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ARTICLE

Exposure-response modeling for extrapolation from adult to pediatric patients who differ with respect to prognostic factors: Application to everolimus

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Abstract

Pediatric extrapolation is essential for bringing treatments to the pediatric population, especially for indications where the recruitment of pediatric patients into clinical trials is difficult and where fully powered trials are impossible. Often a similar exposure-response relationship between adult and pediatric patients can be assumed, but just matching exposures can be misleading when some prognostic factors for efficacy differ between those two patient populations. We present an example in liver transplantation where different study designs led to different (time-dependent) hazards between populations. Only after accounting for this difference an apparent mismatch between the extrapolation from adults and the pediatric study could be resolved. This article also exemplifies a clear scientific, methodological approach of pediatric extrapolation, including model building in adults, extrapolation to pediatrics, qualification of the extrapolation, and derivation of the actual pediatric efficacy.

STUDY HIGHLIGHTS

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Pediatric extrapolation is an essential tool for bringing treatments to the pediatric population. It generally relies on the standard extrapolation assumption of similarity of the exposure-response relationship between adults and pediatric patients.

WHAT QUESTION DID THIS STUDY ADDRESS?

In the current study, the pediatric and adult populations differ with respect to a prognostic factor for response. In such a case, the standard extrapolation assumption can be misleading, and the question is how to adapt it.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

It is necessary to identify the risk factors that differ between adult and pediatric populations and to account for them in the extrapolation assumption to yield realistic predictions of pediatric efficacy.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

This approach leads to credible extrapolation that can increase the acceptance of the results by the health authorities, thereby accelerating the approval of pediatric medicines.

INTRODUCTION

Conducting clinical trials with a new drug regimen in children may be challenging due to ethical and feasibility reasons.[1] In particular, parents may not consent to including their children in clinical trials, specifically if effective treatments already exist for the condition. Consequently, the number of patients available for pediatric clinical trials is often limited.

Pediatric extrapolation is an approach that allows reduced sample sizes and that is accepted by health authorities[2,3] and the scientific community. This approach is increasingly being used[4,5]: between 2009 and 2014, 63% of the 388 pediatric studies submitted to the US Food and Drug Administration were based on some form of extrapolation.

Pediatric extrapolation is based on assumptions. These include the similarity of the course of disease and response to intervention between pediatric and adult patients and the similarity of the drug exposure-response relationship between adult and pediatric patients.[2,3,6] Under these assumptions, the evaluation of the efficacy of a pediatric regimen in a target pediatric population can be predicted by combining the adult exposure-response relationship with the exposure achieved by the pediatric regimen in the pediatric population.

If there are no doubts about the validity of these assumptions, collection of efficacy data may not be required. Often, there are doubts remaining about the similarity of the exposure-response relationship, and it may be necessary to run a small dedicated pediatric efficacy "verification" study to relieve those doubts. The verification of this assumption could be done by predicting the outcome of the pediatric study from an adult exposure-response model (conditional on the observed exposure data in the pediatric trial) and comparing the prediction with the observed outcome.

The evaluation of the pediatric efficacy can be further simplified when the exposure observed (or predicted) in pediatric patients treated with the pediatric regimen is similar to the exposure achieved in adults by the approved adult regimen; in this case, the efficacy of the pediatric regimen is expected to be the same as the efficacy of the adult approved regimen.

The extrapolation assumption of a similar exposure-response relationship in children and adults implies that the same exposure in adult and pediatric patients leads to the same efficacy response. However, there are factors other than drug exposure that influence efficacy response, and it is not reasonable to believe that the same exposure leads to the same efficacy response in adult and pediatric patients that differ with respect to those prognostic factors. In this case, the extrapolation assumption must be adapted. A corresponding exposure-response model should include all those factors that may impact response and that may differ in distribution between the adult and pediatric patient populations.

Such a situation occurred for a combination of the drug everolimus with tacrolimus used for the prevention of acute rejections after liver transplantation. This combination was approved in adults based on a single registration study. The pediatric strategy was to establish pediatric efficacy by extrapolation from the adult data under the extrapolation assumption of a similar exposure-response relationship and to use the efficacy data from a small pediatric study to qualify the assumption. The adult-approved regimen and the regimen used in the pediatric study achieved the same tacrolimus and everolimus exposure, therefore it is expected that, under the extrapolation assumption, the pediatric regimen in the pediatric study should achieve the same efficacy as that of the adult-approved regimen. However, because of a difference in study design discussed in the Method section, pediatric patients were less at risk of efficacy failure than adult patients, therefore it was necessary to adapt the extrapolation assumption to account for this risk (or prognostic factor) difference.

This article describes in the Method section how the risk difference was identified, how the extrapolation assumption was adapted and subsequently verified, and how the extrapolation was ultimately performed. After presentation of the results of those analyses, a discussion of how the pediatric study results would have led to different interpretations if the extrapolation assumption had not been properly adapted is provided.

The focus of this article is on the extrapolation concept and how to include the prognostic factors, not on the technical aspects of the dose-exposure-response analysis that was performed to implement the extrapolation. Only selected aspects of the dose-exposure-response analysis are presented in the article. More substantial methods and results are presented in Supplemental Materials S1 and S2. Note also that, because of therapeutic drug monitoring, the exposure was forced to match between adults and pediatrics, which removed most of the emphasis from the exposure for extrapolation.

