A single-centre comparison of the clinical outcomes at 6 months of renal transplant recipients administered Adoport® or Prograf® preparations of tacrolimus

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Abstract

Background. The use of generic formulations of immunosuppressive drugs in place of brand name drugs offers considerable cost savings. Brand name tacrolimus (Prograf®) came off patent in April 2008. However, published evidence supporting therapeutic equivalence of generic formulations of tacrolimus in solid organ transplantation is lacking. The South West Transplant Centre switched from administering Prograf® to a generic formulation (Adoport®) for de novo transplant recipients in November 2010. This study sought to compare the clinical outcomes of renal transplant recipients administered Prograf® with those receiving Adoport®.

Methods. Data regarding patient characteristics and clinical outcomes were collected retrospectively for all patients undergoing renal transplantation at the South West Transplant Centre between 8 November 2009 and 8 November 2011 to whom tacrolimus was prescribed.

Results. A total of 48 patients received Prograf® and 51 received Adoport®. At 6 months, no statistically significant differences were identified in the rates of patient survival, graft survival, acute allograft rejection, delayed graft function, calcineurin inhibitor toxicity or cytomegalovirus infection occurring within the two groups.

Conclusions. This is the first study to compare the clinical outcomes of patients receiving Adoport® with those receiving brand name tacrolimus. We report comparable clinical outcomes at 6 months in patients receiving either Prograf® or Adoport® from the time of renal transplantation. These early outcome data therefore support the use of Adoport® in place of Prograf® as a potential cost-saving measure.

Keywords: Adoport; Prograf; renal transplant; tacrolimus

Introduction

The use of generic formulations of immunosuppressive drugs in place of brand name drugs offers considerable cost savings. Brand name tacrolimus (Prograf®, Astellas Pharma, USA) came off patent in April 2008. Adoport® (Sandoz, UK), an immediate-release, twice-daily, oral tacrolimus preparation licensed for the prevention and treatment of transplant rejection resistant to other immunosuppressants [1], was introduced to the UK in August 2010.

Both pharmaceutical and bio-equivalence with the originator product, Prograf®, have been demonstrated for Adoport® for licensing purposes [2]. However, whether these data, derived from single-dose studies in healthy adults, offer sufficient guarantee of therapeutic equivalence in a recipient of a renal transplant remains unclear. Published evidence supporting therapeutic equivalence of generic formulations of immunosuppressive medications, including tacrolimus, in solid organ transplantation is lacking [3].

Three studies have evaluated the clinical outcomes of patients receiving generic tacrolimus preparations (including PanGraf® and Tacro-Bell®) and have reported that these medications are safe and effective [4–6]. However, the reliability of these conclusions is undermined by the non-comparative nature of these studies. Meanwhile, a post-hoc analysis of an open-label, randomized, controlled study, which reported higher rates of acute rejection (although not statistically significant) amongst patients receiving generic tacrolimus (Tenacrine®), has not come to peer-reviewed publication [7]. There have been no published studies comparing the clinical outcomes of patients receiving Prograf® with those receiving Adoport®.

For cost reasons, the South West Transplant Centre switched from administering Prograf® to Adoport® for de novo transplant recipients on 8 November 2010. In the absence of any published studies directly comparing the clinical outcomes of patients receiving brand name
and generic preparations of tacrolimus, and in order to meet local governance requirements, we sought to demonstrate non-inferiority between the clinical outcomes of renal transplant recipients administered either Prograf® or Adoport®.

Subjects and methods

Data regarding patient characteristics and clinical outcomes were collected retrospectively for all patients undergoing renal transplantation at the South West Transplant Centre between 8 November 2009 and 8 November 2011 to whom tacrolimus was prescribed.

The induction and maintenance immunosuppression regimens administered to the patients included in this study are shown in Figure 1. During the 12-month period commencing 8 November 2009, Prograf® was commenced in 48 adult patients on the day of transplantation at a total daily dose of 0.10 mg/kg in two divided doses. The target whole blood concentration was 10–12 ng/mL for donation after brain death (DBD) organ recipients and 8–10 ng/mL for donation after cardiac death (DCD) organ recipients for the first 6 months. The patients received 20 mg basiliximab (Simulect®) and 500 mg methylprednisolone intravenously as induction therapy. Basiliximab 20 mg was also administered on Day 4 post operatively. Mycophenolate mofetil 1 g twice daily and prednisolone (reduced from 20 mg once daily to 5 mg once daily over 6 weeks) were administered as initial maintenance therapy. Two patients received azathioprine in place of mycophenolate mofetil due to previous intolerance.

