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REVIEW OF ANTI-CD25 MONOCLONAL ANTIBODIES

in SOLID ORGAN TRANSPLANTATION

A Position Statement of the NSW Therapeutic Assessment Group Inc.

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EXECUTIVE SUMMARY

Solid organ transplantation is an established treatment entity for organ failure. Rejection remains a cause of patient morbidity and of graft loss both in the short and long term. There has been a marked increase in the number and types of immunosuppressive agents developed over the last decade. This has resulted in the ability to successfully rescue the majority of allografts with steroid resistant rejection. These newer agents have generally resulted in better prevention and/or treatment of rejection. There has not, however, been any improvement in the toxicity profile of immunosuppressive drugs and indeed, agents such as the anti-CD3 antibodies have greatly increased the incidence of side effects, including neoplasia and infection. In addition, each new therapy has been expensive, rendering cost benefit issues critical in the use and evaluation of individual agents

Advances in monoclonal antibody (Mab) technology have resulted in a new clinically viable class of immunosuppressives being developed against a large number of antigens known to play a role in allorecognition. The anti-CD25 (anti-IL-2R α) monoclonal antibodies basiliximab (Simulect®) and daclizumab (Xenapax®) are the first of these new Mabs approved for use in the prevention of rejection in renal transplantation.

Basiliximab and daclizumab are identical in their antigenic specificity but have different structures (chimaeric versus humanised), dosage regimens (two doses versus five) and half lives (7 versus 20 days). Nevertheless, these differences do not appear to have a clinically significant impact in antigenicity, efficacy or tolerability. The agents have not been compared directly in clinical studies.

Basiliximab and daclizumab have marketing approval for renal transplantation in many countries, and apparently lack toxicity. Their approval resulted from four large Phase III trials in prophylaxis of rejection in primary renal allograft recipients. The results between the trials and the two agents were remarkably uniform with a reduction in acute rejection by one third compared to standard therapy. No side effects attributable to these Mabs were reported. Anti-CD25 Mabs have therefore provided an immunosuppressive effect without apparent collateral damage to other organs or increase in infections.

Controlled trials to date only provide evidence for use of these agents in prevention of acute rejection in renal transplantation. There are no similar Phase III studies in other solid organ transplants available. The uniform use of these drugs in all renal recipients is, however, difficult to justify. Firstly, such a practice would have significant cost implications, with a course of Mab costing about \$6000-\$8000. In addition, the incidence of acute rejection in renal transplantation is 20-40%. Of these, only a minority are steroid resistant and less than 50% are recurrent. Uniform use in all recipients (as suggested by trial data and approved indication) would therefore result in an unnecessary increase in immunosuppression in the majority of patients. It is important to note that these agents have not had an impact on 12 month graft survival.

The efficacy and lack of toxicity do, however, make Basiliximab and Daclizumab attractive immunosuppressives and their exact role needs to be further explored. It is tempting, for example, to propose that their use is indicated in recipients at high risk of rejection. However,

their efficacy in these cohorts (regrafts, sensitised or poorly matched recipients) needs to be examined, as does their efficacy compared to the anti-CD3 preparations often used in these patients with associated high levels of toxicity.

Nephrotoxicity and acute rejection have been shown by multivariate analysis to be the most significant predictors of chronic allograft nephropathy, which remains the main cause of graft loss. Sparing the use of cyclosporin or tacrolimus and reduction of acute rejection therefore remain important goals in transplantation. Anti-CD25 Mabs may potentially allow a reduction in other more toxic baseline immunosuppressive drugs such as cyclosporin. To date, the well tolerated degree of immunosuppression provided by anti-IL-2R Mabs has been against a background of standard immunosuppression with other agents. How immunosuppressive these monoclonals are by themselves remains to be seen. A third of patients on effective CD25 Mab treatment experience an acute rejection.

The role of these agents in the treatment of rejection has not been systematically evaluated.

At present the exact clinical role of anti-CD25 Mabs in solid organ transplantation can only be defined by further controlled clinical trials.

1. INTRODUCTION

The increasing number of relatively new immunosuppressive agents now available for use in organ transplantation raises the issue of appropriate indications and carries significant cost implications. Data from clinical trials help delineate some of these issues but lack of study in other areas make the definition and justification of use difficult.

