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episodes in kidney transplant recipients (Review)
Webster AC, Wu S, Tallapragada K, Park MY, Chapman JR, Carr SJ
Webster AC, Wu S, Tallapragada K, Park MY, Chapman JR, Carr SJ. Polyclonal and monoclonal antibodies for treating acute rejection episodes in kidney transplant recipients. Cochrane Database of Systematic Reviews 2017, Issue 7. Art. No.: CD004756. DOI: 10.1002/14651858.CD004756.pub4.

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[Intervention Review]

Polyclonal and monoclonal antibodies for treating acute rejection episodes in kidney transplant recipients

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Editorial group: Cochrane Kidney and Transplant Group.

Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 7, 2017.

Citation: Webster AC, Wu S, Tallapragada K, Park MY, Chapman JR, Carr SJ. Polyclonal and monoclonal antibodies for treating acute rejection episodes in kidney transplant recipients. *Cochrane Database of Systematic Reviews* 2017, Issue 7. Art. No.: CD004756. DOI: 10.1002/14651858.CD004756.pub4.

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ABSTRACT

Background

Registry data shows that the incidence of acute rejection has been steadily falling. Approximately 10% to 35% of kidney recipients will undergo treatment for at least one episode of acute rejection within the first post-transplant year. Treatment options include pulsed steroid therapy, the use of an antibody preparation, the alteration of background immunosuppression, or combinations of these options. Over recent years, new treatment strategies have evolved, and in many parts of the world there has been an increase in use of tacrolimus and mycophenolate and a reduction in the use of cyclosporin and azathioprine use as baseline immunosuppression to prevent acute rejection. There are also global variations in use of polyclonal and monoclonal antibodies to treat acute rejection. This is an update of a review published in 2006.

Objectives

The aim of this systematic review was to: (1) to evaluate the relative and absolute effects of different classes of antibody preparation in preventing graft loss and resolving cellular or humoral rejection episodes when used as a treatment for first episode of rejection in kidney transplant recipients; (2) evaluate the relative and absolute effects of different classes of antibody preparation in preventing graft loss and resolving cellular or humoral rejection episodes when used as a treatment for steroid-resistant rejection in kidney transplant recipients; (3) determine how the benefits and adverse events vary for each type of antibody preparation; and (4) determine how the benefits and harms vary for different formulations of antibody within each type.

Search methods

We searched the Cochrane Kidney and Transplant Specialised Register to 18 April 2017 through contact with the Information Specialist using search terms relevant to this review.

Selection criteria

Randomised controlled trials (RCTs) in all languages comparing all mono- and polyclonal antibody preparations, given in combination with any other immunosuppressive agents, for the treatment of cellular or humoral graft rejection, when compared to any other treatment for acute rejection were eligible for inclusion.



Data collection and analysis

Two authors independently assessed the risk of bias of the included studies and extracted data. Statistical analyses were performed using a random-effects model and results expressed as risk ratio (RR) or mean difference (MD) with 95% confidence intervals (CI).

Main results

We included 11 new studies (18 reports, 346 participants) in this update, bring the total number of included studies to 31 (76 reports, 1680 participants). Studies were generally small, incompletely reported, especially for potential harms, and did not define outcome measures adequately. The risk of bias was inadequate or unclear risk for random sequence generation (81%), allocation concealment (87%) and other bias (87%). There were, however, a predominance of low risk of bias for blinding (75%) and incomplete outcome data (80%) across all the studies. Selective reporting had a mixture of low (58%), high (29%), and unclear (13%) risk of bias.

Seventeen studies (1005 participants) compared therapies for first acute cellular rejection episodes. Antibody therapy was probably better than steroid in reversing acute cellular rejection (RR 0.50, 95% CI 0.30 to 0.82; moderate certainty) and preventing subsequent rejection (RR 0.70, 95% CI 0.50 to 0.99; moderate certainty), may be better for preventing graft loss (death censored: (RR 0.80, 95% CI 0.57 to 1.12; low certainty) but there was little or no difference in death at one year. Adverse effects of treatment (including fever, chills and malaise following drug administration) were probably reduced with steroid therapy (RR 23.88, 95% CI 5.10 to 111.86; I² = 16%; moderate certainty).

