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Interleukin-2 receptor antagonists for pediatric liver transplant recipients: A systematic review and meta-analysis of controlled studies

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Abstract: IL-2RA are frequently used as induction therapy in liver transplant recipients to decrease the risk of AR while allowing the reduction of concomitant immunosuppression. The exact association with the use of IL-2RA, however, is uncertain. We performed a systematic literature search for relevant studies. Random effects models were used to assess the incidence of AR, steroid-resistant rejection, graft loss, patient death, and adverse drug reaction, with or without IL-2RA. Six studies (two randomized and four non-randomized) met the eligibility criteria. Acute rejection at six months or later favored the use of IL-2RA significantly (RR 0.38; 95% CI 0.22–0.66, p = 0.0005). Although not statistically significant, IL-2RA showed a substantial reduction of the risk of steroid-resistant rejection (RR 0.32; CI 0.19–1.03, p = 0.0594). Graft loss and patient death showed a reductive tendency through the use of IL-2RA. The use of IL-2RA is safe and is associated with a statistically significantly lower incidence of AR after transplantation and substantial reduction of steroid-resistant rejection, graft loss, and patient death.

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Key words: liver transplantation – immunosuppression – interleukin-2 receptor antagonist – meta-analysis – pediatric – basiliximab – daclizumab – controlled study

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Abbreviations: ACA, available case analysis; ADR, adverse drug reaction; AR, acute rejection; Bas, basiliximab; BG, basiliximab group; CI, confidence interval; CMV, cytomegalovirus; CNI, calcineurin inhibitor; Cont, control group; Cya, cyclosporine A; Dac, daclizumab; EBV, Epstein–Barr virus; eGFR, estimated glomerular filtration rate; EPAR, European Public Assessment Report; Exp, experimental group; GFR, glomerular filtration rate; HCV, hepatitis C virus; HLP, hyperlipoproteinemia; HTN, arterial hypertension; i.o., intra-operative; IgG, immunoglobulin G; IL-2RA, interleukin-2 receptor antagonist/s; IL-2R, interleukin-2 receptor; IQR, interquartile range; ITT, intention-to-treat analysis; KG, body weight; LOCF, last-observation-carried-forward; MD, mean difference; MDRD, Modification of Diet in Renal Disease; MMF, mycophenolate mofetil; na, not applicable; NNT, number needed to treat; ns, not stated; OLT, orthotopic liver transplantation; POD, postoperative day; PP, per-protocol; PRISMA, Preferred Items for Systematic Reviews and Meta-Analysis; PTDM, post-transplant diabetes mellitus; PTLD, post-transplant lymphoproliferative disease; REML, restricted maximum likelihood; RR, relative risk; SADR, serious adverse drug reaction; SRAR, steroid-resistant (acute) rejection; Tac, tacrolimus; tl, target level.

The ultimate purpose of pediatric liver transplantation is to grant an expectance of life of several decades. Immunosuppression should be tailored to ensure best management of both short- and long-term complications. Currently the immunosuppressive strategy is not standardized among different transplantation centers mainly because very few comparative studies with adequate number of patients and duration of follow-up are published (1–3). In particular, only a few published controlled clinical studies report on the use of a relatively new immunosuppressive agent called Bas (Simulect®, Novartis AG, Basel, Switzerland) or Dac (Zenapax®, F. Hoffmann-La Roche AG, Basel, Switzerland). These are monoclonal antibodies targeting the IL-2R. Initially they were approved for therapy of patients after renal transplantation. The two IL-2R antibodies (IL-2RA) Dac and Bas were commercially available, but Dac has recently been withdrawn

from the EU market for commercial reasons. Now Bas is regularly used in adult as well as in pediatric liver transplant both in Europe (4) and in the USA (5).

The aim of induction therapy with IL-2RA is mainly to decrease the risk of AR. Acute rejection should be prevented because a graft is damaged with each rejection and loses part of its function. There are histopathologic features of acute and chronic rejection proved by core needle biopsy (6). Avoiding AR or SRAR improves the long-time function of a liver graft. For children, a good functioning and long-living liver graft is particularly important due to the high expected lifespan. Acute rejection is a strong risk factor for chronic rejection in kidney transplant patients (7). Acute rejection after liver transplantation can progress to chronic injury; it shows a prolonged liver dysfunction, and all lead on to chronic rejection (6). It could be a similar strong risk factor for liver recipients, but the development is not well understood by now (8). Chronic rejection is also described as a potentially reversible process with a dynamic nature (8). There is no evidence based connection between AR and long-term outcome in liver transplantation. FDA regulated clinical research focuses on clinical AR as primary endpoint, leading to less information about long-term data and other endpoints. The idea of using IL-2RA is an exchange of immunosuppressive drugs without increasing the risk of graft damage to reduce long lasting effects of common immunosuppressive substances such as steroids and CNI. Common side effects of steroids include infections, HTN, glucose intolerance, hyperlipidemia, and osteoporosis (9). There are some side effects which differ from adult liver graft recipients. Children suffer from growth impairment (9) and steroids may influence hepatic regeneration and development of immunologic tolerance (10). The use of CNI bears the risk of developing renal dysfunction after liver transplantation because of its nephrotoxicity (1–3).