This review presents available data for the two recently marketed formulations of anti-CD25 (anti-IL-2 α receptor) monoclonal antibodies (Mabs), basiliximab and dacluzimab, in an attempt to define their clinical role in solid organ transplantation.

1.2 History of Immunosuppression for Solid Organ Transplantation

There has been a marked increase in both number and type of immunosuppressive agents available for solid organ transplantation over recent years. This trend reflects the delineation of the components of the allorecognition pathway at a molecular level. New agents are consequently being formulated to target various stages of the process with many of these able to act in an additive or indeed synergistic manner. The generation of new immunosuppressive modalities seeks to reduce the incidence and severity of rejections without augmenting immunosuppression related toxicities such as neoplasia and infection.

Until this decade there were essentially four agents used for immunosuppression in solid organ transplant recipients. Prednisone and azathioprine were in use when transplantation became a treatment entity. The calcineurin inhibitor, cyclosporin, became available in the early 1980s and created the standard 'triple therapy' approach, which has been adopted by the majority of units for induction and maintenance therapy and which has significantly improved short term

graft survival. The next major advance in transplantation therapy was the development of initially polyclonal then monoclonal anti-T cell agents. The latter, for the first time, provided a means of 'rescue' for steroid resistant acute rejections as well as the ability to augment the level of immunosuppression in high risk recipients by forming part of the 'induction' therapeutic regimen.

In 1993-1995 the introduction of two agents: a calcineurin inhibitor tacrolimus (Prograf®) and a purine antagonist Mycophenolate mofetil (Cellcept®) increased treatment options and provided further means of allograft rescue. More recently, rapamycin has been marketed in some countries (not Australia as yet) and again increased the therapeutic armamentarium in transplantation. Each of the new agents introduced in this decade has been shown to reduce rates of acute rejection, although this has not so far impacted on graft or patient survival rates. The indication/s for use of each agent or each potential combination of agents is complex and remains, where defined or critically studied, dependent on a number of variables.

The refinement and availability of monoclonal antibody technology over the last decade has resulted in a new and expanding class of immunosuppressive therapy. Monoclonal antibodies, initially xenogenic in nature, are now chimaeric or humanised preparations, increasing their ability to provide a viable therapeutic modality. This has led to the formulation of a large number of antibodies targeting an increasing number of antigenic entities along the pathway of allorecognition and rejection. The selection of target antigens expressed on a limited population of cells can reduce immunosuppressive toxicity while still maintaining immunosuppressive activity. Although a multitude of structures have been formulated and evaluated both in animal and human models, only the anti CD3 preparations and more recently anti-CD25 agents have been marketed. The latter of these is the subject of this review. A number of other antibodies, in particular those targeting the CD40- CD40ligand and the B7- CD28 co-stimulation pathways of T cell activation, are currently in varying stages of development and remain likely candidates for clinical use in the future.

1.3 Background to Rationale for Anti-CD25 Mabs

Rejection remains the main cause of allograft failure. Immunosuppression is aimed at prevention of acute and if possible chronic rejections. Acute rejection may result in short term graft loss and is a major risk factor for development of chronic allograft nephropathy and graft loss.

Interleukin-2 (IL-2) mediated activation of lymphocytes is the major pathway in the cellular immune response mounted by the host against organ allografts. IL-2, a 15.5kDa glycoprotein, is a critical cytokine largely mediating the clonal expansion of antigen specific T cells. Activation of T cells results in up-regulation of the IL-2 Receptor (IL-2R), which on binding IL-2 triggers the intracellular signalling pathways for productive activation.

The IL-2R and Its Signalling Pathway

During the process of allorecognition, IL-2 binds to its high affinity receptor on the surface of antigen activated T cells. The IL-2R comprises three non-covalently bound chains: the alpha chain (IL-2R α , Tac, later designated CD25, 55 kDa); the beta chain (IL-2R β , CD122,

70/75kDa) and the gamma chain (IL-2R γ , CD132, 64 kDa). CD122 and CD132 (IL-2R β , IL-2R γ) are expressed on resting T cells. In contrast, the level of expression of CD25 (IL-2R α) is low on resting T cells but is induced after allogeneic stimulation following grafting and is restricted to the activated T lymphocyte sub-population.

