Expert Opinion

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Vaccines & Antibodies

Antibodies in the prevention of renal allograft rejection

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The rejection of renal allografts is mediated largely by the intragraft accumulation of alloreactive T lymphocytes. Current immunosuppressive drugs impair lymphocyte function, but also have specific toxicities and lead to nonspecific impairment of immune responses, resulting in an increased risk of infections and malignancy. Initial studies examined the usefulness of antibodies that depleted lymphocytes in preventing rejection. More recently, antibodies that impair lymphocyte function by blocking the interleukin-2 receptor-α (IL-2Rα), thereby reducing IL-2-mediated activation of T cells, were shown to reduce the risk of rejection. As an additional strategy, antibodies that impair lymphocyte trafficking have been investigated for their effect on acute rejection. This review describes the results of clinical trials of depleting antilymphocyte antibodies, IL-2Rα blockers and antibodies to intercellular adhesion molecule-1, lymphocyte function-associated antigen-1, CD154 and CD52 in the prevention of allograft rejection. Particular emphasis has been placed on therapies for which there is evidence obtained from good, randomised, controlled trials or registry data.

Keywords: antilymphocyte antibodies, interleukin-2, kidney, rejection, transplantation

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1. Introduction

The short-term results of renal transplantation are now excellent, with 1-year allograft survival rates of > 90%. Standard immunosuppressive regimes cause nonspecific immunosuppression, leading to infections and, in the long-term, malignancy in a proportion of patients. In addition, the mainstay immunosuppressants, the calcineurin inhibitors cyclosporin and tacrolimus, lead to nephrotoxicity and hypertension, and steroids have numerous well-recognised side effects. Adjunctive therapy with antibodies directed at lymphocytes opens up the possibility of improving graft outcome and at the same time minimising the toxicity associated with the use of other immunosuppressants.

2. Allograft rejection

The CD4+ T lymphocyte plays a critical role in allorecognition of donor antigens. Both indirect allorecognition (in which the T cell receptor binds to antigen presented as a peptide bound to the major histocompatibility complex [MHC] molecules of donor antigen-presenting cells) and direct allorecognition of intact donor MHC molecules play a role in transplant rejection [1,2]. T cell activation requires a second signal provided by costimulatory molecules on the antigen-presenting cell and this leads to IL-2 production (reviewed by Sayegh [3]). IL-2 is a potent stimulus to T cell proliferation and survival. These costimulatory molecules include B7-1 (CD80) and B7-2 (CD86), inducible costimulatory molecule (ICOS) ligand, PD-L1 and PD-L2, which ligate CD28 and ICOS on the T cell surface. Without secondary signals, the T cell undergoes anergy [4] or apoptosis [5]. CD28 upregulates

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CD40 ligand expression, which further stimulates B7 expression. Cytotoxic T lymphocyte antigen-4 and PD-1 are members of the CD28 family and are involved in downregulation of T cell responses. A further costimulatory molecule is CD154 (CD40 ligand) on T cells, which interacts with CD40 on antigen-presenting cells and enhances T cell activation, probably via an increase in the expression of B7 molecules. Alloantigen-activated CD4+ T cells promote the effector arm of the alloreaction process by activating CD8+ T lymphocytes, monocyte/macrophages and B lymphocytes.

3. Antibodies used in prevention of renal allograft rejection

The ideal immunosuppressant would specifically target only those T cells that have responded to donor antigen, thus leaving the immune system otherwise intact, and would also achieve donor-specific tolerance.

3.1 Non-selective depleting antibodies

3.1.1 Polyclonal antibodies

The first antibodies to be developed and used in renal transplantation were polyclonal antibodies directed against multiple T cell epitopes [6,7]. These were raised by immunising horses or rabbits with human lymphocytes (antilymphocyte globulin [ALG]) or thymocytes (antithymocyte globulin [ATG]). The IgG fraction of the antibodies was then purified. It is important to realise that there were considerable differences in these antibodies and batch-to-batch differences even in antibodies raised in a single species. These antibodies were initially used to treat acute rejection episodes, but have subsequently been widely used as induction therapy to prevent rejection.

3.1.2 Monoclonal antibodies

OKT3 is a murine monoclonal IgG2a antibody directed against the CD3 molecule in the T cell receptor complex. OKT3 is a depleting antibody that is used as induction therapy following renal transplantation and also to treat rejection [8,9].

