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The Long-Term Efficacy of Erythropoiesis-Stimulating Agents in Patients With Low-Risk or Intermediate-1-Risk Myelodysplastic Syndrome: Multicenter Real-Life Data (Eritropoezi Stimüle Edici Ajanların Düşük Riskli veya Orta-1 Riskli Miyelodisplastik Sendromlu Hastalarda Uzun Dönem Tedavi Etkinliğinin Değerlendirilmesi: Çok Merkezli Gerçek Yaşam Verisi)

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Abstract

Objective: To evaluate the long-term clinical efficacy of epoetin alfa and darbepoetin alfa in patients with myelodysplastic syndromes (MDS) in the real-life setting.

Materials and Methods: A total of 204 patients with low-risk or intermediate-1–risk MDS who received epoetin alfa or darbepoetin alfa were included. Hemoglobin levels and transfusion need were recorded before and during 12-month, 24-month, 36-month and 48-month treatment.

Results: At 36-month (p=0.025) and 48-month (p=0.022) visits, epoetin alfa vs. darbepoetin alfa yielded significantly higher hemoglobin levels. Transfusion-need was also significantly lower in epoetin alfa vs. darbepoetin alfa groups at 24-month (p=0.012), and in low risk vs. intermediate risk groups at 24-month (p=0.018), 36-month (p=0.025) and 48-month (p<0.001) visits. Treatment response rates at 24-month, 36-month and 48-month visits in epoetin alfa (43.0, 33.6 and 27.1%), darbepoetin alfa (29.9, 22.7 and 16.5%), low risk (39.3, 30.0 and 26.0 %) and intermediate risk (29.6, 24.1 and 11.1%) groups were lower than 12-month response rates, significantly at 36-month and 48-month visits (p ranged <0.05 to <0.001).

Conclusion: This real-life long-term ESA extension study investigated the clinical efficacy of epoetin alfa and darbepoetin alfa for up to 48 months, revealed the treatment efficacy to reach plateau starting from the 24th month of therapy with a continuing decrease in treatment response rates, regardless of treatment type, risk status or gender. Nonetheless, significantly

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higher hemoglobin levels and marked improvement in transfusion-need was evident in the epoetin-treated vs. darbepoetin-treated groups and in the low risk vs. intermediate risk groups.
Keywords: Myelodysplastic syndrome; low-risk- intermediate-1–risk; epoetin alfa; darbepoetin alfa; long-term; treatment response; duration of response; transfusion dependence

Öz

Amaç: Miyelodisplastik sendromlu (MDS) hastalarda epoetin alfa ve darbepoetin alfa tedavisinin gerçek yaşam ortamında uzun-dönem klinik etkinliğini değerlendirmek

Gereç ve Yöntemler: Bu çalışmaya düşük veya orta-1 risk grubu MDS tanısı ile epoetin alfa veya darbepoetin alfa tedavisi almış 204 hasta dahil edildi. Hemoglobin düzeyleri ve transfüzyon gereksinimi, tedaviden önce ve tedavinin 12., 24., 36. ve 48. aylarında değerlendirildi.

Bulgular: Epoetin alfa, darbepoetin alfa ile kıyaslandığında, 36. ay (p=0.025) ve 48. aylarda (p=0.022) anlamlı şekilde daha yüksek hemoglobin düzeylerini sağladı. Transfüzyon gereksinimi 24. ayda (p=0,012) epoetin alfa grubunda darbepoetin alfa grubuna göre, 24. ay (p=0,018), 36. ay (p=0,025) ve 48. aylarda (p<0,001) ise düşük risk grubunda orta risk grubuna göre anlamlı şekilde daha düşük olarak bulundu. Tedavi yanıt oranları 24. ay, 36. ay ve 48. aylarda epoetin alfa (%43,0, %33,6 ve %27,1), darbepoetin alfa (%29,9, %22,7 ve %16,5), düşük risk (%39,3, %30,0 ve %26,0) ve orta risk (%29,6, %24,1 ve %11,1) gruplarında 12. ay yanıt oranlarına göre daha düşük olup, 36. ve 48.aylarda bu değişim istatistiksel olarak anlamlı idi (p <0,05 ile <0,001 arası).

