Received: 27 November 2020 | Revised: 24 December 2020 | Accepted: 18 January 2021

DOI: 10.1111/bcp.14748

SHORT REPORT

The potential of individualized dosing of ravulizumab to improve patient-friendliness of paroxysmal nocturnal haemoglobinuria treatment at reduced costs

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Ravulizumab is a very expensive complement C5-inhibitor for the treatment of paroxysmal nocturnal haemoglobinuria, with a fixed-dosing interval of 8 weeks. For lifelong treatment, a cost-effective and patient-friendly dosing strategy is preferred. We therefore explored alternative ravulizumab dosing regimens *in silico* based on the thorough dose-finding studies of the manufacturer. Extending the interval to 10 weeks or individually extending the interval to a mean of 12.8 weeks based on pharmacokinetic monitoring resulted in noninferior efficacy in terms of lactate dehydrogenase normalization, with drug cost savings up to 37%. We here show the potential of individualized ravulizumab dosing to improve patient-friendliness at reduced costs.

KEYWORDS
paroxysmal nocturnal haemoglobinuria, pharmacodynamics, pharmacokinetics, ravulizumab

1 | INTRODUCTION

Ravulizumab (ravulizumab-cwvz; ULTOMIRIS) is a recently approved complement C5 inhibitor for the treatment of paroxysmal nocturnal haemoglobinuria (PNH) in adults.[1,2] Ravulizumab binds to complement C5 and prevents the formation of the terminal complement complex (C5b-9). In PNH patients, ravulizumab reduces the complement-mediated intravascular haemolysis, thereby reducing PNH-related symptoms and complications. Before the introduction of ravulizumab, eculizumab was the only drug in class for treatment of PNH. Ravulizumab was developed by substituting 4 amino acids in eculizumab, which resulted in a therapeutic monoclonal antibody with a terminal elimination half-life of approximately 32 days, allowing a dosing interval of 8 weeks compared to the 2-week dosing interval of eculizumab.[3] The efficacy of ravulizumab was recently shown to be noninferior to eculizumab in treatment-naïve and eculizumab-experienced/treated PNH patients.[4,5]

Ravulizumab has shown a robust exposure–response relationship: serum concentrations >100 μg/mL result in complete complement C5 blockade.[6] This therapeutic threshold was confirmed by pharmacokinetic–pharmacodynamic modelling of the lactate dehydrogenase (LDH) response of ravulizumab, showing that the ravulizumab serum concentration leading to 95% reduction of LDH levels was similar at 146 μg/mL.[2] The observed mean (± standard deviation) ravulizumab serum trough concentration at the approved dose in the maintenance phase is 473 (±158) μg/mL.[2] This exposure is way above the efficacy threshold of 100 μg/mL, implying that the vast majority of patients on ravulizumab are receiving supratherapeutic doses.

Complement C5-inhibitors have shown substantial impact on PNH-related symptoms, complications and patient survival compared to supportive care, which was the only treatment option before their introduction.[7] However, treatment of PNH with complement C5-inhibitors comes at enormous costs. The annual costs for treatment of PNH with eculizumab in the USA are approximately US$ 500 000 per patient[8] and ravulizumab is priced similarly.[9] In many countries, expensive drugs need to be cost effective compared to the best alternative before they get reimbursed.

With biosimilars for eculizumab in the pipeline and subsequent expected price reductions and the development of other complement inhibitors, the cost effectiveness of ravulizumab is threatened.[10,11] As ravulizumab is dosed supratherapeutically in the majority of patients, an individualized treatment could be of benefit for both patients and society. We, therefore, investigated alternative dosing strategies for PNH treatment with ravulizumab, based on well-established pharmacokinetic–pharmacodynamic knowledge.

What is already known about this subject

- Ravulizumab is a very expensive C5-inhibitor for the treatment of paroxysmal nocturnal haemoglobinuria, with a fixed dosing interval of 8 weeks. It is known that ravulizumab exposure in the maintenance phase far exceeds the efficacy threshold, implying that that the vast majority of patients are receiving supratherapeutic doses.

What this study adds

- This study shows the potential of individualized ravulizumab dosing to improve patient-friendliness and to reduce costs.

2 | METHODS

We performed a clinical trial simulation of 3 different dosing strategies of ravulizumab in treatment-naïve PNH patients in the maintenance phase of dosing for 1 year. The simulations were performed using the validated population pharmacokinetic–pharmacodynamic model as described by the manufacturer in the approval review documents of the Food and Drug Administration and European Medicines Agency.[1,2] In short, the pharmacokinetics was described with a linear 2-compartment model, with weight, sex and haemoglobin at baseline as covariates on clearance and weight, body mass index (BMI) and haemoglobin at baseline as covariates on volume of distribution. The relationship between drug concentrations and LDH kinetics were described with an indirect response model. The model code and a schematic representation of the model can be found in the supplemental material. We simulated the approved dosing regimen (maintenance dose every 8 weeks), an extended dosing interval (maintenance dose every 10 weeks) and a therapeutic drug monitoring (TDM)-based dosing interval. For the TDM scenario, we simulated the effect of extending or shortening the dosing interval, based on trough level measurements (see Table 1). Pharmacokinetic steady-state of ravulizumab was achieved immediately after the initial loading dose, therefore TDM was performed before the second and third dose.[1,12] The trough concentration before the second dose was used to determine the dosing interval for the third dose and the trough