METHOD

Design of the adult and pediatric studies

NCT00622869 is a 24-month, double-blind, phase III study in which 729 adult liver transplant recipients, previously treated with a standard dose of tacrolimus for 30 days following transplantation, were randomized and treated for graft rejection prophylaxis with any of the following three drug regimens:

- A first investigational regimen with everolimus combined with a reduced dose of tacrolimus

- A second investigational regimen similar to the first one during the first 3 months and then tacrolimus is discontinued and everolimus dose is increased
- An active control regimen (standard dose of tacrolimus).

The first investigational regimen was approved in 2014.[7,8]

For the purpose of the analyses presented here, data from the second investigational regimen were censored at the end of the first 3 months and were pooled with the (uncensored) data from the first investigational regimen. This pool is referred to as "investigational regimen" here.

NCT01598987 is a 24-month, open-label, single-arm pediatric study in which 50 pediatric liver transplant recipients, aged 2 to 18 years old, previously treated with a standard exposure to a calcineurin inhibitor (CNI; 44 patients treated with tacrolimus and 6 patients treated with cyclosporine) for 30 to 180 days following transplantation, started a combination of everolimus with a reduced CNI dose.[9]

The primary efficacy end point in the two studies was incidence of treated biopsy proven acute rejection (tBPAR), graft loss, or death during the first 12 months of the treatment period, simply referred to as "rejection" here.

Pediatric Investigation Plan (PIP) including initial extrapolation assumption

The PIP agreed with the European Medicines Agency's (EMA) Pediatric Commitee (PDCO) included the requirement to submit the pediatric data as soon as at least 25 patients had reached the 1-year primary endpoint and to use extrapolation from the adult study to compensate for the small sample size.[10]

The agreed extrapolation assumption was that the relationship between exposure and response (probability of rejection) was expected to be similar between adult and pediatric patients (in analogy to the more immunologically reactive kidney[11]). It was decided to use the efficacy data of the patients treated with everolimus and tacrolimus, specifically the data of the first 12 months after the first everolimus dose ("analysis period"; represented by a yellow area in Figure 1) to verify the extrapolation assumption. The six cyclosporine-treated pediatric patients, who are not included in the extrapolation analysis, are not further discussed in the manuscript.

Therapeutic drug monitoring was used to maintain tacrolimus and everolimus concentrations in target ranges; the target ranges for the investigational regimen were the same in the adult and pediatric studies,[7,9] ensuring similar everolimus and tacrolimus concentrations in the adult and pediatric patients during the analysis period, which is schematically represented in Figure 1 by a dash-dotted blue line and a dashed red line, respectively.

Identification of the risk difference and adaptation of extrapolation assumption

Given the similarity of exposure, the probability of rejection during the analysis period in adults treated with the

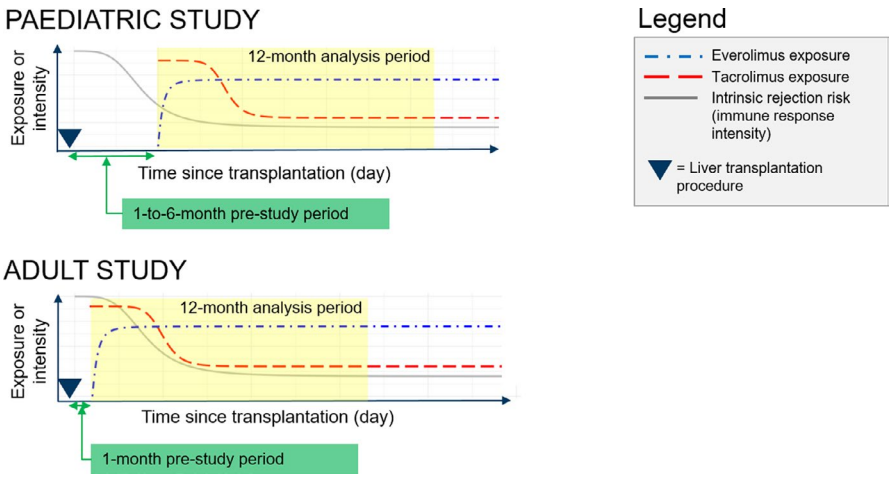

FIGURE 1 Time profiles of drug concentration and immune response intensity in the pediatric study and in the investigational arm of the adult study. The figures grossly depict the expected time profiles of tacrolimus concentration during the study (dashed red line), everolimus concentration (dash-dotted blue line), and immune response intensity after the transplantation procedure (solid gray line) in the pediatric study (top; NCT01598987) and in the investigational regimen of the adult study (bottom; NCT00622869). Those profiles are for qualitative but not quantitative interpretation; in particular (1) the intrinsic immune response intensity in a pediatric patient is expectedly the same as in an adult patient on the same day relative to the day of transplantation and (2) the everolimus and tacrolimus concentration profiles are the same during the 12-month analysis period (yellow area) in the adult and pediatric studies. The 12-month analysis period is the first 12 months of the 24-month treatment period in the adult and pediatric studies

investigational regimen is expected to be the same as that of pediatric patients under the extrapolation assumption mentioned previously.

