The cost-effectiveness of induction immunosuppression in kidney transplantation

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Abstract

Background. Induction immunosuppression is perceived as an expensive therapy, so is often given only to select patients. This study evaluated the cost-effectiveness of antibody induction comparing interleukin-2 receptor antagonists (IL2Ra) to standard therapy with no induction or induction with polyclonal antibodies.

Methods. A Markov model was developed to estimate costs and health outcomes [survival (life years saved, LYS) and quality-adjusted survival (QALYs)] for the alternative strategies. Outcome data were obtained from a meta-analysis of randomized trials and large-scale renal registries.

Results. IL2Ra offers improved survival of 0.21 LYS (2.5 months) and 1.42 QALYs compared with no induction, with a cost saving over 20 years of $79,302 per patient treated regardless of risk profile. The incremental benefits of IL2Ra compared with polyclonal antibody induction therapy were 0.35 LYS (4.3 months) and 0.20 QALYs, with an incremental cost of $5144 per patient. The incremental cost-effectiveness ratio (ICER) of IL2Ra compared to polyclonal induction was $14,803 per LYS and $25,928 per QALY. Sensitivity analyses showed that IL2Ra remained more effective and less expensive than no induction. When IL2Ra was compared to polyclonal induction, the model was sensitive to changes in the cost of induction and the probability of malignancy. Over the range of all other variables tested, IL2Ra was cost-effective compared to polyclonal induction.

Conclusions. Adopting IL2Ra as induction immunosuppression for kidney transplant recipients improves survival and QALYs and is less costly than no induction. It also represents good value for money compared to polyclonal induction.

Keywords: cost-effectiveness; immunosuppression; kidney transplant; QALYs

Introduction

Induction therapy given at the time of transplantation is used to decrease the incidence of acute rejection or in situations where delayed graft function might be anticipated, to provide alternative immunosuppression whilst allowing reduction in exposure to nephrotoxic calcineurin inhibitors. Monoclonal antibodies, particularly the non-lymphocyte depleting interleukin-2 receptor antagonists (IL2Ra), have demonstrated therapeutic advantage over no induction therapy and produce less toxicity compared with lymphocyte depleting polyclonal antibodies [1,2].

Despite recommendations in clinical practice guidelines [3–5], the use of IL2Ra varies between and within countries. Polyclonal antibodies are prescribed to 39% of transplant recipients in the United States [6], whereas in the United Kingdom and Australia, IL2Ra predominate [7,8]. In Asian countries and also New Zealand, induction immunosuppression with any agent is low [7,9], due to funding policies and the perceived additional expense of the therapy [10].

Kidney transplantation in many countries is largely funded via public health care providers [11–13]; however, no formal economic evaluations of IL2Ra using data from meta-analyses have previously been done. Therefore, the aim of this analysis was to determine from a national health system perspective, the incremental costs and incremental health outcomes of using IL2Ra for induction immunosuppression compared to (1) no induction and (2) polyclonal induction immunosuppression.

Subjects and methods

A Markov model was developed using the TreeAge Pro 2008 software (Williamstown, USA) to simulate the transplant outcomes in hypothetical cohorts of kidney transplant recipients treated with the three treatment strategies [14]. IL2Ra induction used a standard basiliximab dosing regimen of 2 × 20 mg on Day 0 and Day 4. Polyclonal antibody induction included all contemporary formulations of anti-thymocyte or anti-lymphocyte depleting antibodies, derived from rabbit or horse at a dose of 2–5 mg/kg for 7 days. Other monoclonal antibodies such as muromonab CD3 were excluded because of their lymphocyte depleting action, and rituximab and alemtuzumab were excluded on the basis of short-term or preliminary data from few randomized controlled trials (RCTs). The third
strategy of ‘no induction’ or standard therapy only was considered an appropriate comparator in this model, as ~26% of transplant recipients in the United States and 15% in Australia do not receive induction immunosuppression [7,15]. The no induction strategy was a triple immunosuppression regimen of a calcineurin inhibitor (tacrolimus or cyclosporine), with an antiproliferative agent (mycophenolate mofetil) and a steroid (prednisolone) based on current usage reported by the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) [16].

