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Individualized dosing of evinacumab is predicted to yield reductions in drug expenses

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Background: Evinacumab is a first-in-class inhibitor of angiopoietin-like protein 3 (ANGPTL3) for treatment of the rare disease homozygous familial hypercholesterolemia (HoFH). With projected drug costs of $450,000 per person per year, the question rises if cost-efficacy of evinacumab can be further improved.

Objectives: To develop an individualized dosing regimen te reduce drug expenses.

Methods: Using the clinical and pharmacological data as provided by the license holder, we developed an alternative dosing regimen *in silico* based on the principles of reduction of wastage by dosing based on weight bands rather than a linear milligram per kilogram body weight (mg/kg) dosing regimen, as well as dose individualization guided by low density lipoprotein cholesterol (LDL-C) response.

Results: We found that the average quantity of drug used for a dose could be reduced by 34% without predicted loss in efficacy (LDL-C reduction 24 weeks after treatment initiation).

Conclusion: Dose reductions without compromising efficacy seem feasible. We call for implementation and prospective evaluation of this strategy to reduce treatment costs of HoFH.

Introduction

Homozygous familial hypercholesterolemia (HoFH) is a rare genetic disorder of lipid metabolism. It results in very high levels of low-density lipoprotein cholesterol (LDL-C) starting at birth and, when left untreated, is often lethal during childhood.[1] If target LDLC levels are not reached with statins and ezetimibe, additional therapies are needed such as lipoprotein apheresis or PCSK9 inhibiting therapies or MTP inhibitors.[2] Lipoprotein apheresis is a costly, invasive and time-consuming procedure with major impact on quality of life.[3,4]

The recent approval of the drug evinacumab for treatment of HoFH as an adjunct to other LDL-C lowering therapies has the potential to have a large impact on the treatment of HoFH and the quality of life of these patients.[5] This monoclonal antibody can be administered every four weeks. It acts by inhibiting angiopoietin-like protein 3 (ANGPTL3), which plays an essential role in lipoprotein metabolism, thereby reducing LDL-C synthesis. Its inhibition by evinacumab results in drastic LDL-

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receptor-independent reduction of LDL-C of >50% from baseline in approximately half of the population 24 weeks after treatment initiation.[6,7] This treatment is expected to replace plasmapheresis in approximately 50% of patients and other therapies with a less favorable safety profile such as lomitapide.[8]

Evinacumab comes with a substantial price tag: in the United states the annual drug expenses are likely to be $450,000 per person in the approved dose[5], based on an undiscounted list prices of $11,212.50 for a 345 mg vial and $39,000 for a 1200 mg vial.[9] Drug expenses are, therefore, directly related to the used number of vials and vial size. With ever increasing costs of drugs seriously straining already limited healthcare budgets[10], there is an urgent need to prevent unnecessary drug expenses in case of overdosing.

Evinacumab is dosed at 15 mg per kilogram (mg/kg) bodyweight dose every 4 weeks (Q4W).[11] Although the mg/kg dosing paradigm is often applied to monoclonal antibodies, this strategy leads to relative underdosing in people with a low bodyweight and relative overdosing in people with a high bodyweight.[12] Furthermore, as evinacumab is only available in 345 and 1200 mg vials[11], the approved mg/kg dosing algorithm will result in considerable drug wastage when a vial is partially used. In addition, the rarity of the disease is a hurdle for vial sharing to prevent drug waste.

The license holder of evinacumab has performed thorough dose finding studies and investigated the relationship between dose, patient characteristics and LDL-C reduction.[6,13] A clear relationship between evinacumab plasma concentrations and LDL-C kinetics was found. Furthermore, it was found that evinacumab doses higher than 15 mg/kg do not relevantly improve LDL-C reduction. The latter indicates that evinacumab is dosed at or near the plateau of the dose-response curve. We postulate that a rational dosing regimen that prevents drug wastage has the potential to reduce costs without loss of efficacy. We, therefore, set out to develop an alternative dosing regimen for evinacumab.

Materials and methods

We performed an *in silico* dosing evaluation of both the approved 15 mg/kg Q4W dosing regimen as an alternative dosing regimen. *In silico* dosing evaluation consists of evaluation of different dosing regimens for a representative population with regards to pharmacokinetics and predicted treatment effect using a validated population pharmacokinetic-pharmacodynamic model. We used the population pharmacokinetic-pharmacodynamic model as described by the license holder of evinacumab and reported in the FDA approval package.[6,13] This validated model describes the relationship between dose, patient characteristics, systemic exposure to evinacumab and LDL-C levels as a function of time. In short, it was found that plasma concentrations of evinacumab are directly related to the inhibition of LDL-C production, with a high inter-individual variability in drug sensitivity, a higher drug sensitivity in patients with higher baseline LDL-C levels and a different clearance in healthy volunteers.[6]

