Emerging Drug List

**EVEROLIMUS**

**Generic (Trade Name):** Everolimus (Certican™)

**Manufacturer:** Novartis Pharmaceuticals

**Indication:** For use with cyclosporine for the prevention of rejection episodes after heart or kidney transplantation.¹

**Current Regulatory Status:** In October 2003, the US Food and Drug Administration (FDA) issued an “approvable” letter regarding Certican™ for use with cyclosporine to prevent rejection episodes after heart or kidney transplantation. Final approval depends on the results of a FDA review of additional clinical information submitted by Novartis.¹ Novartis also completed the European Mutual Recognition Procedure in December 2003.² Health Canada is reviewing Certican™ for use in patients undergoing renal transplantation; and under the fast-track program, for use in patients undergoing heart transplants.¹ In early 2002, Novartis announced that it had partnered with Guidant Corporation, to extend the right to use everolimus in drug eluting stents for patients with coronary or peripheral vascular conditions.³

**Description:** Everolimus, an oral immunosuppressant, is a derivative of sirolimus. Its mechanism of action is based on the suppression of growth-factor stimulated activation and proliferation of lymphocytes and mesenchymal cells.⁴

**Current Treatment:** There are consequences from under-immunosuppression and over-immunosuppression after transplantation. Under-immunosuppression may lead to acute and chronic rejection, while over-immunosuppression may lead to renal compromise, infectious complications and development of malignancies. The combination of pharmaceuticals that is generally used in transplant patients, is individually tailored to their point in therapy (i.e., induction, maintenance, acute rejection episode).⁵⁻⁸ Medications include cyclosporine; tacrolimus; azathioprine; mycophenolate mofetil; sirolimus; corticosteroids; and polyclonal and monoclonal antibodies.⁵⁻¹⁰ Further discussion on immunosuppression in renal and cardiac allografts appears elsewhere.⁵⁻⁸,¹⁰

**Cost:** A cost for Certican™ was unavailable at the time that this review was written.

**Evidence:** A phase III, randomized, multi-centre, double-blind trial assessed the value of everolimus in 634 primary cardiac transplant patients. Patients received everolimus 0.75 mg or 1.5 mg twice daily; or azathioprine 1 to 3 mg/kg/day (maximum of 300 mg), in combination with cyclosporine, corticosteroids and statins. Peripheral therapies, such as cytomegalovirus (CMV) prophylaxis, were used as required. The primary end point was a composite of death, graft loss or retransplantation, loss to follow-up, biopsy-proven rejection (at least grade 3A) or rejection with compromised hemodynamics. At six
months, the composite end point was evident in 27%, 36.4% and 46.7% of patients receiving everolimus 1.5 mg, everolimus 0.75 mg and azathioprine respectively \( [p<0.001 \text{ (everolimus 1.5 mg twice daily versus azathioprine)}; \quad p=0.03 \text{ (everolimus 0.75 mg twice daily versus azathioprine)}] \). At 12 months, 32.2%, 41.6% and 52.8% met the criteria \( [p<0.01 \text{ (everolimus 1.5 mg twice daily versus azathioprine)}; \quad p=0.02 \text{ (everolimus 0.75 mg twice daily versus azathioprine)}] \). The rate of death was not significantly different among the groups. After adjustment for rejection, cardiac vasculopathy was less frequent in the everolimus groups compared with azathioprine \( (p=0.02 \text{ for low dose}; \quad p=0.002 \text{ for high dose}).^4 \)

A 12-month open-label extension of the trial is described in an abstract. At 24 months, the primary end point was evident in 36.0%, 45.9% and 57.5% of patients who received high- and low-dose everolimus and azathioprine respectively \( (p<0.001 \text{ for high dose}; \quad p=0.016 \text{ for low dose versus azathioprine}) \). The incidence of acute rejection was lower in the everolimus-treated patients \( (p=0.005 \text{ for low dose}, \quad p<0.001 \text{ for high dose, everolimus versus azathioprine}) \). The incidence of CMV infections was significantly lower in everolimus-treated patients compared with those receiving azathioprine \( (p<0.001 \text{ for both}) \). The rate of death, which ranged from 10% to 13.7%, was not significant between the arms. Cardiac allograft vasculopathy was only statistically superior in the everolimus 1.5 mg/day group when compared with the azathioprine group \( (p=0.017)^{11} \).