Model structure
The model was structured to include all potential consequences of kidney transplantation including acute rejection, graft loss and dialysis. We considered time after transplantation by dividing the post-transplant period into three stages: within the first 12 months (Year 0); Year 1; and Years 2+. These time frames were chosen to reflect time-dependent rates of events such as risk of acute rejection, graft loss and malignancy. The starting age for the cohorts was 46 years (median age of kidney transplantation) [16]. Each year, for 20 years, patients moved between the health states (functioning transplant, recurrence of primary disease, chronic dysfunction, dialysis, malignancy or dead) (Figure 1), with the likelihood of moving between health states dependent on published event rates. A 20-year time frame was chosen to capture the longer term effects of induction immunosuppression on graft survival, transition to dialysis and overall survival [17,18]. All costs were valued in 2008 Australian dollars (AUS$) [19]; outcomes were calculated in terms of survival [Life years (LY)] and quality-adjusted survival (Quality adjusted life years (QALYs)]. Future costs and benefits were discounted at a standard rate of 5% per annum [20]. Annual probabilities for death with a functioning graft and death on dialysis were calculated from event rates based on age-specific survival data from the United States Renal Data Systems (USRDS) and ANZDATA registries (Table 1) [16,17,21].

Figure 2A and B illustrate the possible pathways taken by cohorts of hypothetical patients in the model for the first and subsequent years after transplantation. Patients with peri-transplant technical problems transitioned to graft loss and maintenance dialysis. Patients with no technical problems who had no acute rejection transitioned to a discharge home—functioning graft state. Patients with acute rejection were either steroid responsive or steroid resistant. Steroid-resistant patients were either discharged home, had a prolonged hospitalization, or had graft loss and transitioned to dialysis. Once discharged home, patients could remain event free with a functioning transplant or die from other causes (e.g. myocardial infarction). In Year 0, patients could also develop infectious complications, recurrence of their primary disease, malignancy, lose their graft through other causes (e.g. non-adherence with immunosuppression) or die with a functioning graft. Patients treated with dialysis could stay on maintenance dialysis or die on dialysis.

In Year 1 (Figure 2B), patients could develop chronic allograft nephropathy, and patients on dialysis could receive a second transplant, stay on maintenance dialysis or die on dialysis.

Clinical data
Outcomes for this model were taken from a previously published meta-analysis of 38 RCTs [1,2]. This meta-analysis covered published data from RCTs over the time period 1989–2003 involving 4893 participants. Seven of 38 trials were conducted in recipients of a first deceased donor graft and nine trials included living donor grafts. Only two small trials were conducted exclusively in ‘high-risk’ recipients, with the RCTs containing mixed-risk participants not reporting stratified results. A summary table of the characteristics of studies included in the meta-analysis are provided in Appendix 1, and additional detail on the methods and results of this meta-analysis are available elsewhere [1,2]. In the initial analysis (base case), event probabilities for patients receiving no induction and IL2Ra induction were taken directly from point estimates [1,2], while event probabilities for patients treated with ‘polyclonal induction’ were calculated based on the relative risk compared to IL2Ra (Table 1). Data for end points in the model that were beyond the follow-up of the RCTs in the meta-analysis were estimated based on long-term observational data of transplant outcomes from the ANZDATA registry [16], with ranges tested using long-term graft survival from the USRDS registry [17] and the European renal registry [18].

Quality of life
QALY weights used for the dialysis and transplant populations were sourced from direct patient measures in the published literature (Table 1) [22,23]. These weights represent quality of life on a standard 0–1 scale, where 1 is equal to perfect health and 0 represents death. QALY weights for malignancy were obtained from a large study of 1157 patients with cancer using the EuroQol (EQ-5D) instrument [24].

Costs
Unit costs for transplantation and dialysis were obtained from the National Hospital Cost Data Collection based on Australian-Refined Diagnosis-Related Groups (AR-DRGs) [25] and the Medicare Benefits Schedule (MBS) [26]. The costs for dialysis were calculated based on the proportion of patients receiving each modality in 2006 [in-centre and satellite (69%), home haemodialysis (9%) and peritoneal dialysis (22%)] and included equipment and overheads, hospitalizations for dialysis-related procedures and concomitant medications [21,25,27]. Costs for publicly subsidized pharmaceuticals were obtained from the Pharmaceutical Benefits Schedule or actual costs to Australian transplant hospitals (Table 2) [28]. Incremental cost-effectiveness ratios (ICERs) were calculated according to the following formula:

\[
\text{ICER} = \frac{\text{TotalCost}_{\text{new}} - \text{TotalCost}_{\text{comparator}}}{\text{Effectiveness}_{\text{new}} - \text{Effectiveness}_{\text{comparator}}}.
\]

The ICER represents a measure of value for money. Using an outcome of QALYs means we can compare to other interventions in health care. Data suggest that in many high income countries, for example the United States, United Kingdom and Australia, interventions that have an ICER of ~US$50 000 per QALY gained are more likely to be funded by the respective governments compared to interventions that have a higher cost per QALY [29–31].

