Aims

To produce a comprehensive review of generic tacrolimus (immediate release) capsules that will be used as part of a toolkit that PMSG will produce to support key decision makers in the NHS on the use of generic and branded generic immunosuppressants.

Introduction

Prograf® (0.5 mg, 1 mg, 5 mg) is an immediate-release capsule formulation of tacrolimus that is taken twice daily. It is licensed for the prophylaxis of transplant rejection in liver, kidney or heart allograft recipients; and for the treatment of allograft rejection resistant to treatment with other immunosuppressive drugs. Sandoz (Adoport®), Teva (Tacrolimus CINFA®) and Dexcel Pharma (Vivadex®) have now launched generic versions in the UK2,3,4. These generic preparations have identical product licenses to the originator product.2-4

Nb: Arrow and Accord have no plans to launch their generic tacrolimus products at present. The MHRA has granted PharOS Ltd Marketing Authorisations for the following tacrolimus (0.5, 1.0, 5.0mg) capsules: Evenil®, Taliximun®, Tacni®, Aletrix®, Takon® and Capexion®, but apart from Tacni (for Teva), it is not clear which of these will be supplied by other companies in the UK.5

Therapeutic drug monitoring

Dosing of tacrolimus should primarily be based on clinical assessments of rejection and tolerability in each individual patient. Blood trough levels should be monitored during the post-transplantation period, approximately twice weekly, initially, and then periodically during maintenance therapy. Levels should also be monitored following dose adjustment, changes in the immunosuppressive regimen, or following co-administration of substances which may alter tacrolimus whole blood concentrations. Clinical study analysis suggests that the majority of patients can be successfully managed if tacrolimus blood trough levels are maintained below 20ng/mL. In clinical practice, whole blood trough levels have generally been in the range 5 -20ng/mL in liver transplant recipients and 10-20ng/mL in kidney and heart transplant patients in the early post-transplant period. Subsequently, during maintenance therapy, blood concentrations have generally been in the range of 5-15ng/mL in liver, kidney and heart transplant recipients.1

The cost of a tacrolimus assay is approximately £11.69 excluding VAT.6

Comparison of generic products to Prograf

Bioequivalence

The underlying assumption of bioequivalence is that if two products have an essentially similar plasma drug concentration-time course, this will result in essentially similar drug concentrations at the site of action and therefore in an essentially similar therapeutic effect. Bioequivalence tests are typically single-dose crossover studies in healthy volunteers that assess the drug’s absorption (bioavailability) by measuring its maximum plasma concentration (Cmax) and the extent of the body’s exposure to the drug, determined by plotting plasma concentration against time and calculating the area under the curve (AUC). Products are considered bioequivalent if their bioavailabilities are sufficiently similar and lie within limits defined by the European Medicines Agency i.e. the
90% confidence interval for the ratio of the test and reference products should be within -20% to +25% (i.e. 80–125%).

In specific cases of products with a narrow therapeutic index, the acceptance interval for AUC should be tightened to 90.00-111.11%. Where Cmax is of particular importance for safety, efficacy or drug level monitoring the 90.00-111.11% acceptance interval should also be applied for this parameter. A Therapeutic Subgroup of the European Medicines Agency considers that tacrolimus is a drug with a narrow therapeutic index, and thus it is necessary to apply tighter bioequivalence acceptance criteria of 90-111% for AUC, but the 80-125% acceptance interval remains for Cmax.

**Bioequivalence of generic tacrolimus capsules (single dose) vs. reference product (Prograf®)**

<table>
<thead>
<tr>
<th>Product</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL) [ratio test/ref % (90% CI)]</th>
<th>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng.h/mL) [ratio test/ref (90% CI)]</th>
<th>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (ng.h/mL) [ratio test/ref (90% CI)]</th>
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<tbody>
<tr>
<td>Tacrolimus® (Adoport®) 0.5mg (Sandoz)</td>
<td>3.47 Ratio = 0.93 (0.9 to 0.97) Prograf= 3.71</td>
<td>32.8 Ratio = 1.05 (1.02 to 1.08) Prograf = 31.6</td>
<td>41.0 Ratio = 1.04 (1.01 to 1.07) Prograf = 39.8</td>
</tr>
<tr>
<td>Tacrolimus® (Adoport®) 5mg (Sandoz)</td>
<td>39.2 Ratio 1.01 (0.92- 1.11) Prograf= 39.3</td>
<td>402 Ratio 1.05 (0.99-1.11) Prograf= 388</td>
<td>424 Ratio 1.04 (0.99-1.1) Prograf = 410</td>
</tr>
<tr>
<td>Tacrolimus® 5mg (TEVA) Biowaiver for lower strengths as per EMA guidance</td>
<td>32.534 Ratio = 1.12 (1.05 to 1.18) Prograf= 29.526</td>
<td>260.236 Ratio = 0.99 (0.93 to 1.05) Prograf= 261.606</td>
<td>279.685 Ratio = 0.99 (0.94 to 1.05) Prograf = 281.575</td>
</tr>
<tr>
<td>Tacrolimus (Vivadex®) 5mg (Dexcel Pharma)</td>
<td>32.53 [111.57] Prograf = 29.53</td>
<td>Data not provided</td>
<td>279.69 [99.01] Prograf = 281.57</td>
</tr>
</tbody>
</table>

The 90% confidence intervals for AUC and Cmax for tacrolimus are within the required bioequivalence acceptance ranges and thus these products can be considered bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements of the European Medicines Agency (EMA).