IL-2RA specifically bind and block the IL-2R α-chain (which corresponds to CD25), which is present only on the surface of activated T-lymphocytes (11). The IL-2 signal is essential for the activation of lymphocytes; it induces second messenger signals to stimulate T cells to enter the cell cycle and proliferate, resulting in clonal expansion and differentiation. The commercially available IL-2RA are both monoclonal anti-CD25 IgG antibodies, but their structure and synthesis are different. Dac is a humanized antibody built by total gene synthesis using oligonucleotides (12), whereas Bas is a chimeric murine–human antibody (13). The competitive block of IL-2R, and thereby of IL-2-mediated activation, lasts for four to 12 wk, depending on the antibody and the administration protocol (11). The following side effects have commonly been observed in conjunction with the use of IL–2RA: CMV or EBV infection/reactivation, lymphoproliferative disorders, anaphylaxis, fever, opportunist infection, hypotension/hypertension, digestive disturbances, hyperglycemia, hirsutism, pruritus, and antibody formation (14).

In this study, we conduct an analysis of published controlled trials examining the effect of IL-2RA in children after liver transplantation. We would like to investigate whether the use of IL-2RA in addition to concomitant immunosuppressive therapy reduces AR and steroid-resistent rejection after pediatric liver transplantation. We expect that the potential reduction of concomitant medication such as CNI or steroids through the additional therapy with IL-2RA will reduce the long-term ADR such as kidney failure, disturbance of growth, diabetes mellitus, and other metabolic disorders.

Material and methods

The methods of literature search, the inclusion and exclusion criteria, outcome measures, and methods of statistical analysis were established according to the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions (15, Part 2). We also used the PRISMA (16) to structure this report. The methods of this meta-analysis were similar to those used in (17).

Literature search

A systematic literature search was performed without language restrictions in December 2012 in the following databases: PubMed, Transplant Library, and Cochrane Library. The following search terms were used: "liver transplantation," "interleukin 2 receptor inhibitor/antagonist," "Bas," "Dac," "Zenapax," "Simulect," "pediatric," "child," "children," and abbreviations thereof. The keywords were combined with Boolean operators.

Inclusion and exclusion criteria

All prospective, controlled pediatric studies and pediatric studies with prospective Exp and historical Cont in which IL-2RA induction therapy in liver transplant recipients was compared with placebo or no add-on were included. A first non-systematic review of the literature showed that in pediatric liver transplantation, IL-2RA are used in addition to standard immunosuppression therapy concepts to reduce other immunosuppressive drugs, such as CNI (3) and corticosteroids (9, 10). We have therefore structured this meta-analysis into three separate comparisons as follows: In the first group, IL-2RA are added to the Exp and are compared to no add-on or placebo, while both study arms got equal concomitant immunosuppressive medication. This group is referred to as the *IL-2RA only* comparison in the following.

In the second group, IL-2RA are additionally combined with delayed CNI in the experimental arm (*delayed CNI* comparison). The third group compared IL-2RA with a standard immunosuppressive protocol with reduced or even dropped steroids in the experimental arm (the *no/low steroids* comparison). Other immunosuppressive medication had to be the same in both treatment arms, for example, MMF.

All retrospective, non-controlled pediatric studies and pediatric studies with multi-organ transplantation or re-transplantation were excluded. Pharmacological studies that did not provide data on clinical outcome measures were excluded as well because of their very short follow-up time. The literature search strategy was designed and performed by two reviewers (N.D.C., A.D.G.). Publications were screened independently by two reviewers (N.D.C., A.D.G.). Disagreement and any discrepancies were resolved by discussion of all four reviewers.

Outcome measures

The primary outcomes analyzed were AR, steroid-resistant rejection, graft loss, and patient death. Secondary outcomes were ADR namely renal dysfunction by need of dialysis or oliguria, de novo malignancy (excluding recurrence of hepatocellular carcinoma), PTLD, infection complications, including fungal, viral, and bacterial infections, new onset of metabolic and cardiovascular disorders such as HTN, HLP, and PTDM.

Study quality

The quality items assessed were blinding, randomization, allocation concealment, ITT analysis, completeness of follow-up, and the method of handling missing values. Assessment was performed according to definitions stated in the Cochrane Handbook (15, Ch. 8). Quality of studies was assessed independently by two reviewers (N.D.C., A.D.G.) without blinding to journal and authorship. Furthermore, completeness of follow-up was defined as the number of patients that were not lost to follow-up. We reported completeness of follow-up as stated by the authors. Methods of handling missing values are stated as reported by the authors of the respective study.

Data extraction

All available data for the described outcome measures were extracted at all available timepoints from individual trials. In contrast to kidney transplants, it has been shown that morphological signs of rejection in protocol biopsies of transplanted livers without clinical correlates require no treatment and have no long-term ADR (18). Therefore, we only included treated ARs in the primary analysis, when the reported AR was stratified into "treated" and "non-treated." When data on outcome measures were not provided or studies seemed to be duplicates, the authors were contacted to provide more data. Data extraction was performed by one reviewer (N.D.C.) using a standardized form and checked by two reviewers (A.D.G, C.R.).