Allowance for uncertainty
One-way sensitivity analyses. All variables in the model were tested in one-way sensitivity analyses using the 95% confidence intervals from the meta-analysis pooled estimates of effect, registry data outcomes and published utilities (Table 1). This included acute rejection outcomes in both low- and high-risk recipients and the probability of cytomegalovirus infection [1,17]. Plausible ranges for costs covered variations in immunosuppression costs, the extremes for inpatient hospital admissions with up to 100% complication rates and the variation in dialysis costs based on published literature [32].

Multi-way sensitivity analyses. Multi-way sensitivity analyses were conducted using combinations of the most influential variables identified by the one-way sensitivity analyses.
Table 1. Clinical data and quality of life weights (utilities)

<table>
<thead>
<tr>
<th>Clinical data variables</th>
<th>No induction</th>
<th>IL2Ra</th>
<th>Polyclonal</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of functioning transplant no events</td>
<td>Base case</td>
<td>Range</td>
<td>Base case</td>
<td>Base case</td>
</tr>
<tr>
<td>Probability of graft loss post-acute rejection</td>
<td>0.3727</td>
<td>0.3427–0.4027</td>
<td>0.2703</td>
<td>0.2431–0.2974</td>
</tr>
<tr>
<td>Probability of graft loss post-acute rejection</td>
<td>0.0879</td>
<td>0.0719–0.1037</td>
<td>0.0712</td>
<td>0.0447–0.0976</td>
</tr>
<tr>
<td>Probability of CMV infection in Year 1</td>
<td>0.1517</td>
<td>0.1264–0.1770</td>
<td>0.1533</td>
<td>0.1276–0.1790</td>
</tr>
<tr>
<td>Probability of malignancy in Year 1 post-transplant</td>
<td>0.0232</td>
<td>0.0136–0.0329</td>
<td>0.0150</td>
<td>0.0016–0.0284</td>
</tr>
</tbody>
</table>

Results

IL2Ra compared to no induction

Treatment with IL2Ra was more effective and less expensive than no induction; therefore, it was not appropriate to calculate an ICER. Over the 20-year period of the model, recipients treated with IL2Ra induction had better survival and QALYs than recipients having no induction. IL2Ra patients gained an extra 0.21 LY (2.5 months) and 1.42 QALYs, predominantly due to less graft failure and a better quality of life with a functioning transplant compared to life on dialysis. IL2Ra induction was also associated with $79 302 lower costs over 20 years.

IL2Ra compared to polyclonal induction

When compared to polyclonal induction, IL2Ra produced 0.35 additional LY (4.3 months) and 0.2 additional QALYs. This was related to a lower probability of graft loss and malignancy with IL2Ra induction. After 20 years, the total average cost per patient was approximately $266 000 for IL2Ra induction and $261 000 for polyclonal induction, both strategies less expensive than no induction (Table 3). IL2Ra was associated with an incremental cost of $5144 over polyclonal induction. The ICER for IL2Ra compared to polyclonal induction was $14 803 per life years saved (LYS) and $25 928 per QALY gained.

Sensitivity analyses

The model results were robust to changes in all variables comparing IL2Ra with no induction therapy. IL2Ra remained both more effective and less expensive than standard therapy with no induction. One-way sensitivity analyses indicated that IL2Ra compared to polyclonal induction remained cost-effective over the range of variables tested.
in almost all circumstances (Figure 3). Our results indicate that IL2Ra was cost-effective compared to polyclonal induction across all recipient risk profiles. The model was sensitive to changes in the cost of induction treatment (i.e., the cost of drug plus the cost of additional hospitalization due to adverse events). When the cost of polyclonal induction was as low as $5270, reflective of a short duration of treatment and minimal toxicity, and the cost of IL2Ra was at the base case value of $6540, the ICER for IL2Ra compared to polyclonal induction rose above $50,000 per QALY. The model was also sensitive to changes in the probability of malignancy in the polyclonal arm.

A two-way sensitivity analysis for the cost of induction therapy was undertaken. The cost of the two induction strategies used in the base case is marked with an ‘X’ (Figure 4). If the cost of IL2Ra was $6400 or higher and the cost of polyclonal induction was $5270, then polyclonal induction would be the more cost-effective strategy. Likewise, if the cost of IL2Ra was $13,000 when the cost of polyclonal induction was $12,000 or lower then induction with polyclonal antibodies would be the more cost-effective therapy.