**Concerns about generic substitution of immunosuppressants:**

Frequent arguments against generic drugs from physicians and patients include the following:

- The quality of generics is sometimes lower than that of the originator drug.
- The FDA acceptance limits for generics are 80–125%- this is a potential difference of as much as 45%.
- Generic drugs are tested only in healthy volunteers and may act differently in the target disease population, resulting in uncontrolled clinical risks.
- Generics of so-called ‘critical dose’ drugs are especially dangerous.

The authors of a recent review on bioequivalence testing attempt to address these arguments, highlighting that it is the upper and lower limit of the 90% confidence interval for the true mean ratios and not only the mean ratio (point estimate) that must be within the bioequivalence acceptance limits; and to fit the 90% confidence interval within the 80–125% acceptance limits, the generic drug and the innovator have to be almost identical. They reiterate that generic drugs approved by the FDA and other regulatory agencies.
• contain the identical active molecule as the innovator’s version of the drug;
• are manufactured following precisely the same quality standards;
• have to meet bioequivalence criteria that can only be met if both the point estimate and the 90% confidence interval of the true mean ratios fall within 80–125% acceptance limits;
• can be tested adequately in healthy volunteers, whereas testing in the target patient population will not necessarily generate additional information or uncover previously unknown risks.

Patient switching programmes

A search of Medline and Embase did not identify any published data on switching programmes. There has been a report of the inadvertent switching of four patients with stable renal allografts on Prograf to generic tacrolimus. None of these patients had experienced any acute rejection in the 12 months prior to the switch. A retrospective analysis of pre- and post-switch trough tacrolimus and serum creatinine levels was conducted. When pooling the data from all 4 patients, trough 12-hour drug levels appeared similar between Prograf and generic tacrolimus, although individual differences were apparent. The mean ± s.e. tacrolimus levels pre- and post-switch, were as follows:

(i) 12-yr-old girl: 7.0 ± 0.69 and 9.7 ± 3.5 (p = NS)
(ii) 8-yr-old boy: 4.7 ± 0.68 and 3.4 ± 0.84 (p = 0.04)
(iii) 22-yr-old woman: 6.8 ± 0.17 and 6.6 ± 0.4 (p = NS)
(iv) 20-yr-old woman: 5.4 ± 0.25 and 4.9 ± 1.4 (p = NS).

Serum creatinine levels were virtually identical pre- and post-switch (eGFR > 75 mL/min/1.73 m²) in the first three patients. Patient 4 experienced an acute rejection episode immediately after the switch, with immediate marked rise in serum creatinine from 1.04 to 2.38 mg/dL. She was treated with a three-day pulse of intravenous methylprednisolone but serum creatinine did not return to baseline. The mean serum creatinine levels rose from 1.15 ± 0.05 before switch to 2.168 ± 0.07 and stayed at that level after the switch (p < 0.001). The authors of this report suggest careful monitoring of paediatric patients who are switched to generic tacrolimus.

The majority of published data on generic tacrolimus preparations relate to bioequivalence studies. There have been some reports from several single arm studies of their use in India, South Korea and Chile:

• The study conducted in India assessed the safety and efficacy of generic tacrolimus (Pan Graf) as de novo therapy in 155 consecutive recipients of living donor renal allografts. Six patients were diabetic prior to transplantation and 9 patients were hepatitis C virus (HCV) positive. Immunosuppression consisted of tacrolimus, mycophenolate mofetil or azathioprine, and steroids. The dose of tacrolimus was adjusted according to levels. All patients were followed for 3 to 33 months. The incidence of acute rejection was 3.87%; 17.93% developed new onset diabetes mellitus; and 77.7% of HCV-positive patients and 14.07% of HCV-negative patients developed post-transplantation diabetes mellitus. The patient survival at the current follow-up was 94.19%.

• The efficacy and safety of generic tacrolimus capsules (TacroBell) was evaluated in 96 renal transplant recipients from 9 transplantation centres in South Korea, 94 of whom were administered study drug at least one time in the intent-to-treat (ITT) analysis. An acute rejection episode developed in 10/94 recipients (10.6%). There were no patient deaths during the study. The 6-month graft survival rate was 96.8%.

