Antibody-mediated pure red cell aplasia (PRCA) treatment and re-treatment: multiple options

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Abstract

In the vast majority of patients with antibody (Ab)-mediated pure red cell aplasia (PRCA), simple withdrawal of the erythropoiesis-stimulating agent (ESA) does not effectively reverse PRCA. In contrast, immunosuppressive treatments can induce the disappearance of anti-erythropoietin Abs and a reversal of PRCA. Consensus opinion on the optimal therapy has not been established, but individual case reports or case series suggest that kidney transplantation or treatment with corticosteroids plus cyclophosphamide are the most effective therapies. However, treatment with cyclosporine is an interesting alternative, since it appears to be effective in at least two-thirds of patients and with minimal side effects. Due to the key role of ESAs in the management of patients with chronic kidney disease (CKD), some patients have been re-treated with an ESA following resolution of Ab-mediated PRCA. In all reported cases, this treatment increased haemoglobin levels, alleviated the need for transfusions and did not have side effects. However, one should be extremely cautious when deciding to re-treat a patient with ESA, due to the small number of reported cases and the possibility of publication bias.

Keywords: epoetin; erythropoietin; immunosuppression; outcomes; pure red cell aplasia

Introduction

As described in detail in this Supplement, epoetin-induced pure red cell aplasia (PRCA) is due to the production of neutralizing anti-erythropoietin (EPO) antibodies (Abs) that cross-react with all available erythropoiesis-stimulating agents (ESAs) and with endogenous EPO. It is marked by a severe, transfusion-dependent anaemia, a virtual absence of reticulocytes and an almost complete lack of red blood cell precursors in an otherwise normal bone marrow [1,2].

Here, we review available data regarding treatment of epoetin-induced PRCA and discuss the possibility of recommencing therapy with ESAs once patients have recovered.

Therapy for antibody-mediated PRCA

In patients with Ab-mediated PRCA, stopping the administration of ESAs appears to be a logical step, since continued treatment is completely ineffective. In vitro studies show that even massive doses of an ESA could not overcome the neutralizing capacity of anti-EPO Abs [3]. Furthermore, continued exposure to ESAs carries the risk of severe systemic immune reactions [4].

Few cases of patients who spontaneously recovered from Ab-mediated PRCA have been reported [2,5,6]. However, it seems that in the vast majority of patients, simply withdrawing ESA treatment is not sufficient to reverse Ab-mediated PRCA [7]. This is probably due to the fact that, in most cases, after cessation of treatment with ESAs, the levels of anti-EPO Abs decrease slowly, while no recovery is observed as long as Abs can be detected. An example of the evolution of Abs titres over time in a patient with Ab-mediated PRCA who did not receive immunosuppressive therapy is shown in Figure 1.
In contrast, a retrospective study in 47 patients with epoetin-induced PRCA suggests that immunosuppressive therapy can accelerate recovery from this disorder [7]. In this study, recovery was defined as an increase in blood reticulocyte counts to >20,000/mm³ in patients who were no longer transfusion dependent. Twenty-nine (78%) of the 37 patients who were treated with one or more immunosuppressive therapies responded successfully, while none of the patients who did not receive such therapy recovered (Figure 2).

For very rare diseases such as epoetin-induced PRCA, identification of the most effective therapy can only be based on extensive retrospective analysis of individual cases, and a database is being created that will include most cases of epoetin-induced PRCA. So far, the largest series of patients with epoetin-induced PRCA includes 47 subjects [7]. As shown in Figure 3 and Table 1, in this series, the percentage recovery (as defined by blood reticulocyte counts >20,000/mm³ in patients who were no longer transfusion dependent) was most impressive in patients who received a kidney transplant, or who were treated with corticosteroids plus cyclophosphamide. All six patients who received a kidney transplant recovered within a month, while seven out of eight patients who were treated with corticosteroids plus cyclophosphamide recovered. The effectiveness of kidney transplantation has been confirmed by other case reports [8,9], although Nigg and colleagues have reported the case of a patient who had persistent PRCA after receiving a kidney transplant [1]. In the series reported by Verhelst and colleagues, the ability of cyclosporine to induce rapid recovery in four out of six patients should also be stressed, since a short course of cyclosporine carries almost no risk of side effects for patients on dialysis [7]. The possibility of using cyclosporine as a first-line therapy is reinforced by analysis of other published case reports, where it induced recovery in nine out of 11 cases [5,8,10–15].

In conclusion, based on the available data, our recommendations for patients with epoetin-induced
PRCA would be: (i) to stop administration of all ESAs; (ii) to initiate cyclosporine therapy; and (iii) to consider kidney transplantation or treatment with other immunosuppressive drugs such as corticosteroids plus cyclophosphamide if cyclosporine therapy does not rapidly induce an increase in reticulocyte counts and a disappearance of anti-EPO Abs.