Two-way sensitivity analysis around the rates of malignancy at 1 year for both induction strategies using published
Table 2. Cost input data (AU$)

<table>
<thead>
<tr>
<th>Cost Base case</th>
<th>Low</th>
<th>High</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplant costs—no induction</td>
<td>8 days recipient hospitalization, all drugs, donor hospitalization or retrieval</td>
<td>$39,249</td>
<td>$19,625</td>
</tr>
<tr>
<td>IL2Ra induction drug costs</td>
<td>$6,540</td>
<td>$3,270</td>
<td>$13,080</td>
</tr>
<tr>
<td>Polyclonal induction drug costs and extended hospitalization for toxicity in 40% of patients</td>
<td>$10,042</td>
<td>$6,318</td>
<td>$25,273</td>
</tr>
<tr>
<td>Delayed graft function</td>
<td>7 haemodialysis sessions</td>
<td>$3,304</td>
<td>$1,652</td>
</tr>
<tr>
<td>Technical problems</td>
<td>Cost of surgical complications, e.g. return to operating theatre, additional drugs, consumables, etc.</td>
<td>$21,622</td>
<td>$10,811</td>
</tr>
<tr>
<td>Steroid responsive acute rejection</td>
<td>$6,056</td>
<td>$3,028</td>
<td>$12,114</td>
</tr>
<tr>
<td>Steroid-resistant acute rejection</td>
<td>$43,339</td>
<td>$21,670</td>
<td>$86,679</td>
</tr>
<tr>
<td>Polyclonal antibodies, additional physician consultations</td>
<td>$10,042</td>
<td>$6,318</td>
<td>$25,273</td>
</tr>
<tr>
<td>Prolonged hospitalization due to acute rejection</td>
<td>$4,255</td>
<td>$2,128</td>
<td>$8,510</td>
</tr>
<tr>
<td>Graft loss and transition to dialysis</td>
<td>Access creation, 50% nephrectomy</td>
<td>$17,663</td>
<td>$8,831</td>
</tr>
<tr>
<td>Maintenance dialysis</td>
<td>69% centre HD, 22% PD, 9% home HD, hospitalizations concomitant medications and transport</td>
<td>$75,643</td>
<td>$37,821</td>
</tr>
<tr>
<td>Transplant follow-up year 0</td>
<td>Immunosuppression, physician consultations, blood tests</td>
<td>$33,447</td>
<td>$16,724</td>
</tr>
<tr>
<td>Transplant follow-up year 1</td>
<td>$13,211</td>
<td>$6,606</td>
<td>$26,423</td>
</tr>
<tr>
<td>Transplant follow-up years 2+</td>
<td>$12,933</td>
<td>$6,467</td>
<td>$25,868</td>
</tr>
<tr>
<td>Diagnosis of cytomegalovirus</td>
<td>$3,589</td>
<td>$1,795</td>
<td>$7,180</td>
</tr>
<tr>
<td>Treatment of cytomegalovirus disease (invasive)</td>
<td>30-day hospitalization, anti-viral medications</td>
<td>$4,843</td>
<td>$2,242</td>
</tr>
<tr>
<td>Treatment of cytomegalovirus viraemia</td>
<td>$2,150</td>
<td>$1,075</td>
<td>$4,301</td>
</tr>
<tr>
<td>Diagnosis of chronic allograft nephropathy</td>
<td>Renal biopsy, concomitant medications, physician consultations</td>
<td>$3,214</td>
<td>$1,607</td>
</tr>
<tr>
<td>Recurrence of primary disease</td>
<td>$3,214</td>
<td>$1,607</td>
<td>$6,429</td>
</tr>
<tr>
<td>Diagnosis of malignancy</td>
<td>CT/PET/MRI, med/surgical oncology consultation</td>
<td>$4,715</td>
<td>$2,357</td>
</tr>
<tr>
<td>Treatment for malignancy for 50% of diagnosed patients</td>
<td>Surgery, 10 × 3 cycles chemotherapy, 10 sessions radiotherapy</td>
<td>$4,912</td>
<td>$2,456</td>
</tr>
<tr>
<td>Palliative care</td>
<td>14-day hospice admission, physician consultations, concomitant medications</td>
<td>$17,952</td>
<td>$8,976</td>
</tr>
<tr>
<td>Second or subsequent transplant</td>
<td>$39,249</td>
<td>$19,625</td>
<td>$78,498</td>
</tr>
<tr>
<td>Discount rate</td>
<td>5.00%</td>
<td>2.50%</td>
<td>10.00%</td>
</tr>
</tbody>
</table>

*aActual resource costs by Australian Transplant Hospitals.