However, the immune response is expected to be more intense during the first months following transplantation (which is why the tacrolimus concentration is maintained high during this period[7] and which is additionally supported by the larger incidence of rejection during the first months after transplantation[12]) and to decrease afterward, as schematically represented by a solid gray line in Figure 1. As the pediatric analysis period is further away from the transplantation day than the adult analysis period (Figure 1), the probability of rejection of the pediatric patients should be lower than that of the adult patients despite the similar everolimus and tacrolimus exposure time course during that period.

It is therefore necessary to adapt the extrapolation assumption to account for the immune response intensity. Note that, in the absence of a good measure of immune response intensity, it is necessary to make the additional assumption that, everything else (i.e., exposure) being the same, the immune response on a given time (e.g., day) relative to the time of transplantation has similar intensity in adults as in pediatric patients. Based on discussions with clinicians as well as indirectly by the relative similarity of the acute rejection time course between adult and pediatric patients,[12] this additional assumption was considered plausible.

Accordingly, the adapted extrapolation assumption is that the probability of rejection of a pediatric patient on a given day (relative to the day of transplantation) is expected to be the same as that of an adult patient on that same day similarly exposed to everolimus and tacrolimus.

Prediction of tacrolimus and everolimus exposures for adult and pediatric patients

Because of the sparse pharmacokinetics (PK) sampling and the numerous therapeutic drug monitoring–induced changes of dose, two population PK models, one for everolimus and one for tacrolimus, were used to provide a precise prediction of the actual concentration at any timepoint during the study for each pediatric and adult patient.

Those population PK analyses are described in Supplemental Material S1.

Estimation of the exposure-response relationship in adults

The incidence of rejection was modeled in the time-to-event framework by means of the hazard function because of its convenience in handling time-varying covariates, for example, drug exposure, and different patients' follow-ups. See Dumortier et al.[13] and Wang et al.[14] for detailed discussions of the necessity to handle exposure as a time-varying covariate.

As only the rejection date was recorded, the calendar day was used as time unit for the analysis, with the day of transplantation used as origin ($t = 0$) to be compatible with the adapted extrapolation assumption. Note that the adult rejection hazard is defined from day 30 after randomization ($t \geq 30$), that is, from the start of the adult study; this is sufficient for the extrapolation purpose as no pediatric patients entered the study treatment period before day 30 after transplantation.

The final exposure-response model was selected at the end of a model-building procedure (described in Supplemental Material S2). This final model includes the effect of tacrolimus concentration and treatment effect (investigational vs. control arm). The treatment effect reflects the effect of being treated with versus without everolimus and is assumed to be constant over time and additive to the effect of tacrolimus. Note that the actual everolimus concentration is not part of the model. Note also that the tacrolimus concentration variable specifically used to predict the rejection hazard on a given day t is the minimum tacrolimus concentration on the previous day, which is denoted by $C_{TAC,i}(t-1)$ for (adult or pediatric) patient i and was predicted from the tacrolimus population PK model.

The structure of the final adult model is:

$$h_\theta\left(t, 1_{EVR,i}, C_{TAC,i}(t-1)\right) = h_0\left(t;\mu_1,\mu_2,\mu_3\right) e^{\gamma 1_{EVR,i} + \beta\, min\left(\delta, C_{TAC,i}(t-1)\right)},$$

where $h_\theta\left(t, 1_{EVR,i}, C_{TAC,i}(t-1)\right)$, in short $h_{\theta,i}(t)$, is the hazard of rejection on day t(relative to the day of transplantation) for adult patient $i$in the investigational arm ($1_{EVR,i} = 1$) or in the control arm ($1_{EVR,i} = 0$), with tacrolimus minimum concentration on the previous day equal to $C_{TAC,i}(t-1)$, where

$$min\left(\delta, C_{TAC,i}(t-1)\right) = \begin{cases} C_{TAC,i}(t-1) & if\, C_{TAC,i}(t-1) < \delta \\ \delta & if\, C_{TAC,i}(t-1) \geq \delta \end{cases}.$$

The function $h_0(t)$ is the nonnegative piecewise constant parametric baseline hazard with three periods equal to:

$$h_0\left(t;\mu_1,\mu_2,\mu_3\right) = \begin{cases} \mu_1 & if\, t > 120 \\ \mu_1+\mu_2 & if\, 70 < t \leq 120 \\ \mu_1+\mu_2+\mu_3 & if\, t \leq 70 \end{cases},$$

where $\theta = \left(\mu_1, \mu_2, \mu_3, \gamma, \beta, \delta\right)$ is the vector of parameters of the exposure-response model.

The model was estimated using maximum likelihood method. $\widehat{\theta}$ denotes the maximum likelihood estimate of θ.

The goodness of fit of the final hazard model was assessed via visual predictive checks[15] (VPC) and Kaplan-Meier mean covariate[16] (KMMC) plots.

Use of the estimated adult exposure-response model to predict the probability of rejection in pediatric patients

Under the adapted extrapolation assumption, the adult exposure-response model is valid for pediatric patients treated with everolimus in combination with tacrolimus.

