Patients with and without rheumatoid arthritis benefit equally from preoperative epoetin-α treatment

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Background **Preoperative epoetin-α administration is said to have a limited effect in patients with chronic inflammatory diseases such as rheumatoid arthritis (RA), due to lower iron availability. We studied the effects of preoperative epoetin-α treatment in orthopedic surgery patients in a daily life setting in which iron supplementation was assured, and compared the effects in RA and non-RA patients.**

Methods **In an open, naturalistic, randomized controlled trial, 695 orthopedic surgery patients with preoperative hemoglobin (Hb) values of 10–13 g/dL, either with RA (113) or without RA (582), received either preoperative epoetin-α treatment added to standard care, or standard care alone. Hb values and transfusions were evaluated from entry into the study until 4–6 weeks after surgery.**

Results **Both in RA and non-RA patients, perioperative Hb values were significantly higher and transfusion requirements were significantly lower in epoetin-α treated patients than in control patients ($p < 0.001$). In RA patients, the outcomes regarding Hb values were not significantly or relevantly different from non-RA patients.**

Interpretation **Just as with orthopedic patients in general, RA patients benefit from preoperative epoetin-α treatment in combination with iron supplementation. We postulate that iron supplementation during epoetin-α therapy in RA patients is important for optimal efficacy.**

Major orthopedic surgery is associated with large blood loss, frequently exceeding 700 mL (Rosencher et al. 2003). As a consequence, blood transfusions are often required, which may cause serious complications, increased susceptibility to postoperative infections, and delayed postoperative recovery (Innerhofer et al. 1999; for a review, see Landers et al. 1996). An effective way to reduce transfusion requirements is the preoperative administration of epoetin-α once weekly for 4 weeks (Adamson 1996, Goldberg et al. 1996, Bierbaum et al. 1999). Patients with chronic inflammatory diseases such as rheumatoid arthritis (RA) frequently suffer from anemia. Many RA patients exhibit functional iron deficiency, characterized by high iron stores (high ferritin levels) but low iron availability (low transferrin saturation) (for a review, see Marx 2002). Also, endogenous erythropoietin synthesis appears to be impaired in RA patients (Kendall et al. 1993) and other types of anemia in chronic disease such as cancer (Miller et al. 1990). This might result in lower responsiveness to epoetin-α treatment compared to otherwise healthy people. Consequently, patients with RA have been excluded from most studies on the subject of blood management in orthopedic patients.

We studied the effects of epoetin-α treatment on hemoglobin (Hb) values and transfusion require-

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ments in a general (daily life) population of orthopedic surgery patients, the results of which are described in another publication (Weber et al. 2005). As the number of patients with RA was substantial, it was possible to compare the effects of epoetin-α on patients with and without RA, in order to confirm or refute the theory of a worse response in RA patients.

Methods

This article focuses on a post-hoc analysis of RA versus non-RA patients (not randomized) from an earlier naturalistic, prospective, open randomized trial on the effects of preoperative epoetin treatment in 733 patients scheduled for elective major orthopedic surgery, as described by Weber et al. (2005). Patients with a preoperative Hb value between 10–13 g/dL were included. Patients were considered to have rheumatoid arthritis if this was part of their medical record.

Patients received either best standard of care alone (control treatment) or best standard of care and epoetin-α, in a 1:2 ratio. Epoetin-α (Eprex; Ortho Biotech, commercially available, produced in Puerto Rico, packed in Schaffhausen, Switzerland) was administered subcutaneously in a 40,000-IU dose once weekly for 3 weeks before surgery and on the day of surgery, in combination with oral iron. Patients were not randomized for rheumatoid arthritis. Patients in the control group could also take iron orally or receive it by intravenous injection, if this was part of the usual standard care in the hospital. Irrespective of their group allocation, all patients received blood transfusions when needed. Blood transfusions were only given according to an Hb-based transfusion trigger, as stated in the hospital transfusion protocol. Blood volume loss alone was not a reason for transfusion. In hospitals in which no transparent local protocol was available, transfusion with packed cells could only be given during and after surgery if the Hb concentration had dropped below 8.0 g/dL, according to Slappendel et al. (2003). Before any blood transfusion, the Hb value was recorded.

Patients were evaluated for Hb values during the whole study period and for transfusion requirements during and after surgery until discharge (type of transfusion, numbers of patients transfused, and numbers of units transfused). Evaluations were carried out at entry into the study, just before surgery, 1 day after surgery, at discharge from hospital, and at follow-up (4–6 weeks after surgery, depending on hospital procedures).