The expression of all three receptor subunits confers high affinity binding status to the IL-2R for IL-2. CD25 does not transduce a signal but is responsible for the rapid association of IL-2 with the beta and gamma chains of the IL-2R, which in turn trigger the antigen activated T lymphocyte to undergo clonal expansion.

The IL-2R in T cells and natural killer cells does not possess intrinsic protein tyrosine kinase domains; but receptor stimulation evokes rapid tyrosine phosphorylation of intracellular proteins including the receptors themselves. The IL-2R binds Jak1 and Jak3 – members of Janus kinase (Jak) family of protein tyrosine kinases. Jak activation by IL-2 in turn leads to phosphorylation and nuclear translocation of STAT-3 and STAT-5 – two members of the transcription factor family known as signal transducers and activators of transcription (STATs).

Importantly, there is redundancy within the IL-2R due to the sharing of receptor sub-units among members of the cytokine receptor family. IL-2 shares two of its receptor sub-units: the β chain is shared with receptor for IL-15 and the γ chain by other cytokines that can also activate T cells. Thus, blockade of the IL-2R results in partial and not total immunosuppression.

Nevertheless, the predominant role of the IL-2/IL-2R pathway in T cell activation led to identification of CD25 as a potentially important target for monoclonal therapy.

1.4 Pre and Early Clinical Experience with Murine Anti-CD25 Mabs

A number of rodent monoclonal anti-CD25 antibodies were developed in the 1980s. Their immunosuppressive efficacy was shown in animal models. Two groups showed prolongation of cardiac allografts with murine Mab (AMT-13 or M7/20 and ART-18)^{1, 2, 3}. Similar results were obtained in renal allografts with anti-Tac⁴. Increased survival was confirmed for cardiac xenografts in primate models⁵. Prolonged survival of neural allografts was later demonstrated⁶.

Early clinical experience in the transplant setting included the comparison anti-IL-2R Mab 33.B.3.1 to anti-thymocyte globulin (ATG) in cadaveric renal recipients demonstrating equivalent efficacy and good tolerability⁷. Another Mab formulation BT563 similarly yielded better tolerance and equal efficacy to ATG in liver allografts⁸. In 1991 anti-Tac was compared to standard triple therapy for prevention of rejection in 80 renal recipients, and was shown to result in significant delay to the time of first rejection⁹.

The use of murine Mabs in humans, however, was limited by the development of neutralising antibodies in about 80% of recipients. This problem was successfully resolved when advances in molecular engineering enabled the formulation of chimaeric or humanised Mabs, which did not elicit a clinically significant host immune response. Theoretically, humanised Mabs should be less immunogenic than chimaeric Mabs but there is little practical evidence from human studies to support this. Most antibodies raised against chimaeric Mabs are directed against idiotypes present on both chimaeric and humanised Mabs.

1.5 Anti-CD25 Mabs Available for Clinical Use

Two monoclonal antibodies directed against the alpha chain of the IL-2R (ie.CD25) have been developed using molecular engineering. These are basiliximab (Simulect®) which is a chimaeric formulation by Novartis and dacluzimab (Zenapax®) being a humanised Mab preparation by Roche.

Daclizumab is derived from a recombinant gene in which the hypervariable region from the mouse antibody anti-Tac has been introduced into a human framework. Basiliximab is also derived from a recombinant gene but is chimaeric where the entire mouse variable region and human constant region of immunoglobulin are utilised.

Both strategies reduce antigenicity and give a half-life approximating human IgG (about 22 days). Each dose therefore acts for several weeks. They can be administered repeatedly as there is little neutralising antibody or anti-idiotypic response to them. Their use is associated with a decline in the percentage of circulating lymphocytes expressing CD25 without an accompanying decrease in the absolute number of lymphocytes. These monoclonal antibodies probably act by prolonged saturation of the IL-2R including both blocking and disrupting (shedding or internalising) the receptor.