Therefore, the probability that patient i of the pediatric study experiences rejection during its analysis period (delimited by days $\tau_{s,i}$ and $\tau_{e,i}$), which we denote by $Q_{\theta,i}$, can be estimated by [17]:

$$Q_{\hat{\theta},i} = 1 - e^{-\int_{\tau_{s,i}}^{\tau_{e,i}} h_{\hat{\theta}}(t|1_{EVR,i}=1, C_{TAC,i}(t-1))dt}.$$

Verification of the extrapolation assumption—qualification of the adult model for extrapolation

Under the extrapolation assumption, the adult model holds for pediatric patients. Therefore, a verification of the extrapolation assumption can be done by comparing the pediatric efficacy predicted from the model to that observed in the pediatric study. In our case, this was done by comparing the proportion of patients in the pediatric study who experienced rejection during the analysis period (denoted by r_{obs}) to its predictive distribution.

This prediction distribution was approximated by a Monte Carlo simulation, that is, by repeated simulations of the pediatric study from the adult model. Each repeated study b (b = 1, . . , 1000) used the probability $Q_{\hat{\theta}_b,i}$ of the N_p patients of the pediatric study ($i = 1, . . , N_p$) to randomly generate the incidence of rejection for the pediatric patients and thus obtain$r_{b,obs}$, the proportion of patients in the repeated study b who experienced (simulated) rejection. The probability $Q_{\hat{\theta}_b,i}$ is defined analogously to$Q_{\hat{\theta},i}$, replacing the $\hat{\theta}$ by a bootstrap version $\hat{\theta}_b$, thereby accounting for the parameter estimate uncertainty.[18] The empirical distribution of $r_{b,obs}$ is the prediction distribution ofr_{obs}. The 90% prediction interval for r_{obs} is delimited by the 5th and 95th percentiles of that empirical distribution.

Calculation of the pediatric efficacy by extrapolation

The estimand is the probability, which we denote by Q_θ^{365}, that a pediatric patient randomly selected from the pediatric population of interest experiences rejection during a 365-day period.

The example that we consider here is that the patients of the pediatric study are representative of our pediatric population of interest in terms of the distribution of treatment start day (relative to the day of transplantation) and daily minimum tacrolimus concentration. Therefore, Q_θ^{365} can be approximated by $\frac{1}{N_p}\sum_{i=1}^{N_p} Q_{\theta,i}^{365}$, and $Q_{\theta,i}^{365}$ is estimated by $Q_{\hat{\theta},i}^{365} = 1 - e^{-\int_{\tau_{s,i}}^{\tau_{s,i}+365} h_{\hat{\theta}}(t|1_{EVR}=1, C_{TAC,i}(t-1))dt}$.

The 90% confidence interval (CI) for Q_θ^{365} is obtained from the 5th and 95th percentiles of the bootstrap distribution of $\frac{1}{N_p}\sum_{i=1}^{N_p} Q_{\hat{\theta}_b,i}^{365}$, where $\hat{\theta}_b$ is obtained as noted previously and $Q_{\hat{\theta}_b,i}^{365}$ is defined analogously to $Q_{\hat{\theta},i}^{365}$.

RESULTS

Descriptive results of the original adult and pediatric studies

The adult registration study included 239 and 461 patients in the control and the investigational arms, respectively. The estimated probability of experiencing rejection during the 365-day analysis period was equal to 0.06 (95% CI, 0.03–0.09) in the investigational arm and 0.09 (95% CI, 0.06–0.12) in the control arm (Table 1).

Twenty-two patients from the pediatric study were included in the analysis agreed with the PDCO. None of those 22 patients experienced rejection; the estimated probability to experience rejection during the 365-day analysis period was thus equal to 0 (95% CI, 0.00–0.21). This large CI expresses the uncertainty about this probability due to the small sample size of the pediatric study.

Prediction of tacrolimus and everolimus concentration exposures

Figure 2 displays the time course of the predicted tacrolimus and everolimus daily minimum concentrations for each patient (one line by patient) plotted from the start of the treatment period in the adult and pediatric studies. In this figure, the dots represent the rejections displayed on the day when the event happened at the minimum concentration on that day.

Estimation of the exposure-response relationship in adults

Several exposure-response models, described in Supplemental Material S2, were estimated using the data of the adult study.

Those models generally showed a significant effect of daily minimum tacrolimus concentration and a significant effect of treatment with everolimus. None of the models showed an additional effect of daily minimum everolimus concentration.

This does not mean that everolimus has no concentration effect. This can be explained by the plateau of the sigmoid

TABLE 1 Number of subjects and rejection events by study and treatment group

Study	Treatment group	Number of patients	Treatment period	Analysis period (first 365 days of treatment period)	
			Number of patients with rejection	Number of patients with rejection	Estimated rejection rate (95% CI)
Adult	Control	239	25	20	0.09 (0.05–0.13)
	Investigational	461	21	18	0.06 (0.03–0.08)
Pediatric	Investigational	22	0	0	0.00 (0.00–0.21)

Note: Only the patients with available tacrolimus concentrations are included in the table. As discussed in the Method section, the investigational arm in the adult study is the pool of the first and second investigational arms, the second being censored when tacrolimus was interrupted. Kaplan-Meier (KM) methods were used to estimate the rejection rate to account for the fact some patients, mostly the patients of the second adult investigational arm, were censored before reaching day 365. For the pediatric study, an exact method for small sample size described in Fay et al.[20] was used to obtain the KM estimate. The KM estimate of the rejection rate is calculated as one minus the standard KM survival estimate.

Abbreviation: CI, confidence interval.