From 8 November 2010, de novo renal transplant recipients were prescribed Adoport® in place of Prograf®. During the subsequent 12-month period, a total of 63 adult patients underwent transplantation. The South West Transplant Centre recruited patients to the national clinical trial of alemtuzumab (Campath-1H®) and sirolimus (3C study) [8] from 11 January 2011, and 36 of the 63 patients were enrolled in this trial. Twelve of these patients were randomized to receive alemtuzumab in place of basiliximab at induction and have therefore been excluded from the analysis reported here. The immunosuppression regimen provided to the remaining 51 recipients of Adoport® was identical to that described for the Prograf® recipients with the exception of the use of mycophenolate sodium (720 mg twice daily) in place of mycophenolate mofetil in approximately half of the patients (in accordance with the 3C study protocol).

Data were collected for the following parameters: age; sex; primary renal disease; type of transplant (DBD; DCD; living donor genetically related; and, living donor genetically unrelated); induction and initial maintenance immunosuppression regimens; whole blood trough tacrolimus levels at 1, 3 and 6 months; period of follow-up; patient survival; graft survival; delayed graft function (DGF); biopsy-proven acute rejection (BPAR) episodes; calcineurin-inhibitor toxicity; thrombotic microangiopathy (TMA); post-transplant lymphoproliferative disorder (PTLD) or new malignancy; cytomegalovirus (CMV) viraemia and disease; BK polyoma virus nephropathy (BKV); pneumocystis jiroveci pneumonia (PJP); excretory renal function at six months (estimated glomerular filtration rate (eGFR) and serum creatinine); and reported adverse prescribing incidents.

DGF was defined, in accordance with the most commonly used definition in the medical literature [9], as the need for one or more sessions of dialysis within the week following transplantation.

Fig. 1. The induction and initial maintenance immunosuppression regimens.
Clinical outcomes with generic tacrolimus in transplantation

The diagnosis of acute rejection required histological confirmation based on the 2007 revision of the 1997 Banff criteria [10]. The diagnosis of calcineurin-inhibitor toxicity required that three criteria were met: histological features compatible with calcineurin-inhibitor toxicity (for example, arteriolar hyalinosis, isometric tubular epithelial cell vacuolization or a ‘striped’ pattern of interstitial fibrosis); the absence of any other identifiable cause of graft dysfunction; and an improvement in graft function as a result of a subsequent reduction in the tacrolimus dosage.

The definition of TMA required either a fulminating de novo haemolytic uraemic syndrome (characterized by acute kidney injury, microangiopathic haemolytic anaemia and thrombocytopenia) or an acute kidney injury associated with histological changes compatible with TMA (such as glomerular involvement with endothelial cell swelling, capillary thrombi and mesangiolysis, and fibrinoid necrosis in the arterioles and interlobular arteries) in the absence of serological evidence of anti-body or T-cell mediated rejection.

In the South West Transplant Centre, all recipients at high risk of developing CMV infection (D+ R− recipients) receive antiviral prophylaxis with valganciclovir for 6 months from transplantation, after which surveillance with CMV polymerase chain reaction (PCR) testing is undertaken for a further 3 months. For recipients with latent infection (D+ R+ and D− R+), CMV prophylaxis is dependent upon immunosuppressive treatment: patients receiving T-cell-depleting antibodies, including alemtuzumab (at induction) or anti-thymocyte globulin (for the treatment of rejection), receive prophylaxis with valganciclovir, whilst the remainder undergo surveillance with CMV PCR for the first 3 months after transplantation. No surveillance or routine prophylaxis was undertaken for D− R− recipients.

