Hyporesponsiveness to recombinant human erythropoietin

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Abstract

The introduction of recombinant human erythropoietin (rh-Epo, epoetin) as a treatment for the anaemia of renal failure has transformed the management of this condition. Nevertheless, a significant number of patients fail to respond. There are many different possible causes of inadequate response to epoetin. Iron deficiency, whether absolute or functional, is considered to be the most important, and it is widely accepted that maintaining adequate iron levels reduces rh-Epo dosage requirement and improves efficacy in haemodialysis patients. Infection and inflammation have been shown to influence responsiveness to rh-Epo by disrupting iron metabolism and eliciting the release of cytokines that inhibit erythropoiesis. Another factor for consideration is severe hyperparathyroidism, which can lead to a reduced number of responsive erythroid progenitor cells. Inadequate dialysis can also negatively impact on rh-Epo therapy, and aluminium overload interferes with iron metabolism and reduces the efficacy of rh-Epo. Deficiencies in vitamin B12, folic acid and potentially vitamin C can all reduce the efficacy of treatment with rh-Epo. Optimizing patient response to rh-Epo therapy, therefore, requires consideration of many factors, some well established and others that are more controversial, and the list continues to grow with the identification of new factors.

Keywords: anaemia; dialysis; epoetin; hypoparathyroidism; hyporesponsiveness; iron deficiency

Introduction

The introduction in the late 1980s of recombinant human erythropoietin (rh-Epo, epoetin) as a treatment for the anaemia of renal failure has transformed the management of this condition. However, while rh-Epo is effective in correcting anaemia in most cases, there are a significant number of patients who fail to respond. According to the European Best Practice Guidelines (EBPG), a continued need for >300 IU/kg per week when administered subcutaneously is defined as an inadequate response to rh-Epo, while a somewhat higher threshold of 400 IU/kg per week is suggested if epoetin is administered intravenously [1]. US guidelines define hyporesponsiveness as a failure, in the presence of adequate iron stores, to achieve and maintain the target haemoglobin (Hb) level at a rh-Epo dose of 450 IU/kg per week when administered intravenously or 300 IU/kg per week when administered subcutaneously [2].

There are many different possible causes of inadequate response to epoetin (Table 1), and while some are well established, others remain controversial. This paper will discuss some of the more important factors in detail, and review a case study that highlights the factors requiring consideration when attempting to identify the cause of resistance to rh-Epo therapy.

Iron deficiency

The most common cause of inadequate response to epoetin therapy is absolute or functional iron deficiency [3]. Iron deficiency may be considered absolute when total body iron stores are depleted, as indicated by a serum ferritin concentration <20 μg/l [1], and functional when serum ferritin concentrations are normal, but insufficient iron can be made available to meet the needs of erythropoiesis and the Hb concentration fails to increase as expected with usual doses of epoetin [1]. Iron deficiency can also occur as a result of interference with normal iron metabolism by aluminium toxicity [4]. All patients with chronic renal failure (CRF) must be iron-replete in order to achieve and maintain optimum Hb levels at the minimum possible dose of rh-Epo, and the benefits of intravenous iron supplementation for increasing rh-Epo efficacy have been demonstrated in numerous studies [5,6]. Adequate intravenous iron therapy is increasingly recognized as a means of enhancing the response to rh-Epo, allowing a reduction in the required dose with

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obvious implications for an improved cost:benefit ratio [7].

Inflammation

The role of inflammation and pro-inflammatory cytokines in resistance to epoetin therapy is gaining increased recognition (see article by Stenvinkel [8]). Erythropoiesis is inhibited by cytokines such as tumour necrosis factor-α (TNF-α), interleukin-1 (IL-1) and interferon-γ (IFN-γ). These cytokines are particularly involved in the inflammatory process as they are directly produced by macrophages (TNF-α, IL-1) or because their production by another cell is induced by a macrophage cytokine (IFN-γ). Several studies have shown that markers of inflammation are associated with a decreased response to rh-Epo [9,10]. In particular, high levels of serum C-reactive protein (s-CRP) have been shown to predict resistance to epoetin therapy in haemodialysis (HD) patients [9]. The weekly rh-Epo dose in patients with s-CRP ≥20 mg/l was, on average, 80% higher than in patients with s-CRP ≤20 mg/l. These data are supported by findings from the European Survey on Anaemia Management (ESAM) [3], which found that the rh-Epo dose in patients with elevated CRP levels (≥50 mg/l) was significantly higher than in patients with CRP levels ≤50 mg/l (Figure 1). Moreover, the epoetin dose in the high CRP group was found to increase over a 6-month observation period [3].

