Letters

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Fetal malformations associated with mycophenolate mofetil for lupus nephritis

Sir,

Mycophenolate mofetil (MMF) has become a major therapeutic option as an induction and maintenance therapy for lupus nephritis [1,2]. Many patients with lupus are women of child-bearing age, so the issue of teratogenicity associated with MMF is important. MMF has been classified as category C by the American Food and Drug Administration. In other words, animal reproductive studies have shown a teratogenic effect and the required human reproductive studies are lacking; however, the potential clinical benefits may warrant the use of MMF during pregnancy, despite the potential risk.

In a recent paper, Sifontis et al. [3] analysed the outcomes of pregnancies in patients who had received solid organ transplants, and were also exposed to MMF. The rate of live births was 57.7%, and 26.7% (4 cases) of the live births had structural malformations. Combining these four cases with another reported case [4], recurrent structural malformations can be identified: microtia (4/5), cleft lip and palate (3/5). There are also other birth-associated defects, including hypoplastic nails, shortened fingers, external auditory duct atresia, diaphragmatic hernias and heart malformations. Despite this recurrent pattern, the authors suggest that the multiplicity of medications in transplant recipients may be involved, and particularly the fact that MMF is always associated with calcineurin inhibitors, drugs also classified in category C. The effects of MMF during pregnancy may be assessed by studying a non-transplant, MMF-exposed population.

Here we report a case of a 21-year-old woman who had two flares of class IV lupus nephritis, treated in 2003 and 2005 by 6-month courses of intravenous cyclophosphamide. The lupus was in remission after the last course of cyclophosphamide. She had been on MMF maintenance therapy (1000 mg b.i.d) for 10 months when pregnancy was discovered at 25 weeks gestation. She was also receiving prednisone, hydroxychloroquine and perindopril. The pregnancy was terminated because fetal ultrasonography showed multiple malformations. The feto-pathology examination showed multiple defects affecting the head (bilateral anopia, external auditory duct atresia), lower limb (polydactyly and nail hypoplasia), heart (anterior positioning of the aorta, interventricular communication) and kidneys (asymmetry). Cytogenetic studies revealed a normal karyotype.

Several studies have shown safety of hydroxychloroquine during pregnancy [5]. Exposure to perindopril, an angiotensinogen-converting enzyme (ACE) inhibitor, in the first trimester may explain the heart and kidney malformations [6]. However, we also observed malformations, including microtia, external auditory duct atresia and limb abnormalities, similar to those reported in transplant recipients receiving MMF, but not in patients receiving ACE inhibitors. To our knowledge, this is the first case to illustrate the teratogenicity of MMF alone, when treating lupus nephritis. The European recommendations for organ recipients should, therefore, also be applied to women suffering from rheumatological disease treated with MMF [7]. A different immunosuppressive agent should be used from at least 6 weeks before conception. Azathioprine, a drug that is not teratogenic, appears to be the best alternative for treating lupus nephritis.

Conflict of interest statement. None declared.

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Is implanto-prosthodontic treatment available for haemodialysis patients?

Sir,

Dental problems and complications in renal patients are infrequently discussed in nephrological journals. In this context, the appearance of two publications (Original Article and Editorial Comment) dedicated to this underestimated, but very important problem in NDT seems a very positive exception [1,2]. Underdiagnosed and untreated
periodontitis and other gingival changes may in consequence lead to odontogenic bacteriemic episodes and the development of potentially serious infections, e.g. infective endocarditis. One must remember that ESRD patients are immunodeficient, a condition caused by disturbances of the cellular and humoral immunological response [3]. On the other hand, patients after renal transplantation may develop a very specific type of gingival hyperplasia and subsequent periodontitis caused by cyclosporine. We recently published our experience with this subject, taking into account treatment performed on patients after successful renal transplantation [4,5]. In the second paper, we proposed a diagnostic and therapeutic algorithm based on our experience and literature search. We wish to draw attention to another important issue related to the availability of modern dental implantology in ESRD patients. In their comments, Craig et al. [1] suggested that ‘osseous periodontal surgical procedures such as bone grafting or dental implants may be contraindicated in patients with significant renal osteodystrophy’. This suggestion was based on the results of studies performed several years ago. Unfortunately, this type of opinion is quite common both in dental and nephrological literature [6]. In the last 5 years, we have performed several studies in patients treated with maintenance haemodialysis and after successful renal transplantation leading to opposite conclusions, showing that this type of treatment is applicable to ESRD patients [7–9]. In Table 1, the availability of implants in 100 haemodialysis patients is shown. Results were compared with a control group of 50 healthy persons, with similar age and gender. Studies included radiometric analysis in digital dental panoramic tomography (DPT) using implantological template by Nobel Biocare. Multivaricance analysis consists of:

- radiometric, mathematical Fourier’s and densitometric analysis of the jaw bones;
- Nobel Direct implants simulation, using implantological template and digital pantomography system Planmeca, Vix Win 2000;
- histological and histomorphometrical analysis of jaws bone tissue samples;
- jaws mineral bone qualitative analysis using EPR (electron paramagnetic resonance methodology);
- evaluation of biochemical markers of bone metabolism (calcium, phosphate, PTH, alkaline phosphatase). Analysis of the obtained results performed using multiple regression and correlation tests (Statistica 7.0, StatSoft, Tulsa, USA).

Table 1. Comparison of the availability of implant installation at maxilla or mandible between control group and HD patients

<table>
<thead>
<tr>
<th>Availability of implant installation Place/Group (%)</th>
<th>No possibility</th>
<th>10 mm length implant (%)</th>
<th>13 mm length implant (%)</th>
<th>16 mm length implant (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maxilla Control group n = 50</td>
<td>–</td>
<td>28</td>
<td>24</td>
<td>48</td>
</tr>
<tr>
<td>HD Patients n = 100</td>
<td>–</td>
<td>40</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Dialysed ≤2 years</td>
<td>–</td>
<td>30</td>
<td>53</td>
<td>17</td>
</tr>
<tr>
<td>Dialysed ≤4 years</td>
<td>–</td>
<td>28</td>
<td>55</td>
<td>28</td>
</tr>
<tr>
<td>Dialysed ≤6 years</td>
<td>–</td>
<td>20</td>
<td>52</td>
<td>28</td>
</tr>
<tr>
<td>Mandible Control group n = 50</td>
<td>–</td>
<td>20</td>
<td>52</td>
<td>28</td>
</tr>
<tr>
<td>HD Patients n = 100</td>
<td>–</td>
<td>44</td>
<td>44</td>
<td>8</td>
</tr>
<tr>
<td>Dialysed ≤2 years</td>
<td>11</td>
<td>51</td>
<td>33</td>
<td>5</td>
</tr>
<tr>
<td>Dialysed ≤4 years</td>
<td>13</td>
<td>37</td>
<td>42</td>
<td>8</td>
</tr>
<tr>
<td>Dialysed ≤6 years</td>
<td>–</td>
<td>40</td>
<td>20</td>
<td>–</td>
</tr>
</tbody>
</table>

Detailed data showing the results of consecutive steps of examination performed in ESRD patients were published elsewhere [7–9].

The analysis shows a decreased quantity and quality of bone tissue of the maxilla and mandible in renal osteodystrophy. Nevertheless, according to internationally recognized standards, these changes were not a contraindication to implantological treatment. This thesis was confirmed in clinical practice because we observed normal function of the implants in patients suffering from renal osteodystrophy, who had received implants many years previously. In general, these patients need more frequent professional advice on oral hygiene and microbiological control using RT-PCR (unpublished data).

Only four patients were potentially excluded from this procedure dependent on the time of haemodialysis therapy, due to the inappropriate state of their mandible (low bone density and considerable bone decrease). No exclusions were noted on potential implant installation in the maxilla.

In conclusion, the results of our studies clearly show that in the large majority of patients on renal replacement therapy, implantological treatment is possible. Nevertheless, taking into account all specific circumstances (potential use of immunosuppression, higher risk of infection, etc.) it is necessary to establish a special diagnostic and therapeutic algorithm regulating implantological procedures in these patients [10].

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Calcimimetic increases osteoprotegerin and decreases fetuin-A levels in dialysis patients

Sir,

The calcimimetic drug cinacalcet, recently introduced as therapy for Secondary Hyper-Parathyroidism (SHP) in dialysis patients, has greatly enhanced the ability to achieve simultaneous control of parathyroid hormone (PTH), calcium and phosphate [1].

However, there have been no data to show that a better control of mineral metabolic parameters is matched with improved clinical outcomes of vascular calcification processes, and hence, of vascular morbidity and mortality.

Recent studies have shown that both osteoprotegerin (OPG) and Fetuin-A are associated with the vascular calcification process in uremic patients [2,3].