3.2 Non-depleting antibodies

3.2.1 IL-2 receptor-α antibodies

IL-2 receptor-α (IL-2Rα) blockade with anti-CD25 monoclonal antibodies inhibits T lymphocyte proliferation. As the α-subunit is only expressed on activated T lymphocytes, monoclonal antibodies against the IL-2Rα offer immunosuppression that is targeted at activated lymphocytes. The original IL-2 monoclonal antibodies were rapidly degraded because of the development of human anti-rat or anti-mouse antibodies. Through genetic engineering, these antibodies have been modified to fuse either the entire variable region of the mouse antibody to human heavy and light chain constant regions (basiliximab [Simulect®; Novartis Pharmaceuticals Corporation]) or murine hypervariable regions to the human IgG molecule (daclizumab [Zenapax®; F. Hoffmann-La Roche, Inc.]).

3.3 Antibodies that block lymphocyte trafficking

Adhesion molecules coordinate lymphocyte migration to sites of inflammation. Monoclonal antibodies to lymphocyte function-associated antigen (LFA)-1 and intercellular adhesion molecule (ICAM)-1 have been developed and studied in patients receiving renal allografts.

4. Polyclonal depleting antibodies (ATG, ALG)

Antithymocyte (lymphocyte) antibodies act by depleting lymphocytes through antibody-dependent cell-mediated cytotoxicity, complement activation and opsonisation and clearance. Preparations available at present comprise rabbit ATG and equine ATG. These antibodies are given as induction therapy for 7 – 14 days following renal transplantation, and this allows withholding of cyclosporin until graft function is established.

4.1 Early studies

Antilymphocyte antibodies have been used in transplantation since the 1960s and were initially introduced to treat acute rejection in patients on prednisolone and azathioprine. More recently, they have been used as induction therapy in patients on calcineurin inhibitors. The early studies in the precalcineurin era suggested that antilymphocyte antibodies reduced the risk of acute rejection [10-13] or were of no benefit [14-16]. In the Medical Research Council study, the use of antilymphocyte antibodies was associated with an excess risk of fatal infections as compared with controls [16].

4.2 Studies in the calcineurin era

There have been many cohort and randomised controlled studies of antilymphocyte antibodies in patients on calcineurin inhibitors [17-19]. The accepted advantage of these antibodies was that they provided effective immunosuppression during a period of delayed graft function and, therefore, allowed the introduction of potentially nephrotoxic calcineurin inhibitors to be delayed. The Transplant Community has been divided into two camps; one, which uses antilymphocyte antibody induction, and the other, which, like the authors, does not. Some studies of induction therapy with antilymphocyte antibodies showed benefit in terms of a reduction in acute rejection, whereas others did not. The evidence for the utility of these antibodies in renal transplantation is considered later.

4.3 Polyclonal antilymphocyte antibodies: side effects

Because these antibodies are non-human, they induce an antibody response in patients that may rarely lead to serum sickness and, in addition, limits their repeated use. They are commonly associated with systemic reactions, such as fever and chills, and with neutropenia and thrombocytopenia [20,21]. More importantly, these antibodies are associated with an increased risk of infections, particularly cytomegalovirus (CMV) infections, and malignancy.

5. Monoclonal depleting antibodies

5.1 Monoclonal antibody to CD3 (OKT3, muromonab-CD3)

OKT3 is a mouse monoclonal IgG2a antibody that reacts with the T cell/CD3 complex on T cells, thereby blocking its effector function and also causing activation with cytokine release. OKT3 is a depleting antibody that is given intravenously for 10 – 14 days as induction therapy following renal transplantation [22]. One reason for its use is that it allows delayed introduction of cyclosporin, avoiding the potential for nephrotoxicity in the early post-transplant period.

