens were explored for different albumin categories. In our simulations, we observed that patients >35 kg may benefit from dose adjustments based on the albumin level to achieve similar emicizumab $C_{av,ss}$ levels. However, this is caused by the fact the population PK model describes that a deviating albumin level is associated with a larger absolute deviation in emicizumab apparent clearance in patients with a higher body weight.[9] Possibly dosing adjustments could also be made for elderly patients, as Retout et al[9] described a 31% reduction in steady-state exposure for a patient with hemophilia A of 77 years old.

Importantly, the results of this study are based on Monte Carlo simulations and describe dosing regimens that have not yet been validated in clinical practice or evaluated with a prospective study. Hence, when these dosing schemes are applied, we recommend monitoring of emicizumab levels as clinical experience with emicizumab is limited and up to now the drug has only been administered to a limited number of patients. More detailed information is needed with respect to drug efficacy and the occurrence of side effects. Nonetheless, the results of the Monte Carlo simulations are based on the published population PK model, which is based on data from 389 patients with hemophilia A with or without inhibitors recruited in five different clinical studies.[2,4–6,9] In this dataset patient weighted between 9.5 and 156 kg. The suggested doses for patients <9.5 kg are therefore based on an extrapolation, and should be interpreted with more caution. Especially since young infants have physiologically reduced factor IX levels, which may impair emicizumab efficacy.[18]

A limitation of our study was that it was difficult to define which emicizumab $C_{av,ss}$ levels are acceptable as only sparse data on the exposure–effect and pharmacodynamics of emicizumab have been published. Due to this lack of data, we have chosen to define requirements based on clinical trials, the results described in Retout et al[9] and the obtained simulated emicizumab $C_{av,ss}$ after dosing with the currently registered 1.5 mg/kg every week, as this specific dosing regimen has been tested extensively. The exposure–effect relation described by Yoneyama et al,[7] implies that when emicizumab levels range between 25 and 95 µg/mL, the proportion of patients with an annual bleeding rate of zero is between 35 to 65%.[7] However, this report included bleeding data of only 18 patients, therefore lacking statistical power. Moreover, it is unclear which PK parameter of emicizumab (trough level, AUC, $C_{av,ss}$, etc.) correlates best with the annual bleeding rate in patients. Momentarily, we have chosen to focus on $C_{av,ss}$ levels as a prior study has shown that similar emicizumab $C_{av,ss}$ levels were achieved after dosing of 1.5 mg/kg every week, 3 mg/kg every 2 weeks, or 6 mg/kg every 4 weeks, while clinical trials show similar efficacy of these dosing schemes in terms of bleeding control.[2,9] Additionally, a decreasing $C_{av,ss}$ level was associated with a minimal increase in annualized bleeding rate.[9]

Interestingly, a high inter-individual variability was observed in the achieved emicizumab $C_{av,ss}$ levels. This implies that therapeutic drug monitoring (PK-guided dosing) of emicizumab levels may be of added value, especially because the hemostatic effect of emicizumab is not directly measurable either clinically or by laboratory parameters. However, as discussed above the exposure–effect relation of emicizumab and its inter-individual variability are still to be evaluated more extensively, before the therapeutic window can be precisely defined. In the meantime, we hope that this alternative user-friendly economical dosing scheme will contribute to a high quality of care with an optimized cost–benefit ratio for patients and society at large.

 

## What is known about this topic?

- When emicizumab is dosed according to label, clinicians are often obligated to discard or overdose medication.

## What does this paper add?

- An alternative maintenance dosing regimen was developed based on Monte Carlo simulations.
- The developed regimen reduces financial costs, avoids medication spillage, and is patient-friendly without loss of efficacy.

### Author Contributions

L.H.B. and R.A.A.M. performed the analysis and wrote the manuscript. K.Fisher, I.K.-H., and R.E.G.S. proposed the idea of changing the dosing interval proportional to the dose increase. K.Fisher, I.K.-H, A.A.M.D., K. Fijnvandraat, and M.H.C. gave clinical input. K.Fisher, M.H.C., and R.A.A.M. supervised the study. All authors contributed substantially to the critical revision of the manuscript and approved the final draft.

### Note

This study was performed as part of the OPTI-CLOT international multicenter research consortium, "Patient tailOred PharmacokineTIc-guided dosing of CLOTting factor concentrates and desmopressin in bleeding disorders," which is currently WP6 within the SYMPHONY consortium.

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### Conflict of Interest

K.Fischer has received speaker's fees from Bayer, Baxter/Shire, Sobi/Biogen, CSL Behring, Octapharma, Pfizer, and Novo Nordisk, and has performed consultancy for Bayer, Baxter, Biogen, CSL Behring, Freeline, Novo Nordisk, Pfizer, Roche, and Sobi. She and/or her institution has received research support from Bayer, Pfizer, Baxter/Shire, and Novo Nordisk. The institution of K. Fijnvandraat has received unrestricted research grants from CSL Behring, Bayer, Sobi, and Novo Nordisk, and her institution has received consultancy fees from Shire, Roche, Novo Nordisk, and Bayer. M.H.C. has received investigator-initiated research grants over the years from the Netherlands Organization for Scientific Research (NWO), the Netherlands Organization for Health Research and Development (ZonMw), the Dutch "Innovatiefonds Zorgverzekeraars," Baxter/Baxalta/Shire, Pfizer, Bayer Schering Pharma, CSL Behring, Sobi, Biogen, Novo Nordisk, Novartis, and Nordic Pharma, and has served as a steering board member for Roche and Bayer. All grants, awards, and fees go to the Erasmus MC as institution. R.A.A.M. reports grants from Bayer, grants from Shire, grants from Merck Sharpe Dome, grants from CSL Behring, other from Bayer, other from Shire, outside the submitted work. The remaining authors declare no competing financial interests. All unrestricted research grants, awards, educational grants, and consultancy fees have been forwarded to the respective institutions.

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