

Lung transplantation in Australia: barriers to translating new evidence into clinical practice

Greg Snell, Tom Kotsimbos and Trevor J Williams

Evidence “beyond reasonable doubt” may never be achievable for low-volume drugs

The recent publication of a randomised controlled trial (RCT) of inhaled cyclosporin in the *New England Journal of Medicine* represents another milestone in the evolution of lung transplantation (LTx) as a standard therapy in the management of severe lung and pulmonary vascular diseases.^{1,2} RCTs have been few and far between in lung transplantation, and this is the first in such a high-profile general journal. However, the big question is: how will we integrate the study results into the clinical practice in Australia?

Lung transplantation is a relatively recent and very demanding form of solid organ transplantation. The first long-term survivor received a lung transplant in 1981,³ and, compared with kidney and liver transplantation, there have been proportionally fewer lung transplantation procedures performed annually in Australia (100 lung, 400 kidney and 170 liver cadaveric transplants in 2004⁴). Nonetheless, the four Australian lung transplant programs have performed about 6% of all lung transplants worldwide.⁵ At present, 100 Australians are awaiting suitable donor lungs.

The efficacy of the various lung transplantation procedures themselves is determined primarily by comparison with historical control data, and the results of small cases series. The clinical practice of lung transplantation has generally developed by inference from other types of solid organ transplantation, as well as clinical anecdote and deduction. Indeed, we can identify only a handful of RCTs performed in lung transplant recipients that directly guide therapeutic decision making. Typically, the conduct of RCTs requires substantial resources and patient numbers. In lung transplantation, unless the effect size is huge, this typically mandates multicentre, multinational trials.^{6,7}

Australian lung transplantation centres have recognised the need for good quality trials, and have consistently taken lead or major roles in virtually every significant RCT of an immunosuppressant published over the last decade.⁶⁻⁸ Five-year survival after lung transplantation (50%) lags well behind that of other forms of solid organ transplantation (kidney, 85%; liver, 80%⁴), and we continue to strive to increase our evidence base with the ultimate objective of improving clinical outcomes. Therefore, it seems somewhat ironic that, despite core Australian involvement in clinical trials generating evidence of the utility of newer immuno-

suppressant agents (tacrolimus, sirolimus, mycophenolate mofetil, everolimus), this evidence has not been readily integrated into Australian clinical practice. The reimbursed immunosuppressive protocols employed by lung transplantation programs in this country (cyclosporin, azathioprine and prednisolone) reflect decade-old practices. By contrast, in the United States, United Kingdom and Europe, newer agents have been rapidly integrated into practice. In Australia, there appears to be a progressively widening gap between the point at which there are sufficient data to support the use of a drug in a clinical situation (clinical risk versus benefit), and the point at which funding can be achieved that will allow the drug to actually be administered to patients.

We submit that central to the problem in Australia is the extremely complex system of health care funding. Gaining Therapeutic Goods Administration (TGA) registration of a drug allowing it to be prescribed for a series of indications is only the first (relatively small) step. After that, there is extreme complexity as to who (if anyone) will pay. Previously, public hospitals have provided drugs that were indicated on clinical grounds but not subsidised by the (federal) Pharmaceutical Benefits Scheme (PBS). With a shift to predominantly casemix funding, hospitals with cutting-edge clinical programs have been forced to limit access to non-PBS items to prevent institutional “fiscal meltdown” from these largely unsupported costs.

Generally, equitable access to an expensive drug in Australia requires listing on the PBS on the advice of the Pharmaceutical Benefits Advisory Committee (PBAC). The process is rigorous, evidence-based, and includes detailed pharmacoeconomic evaluation with a benchmark of cost-effectiveness. Our concerns are that the same level of evidence is required for frequently used medications (such as statins) compared with low volume drugs (such as anti-rejection drugs for lung transplant recipients) and the cost-effectiveness benchmark is not stated specifically.