5.2 Randomised controlled studies

OKT3 was initially introduced to treat rejection in patients undergoing renal transplantation [9]. Subsequently, OKT3 was used as induction therapy following renal transplantation, usually with the delayed introduction of cyclosporin. There were many small cohort studies and several randomised controlled trials, but many of these were small and lacked statistical power. Norman and colleagues [23] randomised 215 cadaveric allograft recipients to treatment with steroids, azathioprine and cyclosporin (n = 102) or with OKT3 (5 mg/day i.v. for 10 – 14 days), steroids, azathioprine and the delayed introduction of cyclosporin on day 11 postoperatively (n = 105). Patients treated with OKT3 had fewer rejection episodes than control patients (51 versus 66%; $p = 0.032$). Graft survival at 2 years was better at 84% in OKT3-treated patients than in control patients (75%), but the difference was not significant ($p = 0.077$). There were no differences in overall infections and although more OKT3-treated patients than control patients had CMV infections (13 versus 5%), the difference was not significant ($p = 0.055$). In another study, 108 recipients of cadaveric renal allografts were randomised to treatment with OKT3 (5 mg/day i.v. for 14 days), steroids, azathioprine and the delayed introduction of cyclosporin (day 11, postoperatively) (n = 56), or to treatment with steroids, azathioprine and cyclosporin (n = 52) [24]. Rejection episodes occurred less frequently in OKT3-treated patients (61/1455 patient months) than in control patients (81/1320 patient months; $p < 0.05$). There was no difference in overall graft survival (83% in OKT3-treated patients and 75% in control patients, $p = 0.12$) or in patient survival. The combined results from the above two trials [25] showed that actuarial graft survival was significantly higher in OKT3-treated patients (83.6%) than in control patients (73.6%) ($p = 0.03$) at 2 years, but not at 5 years, when it was 71.2 and 65%, respectively ($p = 1.52$). The Spanish Monotherapy Study Group randomised first cadaveric allograft recipients aged > 50 years to treatment with cyclosporin monotherapy (n = 41), OKT3 (5 mg/day i.v. for 4 days) followed by cyclosporin monotherapy (n = 41), or steroids and cyclosporin (n = 44) [26]. Acute rejection occurred more often in patients on cyclosporin monotherapy (73%) than in patients treated with OKT3 and cyclosporin (54%; $p < 0.05$) or in patients treated with steroids and cyclosporin (41%; $p < 0.01$). Actuarial graft and patient survival was comparable in the three treatment groups. A retrospective study of the United Network for Organ Sharing Registry of 24191 cadaveric renal transplant procedures from October 1987 to January 1991 showed that the use of OKT3 for ≥ 7 days was associated with improved graft survival at 60 and 400 days when compared with patients not receiving antilymphocyte antibody therapy [27].

5.3 OKT3 side effects

The first doses of OKT3 may be associated with fevers, chills, headaches and hypotension due to the release of cytokines including TNF-α, IL-2, IL-6, IL10 and IFN-γ [28,29]. Less commonly, there may be more severe illness, including pulmonary oedema or aseptic meningoencephalitis, which may cause fits in some instances, and allograft thrombosis [9,30]. High-titre human anti-mouse antibodies develop in 5.8% of patients and this may limit further use of OKT3 [31].

6. Meta-analysis of depleting antilymphocyte antibodies in renal transplantation

There have been several randomised and many non-randomised studies of the efficacy of antilymphocyte antibodies in renal transplantation in the calcineurin era. Most of these studies were too small to demonstrate benefit in terms of allograft survival.

The question of efficacy was studied in a meta-analysis of seven randomised clinical trials [32]. Background immunosuppression was with cyclosporin, prednisolone and azathioprine, and induction therapy was with OKT3 in three trials [23,24,26] and antilymphocyte or antithymocyte antibodies in four trials [17-19,33]. The meta-analysis showed a rate ratio for allograft failure at 2 years of 0.69 (95% confidence interval [CI] 0.49 – 0.97; $p = 0.03$), indicating benefit from antibody therapy. A subsequent meta-analysis from the same authors [34] using individual patient data and a 5-year follow-up from five of these studies where it was available (three with OKT3 [23,24,26] and two with antilymphocyte globulin [18,33]) showed that antibody therapy reduced allograft failure as compared with controls at 2 years (rate ratio 0.62; 95% CI 0.43 – 0.90; $p = 0.012$), but not at 5 years (rate ratio 0.82; 95% CI 0.62 – 1.09; $p = 0.17$). Antibody therapy was associated with an improved outcome at five years in presensitised patients (rate ratio 0.20; 95% CI 0.09 – 0.47; $p = 0.001$). There was no evidence of benefit in African–Americans, patients with previous transplants and patients with delayed graft function. The conclusion from these studies was that antilymphocyte antibodies were of short-term benefit in all patients (for up to 2 years) and of long-term benefit only in presensitised patients. The key question is whether these short-term benefits outweigh their toxicity.