For the purposes of this study, a diagnosis of CMV viraemia required the presence of >1 × 10³ copies/mL on PCR. A diagnosis of CMV disease required one or both of the following two criteria to be met. First, CMV viraemia in the presence of one or more of the following clinical symptoms: fever, night sweats, weight loss, myalgia, arthralgia, or malaise; lymphopaenia; thrombocytopenia; or subclinical hepatitis (serum transaminases greater than two times the upper limit of normal). Secondly, tissue invasive disease such as biopsy-proven gastrointestinal disease; radiological evidence of pneumonitis associated with typical symptoms; the typical fundoscopic appearances of CMV chorioretinitis; or graft dysfunction (diagnosed on the basis of either histological evidence at renal biopsy or a rise in serum creatinine in the absence of an alternative explanation and in the presence of CMV viraemia).

The diagnosis of pneumocystis jiroveci pneumonia (PJP) required the identification of infected material (from either induced sputum and broncho-alveolar lavage). The diagnosis of BK polyoma virus nephropathy required positive immunohistochemistry using a commercial antibody directed against the SV40 large-T-antigen. The diagnosis of both post-transplant lymphoproliferative disorder and other forms of malignancy required histological confirmation.

The eGFR was determined using the Modification of Diet in Renal Disease formula [11]. Reported adverse prescribing incidents were identified through the Datix® patient safety software system used throughout the hospital Trust.

Statistical analysis

Differences between means were tested using Student’s t-test or Mann–Whitney U test for non-normal data. Normality was assessed by visual inspection of probability plots. Differences between proportions were tested using Fisher’s exact test. Kaplan-Meier analysis of graft and patient survival, and time to first rejection, was performed using the software ‘R’ [12] and the ‘survival’ package [13]. The groups were compared using a log-rank test. P-values <0.05 were considered statistically significant. All tests were two-tailed.

Results

The characteristics of the patients included in this study are presented in Table 1. There was little evidence of a difference in whole blood trough tacrolimus levels at 1, 3 and 6 months post-transplant between patients receiving Adoport® and those receiving Prograf®. These data are presented in Table 2 and Figure 2. Overall, the estimated median trough levels decreased from 9.01 to 7.23 ng/mL between the 1- and 6-month observations.

There was little evidence of a difference in the rates of patient survival at 6 months between the Prograf® and Adoport® groups (95.8 and 96.1%, respectively, P = 1.000; Table 3 and Figure 3). Similarly, there was little evidence of a difference in graft survival at 6 months between the Prograf® and Adoport® groups (87.5 and 84.3%, respectively, P = 0.776; Table 3 and Figures 4 and 5), although those deceased donor organ recipients to whom Adoport® was prescribed had numerically lower graft survival rates than those to whom Prograf® was administered (78.9 and 88.2%, respectively).

The degree of graft function at 6 months was compared between the two groups. Although the use of Prograf® appeared to be associated with improved serum creatinine and eGFR results, statistical significance was not reached (Table 4). There was no statistical difference in the BPAR rates between Prograf® (16.7%) and Adoport® (17.6%) recipients (P = 1.000; Table 5 and Figure 6). In deceased donor recipients, BPAR occurred more frequently in patients receiving Adoport® than Prograf® (21.1 and 8.8%, respectively) although this difference was not statistically significant. Amongst the Prograf® recipients, the rate of BPAR was unexpectedly high within the live donor group (35.7%), although the patient numbers are small (n = 14).

The incidence of DGF was higher amongst Prograf® recipients (33.3%) than Adoport® recipients (21.6%) although this difference was not statistically significant (P = 0.292, Table 5). This was the case for both live donor organ recipients (no patients receiving Adoport® developed DGF compared with 14.3% of those receiving Prograf®) and deceased donor recipients (41.2% of those taking Prograf® developed DGF compared with 28.9% of those taking Adoport®).

There were higher rates of calcineurin inhibitor toxicity amongst those patients receiving Adoport® than those receiving Prograf® (23.6 and 12.5%, respectively), for recipients of both deceased donor and live donor organs, although this finding was not of statistical significance (P = 0.186, Table 5).