2. CLINICAL TRIALS OF ANTI-CD25 MABS

Daclizumab and basiliximab were each evaluated in large Phase III clinical trials in renal transplantation. Both agents resulted in around 30% reduction in the incidence of rejection with no apparent associated toxicity. The clinical application of these Mabs is likely to be similar given the lack of clinically significant differences between them in controlled trials.

The findings from Phase I and Phase II trials relevant to the use of the agents are summarised but not detailed below. Four Phase III studies (2 for each agent) have been performed and resulted directly in marketing of this class of immunosuppressives. These and selected other studies, which provide clinically relevant insights into the role anti-CD25 Mabs, are presented in some detail, as this reflects the current level of knowledge and experience with the two available agents.

2.1 Daclizumab (Xenapax®)

2.1.1 Phase I & II Clinical Trials

- Daclizumab, first marketed in 1997 (1999 in Australia), is a genetically engineered humanised antibody comprising 90% human and 10% mouse antibody sequences.
- The half-life of the drug is approximately 20 days.
- The recommended dosage regimen is 1mg/kg administered by intravenous infusion over a 15 min. period. The standard course of therapy is five doses, at fortnightly intervals, with the first dose given within 24 hours prior to transplantation.

- This dosage regimen maintains IL-2R saturating serum daclizumab concentrations of 5-10µg/ml for 90-120 days¹⁰. The duration of clinically significant IL-2R blockade after recommended treatment is not defined.
- Re-administration of the drug has not been studied.

2.1.2 Phase III Clinical Trials

Two large multi-centre clinical studies in renal transplantation have been performed in which daclizumab was compared to placebo when added either to cyclosporin and prednisone (double therapy) or to cyclosporin, prednisone and azathioprine (triple therapy) for prevention of acute rejection. When added to double therapy, Daclizumab significantly reduced acute rejection from 47% to 28% compared to placebo. When added to the triple therapy the incidence of acute rejection was reduced from 35% to 22%. Therefore, acute rejection was reduced by 37-40% in these trials. Rebound rejections were not observed. No Daclizumab related toxicities were reported, with adverse events being comparable to those seen in placebo control groups.

TRIAL (Double Therapy)^{11, 12}

Randomised, placebo controlled, double blind trial in 275 recipients of a first cadaveric renal allograft. Baseline immunosuppression consisted of cyclosporin and prednisone.

Results:

- At 6 months acute rejection was significantly reduced from 47% in placebo arm to 28% in daclizumab arm (p= 0.001) representing a reduction in acute rejection of 40%.
- Recurrent acute rejection was found in 13% of patients receiving daclizumab compared to 22% of control patients (p=0.056).
- Patients on daclizumab received significantly less anti-lymphocyte therapy (8% active versus 16% of control group; p=0.02).
- Time to onset of first rejection was significantly prolonged (81 days daclizumab group compared with 17 days for placebo group). However, this did not account for the reduction in acute rejection rate as the incidence at 12 months was still low at 36%.
- There was no significant difference in the rates of delayed graft function between groups.
- Graft function at 6 and 12 months was significantly better in the daclizumab group with serum creatinine of 1.7±0.7 versus 1.9±0.9mg/ml in controls (P=0.02); and 1.7±0.9 versus 2.1 ± 0.14mg/ml in controls (p= 0.04) respectively.
- There was no significant difference in graft survival at six and 12 months post transplantation.

TRIAL (Triple therapy)¹³

Randomised, placebo controlled, double blind trial of 260 recipients of a first cadaveric renal allograft. Baseline immunosuppression consisted of cyclosporin, azathioprine and prednisone.

Results:

- At 6 months acute rejection was significantly reduced from 35% in placebo arm to 22% in daclizumab arm (p=0.03) representing a reduction in acute rejection of 37%.

- Graft function (serum creatinine) at 6 months was similar between trial groups.
- Graft survival at 6 months was significantly better in daclizumab group (98% versus 91% in control group; $p=0.02$). However, there was no significant difference in graft survival at 12 months post transplantation ($p=0.08$).

Combined analysis of these two trials (which had similar design but used different baseline immunosuppression regimens) was published in 1999¹⁴. In combination there were 535 patients randomised to receive daclizumab ($n=267$) or placebo ($n=268$).