Data analysis

We expressed the results of dichotomous outcomes as RR with values smaller than one favoring IL-2RA. When no event was observed in both arms, we excluded it from the corresponding comparison (15, Ch.16.9.3). We performed the analysis using a random effects model, as in case of doubt, it makes more sense to use the more general approach (including the fixed-effects model as a special case), which will usually lead to more conservative results (19). For the random effects models, the amount of residual heterogeneity (i.e., τ^2) was estimated by the REML method (20). CIs for τ^2 were obtained by the Q-profile method (21). The model parameters were estimated by way of weighted least squares, with weights equal to the inverse sum of the variance of the estimate and the estimate of the residual heterogeneity. Then, Wald-type tests and CIs were obtained for the parameter estimates (20). We analyzed heterogeneity among studies using Cochrane's Q test and calculating I^2 to measure the proportion of total variation due to heterogeneity beyond chance (22). We performed subgroup analyses for primary outcomes which had significant results. Subgroups and factors defined *a priori* were methodological quality of trial (i.e., randomized vs. non-randomized), comparison group, type of IL-2RA, type of CNI, and use of MMF. For the primary analysis, we pooled effect measurements from trials with different follow-up time; but timepoint of measurement (grouped by six months vs. 12 months and later) was evaluated in a subgroup analysis. In some of the subgroups, a valid analysis was not possible. To examine the influence of covariates affecting the direction and/or strength of the relation between dependent and independent variables, we used the moderator test. For statistically significant results, we calculated the NNT describing how many patients are needed to be treated with an intervention, here IL-2RA, to prevent one patient from having one additional bad outcome, here for example AR. Publication bias was assessed using funnel plots (23) and tests for funnel plot asymmetry (20). The R environment for statistical computing (v. 2.11.0) (24) with packages "meta" (v. 2.5-0) (25), "metafor" (v. 1.4-0) (20), and "lme4" (v. 0.999375-37) (26) was used for all analyses.

Results

Literature search

Database searches yielded 325 entries (see Fig. 1), of which 15 were excluded as duplicates. Of the remaining 310 publications that qualified for abstract review, 252 were excluded primarily because they were not controlled trials, the effect of IL-2RA was not investigated, they were not dealing with pediatric patients, or they were not conducted in patients undergoing first liver transplantation. Also retrospective studies were excluded. The remaining 58 publications underwent full article review and 38 further publications were excluded. Most common reasons were retrospective studies, other comparator than IL-2RA, studies with adult patients, non-controlled studies, and reviews. A total of 20 trials qualified for inclusion in this review. Thirteen studies were excluded because of being duplicates, preliminary reports, and follow-up reports of the included studies. One study was excluded because of having no reported follow-up time and the authors did not respond to our requests

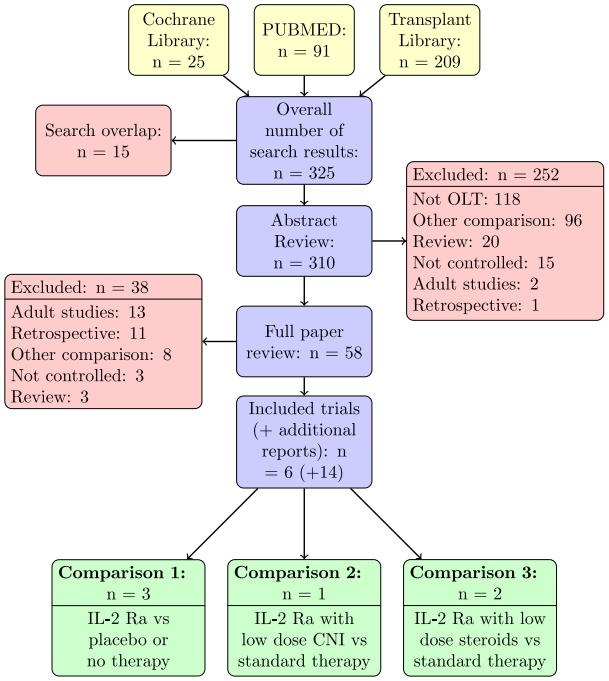

Fig. 1. Flow chart of systematic review: IL2-RA (according to PRISMA (16)).

of further information. Six studies were eventually included for analysis (1–3, 9, 10, 27). All trials were obtained as full-text publications. In case of multiple reports on the same study, we cited the most recent full-text publication as the index publication. Two authors of reports were contacted to resolve ambiguities. One author answered, and the other author did not respond.

Included studies

Table 1 shows the characteristics of the included studies. Three trials (1, 2, 27) compared IL-2RA to no add-on without modification of concomitant immunosuppressive medication (*IL-2RA only* comparison). Only one trial (3) compared IL-2RA in combination with delayed CNI to no add-on with standard immunosuppression (*delayed CNI* comparison). Two trials (9, 10) compared IL-2RA in combination with early discontinuation or reduction of steroids to no add-on with standard immunosuppression (*no/low steroids* comparison). One study (9) excluded patients with a severe renal dysfunction and another trial (10) excluded children with autoimmune hepatitis. In two-thirds of the included studies, Bas was used for induction (1, 9, 10, 27) and another two-thirds of the trials used Tac as CNI (2, 3, 9, 10). Two of the six studies used MMF (2, 3) and all but the experimental arms of the studies of *no/low steroids* comparison (9, 10) used steroids as concomitant medication. Most trials had a study duration of 12 months or more (3, 9, 10, 27).

Quality of included studies

Table 2 shows the quality assessment of the included studies. None of the studies were classified as blinded, whereas two of them did not report the status of blinding and were classified as "not stated." Two studies (3, 9) were prospective and randomized, a third study (2) was entirely prospective, and three studies (1, 10, 27) had a prospective Exp and historical Cont. Of the randomized trials, allocation concealment was found to be adequate in none of the studies, but unclear in one study (9) and inadequate (3) in another. For the four non-randomized studies (1, 2, 10, 27) allocation concealment was na. ITT analysis was stated and performed in one study (9) and was assessed as adequate. In three further

Table 1. Characteristics of included trials stratified by the three prespecified comparison groups