In patients with and without RA, Hb values and transfusion requirements between patients receiving epoetin-α and patients receiving only best standard of care were compared.

In the study, 733 patients were enrolled. The intention-to-treat study population (704 patients) included 113 RA patients (75 epoetin-α, 38 control), and 591 non-RA patients (392 epoetin-α, 199 control). Patients for whom the operation was postponed for more than 10 days were excluded, which brought the actual surgery population to 695, including 113 RA patients (75 epoetin-α, 38 control) and 582 non-RA patients (385 epoetin-α, 197 control).

The protocol for this study was approved by the local ethics committees of the participating sites. All subjects gave informed consent prior to entry into the study.

Statistics

Demographic variables, characteristics of the surgical procedure, efficacy parameters and adverse events were categorized and tabulated. An intention-to-treat analysis was performed in all patients who were included in the trial and had a study evaluation on the day before surgery. The on-treatment population was defined as those patients included in the trial who underwent surgery. Nominal variables were analyzed using Pearson's chi-squared test and Fisher's exact test. Ordinal and interval variables were analyzed by means of the Wilcoxon two-sample test for between-group comparisons. Hemoglobin changes were analyzed by means of Student's t-test. Transfusion requirements were analyzed using Pearson's chi-squared test. The actual tests are mentioned with the results as Fisher, Pearson, Wilcoxon, and Student, respectively. All statistical comparisons were made using two-tailed analyses with $p = 0.05$ required for significance. Statistical analysis was performed by Dimensione Ricerca, Rome, Italy, using SPSS 11.0.

Table 1. Baseline characteristics in intention-to-treat population. Values are mean (SD). No significant differences were found

Characteristic	RA [a] n = 113	non-RA [a] n = 591	P-value
Age (years)	65.4 (12.9)	67.2 (10.5)	0.4 [b]
Sex (male/female)	13/100	59/532	0.6 [c]
Height (cm)	165 (7.4)	165 (8.0)	0.9 [b]
Weight (kg)	71 (13)	73 (13)	0.4 [b]
MBP [d] (mmHg)	146/81	146/82	0.8/0.4 [b]

[a] RA: rheumatoid arthritis
[b] Wilcoxon's two-sample test.
[c] Pearson's chi-square test.
[d] MBP: mean systolic/mean diastolic blood pressure at baseline

Table 2. Surgery characteristics (n = 695)

Characteristic	RA [a] n = 113 n (%)	non-RA [a] n = 582 n (%)
Type of surgery: p = 0.000 [b]		
Total hip replacement	53 (47)	420 (72)
Total knee replacement	53 (47)	147 (25)
Spinal surgery	6 (5)	14 (2)
Other surgery	1 (0.9)	1 (0.2)
Type of anesthesia: p = 0.9 [b]		
General	28 (25)	158 (27)
Local	3 (3)	14 (2)
Spinal	80 (71)	402 (69)
Mixed spinal and general	2 (2)	8 (1)

[a] RA: rheumatoid arthritis
[b] Pearson's chi-square test

Table 3. Mean (SD) Hb values (g/L) for patients with and without rheumatoid arthritis and treated with or without epoetin-α (population: intention-to-treat)

	RA [a]			non-RA [a]		
	Epoetin-α n = 75	Control n = 38	P-value [b]	Epoetin-α n = 392	Control n = 199	P-value [b]
At screening	119 (8)	121 (9)	0.4	124 (7)	123 (07)	0.09
Day of surgery	136 (13)	121 (10)	< 0.001	145 (11)	123 (08)	< 0.001
Day after surgery	112 (12)	98 (13)	< 0.001	114 (14)	96 (11)	< 0.001
At discharge	116 (12)	103 (11)	< 0.001	118 (14)	105 (12)	< 0.001
At follow-up	119 (10)	119 (12)	0.3	124 (10)	119 (09)	< 0.001

[a] RA: rheumatoid arthritis
[b] Student's t-test

Results

Patient characteristics

Baseline and demographic characteristics were not significantly different between patients with and without RA (Table 1), but the RA population included relatively less hip surgery and more knee surgery patients than the non-RA patients (Table 2).