TABLE 1 Evaluated dosing strategies for ravulizumab

	Approved dosing interval	Extended dosing interval	TDM-based dosing interval
Loading dose on d1	According to drug label, based on body weight 40–60 kg: 2400 mg 60–100 kg: 2700 mg >100 kg: 3000 mg		
Maintenance dose starting on d15	According to the drug label, based on body weight 40–60 kg: 3000 mg 60–100 kg: 3300 mg >100 kg: 3600 mg		
Maintenance dose interval	According to the drug label: Every 8 wk, starting 2 wk after loading dose	Every 10 wk, starting 2 wk after loading dose	The standard interval of 8 wk was shortened or extended based on trough concentrations (mg/L) (C_{trough}) before the second and the third dose by the following algorithm: C_{trough} — Interval <150 — - 2 wk 150–200 — + 0 wk 200–400 — + 2 wk > 400 — + 4 wk

TDM, therapeutic drug monitoring

concentration before the third dose was used to determine the dosing interval for the fourth and subsequent doses. The dosing regimens were chosen at the discretion of the researcher and based on empiric rationale. Simulations were based on the demographic data of 1171 adult patients, sampled from the NHANES database.[13] The population characteristics at baseline were as follows: sex (female: 49.8%); weight (median: 73.8 kg, interquartile range: 63.6–83.9 kg); height (1.67 m, 1.60–1.75 m); haemoglobin (101 g/L, 88–115 g/L). These population characteristics are representative for patients with PNH.[4] Table 1 summarizes the 3 regimens. All simulations were performed with the software package NONMEM v7.4 (Icon PLC, Dublin, Ireland).

For each scenario, we predicted LDH at baseline, as well as LDH and a ravulizumab trough serum concentration during the maintenance phase. Furthermore, the average proportion of LDH normalization from day 29 to 183 was determined, comparable with the analysis in the pivotal phase-3 trial of ravulizumab,[4] as well as the mean yearly maintenance dosing costs per person, assuming costs of US$6404 per 300-mg ravulizumab vial.[14] Lastly, for the TDM-based regimen, we also calculated the mean maintenance dosing interval.

3 | RESULTS AND DISCUSSION

The predicted serum trough concentration of ravulizumab at a single time point in the maintenance phase and associated LDH response are depicted in Figure 1. As can be observed in these plots, a large variability in ravulizumab concentration was observed for the approved dosing interval, which can largely be diminished with an individualized dosing interval, while maintaining therapeutic exposure. For the standard dosing interval and for the TDM-based interval, none of the patients exhibited a ravulizumab trough concentration <100 mg/L during our simulation study. For the 10-week interval, 7 patients out of 1171 exhibited a ravulizumab trough concentration <100 mg/L at 1 or several time points.

LDH concentrations at steady state are comparable for each dosing interval, suggesting that ravulizumab serum concentrations remain in the plateau phase of the concentration–effect curve. The predicted average of proportions of LDH normalization from day 29 to 183 in the approved, extended dosing interval and individualized dosing regimen, were 50.1, 49.6 and 49.1%, respectively. The mean yearly maintenance dose costs for the approved dosing regimen, the extended dosing interval regimen and the individualized dosing regimen of treatment were US$454365, US$363493 and US$288279, respectively, showing a potential of ∼37% reduction in drug costs. The mean (SD) dosing interval of the TDM-based regimen was 12.8 (±1.6) weeks.

In the pivotal phase-3 trial of ravulizumab *vs.* eculizumab in treatment-naïve PNH patients, the weighted average of proportions of LDH normalization (LDH < 246 U/L) from day 29 to 183 was the co-primary endpoint of the study.[4] 53.6% (95%CI 45.9–61.2%) in the ravulizumab group was considered noninferior to 49.4% (95%CI 41.7–57.0%) in the eculizumab group (noninferiority margin of 0.39 for the odds ratio of ravulizumab *vs.* eculizumab for LDH normalization).[4] We show in our study that noninferior LDH normalization is predicted for the extended and individualized dosing regimens, compared with the approved dosing regimen or eculizumab treatment. Furthermore, when employing a TDM-based dosing interval, the mean dosing interval could be extended to 12.8 weeks. Therefore, a substantial proportion of patients could benefit from a decreased number of yearly hospital visits, which translates to a more patient-friendly regimen of a lifelong treatment and further cost reductions.