Trial		Sample size		Age†		Sex (male)						
Author (year)	Patient subgroup*	Exp	Cont	Exp	Cont	Exp	Cont	Type of IL-2RA	Control substance	CNI	MMF	Follow-up‡
IL-2RA only comparison: IL-2RA vs. placebo/no treatment												
Ganschow (2005)		54	54	4.2 (0.3–8.9)§	Matched	ns	ns	Bas	No	Cya	No	36
Gibelli (2004)		28	28	3 (1.3–16)§	Matched	ns	ns	Bas	No	Cya	No	6
Schuller (2005)		18	12	3.95 ± 0.33	3.9 ± 0.26	9	4	Dac	No	Tac	Yes	6
Delayed CNI comparison: IL-2RA and delayed and/or reduced CNI vs. placebo/no treatment and standard immunosuppressive co-medication												
Heffron (2003)		61	20	6.8 ± 6.3	5.3 ± 6.6	24	7	Dac	ns	Tac	Yes	24
No/low steroids comparison: IL-2RA and minimized steroids or no steroids vs. placebo/no treatment and standard immunosuppressive co-medication												
Spada (2006)	Renal function	36	36	2.9 (1.5–4.3)§	2.8 (1.5–4.3)	18	15	Bas	No	Tac	No	12
Gras (2008)	No auto-immune hepatitis	50	34	1.7 (0.4–14.0)§	2.0 (0.4–14.0)	27	16	Bas	No	Tac	No	36

*Patient subgroup: special inclusion criteria used by the authors.
†Age is given in mean ± s.d. if available.
‡Length of follow-up, time is given in months.
§Age is given in mean with (minimum–maximum).

Table 2. Summary of quality assessment of included trials

Trial Author (year)	Blinding	Randomized	Cont	Allocation concealment	ITT analysis	Missing values	Completeness of follow-up* Exp (%)	Cont (%)	Month
IL-2RA only comparison: IL-2RA vs. placebo/no treatment									
Ganschow (2005)	No	No	Historical	na	Yes† (ns)	ns	ns	ns	28–52
Gibelli (2004)	No	No	Historical	na	Yes‡ (PP)	ns	ns	ns	6
Schuller (2005)	No	No	Concurrent§	na	Yes† (ns)	ns	ns	ns	6
Delayed CNI comparison: IL-2RA and delayed and/or reduced CNI vs. placebo/no treatment and standard immunosuppressive co-medication									
Heffron (2003)	ns	Yes	Concurrent	Inadequate	ns	ns	ns	ns	24
No/low steroids comparison: IL-2RA and minimized steroids or no steroids vs. placebo/no treatment and standard immunosuppressive co-medication									
Spada (2006)	ns	Yes	Concurrent	Unclear	Yes	ns	90	90	12
Gras (2008)	No	No	Historical	na	Yes† (ns)	ns	100	100	36

*As stated by authors or calculated from available data.
†ITT analysis is assumed, because the author reported about at least one analysis with the total number of included patients.
‡Author reported that ITT analysis was performed, but also stated conditions that must be met for patient to be included in analysis, such as "patient received at least one dose of medication" and/or "at least one follow-up available."
§Prospective study.

trials (2, 10, 27), ITT analysis was assumed and considered adequate because the authors reported on all patients at the end-points of the study. One study (1) reported ITT analysis, but it was assessed as inadequate. According to the definition given in (15, Ch. 16.2.1), the authors of that trial did a PP analysis. In only one trial (3), we could not assess ITT analysis and it was therefore classified as "not stated." None of the authors stated how missing values were handled. Only two studies (9, 10) described completeness of follow-up.

Application of IL-2RA

Table 3 summarizes the immunosuppressive therapy of included pediatric trials. Bas was used in four studies (1, 9, 10, 27). All of them administered Bas on POD 0 and 4 in a dosage of 10 mg for children with a weight below 30 kg or a dosage of 20 mg for children with a weight of more than 30 kg. In addition, Spada et al. (9) administered Bas on PODs 8 until 10 if the recipient had lost more than 70 mL/kg fluid from the abdominal drains, because Bas crosses into the ascitis fluid (3). Dac was used as induction therapy adapted to patient's weight (1 mg/kg) in two trials (2, 3) and was therefore administered on POD 0. Schuller et al. (2) in addition gave a second dose on POD 14. In the immunosuppressive concepts of the studies discussed here, the authors tried to limit the overall immunosuppression (3). Dac has a half-life of 99 h, and its loss in ascitic fluid has been only weakly correlated to the monoclonal antibody clearance (3, p. 2040). Heffron et al. (3) used it in the first week after transplantation instead of CNI, whereas Schuller et al. (2) used Dac induction to reduce the tl of Tac from the beginning.

Definition of primary outcomes

Most studies defined AR as a rejection episode (1, 2, 9, 10), confirmed by liver biopsy (1, 3, 9, 10, 27), and for which therapy was given (2, 3, 9, 10, 27). Some trials described a clinical and laboratory diagnosis in addition (3, 27). The severity of AR was graded using the Banff criteria (28) in two studies (9, 27). A steroid-resistant AR was defined as not past using steroids (2, 3, 9, 27), and therefore a treatment with, for example, OKT3 (3, 9) was needed. Some studies proved it by biopsy (3, 27). Spada et al. (9) also used CNI in standard dose first before adding steroids.

Follow-up time of included studies

Follow-up times varied from six to 52 months. They also differed between control and Exp and were not necessarily identical for all outcomes. Because of the different follow-up times, a comparison is difficult, but the first six months are the crucial period in which IL-2RA are acting. The long-time effects on outcome of patients should be measured over years. We have not found enough data on long-term outcomes. Most follow-up is about three yr only.

