Table 1. Cases of ATIN associated with the selective COX-2 inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Author</th>
<th>Peak SCr</th>
<th>Treatment</th>
<th>Final SCr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>Alper [3]</td>
<td>186 μmol/l</td>
<td>Steroids</td>
<td>97 μmol/l</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>Brewster</td>
<td>522 μmol/l</td>
<td>Steroids</td>
<td>106 μmol/l</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>Rocha [5]</td>
<td>769 μmol/l</td>
<td>Haemodialysis, steroids</td>
<td>124 μmol/l</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>Alim [6]</td>
<td>1202 μmol/l</td>
<td>Haemodialysis</td>
<td>115 μmol/l</td>
</tr>
</tbody>
</table>

SCr, serum creatinine concentration.


DOI: 10.1093/ndt/gfh033

Enzyme replacement in the treatment of Fabry’s disease. Is there a point-of-no-return?

Sir,

We read with interest the recently published article by De Schoenmakere *et al.* [1] on enzyme replacement therapy in Fabry’s disease and the Editorial Comment by Breunig and Wanner [2] in the same issue of NDT. In both papers the question raised is whether there is or not a point-of-no-return beyond which organ damage cannot be reversed in spite of correct enzyme replacement treatment. Our experience with a patient may help to answer to this question.

A young man, 29 years old, presented in our outpatient clinic with ankle oedema and was diagnosed with nephrotic syndrome with microhaematuria. The serum creatinine at that time was 1.1 mg/dl. The clinical exam discovered angiookeratomas in pelvic localization. He had suffered acroparaesthesias, hypohidrosis and dizziness for years. Kidney and skin biopsies suggested Fabry’s disease. Very low levels of alpha-galactosidase were demonstrated in the patient and in his mother. He received treatment with carbamazepine and phenytoin for 30 months. The clinical symptoms did not change very much and the renal function declined progressively.

During the month of June 2001 it became possible to start enzyme replacement treatment with agalsidase beta 1 mg/kg every 15 days by i.v. route. At that time the serum creatinine was 4.06 mg/dl and the calculated GFR 20 ml/min.

Three months later the patient began renal replacement treatment with haemodialysis. An echocardiography carried out at that time showed left ventricular hypertrophy. He developed arterial hypertension and was treated with amlodipine and irbesartan. Agalsidase beta treatment was continued at the same dose and was administered during the dialysis session every 14 days.

The clinical symptoms did not change significantly. In July 2002 the patient suffered from a cerebrovascular event diagnosed as ischaemic after a normal cranial CT. The arterial pressure was very difficult to control and he died 48 h later. The necropsy found that cerebral haemorrhage was the cause of death. Cardiac hypertrophy persisted and there were multiple deposits of globotriaosylceramide particularly in endothelial cells (Figure 1).

Enzyme replacement therapy was unable to stop the progression of Fabry’s disease in our patient. This treatment was initiated when the renal function was very low and probably the organ damage was very advanced. We think that in our patient the kidney fibrosis and the damage in other organs like heart, vascular endothelium, etc., had reached a point beyond which the treatment was not useful. The conclusion is that enzyme replacement therapy in Fabry’s disease patients must be initiated as soon as possible to avoid reaching that point-of-no-return.

Conflict of interest statement. None declared.

Sir,

Erythropoietin (EPO) requirements vary in haemodialysis patients. The most commonly recognized causes of EPO resistance are iron deficiency and chronic inflammation. We have previously noted a correlation between serum albumin and extracellular fluid volume (Vecf) in HD patients [1]. If serum albumin is lower in subjects with an increased Vecf, then haemoglobin may be too. However, unlike albumin,
the haemoglobin concentration can be manipulated by the administration of drugs, particularly EPO and iron. We use a computerized anaemia management algorithm to manage the haemodialysis population. EPO and iron doses are determined by: (i) the actual haemoglobin, i.e. the threshold (below which EPO dose increases) and ceiling (above which the EPO dose decreases); (ii) the relative change in haemoglobin, i.e. the size of change in the EPO dose; (iii) the ferritin, i.e. the ceiling for iron administration; and (iv) the percentage iron saturation (TSAT), i.e. the prescribed iron dose.

