Title: Basiliximab for Immunosuppression During a Calcineurin Inhibitor “Holiday” in Renal Transplant Patients with Acute Renal Dysfunction: Guidelines for Use and a Clinical and Cost-Effectiveness Review

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Context and policy issues:

Patients who receive kidney transplants require immunosuppressive therapy in two phases — usually termed induction and maintenance therapy — to help prevent acute rejection and the loss of the renal allograft.1,2 During the induction phase, recipients receive higher doses of several concurrent drugs to induce a partially immunosuppressed state. Immunosuppressant drugs are selected that work at various sites in the cell cycle and have non-overlapping toxic effects.2 The doses are gradually tapered during the first two to four months after transplantation until maintenance levels are achieved. In addition, many transplant centres include a short course of anti-CD25 monoclonal antibodies (also called IL-2-receptor antagonists) during the induction phase.2 Anti-CD25 monoclonal antibody agents include daclizumab and basiliximab. These agents block the interleukin-2 receptor on activated T lymphocytes, which impedes the immune cascade that causes acute cellular rejection in solid organ transplantation.3,4

Most transplant centres use an induction/maintenance immunosuppression regimen consisting of a calcineurin-inhibitor (CNI) drug (cyclosporine or tacrolimus) and an anti-metabolite drug (azathioprine or mycophenolate mofetil), with or without corticosteroids.1 CNI drugs remain the cornerstone agent of the maintenance immunosuppressive regimen.1 However, there is increasing concern about CNI-induced nephrotoxicity, which is an important contributor to post-transplant chronic allograft dysfunction.5 The nephrotoxic properties of CNI drugs may delay renal allograft function, hinder diagnosis of clinical rejection, prolong the need for dialysis and result in poorer long-term outcomes.3

There is no gold standard protocol for managing acute renal dysfunction after solid organ transplant.6 Various strategies have been used to reduce CNI-induced nephrotoxicity, including decreasing the dose or eliminating the CNI altogether from the treatment regimen.5 Mammalian
target of rapamycin (mTOR) inhibitor agents, including sirolimus and everolimus, are increasingly being used as CNI-sparing substitutes. CNI treatment may also be delayed during the early postoperative period while the patient is covered by the immunosuppressant effects of anti-CD25 monoclonal antibodies that are given during the induction phase.

Another treatment strategy for transplant patients experiencing acute renal dysfunction is to introduce a CNI “holiday” (i.e. withhold CNI for a short period of time) to allow kidney function to return to baseline function. However, there is a risk of acute rejection if CNI drugs are withheld. It has been suggested that basiliximab could be used “off label” (i.e. outside of the induction phase in the immediate transplantation period) to provide immunosuppression while patients with acute renal dysfunction take a temporary CNI drug “holiday” to allow kidney function to recover and return to baseline function. A review of the guidelines and the clinical effectiveness of basiliximab for this off label use is necessary. In addition, due to the high cost of basiliximab ($1,517.83 per 20 mg dose) it is important to assess the cost-benefit of the off-label use of this drug.

**Research question(s):**

1. What is the clinical effectiveness of switching patients experiencing acute renal dysfunction as a result of using cyclosporin or tacrolimus to basiliximab post-renal transplantation?

2. What is the cost-effectiveness of switching patients experiencing acute renal dysfunction as a result of using cyclosporin or tacrolimus to basiliximab post-renal transplantation?

3. What are the guidelines for the use of basiliximab in renal transplant patients experiencing acute renal dysfunction as a result of using cyclosporin or tacrolimus?

**Methods:**

A limited literature search was conducted on key health technology assessment resources, including OVID Pre-Medline, Medline and Embase, Pubmed, The Cochrane Library (Issue 2, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2000 and May 2008, and are limited to English language publications only. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analysis, clinical guidelines, randomized clinical trial (RCT) studies, observational and non-randomized studies, and economic evaluations.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews and meta-analyses are presented first. These are followed by economic evaluations, randomized controlled trials, observational studies and evidence-based guidelines.

**Summary of findings:**

No relevant health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, economic analyses or clinical practice guidelines were identified regarding the clinical effectiveness or cost-effectiveness of switching patients experiencing acute renal dysfunction caused by CNI drugs (cyclosporin or tacrolimus) to basiliximab post-renal transplantation. One published observational study was identified, as well as an abstract of another observational study.
Observational studies