• In the report from Chile, the use of generic tacrolimus and mycophenolate mofetil was evaluated as primary immunosuppression in 6 living related and 11 cadaveric donor renal transplant recipients. Mean follow-up was 7.6 months. No biopsy-proven acute rejection episodes, graft loss, or recipient deaths were observed.

The results of one relatively large conversion programme involving 102 transplant recipients switched from Prograf® (Astellas) to generic tacrolimus (Sandoz) has been
presented at conference\textsuperscript{17}. In this study patients from four centres in the US were switched on a mg:mg basis if they were on a stable tacrolimus dose (unaltered in previous 4 weeks), had an unchanged target tacrolimus trough level, were not starting or stopping drugs known to interact with tacrolimus and attended follow up appointments reliably. In the cohort recruited 57\% had received a renal transplant, 36\% a liver transplant and 7\% another organ transplant. The average time from transplant was 57 months and the average time from last change in tacrolimus dose was 17 months. It was reported that the average tacrolimus trough level was 6.5\textpm 2.4 ng/mL prior to switch and 6.4 \textpm 2.9 ng/mL after the switch (p=0.72). It was also reported that the average tacrolimus dose was 4.7 \textpm 3.2 mg per day prior to the switch and 4.5 \textpm 3.0 mg afterwards (p=0.17). Of the 102 patients switched 71\% required no dose adjustment, 14\% required an upward titration and 16\% a downward titration. Four spontaneous reports of adverse events were noted (1x mouth sores, 1x rash, 1x vision changes and 1x nausea). The authors conclude that dose requirements and trough concentrations are similar between brand and generic tacrolimus but additional drug monitoring post conversion is recommended as 1 out of every 3 to 4 patients may require dose titration.

**UK national body advice or guidance**

**BNF**

The BNF recommends that switching between Adoport®, Prograf®, Modigraf®, and Advagraf® requires careful therapeutic monitoring. Substitution should be made only under the close supervision of a transplant specialist.\textsuperscript{18}

**MHRA**

The MHRA has recommended measures to minimise the risk of medication errors arising from different formulations of tacrolimus (capsules or granules, immediate-release or prolonged-release). It stressed that it is not safe to switch between these formulations of tacrolimus; and any changes between different formulations, and changes in dosing regimen, should always be accompanied by careful therapeutic monitoring under the supervision of a transplant specialist. However, it did state that “generic immediate-release tacrolimus capsules are bioequivalent with Prograf and may be interchanged.” The Commission on Human Medicines and the MHRA require that all generic oral tacrolimus products be approved with a brand name.\textsuperscript{19}

**The Efficacy and Safety of PRescribing In Transplantation (ESPRIT) Group recommendations**

This independent group of multidisciplinary healthcare professionals, promoting the safety and wellbeing of transplant patients, (www.esprit.org.uk) recently issued recommendations on generic immunosuppressants.\textsuperscript{20} The ESPRIT Group is an independent company supported by educational grants from interested parties including a number of pharmaceutical companies. With regards to tacrolimus, the group does not support generic substitution; and suggest that switching should only be contemplated in the specialist transplant setting with appropriate monitoring. The rationale for this position being that there is limited experience with generic tacrolimus to date and because:

- Tacrolimus is a similar drug (in the same class of calcineurin inhibitors) to ciclosporin and has essentially the same critical indications in transplantation.
- There is currently no evidence that different immediate-release tacrolimus products can be safely interchanged.
- Issues encountered with ciclosporin only became apparent over the years, as experience grew.

**Summary**

Generic immediate-release tacrolimus capsules have identical product licenses to the originator product (Prograf®) and fulfil the bioequivalence requirements of the European Medicines Agency. The MHRA in its May 2010 Drug Safety update stated that as these generic preparations are “bioequivalent with Prograf, they may be interchanged.” There are insufficient data to determine if additional blood levels of tacrolimus would be
required when switching to generic preparations but given the clinical experience described above it would seem prudent to do so. There is limited experience with use of generic tacrolimus to date and there have been no published data on the outcome of switching programmes. The largest cohort study identified is an unpublished report of experience in 102 patients switched in 4 transplant centres in the US in which it is shown that there is a good correlation between dose requirements and trough concentrations pre and post switch although it is noted that 1 in every 3 to 4 patients switched may require dose titration following the switch to the generic version. The Efficacy and Safety of PRescribing In Transplantation (ESPRIT) Group does not support generic substitution and suggest that switching should only be contemplated in the specialist transplant setting with appropriate monitoring.

Ref

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4. Dexcel Pharma Ltd: Vivadex 0.5, 1.0 and 5.0 mg Capsules Summary of Product Characteristics DOR: 20th Feb 2011
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13. Dexcel Pharma. Bioequivalence data for Tacrolimus (Vivadex®) 5mg