This algorithm gives a stable haemoglobin and ferritin outcome. Within this framework, we have looked for factors that influence the achieved haemoglobin and the dose of EPO required to obtain it. In particular, we have explored the influence of inflammatory markers and of Vecf.

This was an observational cohort study using data that are collected routinely in our haemodialysis population. We measure pre-dialysis Vecf and total body water (Vtbw) as part of our hypertension management programme. Vecf and Vtbw are measured by multiple frequency bio-electric impedance (Hydra, Xitron technologies) as previously described [2]. Vecf was normalized as a ratio of Vtbw (Vecf/Vtbw). Haemoglobin, serum ferritin, albumin, and C-reactive protein (CRP) were measured by standard assays in a fully accredited hospital laboratory. Correlations were sought between haemoglobin, CRP, serum ferritin, albumin, EPO dose/kg body weight and Vecf/Vtbw.

Bio-impedance data were available in 61 non-selected patients. The median (25th and 75th centile) haemoglobin, CRP, serum ferritin, serum albumin, EPO dose/kg and Vecf/Vtbw were 11.6 g/dl (10.7–12.8), 10 mg/l (5–26.3), 473 μg/l (348–582), 38 g/l (34.8–40), 124 U/kg/week (47–208) and 0.51 (0.48–0.52), respectively. A correlation matrix is shown in Table 1. The achieved haemoglobin was negatively correlated with CRP ($r = -0.311$, $P = 0.01$) and EPO dose/kg ($r = -0.344$, $P = 0.006$) and positively correlated with serum albumin ($r = 0.344$, $P = 0.006$). EPO dose/kg was positively correlated with Vecf/Vtbw ($r = 0.249$, $P = 0.049$; Figure 1) and negatively correlated with serum albumin ($r = -0.312$, $P = 0.013$).

Under the influence of a treatment algorithm that maintains a stable haemoglobin outcome and iron status, inflammation is the major determinant of achieved haemoglobin. This is indicated by a negative correlation with CRP (an acute phase protein) and a positive correlation with serum albumin (a negative acute phase protein). The quantity of EPO required to achieve this haemoglobin outcome was positively correlated with the Vecf as a ratio of total body water. This suggests that under the influence of a treatment algorithm, volume expansion will result in a greater EPO requirement.

**Table 1.** Correlation between haemoglobin (Hb), serum ferritin, serum albumin, CRP, EPO dose/kg body weight per week and extracellular fluid volume as a ratio of total body water (Vecf/Vtbw)

<table>
<thead>
<tr>
<th></th>
<th>Hb</th>
<th>Ferritin</th>
<th>Albumin</th>
<th>CRP</th>
<th>EPO/kg</th>
<th>Vecf/Vtbw</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>-0.155</td>
<td>-0.155</td>
<td>0.344*</td>
<td>-0.311**</td>
<td>-0.344*</td>
<td>-0.085</td>
</tr>
<tr>
<td>Ferritin</td>
<td>-0.155</td>
<td>-0.303**</td>
<td>-0.311**</td>
<td>0.642****</td>
<td>0.014</td>
<td>0.072</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.344*</td>
<td>-0.303**</td>
<td>-0.470***</td>
<td>-0.312**</td>
<td>-0.420***</td>
<td>0.117</td>
</tr>
<tr>
<td>CRP</td>
<td>-0.311**</td>
<td>0.642****</td>
<td>-0.470***</td>
<td>-0.312**</td>
<td>0.117</td>
<td>0.249***</td>
</tr>
<tr>
<td>EPO/kg</td>
<td>-0.344*</td>
<td>0.014</td>
<td>-0.312**</td>
<td>0.117</td>
<td>0.249***</td>
<td></td>
</tr>
<tr>
<td>Vecf/Vtbw</td>
<td>-0.085</td>
<td>0.072</td>
<td>-0.420***</td>
<td>0.117</td>
<td>0.249***</td>
<td></td>
</tr>
</tbody>
</table>

Pearson correlation coefficient ***$P < 0.0001$, **$P < 0.01$, *$P < 0.02$, ****$P < 0.05$. 