Daclizumab prophylaxis resulted in a significant reduction in incidence of biopsy proven acute rejection at six and 12 months post transplantation ($p<0.001$). The use of anti-lymphocyte preparations was significantly lower in patients receiving daclizumab ($p=0.007$). There was no significant difference in renal function or graft survival.

Other Clinical Trials

An open single arm pilot study to examine whether calcineurin inhibitors (which are problematic in renal transplantation due to nephrotoxicity) can be avoided by daclizumab prophylaxis has been undertaken¹⁵. One hundred recipients of primary renal allografts received daclizumab, in combination with mycophenolate mofetil (MMF) and prednisone. Patients with panel reactive antibody of $>20\%$ and whose donor kidneys had ischaemic times of >48 hrs were excluded. Subjects received 2mg/kg of daclizumab pre-operatively and then 1mg/kg for a further four doses fortnightly. MMF was administered at 3g daily for 6 months and 1g daily thereafter. Preliminary results at a 180 days median follow up show biopsy proven rejections were observed in 45% of patients (most occurring in the first 90 days post transplantation). Calcineurin inhibitors were initiated in 40 of 44 patients experiencing rejection. Patient survival was 100% and graft survival 98%.

Studies are currently underway to examine the ability of daclizumab to allow avoidance of other immunosuppressive agents such as corticosteroids.

A retrospective study in liver transplantation recently reported experience in 32 patients in whom daclizumab was used to avoid or delay the use of calcineurin inhibitors³¹. Both the cohort and the reasons to avoid calcineurin inhibition were heterogeneous but the following observations were useful. Seven of the patients were part of a pilot to determine efficacy of daclizumab used in conjunction with prednisone and mycophenolate mofetil. The pilot study was stopped due to an unacceptably high incidence of rejection (100%). Significantly, 4 of these were corticosteroid resistant rejections. The remaining 25 patients in this report received similar induction, but calcineurin inhibition with tacrolimus or cyclosporin was introduced within the first 7 days post transplant. The rejection rate in this group was 36%. It was also found that the use of standard dosage regimen of daclizumab resulted in lower than expected serum levels of daclizumab compared with renal transplant study cohorts.

2.2 Basiliximab (Simulect®)

2.2.1 Phase I & II Clinical Trials

- Basiliximab is a 156 kD chimaeric human and mouse Mab of the IgG1kappa isotype. The murine genes conferring specificity for CD25 variable region originate from a murine hybridoma (RFTgamma2a) and the human genes code for the constant regions of heavy and light chains of IgG1kappa. The purified preparation is formulated as a lyophilysate.
- The half-life of the drug is 7.5 ± 2.5 days.
- The recommended dosage regimen is 20mg administered by intravenous infusion over 15 minutes. The standard course of therapy is two doses on days 0 and 4 of transplantation with the first dose administered within 2 hours prior to transplantation.
- This dosage regimen saturates the CD25 component of the IL-2R for about 30-45 days¹⁶. In detailed pharmacokinetic studies^{17, 18} receptor saturating serum basiliximab concentrations ($>0.2 \mu\text{g/ml}$) were maintained for 41 ± 23 days. The duration of clinically significant IL-2R blockade after recommended regimen is not known. No relationship between acute rejection and drug concentration has been found.
- Re-administration has not been studied.
- Basiliximab has been used to a limited extent in paediatric renal transplant recipients. For children between the ages 2-15, the recommended regimen is two doses of 12mg/m^2 (to a maximum of 20mg/dose).
- The drug has a relatively restricted distribution volume ($7.5 \pm 1.7 \text{L}$) attributable to its highly selective binding affinity and a relatively slow clearance from the body ($33 \pm 12 \text{ ml/h}$)^{17, 18}. Moderate inter-patient variability in clearance, half-life and distribution volume have been reported with coefficients of variation of 32-35%¹⁷. No clinically relevant influence of weight, age or gender has been found.
- Pharmacokinetic parameters in liver graft recipients have been found to differ from renal patients¹⁹. Total body clearance of basiliximab is significantly faster for liver transplants (75 ± 24 versus $46 \pm 16 \text{ ml/hr}$; $p=0.0001$) with a correspondingly shorter elimination half-life (4.1 ± 2.1 versus 5.8 ± 2 days; $p=0.0071$). A significant positive correlation exists between cumulative blood loss and total body clearance of drug. Differences in disposition between liver and renal recipients are contributed to by blood loss and loss in ascitic fluid with latter accounting for 20% total clearance. Complete saturation of CD25 is maintained as long as serum concentrations exceeds $0.1 \mu\text{g/ml}$. The duration of receptor saturation was 23 ± 7 days post transplantation (range 13-41 days).