Re-treatment following resolution of antibody-mediated PRCA

In addition to the challenge of determining the optimal treatment for EPO-induced PRCA, nephrologists are faced with the dilemma of whether or not therapy with ESA may be restarted in patients who have recovered from Ab-mediated PRCA. It is quite unusual to rechallenge patients who have developed a severe drug-induced immune reaction. However, in the case of Ab-mediated PRCA, this approach is supported by at least two considerations. First, even patients with end-stage renal failure still produce small amounts of EPO, and thus all patients are continuously exposed to the antigen. Secondly, for many patients with CKD, the benefits of treatment with ESA are so important that it would be difficult not to consider resuming it. This probably explains that, so far, 14 cases of patients re-treated with an ESA after recovering from Ab-mediated PRCA have been reported. Encouragingly, in all these cases, treatment with an ESA successfully increased haemoglobin levels, but we should remain cautious in view of the possibility of a positive publication bias.

Eight patients have been rechallenged with an ESA following recovery from Ab-mediated PRCA. Three patients who had been successfully treated with cyclosporine were rechallenged with darbepoetin-α (two cases) injected intravenously (i.v.) or epoetin-β (one case) injected subcutaneously (s.c.) [12,13,16]. One patient who had been treated with anti-CD20 Abs was re-treated with epoetin-α i.v. [17]. Two patients who had received corticosteroids plus cyclophosphamide were rechallenged with epoetin-α (one case) or darbepoetin-α (one case) given i.v. [16]. The latter patient also received cyclosporine at the time of rechallenge. One patient was treated with corticosteroids and then rechallenged with epoetin-α i.v. [18]. Another patient was treated with corticosteroids and then rechallenged [19]. Although these are isolated case reports that should be interpreted cautiously, they indicate that at least some patients with previous epoetin-induced PRCA can be successfully rechallenged with an ESA.

Table 1. Outcome of immunosuppressive therapy, in a series of 37 patients with Ab-mediated PRCA [7]

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of patients who recovered (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No therapy</td>
<td>0/10 (0%)</td>
</tr>
<tr>
<td>Rituximab (anti-CD20 mAb)</td>
<td>0/2 (0%)</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>0/1 (0%)</td>
</tr>
<tr>
<td>I.v. Ig</td>
<td>1/9 (11%)</td>
</tr>
<tr>
<td>Cs ± i.v. Ig</td>
<td>10/18 (58%)</td>
</tr>
<tr>
<td>CyA</td>
<td>4/6 (67%)</td>
</tr>
<tr>
<td>Cs + i.v. Ig + plasmapheresis</td>
<td>1/1 (100%)</td>
</tr>
<tr>
<td>Cs + cyclophosphamide</td>
<td>7/8 (87%)</td>
</tr>
<tr>
<td>Kidney transplant</td>
<td>6/6 (100%)</td>
</tr>
</tbody>
</table>

Cs = corticosteroids; CyA = cyclosporine A; IVIg = intravenous immunoglobulins; mAb = monoclonal antibody.

Fig. 3. Rate of recovery following various immunosuppressive therapy regimens, in 37 patients with confirmed Ab-mediated PRCA [7]. Some patients received more than one treatment. CS = corticosteroids; CyP = cyclophosphamide; CyA = cyclosporine A; IVIg = intravenous immunoglobulins.
Five patients have been reported for whom treatment with an ESA was not stopped while they had developed Ab-mediated PRCA [5,6,13,14]. In all these patients, recovery from PRCA was associated with restoration of a response to ESA. Three patients recovered after receiving cyclosporine, either alone (two patients) or in association with anti-thymocyte globulins (one patient) [5,13,14]. Two patients recovered after being treated with corticosteroids alone (one patient) or in association with azathioprine (one patient) [6,20]. In these patients, at the time of recovery, two were receiving epoetin-α formulated with human serum albumin stabilizer, and three epoetin-β. Epoetin was injected s.c. in at least three of these patients.

A final case reported recently by Asari and Gokal demonstrates the positive response to re-treatment in a patient who had low but detectable levels of anti-EPO Abs at the time of rechallenge, and thus who had not completely recovered from PRCA [2]. Continued transfusion requirements over 2 years following cessation of epoetin-α without adjunctive immunosuppression initiated the patient's request for an alternative treatment. Darbepoetin-α was introduced at a time when anti-EPO Abs could still be detected but with declining titres. Within a month of re-treatment, this patient achieved transfusion independence, and sustained haemoglobin levels of 12–13 g/dl could be achieved. At the same time, there was a disappearance of anti-EPO Abs.

In conclusion, from isolated case reports, it is clear that some patients can be re-treated with ESAs following remission from PRCA and decline of anti-EPO Ab to very low levels. Our recommendations would be (i) to consider rechallenging a patient only if anti-EPO Abs are below or around the lower limit of detection; (ii) to perform such a rechallenge with careful monitoring of reticulocyte counts and anti-EPO Ab levels, but also of systemic reactions; and (iii) to inject ESA by the i.v. route whenever it is feasible.

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References