7. Side effects of depleting antilymphocyte antibodies

In a registry study, Meier-Kreische *et al*. studied 73,707 primary renal transplants reported to the USRDS database between 1988 and 1997 [35]. Thirty two per cent of these patients received antibody induction with either polyclonal antibodies or OKT3. Antibody induction was associated with an overall increased risk of early death within 6 months of transplantation, with a relative risk (RR) of 1.13 (CI: 1.04 – 1.22). There was also an increased risk of infection-related death (RR = 1.32; CI: 1.14 – 1.45). In a long-term follow-up, antibody induction was associated with an overall risk of patient death (RR = 1.10; CI: 1.05 – 1.15), increased risk of cardiovascular death (RR = 1.117; CI: 1.10 – 1.25), infection-related death (RR = 1.16; CI: 1.04 – 1.30) and death due to malignancy (RR = 1.35; CI: 1.15 – 1.59). Other studies have shown an increased risk of infections, particularly of CMV infections [36,37], and also of post-transplant lymphoproliferative disorder [38,39]. These risks must be balanced against the potential benefits of antilymphocyte antibody induction.

8. Antibodies against the IL-2 receptor

8.1 IL-2 and its receptor

Following activation, CD4+ T cells produce IL-2, which is an autocrine growth factor that stimulates T cell proliferation and cytokine production [40]. IL-2 acts on the IL-2 receptor, which consists of three transmembrane, non-covalently associated proteins, α (CD25) (Tac), β (CD122) and γ (CD132) [41,42]. IL-2Rα is not expressed on resting T cells and is induced by activation such as that induced by alloantigens. IL-2Rα binds to IL-2Rβ and IL-2Rγ to form the high affinity IL-2R. The IL-2R shares the β- and γ- chain with the IL-15 receptor and the γ-chain with the IL-4, IL-7 and IL-9 receptors [41]. Natural killer cells express functional IL-2Rβ and IL-2Rγ, which allows these cells to be spontaneously responsive to IL-2. Stimulation of the IL-2R evokes rapid tyrosine kinase phosphorylation of Janus kinase (JAK)-1 and JAK-3, which results in phosphorylation and nuclear translocation of signal transducer and activator of transcription (STAT)-3 and STAT-5 [43]. Since IL-2Rα is only expressed by activated T cells, this provides a logical basis for the development of blocking antibodies, which would be expected to be immunosuppressive.

8.1.1 Early studies in humans

Initial studies were with rat or murine monoclonal antibodies directed at the IL-2Rα (Tac). In 1987, Soulillou *et al*. [44] reported that administration of a rat monoclonal antibody to the IL-2Rα to renal transplant recipients treated with prednisolone and azathioprine reduced the rate of rejection as compared with historical controls. In a subsequent randomised controlled trial, they reported that this antibody was as effective as rabbit antilymphocyte globulin in preventing rejection and was associated with fewer infections and side effects [45]. The studies of Kirkman *et al.* with a murine anti-IL-2Rα monoclonal antibody [46], Kriaa *et al.* with a rat monoclonal anti-IL-2Rα antibody, and Van Gelder with a murine monoclonal anti-IL-2Rα antibody [47] confirmed the efficacy of this approach. However, the use of these antibodies was associated with the development of human anti-rat or anti-mouse antibodies, with the potential for loss of efficacy.

This prompted the development of humanised and chimaeric antibodies which were predicted to be less likely to induce an immune response. Two such antibodies, daclizumab and basiliximab, have now been licensed for clinical use.

8.1.2 Pharmacokinetics

8.1.2.1 Daclizumab

Daclizumab is a recombinant, humanised IgG1 antibody that binds with high affinity to the IL-2Rα and inhibits IL-2 binding and lymphocyte activation (reviewed in [101]). At a dose of 1 mg/kg i.v. every 14 days, the mean (sd) peak serum concentration rose from 21 ± 14 μg/ml after the first dose to 32 ± 22 μg/ml at the fifth dose, and at this latter time the mean trough serum concentration was 7.6 ± 4 μg/ml. These levels were adequate to saturate the IL-2Rα. The estimated terminal elimination half-life was 20 days. Between 12 and 22% of patients in the initial studies developed antibodies to daclizumab, but these did not appear to affect the pharmacokinetics or efficacy of daclizumab.

