Background and aims

Tacrolimus is a potent macrolide immunosuppressive agent that is highly effective in the prophylaxis of transplant rejection and in the treatment of allograft rejection in patients resistant to treatment with other immunosuppressive agents. Numerous studies have demonstrated that tacrolimus is safe and effective in reducing the risk of post-transplantation graft rejection. However, doses that result in tacrolimus exposure outside of the therapeutic range can result in an increased risk of rejection (with low tacrolimus concentrations) or toxicity (with high tacrolimus concentrations). Therapeutic drug monitoring of whole-blood tacrolimus trough concentrations is therefore used to establish the appropriate dose for a given patient. In spite of this, the process of ascertaining the appropriate dose is complicated by the considerable within-patient pharmacokinetic variability exhibited by tacrolimus (a phenomenon typically measured using the coefficient of variability ($\text{CoV}$)).

In 2007, the European Commission granted EU-wide marketing authorization for Advagraf, a once-daily, prolonged-release formulation of tacrolimus. The scientific discussion that accompanied the marketing authorization noted that phase II trial data had already demonstrated that conversion from Prograf (an existing twice-daily, immediate-release tacrolimus formulation) to Advagraf had resulted in reduced within-patient variability. More recently, a 2011 prospective study showed that, when stable renal transplant recipients were switched from Prograf to Advagraf, the proportion of patients with a tacrolimus CoV greater than 22.5% decreased from 17.4% to 3.1% ($p < 0.01$ at three months after conversion).

The aim of the present study was to use these clinical data to evaluate the budgetary implications of using Advagraf in place of Prograf, a twice-daily, immediate-release tacrolimus formulation, in renal transplant recipients in the UK.

Methods

A budget impact model was constructed to evaluate the direct medical costs associated with using prolonged-release tacrolimus (Advagraf) relative to immediate-release tacrolimus (Prograf) in patients undergoing kidney transplant from the perspective of a UK healthcare payer. The model was constructed in Microsoft Excel and was designed to report the clinical endpoints of graft failure, acute rejection and patient mortality. The underlying evidence of graft failure and patient mortality was based on data from the 2011–2012 National Health Service Blood and Transplant (NHSTB) Organ Donation and Transplantation Activity Report.

Specifically, data from 2,469 UK patients who underwent first kidney transplantation (from donors after brain death) in 2004–2006 were used to establish the baseline proportion of grafts and patients surviving at years 1, 2 and 5 after transplant.

Table 1 Costs used in the base case analysis

<table>
<thead>
<tr>
<th>Cost item</th>
<th>Cost (GBP per milligram)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advagraf</td>
<td>1.43</td>
<td>British National Formulary</td>
</tr>
<tr>
<td>Prograf</td>
<td>1.61</td>
<td>British National Formulary</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>0.00126</td>
<td>British National Formulary</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>0.184</td>
<td>British National Formulary</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cost item</th>
<th>Cost (GBP)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute rejection (AR) episode</td>
<td>28.50</td>
<td>British National Formulary</td>
</tr>
<tr>
<td>Refractory AR episode</td>
<td>6,701.65</td>
<td>British National Formulary</td>
</tr>
<tr>
<td>Peritoneal dialysis (per day)</td>
<td>53.00</td>
<td>NHS Tariff (HRG LD12A)</td>
</tr>
<tr>
<td>Hemodialysis session</td>
<td>123.00</td>
<td>NHS Tariff (HRG LD11A)</td>
</tr>
</tbody>
</table>

Cohort bodyweight and dosing assumptions were based on a multicenter randomized trial, published in 2010 by Krämer and colleagues, that compared Advagraf and Prograf in 667 de novo renal transplant recipients. All drug costs were taken from the British National Formulary (BNF), while costs associated with dialysis were taken from 2012-13 National Health Service tariff information (Table 1). Future costs were not discounted in the base case analysis.

The proportion of patients with high within-patient variability and the effects of high within-patient variability on the incidence of graft failure were modeled using data from two studies. The first, published in 2011 by Wu et al., reported that, after conversion of stable renal transplant recipients (N=129) from Prograf to Advagraf, the proportion of patients with a trough concentration CoV greater than 22.5% decreased from 17.4% to 3.1% ($p<0.01$ at three months after conversion).

For the purposes of the analysis, these patients were considered to have “high” within-patient variability. The second study, by Borra and colleagues, was a retrospective analysis of 207 patients who had undergone kidney transplantation between 2001 and 2004 and had a functioning graft at 12 months after transplantation. The patients were divided into two groups based on the median tacrolimus concentration CoV; CoV to give “low” and “high” within-patient variability groups. The incidence of the primary composite endpoint (of graft loss, biopsy-proven chronic allograft nephropathy and doubling of plasma creatinine concentration) was calculated for each group and the relative risk of reaching the composite endpoint was 2.38 in patients with high within-patient variability relative to those with low within-patient variability.

The base case analysis assumed that there would be no differences in concomitant medication use or in the incidence of acute rejection or mortality in patients on Advagraf relative to those on Prograf.

Results

Over a five-year time horizon, the mean cost per patient (including costs of tacrolimus, concomitant immunosuppressive medications, dialysis after graft failure, and treatment for acute rejection) was GBP 29,941 (standard deviation [SD] GBP 2,765) for Advagraf versus GBP 30,386 (SD GBP 3,085) for Prograf ($p<0.01$). The total cost saving of GBP 3,415 (SD GBP 516) was driven primarily by reduced dialysis costs arising from the lower risk of graft failure in the greater proportion of patients with low within-patient in the Advagraf arm. After 5 years, 14.8% of patients on Advagraf had experienced graft failure, compared with 17.6% of patients on Prograf (Figure 2).

Advagraf remained cost saving in a sensitivity analysis in which the relative risk of graft failure with high within-patient variability was set to 1, although the magnitude of the savings was reduced to GBP 1,563 (SD GBP 513). Advagraf also remained cost saving in an analysis in which the cost of Advagraf was set to the same as that of Prograf, although the saving was reduced to GBP 1,848 (SD GBP 420) over five years.

Discussion and conclusions

The present study showed that, over a 5-year time horizon, using a prolonged-release tacrolimus formulation in renal transplant recipients would result in substantial cost savings in the UK setting relative to immediate-release tacrolimus. Savings were driven primarily by a reduction in the incidence of graft failure in patients with lower within-patient variability (of which there were more in the Advagraf arm than the Prograf arm).

The analysis used a straightforward and transparent modeling approach; recent, robust and UK-specific data to model graft failure and mortality; and up-to-date UK cost data and resource-use assumptions. However, there are limitations that should be considered when interpreting the findings. Notably, graft failure was captured used data from heterogeneous sources that used different CoV thresholds to distinguish between high and low within-patient variability. This was, however, addressed in sensitivity analyses in which Advagraf remained cost saving.

Advagraf is well-established as a safe and efficacious therapy in the prophylaxis of graft rejection and the study provides evidence that it may also result in substantial cost savings in the UK setting. Given that recent research indicates that patients overwhelmingly prefer once-daily immunosuppressive medication to twice-daily, there should be no clinical or economic barriers to its use in renal transplant recipients in the UK.

References