Primary outcomes

Acute rejection

Reduction of AR favored the use of IL-2RA (RR 0.38; CI 0.22–0.66; $p = 0.0005$; six trials; Fig. 2). The effect is also seen in the subgroup of randomized trials (RR 0.31; CI 0.20–0.47; $p < 0.0001$; three trials), but is not statistically significant in non-randomized studies (RR 0.46; CI 0.18–1.18; $p = 0.1039$; three trials). The RR of all studies had a statistically significant heterogeneity ($p = 0.0126$) which is due to the study of

Table 3. Immunosuppressive therapy of included pediatric trials

Trial Author (year)	IL-2RA (type and dosage)	CNI Type, first day of therapy, dosage and tl Exp	CNI Type, first day of therapy, dosage and tl Cont	Corticosteroids dosage* Exp	Corticosteroids dosage* Cont	MMF dosage
IL-2RA only comparison: IL-2RA vs. placebo/no treatment						
Ganschow (2005)	Bas POD 0 and 4 i.v. 10 mg (KG < 30 kg) 20 mg (KG > 30 kg)	Cya tl 150–200 μg/L after one yr tl 80–100 μg/L		Prednisolone 60 mg/m² after one wk 30 mg/m² thereafter weekly reduction about 5 mg/m² break off after one yr		No
Gibelli (2004)	Bas POD 0 and 4 i.v. 10 mg (KG < 30 kg) 20 mg (KG > 30 kg)	Cya 7–13 mg/kg/d tl 850–1000 mg/dL	Cya 5–7 mg/kg/d tl 850–1000 mg/dL	Steroids		No
Schuller (2005)	Dac POD 0 and 14 i.v. 1 mg/kgKG	Tac 0.2 mg/kg/d tl 10–12 ng/mL Start: POD 3	Tac 0.2 mg/kg/d tl 6–8 ng/mL Start: POD 3	Methylprednisolone 20 mg/kg Start: POD 0 fast reduction break off after 4th months		1200 mg/m²/d Start: POD 14
delayed CNI comparison: IL-2RA and delayed and/or reduced CNI vs. placebo/no treatment and standard immunosuppressive co-medication						
Heffron (2003)	Dac POD 0 i.v. 1 mg/kgKG	Tac 0.15/mg/kg/d tl 10–14 ng/mL Start: POD 7	Tac 0.15/mg/kg/d tl 10–14 ng/mL Start: POD 0	Methylprednisolone: POD 0: 20 mg/kg/d, POD 6: 0.3 mg/kg/d		30 mg/kg/d, p.o.
No/low steroids comparison: IL-2RA and minimized steroids or no steroids vs. placebo/no treatment and standard immunosuppressive co-medication						
Spada (2006)	Bas POD 0 and 4 POD 8–10 i.v. 10 mg (KG < 35 kg) 20 mg (KG > 35 kg)	Tac 0.04 mg/kg/d, p.o. tl 1st month 10–15 ng/mL tl 2nd–3rd month 10–15 ng/mL tl 4th–6th month 6–8 ng/mL thereafter 5–7 ng/mL		Methylprednisolone i.o. 10 mg/kg i.v.	Methylprednisolone i.o. 10 mg/kg i.v. POD 1–6: 2 mg/kg/d POD 7: 1 mg/kg/d break off after 3rd–6th months maximum: 40 mg	No
Gras (2008)	Bas POD 0 and 4 i.v. 10 mg (KG < 35 kg) 20 mg (KG > 35 kg)	Tac 0.2 mg/kg/d, p.o. Start: POD 0 tl 1st month 8–12 ng/mL thereafter 5–8 ng/mL		No	Methylprednisolone 10 mg/kg/i.v. POD 1–6: 2 mg /kg/d i.v. POD 7–13: 1 mg/kg/d p.o. POD 14–20: 0.75 mg/kg/d POD 21–28: 0.5 mg/kg/d thereafter 0.25 mg/kg/d POD 90: 0.25 mg/kg/d (cave: alternative therapy in 2nd–6th months)	20 mg/kgKG/d (only the first nine children took it)

*All trials used methylprednisolone intra-operatively. In the postoperative period, they used methylprednisolone or prednisolone.

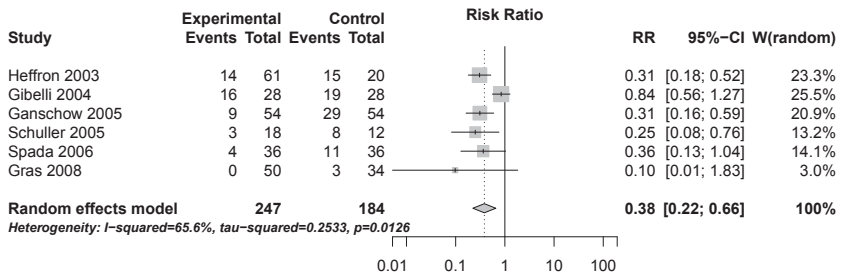

Fig. 2. Forest plot of AR of all included studies. The forest plot shows a reduced RR of AR for pediatric patients which have used IL-2RA (Exp). The result is significant, but also shows significant heterogeneity (p = 0.0126).