Twelve studies (576 patients) investigated antibody treatment for steroid-resistant rejection. There was little or no benefit of muromonab-CD3 over ATG or ALG in reversing rejection, preventing subsequent rejection, or preventing graft loss or death. Two studies compared the use of rituximab for treatment of acute humoral rejection (58 patients). Muromonab-CD3 treated patients suffered three times more than those receiving either ATG or T10B9, from a syndrome of fever, chills and malaise following drug administration (RR 3.12, 95% CI 1.87 to 5.21; I² = 31%), and experienced more neurological side effects (RR 13.10 95% CI 1.43 to 120.05; I² = 36%) (low certainty evidence).

There was no evidence of additional benefit from rituximab in terms of either reversal of rejection (RR 0.94, 95% CI 0.54 to 1.64), or graft loss or death 12 months (RR 1.0, 95% CI 0.23 to 4.35). Rituximab plus steroids probably increases the risk of urinary tract infection/pyelonephritis (RR 5.73, 95% CI 1.80 to 18.21).

Authors' conclusions

In reversing first acute cellular rejection and preventing graft loss, any antibody is probably better than steroid, but there is little or no difference in subsequent rejection and patient survival. In reversing steroid-resistant rejection there was little or no difference between different antibodies over a period of 12 months, with limited data beyond that time frame. In treating acute humoral rejection, there was no evidence that the use of antibody therapy conferred additional benefit in terms of reversal of rejection, or death or graft loss.

Although this is an updated review, the majority of newer included studies provide additional evidence from the cyclosporin/azathioprine era of kidney transplantation and therefore conclusions cannot necessarily be extrapolated to patients treated with more contemporary immunosuppressive regimens which include tacrolimus/mycophenolate or sirolimus. However, many kidney transplant centres around the world continue to use older immunosuppressive regimes and the findings of this review remain strongly relevant to their clinical practice.

Larger studies with standardised reproducible outcome criteria are needed to investigate the outcomes and risks of antibody treatments for acute rejection in kidney transplant recipients receiving contemporary immunosuppressive regimes.

PLAIN LANGUAGE SUMMARY

Polyclonal and monoclonal antibodies for treating acute rejection episodes in kidney transplant recipients

What is the issue?

Kidney transplantation is the treatment of choice for most patients with end-stage kidney disease. Strategies to increase donor organ availability and to prolong the transplanted kidney's survival have become priorities in kidney transplantation. About 10% to 35% of all kidney transplant recipients will experience one episode of acute rejection in the first year. Options for treating these episodes include pulsed steroid therapy, the use of an antibody preparation, the alteration of background immunosuppression, or combinations of these options.

What did we do?

This review investigated the role of mono- or polyclonal antibodies in the treatment of acute cellular or acute humoral rejection in kidney transplant recipients. Thirty one studies (1680 patients) were included.

What did we find?

We identified 31 studies enrolling 1680 people. Any antibody was better than steroid treatment for reversing the first acute cellular rejection episode and preventing graft loss, but showed little or difference in reversing steroid-resistant rejection episodes. Polyclonal antibody-treated patients were more likely to experience an immediate reaction of fever, chills and malaise than those receiving steroid treatment.



Conclusions

Antibody treatment was better than steroid treatment for reversing first acute cellular rejection and preventing graft loss but this treatment was associated with a high incidence of adverse effects. The main limitation of this review is that many of the included studies were performed during the cyclosporin/azathioprine era of kidney transplantation and therefore conclusions cannot necessarily be extrapolated to patients treated with more contemporary immunosuppressive regimens which include tacrolimus/mycophenolate or sirolimus.