2.2.2 Phase III Clinical Trials

Two large multi-centre clinical studies in renal transplantation have been performed in which basiliximab was compared to placebo when added to cyclosporin and prednisone (double therapy) for prevention of acute rejection.

In both studies, patients receiving basiliximab experienced significantly fewer rejections at six and 12 months post transplantation. Incidence of acute rejection was reduced by 28-32%. There was no difference in rate of delayed graft function, patient or graft survival between study

groups in either study. No basiliximab related toxicities were reported, with adverse events being comparable to those seen in placebo control groups in the pivotal trials.

TRIAL- (CHIB 201)²⁰

Randomised, placebo controlled, double blind trial in 376 recipients of a first cadaveric renal allograft. Baseline immunosuppression consisted of cyclosporin and prednisone. Highly sensitised patients were excluded from the trial. 333 patients completed 12 month assessment period.

Results:

- At 6 months, biopsy confirmed acute rejection was significantly reduced from 44% in placebo arm to 30% in basiliximab arm ($p=0.012$) representing a reduction in acute rejection of 32%.
- There was no difference between treatment groups in incidence of recurrent rejection.
- Significantly fewer patients in basiliximab group (10% compared to 23.1% in placebo group) had a steroid resistant first rejection episode requiring antibody therapy ($p<0.001$).
- There was no significant difference in graft survival at 12 months post transplantation.

TRIAL (US Study Group)^{16,21}

Randomised, placebo controlled, double blind trial in 348 recipients of a first renal allograft. Baseline immunosuppression consisted of cyclosporin and prednisone. Recipients of first living donor grafts were enrolled.

Results:

- Incidence of biopsy proven acute rejection at 6 months was reduced by 29% (32.9% in basiliximab group versus 45.7% in placebo group $p=0.017$).
- Significantly fewer patients (39%) in basiliximab group had steroid resistant rejection episodes (25.4% compared to 41.6% in placebo group; $p=0.001$).
- There was no significant difference in rates of delayed graft function.
- Incidence of death, graft loss or acute rejection at 6 months was reduced by 40% (basiliximab 29.6% versus placebo 49%; $p=0.038$) in living donor recipients and by 27% in cadaveric donor recipients (basiliximab 42% versus placebo 57.4%; $p=0.016$).
- Incidence of biopsy proven acute rejection was reduced by 43% in living donor recipients (basiliximab 24.8% versus placebo 43.2%; $p=0.028$) and by 21% in cadaveric donor recipients (basiliximab 37.7% versus placebo 47.6%; $p=0.021$).

Other Clinical Trials

Open label multi-centre dose escalation study¹¹ for pharmacokinetic analysis was performed using basiliximab in a single dose regimen of 40-60mg with steroids and azathioprine. Cyclosporin was withheld until day 10 post transplantation. One important finding of this trial was that 17 of 22 rejections observed occurred in the first 11 days (in absence of CSA) despite systemic concentrations of basiliximab exceeding those needed to saturate the CD25 component of the IL-2R. This observation suggests that the efficacy of basiliximab may be dependent on drugs that inhibit IL-2 production.

2.3 Clinical Trials for the Formulation of Recommendations

There is only limited literature regarding the use of daclizumab and basiliximab in non-renal solid organ transplantation. In addition, no controlled prospective studies exist to compare the efficacy of these antibodies to anti-CD3 monoclonals used for induction in recipients at high risk of rejection. There has also not been a systematic examination of the role of the two agents in the treatment of acute rejections.