TMA was diagnosed in 4.2% of patients receiving Prograf® and 5.9% of patients receiving Adoport® (Table 5).
The rates of CMV infection are shown in Table 6. High-risk (D+ R−) recipients treated with Prograf® developed CMV disease in 5.3% of cases. A higher, although not statistically significant, incidence occurred amongst those treated with Adoport® (13.3%). The use of Adoport® for recipients with latent infection (D+ R+ and D− R+) was associated with CMV disease rates of 15.4 and 0%, respectively; lower than the rates amongst Prograf® recipients of 22.2 and 11.1%. Although the incidence of CMV viraemia amongst D+R+ and D−R+ patients was higher in those taking Adoport® than in those taking Prograf® (38.5 and 40% compared with 22.2 and 11.1%), this did not reach statistical significance.

During this study, a single patient (receiving Adoport®) developed PTLD. There were no identified cases of BK polyoma virus nephropathy or PJP in patients receiving either Adoport® or Prograf®.

### Discussion

We have undertaken a retrospective comparison of the clinical outcomes at 6 months of patients commencing Prograf® or Adoport® at the time of renal transplantation at a single centre.
There was little evidence for the difference in patient or graft survival at 6 months between the Prograf® and Adoport® groups. Although those deceased donor organ recipients to whom Adoport® was prescribed had numerically lower graft survival rates than those to whom Prograf® was administered, this finding was not statistically significant (P = 0.354). Furthermore, the use of Adoport® was not obviously implicated in this finding: of the eight Table 3. Patient and graft survival rates at six months for patients administered Prograf® and Adoport®

<table>
<thead>
<tr>
<th>Outcome parameter</th>
<th>Donor organ</th>
<th>Prograf® recipients</th>
<th>Adoport® recipients</th>
<th>Prograf® versus Adoport® P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient survival</td>
<td>DCD and DBD</td>
<td>33/34</td>
<td>36/38</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>LD</td>
<td>13/14</td>
<td>13/13</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>46/48</td>
<td>49/51</td>
<td>1.000</td>
</tr>
<tr>
<td>Graft survival (death not censored)</td>
<td>DCD and DBD</td>
<td>30/34</td>
<td>30/38</td>
<td>0.354</td>
</tr>
<tr>
<td></td>
<td>LD</td>
<td>12/14</td>
<td>13/13</td>
<td>0.482</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>42/48</td>
<td>43/51</td>
<td>0.776</td>
</tr>
</tbody>
</table>

Graft survival treats death with graft function as graft failure.

Table 4. Additional clinical outcome data at 6 months for patients administered Prograf® and Adoport®

<table>
<thead>
<tr>
<th>Donor organ</th>
<th>Prograf® recipients</th>
<th>Adoport® recipients</th>
<th>Prograf® versus Adoport® P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median serum creatinine, with inter-quartile range (µmol/L)</td>
<td>DCD and DBD</td>
<td>112 (96–142)</td>
<td>127 (114.2–153)</td>
</tr>
<tr>
<td>LD</td>
<td>122.5 (98.5–188)</td>
<td>134.5 (101–159.2)</td>
<td>0.9737</td>
</tr>
<tr>
<td>All</td>
<td>127 (111.8–157.2)</td>
<td>112 (96–167)</td>
<td>0.1632</td>
</tr>
<tr>
<td>Mean estimated glomerular filtration rate, ±SD (mL/min/1.73 m²)</td>
<td>DCD and DBD</td>
<td>54.7 ± 20.2</td>
<td>48.3 ± 15.2</td>
</tr>
<tr>
<td>LD</td>
<td>53</td>
<td>45.2</td>
<td>0.2754</td>
</tr>
<tr>
<td>All</td>
<td>54.3 ± 20.2</td>
<td>47.6 ± 15.2</td>
<td>0.0887</td>
</tr>
</tbody>
</table>

Grafts failing prior to 6 months were excluded from this analysis.