Based on this knowledge, we explored two alternative dosing regimens. Alternative dosing regimen 1 was based on the principles that systemic evinacumab exposure in the alternative dosing regimen should be equivalent to the exposure reached with the approved dosing regimen and that the administered dose should be based on administration of complete vials to prevent drug wastage. The criteria for equivalent exposure were based on a recent FDA draft guideline for *in silico* dose development for monoclonal antibodies for treatment of cancer to update the dosing information in the label based solely on modelling and simulation.[14] This draft guideline proposes that, if the average concentration just before administration of the next dose (trough concentration (C_{trough}) and the cumulative exposure (defined as area under the concentration time curve (AUC) or average concentration (C_{avg}) of the alternative dosing regimen are not more than 20% lower than associated predicted for the reference approved dosing regimen, exposure is clinically equivalent. Furthermore, this guidelines states that the average maximum concentration (C_{max}) of the alternative dosing regimen should not be >20% higher than predicted for the approved reference dosing regimen. Alternative dosing regimen 2 was an extension of dosing regimen 1. Since it is known that some people have a higher sensitivity for evinacumab due to variability in individual drug sensitivity or due to an increased sensitivity in patients with a high LDL-C at baseline[6], LDL-C-guided dose reductions may be useful to further reduce the dose without compromising efficacy. Therefore, for alternative dosing regimen 2 treatment initiation was based on alternative dosing regimen 1 and further dose reductions during the first 12 weeks of treatment were based on LDL-C-response. If the LDL-C reduction during the first 12 weeks of treatment was >70%, the dose was further reduced by 345 mg (1 vial).

The *in silico* dosing evaluation was performed by means of a Monte Carlo simulation using the software package NONMEM V7.5 (Icon, Ireland). A population of 1000 virtual patients with a body weight of 71 kg was constructed, with an interindividual variability of 20%, a baseline LDL-C of 211 mg/dL (5.46 mmol/L) with an interindividual variability of 62.5% and a baseline total AngPTL3 of 0.08 mg/L with an interindividual variability of 44.4%. These assumptions were based on the patient characteristics in the pivotal clinical studies for evinacumab in the FDA drug approval package.[13] The NONMEM code for the simulations is provided in the supplemental material of this manuscript. From the Monte Carlo simulations we calculated the average evinacumab C_{trough}, the average evinacumab C_{avg} as well as the fractional reduction in LDL-C and the fraction of patients with an LDL-C reduction of >50% at 24 weeks after treatment initiation. Furthermore, we calculated the average dose administered per administration, as well as the average quantity of drug used for preparation of a single dose, assuming

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Table 1 Results of the Monte Carlo simulation for different dosing regimens.

Dosing regimen Q4W	Average C_{trough} at 24 weeks (%CV)	Average C_{avg} at 24 weeks (%CV)	Average dose administered per administration at 24 weeks (%CV)	Average quantity of drug used per administration at 24 weeks (%CV)[a]	Average LDL-C reduction (%CV) at 24 weeks	Patients with LDL-C reduction >50%
Approved 15 mg/kg	219 mg/L (46%)	273 mg/L (31%)	1080 mg (21%)	1255 mg (19%)	48% (69%)	58%
Alternative dose 1 <65 kg: 690 mg 65-100 kg: 1035 mg >100 kg: 1380 mg	181 mg/L (48%)	230 mg/L (34%)	930 mg (20%)	930 mg (20%)	46% (72%)	57%
Ratio alternative dose 1 to approved dose	0.83	0.84	0.86	0.74	0.95	0.98
Alternative dose 2 <65 kg: 690 mg 65-100 kg: 1035 mg >100 kg: 1380 mg Followed by LDL-C-guided dose reduction	156 mg/L (57%)	209 mg/L (38%)	832 mg (33%)	832 mg (33%)	46% (72%)	56%
Ratio alternative dose 2 to approved dose	0.71	0.77	0.77	0.66	0.95	0.97

[a]The average quantity of drug used per dose administered, assuming wastage of the smallest vial size available when partially used %CV: coefficient of variation.

wastage of the remaining drug in the smallest vial if it was partially used.

Results

For alternative dosing regimen 1, a regimen based on weight bands was developed. People with a body weight <65 kg were administered a dose of 690 mg (2 vials of 345 mg), people with a body weight of 65-100 kg were administered a dose of 1035 mg (3 vials of 345 mg) and people with a body weight >100 kg were administered a dose of 1380 mg (4 vials of 345 mg). The predicted pharmacokinetics and pharmacodynamics of this alternative dose and the comparison with the approved dosing regimen are presented in Table 1. Alternative dosing regimen 2 was similar to dosing regimen 1, with a dose reduction of 345 mg (1 vial) when individual LDL-C reduction was >70% during the first 12 weeks.

As observed, the alternative dosing regimen 1 resulted in a slightly lower (~15%) average exposure compared to the approved dosing regimen, yet within the predefined boundaries of pharmacokinetic equivalence (<20% deviation). Furthermore, switching from a mg/kg to a dosing regimen based on weight bands and administration of complete vials did not result in a relevant increase in variability in pharmacokinetics and the predicted LDL-C reduction for alternative dose 1 was not relevantly different compared the predicted LDL-C reduction in the approved dosing regimen (46% versus 48% LDL-C reduction, respectively). The maximum savings in expenses for alternative dose 1 were predicted to be 26% due to both a lower dose on average as well as prevention of wastage of partially used vials. Furthermore, it can be observed that for alternative dosing regimen 2, with addition of LDL-C guided dose reductions, a further decrease in drug use can be established with maximum savings of 34%, without relevant effect on predicted LDL-C response.

