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Recombinant human erythropoietin in patients with inflammatory bowel disease and refractory anemia: A 15-year single center experience

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Abstract

Aim of the study: To describe our 15-year experience on the patients' response and safety to the use of EPO in IBD patients with refractory anemia.
Patients–Methods: Single center retrospective chart analysis of all IBD patients receiving EPO for the period 1994–2009. Patients with resistant anemia not responding to I.V. iron therapy were enrolled. Concommitant medication, medical and laboratory data on short and long-term patients' responses and safety were recorded.
Results: In total 820 IBD files were reviewed and among 78 patients treated with I.V. iron we identified 26 patients who received EPO in concordance to our inclusion criteria. Azathioprine or methotrexate was administered in 17 patients and 7 patients received concomitant Infliximab. After EPO, 22/26 patients (84.6%) responded and peripheral blood parameters were significantly improved and blood transfusions were significantly decreased ($p<0.001$). Erythropoietin dose was increased in three non-responders while two patients required emergency transfusions. No adverse events were recorded.
Conclusions: In anemic IBD patients who are refractory to I.V. iron monotherapy, administration of EPO significantly improved peripheral blood parameters with safety. Prospective controlled trials are needed to confirm positive patients' response to EPO and identify those patients who are more likely to benefit.

Abbreviations: EPO, erythropoietin; IBD, inflammatory bowel disease; IFX, infliximab; I.V., intravenous.

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1. Introduction

Anemia is a common complication of inflammatory bowel disease (IBD) with a prevalence ranging from 9%[1] up to 74%[2,3] and has been used as an indicator of disease severity.[4] In addition, one third of IBD patients suffer from recurrent anemia.[5,6]

Multiple factors can contribute to the anemia in IBD, such as iron, folic acid or B12 deficiency, treatment with immunosuppressive drugs or sulfasalazine-induced hemolysis, and anemia of chronic disease.[7–9]

Anemia of chronic disease probably results from decreased erythropoiesis, secondary to increased levels of proinflammatory cytokines, reactive oxygen metabolites and nitric oxide and is characterized by impaired iron utilization, lower erythropoietin (EPO) production than needed, and a low response of bone marrow erythroid progenitor cells to EPO.[10,11]

Anemia of chronic inflammation in IBD can result for a variety of reasons. Animal studies have pointed to an inadequate erythropoietin synthesis under chronic inflammatory conditions.[12] However, erythropoietin levels in chronic disease anemia are generally higher than in normal subjects, but they may be low in relation to the degree of anemia. There have been studies on the higher than expected serum EPO levels in IBD patients compared with control population.[13–15] However, in IBD anemic patients this EPO increase is inadequate in relation to the degree of anemia.[16,17]

Correction of anemia through the administration of oral or intravenous (I.V.) iron and/or supplemental recombinant human EPO or darbepoetin[19] in refractory patients has been shown to improve hematologic indices and quality of life.[20–22]

In this study we aimed to report our experience on patients' response and safety to EPO administration in a cohort of refractory to I.V. iron anemic patients with IBD.

2. Materials and methods

2.1. Study population

This was a single center descriptive study. We conducted a retrospective chart analysis of all IBD patients who received EPO during the period 1994–2009. Data were retrieved from our electronic records and included all medical and laboratory data of our IBD patients.

Patients were included in our analysis if they were diagnosed with documented resistant anemia not responding to I.V. iron therapy.[16] An additional criterion for EPO administration was poor tolerance or severe adverse reaction to I.V. iron. All patients were living in between 0 and 1200 m above sea level and were followed from their IBD diagnosis until their inclusion to our study in our outpatient clinic.

We investigated in all patients any history of severe bacterial or viral infection, other than IBD causes of anemia (e.g. vitamin B12 deficiency, folic acid deficiency, hemolytic disorder, hemoglobinopathy, splenomegaly), anticipated need for blood transfusion, asthma, eczema or other atopic allergy, history of drug allergy, history of previous allergic reaction to EPO molecules, pregnancy, hematologic or other malignancy, severe cardiac, severe hepatic or renal or psychiatric disorders, evidence of iron overload (ferritin >800 ng/ml) or administration of antihistamines and history of previous exogenous EPO or other erythropoietic factor administration.