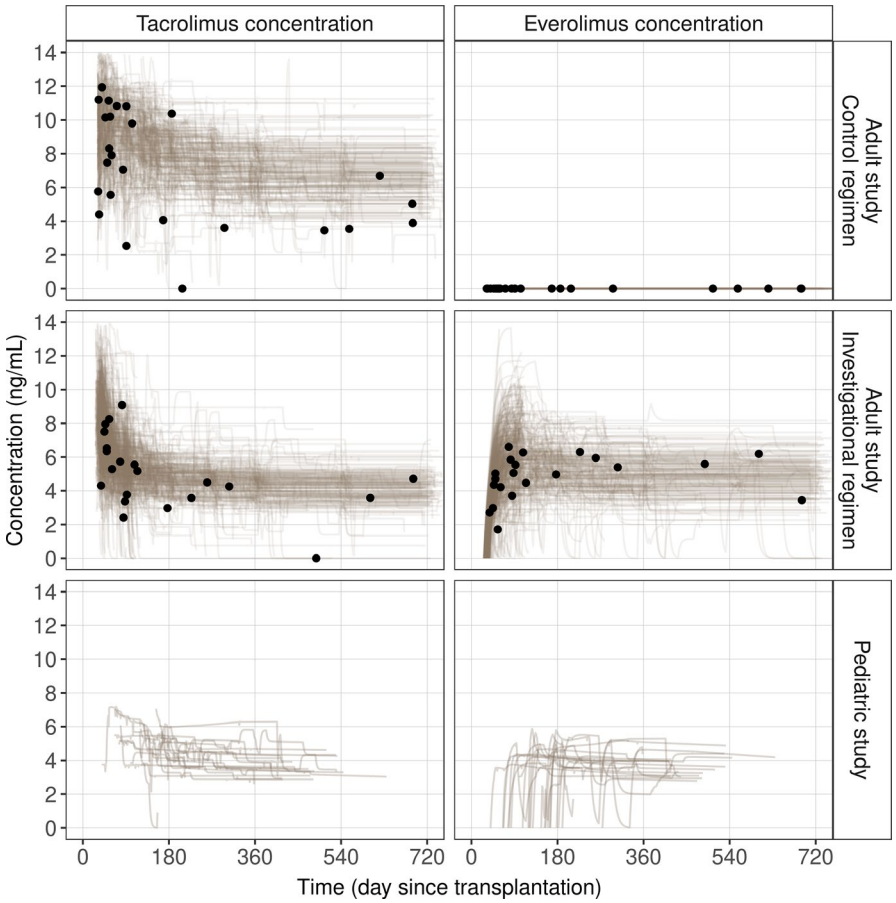

FIGURE 2 Time course of predicted tacrolimus and everolimus daily minimum concentration and the rejection events. The figure displays the individual tacrolimus and everolimus daily minimum concentration profiles predicted from four population pharmacokinetic models estimated using the tacrolimus and everolimus data from the adult and pediatric studies. One curve corresponds to the time-varying daily minimum concentration for one patient. Rejection events are also displayed on the figure: a dot represents an event plotted on day of event (x axis) at the minimum concentration on that day (y axis). More information about the four population pharmacokinetic models for everolimus and tacrolimus for adult and pediatric patients is provided in Supplemental Material S1

exposure-response curve being reached below or in the low part of the everolimus concentration levels observed in the study (3 to 6 ng/ml; see Figure 2).

The functional relationship of the tacrolimus concentration effect as well as the parametric form of the baseline hazard were further investigated (see Supplemental Material

S2). Eventually, the model presented in the Method section and in the footnotes of Table 2 showed goodness of fit (VPC and KMMC displayed in Supplemental Material S2) and was considered final.

TABLE 2 Final model parameters: estimates and standard errors

Parameter	Estimate (SE)
Baseline hazard, log scale	$\hat{\mu}_1 = -5.43\,(0.686)$
Additional baseline hazard before day 120, log scale	$\hat{\mu}_2 = 2.27\,(0.378)$
Additional baseline hazard before day 70, log scale	$\hat{\mu}_3 = 0.839\,(0.374)$
Effect of 1 ng/ml of daily minimum tacrolimus concentration on the log hazard	$\hat{\beta} = -0.645\,(0.099)$
Threshold daily minimum tacrolimus concentration—maximum daily minimum tacrolimus concentration value with effect, ng/ml	$\hat{\delta} = 7.10\,(0.046)$
Treatment with—versus without—everolimus, effect on the log hazard	$\hat{\gamma} = -1.65\,(0.418)$

Final adult model: $e^{\gamma 1_{EVR,i} + \beta\, min\left(\delta, C_{TAC,i}(t-1)\right)}$, where

$$h_0\left(t;\mu_1,\mu_2,\mu_3\right) = \begin{cases} \mu_1 & if\, t > 120 \\ \mu_1 + \mu_2 & if\, 70 < t \le 120 \\ \mu_1 + \mu_2 + \mu_3 & if\, t \le 70 \end{cases}.$$

The parameter estimates of that model are presented in Table 2. Besides a significant effect of treatment with everolimus, the final model includes a linear effect of tacrolimus concentration that plateaus at 7.1 ng/ml and a baseline hazard that decreases over time in a stepwise fashion consistently with the assumption mentioned in the Method section.

