Impacts of dose titration on logistic exposure-response in simulated flexible-dose clinical trials

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Titrating based on early response can obscure or reverse exposure-response. Change from baseline response may be less susceptible to the titration paradox than absolute response or a binary response measure. A titration flag helps to unveil the true E-R relationship.

Background & Objective

Dose titration based on response seeks to optimize individual responses while minimizing the risk of side effects. However, this technique is not widely adopted in drug development due to the selection bias it creates, where responders tend to receive lower doses and non-responders tend to receive higher doses. This bias can sometimes obscure or even reverse the expected dose-response exposure-response (E-R) relationship, a phenomenon known as the "titration paradox" [1].

The objective of this work was to illustrate the effects of dose titration on E-R analysis for a binary endpoint and to examine factors that could help resolve the paradox.

Methods

A simple dose titration study was simulated: 200 patients treated for 24 weeks for a liver disease resulting in elevated alkaline phosphatase (ALP) levels at baseline, with no dropouts. Participants were randomly assigned to either the 50 mg or the 100 mg dose arm in a 1:1 ratio, and a 2-fold increase in dose was permitted at 12 weeks if a participant had an ALP >1.67×upper limit of normal (ULN). At 24 weeks, the relationship between drug exposure and a binary efficacy endpoint of ALP (BALP) was evaluated: whether a patient achieved ALP ≤ 1.67×ULN or not.

Baseline ALP, steady-state drug exposure, and the intrinsic half-maximal effective exposure (EC_{50}) for percent change in ALP were simulated to follow a lognormal distribution across subjects, while maximal percent decrease in ALP (Emax) was assumed to follow a normal distribution.

Responses in terms of absolute ALP, change from baseline ALP, and the BALP endpoint were derived from the simulated percent change in ALP values, modeled as:

$$E_0 + \frac{E_{max} \times Exposure}{EC_{50} + Exposure} + Random\ Error$$

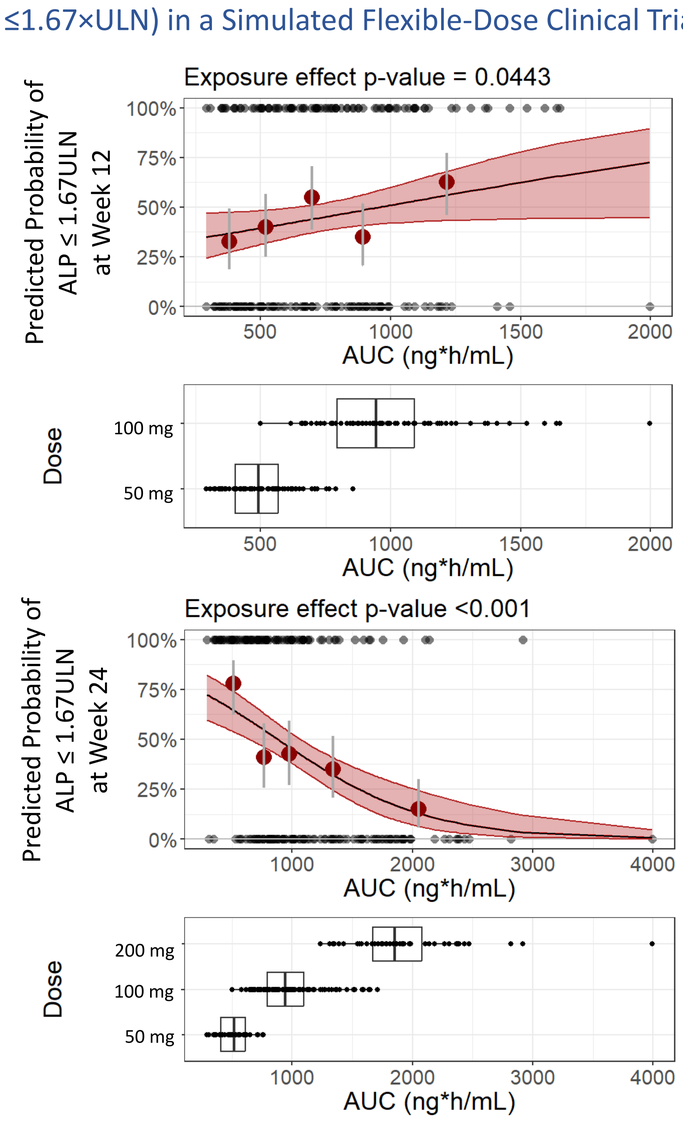
Discussion

The simulations suggest continuous response measured as change from baseline may be less susceptible to the titration paradox than absolute response or a binary response measure. This is likely because baseline values are correlated with early responses. For instance, in the simulated trial, baseline was positively correlated with absolute ALP and negatively correlated with binary ALP. As a result, change from baseline effectively accounts for the baseline effect, whereas absolute response or binary response does not. In addition, a titration flag based on early response helps to unveil the true E-R relationship.

Results

The simulations demonstrated the titration paradox, where the E-R relationship for BALP in a logistic model unexpectedly reversed at week 24. Adding a titration flag as an interaction term to drug exposure in the logistic model allowed for dynamic E-R relationships in subgroups of patients with and without up-titration. Results showed that the titration flag helped resolve the paradox in patients without up-titration, as higher drug exposure increased the probability of achieving BALP. The positive E-R relationship became less significant with increasing random dropouts. The titration paradox was also observed in the E-R relationship of continuous absolute ALP but not continuous change from baseline ALP.