8.1.2.2 Basiliximab

Basiliximab is a chimaeric human/mouse antibody that has a high affinity for the IL-2Rα. In a pharmacodynamic study, peak levels were 9.3 ± 4.5 μg/ml after a 40 mg dose and 11.6 ± 4.2 μg/ml after a 60 mg dose of basiliximab. The estimated terminal half-life was 6.5 ± 2.1 days and the period of time that serum drug concentrations exceeded concentrations that are known to saturate IL-2Rα was 26 ± 8 days at the 40 mg dose and 32 ± 11 days at the 60 mg dose [48]. Thus, these doses would maintain saturation of the IL-2Rα for a 4 – 6-week period post-transplantation. No anti-idiotypic antibodies were seen in these studies [48].

8.1.2.3 Randomised controlled trials

There are now at least eight randomised controlled trials of IL-2Rα antibodies versus placebo or no treatment in patients undergoing a renal transplant. The first studies were with monoclonal murine or rat antibodies [46,47] which, although effective in reducing the incidence of acute rejection, were associated with the development of anti-mouse and anti-rat antibodies. Subsequently, there have been four randomised controlled trials using basiliximab [49-52] and two using daclizumab [53,54].

8.1.2.4 IL-2 receptor antibodies: meta-analysis

The authors recently reported a meta-analysis of these eight trials, which involved a total of 1858 patients [55]. The trial characteristics are shown in Figure 1. In four trials, immunosuppression was with prednisolone and cyclosporin [47,49,50,54]; three trials used prednisolone, azathioprine and cyclosporin [46,52,53]; one

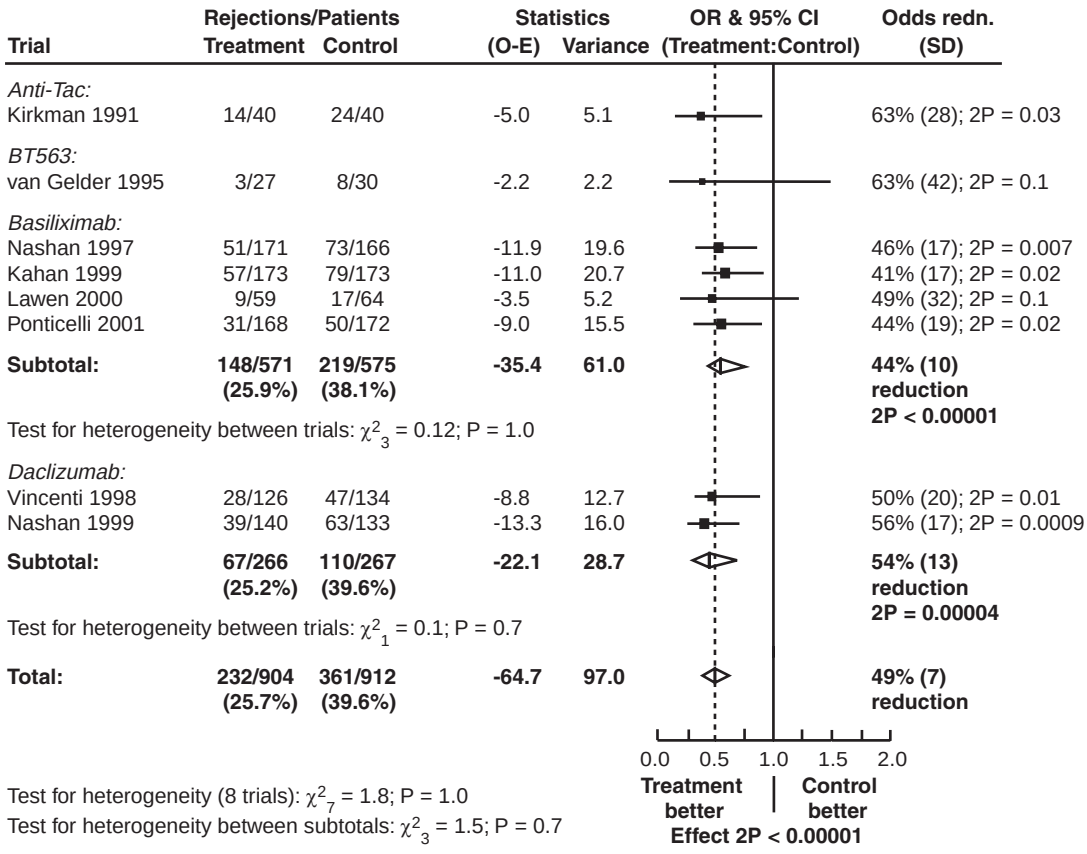

Figure 1. Incidence of acute rejection by type of IL-2 receptor antibody. Note that only overall follow-up data (6 – 26 months) for anti-Tac (Kirkman) and 12-week data for BT563 (van Gelder) were available. Reprinted with permission from the BMJ Publishing Group: *BMJ* 2003; **326**:789; Adu D *et al*.