It is quite appropriate for regulatory authorities, hospitals and individual transplant physicians to appreciate the financial implications of novel agents, and not just focus on the evidence of efficacy. It is also important for 21st century physicians to recognise the commercial reality of drug patent laws, generic alternatives and pharmaceutical company marketing strategies.

Key findings of the inhaled cyclosporin lung transplant study²

Design and primary outcome

- 58 patients were randomly allocated, early after transplant, to receive 300 mg inhaled cyclosporin or placebo for 2 years, in addition to standard therapy.
- The primary outcome was rate of histological acute rejection.

Results

- Acute rejection rates were the same for the two groups (0.44 v 0.46 episodes per patient; $P=0.87$)
- Nephrotoxicity and opportunistic infection rates were similar.
- Survival was improved in the inhaled cyclosporin group (relative risk of death, 0.2; $P=0.01$)
- Chronic rejection-free survival was improved in the inhaled cyclosporin group (relative risk of chronic rejection, 0.38; $P=0.01$) ♦

However, these issues create particular difficulties in small clinical fields like that of lung transplantation, where there may be sufficient evidence to support the use of a therapy, despite the absence of the multiple randomised trials specific to lung transplantation. It becomes apparent that it may not be commercially viable for a pharmaceutical company to perform the necessary trials and successfully negotiate registration and reimbursement for such a small patient group as lung transplant recipients.

These issues are again brought to our attention by the recent RCT in the *New England Journal of Medicine*.^{2,8} This small single-centre RCT in lung transplantation is welcomed with great interest, as it shows efficacy for a novel inhaled cyclosporin formulation in enhancing key outcomes, including chronic rejection-free and overall survival (Box).² The study had an accompanying editorial noting several methodological issues and, consistent with conservative evidence-based medicine, the editorial suggests the lung transplantation community undertake multicentre trials to avoid being “doomed to recreate a series of anecdotal experiences”.⁸ We are concerned, however, that repeating the RCT will take years to complete. Indeed, given the particular complexities of this agent, where multiple entities hold patents and licensing rights to different components of the therapy, no trial may ever be undertaken. There is a push to market the treatment on the existing evidence, and a case could be made that not to facilitate access to this novel therapy for Australian lung transplant recipients may cause greater harm by preventing the use of what appears to be a safe agent that strikingly reduces the risk of chronic rejection and death.

We face a dilemma as lung transplant physicians (which we believe will resonate with many other clinicians) that on the “balance of probabilities” (to use a legal analogy), the benefits to our patient are likely to be greater than the risks, so it would be better to use the drug than not. However, to have the drug funded (and thus, available to our patients in a practical sense) realistically requires evidence “beyond reasonable doubt”. For the many reasons alluded to, this standard may never be achievable for low-volume drugs.

Australia has been very well served by a centralised drug reimbursement system like the PBS, but we also believe it disadvantages patients with uncommon diseases who need high-cost drugs. If health economics are to be the principle determinant of funding, we need a transparent, consistent benchmark of cost-effectiveness across the entire health system. In the meantime, we ask that the thresholds of support for pharmaceutical funding be based on clinical appropriateness from the best available evidence, otherwise evidence-based medicine is in danger of becoming an economic weapon rather than a key clinical tool.

Competing interests

Greg Snell serves on the Transplant Advisory Board of Roche Pharmaceuticals. Both Greg Snell and Tom Kotsimbos have received speakers’ fees for delivering talks at Roche and Novartis Pharmaceutical meetings over the past 2 years, and travel assistance from Novartis Pharmaceuticals to attend the 2006 meeting of the International Society for Heart and Lung Transplantation.

Author details

Greg Snell, MB BS, Head (Medical) Lung Transplant Service,¹ and Associate Professor²
Tom Kotsimbos, MD, FRACP, Respiratory Physician, Lung Transplant Service,¹ and Associate Professor²
Trevor J Williams, MB BS, FRACP, Clinical Director, Department of Allergy, Immunology and Respiratory Medicine,¹ and Associate Professor²

1 The Alfred Hospital, Melbourne, VIC.

2 Monash University, Melbourne, VIC.

Correspondence: g.snell@alfred.org.au

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