Basiliximab application on liver recipients: a meta-analysis of randomized controlled trials

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BACKGROUND: The benefits of the application of basiliximab induction therapy in liver transplantation are not clear. The present meta-analysis was to evaluate the pros and cons of basiliximab use in liver transplantation.

DATA SOURCES: We searched the associated publications in English from July 1998 to December 2015 in the following databases: MEDLINE, PubMed, Ovid, EMBASE, Web of Science and Cochrane Library.

RESULTS: Basiliximab significantly decreased the incidence of *de novo* diabetes mellitus after liver transplantation (RR=0.56; 95% CI: 0.34-0.91; *P*=0.02). Subgroup analysis showed that basiliximab in combination with steroids-free immunosuppressant significantly decreased the incidence of biopsy-proven acute rejection (RR=0.62; 95% CI: 0.39-0.97; *P*=0.04) and new-onset hypertension (RR=0.62; 95% CI: 0.42-0.93; *P*=0.02).

CONCLUSIONS: Basiliximab may be effective in reducing *de novo* diabetes mellitus. What is more, basiliximab in combination with steroids-free immunosuppressant shows statistical benefit to reduce biopsy-proven acute rejection and *de novo* hypertension.

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KEY WORDS: liver transplantation; basiliximab; induction; immunosuppression; meta-analysis

Introduction

Induction immunosuppression[1] is a short-term, intense therapy administered around the time of transplantation to prevent acute rejection (AR) in the first month post-transplant. Induction therapy is used widely in a variety of solid organ transplantations.[2-9] Since basiliximab, a strong immunosuppressant, was approved for clinical use,[10] researches have shown that basiliximab induction therapy reduces the incidence of acute cellular rejection without increasing the risk of infection or other side effects in renal transplantation.[11-15] However, the role of basiliximab induction therapy in liver transplantation remains contentious. The present meta-analysis was to evaluate the basiliximab induction therapy in liver transplantation and mainly on biopsy-proven AR (BPAR), graft survival, mortality and other adverse events.

Methods

Literature search

A systematic literature published in English from July 1998 (basiliximab was first approved for clinical use in 1998) to December 2015 was searched in the following databases: MEDLINE, PubMed, Ovid, EMBASE, Web of Science and Cochrane Library. The keywords used were "liver transplantation", "basiliximab", "simulect", "interleukin-2 receptor antagonist", "anti CD-25 monoclonal antibody", and abbreviations thereof. The key words were combined with appropriate Boolean operators. And for further relevant articles, we also checked the reference lists in all identified trials.

Inclusion and exclusion criteria

All prospective, controlled, randomized studies published as full papers or abstracts in which basiliximab was used to treat liver transplant recipients were reviewed. The inclusion criteria were: 1) patients underwent primary liver transplantation from a living or cadaveric donor; 2) the experimental group received basiliximab

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in combination with steroids-based/free immunosuppressant; 3) the control group received standard steroids induction therapy; 4) the stated primary outcomes and secondary outcomes were reported and all studies had a minimum follow-up duration of 12 months.

To avoid intrinsic bias, we excluded nonrandomized controlled studies and pharmacological studies that did not provide data on clinical outcome due to their short follow-up duration (less than 12 months). We also excluded trials with patients who underwent multi-organ transplantation or re-transplantation.

Outcomes

The primary outcomes analyzed were BPAR rate, graft survival, and mortality. Secondary outcomes were new-onset of hypertension and diabetes mellitus, overall infection, cytomegalovirus (CMV) infection, recurrence of hepatocellular carcinoma (HCC) and hepatitis C virus (HCV).

Data extraction and study quality

Data extraction was performed independently by two authors using a standardized form; any disagreement was resolved by discussion among all of the authors. The methodology quality of each trial was assessed according to the instructions given in the *Cochrane Handbook for Systematic Reviews of Intervention*, including blinding, randomization, allocation concealment, intention-to-treat (ITT) analysis, completeness of follow-up, and the method of handling missing values.

Statistical analysis

All statistical analyses were performed using RevMan 5.3 provided by Cochrane Collaboration. Pooled relative risk (RR) with 95% confidence intervals (CI) were calculated for each principal dichotomous variable outcome using either the fixed effects model or random effects model, where values of <1 favored basiliximab regimens and values of >1 favored basiliximab-sparing regimens. We analyzed heterogeneity among studies using Cochrane's Q test and calculating I^2, with $P<0.05$ used to denote statistical significance, and with I^2 calculated to measure the proportion of total variation in the estimates of treatment effect that was due to heterogeneity beyond chance.

Results

Trial selection

Database searches yielded 192 entries (Fig. 1), of which 20 were excluded as duplicates. Of the 172 publications that qualified for abstract review, 158 were excluded because they were not controlled trials. The remaining 14 trials underwent full article review and a further 8 publications were excluded mainly because they were entirely retrospective, or because of the short follow-up duration.

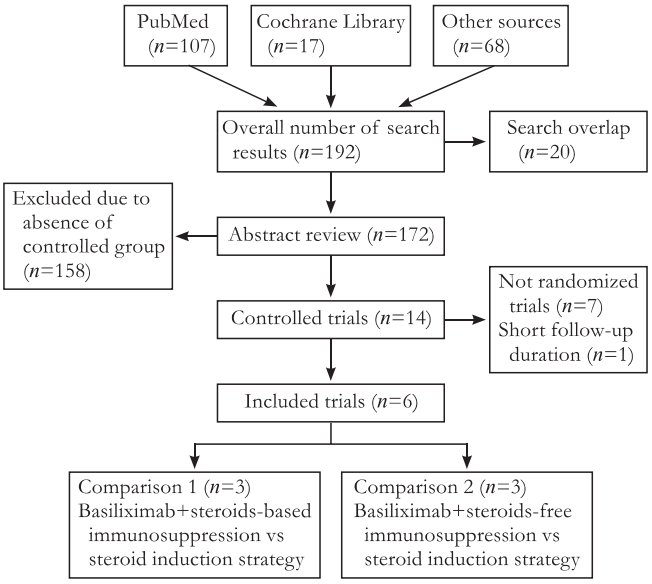

Fig. 1. Flow chart of publication search and selection.

A total of 6 randomized controlled trials (RCTs)[16-21] fulfilled the inclusion criteria, one[18] was in conference abstract. Among 887 patients in these trials, 446 treated with basiliximab regimens and 441 with basiliximab-sparing regimens.

Included trials in the systematic review

Previous literatures[22-25] showed that in liver transplantation, basiliximab was used in addition to standard immunosuppressant to reduce other immunosuppressive drugs, such as calcineurin inhibitor (CNI) and corticosteroids. We have therefore classified the 6 included trials into 2 comparisons: comparison 1, basiliximab is added to the steroids-based immunosuppressant, which is compared to steroid; comparison 2, basiliximab is added to the steroids-free immunosuppressant, which is compared to steroid.

Table 1 shows the characteristics of the included RCTs. Three trials[16, 20, 21] compared basiliximab in combination with steroids-based immunosuppressant to standard steroids; the other three trials[17-19] compared basiliximab in combination with steroids-free immunosuppressant to standard steroids. Four studies[16, 17, 20, 21] were restricted to adult patients and one[19] included only pediatric patients, whereas the study of De Simone et al[18] does not give any details on patients' age.

The trials had greatly varied follow-up durations from 12 to 114 months: four trials[16, 18, 19, 21] reported outcomes at 12 months, one[17] at 21.6 months and the remaming one[20] at 76-114 months.