Table 3. Present value of costs and outcomes per patient (AU$)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost per patient (12 months)</th>
<th>Cost per patient (20 years)</th>
<th>Life years gained (20 years)</th>
<th>QALYs gained (20 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No induction</td>
<td>$89,188</td>
<td>$345,649</td>
<td>7.05</td>
<td>3.86</td>
</tr>
<tr>
<td>IL2Ra induction</td>
<td>$85,227</td>
<td>$266,347</td>
<td>7.26</td>
<td>5.28</td>
</tr>
<tr>
<td>Polyclonal induction</td>
<td>$88,860</td>
<td>$261,203</td>
<td>6.91</td>
<td>5.08</td>
</tr>
</tbody>
</table>

Confidence intervals from meta-analytic data showed that IL2Ra induction remained the most cost-effective intervention over almost all combinations of probabilities. Only when the probability of malignancy with polyclonal induction was <3% and the probability of malignancy with IL2Ra was >2%, did IL2Ra cease to be the more cost-effective intervention.

Discussion

Using the best available data, we have shown that induction therapy using IL2Ra at the time of kidney transplantation is likely to offer both lower costs and improved health outcomes, (0.21 LY and 1.42 QALYs) compared to no induction in both low- and high-risk recipients. In addition,
our results show an increase in survival time (0.35 LYS or 4.3 months) and an increase in QALYs of 0.2 LY with IL2Ra induction compared with polyclonal induction, suggesting that IL2Ra induction provides transplant recipients a longer and better quality of life over time. The incremental benefit of IL2a induction comes at an increased cost, but well within the realm of what is considered good value for money, with an ICER of $25928 per additional LY in full health compared with polyclonal induction [33].

Our study highlights that induction immunosuppression with IL2Ra prolongs the time a person lives with a functioning transplant and is associated with improved survival, quality of life and lower overall costs. As would be expected, the Year 0 healthcare costs for transplantation (≈$85000–90000) were higher than the Year 0 costs for dialysis ($75000) with the costs for dialysis in subsequent years being higher than the maintenance costs for transplantation. While induction therapy using IL2Ra does add an incremental cost to the transplant procedure, the consequent reduction in the incidence of acute rejection and improved long-term graft survival, more than recoups the initial outlay.

The quality of life weight for patients with a transplant (0.75) was higher than that reported for patients on dialysis (0.57) [22]. Application of these QALY weights in the model meant that time spent with a functioning transplant compared to time on dialysis accrued more QALYs.

The benefit of induction immunosuppression appears to be realized in both low- and high-rejection-risk recipients. Although only a small contribution of meta-analytic data was from trials conducted exclusively in high-risk recipients, the high level of homogeneity of results between RCTs for the majority of outcomes, particularly the primary outcomes of graft loss and acute rejection, suggests that the results are likely to be generalizable to populations of greater and lesser risk. In the past, studies from single centres and registries, as well as meta-analyses have found that induction with monoclonal antibodies offers clinical advantages primarily in low-risk recipients [34–36]. One trial comparing IL2Ra with no induction in a population of 100 first transplant, living donor recipients, found a relative risk of acute rejection of 0.58 (95% C.I. 0.38–0.89) in the IL2Ra group [37].

Induction with polyclonal antibodies, particularly thymoglobulin, has gained popularity in the United States. Published results suggest, however, that IL2Ra have fewer side effects and have been shown to produce lower overall rates of graft loss and lower rates of CMV. Our model captured a reduction in the quality of life weight for polyclonal antibodies associated with toxicity, which meant that polyclonal antibodies were associated with lower overall health gain (in QALYs) than IL2Ra. This is consistent with a trial-based economic evaluation [38] that reported more hospitalized days from adverse drug reactions, and a lower quality of life at 1 year with polyclonal induction, coupled with higher drug costs at 12 months [mean US$6292 (95% C.I. US$5765–7419)].

Our results are consistent with two recent health technology assessments conducted by the National Institute for Clinical Excellence (NICE) in the United Kingdom [39,40]. These reports concluded that basiliximab and daclizumab consistently reduced the incidence of 1-year acute rejection compared with standard therapy, but acknowledged that long-term benefits were contingent on extrapolations from short-term trial outcomes. Basiliximab afforded a QALY gain of 0.06 (21 days) at 10 years with a reduced cost when compared to no induction. Likewise, daclizumab was also cost-effective compared to no induction therapy even when the probability of acute rejection was very low (ICER £12000 per QALY).

The Scottish Medicines Consortium (2008) has recently recommended against anti-thymocyte globulin for induction immunosuppression. They report a lack of beneficial health outcomes compared to IL2Ra and side effects that are considered unacceptable where an alternative agent exists [8]. Our results add further weight to this recommendation.