Those effects can be visualized in Figure 3: the left panel displays the estimated baseline hazard, and the right panel displays the predicted probability of rejection for hypothetical adult patients with the tacrolimus concentration constant during the analysis period; this panel shows that this probability decreases when the tacrolimus concentration increases to reach a minimum probability at concentration equal to 7.1 ng/ml and that the predicted probability for a patient in the investigational arm is lower than for a patient in the control arm with the same tacrolimus concentration: this reflects the effect of everolimus treatment.

Use of the adult model to predict the probability of rejection for pediatric patients

Under the extrapolation assumption, the adult exposure-response model can be used to predict the cumulative probability of rejection over time for each patient of the pediatric study (Figure 4, right panel). For comparison purpose, the cumulative probability curve is also displayed for

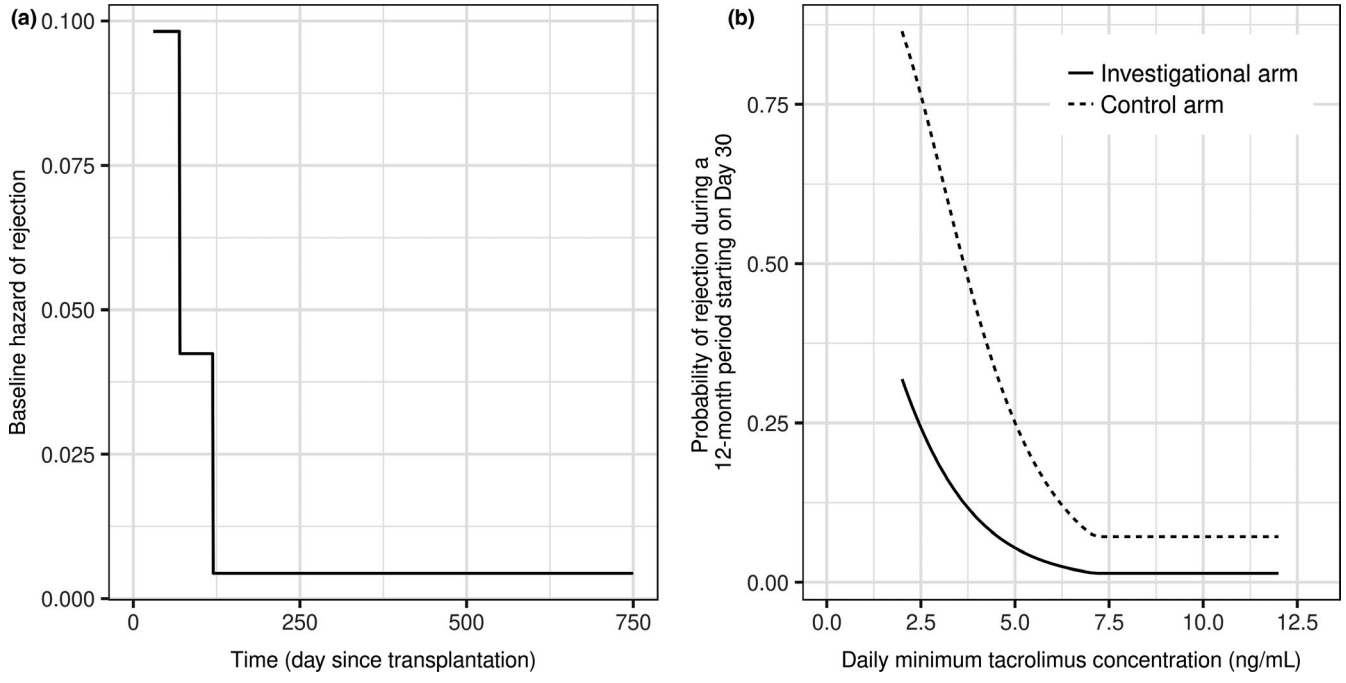

FIGURE 3 Selected characteristics of the estimated final adult model. Left: the estimated baseline hazard, only defined from day 30 on; note that its piecewise constant shape was selected based on a preliminary semiparametric analysis (Supplemental Material S2). Right: the probabilities of rejection during the 12-month period starting on day 30 for a hypothetical adult patient of the investigational and control arms exposed to a daily minimum tacrolimus concentration $C_{TAC,cst}$ constant over time are equal to $1 - e^{-\int_{30}^{395} h_{\hat{\theta}}\left(t,1_{EVR}=1,C_{TAC,cst}\right)dt}$ (plain line) and $1 - e^{-\int_{30}^{395} h_{\hat{\theta}}\left(t,1_{EVR}=0,C_{TAC,cst}\right)dt}$ (dotted line), respectively