Pro-inflammatory cytokines can also influence the response to rh-Epo through disruption of iron metabolism [11]. Hypoferraemia is often observed in the presence of infection or inflammation despite adequate iron stores, and this is probably a consequence of impaired release of iron from the monocyte–macrophage system [11].

Quality of dialysis

The adequacy of dialysis also impacts on the responsiveness to rh-Epo therapy. The association between dialysis dose, evaluated by the urea reduction rate (URR), and haematocrit and rh-Epo dose has been assessed in a random sample of 7092 HD patients in the US [12]. The authors of this study found that the rh-Epo dose requirement decreased as URR increased (P<0.001), while the haematocrit increased as URR increased (P<0.001). Similar results were reported from a second study investigating the relationship between \( K_f/V \) and the weekly dose of rh-Epo in 68 HD patients, which found that rh-Epo dose requirement decreased as \( K_f/V \) increased [13]. The division of patients into two groups according to \( K_f/V \) levels revealed a 45% reduction in dose needed to maintain the target haematocrit in patients with better \( K_f/V \) levels.

Hyperparathyroidism

Secondary hyperparathyroidism is a well-known consequence of renal failure, and results from a combination of phosphate retention, hypocalcaemia and reduced plasma levels of 1,25-(OH)\(_2\)D\(_3\) [14]. The hypothesis of a potential role of hyperparathyroidism in rh-Epo resistance was initially based on observations that primary hyperparathyroidism is sometimes associated with anaemia and that surgical ablation of a parathyroid adenoma has been shown to correct such anaemia [15,16]. There are several potential mechanisms by which hyperparathyroidism can exacerbate anaemia in CRF and particularly dialysis patients. These include a direct toxic effect of parathyroid hormone (PTH) on erythropoietin synthesis, as well as on red blood cell production and survival (toxic effect on bone marrow erythroid progenitors), and an

<table>
<thead>
<tr>
<th>Table 1. Potential causes of inadequate response to rh-Epo</th>
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<tr>
<td>Major factors</td>
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<tr>
<td>Iron deficiency</td>
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<tr>
<td>Infection</td>
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<td>Non-infectious inflammatory states</td>
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<td>Chronic blood loss</td>
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![Fig. 1. Relationship between the level of CRP and rh-Epo dose.](image)
indirect effect via the induction of marrow fibrosis and interference with erythropoiesis [17].

The beneficial effects of parathyroidectomy (PTX) on anaemia and rh-Epo response in dialysis patients would appear to support a role for secondary hyperparathyroidism in resistance to rh-Epo therapy [18]. Surgery improved anaemia in patients both receiving and not receiving rh-Epo before PTX, and the improvement of anaemia following PTX in patients receiving rh-Epo was further emphasized by concomitant lowering of the weekly mean rh-Epo dose by 30–45% (Table 2).

### Other factors affecting rh-Epo responsiveness

Aluminium overload can interfere with iron metabolism and with enzymes of haeme synthesis, resulting in microcytic anaemia. This interaction of aluminium with iron handling can induce some resistance to rh-Epo [11]. Vitamin deficiency states such as folic acid or B₁₂ deficiency, can aggravate the anaemia of CRF and contribute to resistance to rh-Epo treatment. There is some evidence that vitamin C deficiency is associated with decreased availability of stored iron [19], and systematic administration of vitamin C supplements can improve iron availability, although large exogenous doses of vitamin C may increase the risk of oxalate deposition. Blood loss is a common factor in rh-Epo hyporesponsiveness, and patients with various forms of solid tissue malignancy may show chronic anaemia that is resistant to rh-Epo [1].

### Case study review

An interactive case study was presented to delegates to highlight the different factors that require consideration when attempting to identify the cause of rh-Epo resistance. Delegates’ opinions were sought on various aspects of diagnosis and treatment.

The patient is female, 60 years of age, body weight 63 kg, height 1.68 m and suffering from chronic interstitial nephritis. She was started on intermittent dialysis in September 1997 (left radial AV fistula). Anaemia was treated with rh-Epo at a dose of 6000 IU three times weekly. Her Hb level was 11.5 g/dl.