2.2. Previous I.V. iron therapy

Previously to EPO therapy, all patients had received consecutive iron infusions to achieve a pre-calculated total dose. The cumulative dose per FeS treatment cycle was calculated using the formula: total iron deficit (mg) = W [kg] × [target Hb − actual Hb]g/l × 0.24 + depot iron (500 mg) [W = weight, Hb = hemoglobin]. I.V. iron was administered on a day care basis with consecutive infusions paced over several days to achieve the calculated dose.[17]

2.3. EPO administration protocol

EPO was subcutaneously administered at a dose of 150–300 UI//kg of body weight three times per week for 4–12 weeks as suggested.[16,20,23,24] EPO dose modifications (dose increase) were separately recorded. A new EPO cycle was started when needed and iron stores were also replenished. Peripheral blood analysis was routinely performed before the initiation of EPO and during patients' visits in our clinic. Endogenous EPO levels were also measured. Disease activity was monitored during every scheduled visit or on emergency.

2.4. Patients' short and long-term responses to EPO and EPO safety

In addition to demographic data and clinical disease characteristics we recorded the total number of EPO doses, the mean EPO dose (UI/kg) and the duration of EPO therapy in each patient.

Short-term response to EPO was assessed three-months after the end of the first EPO cycle. Hematological parameters were assessed prior to EPO and after the end of the EPO cycle, while changes between pre- and post-EPO values were also calculated.

A good response was defined as an increase in Hb of at least 2.0 gr/dl and partial response as a Hb increase between 1.0 and 2.0 gr/dl. We also recorded the percentage of patients with Hb > 12 g/dl three-months after EPO administration.[23] Disease activity (relapse or remission) before and after EPO administration was also recorded.

We recorded any new I.V. iron, EPO cycle, and blood transfusion at 12-months and 12-month beyond EPO administration. Cases who underwent surgery during or after EPO therapy were also recorded.

Adverse events potentially related to EPO administration were recorded.

2.5. Concomitant medications

Patients were co-administered B12 or folic acid according to laboratory results. We also recorded concomitant azathioprine, methotrexate and infliximab.

2.6. Ethical considerations

Since 1981 all patients are routinely giving informed consent for data collection and blood sampling for our IBD database. Every procedure in our IBD patients is performed according to the rules of good clinical practice.

2.7. Statistical analysis

Percentages were calculated for binary and categorical variables while continuous variables were described with median and interquartile range (IQR). Comparison between groups was performed using Fisher's exact test and *t*-test. A two tailed p value <0.05 was considered to be significant and for calculations we used the SPSS 17.0 (SPSS Inc., Chicago, IL).

3. Results

3.1. Clinical and laboratory characteristics of study population

In total 820 files of IBD patients in our database were reviewed. We identified 78 patients treated with I.V. iron and among them 26 patients who received EPO in concordance with our inclusion criteria. The clinical and demographic characteristics of the IBD patients who received exogenous EPO are presented in Table 1.

Table 1 Demographic and clinical data of the IBD patients on erythropoietin (EPO).

Number of IBD patients on erythropoietin (EPO)	26
Sex (male/female)	12/14
Age of patients in years (median, IQR)	49.5 (34–68)
Weight of patients in kg (median, IQR)	71 (64–75)
Patient follow up in years (median, 25–75 percentiles)	11.5 (8–18)
IBD diagnosis (UC/CD)	16/10
IBD location	
Ulcerative colitis (n=16)	
Pancolitis	4
Left-sided colitis	12
Crohn's disease (n=10)	
Pancolitis	3
Ileitis	2
Upper GI tract/ileitis	3
Ileocolitis	2
Immunomodulators (azathioprine or methotrexate)	17 (65.4%)
Infliximab (dose 5 mg/kg)	7 (27%)
Infliximab doses (median, range)	11 (2–24)
Infliximab months (median, range)	17 (4–46)
Indication for EPO	
I.V. iron refractory anemia	23 (88.5%)
I.V. iron allergy	3 (11.5%)
EPO administration in hospital/outpatient basis	16 (61.5%)/10
EPO therapy duration in weeks (median, 25–75 percentiles)	4 (2–11)
EPO doses per patient (median, 25–75 percentiles)	12 (7–39)
EPO cycles per patient (median, range)	1 (1–6)
EPO dose escalation due to non-response	3 (11.5%)*
Endoscopy within 3 months before EPO	9 (34.6%)
Surgery at beyond 12-month follow up after EPO	5 (24.8%)
Adverse events to EPO	0

* Two of those patients turned to partial responders.