Gibelli et al. (1). Omitting the study by Gibelli et al. (1) the risk reduction is larger (RR 0.30; CI 0.21–0.43; p < 0.0001; five trials). Considering the three prespecified subgroups of studies, we have data on the *IL-2RA only* comparison (RR 0.44; CI 0.19–1.002; p = 0.0507; three trials) and on the *no/low steroids* comparison (RR 0.31; CI 0.12–0.84; p = 0.0211; two trials). Only the *no/low steroids* comparison was significant in reduction of AR, favoring the use of IL-2RA. Stratifying studies by follow-up time showed a statistically significant reduction of ARs with IL-2RA at 12 months and later (RR 0.31; CI 0.21–0.45; p < 0.0001; four trials), but not at six months (RR 0.51; CI 0.16–1.66; p = 0.2654; two trials). Furthermore, subgroup analysis stratified by the type of IL-2RA used showed a statistically significant effect of both Bas (RR 0.44; CI 0.21–0.92; p = 0.0299; four trials) and Dac (RR 0.29; CI 0.18–0.47; p < 0.0001; two trials). The subgroup with Dac induction therapy got additional MMF as immunosuppressive concomitant medication, and it showed a lower p value and showed no statistically significant heterogeneity. Stratifying trials by type of CNI used showed a statistically significant effect of Tac (RR 0.30; CI 0.19–0.46; p < 0.0001; four trials) but not for Cya (RR 0.53; CI 0.20–1.40; p = 0.1999; two trials). Finally, we analyzed the subgroup stratified by Cont. Studies with retrospective Cont showed no statistically significant reduction of AR (RR 0.46; CI 0.18–1.18; p = 0.1039; three trials) in comparison to these with prospective Cont (RR 0.31; CI 0.20–0.47; p < 0.0001; three trials). The NNT is 3.6, which means that four children after liver transplantation have to be treated with IL-2RA in addition to standard immunosuppressive therapy to prevent one patient of having an AR. Four studies defined AR clinically and confirmed it by biopsy (1–3, 27). Analysis of this subgroup showed a statistically significant reduction of AR (RR 0.40; CI 0.21–0.76; p = 0.0052; four trials). One trial (9) used the term of an episode of AR as outcome measurement and another study (10) did not state a definition. None of the trials were taking protocol biopsies.

Steroid-resistant rejection

All trials reported data on steroid-resistant rejection. One study (9) reported about no steroid-resistant rejection in both arms, so that we excluded it from analysis. IL-2RA in addition to standard double or triple immunosuppressive therapy after liver transplantation in children did not reduce steroid-resistant rejection statistically significantly (RR 0.44; CI 0.19–1.03; p = 0.0594; five trials). If we exclude one of the older studies (1) with the most extreme effect from the analysis, we get a statistically significant reduction of steroid-resistant rejection without significant heterogeneity (RR 0.34; CI 0.14–0.79; p = 0.0123; four trials). Stratifying trials by randomization status (randomized subgroup: RR 0.18; CI 0.04–0.74; p = 0.0177; two studies (2, 3) and non-randomized subgroup: RR 0.65; CI 0.24–1.78; p = 0.3971; four trials (1, 9, 10, 27)) and comparison did not show statistically significant effects (*IL-2RA only* comparison: RR 0.77; CI 0.30–1.98; p = 0.5894; three trials (1, 2, 27); *delayed CNI* comparison (3) and *low/no steroids* comparison (10) only one study each) except the subgroup of randomized studies. However, we saw a statistically significant reduction of steroid-resistant rejection in studies (3, 10, 27) with follow-up measurements at 12 months and later (RR 0.33; CI 0.12–0.89; p = 0.0281; three trials; Fig. 3), but not at six months (RR 0.93; CI 0.18–4.67; p = 0.9269; two trials (1, 2)). There was a statistically significant reduction in steroid-resistant rejection using IL-2RA in subgroups using Tac (RR 0.17; CI 0.05–0.57; p = 0.0041; three trials (2, 3, 10)) and Dac induction therapy combined with additional MMF dose and prospective Cont (RR 0.18; CI 0.04–0.74; p = 0.0177; two trials (2, 3)).

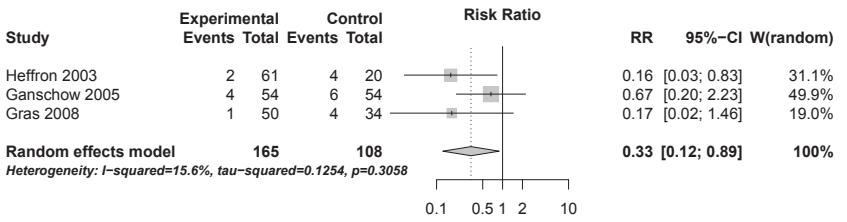

Fig. 3. Forest plot of steroid-resistant rejection stratified by follow-up measurement, here follow-up 12 months and later. The forest plot shows a reduced RR of steroid-resistant rejection for pediatric patients which have used IL-2RA (Exp). The result is significant and shows no significant heterogeneity (p = 0.3058).

Graft loss and patient death

Four studies (3, 9, 10, 27) reported data on graft loss and patient death. Neither graft loss (RR 0.65; CI 0.34–1.21; p = 0.1737; four trials) nor patient death (RR 0.61; CI 0.27–1.37; p = 0.2296; four trials) was statistically significantly reduced using additional IL-2RA in combination to standard immunosuppressive medication in the observation period. In the forest plot, one study (9) is prominently deviating from the remaining studies. After excluding this study from the analysis, we saw a statistically significant result for reducing graft loss by the use of IL-2RA (RR 0.44; CI 0.21–0.92; p = 0.0298; three trials), but not for death (RR 0.42; CI 0.16–1.12; p = 0.0831; three trials). However, all analyses show a trend toward a lower incidence of graft loss and patient death in the Exp using IL-2RA in addition to standard double-drug or triple-drug therapy.