The only data in relation to these largely unanswered areas is from early studies using murine monoclonal anti-CD25 preparations prior to the development of the two humanised forms currently available.

2.3.1 Clinical Trials in Earlier Murine Formulations of Anti-CD25 Mabs

- BT563, a mouse IgG1 anti-IL-2R monoclonal antibody was used in a pilot study for rescue treatment for steroid resistant acute rejection in 19 patients²². The initial response rate of 84% and a graft survival rate of 68% at 3 years were comparable to a historical control group of tacrolimus or OKT3 rescue and resulted in fewer side effects. The limiting factor was the development of anti-mouse antibodies that neutralised administered antibody.
- BT563 was also examined in a prospective, randomised trial²³ of 51 liver allograft recipients for rejection prophylaxis administered on a background of standard triple therapy. There was significantly less acute rejection in BT563 group (10.5% versus 42.9%). None of BT563 cohort developed steroid resistance compared with 56% of those in placebo group who required OKT3 or tacrolimus rescue.
- In two further BT563 studies^{24, 25, 26} in liver transplantation, equivalence to OKT3 or ATG was demonstrated in prophylaxis of rejection. Side effect profile, with the exception of the formation of anti-mouse antibodies, was minimal in the BT563 cohort. Patient and graft survival rates were equivalent, as was the incidence of steroid resistant rejections. Another murine Mab preparation, LO-Tac-1 yielded similar results of equivalence with reduced toxicity when compared to OKT3 in 129 liver transplant recipients²⁷.
- BT563 was also compared to OKT3 in 60 cardiac recipients^{28, 29}. Cyclosporin was started on day 3. Patients receiving BT563 experienced less toxicity, but earlier rejections, than the OKT3 group.
- In a further cardiac transplantation rejection prophylaxis study,³⁰ BT563 was administered with Cyclosporin from day 0 in 20 patients. A control group of 31 patients also received BT563 but Cyclosporin was delayed until day 3 post transplant. There was no significant difference in the incidence of acute rejection between groups. Importantly, immunohistochemistry showed that during rejection, IL-2R bearing cells were present in only 20% of patients on BT563 (compared to 75% in absence of BT563). This study suggested that despite adequate blockade of the IL2/IL-2R pathway patients develop rejection, probably due to the redundancy of cytokine network.

3. ADVERSE EFFECTS AND INTERACTIONS OF ANTI-CD25 MABS

The anti IL-2R antibodies have been remarkably free of adverse effects in all studies to date. Unlike the various anti-CD3 monoclonal preparations (eg.OKT3, ATG, ALG), cytokine release syndrome (first dose reaction) has not been reported and premedication is not required.

Importantly, there has not been an increase in the incidence of infections or other side effects compared to placebo to date, either in the short or longer term. It is worth noting, however, that the placebo arms in controlled trials experienced more rejections and therefore received higher steroid doses. The anti-CD25 Mabs therefore had equivalent adverse effects to the anti-rejection therapies they replaced.

The use of anti-CD25 antibodies does not alter the pattern, frequency and severity of known toxicities associated with immunosuppressive agents with which they have been used. The apparent lack of toxicity has been attributed to the selective binding to activated cells without affecting resting cells.

Status of these agents in relation to the foetus remains unknown in humans. Basiliximab is classified in Pregnancy Category B and Daclizumab in Category C.

4. COST

There are no published pharmaco-economic data. The current cost of a course of basiliximab (2 doses) is \$6000 and of daclizumab (5 doses) \$8000. This compares with a course of anti-T cell therapy of between \$3500 - \$5000. These costs relate to the drug and do not take into account other variables (eg. potential savings due to the reduced incidence of rejections). A detailed pharmaco-economic analysis of the use of these agents needs to be undertaken.

5. RECOMMENDED INDICATIONS

5.1 Recommended Usage

The anti-IL-2R monoclonal antibodies daclizumab and basiliximab are marketed in many countries, including Australia, for use in the prevention of acute rejection in renal transplantation.