3.2. Short and long-term patients' responses to EPO

After EPO therapy peripheral blood parameters (Ht, Hb, Fe) were significantly improved on the three- and 12-month visit. Blood transfusions 12-months after EPO administration were significantly decreased (Table 2).

Response (Hb increase at least 2.0 g/dl) was achieved in 16 (61.5%) patients. Partial response (Hb increase between 1.0 and 2.0 g/dl) was achieved in 6(23.1%) patients. In total 22/26 (84.6%) of patients fully or partially responsed to EPO and Hb>12 gr/dl was achieved in 14 (53.8%) patients.

Non-response was evident in 4 (15.4%) patients, and two of them required blood transfusion on emergency.

In total 9 (34.6%) patients required blood transfusions before EPO administration. Twelve months after EPO administration I.V. iron was administered in 10 (38.5%) patients and 1 (3.8%) patient received blood transfusion.

I.V. iron was administered in 9 (34.6%) patients and 10 (38.5%) patients received blood transfusions beyond 12 months since EPO administration.

On the long-term follow up (12 month and beyond) a new EPO cycle was required in 7 (27%) patients. Surgery was performed in 5 (24.8%) patients.

At the initiation of EPO 18 (70%) patients had active disease while at three-months, disease was active in 8 (30.8%) patients. All clinical parameters of efficacy on short and long-term follow-up are presented in Table 2.

3.3. EPO dose modifications and adverse events

Erythropoietin dose was increased in 3 non-responders at a dose of 300 UI/kg of body weight. Maximal weekly EPO administration was 40,000 UI. Two of these patients had a partial response.

Adverse events potentially related to EPO administration were not recorded.

3.4. Concomitant medications

Azathioprine or methotrexate was administered in 17 (65.4%) patients and 7 (27%) patients received Infliximab (IFX) parallel to EPO. Minimal and maximal EPO doses were 150 UI/kg and 200 UI/kg for immunomodulator, 150 UI/kg and 200 UI/kg for IFX patients, and 180 UI/kg and 220 UI/kg for non-IFX treated patients.

4. Discussion

This descriptive study found that in I.V. iron refractory anemic IBD patients exogenous EPO administration seemed safe and that EPO together with effective treatment of

Table 2 Clinical and laboratory short and long term response parameters for IBD patients on erythropoietin (EPO) [n=26].

	Before EPO	3 months after EPO	12 months after EPO	p-value
Hematocrit (%)	30.9 (27.9–33.8)	39.3 (34.3–43.5)	38.3 (34.3–42.6)	<0.001
Hemoglobin (gr/dl)	10 (8.7–10.9)	12.6 (10.9–14.3)	12.1 (11.1–14.1)	<0.001
Fe (μg/dl)	39 (23–70)	62 (32.7–77.5)	73 (27.2–84)	0.009
Ferritin (ng/ml)	122 (36–258)	37 (21.5–204.5)	36.5 (16.5–186.2)	NS
EPO endogenous (mUI/ml)	15.3 (11.2–29.8) *	19.5 (9.5–56.1) **	20.2 (12.1–62.2) ***	0.008
Blood transfusion	9	2 (on emergency)	1	0.008
Response (Hb increase at least 2 gr/dl)		16 (61.5%)		
Hemoglobin>12 gr/dl	0	14 (53.8%)		
Partial response (Hb increase 1–2 gr/dl)		6 (23.1%)		
Non response (Hb increase <1 gr/dl)		4 (15.4%) **		
New I.V. iron cycle			10 (38.5%)	
New EPO cycle			7 (27%)	
Active IBD	18 (69.8%)	8 (30.8%)	11 (42.3%)	

For Ht and Hb, p-value corresponds to the comparisons: Before EPO vs. 3 months after and Before EPO vs. 12 months after.
For Fe p-value corresponds to the comparisons: Before EPO vs. 12 months after; for Before EPO vs. 3 months after, p-value NS.
* n=11 patients.
** n=12 patients.
*** n=6 patients.

inflammation controls anemia in most patients by improving specific parameters such as Ht, Hb, and Fe. EPO administration also decreased blood transfusions.