Strengths and limitations

Meta-analytic data are considered the highest level of evidence for both assessment of effectiveness and cost-effectiveness as it incorporates evidence from multiple RCTs into a summary estimate of effect, thus minimizing selection bias compared with utilising data from a single randomized trial [41,42]. The meta-analysis on which much of the model input was based was not restricted to English language trials, explicitly stated the exclusion and inclusion criteria, and derived pooled estimates of relative risk with 95% confidence intervals around the summary treatment effect. The 38 included trials were judged to be of good quality and were presented with a test statistic for heterogeneity. A complete list of included trials is outlined in Appendices 1 and 2.

In addition, our analyses have the advantage of considering costs and health outcomes over a longer and more clinically relevant timeframe, and specifically incorporating the quality of life of reported by patients with a transplant or on dialysis.

Fig. 4. Two-way sensitivity analysis for the cost of polyclonal induction and the cost of IL2Ra induction immunosuppression, indicating which option is more cost-effective (assuming a cost-effectiveness threshold of $50 000 per QALY gained).
Although our analyses are based on the best data currently available, we recognize that there remains uncertainty around some of the parameters included in our model. Within the timeframe of RCTs, longer term events such as malignancy occur infrequently, and so meaningful assumptions about the association of cancer with induction therapy must be interpreted with care. Overall a non-significant trend of higher rates of malignancy with polyclonal induction has been reported [1,2]. This evaluation is based on the current practice of kidney transplantation in Australia, which may not be completely comparable to other populations where transplant practices or funding for kidney transplantation differs substantially; however, the broad conclusions of our analyses are robust over a wide range of values of costs and effects.

Baseline immunosuppression commonly used in the 1990s (cyclosporin A and azathioprine) has largely been replaced with tacrolimus and mycophenolate mofetil, with two-thirds of patients still managed on steroids [16]. Seven trials in the meta-analysis (Ahsan 2002, Philosophe 2002, Tullius 2003, Garcia 2002, Khan 2000, Vitko 2003 and van Riemsdijk 2002) evaluated induction therapy using this contemporary regimen and demonstrated a consistent incremental benefit of IL2Ra; however, we appreciate the limitations of model findings as a larger number of trials were based on the former regimen.

**Implications for future research**

Alemtuzumab, a newer T-cell depleting monoclonal antibody not evaluated in this model, has shown promising early results in a few RCTs [43–45]. Alemtuzumab has shown equivalent rejection rates to other induction agents and does not appear to increase the rate of CMV or BK nephropathy. Future meta-analyses and cost-effectiveness analyses of induction immunosuppression should include this new agent. Future analyses may also consider stratifying treatment effects by donor type, for example living donors and expanded criteria donors.

Induction therapy using IL2Ra offers better overall survival, QALYs and lower costs than no induction. IL2Ra provides significant long-term cost savings compared with no induction therapy. IL2Ra affords an increase in both length of life and importantly QALYs time when compared with no induction or polyclonal induction. Induction therapy using IL2Ra appears to be good value for money, with an ICER of $25 928 per QALY compared with polyclonal antibody induction therapy. Based on our analyses, IL2Ra is a preferable induction immunosuppression agent for low-risk kidney transplant recipients that may also benefit high-risk recipients.

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**Conflict of interest statement:** None declared.