CI: Confidence interval; E: Expected; O: Observed; SD: Standard deviation.

trial was with prednisolone, cyclosporin and mycophenolate mofetil [51]. Treatment with IL-2R antibodies was associated with a highly significant reduction in episodes of acute rejection at 6 months (OR 0.51; 95% CI 0.42 – 0.62) ($p < 0.0001$) (Figure 1), but with no significant reductions in graft loss (0.78; 0.58 – 1.04) ($p = 0.09$) or in patient mortality at 1 year (0.75; 0.46 – 1.23) ($p = 0.3$). Treatment with IL-2R antibodies had no significant effect on overall infections (0.97; 0.77 – 1.24) ($p = 0.8$) or on CMV infections (0.81; 0.62 – 1.04) ($p = 0.1$). There was no difference in the risk of lymphoma or other malignancies at 1 year (0.82; 0.39 – 1.70) ($p = 0.6$). The effect on acute rejection was similar for all the anti-IL-2R antibodies. The size of the reduction in acute rejection was comparable in patients treated with cyclosporin and prednisolone (OR 0.52; 95% CI 0.40 – 0.67) ($p < 0.0001$), with cyclosporin, prednisolone and azathioprine (0.5; 0.36 – 0.71) ($p < 0.0001$) or with cyclosporin, prednisolone and mycophenolate mofetil (0.51; 0.22 – 1.21) ($p = 0.1$) (Figure 2). There was no evidence of heterogeneity between the trials for any of the outcomes.

This meta-analysis confirms that the addition of IL-2R antibodies to standard cyclosporin-based immunosuppression provides a very large benefit, with a highly significant 49% reduction in episodes of biopsy-proven acute rejection at 6 months. Although no other end point was statistically significant, both graft loss and mortality were nonsignificantly reduced by IL-2R antibodies and there was no evidence of adverse effects in terms of an increased incidence of infections or risk of malignancy. A reduction in the rate of acute rejection is highly important in renal transplantation, as one or more episodes of acute rejection is associated with a ≥ 50% reduction in long-term graft survival. Because of the excellent overall 1-year graft survival results for renal transplantation of ~ 90% [56,57], the impact of a reduction in acute rejection or graft loss will require a longer duration of follow-up than the 1 year used in these studies.

In this analysis, there was no evidence of any increase in the incidence of infections or malignancies in patients treated with IL-2R antibodies when compared with the placebo group. This is particularly important, as previous analyses of treatment with antilymphocyte antibodies in renal allograft recipients have shown an increased risk of these complications following transplantation. Finally, there was some suggestion of a reduction in the incidence of CMV infections in IL-2R-treated patients as compared with placebo controls.