There was little evidence for the difference in patient or graft survival at 6 months between the Prograf® and Adoport® groups. Although those deceased donor organ recipients to whom Adoport® was prescribed had numerically lower graft survival rates than those to whom Prograf® was administered, this finding was not statistically significant (P = 0.354). Furthermore, the use of Adoport® was not obviously implicated in this finding: of the eight
Table 5. Additional clinical outcome data at 6 months for patients administered Prograf® and Adoport®

<table>
<thead>
<tr>
<th>Outcome parameter</th>
<th>Donor organ</th>
<th>Prograf® recipients</th>
<th>Adoport® recipients</th>
<th>Prograf® versus Adoport® recipients P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed graft function</td>
<td>DCD and DBD</td>
<td>14/34</td>
<td>11/38</td>
<td>28.9%</td>
</tr>
<tr>
<td></td>
<td>LD</td>
<td>2/14</td>
<td>0/13</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>16/48</td>
<td>11/51</td>
<td>21.6%</td>
</tr>
<tr>
<td>Biopsy proven acute rejection</td>
<td>DCD and DBD</td>
<td>3/34</td>
<td>8/38</td>
<td>21.1%</td>
</tr>
<tr>
<td></td>
<td>LD</td>
<td>5/14</td>
<td>1/13</td>
<td>7.7%</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>8/48</td>
<td>9/51</td>
<td>17.6%</td>
</tr>
<tr>
<td>Calcineurin inhibitor toxicity</td>
<td>DCD and DBD</td>
<td>6/34</td>
<td>10/38</td>
<td>26.3%</td>
</tr>
<tr>
<td></td>
<td>LD</td>
<td>0/14</td>
<td>2/13</td>
<td>15.4%</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>6/48</td>
<td>12/51</td>
<td>23.6%</td>
</tr>
<tr>
<td>Thrombotic microangiopathy</td>
<td>All</td>
<td>2/48</td>
<td>3/51</td>
<td>5.9%</td>
</tr>
</tbody>
</table>

Fig. 6. Kaplan–Meier survival analysis showing time to first rejection episode after transplantation (with death and graft loss censored). P = 0.894 (log-rank test).

patients whose grafts failed, five suffered surgical complications (two developed renal vein thrombosis; two developed mycotic transplant artery aneurysms resulting from donor contamination with candida; and one suffered an unexplained transplant artery rupture) whilst a further patient was found to have severe donor vascular disease compounded by surgical re-exploration for poor flow in the renal vein and the subsequent development of an arteriovenous fistula after transplant biopsy. The remaining two patients suffered graft loss as a result of rejection.

No clinically significant changes in the performance of the South West Transplant Centre were detected by the cumulative sum charts produced quarterly by NHS Blood and Transplant during the period of this study to observe 30-day mortality and graft survival rates, indicating that the outcomes obtained using Adoport® are in keeping with the historical performance of the centre.

The mean eGFR at 6 months for patients receiving Prograf was more than 5 mL/min/1.73 m² higher than those in the Adoport® group, though this was not found to be statistically significant. This was investigated further by fitting a multiple regression model to estimate the treatment effect allowing for other prognostic factors: type of donor (living or deceased); donor age; mismatch; DGF; calcineurin inhibitor toxicity; BPAR; and tacrolimus trough levels. The mean eGFR level in the Prograf group was 2.94 mL/min/1.73 m² higher than that in the Adoport group (95% confidence interval –3.28 to 11.17).

Acute allograft rejection complicates between 10 and 25% of renal transplants, and the finding that the rates of BPAR were similar between the Prograf® and Adoport® recipients in this study is therefore important—particularly as more than 90% of episodes occur within the first 6 months.

Although not reaching statistical significance, the rates of calcineurin inhibitor toxicity appeared to be higher in those patients receiving Adoport® than in those receiving Prograf® for recipients of both deceased donor and live donor organs. How these results compare with those in other centres is difficult to ascertain as data regarding the incidence of calcineurin inhibitor toxicity in the early period after transplantation are limited. In a recent prospective study of 158 deceased donor transplant recipients, clinically manifest calcineurin inhibitor toxicity was evident on protocol biopsy in 10.1% of patients at week 3 after transplantation, 9.2% at month 3, and in 8.9% at 1 year [14]. The same study also reported similar incidences (10.8, 9.9 and 9.7%) of subclinical calcineurin inhibitor toxicity at these time points. The results presented here therefore reveal higher rates of calcineurin inhibitor toxicity within the Adoport® group, despite the targeting of lower whole blood trough levels. However, it is possible that differences in the diagnostic criteria used for calcineurin inhibitor toxicity between the two studies may have contributed to their differing results.