**Appendix 1. Characteristics of included studies in meta-analysis [1]**
### Table 1: Co-interventions

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Deceased donor%</th>
<th>First transplant%</th>
<th>IL2RA (n)</th>
<th>Comparator (n)</th>
<th>Calcineurin inhibitor (initial dose, mg/kg/day: trough ng/ml)</th>
<th>Antiproliferative agent (Azathioprine, MMF g/day)</th>
<th>Duration of follow-up (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL2Ra vs. other antibody</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brennan 2002</td>
<td>212</td>
<td>100</td>
<td>Ns</td>
<td>Basiliximab (106)</td>
<td>ATG (106)</td>
<td>Cy (12–16: ns)</td>
<td>MMF (2)</td>
<td>0.5</td>
</tr>
<tr>
<td>Flechner 2000</td>
<td>45</td>
<td>ns</td>
<td>Ns</td>
<td>Basiliximab (23)</td>
<td>OKT3 (22)</td>
<td>Cy (ns: ns)</td>
<td>MMF (2)</td>
<td>0.5</td>
</tr>
<tr>
<td>Hourmant 1994</td>
<td>40</td>
<td>ns</td>
<td>0</td>
<td>33B3.1 (20)</td>
<td>ATG (20)</td>
<td>Cy (8: 150–250)</td>
<td>Aza (2)</td>
<td>1</td>
</tr>
<tr>
<td>Kriaa 1993</td>
<td>40</td>
<td>100</td>
<td>Ns</td>
<td>Basiliximab (52)</td>
<td>ATG (52)</td>
<td>Cy (5: ns)</td>
<td>Aza or MMF (ns)</td>
<td>1</td>
</tr>
<tr>
<td>Kyllonen 2002c</td>
<td>104</td>
<td>100</td>
<td>Ns</td>
<td>Lo-tact-1 (20)</td>
<td>ALG (20)</td>
<td>Cy (ns: ns)</td>
<td>MMF (2)</td>
<td>0.5</td>
</tr>
<tr>
<td>Lacha 2001</td>
<td>28</td>
<td>ns</td>
<td>58</td>
<td>Daclizumab (14)</td>
<td>OKT3 (14)</td>
<td>Cy (8: ns)</td>
<td>MMF (2)</td>
<td>1</td>
</tr>
<tr>
<td>Lebranchu 2002</td>
<td>103</td>
<td>100</td>
<td>100</td>
<td>Basiliximab (52)</td>
<td>ATG (51)</td>
<td>Cy (6–8: 150–200)</td>
<td>MMF (2)</td>
<td>1</td>
</tr>
<tr>
<td>Hourmant 2002</td>
<td>89</td>
<td>98.5</td>
<td>89.5</td>
<td>Basiliximab (46)</td>
<td>ATG (43)</td>
<td>Cy (6: ns)</td>
<td>MMF (2)</td>
<td>0.5</td>
</tr>
<tr>
<td>Philosophe 2002</td>
<td>50</td>
<td>ns</td>
<td>92</td>
<td>Daclizumab (26)</td>
<td>OKT3 (24)</td>
<td>T (ns: ns)</td>
<td>MMF (ns)</td>
<td>1</td>
</tr>
<tr>
<td>Pourfarziani 2003</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>Daclizumab (11)</td>
<td>ALG (14)</td>
<td>Cy (ns: ns)</td>
<td>MMF (ns)</td>
<td>1</td>
</tr>
<tr>
<td>Shidban 2000</td>
<td>42</td>
<td>100</td>
<td>Ns</td>
<td>Basiliximab (22)</td>
<td>OKT3 (20)</td>
<td>Cy (ns: ns)</td>
<td>MMF (ns)</td>
<td>0.5</td>
</tr>
<tr>
<td>Shidban 2003</td>
<td>75</td>
<td>100</td>
<td>100</td>
<td>Basiliximab (25)</td>
<td>ATG (50)</td>
<td>Cy (ns: ns)</td>
<td>MMF (ns)</td>
<td>0.5</td>
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<tr>
<td>Sollinger 2001</td>
<td>135</td>
<td>62</td>
<td>81</td>
<td>Basiliximab (70)</td>
<td>ATG (65)</td>
<td>Cy (6–10: ns)</td>
<td>MMF (2–3)</td>
<td>1</td>
</tr>
<tr>
<td>Soulillou 1990</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>33B3.1 (50)</td>
<td>ATG (50)</td>
<td>Cy (8: 300–600)</td>
<td>Aza (2)</td>
<td>1</td>
</tr>
<tr>
<td>Tullius 2003</td>
<td>124</td>
<td>100</td>
<td>75</td>
<td>Basiliximab (62)</td>
<td>ATG (62)</td>
<td>T (0.2: 10)</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>IL2Ra vs. other antibody</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garcia 2002</td>
<td>49</td>
<td>0</td>
<td>100</td>
<td>Daclizumab, MMF (23)</td>
<td>T, Aza, (26)</td>
<td>T (0.1–0.15: ns),</td>
<td>MMF (2–3), Aza (2)</td>
<td>0.5</td>
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<tr>
<td>Khan 2000</td>
<td>59</td>
<td>ns</td>
<td>Ns</td>
<td>Basiliximab (29)</td>
<td>Daclizumab (30)</td>
<td>T or Cy (ns: ns),</td>
<td>MMF (ns) or Aza (ns)</td>
<td>0.25</td>
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<tr>
<td>Kumar 2002</td>
<td>27</td>
<td>ns</td>
<td>Ns</td>
<td>High basiliximab, low P (17)</td>
<td>Basiliximab, normal P (10)</td>
<td>Cy (ns: ns)</td>
<td>MMF (ns)</td>
<td>1</td>
</tr>
<tr>
<td>Matl 2001</td>
<td>202</td>
<td>100</td>
<td>100</td>
<td>Basiliximab (102)</td>
<td>Basiliximab (100)</td>
<td>Cy (10: ns),</td>
<td>Aza (1–2)</td>
<td>1</td>
</tr>
<tr>
<td>Nair 2001</td>
<td>23</td>
<td>26</td>
<td>100</td>
<td>Basiliximab (10)</td>
<td>Daclizumab (13)</td>
<td>Cy (7: ns)</td>
<td>MMF (2)</td>
<td>0.5</td>
</tr>
<tr>
<td>Van Riemsdijk 2002</td>
<td>130</td>
<td>ns</td>
<td>Ns</td>
<td>Daclizumab, normal P (64)</td>
<td>P (66)</td>
<td>T (ns: ns)</td>
<td>MMF (ns)</td>
<td>0.5</td>
</tr>
<tr>
<td>Vitko 2003</td>
<td>457</td>
<td>ns</td>
<td>Ns</td>
<td>Basiliximab (153)</td>
<td>MMF (151); MMF/P (147)</td>
<td>T (0.2: 5–15)</td>
<td>MMF (2)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