EPO was initially used for patients with a long-standing history of IBD and refractory chronic anemia (Hb <10 gr/dl, plasma EPO concentrations below 100 mU/mL)[24] but in clinical practice its role has been expanded. Exogenous EPO efficacy was demonstrated in multicenter and studies from referall centers.[6,13,16–18,20–23]

Early correction of IBD related anemia is desirable although the evidence for recommending 'target' hemoglobin has not been firmly established. In the study of Schreiber et al.[16] the primary measure of efficacy was an increase in hemoglobin levels of more than 1.0 gr/dl per deciliter while in the study of Gasche et al.[21] treatment response was defined as an increase in Hb of at least 2 gr/dl. In our cohort, more that a half of EPO treated patients achieved the 'target' Hb level of >12 g/dl while many additional patients also demonstrated a clear benefit of 1–2 gr/dl of Hb gain.

The proportion of our patients who repsonded to EPO was similar to that of previous studies although response definition varied among these studies. According to those studies the response to EPO after 6–12 weeks ranged from 82%[16] to 60%.[20–23] In those studies erythropoietin was highly effective in previous I.V. iron nonresponders. In a study with 20 patients on darvopoietin alpha[19] hematopoietic response was observed in 75% of them.

In this study four patients showed EPO treatment failure, either requiring EPO dose increase or new EPO or I.V. iron cycle or even transfusion on emergency. Non-response rate ranged in expected levels and comparable to those in the study of Schreiber et al.[16] where EPO failures were fewer compared to the non-EPO treated group. Our patients composed a rather 'difficult to treat group', mainly consisting of patients with refractory disease in need of infliximab, immunomodulators and surgery.

The optimal EPO dosing has not been firmly established and modifications of dose may be needed as it occurred in three of our patients not responding to the initial EPO dosing. In other studies EPO was administered at doses ranging from 150 UI/kg to 300 UI/kg two to three times per week and for a period of up to 12 weeks.[16,17,20,24] In our patients we preferred to increase EPO dose rather than prolong the period of EPO administration. So far the only adverse effect of EPO was observed in a pediatric study and was pain at the injection site.[20]

There is no ideal method for monitoring EPO therapy on short and long tem. After initiating treatment, careful monitoring of hemoglobin levels and iron parameters is needed in order to avoid recurrence of anemia,[25–27] which could probably be delayed by aiming for high post-treatment ferritin levels.[6] Many of our patients required additional EPO or/and I.V. iron cycles and the frequency was only determined because of regular visits. In other studies EPO was also combined with either oral[16] or I.V. iron.[4,5,17,21,23]

In this study we were not able to identify predictors in patients who clearly did much better with EPO or who failed EPO therapy. Assessment of endogenous EPO production, soluble transferrin receptors (sTR), transferrin and ferritin concentrations may help to identify individuals who benefit the most from additional erythropoietin treatment.[28–31] Higher baseline EPO levels were significantly associated with a higher probability of treatment response and vice versa.[32] However, serum EPO depends from Hb concentration but also from proliferative activity of the RBC.[33,34] In addition, it has been suggested that serum sTR is not specific for tissue iron deficiency in patients on maintenance EPO therapy and that exogenous EPO not only increases erythropoiesis but also raises serum sTR levels.[35]

Concomitant medication is of major importance in IBD anemic patients. Infliximab treatment induces healing of mucosal ulcers that could reduce intestinal iron loss and subsequently alleviate iron deficiency related anemia or refractory anemia.[36–38]

Normalization for the effect of azathioprine in our study was not possible since many were treated with azathioprine. In renal transplant recipients azathioprine can cause an increased production of EPO,[39,40] thereby producing a

condition of endogenous EPO resistance probably as a compensatory phenomenon to bone marrow suppression[41] and ineffective erythropoiesis.[42] In addition, the long-term exposure to the myelosuppressive agent methotrexate might be a contributing factor affecting the bone marrow erythroid cell reserve and function. Finally, a rather positive effect of glucocorticoids in bone marrow progenitor cells has been suggested.[43]

This study demonstrates that erythropoietin may help IBD patients with refractory anemia. Prospective, controlled trials are needed to identify the type of patients at highest risk of developing severe anemia as well as the treatment interventions with the most beneficial effect for these patients.[44–48] New formulations of intravenous iron and new generation of erythropoietic agents should also be evaluated for optimal dosing, efficacy, and safety.

Conflict of interest

There is no conflict of interest in this study.

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