In both epoetin-α treated groups, almost all patients received iron supplementation: 100% of RA patients (mean daily dose 291 mg/day (SD 183)) and 99% of non-RA patients (mean daily dose 280 mg/day (SD 157)); for frequency p = 0.6 (Fisher), for dose p = 0.6 (Wilcoxon). In both control groups iron supplementation was given to more than 75% of the patients (76% of RA patients, 77% of non-RA patients; p = 0.8 (Fisher); mean daily dose in RA patients was 264 mg/day (SD 156) and mean daily dose in non-RA patients was 276 mg/day (SD 149); p = 0.6, Wilcoxon). The percentage of patients receiving iron supplementation was different between epoetin-α treated and control patients in both RA and non-RA groups (both p < 0.001; Pearson/Fisher) but the dose of iron was not significantly different: p = 0.6 and 0.4, respectively (Wilcoxon).

Hemoglobin values

The Hb values at baseline were not statistically significantly different between all groups, and significantly increased Hb values at the day of surgery were seen in both groups of epoetin-α treated patients (Table 3). This increase was statistically significantly (p = 0.002; Student) greater in non-

Table 4. Transfusion rates in patients with rheumatoid arthritis (RA) and patients who did not suffer from rheumatoid arthritis, treated with or without epoetin-α

	Percentage of patients transfused	
	RA	non-RA
Epoetin-α	9	13
Control	40	47
P-value [a]	< 0.001	< 0.001

[a] Pearson's chi-square test

RA patients (by 21 g/L) than in RA patients (by 17 g/L).

Transfusion requirements

In the epoetin-α groups of both RA patients and non-RA patients, transfusion requirements were strongly reduced as compared to the control groups ($p < 0.001$; Pearson) (Table 4). There was no significant difference in percentage of patients transfused between patients with and without RA ($p = 0.3$; Pearson).

No significant difference was observed in mean transfusion trigger between groups: 87 g/L (SD 9.1) in RA patients and 86 g/L (SD 12) in non-RA patients ($p = 0.1$) between the epoetin-α and control treatments ($p = 0.6$ between patients with and without RA; Wilcoxon).

There was no statistically significant difference between patients with or without RA regarding their periods of hospitalization, time to ambulation or postoperative infection rates (Table 5).

Safety data

No differences were seen in the frequency of adverse events between epoetin-α and control treatments in the patients with RA (patients mentioning at least one adverse event: epoetin-α 47/78 = 60%; controls 23/38 = 61%), nor in the patients without RA (patients mentioning at least one adverse event: epoetin-α 234/409 = 57%; controls 112/208 = 54%; $p = 0.4$, Pearson). The frequency of adverse events was not significantly different between RA and non-RA patients (70/116 = 60% as compared to 346/617 = 56%; $p = 0.4$, Pearson).

The most commonly reported adverse events were as follows. In RA patients treated with epoetin-α vs. control, frequencies of adverse events were: nausea 10% vs. 8%, urinary tract infections 10% vs. 3%, headache 10% vs. 0%, paresthesia 9% vs. 5%, and hemorrhage 5 vs. 8%. In non-RA patients treated with epoetin-α vs. control, frequencies of adverse events were: headache 9% vs. 5%, nausea 7% vs. 11%, hemorrhage 6% vs. 6%, constipation 5% vs. 8%, urinary tract infections 4% vs. 8%, and paresthesia 2% vs. 0.5%.

There were no differences in serious adverse events (SAEs) between groups. For RA patients with epoetin-α and control treatment, the frequencies of SAEs were 8% and 6%, respectively ($p = 0.4$, Pearson) and for non-RA patients the rates were 9% and 5%, respectively ($p = 0.7$, Fisher); $p = 0.8$ (Pearson) between RA and non-RA (8% vs. 7%). The most frequent SAEs were joint disorder (1%), abnormal healing (0.8%), and hemorrhage (0.5%).

3 thrombotic events were observed during the study: 1 in an RA patient receiving epoetin-α, 1 in a non-RA patient receiving epoetin-α, and 1 in a non-RA patient receiving the control treatment.

Discussion

In this study, using a post-hoc analysis we compared the responsiveness of patients with and with-

Table 5. Mobilization and hospitalization time and postoperative infection rates for patients with and without rheumatoid arthritis (RA)

	RA	Non-RA	Overall	P-value
Days to ambulation; mean (SD)	3.4 (2.4)	3.3 (2.8)	3.3 (2.7)	0.5 [a]
Days until discharge; mean (SD)	12 (8.0)	11 (4.8)	11 (5.5)	0.8 [a]
Postoperative infection rate (%)	12	9.3	9.8	0.3 [b]

[a] Wilcoxon test
[b] Pearson's chi-square test

out rheumatoid arthritis to preoperative epoetin-α therapy with a control treatment as background. Responsiveness was measured by Hb values and transfusion requirements. From the large number of patients involved, such a post-hoc analysis is justified and solid.

