Role of Registry Analyses in Comparing the Long-Term Benefits of Calcineurin Inhibitors

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Registry analyses complement RCTs

Traditionally, data from randomised controlled trials (RCTs) are considered the gold standard in evaluating competing strategies in clinical medicine. For a number of reasons, RCT data may need to be supplemented in the field of transplantation. RCTs provide the most appropriate information about efficacy and safety of medicines under highly controlled conditions with tight inclusion criteria. They have mostly small or medium sample sizes and have limited follow-up between 6 months to 3 years, with usually high discontinuation rates. Graft survival rates following organ transplantation are outstanding – over 90% of renal transplants are functioning at one year. This remarkable success means that RCTs are no longer powered to detect differences in graft survival rates between interventions. Therefore studies in renal transplantation should rely on intermediate outcomes. However if a new drug improves one intermediate outcome (e.g. acute rejection) whilst worsening another one (e.g. new onset diabetes mellitus), it is difficult to conclude whether the therapy provides significant health gain to patients.

In organ transplantation we have access to uniquely comprehensive and accurate outcomes databases that can help address these issues. Registry analyses, although data is not collected with the rigour of a clinical trial, offer three advantages. First, they have sufficient patient numbers to identify outcomes differences according to risk factors or interventions. Second, they continue for long enough to capture the long-term implications of an intervention or risk factor. Third, results are collected within routine practice in a standard-risk patient population. Results from registry analyses are inherently vulnerable to bias. There are no inclusion or exclusion criteria for patients, as there are in a clinical trial, and patients are not randomly assigned to immunosuppressive regimens or other interventions. It is realistic to assume that selection bias exists - for example, newer immunosuppressive regimens tend to be used in patients at higher risk of graft loss. Neither are patients managed by protocol, so differences in clinical practice between centres or over time may also influence results. However, appropriate selection of datasets and statistical techniques, such as multivariate regression analysis can minimise the potential for bias (1, 2).

The value of registry analyses: A comparison of MMF and azathioprine

Results from the Phase III clinical trials (3, 4) of mycophenolate mofetil (MMF) in renal transplantation showed a significant reduction in the incidence of acute rejection compared to azathioprine. However, the trials showed no significant advantage for MMF in terms of graft survival. By the late 1990s, an analysis of data from over 66,000 patients registered with the UNOS Renal Transplant Scientific Registry and USRDS was undertaken to compare the incidence of chronic renal allograft failure between the two therapies (5). Results showed that after adjustment for confounding variables, the annual rate of graft loss over five years was significantly lower for MMF than azathioprine (18.9 versus 26.5 grafts per 1000 patients, $p<0.0001$). This difference was unlikely to have been revealed in a typical clinical study setting because of insufficient patient numbers and the financial and logistical barriers to conducting a clinical study over a period of several years. Later several additional registry analyses reconfirmed the graft and patient survival benefit of mycophenolate mofetil over azathioprine (6, 7).

The case of Sandimmune vs Neoral

Evidence from randomised, controlled trials showed that the microemulsified cyclosporin (Neoral) is associated with a lower incidence of acute rejection compared with cyclosporin (Sandimmune) (8), however difference in graft survival was not seen in those short time-frame studies. Registry analyses confirmed that Neoral decreases chronic allograft failure and improves long-term graft survival when compared to Sandimmune (9, 10).

The case of Sandimmune vs tacrolimus

Pivotal studies of tacrolimus showed an improvement in acute rejection compared to Sandimmune (11). However intent-to-treat analysis revealed equivalent patient and graft survival between treatment arms at 5 years of follow-up (79.1% vs. 81.4%; P=0.472 and 64.3% vs. 61.6%; P=0.558 among tacrolimus and CsA-treated patients, respectively) (12). Finally only registry analyses could confirm the superiority of tacrolimus over Sandimmune in hard-end points (9).

The case of Neoral vs tacrolimus

Some clinical studies indicate that tacrolimus is more efficacious than microemulsified cyclosporine in preventing

acute rejection (13). These and other studies also indicate that tacrolimus increases the rate of new onset diabetes[i] and BK polyoma virus infection (15) whilst improving renal function (16), lipid levels (17) and blood pressure compared to Neoral. However no multicenter RCTs were able to show that tacrolimus improves graft survival compared to Neoral.

Meier-Kriesche & Kaplan concluded that both Neoral (RR:0.6, 95% CI: 0.5-0.7) and tacrolimus (RR:0.7, 95% CI: 0.5-0.8) were associated with a lower relative risk for chronic allograft failure as compared with conventional cyclosporin (Sandimmun) based upon the USRDS database for kidney transplant recipients between 1994-97. This observation was independent of the use of MMF.

As both Neoral and tacrolimus are superior to Sandimmune, it is difficult to interpret those registry analyses, in which tacrolimus is compared to cyclosporin, including Sandimmune and Neoral or even generic formulations (18).

Irish et al (19) compared Neoral-MMF with tacrolimus-MMF based upon the USRDS registry for kidney transplant recipients between 1995-98. Using Cox proportional hazards modeling, the adjusted relative hazard of 3-year graft failure for cadaveric donor patients taking tacrolimus versus Neoral was 1.02 (95% CI 0.8-1.3) and for living donor recipients it was 1.15 (CI 0.8-1.8).

Bunnapradist et al (20) utilised the UNOS Scientific Registry of Transplant Recipients (SRTR) database in a multivariate analysis comparing cyclosporin plus MMF with tacrolimus plus MMF. The data were taken from 1998 to 1999, a period in which all de novo patients treated with cyclosporin used the Neoral formulation only. A Cox multivariate analysis was performed that adjusted for confounding factors. The study established that 3-year graft survival for living donor recipients was significantly greater for the cyclosporin regimen compared to the tacrolimus based regimen (Hazard ratio 1.28, p=0.004). Calculated half life is 4.7 years longer with the cyclosporin regimen. In this paper the authors pointed out that hazard ratios for graft loss change over time. Statistically significant difference in favour of Neoral is presented only after 1997. This indicates the importance of evolution in the use of immunosuppressant regimens, and the need to correct for a specific period, besides formulation of cyclosporin, adjunct agents and other confounding variables.

Kaplan et al (21) by using the UNOS SRTR database showed that graft survival in living transplant recipients was not statistically different between Neoral vs. Prograf based regimens (95.6% vs. 95.6% survival at one year, and 80.5% vs. 78.2% at five years of follow up for Neoral and Prograf respectively. Five year death censored graft survival was almost identical among paired cadaveric donor kidneys for Neoral vs. Prograf based immunosuppressive regimen.

Opelz et al (22) conducted an analysis of cadaver kidney transplants performed from 1994 to 1998 based on the Collaborative Transplant Study database. This intent-to-treat analysis revealed no significant differences in 3-year graft survival rate between cyclosporin and tacrolimus.

Conclusion

Registry analyses complement randomized clinical studies by providing evidence about graft and patient survival of different immunosuppressant regimens in real life. Registry analyses could prove that mycophenolate mofetil improves long-term graft and patient survival and this is independent of its impact on acute rejection. Also registry data proved that both tacrolimus and Neoral is superior to Sandimmune. However based upon these registry analyses tacrolimus provides no survival benefit compared to Neoral over 3-5 years time-frame, or even Neoral shows superiority in living donor transplantation.

Given the scarcity of health care resources, economic considerations (such as price of immunosuppressants and cost of managing side-effects(14, 17)) should also be taken into account when selecting the appropriate immunosuppressant regimen for the majority of transplanted patients.

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