A small observational study reported using anti-CD25 monoclonal antibody coverage during a temporary CNI “holiday.” Cantarovich et al \(^6\) described a case series of 11 patients with solid organ transplants who experienced 15 events of acute renal dysfunction due to CNI nephrotoxicity between one month and 14 years post transplant. Seven patients were heart transplant recipients, two patients had received a liver transplant, one a renal transplant (12 years after a heart transplant) and one had received a simultaneous heart/kidney transplant. Acute renal dysfunction was defined as a 25% increase in baseline serum creatinine. The CNI “holiday” was implemented and continued until serum creatinine had decreased to baseline. Basiliximab was given to seven patients for the treatment of 11 events of acute renal dysfunction. Basiliximab was given at a dose of 20 mg intravenously, followed by 20 mg four days later, and then 20 mg once every 20 days until CNI drugs were reinstated or replaced by mycophenolate mofetil or sirolimus. The remaining four patients received daclizumab at a dose of 1.5 mg/kg intravenously every seven days until CNI drugs were reinstated or replaced by mycophenolate mofetil or sirolimus. The duration of the CNI “holiday” ranged from 21 ± 51 days (range 6 to 210). Serum creatinine levels (\(\mu\)mol/L) had increased from a mean baseline of 145 ± 48 to 301 ± 92 (P<0.0001) with CNI drug therapy and they decreased to 143 ± 55 with the CNI “holiday.” Six patients had CNI therapy reintroduced and had a slight increase (10.6%) in serum creatinine to 155 ± 67 (range 71 to 277) at one week; 160 ± 51 (range 91 to 238) at one month; and 160 ± 72 (range 92 to 269) at three months. The remaining five patients were put on sirolimus or mycophenolate mofetil. No episodes of acute rejection occurred and anti-CD25 antibody drugs were well tolerated, with no adverse events reported. Six patients died from causes deemed unrelated to basiliximab or daclizumab therapy two weeks to seven months after the CNI “holiday.” The authors concluded that a CNI “holiday” can be implemented in solid organ transplant patients experiencing acute renal dysfunction, under basiliximab or daclizumab coverage. However, observational data obtained from a case series is considered to be weak scientific evidence and the authors stated that prospective randomized studies are required to confirm preliminary results.

Also identified was a brief abstract of an observational study reported by Cantarovich in a newsletter highlighting presentations made at a 2006 scientific symposium on transplantation issues.\(^8\) The abstract reported that 24 heart or liver transplant patients with CNI-induced acute renal dysfunction were managed using prolonged therapy with either basiliximab or daclizumab. CNI drug “retirement” was implemented in six heart transplant patients for 6 ± 2 months and for 14 ± 9 months in seven liver transplant patients. No episodes of acute rejection were recorded. The author concluded that prolonged anti-CD25 monoclonal antibody therapy may allow a CNI holiday or retirement in heart or liver transplant patients with renal dysfunction. The limitations of this preliminary report are that data have not yet been fully reported and the study has not been published in a peer-reviewed journal. Observational data obtained from a case series are considered to be weak scientific evidence and prospective randomized studies are required to confirm these preliminary results.

Conclusions and implications for decision or policy making:

We identified only two studies, from the same group of investigators, that have reported using anti-CD25 monoclonal antibodies (basiliximab and daclizumab) outside of the induction period in renal transplant patients experiencing acute renal dysfunction due to CNI drugs, including cyclosporin or tacrolimus.

Investigators in the Transplantation Division at the Royal Victoria Hospital in Montreal have reported using basiliximab (or daclizumab) to provide immunosuppression coverage during a
calcineurin inhibitor “holiday” in 11 solid organ transplant patients with acute renal dysfunction.\(^6\) Their preliminary findings suggested that a temporary CNI “holiday” could be safely implemented without acute rejection in solid organ transplant patients, under immunosuppressant coverage with either basiliximab or daclizumab. A prospective randomized study is required to confirm this initial finding, with attention paid to outcome measures such as acute rejection episodes, renal function, and allograft survival. Cost-benefit analyses are also needed.

The same Montreal investigators have also reported the preliminary results of using prolonged anti-CD25 monoclonal antibody therapy during CNI “holiday” or “retirement” in 24 heart or liver transplant patients.\(^8\) The full results of this observational study have not yet been published in a peer-reviewed journal.

The use of anti-CD25 monoclonal antibodies (basiliximab and daclizumab) has facilitated the development of steroid- and CNI-sparing regimens during the immediate post-transplantation period. However, the “off-label” use of anti-CD25 monoclonal antibodies outside of the immediate post-transplantation period to allow a temporary drug “holiday” from nephrotoxic CNI drugs requires further evaluation of long-term outcomes in larger numbers of transplant recipients. At present, extremely limited data are available concerning the clinical effectiveness and safety of this regimen; no economic analyses of the regimen were identified.

Since basiliximab is typically administered in the hospital during the peri-transplantation period, it would be covered under hospital drug budgets. Each 20 mg dose of basiliximab costs $1,517.43.\(^7\) Other costs to consider for its off-label use include those related to administering the drug intravenously over 20 to 30 minutes in a health care facility equipped and staffed to treat any potential severe hypersensitivity reactions.

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