Epoetin-α was given in the same dose to both groups of patients. Analysis of the Hb values shows that epoetin-α was effective both in patients with RA and in patients without RA. In both groups, we found that Hb values from the day of surgery until discharge were significantly higher in epoetin-α treated patients than in patients who received the control treatment. Moreover, the changes in Hb values in both the epoetin-α treated and the control-treated RA patients showed the same profiles as those in non-RA patients. This confirms the efficacious effect of preoperative epoetin-α treatment in RA patients.

Whereas the value of preoperative epoetin-α treatment has been proven in non-RA patients (Adamson 1996, Goldberg et al. 1996, Bierbaum et al. 1999), it is important to note that transfusion rates were reduced in epoetin-α treated RA patients to the same extent as in patients without rheumatoid arthritis, as compared to those undergoing the control treatment. In both RA and non-RA patients, transfusion rates were reduced from 40% in the control groups to 10% in the epoetin-α treated groups. Next to the hemoglobin response and transfusion requirements, we found no difference in the incidence of adverse events in RA patients and non-RA patients.

Our data confirm that rheumatic patients may benefit from epoetin-α, just as non-rheumatic patients do, as demonstrated previously by Peeters et al. (1996, 1999) and Matsui et al. (1999). However, the data from clinical practice are contradictory. For example, Nordström et al. (1997) reported poor responsiveness to epoetin-α in patients with anemia of chronic disease and rheumatoid arthritis, and they attributed this to a low iron availability.

It is well known that iron availability is low in patients with chronic inflammatory diseases such as rheumatoid arthritis, as seen from the low transferrin saturation (for a review, see Marx 2002). The good efficacy in our study may be due to the 100% iron supplementation in epoetin-α treated rheumatic patients. This would support the need for iron supplementation in patients receiving epoetin-α as suggested by Nordström et al. (1997), and as has been demonstrated in other applications of epoetin-α (for reviews, see Drueke 1991, Stivelman 1989).

As an open study in daily practice and a post-hoc analysis, this study was not performed in fully controlled circumstances for this subgroup of RA patients. This explains why iron supplementation was not given to 100% of the control patients and why RA patients received relatively more knee surgery and less hip surgery.

Previous studies have shown that iron supplementation alone had no positive effect on Hb values after preoperative administration in otherwise healthy subjects (Olijhoek et al. 2001). An observed increase in Hb values after intravenous iron administration in RA patients with anemia was not found to be clinically relevant (Cimmino et al. 1997). Moreover, in the present study there was no Hb increase in the control groups (with or without RA), in spite of the fact that 77% of patients in those groups received iron. Thus, we believe that, even though there was a statistically significant difference in the number of patients receiving iron supplementation, this did not influence the outcomes. The other different factor (type of surgery) does not seem to have been relevant for the study outcome either. Transfusion triggers were not different between groups, and can therefore not explain any difference in transfusion rates or Hb values.

This study confirms that the hematopoietic effect of epoetin-α is not diminished in patients with RA, provided that patients receive good iron supplementation. As the blood transfusion service in all countries is struggling to meet the demand for blood, epoetin-α may help to reduce the need for packed cells, in RA patients as well as in non-RA patients.

Contributions of authors

All authors were involved in the conception and design of the study, in the analysis and interpretation of the data, and in critically reviewing the manuscript. The first 7 authors included and treated patients in the following numbers: 126 (RS and EWGW), 15 (YH), 7 (SM), 18 (TD), 44 (EFAMR), 43 (JJvO) and 27 (AV) patients.

The sponsoring company was, together with the Study Review Board, consisting of investigators, involved in the design and planning of the study, as well as in interpretation of the data, suggestions of additional analyses and co-authoring of the manuscript (the senior author was an employee of the sponsoring company, Ortho Biotech). Statistics and computer-generated IVRS were performed by M. Bassano and M. Borelli, Dimensione Ricerca, Rome, Italy. An electronic data-capture system owned by Dimensione Ricerca was successfully employed for data management.

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