**a**Additional immunosuppressive agents.

**b**Trials ongoing.

**c**Kyllonen 2002 (156 participants) has three arms comparing IL2Ra with both no treatment and with ATG, and so appears in both comparisons. All trials (except van Riemsdijk 2002 and Vitko 2003) also used steroid therapy in all arms.

**T** = tacrolimus, **Cy** = cyclosporin, **Aza** = azathioprine, **MMF** = mycophenolate mofetil, **= no agent used, **P** = steroid, ns = not stated.
Appendix 2. References for each study included in the meta-analysis (ordered by author)


### Appendix 3. Base case calculations for cost of polyclonal induction

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patient weight</th>
<th>Dose per day</th>
<th>Cost of drug (^a)</th>
<th>Cost/day</th>
<th>No. of days</th>
<th>Hospitalization for toxicity</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATG 100 mg/5 ml (Fresenius)</td>
<td>70 kg</td>
<td>2 mg/kg</td>
<td>$527 per vial</td>
<td>$1054</td>
<td>7</td>
<td>$2664.00</td>
<td>$10 042.00</td>
</tr>
<tr>
<td>Thymoglobuline 25 mg/10 ml (Genzyme)</td>
<td>70 kg</td>
<td>1 mg/kg</td>
<td>$380 per vial</td>
<td>$1140</td>
<td>7</td>
<td>$2664.00</td>
<td>$10 644.00</td>
</tr>
</tbody>
</table>

\(^a\)Cost of drugs to Australian Transplant Hospitals (2008).
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The pharmacokinetics of mycophenolate mofetil in renal transplant recipients receiving standard-dose or low-dose cyclosporine, low-dose tacrolimus or low-dose sirolimus: the Symphony pharmacokinetic substudy

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Abstract

Background. Exposure to mycophenolic acid (MPA), the primary active metabolite of mycophenolate mofetil (MMF), is correlated with therapeutic efficacy of MMF but varies depending on the concomitantly administered immunosuppressive drugs.

Methods. A 3-month pharmacokinetic substudy of the prospective, randomized, multicentre, open-label Symphony study was performed. Eighty-three adult renal transplant patients received standard-dose cyclosporine, MMF 2 g/day and corticosteroids, or daclizumab induction, MMF 2 g/day and corticosteroids plus low-dose cyclosporine, low-dose tacrolimus or low-dose sirolimus. The area under the concentration–time curve (AUC0–12) of MPA and its metabolites between treatment groups was compared. Pharmacokinetic sampling was performed before MMF administration and at 20, 40, 75 min; 2, 3, 6, 8, 10 and 12 h post-dose on Day 7 and Months 1 and 3.

Results. Compared with standard-dose cyclosporine, patients receiving low-dose tacrolimus or low-dose sirolimus had significantly higher AUC0–12 values for MPA at Day 7 and Month 1 and for free MPA at Day 7, and significantly lower AUC0–12 values for 7-O-MPA-glucuronide (MPAG) at Month 1 and for acyl-glucuronide at Months 1 and 3 (P < 0.05). AUC0–12 of MPA and free MPA was significantly greater with low-dose tacrolimus and low-dose sirolimus than with low-dose cyclosporine in the first month (P < 0.05). The ratio of MPA to tacrolimus was significantly higher in the three low-dose groups than in the standard-dose cyclosporine group (P < 0.05).

Conclusions. Standard- and low-dose cyclosporine reduces the exposure of MPA and free MPA compared to low-dose tacrolimus or low-dose sirolimus in patients given the same dose of MMF.

Keywords: mycophenolate mofetil; mycophenolic acid; mycophenolic acid glucuronide; pharmacokinetics; renal transplantation

Introduction

Mycophenolate mofetil (MMF) is a highly effective immunosuppressant that does not adversely affect renal function and has been shown to have a nephroprotective effect in patients with chronic allograft nephropathy [1]. Consequently, MMF has become an integral component of toxicity-sparing regimens that seek to minimize or eliminate exposure to the nephrotoxic calcineurin inhibitors (CNIs).