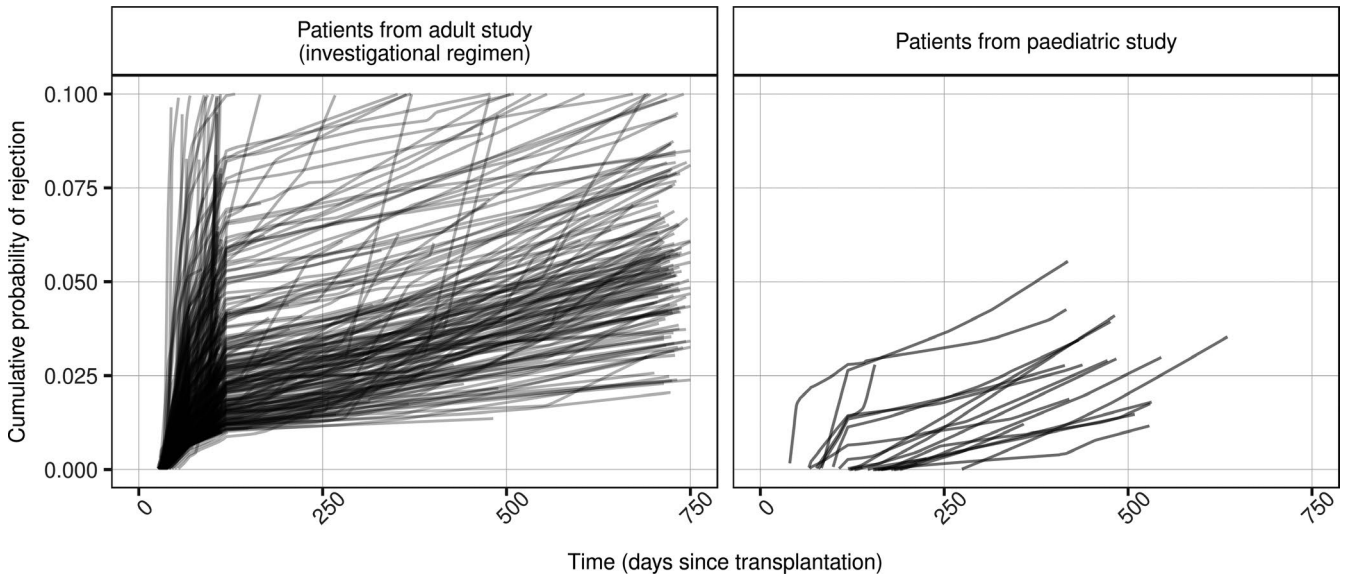

FIGURE 4 Predicted cumulative probability of rejection over time for each pediatric patient and each adult patient treated with the investigational treatment. One line represents the cumulative probability of rejection for one adult or pediatric patient. The cumulative probability of rejection estimated from the final adult model for patient i on day t is equal to $1 - e^{-\int_{\tau_{s,i}}^{t} h_{\hat{\theta}}(t|1_{EVR}=1, C_{TAC,i}(s-1))ds}$, where $\tau_{s,i} \leq t \leq \tau_{e,i}$, $\tau_{s,i}$ and $\tau_{e,i}$ are patient i the first and last days in the study, and $C_{TAC,i}(t-1)$ is the daily minimum concentration of patient i in the study. The minimum, 25th percentile, median, 75th percentile, and maximum study start days of everolimus relative to the day of transplantation in the investigational regimen were equal to 40, 87, 126, 163, and 274, respectively, in the pediatric study and to 26, 30, 32, 35, and 54, respectively, in the adult study; the same statistics for the day of randomization in the adult control regimen were equal to 30, 31, 32, 34, and 35, respectively

each adult patient treated with the investigational regimen (Figure 4, left panel). Note that the curves start on the day (relative to the day of transplantation) patients started study treatment.

The adult patients started the treatment period approximately on day 30 after transplantation when the baseline hazard for rejection is high (Figure 3, left). This is reflected by the steep increase in cumulative probability (Figure 4, left) during that period. This effect does not show for the majority of the pediatric patients (Figure 4, right) who started treatment much later (median treatment start on day 126 relative to day of transplantation; see the legend of Figure 4).

Verification of the extrapolation assumption—qualification of the adult model for extrapolation

Figure 5 displays the predictive distribution of the proportion of the 22 patients from the pediatric study who experience rejection during the analysis period.

The mode of this predictive distribution, that is, the most likely proportion to be observed in the pediatric study under the adapted extrapolation assumption, is equal to zero. This corresponds exactly to the results of the pediatric study

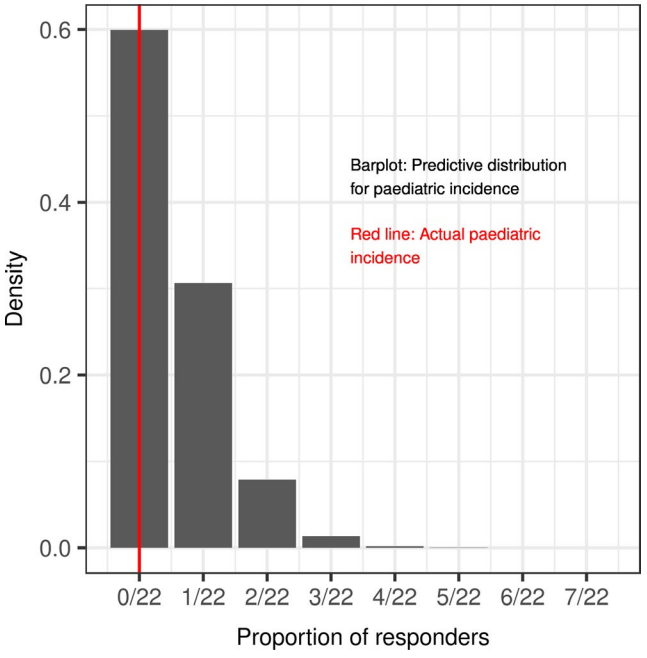

FIGURE 5 Predictive distribution for the rejection rate in the pediatric study. Predictive distribution for the rejection incidence during the analysis period from the final adult model in the 22 pediatric patients exposed to everolimus and tacrolimus in the pediatric study under the adapted extrapolation assumption. The figure also includes the actual event rate in the pediatric study (0 events)

where none of the 22 patients experienced rejection. This result therefore qualifies the extrapolation assumption.