In June 1999, she was given a spine X-ray after presenting with back pain, weakness in the legs following a fall and intermittent temperature elevation. The X-ray revealed a compression fracture of vertebral body L1. Within 4 months, the patient was admitted to hospital due to persistent back pain. On admission, her clinical status was as follows: body weight 60 kg (loss of 3 kg), diminished appetite, body temperature 37.5 °C, blood pressure 125/75 mmHg, heart rate 82 beats/min, no evidence of pulmonary or urinary infection, well functioning AV fistula and URR 70%. Her medical treatment consisted of calcium carbonate (3 g/day) and oral vitamin B₆. In addition, her rh-Epo dose was increased from 6000 to 12 000 IU three times per week, and she received iron supplements once weekly for 8 weeks.

Based on this information, delegates were asked to vote on a possible diagnosis. Thirty-nine per cent opted for ‘malignancy’, 53% for ‘infection’ and 8% for ‘dialysis amyloidosis’. ‘Dialysis amyloidosis’ was ruled out, given that the patient had only been receiving dialysis for 3 years. Delegates were then presented with additional information from hospital laboratory findings. The patient’s white blood cell count was 15 300 μl (78% neutrophils, 15% lymphocytes, 6% monocytes, 1% eosinophils), Hb 8.8 g/dl (despite the high dose of rh-Epo), reticulocytes 35 000 μl and transferrin saturation 24%. The patient had an elevated CRP level (45 mg/l), and serum aluminium and PTH levels were considered normal. The patient also underwent a bone marrow biopsy, which revealed that the marrow was poor in erythroblastic precursor cells, and MRI of the lumbar spine, which identified partial collapse of vertebral body L1 with preserved intervertebral disc.

Based on this additional information, delegates’ opinions on the probable diagnosis were sought again. Sixty-six per cent opted in favour of ‘malignancy’, and 32% felt ‘malignancy’ was still a possibility. When delegates were questioned as to what step they would take next, 33% opted for a CT scan of the liver and lung, 39% opted for a CT scan of the spine, and 22% opted for a test for tumour markers. The patient’s actual treatment involved a test for tumour markers, which proved negative, followed by a biopsy of the paravertebral soft tissue. This revealed the presence of granulomas composed of epithelioid cells and occasional giant cells and pointed to a probable diagnosis of tuberculosis, although the absence of acid-fast bacilli meant that the diagnosis could not be fully established. The audience was then asked whether they would start treatment for tuberculosis immediately or wait for the results of a polymerase chain reaction (PCR) test on the biopsy specimen. There was a 2 : 1 majority in favour of the PCR test. The patient was actually treated for tuberculosis before the PCR test confirmed the presence of mycobacteria tuberculosis, identifying ‘infection’ as the underlying cause of rh-Epo hyporesponsiveness.

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**Table 2. Effects of PTX on anaemia (Mandolfo et al. [18])**

<table>
<thead>
<tr>
<th>PTX</th>
<th>Before</th>
<th>2 months</th>
<th>$P$</th>
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<tbody>
<tr>
<td>Not treated with rh-Epo ($n = 20$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>948 ± 501</td>
<td>51 ± 42</td>
<td>n.a.</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>10.0 ± 1.3</td>
<td>11.1 ± 1.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>rh-Epo treated ($n = 19$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>1023 ± 515</td>
<td>55 ± 41</td>
<td>n.a.</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>8.6 ± 1.0</td>
<td>10.4 ± 1.2</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>rh-Epo dose (IU/kg/week)</td>
<td>170 ± 67</td>
<td>112 ± 48</td>
<td>&lt;0.005</td>
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</table>

n.a.: not available.
Conclusion

Hyporesponsiveness to rh-Epo is an important issue in the treatment of the anaemia of CRF. Iron deficiency is considered the most important factor influencing rh-Epo response, and it is widely accepted that maintaining adequate iron levels reduces dosage requirement and improves efficacy in HD patients. However, many other factors can influence resistance to rh-Epo therapy, especially inflammation and infection, quality of dialysis and hyperparathyroidism. Optimizing response to rh-Epo therapy is important for both patient outcomes and the cost of treatment, and requires consideration of a growing number of factors, some well established and others more controversial.

References