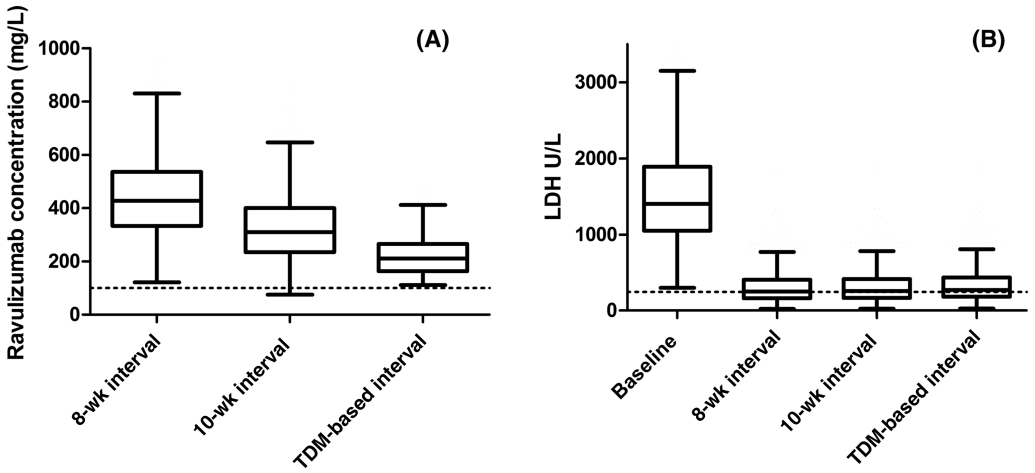

FIGURE 1 (A) Tukey box-and-whisker plots for ravulizumab trough concentrations at a single time point during maintenance phase. From left to right: 8-week interval; 10-week interval; and therapeutic drug monitoring (TDM)-based interval. The dotted line represents a ravulizumab concentration of 100 mg/L (threshold for efficacy). (B) Tukey box-and-whisker plots for lactate dehydrogenase (LDH) at baseline and at a single time point during maintenance phase. From left to right: LDH at baseline and LDH at steady state for 8-week interval; 10-week interval; and TDM-based interval. The dotted line represents the upper limit of normal for LDH (246 U/L)

De Latour *et al.*[12] thoroughly investigated the pharmacokinetics and pharmacodynamics of eculizumab and ravulizumab and found that for patients treated with eculizumab, breakthrough haemolysis events were associated with elevations in free C5, suggesting inadequate C5 control. In contrast, for patients treated with ravulizumab, no breakthrough haemolysis events were associated with elevations in free C5.[12] We expect similar results with our alternative dosing strategies for ravulizumab, as it was shown that all patients stay above the therapeutic threshold.

Although it is known that covariates such as body size and haemoglobin explain some variability in pharmacokinetics,[1] the effect of these covariates is limited and unexplained variability in the pharmacokinetics of ravulizumab remains. These data encourage the investigation of pharmacokinetically-guided dosing, rather than covariate-based dosing in the maintenance phase.

The use of a TDM based dosing regimen for ravulizumab requires the development and validation of an appropriate analytical method and the implementation of the TDM strategy into the clinic, for which resources, staffing and expertise are needed. The generic methodologies for enzyme-linked immunoassays and mass spectrometric assays for eculizumab can also be applied for the bioanalysis of ravulizumab. In general, the unit costs for measurements of monoclonal antibodies are in the order of magnitude of US$20–50 per sample.[15] We consider all these additional costs for treatment with ravulizumab negligible, considering the potential savings.

The presented dosing regimens for ravulizumab were evaluated using the validated pharmacokinetic–pharmacodynamic model by the manufacturer of ravulizumab, based on the clinical studies with ravulizumab. The data and model have been thoroughly reviewed by both the Food and Drug Administration and European Medicines Agency. Although we consider these data reliable, we realize that these clinical trials employ restrictive eligibility criteria and might not be completely representative for the real-world population. Our study shows only a proof of concept for dose individualization of ravulizumab, and we think it is of the essence to prospectively investigate the noninferiority of the proposed alternative dosing regimens, with LDH normalization, pharmacokinetic target attainment, breakthrough haemolysis and treatment costs as endpoints before routinely implementing it in the clinic.

Whether ravulizumab will be cost-effective compared to eculizumab will mainly depend on the price of eculizumab biosimilars. With this study, we show that the costs of ravulizumab can potentially be decreased by ~37% when using an individualized dosing regime and the dosing interval can be prolonged for most patients.

3.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[16]

ACKNOWLEDGEMENTS

The authors would like to thank Stijn van Beek for his review of the model code.

COMPETING INTERESTS

The authors declare no conflicts of interest.

CONTRIBUTORS

M.t.A. and R.t.H. designed the study, analysed and interpreted the data and wrote the manuscript. S.L, S.S, N.K, N.B. and W.K. reviewed drafts of the manuscript, and approved the final version.

DATA AVAILABILITY STATEMENT

The article describes entirely theoretical research.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: ter Avest M, Langemeijer SMC, Schols SEM, et al. The potential of individualized dosing of ravulizumab to improve patient-friendliness of paroxysmal nocturnal haemoglobinuria treatment at reduced costs. *Br J Clin Pharmacol*. 2021;87:3359–3363. https://doi.org/10.1111/bcp.14748