Calculation of the pediatric probability of rejection by extrapolation

Upon qualification, one can proceed with the actual extrapolation to the pediatric population of interest. Here we considered the patients of the qualification study are representative of our pediatric population of interest in terms of their start treatment day (relative to the day of transplantation) and their daily minimum tacrolimus concentration. The predicted probability of rejection in this pediatric population of interest, denoted by Q_{θ}^{365} in the Method section, was estimated equal to 0.023 (95% CI, 0.012–0.039).

DISCUSSION

Our target estimand was the probability of experiencing rejection (a shorthand for tBPAR, graft loss, or death) during a 365-day period for a pediatric patient treated with the investigational regimen. The data of the pediatric study, where none of the 22 patients had experienced an event, provides a direct estimate equal to 0 for this probability (Table 1). The uncertainty around this probability, as expressed by a wide 95% CI equal to 0.00–0.21, illustrates the inadequacy of inferring efficacy from this pediatric study alone, especially given the severity of the disease and the fragile nature of the pediatric population.

Because pediatric and adult exposures are similar (Figure 2), one could be tempted to extrapolate pediatric efficacy directly from the adult data, assuming that similar exposure would lead to similar response. In other words, one would simply use the adult estimate of 0.06 (95% CI, 0.03–0.08; see Table 1) as an estimate for the pediatric risk to experience a rejection during the first 365 days of treatment.

That result would have been valid had the pediatric study started at the same time as the adult study. However, this estimator did not take into account the differences between the start of everolimus treatment (day 30 for adults, usually much later for pediatric patients) and thus the fact that pediatric patients were treated in a period of lower immune response intensity than the adults. When accounting for these differences, the resulting estimate for the predicted pediatric probability of experiencing rejection was equal to 0.023 (95% CI, 0.012–0.039). This reduced risk is reflected in the predictive distribution that assigns a probability of 60% to the event of no rejections among 22 pediatric patients (Figure 5). The observed efficacy data (zero events) of the small pediatric study was fully consistent with this prediction, leading to the qualification of the assumption.

As mentioned in the Method section, the extrapolation analyses presented here were required by the PDCO as part of the PIP agreement.[10] Upon the submission of the pediatric study results to European health authorities, the compliance check was successful, demonstrating/confirming that the pediatric development was conducted in accordance with the PIP decision.

The results of our efficacy extrapolation work presented here supported the hypothesis that the pediatric regimen provides sufficient levels of immunosuppression. Obviously, those efficacy results (zero rejections) could not rule out overimmunosuppression, and overimmunosuppression was actually suggested based on safety findings such as a higher-than-expected rate of posttransplant lymphoproliferative diseases.[9] Eventually, the totality of the pediatric study data along with the extrapolation analyses were included in a benefit/risk assessment that did not support recommendations for pediatric use in liver transplantation.

The need to account for all risk (or prognostic) factors that differ in distribution between two populations is required[19] to elicit the use (“transport”) of a causal relationship (in our case, an exposure-response relationship) established in a source population (in our case, the adult patients) to a target population (in our case, the pediatric patients). This difference in risk factor distribution can be induced by differences in study design as in our case or can be intrinsic to the patient (e.g., disease severity). Accounting for those risk factors can be done via statistical modeling as in this article or via case-matching methods where the adult patients are selected to match the risk factors of the pediatric patients.

The identification of those risk factors is a difficult task. It must be based on literature research and discussions with clinicians. To avoid unnecessary difficulties, it is recommended to keep the design of the pediatric study as similar as possible to the adult study, but this is not always possible as in our case where the pediatric study was delayed to allow a longer monitoring of the recovery from the surgery. The risk factors that need accounting for is expected to be part of the discussions leading to the agreement of the PIP with the health authorities.

An important objective of a pediatric program is to obtain a prediction of the response in the general (broader) pediatric population. In the extrapolation paradigm, the prediction to the general pediatric population is not obtained by inferring from the pediatric study, but by extrapolation from the adult model. This extrapolation is thus not affected by the small sample size of the pediatric study. However, such an extrapolation to the general pediatric population is only possible if the model accounts for all risk factors that differ in distribution between that general pediatric population and the adult population.

Pediatric extrapolation is an approach encouraged by the health authorities to evaluate the efficacy of a drug in children

that reduces the amount of pediatric efficacy data required. It requires assumptions relating the exposure-response relationship in adult and pediatric populations, which accounts for those risk factors that differ between the two populations. When those assumptions are valid, pediatric extrapolation can deliver realistic and credible predictions of pediatric efficacy and increase the acceptance of the results by the health authorities, thereby accelerating the approval of pediatric medicines.

CONFLICTS OF INTEREST

Thomas Dumortier, Günter Heimann, and Martin Fink are employees of Novartis Pharma AG.

AUTHOR CONTRIBUTIONS

T.D., G.H., and M.F. wrote the manuscript. T.D. designed the research. T.D. and M.F. performed the research. T.D., G.H., and M.F. analyzed the data.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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