The 36-month results from a phase III study examining the utility of everolimus compared to mycophenolate mofetil in de novo renal transplant patients has been published in abstract form. Patients \( (n=588) \) received everolimus (1.5 or 3 mg/day) or mycophenolate (2 g daily) in combination with cyclosporine and steroids. At 36 months, the death rate was comparable between the groups (8% to 9%). Patients treated with everolimus 1.5 mg had a lower incidence of a late-occurring composite end point of death, graft loss, biopsy proven acute rejection (BPAR) or loss to follow-up \( [1.2% \text{ (1.5 mg everolimus)} \quad \text{versus} \quad 7.3% \text{ (3 mg everolimus)} \text{ and } 5.9% \text{ (mycophenolate)}] \). The incidence of death or graft loss was higher in those receiving everolimus 3 mg/day \( (24.2%) \) compared with everolimus 1.5 mg/day \( (13.9\%) \) and mycophenolate \( (16.3\%) \). CMV infection occurred more frequently in patients receiving mycophenolate \( (20\% \text{ versus } 6\% \text{ to } 7\%) \). The authors concluded that everolimus treatment was equivalent to mycophenolate in de novo renal patients and that the everolimus 1.5 mg dosage had a preferred efficacy and safety profile.\(^{11}\)

Another phase III trial, which was described in a press release, involved 583 patients. It compared mycophenolate to everolimus at the same dosages as the phase III study just described. At six and 12 months, the frequency of the composite end point was similar between the groups, with an overall survival rate in both groups of 96%. Serum creatinine increases were noted more frequently in the everolimus group.\(^{13}\)
Vitko et al. have highlighted the six-month results of two prospective, randomized studies where everolimus (1.5 and 3 mg/day, titrated to a serum trough level of 3 ng/mL) with steroids and low exposure cyclosporine were evaluated in de novo renal transplant patients. Study 1 included 237 patients who received no induction, while study 2 included 256 patients who received basiliximab on days 0 to 4. The primary end point was renal function at six months. At six months, the median serum creatinine ranged from 130 to 133 µmol/L between the groups in both trials. There were no significant differences between the groups in the composite end point of BPAR, graft loss or death. In study 2, however, BPAR was significantly higher in patients with an everolimus serum trough level <3 ng/mL. There were no significant differences in adverse events in either study.

Further information on everolimus in renal transplantation has been presented elsewhere. A Cochrane review is underway to evaluate the short and long-term benefits and risks of sirolimus and everolimus when used for induction, treatment of refractory rejection or immunosuppression in a maintenance regimen for those with renal transplants. The protocol is available and the review is expected to be published in 2004.

Everolimus is also being evaluated for use in lung transplantation. The 12-month results of a three-year clinical trial assessing everolimus in combined heart-lung transplant procedures are available electronically.

Adverse Effects:

In the Eisen et al. study, no statistically significant differences were noted in withdrawals due to adverse events between the groups. Of the adverse effects recorded, bacterial infection was more prevalent in the higher dose everolimus group compared with azathioprine (p=0.001), while CMV and other viral infections occurred more frequently in the azathioprine group (p=0.001 for both everolimus arms versus azathioprine). Cancer rates were not statistically different between the groups. All arms experienced an elevation in total cholesterol and triglyceride levels from baseline, although it was statistically higher in the everolimus groups (p=0.01).

In the two prospective studies reported by Vitko, reports of infection, particularly of the urinary tract, were prevalent (50% to 60%), while the rates of CMV cases were low (0.9% to 3.2%). Other common side effects (≥10% in all arms across both studies) included anemia (not otherwise specified), hypertension (not otherwise specified), constipation, total cholesterol increase (9.1 mmol/L) and elevated triglycerides (4.5 mmol/L). New-onset diabetes was also noted in 3% to 5% of patients during the investigations.

Commentary:

Immunosuppression is a delicate balancing act. The ideal agent or combination of agents to use has not yet been found. Everolimus is an immunosuppressant that may help to prevent graft rejection in some patients. Efficacy has been shown in heart and kidney transplant procedures and its use in other types of transplantation is being explored.
Much of the data are available in abstract form only; and some are non-comparative. Publication of these studies in full would allow for further analysis. The lower incidence of CMV infection and coronary vasculopathy is of interest.

References:


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This series highlights medical technologies that are not yet in widespread use in Canada and that may have a significant impact on health care. The contents are based on information from early experience with the technology; however, further evidence may become available in the future. These summaries are not intended to replace professional medical advice. They are compiled as an information service for those involved in planning and providing health care in Canada.

These summaries have not been externally peer reviewed.

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