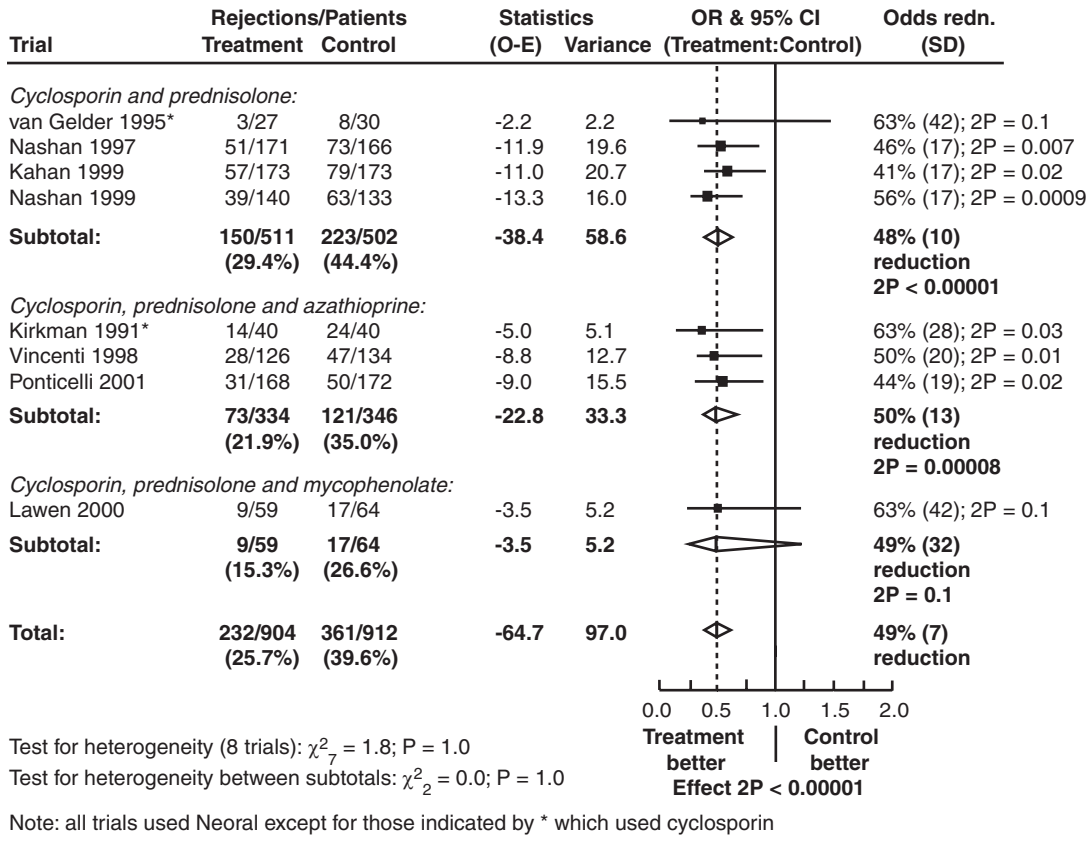

Figure 2. Incidence of acute rejection at 6 months by immunosuppression regimen. Reprinted with permission from the BMJ Publishing Group: *BMJ* 2003; **326**:789; Adu D *et al*.
CI: Confidence interval; E: Expected; O: Observed; SD: Standard deviation.

8.1.2.5 Live donor transplants

The use of basiliximab in live donor transplant recipients was examined using cyclosporin, azathioprine, steroids and basiliximab or placebo [58]. These patients were followed for 3 years. There was significant reduction in acute rejection in the first year and subsequent reduction in the use of steroids. Post-transplant complications were similar in the two groups.

9. IL-2Rα antibodies compared with OKT3 and ATG/ALG

The efficacy and safety of IL-2Rα antibodies are well-established. The question arises as to whether these antibodies are as effective as antithymocyte globulin (ATGAM®; Pharmacia & Upjohn Pharmaceuticals) in reducing the risk of rejection and whether they are also safer. Sollinger *et al*. conducted a randomised, controlled study comparing basiliximab, 20 mg i.v. on days 0 and 4, with ATGAM 15 mg/kg/day beginning within 48 h of transplantation and continuing for up to 14 days [59]. Background immunosuppression was with cyclosporin, prednisolone and mycophenolate mofetil. The rates of biopsy-proven rejection episodes and of graft losses were comparable in basiliximab and ATGAM-treated patients at 21.4 and 23.1%, respectively. Patient and graft survival rates were comparable at 1 year and adverse drug-related events were more common in ATGAM-treated patients (42%) than in patients on basiliximab (11%). The authors concluded that basiliximab was as effective as ATGAM, had fewer side effects and was more convenient to use. A further randomised, controlled trial in recipients of first cadaveric transplants compared basiliximab 20 mg on days 0 and 4, with thymoglobulin 1 – 1.5 mg/kg/day starting within 24 h of transplantation and adjusted to maintain CD2+ and CD3+ lymphocyte counts to < 20/mm^3 [21]. Immunosuppression was with cyclosporin, prednisolone and mycophenolate mofetil. The rate of biopsy-proven rejection was identical at 8%, as was patient and graft survival at 1 year. Symptomatic CMV infections were more common in thymoglobulin-treated patients (12%) than in basiliximab-treated patients (6%). In a third study that has so far only been published in abstract form, Brennan and colleagues randomised high-risk patients to treatment with thymoglobulin or basiliximab [60]. These patients had one or more of the following risk factors: panel-reactive antibodies of > 20%, prolonged cold ischaemic time, six antigen mismatch, were African–Americans and non-heart beating donors. The immunosuppression used was cyclosporin, prednisolone and mycophenolate mofetil. At a mean follow-up of 9.8 ± 3.9 months,

the rate of acute rejection was lower in thymoglobulin-treated patients (14.2%) than in basiliximab-treated patients (25%), $p < 0.013$. As expected, leukopenia and thrombocytopenia were more common in the thymoglobulin group. There were three malignancies in the thymoglobulin-treated patients and one in the patients on basiliximab.