The approved indication of prevention of rejection is based on a reduced incidence of rejection. There has, however, not been any improvement in graft survival in Phase III trials at 12 months. The implications and consequences of acute rejections are not uniform and in particular, early mild rejections do not seem to carry a penalty for the graft or patient outcome. In contrast, late, recurrent or more severe rejections do correlate with poorer graft outcomes. The use of these agents in a blanket fashion for all renal allograft recipients is therefore difficult

to justify and is not likely to be cost effective. Further subgroup analysis and trials are required to define the cohort in whom anti-IL-2R Mabs will be clearly beneficial and cost effective.

The controlled trials have generally examined one type of cohort ie. recipients of a first renal allograft and have excluded recipients of subsequent grafts. The latter, along with sensitised recipients, carry a significantly increased risk of rejection. They may therefore represent the group that anti-IL-2R Mabs would most benefit, in conjunction with other available baseline therapies. Indeed, it is these recipients that routinely receive anti-T cell therapies such as OKT3 and ATG for rejection prophylaxis in some transplant units in Australia. The lack of observed toxicity of anti-IL-2R Mabs is in marked contrast to the high side effect profile of the anti-T cell preparations. A prospective controlled comparison of anti-T cell therapies and basiliximab or daclizumab has not been undertaken.

The four Phase III trials may be able to provide further insights to the role of these drugs if an analysis of outcome for variables such as level of sensitisation or degree of HLA matching were to be performed. Data on such cohort subgroups are not available in the published literature.

Similarly, there is no controlled trials examining the role of these antibodies in non-renal solid organ transplants. There is some literature using earlier formulations of anti-IL-2R Mabs in liver and to a lesser degree in cardiac transplantation. These studies are suggestive of similarly favourable efficacy in rejection prevention with good tolerability. Indeed, markedly reduced toxicity has been suggested compared to other monoclonal induction preparations although this data has not been repeated with either daclizumab or basiliximab in a controlled and prospective manner.

5.2 Recommended for use in controlled clinical trial settings

Controlled, prospective clinical trials would be useful and should be encouraged in:

- non renal solid organ transplantation for prevention of rejection and to determine optimal dosage regimens for different organs (eg. liver transplantation)
- recipients at high risk of rejection (sensitised, regrafts, unmatched) for prevention of rejection. The author's personal experience has been very favourable in a cohort of 15 sensitised recipients (reported TSANZ,2000).
- direct comparison to anti-T cell Mabs in prevention of rejection,
- examining the role of these agents in sparing other more toxic immunosuppressive agents (eg cyclosporin, prednisone etc). There is limited data (in renal and hepatic transplantation) to suggest that optimal results require IL-2 inhibition as well as receptor blockade and their use in the absence of calcineurin inhibitors needs further evaluation.
- assessing the role of these agents in reducing use of calcineurin inhibitors and the duration of dialysis dependence in grafts with initial non function or in recipients of grafts from marginal donors.
- defining the role of these agents in the treatment of rejection. Do the agents work alone or as an adjunct and if so, what combination of therapies would be useful? (For example, is the use

of these agents additive to the rescue regimen of tacrolimus in the face of ongoing or recurrent rejection?).

5.3 Usage not supported by Evidence

- There is no evidence to support a treatment role for these agents in rejection. Anecdotal reports suggest a lack of efficacy in renal allograft rejection. However, a systematic examination has not been undertaken.
- The lack of information of these agents in liver, heart/lung and pancreas transplants make it difficult to propose their use at this time although benefits are likely to be comparable to those observed in renal transplantation.

5.4 Contraindications

There are no known contraindications to the use of anti-CD25 Mabs given the apparent lack of toxicity and absence of cytokine release syndrome. The cost implications and need for intravenous administration (for daclizumab often well after the patient is out of hospital) are relative issues to consider.

6. CONCLUSION

It is important that objective based definition of the role of the anti-CD25 Mabs is achieved through controlled studies. The availability of technology for humanising Mabs and the increasing understanding of the molecules involved in the rejection process suggest that Mabs will be developed in growing numbers. Each of these will need full and critical evaluation to define its precise role.

Transplantation is entering an era where immunosuppressive therapy may be tailored for a given individual and allograft. It is only through specific targeting of an agent that the cost of each new therapy may be justified by improving outcome for a given cohort or setting.

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