Titration Paradox in the Binary ALP Endpoint (ALP ≤1.67×ULN) in a Simulated Flexible-Dose Clinical Trial



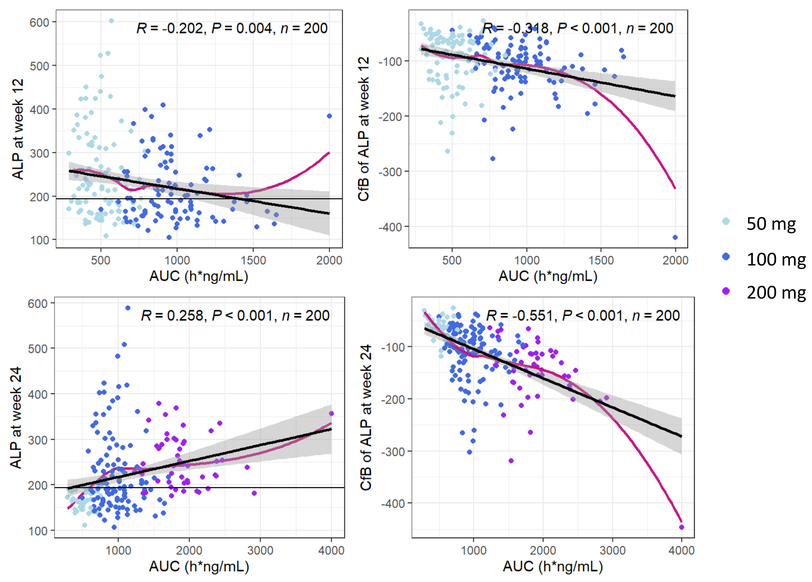
Steady-state AUC was divided into quintiles. Red points and gray error bars represent the observed proportions of patients achieved ALP < 1.67ULN and 95% confidence intervals (CIs) for each group (plotted at the mean AUC within each group), respectively. The curve represents the model prediction, and the shaded region represents its 95% CI. Observed binary ALP endpoint is presented in points at 0% if a subject missed the endpoint, and 100% if a subject achieved the endpoint. Boxplots show distributions of steady-state AUC for each dose group.

Reference

[1] Schnider et al. (2021). *Clinical Pharmacol. Ther*. *110*(2), 401-408.
[2] Kristensen & Agersø (2022). CPT: Pharmacometrics & Systems Pharmacology, 11(12), 1592-1603.

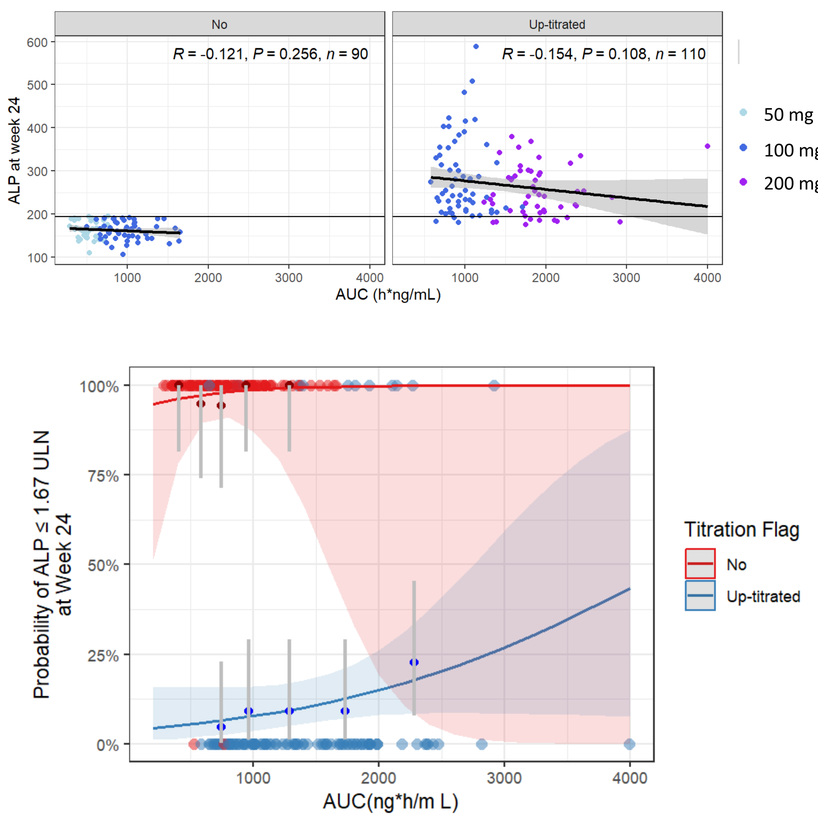
Additional Figures

Titration Paradox Observed in Absolute ALP but NOT in Change from Baseline ALP in a Simulated Flexible-Dose Clinical Trial



CfB=change from baseline. Dots represent the simulated ALP and change from baseline ALP. Black lines represent the linear regressions of the data with shaded area representing the 95% confidence interval. Red lines represent the LOESS (locally weighted smoothing) fit to data.

A titration flag helped unveil the true E-R relationship



Dots represent the simulated change from baseline ALP. Black lines represent the linear regressions of the data with shaded area representing the 95% confidence interval. Red lines represent the LOESS (locally weighted smoothing) fit to data.

Steady-state AUC was divided into quintiles for patients who up-titrated dose and patients who did not, respectively. Points and gray error bars represent the observed proportions of patients achieved ALP ≤ 1.67ULN and 95% confidence intervals (CIs) for each group (plotted at the mean AUC within each group), respectively. The curve represents the model prediction, and the shaded region represents its 95% CI. Observed binary ALP endpoint is presented in points at 0% if a subject missed the endpoint, and 100% if a subject achieved the endpoint.

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