10. Antibodies that block lymphocyte trafficking

10.1 Monoclonal antibodies to the adhesion molecules LFA-1 and ICAM-1

Transmigration of lymphocytes across endothelium to sites of inflammation such as those seen in the allograft reaction is dependent on the regulated expression of adhesion molecules on lymphocytes and endothelium [61]. During this process, lymphocytes bearing the integrins LFA-1 (CD11a/CD18) and very late antigen-4 (CD49d/CD29) bind to endothelial ICAM-1 and vascular cell adhesion molecule-1, respectively. LFA-1 can also act as a costimulatory molecule in T cell/antigen-presenting cell interaction. Animal allograft models showed that antibodies to ICAM-1 or LFA-1 ameliorated the severity of rejection.

10.1.1 Anti-ICAM-1 in renal transplantation

In a randomised controlled trial, cadaveric renal allograft recipients were randomised to treatment with a mouse monoclonal IgG_{2a} antibody directed at ICAM-1 (enlimomab) (n = 131) or to placebo (n = 131) [62]. Background immunosuppression consisted of cyclosporin, prednisolone and azathioprine. There were no significant differences in the rate of acute rejection, delayed graft function or infections, and graft and patient survival at 1 year was comparable. The conclusion was, therefore, that at the doses given, enlimomab was not effective in preventing rejection.

10.1.2 Anti-LFA1 in renal transplantation

There are preliminary studies of a humanised IgG1 monoclonal antibody directed against the CD11a chain of LFA-1 (odulimomab). In a multi-centre randomised study comparing anti-LFA-1 (n = 52) with ATG (n = 49) in patients treated with cyclosporin, azathioprine and prednisolone, there were comparable amounts of rejection, but in the anti-LFA-1 group there were more early episodes of rejection [63]. Anti-LFA-1 was well-tolerated and there was less delayed graft function in the group in which it was used. However, a recent study of efalizumab, a humanised monoclonal antibody to CD11a, reported that of 10 patients given this antibody at a dose of 2 mg/kg together with cyclosporin and mycophenolate mofetil, 3 developed post-transplant lymphoproliferative disorder [64].

11. Other antibodies

11.1 Anti-CD154

The CD154–CD40 pathway provides important costimulation to T cell activation, and blockade of this pathway using anti-CD154 prevented renal allograft rejection in rhesus monkeys [65]. However, thromboembolic complications developed in monkeys given anti-CD154 [66] and also in patients given the humanised anti-CD154 monoclonal antibody (hu5c8). A recent study in patients with systemic lupus erythematosus who were given a different humanised anti-CD154 monoclonal antibody (IDEC-131) reported no evidence of thromboembolic events [67].

11.2 CAMPATH-1

CAMPATH-1 is a monoclonal-depleting antibody directed against CD52 antigen, which is a glycoprotein abundantly expressed on lymphocytes and monocytes. A humanised anti-CD52 monoclonal antibody (CAMPATH-1H) has been used as prophylaxis in cadaveric renal allograft recipients together with cyclosporin monotherapy. The results were promising, but further studies will be required to establish its role in renal transplantation [68].

12. Conclusions/expert opinion

Induction antilymphocyte antibody therapy aimed at reducing the risk of acute rejection has been in use for ~ 30 years. During this time, immunosuppressive strategies have evolved from prednisolone and azathioprine to include drugs such as the calcineurin inhibitors, mycophenolate mofetil and sirolimus. Evaluating the evidence for the effectiveness and safety of antibody therapy on the background of these changes in immunosuppression is difficult. Because of the cytokine release syndrome, OKT3 is now not widely used for induction therapy. Depleting antibodies such as ATGAM and thymoglobulin, although effective, have substantial toxicity. The balance of evidence suggests that anti-IL-2Rα antibodies are as effective as antithymocyte globulin in reducing the risk of rejection in patients at low risk of graft failure. Limited data suggests that antithymocyte globulin may be more effective in highly sensitised patients or patients who are at high risk of graft failure. The potential benefit must, however, be balanced against the long and short-term toxicities.

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