Secondary outcomes: side effects and subgroups

It was not possible to collect enough data to analyze secondary outcomes, namely de novo malignancy, PTDM or HLP. Four studies reported on renal dysfunction (1, 2, 9, 27); data analysis of this outcome showed a slight reductive tendency but no statistically significant reduction using IL-2RA (RR 0.96; CI 0.60–1.54; p = 0.8683; four trials). Furthermore, three studies (1, 9, 27) reported on new onset HTN. Analysis showed no significant reduction of HTN using IL-2RA but a reductive tendency (RR 0.85; CI 0.60–1.21; p = 0.3731; three trials). Three studies (2, 9, 27) reported on PTLD, but one of them (2) yielded no event in both arms, so that we excluded it from analysis. PTLD was not reduced using additional IL-2RA therapy (RR 1.6; CI 0.20–12.67; p = 0.6587; two trials), on the contrary, it showed a higher RR in the Exp. Two studies (9, 27) reported on infection complications and outcomes were also reported on subgroups named viral, bacterial, and fungal infections. Additional IL-2RA therapy with standard immunosuppressive medication did not reduce infection complications statistically significantly (infection complications: RR 0.80; CI 0.60–1.07; p = 0.1363; two trials; viral infection: RR 1.06; CI 0.62–1.80; p = 0.8356; two trials; fungal infection: RR 1.15; CI 0.46–2.87; p = 0.7624; two trials; bacterial infection: RR 0.68; CI 0.34–1.37; p = 0.2838; two trials). Infection complications and bacterial infection showed a reductive tendency, but viral and fungal infections were more frequent in the Cont. Due to limited data, we were unable to do subgroup analyses except for the *IL-2RA only* comparison. The subgroup analysis of AE of the *IL-2RA only* comparison showed no significant reduction using IL2-RA in any of the secondary outcomes renal dysfunction, HTN or PTLD.

Discussion

The use of IL-2RA in addition to standard double-drug or triple-drug therapy significantly lowers the risk of AR in pediatric patients after liver transplantation. Acute rejection rate is reduced by two-thirds through the use of IL-2RA (RR 0.38). These results are similar to those we found in our meta-analysis in adult liver transplant recipients (17). The RR of all studies has a significant heterogeneity which is introduced by the study of Gibelli et al. (1). Most of the subgroup analyses support a statistically significant reduction of AR through the additional use of IL-2RA, and all subgroup analyses showed a substantial reduction by at least 50%.

The use of IL-2RA in addition to standard double-drug or triple-drug therapy also shows a substantial reduction of steroid-resistant rejection after pediatric liver transplantation (RR 0.44). If we exclude one of the older and prominently deviating studies (1) from analysis, we get a statistically significant reduction of steroid-resistant rejection without significant heterogeneity. Subgroup analyses stratified by measurement

time at 12 months and later, randomized subgroup, as well as a subgroup of only prospective controlled trials observed significant reduction of steroid-resistant rejection through the use of IL-2RA.

Although the risk of AR is substantially reduced when IL2-RA is applied, we did not observe a statistically significant reduction in graft loss or patient death. Observed trends suggested that the number of patients may be too small to observe significant effects, but we see a clinically relevant reduction of patient death (RR 0.61) and graft loss (RR 0.65) by about one-third. These results are similar to those we found in adult liver transplanted patients (17).

We also looked at the possibility of reducing concomitant immunosuppressive medication when using IL-2RA because most published studies explored this effect. We could classify published studies into three different experimental immunosuppressive regimens, namely the *IL-2RA only* comparison (1, 2, 27), the *delayed CNI* comparison (3), and the *no/low steroids* comparison (9, 10). Stratifying trials by comparison, there is only the *IL-2RA only* comparison and the *no/low steroids* comparison to analyze. The *no/low steroids* comparison shows a statistically significant reduction of AR favoring the use of IL-2RA. In the analysis of other primary outcomes, the number of studies in each comparison is too small, so that we find no statistically significant effect in any. We see a clinically relevant reductive effect in the *IL-2RA only* and *no/low steroids* comparisons of the risk of steroid-resistant rejection, patient death, and graft loss through the additional use of IL-2RA in the Exp.

Compared to other types of pediatric solid organ transplantations, we see a similar reductive tendency of AR and SRAR in pediatric renal recipients receiving induction therapy with IL-2RA. Swiatecka-Urban et al. (29), a study with retrospective Cont, compared Bas induction and Tac with no treatment in pediatric renal recipients. The use of Bas induction in addition to Tac and steroids reduces the risk of rate of AR (BG: 26% vs. non-BG: 43%; $p = 0.36$) and rate of SRAR (BG: 8.7% vs. non-BG: 12.5%; $p = 0.68$). No patient deaths were observed within one-yr follow-up time. The one-yr graft survival rate was higher in the induction group (BG: 87.5% vs. 75% in non-BG; $p = 0.45$). These results are comparable with results of other studies, for example Vester et al. (30). In this prospective study using Bas as induction combined with cyclosporin A and prednisone, one-yr patient survival rate was 100%, graft survival rate was 95%, AR episodes were observed in six patients and two SRAR were observed. Also a historical controlled study comparing Bas with no medication and triple baseline immunosuppression with cyclosporine or Tac, prednisone, MMF showed a reduction of AR to 10% in the induction group compared to 38% in the Cont (31). There are very few studies using IL-2RA in pediatric patients after lung or heart transplantation. We found occasional controlled studies while most publications were reviews. One controlled study reported about a six-months AR incidence of 30% in the Dac group vs. 60% in the Cont (32). IL-2RA are also used in pediatric patients after heart transplantation (33, 34). It seems to reduce AR if Bas is given before transplantation (35) and reduced AR in critically ill children with heart transplantation (36). IL-2RA induction therapy after lung and heart transplantation showed a reductive tendency of AR along with an acceptable safety profile, but the reductive tendency in pediatric patients seems to be stronger after liver transplantation compared to published data on renal, heart, or lung transplant recipients.