Discussion

Based on the clinical data and the relationship between dose, pharmacokinetics and efficacy reported by the license holder of evinacumab[6,13], we predict that a practical dosing regimen based on weight bands, administration of complete vials and further LDL-C guided dose reductions has the potential to save up to 34% of evinacumab treatment costs without compromising efficacy. With projected drugs costs of $450,000 per person per year[5], this translates to savings of $153,000 per person per year. Although costs in other settings are currently unknown, it is likely that evinacumab treatment costs are high in other parts of the world as well. The extension of the indication of evinacumab, e.g. to patients with refractory hypercholesterolemia[15], total drug expenses are likely to increase if the price is not reduced.

As observed in our analysis, a lower dose resulted in a lower exposure, yet within the prespecified boundaries of equivalence for alternative dosing regimen 1 and without predicted relevant loss in efficacy for both alternative dosing regimens. The reported evinacumab concentration inducing 50% of the effect (IC50) is 57.4 mg/L with an interindivid-

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ual variability (standard deviation) of 3.11 mg/L)[6]. The predicted C_{avg} at 24 weeks for both the approved and alternative dosing regimens 1 and 2 of 273 mg/L, 230 mg/L and 156 mg/L is above this IC50. This shows that evinacumab in the approved dose is dosed in the plateau of the dose-response curve and that dose reductions only have minimal effect on LDL-C response. Apheresis rates may vary between different clinics and patients. This may result in different "baseline" LDL-C levels, but our proposed evinacumab dosing algorithm can be implemented independent of apheresis strategy.

Annual per-person costs of lipoprotein apheresis in the United States were estimated to be $228,956 in 2016.[4] This does not account for social burden and personal costs, e.g. as a result of lost working days. Therefore, also from a patient perspective, there is an urgent need to make evinacumab treatment cost-effective. The basis for our claim that drug expenses can be reduced using the proposed dosing algorithm, is based on the fact that the administered evinacumab dose currently directly relates to drug expenses. If a different pricing strategy is applied, e.g. "pay for performance" this no longer holds true. Moreover, we consider it good practice to not expose patients to more drug than strictly required.

One may argue that our findings are not directly derived from a clinical study and that the alternative dosing regimens should be thoroughly tested in clinical studies before implementation in routine clinical care. The rarity of HoFH complicates the execution of such a trial. Although evinacumab is currently not approved for other indications than HoFH, it may be postulated that proof-of-concept of our dosing algorithm can also be shown in heterozygous or wildtype individuals. However, as patients with a low baseline LDL-C may be less sensitive to evinacumab and disease state may impact the pharmacokinetics of evinacumab[6], it is uncertain whether similar dose reductions can be achieved in patients without HoFH. The source for drug costs in the United States in this analysis is based on the wholesale (undiscounted) acquisition costs of evinacumab as communicated by the license holder. The drug cost estimates of this analysis do not reflect effects of manufacturing cost or nonmanufacturing costs such as advertisement, marketing, infrastructure, drug company personnel, taxes, distribution, manufacturer recovery of past research and development, pharmacy benefit manager rebates, and negotiation with insurers.

Our predictions are derived from the model developed by the license holder of evinacumab based on all pharmacokinetic and pharmacodynamic data during clinical development of this drug. Therefore, there is much certainty about the validity of the developed model and our predictions. Moreover, changes in the labels for the dosing of monoclonal antibodies used for oncological indications, based solely on modelling and simulation, are becoming common practice. This strategy is supported by a recent draft guideline by the FDA[14] and the provided level of evidence for alternative dosing regimen 1 complies with these FDA criteria. Since LDL-C can be easily monitored, sub-therapy can be diagnosed early and treatment adjusted accordingly. We, therefore, think that direct implementation of the proposed alternative dosing regimen 2, with addition of frequent LDL-C monitoring, is a safe strategy. Ideally, if the proposed individualized dosing algorithm is proven cost-effective in clinical practice, this dosing algorithm should be adopted in the label. However, as only the license holder is allowed to request a label change, we strongly encourage professional societies to adopt proven alternative dosing regimens in guidelines to facilitate their implementation.

Since HoFH is a rare disease, we call for an international cooperation to directly implement the proposed alternative dosing regimen to save costs and to prospectively confirm its efficacy in a phase IV study.

Author contributions

Rob ter Heine: conceived and designed the analysis, collected the data, performed the analysis, wrote the paper. **Gerard Rongen**: conceived and designed the analysis, wrote the paper conceived and designed the analysis, wrote the paper. **Jeanine Roeters van Lennep**: wrote the paper. **Joost Rutten**: conceived and designed the analysis, wrote the paper conceived and designed the analysis, wrote the paper.

Declarations of Competing Interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jacl.2023.03.004.

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