This observation cannot be fully explained by the present study. The relationship may be straightforward; the intravascular volume is expanded and haemoglobin concentration is diluted. Alternatively, a high CRP may indicate an inflammatory process that both impairs haemoglobin production and increases vascular permeability, resulting in an increased Vecf.

The findings could have important implications in clinical practice. First, increased EPO doses may not be needed in volume-expanded patients, as one might accept a lower predialysis haemoglobin. It might be possible in the future to incorporate Vecf into the anaemia management algorithm. Secondly, one way of achieving an improved haemoglobin outcome might be to increase the ultrafiltration volume and thus decrease the dry weight of the patient population. Whether this could lead to a sustained improvement in haemoglobin outcome has not been tested. Thirdly, achieving a pre-dialysis haemoglobin concentration in the normal range in a volume-expanded subject will mean that the post-dialysis haemoglobin will be greater than normal, with potential detrimental consequences. This might be particularly relevant in avoiding post-dialysis polycythaemia where clinicians are attempting to comply with the European Best Practice Guidelines [3] for anaemia (pre-dialysis Hb > 11 g/dl), which requires a population mean haemoglobin of 12.7 g/dl with an SD of ~1.7 g/dl [4].

In conclusion, an expanded Vecf may increase the amount of EPO prescribed in order to obtain recommended predialysis haemoglobin values. Perhaps routine assessment of
Vecf, or ideally but less practically plasma volume, should become part of an anaemia management protocol.

Conflict of interest statement. D.R. and C.H.J. have received sponsorship to attend national and international meetings from the manufacturers of all EPO brands. D.R. has acted as medical adviser to the manufacturers of all EPO brands.

Renal Unit
York Hospital
York
UK
Email: colinjones@doctors.org.uk


DOI: 10.1093/ndt/gfh072

Hypothyroidism and resistance to human recombinant erythropoietin

Sir,

Many possible causes of resistance to human recombinant erythropoietin (rh-EPO) have been reported in patients with renal failure [1]. However, some factors remain controversial. We report a haemodialysis patient with a diminished response to rh-EPO in association with hypothyroidism.

The patient was a 62-year-old female who was treated with regular haemodialysis since 1993. She had a past medical history of primary hypertension and pulmonary tuberculosis. During 5 years, haemoglobin level ranged between 10.2 and 11.7 g/dl with rh-EPO alpha treatment of 9000 IU/week. In 1998, the patient developed secondary hyperparathyroidism (iPTH 1845 pg/ml) and worsened anaemia (Hb 9 g/dl) despite increasing doses of rh-EPO up to 15000 IU/week. Successful subtotal parathyroidectomy was performed in October 1998 together with subtotal thyroidectomy because of nodular goiter. Haemoglobin level remained unchanged with normochromic, normocytic erythrocytes and normal leukocytes and platelets. All usual causes of epoietin resistance were ruled out, such as infection, malignancy, iron or vitamin deficiency states, aluminum overload and underdialysis. A few months later, hypercholesterolaemia appeared and subclinical hypothyroidism was diagnosed. Thyroid-stimulating hormone was >50 mIU/l, free triiodothyronine 4.4 pmol/l and free thyroxine 9 pmol/l. Thyroxine replacement therapy was started in April 1999 and the dose was progressively increased to 225 µg/day. Normalization of serum thyroid hormone levels was accompanied by improved response to epoetin (Figure 1). Haemoglobin level increased to 11.5 g/dl with a parallel reduction of rh-EPO dose to 6000 IU/week. These findings, as in two previous reports [2,3], strongly support the hypothesis that hypothyroidism may contribute to epoetin resistance in chronic haemodialysis patients.

Conflict of interest statement. None declared.

1Service de Néphrologie and Inserm U507
Hôpital Necker
Paris
France
Email: malikpablo@wanadoo.fr


Fig. 1. Evolution of haemoglobin level and thyroid stimulating hormone.