Of 164 patients from our dialysis centre, we submitted 29 of these having serum i-PTH >300 pg/ml while on standard therapy (calcitriol + phosphate binders) to cinacalcet treatment over a 6-month period.

After an observation period of 3 weeks that included the standard therapy, cinacalcet was started at an initial dose of 30mg per day. Thereafter, cinacalcet, vitamin D metabolites and phosphate binder doses were adjusted according to i-PTH, c-Ca and Pi levels. Cinacalcet was allowed to be increased by 30mg steps every 15 days to a maximal allowed dose of 180mg per day. The drug was reduced or withdrawn if i-PTH levels were <150pg/ml, if c-Ca was <8.4mg/dl, or if any adverse events appeared.

Blood levels of i-PTH, c-Ca, inorganic phosphate (Pi), albumin, IL-6, Fetuin-A, OPG were assessed at baseline and at the end of the study period. Intact PTH, c-Ca and Pi levels were also checked every 15 days. Over the 6-month study period, the doses of cinacalcet, vitamin D metabolites, phosphate binders, erythropoietin (EPO), anti-hypertensive (antiHT) drugs and any major and minor adverse events were recorded.

OPG and Fetuin-A were assessed by ELISA (Normal values: OPG 4.1 ± 0.33 pmol/l; Fetuin-A 0.35–0.95 g/l).

IL-6 was determined with a solid-phase, enzyme-labelled, chemiluminescent sequential immunometric assay (Normal values were 0–5.9 pg/ml).

Five of the original 29 patients did not complete the study (two due to cardio-vascular deaths; one for withdrawal after a non-fatal cardio-vascular event; two for receiving renal transplantation), resulting in 24 patients included in the final analysis (16 males; aged 38–78).

Table 1 shows the effects of cinacalcet treatment on i-PTH, c-Ca, Pi and the c-Ca × Pi product. All of these parameters were significantly decreased after cinacalcet therapy.

The mean dose of cinacalcet utilized at the end of the study was 63.12 ± 40.3 mg per day. There were no significant changes in Vitamin D, Sevelamer, Ca based Pi binder, antiHT drugs or EPO doses.

Following cinacalcet treatment, mean serum OPG levels were significantly increased and serum Fetuin-A levels were significantly decreased (Table 2). On the other hand, there were no significant changes in mean IL-6 values. OPG increments were significantly correlated with the degree of c-Ca reduction (r = 0.445; P = 0.029), whereas Fetuin-A levels were not significantly affected by cinacalcet therapy.

Table 1. Effects of 6-month Cinacalcet treatment on the main mineral metabolic parameters and doses of concomitant therapy (mean ± SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>6th month</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>i-PTH (pg/ml)</td>
<td>410.1 ± 0.34</td>
<td>379.8 ± 0.43</td>
<td>0.0002</td>
</tr>
<tr>
<td>c-Ca (mg/dl)</td>
<td>10.5 ± 0.52</td>
<td>9.10 ± 0.70</td>
<td>0.0001</td>
</tr>
<tr>
<td>Pi (mg/dl)</td>
<td>4.93 ± 0.31</td>
<td>4.20 ± 0.19</td>
<td>0.0003</td>
</tr>
<tr>
<td>Ca × Pi (mg/dl²)</td>
<td>51.9 ± 0.31</td>
<td>38.1 ± 0.50</td>
<td>0.00001</td>
</tr>
<tr>
<td>Vitamin D (μg/week)</td>
<td>2.05 ± 0.31</td>
<td>1.63 ± 0.36</td>
<td>0.331</td>
</tr>
<tr>
<td>Ca carbonate (g/day)</td>
<td>0.442 ± 0.31</td>
<td>0.480 ± 0.556</td>
<td>0.726</td>
</tr>
<tr>
<td>Sevelamer (g/day)</td>
<td>5.43 ± 0.31</td>
<td>5.00 ± 0.28</td>
<td>0.319</td>
</tr>
</tbody>
</table>

Table 2. Effects of cinacalcet on OPG, Fetuin-A and IL-6 levels (mean ± SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>6th month</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPG (pmol/l)</td>
<td>16.6 ± 0.34</td>
<td>22.20 ± 0.43</td>
<td>0.001</td>
</tr>
<tr>
<td>Fetuin-A (g/l)</td>
<td>0.766 ± 0.44</td>
<td>0.430 ± 0.24</td>
<td>0.01</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>5.75 ± 0.43</td>
<td>5.93 ± 0.51</td>
<td>0.847</td>
</tr>
</tbody>
</table>


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