The following side effects were observed after Bas application in about 20% of pediatric patients by the EPAR: urinary tract infections, hypertrichosis, rhinitis, fever, hypertension, upper respiratory tract infection, viral infection, sepsis, and constipation (37, p. 2). The EPAR reported about side effects of Dac such as insomnia, tremor, headache, hypertension, dyspnoea, constipation, diarrhea, vomiting, nausea, dyspepsia, musculoskeletal pain, edema, impaired healing, and post-traumatic pain being observed in more than one of ten patients (38, p. 2). Of these named potential side effects, the analyzed studies reported mostly about metabolic disorders, for example HTN, and observed infection complications which were not reported in detail. Major side effects as lymphoma were observed rarely.

Due to the limited amount of data, we were unable to perform subgroup analyses except for the *IL-2RA only* comparison. Also it was not possible to collect enough data to analyze secondary outcomes, namely de novo malignancy, PTDM, or HLP. Analysis of included studies shows a reductive tendency of renal dysfunction, new onset post-transplant HTN, and infection complication especially bacterial infections in Exp which uses IL-2RA in addition to standard immunosuppressive therapy. The subgroup analysis of the *IL-2RA only* comparison showed no statistically significant reduction using IL2-RA in any of the secondary outcomes called renal dysfunction, HTN, or PTLD.

In the published EPAR about Simulect, the weight limit for a higher dose is 35 kg (37). Bas was studied in pediatric and adult kidney-transplanted patients. It was given on POD 0 and 4 (37). According to the EPAR, Dac should be given in 1 mg/kg on PODs 0, 14, 28, 42, and 56 after kidney transplantation (38). By comparing the mode of application between analyzed studies and EPAR statement, we see that the authors have used the common dose of Bas. Only Spada et al. (9) added a third dose, which might hold the level of IL-2RA intracorporeal. The limit of weight for a higher dose was lower than proposed by EPAR. Dac was given only once or twice after liver transplantation. Giving a drug in one or two single dose is a good practical application, promotes the compliance, and may shorten the day of hospitalization.

Strengths and limitations

The main limitation of this review is the small number of randomized controlled trials, even compared to trials in kidney transplantation (39), and our systematic review and meta-analysis of adult patients after liver transplantation (17). The low number of studies makes it difficult to acquire enough data to demonstrate statistical significance. Corresponding to our experience with studies of adult liver transplant recipients (17), we decided to include not only randomized trials but also non-randomized controlled trials and studies with prospective Exp and retrospective Cont in this review. Half of them compared IL-2RA to no add-on. The other half explored the effects of reduced or delayed concomitant immunosuppression. Therefore, we decided to include those studies to increase the total number of included trials. We also allocated them to predefined comparisons of concomitant medication. Furthermore, we included and pooled studies that used a different type of IL-2RA, had different concomitant medication (type of CNI and MMF), or had different follow-up times. Because all these differences may be sources of heterogeneity, it was planned to explore differences of effect by performing subgroup analyses. Because of the small number of included studies, some studies dominate the results as we have seen in analyses including Gibelli et al. (1) or Spada et al. (9). Both studies met the inclusion criteria. Due to the paucity of data on secondary outcomes, we were only able to extensively analyze the primary end-points. Another problem was the insufficient detailed reporting of outcomes; this was noticed most evidently regarding the ADR of immunosuppression. Few studies give data on complications and ADR, but also these were measured or grouped differently in the various trials. We endeavored to overcome this limitation by grouping data on side effects into broader categories, but this may further limit the interpretation of the results. However, we attempted to minimize publication bias by searching for and including data from different databases. Nonetheless, this systematic review and meta-analysis gives us a first impression of the evidence and the order of magnitude of the effect of using IL-2RA as an induction therapy in addition to standard double-drug or triple-drug therapy in pediatric liver transplant recipients. For further analysis, we require more studies, but we do not expect more data to accumulate over the next years. To gain information on long-term effects of reduced or delayed concomitant immunosuppression, which is urgently needed in pediatric liver transplant recipients, more prospective controlled trials are needed.

Clinical implications

Four pediatric patients would need to be treated with IL-2RA to prevent one AR (NNT $\approx$ 4). The risk reduction for AR is higher than would be expected from experience with adult liver transplantation (17) which could be a result of differences in the pediatric metabolism. We have no evidence for a difference in effectiveness between Bas and Dac in reducing the risk of rejection. In conclusion, the use of IL-2RA reduces the risk of AR without a significant increase of harmful effects. This effect may allow for reduction of coimmunosuppression to avoid the ADR of CNI or steroids. Also we observe a substantial reduction of the risk of steroid-resistant rejection, patient death, and graft loss using IL-2RA in addition to standard double-drug or triple-drug therapy, and therefore, we should value this result as clinical relevant.

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Authors' contributions

Nicola D. Crins: Participated in concept/design, data collection, studies selection, data analysis/interpretation, statistics; Dr. Christian Röver: Participated in statistics, critical revision of article, discussion of results, data extraction; Dr. Armin D. Goralczyk: Participated in concept/design, statistics, data collection, studies selection; Prof. Dr. Tim Friede: Participated in statistics, critical revision, discussion of results and problems, approval of article.

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