The rates of TMA for both the Adoport® and Prograf® patients were higher than those reported elsewhere in the literature. None of these patients had haemolytic uraemic syndrome as their primary renal disease. There is a genetic predisposition to atypical haemolytic uraemic syndrome amongst clusters of families in the North Devon area of the UK.

Data regarding the incidence of CMV infection vary between studies as a result of the varying intensities of immunosuppression, differing definitions of CMV viraemia and disease, and alternative protocols for prophylaxis and pre-emptive treatment. We report a relatively low incidence of CMV disease amongst high risk (D+ R–) recipients treated with Prograf® (5.3%) and a higher, although not statistically significantly different, incidence amongst those treated with Adoport® (13.3%) when compared with the incidence of 11.5% reported (at 1 year) in a recent study of patients receiving the same prophylaxis...
regimen [15]. The use of Adoport® for recipients with latent infection (D+ R+ and D− R+) was associated with the rates of CMV disease in keeping with those reported with other immunosuppressants. Although the incidence of CMV viremia amongst D+R+ and D−R+ patients was higher in those taking Prograf® than in those taking Prograf® (and than has typically been reported elsewhere), this did not reach statistical significance.

In this study, 46 of the 48 patients receiving Prograf® were administered mycophenolate mofetil (with two patients receiving azathioprine). Meanwhile, 26 of the 51 patients receiving Adoport® were administered mycophenolate mofetil with the remaining 25 receiving mycophenolate sodium. This discrepancy in immunosuppressive regimens is unlikely to be of clinical significance as strong evidence favouring one or more of these preparations is lacking. Although a retrospective study of 1709 transplant recipients found that mycophenolic sodium was associated with lower rates of BPAR, possibly as a result of fewer dose reductions or discontinuations, this graft survival rates were the same as those for patients receiving mycophenolate mofetil [16]. Furthermore, a prospective study of 105 patients receiving tacrolimus, steroid and one or more of the mycophenolic acid preparations after renal transplantation reported no significant differences in clinical outcomes [17]. A similar finding was reported from a randomized study comparing the use of mycophenolate mofetil and mycophenolate sodium in 150 patients taking tacrolimus but no steroid and followed for 4 years [18].

Finally, changes to routine clinical practice—such as the use of Adoport® in place of Prograf®—may result in human error. We identified one patient in whom Adoport® had been inadvertently switched to Prograf®. Whole blood tacrolimus concentrations remained consistent and the patient experienced no adverse effects. Although the MHRA states that Prograf® and Adoport® may be interchanged [19], there is little published evidence to support this. In one study, 43% of the 41 mixed transplant patients switching from Prograf® to generic formulations experienced alterations in whole blood concentrations greater than 20% [20]. Dose adjustments were required more frequently after switching to generic formulations during a further study of 70 mixed transplant patients, in whom there were no recorded episodes of allograft rejection [21]. Post-conversion monitoring is therefore advisable, and inadvertent switching may result in adverse outcomes. In a case series of four inadvertent switches from Prograf® to generic tacrolimus in paediatric renal transplant recipients, one patient developed biopsy-proven acute rejection [22]. Guidance intended to reduce the risk of medication errors with tacrolimus advocates that prescribers use either the exact and full pharmaceutical form (capsules or granules; intermediate or prolonged release) or the brand name, including the dose and frequency in both cases [19]. Patients should be advised to note the brand name of their tacrolimus medicine [19].

**Limitations**

This was a retrospective study in which the patient cohorts were separated by time, increasing the possibility of confounding influences, and in which only the short-term clinical outcomes were assessed.

**Conclusions**

Recent studies have reported that Adoport® has a similar pharmacokinetic profile to brand name tacrolimus (Prograf®) and is bioequivalent in kidney transplant recipients [23, 24]. This is the first study to compare the clinical outcomes of patients receiving Adoport® with those of patients receiving Prograf®. We report comparable clinical outcomes at 6 months in patients receiving either Prograf® or Adoport® from the time of renal transplantation. These early outcome data therefore support the use of Adoport® in place of Prograf® as a potential cost-saving measure.

**Authors’ contributions**

AC and PAR conceived the idea for the paper. AC collected the data and wrote the initial manuscript. All authors contributed to the analysis of the data and to subsequent revisions of the manuscript.

**Conflict of interest statement.** None declared.

**References**


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