Sonuç: Epoetin alfa ve darbepoetin alfanın 48 aylık klinik etkililiğinin değerlendirildiği bu gerçek-yaşam uzun-dönem ESA çalışmasında, tedavi etkililiğinin tedavinin 24. ayından başlayarak plato evresine eriştiği ve devamında tedavi yanıt oranlarında, tedavi tipi, risk durumu veya cinsiyetten bağımsız olarak süregiden bir düşüşün gerçekleştiği saptandı. Bununla birlikte, epoetin tedavisi alan grupta darbepoetin ile tedavi edilen gruba göre ve düşük risk grubu hastalarda orta risk grubu hastalara göre, hemoglobin düzeyleri anlamlı şekilde daha yüksek olup, transfüzyon gereksiniminde de belirgin azalma olduğu tespit edildi.
Anahtar Sözcükler: Miyelodisplastik sendrom; düşük risk; orta-1 risk; epoetin alfa; darbepoetin alfa; uzun-dönem; tedavi yanıtı; yanıt süresi; transfüzyon bağımlılığı

Introduction

Epoetin alfa (short-acting) and darbepoetin alfa (long-acting) are commonly used erythropoiesis-stimulating agents (ESAs) in clinical practice for the treatment of anemia in patients with low or intermediate-1 risk myelodysplastic syndromes (MDS) to reduce the transfusion requirements and the transfusion-related risks (1-5).

However, ESA response rates in routine practice may differ from those reported in clinical trials with use of higher doses of ESAs (6,7). The value of continuing ESAs in the absence of an early response also remains unclarified due to investigation of response rate rather than the duration of response by most of the previous ESA studies (3,8-11).

We have previously reported the comparative efficacy of 12-month epoetin alfa and darbepoetin alfa in improving hemoglobin levels and reducing transfusion-need in patients with low-risk or intermediate-1–risk MDS in the real-life setting (12).

This extension study aimed to evaluate the long-term clinical efficacy of epoetin alfa and darbepoetin alfa in terms of rate and durability of treatment response and the transfusion dependence up to 48 months in patients with low-risk or intermediate-1-risk MDS in a retrospective real-life setting.

Materials and Methods

Study population

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A total of 204 patients newly diagnosed with low-risk or intermediate-1–risk MDS who received ESA treatment with epoetin alfa (Eporon®, Dem Pharmaceuticals; maintenance: 75-300 U/kg/week; maximum dose: 900 U/kg per week) or darbepoetin alfa (Aranesp®, Amgen Pharmaceuticals; maintenance: 0.13-0.35 µg /kg/week; maximum dose: 150 µg per week) after the diagnosis were included in this retrospective multicenter, non-interventional hospital-registry study. Pre-treatment EPO levels of <500 IU/mL and presence of hemoglobin levels <10g/dL with or without a need for ≥2 units of erythrocyte suspension transfusion per month were the inclusion criteria of the study. Patients with high risk MDS, AML, EPO levels of >500 IU/mL and hemoglobin levels >12 g/dL, anemia related to iron deficiency or chronic disease, uncontrolled hypertension and chronic kidney disease and those receiving MDS treatment other than ESAs were excluded.

Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study which was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the institutional ethics committee (Date of Approval: 01/12/2021; Protocol No: 2021/23).

Data collection

Data on baseline characteristics including patient demographics, EPO and hemoglobin levels, rate of transfusion need and type of ESA treatment were recorded. Data on hemoglobin levels and transfusion need were recorded in the pre-treatment period as well as at four consecutive visits (12th month, 24th month, 36th month and 48th month visits) after the onset of treatment. Treatment response was evaluated in subgroups of ESA treatment (epoetin alfa vs. darbepoetin alfa), risk groups (low vs. intermediate risk) and gender (female vs. male).

MDS diagnosis, risk grouping and treatment response

MDS risk stratification and assessment of response to treatment were performed as previously described (13,14).

ESA treatment

Treatment doses for epoetin alfa (Eporon®, Dem Pharmaceuticals; initial dose of 50-150 U/kg/week, maintenance: 75-300 U/kg/week; maximum dose: 900 IU/kg per week) and darbepoetin alfa (Aranesp®, Amgen Pharmaceuticals; initial: 0.25-0.75 µg /kg/week; maintenance: 0.13-0.35 µg /kg/week; maximum dose: 150 µg per week) were determined in accordance with the Ministry of Health's Health Implementation Directive (SUT) in Turkey. Treatment was continued till the loss of response in any patient. In patients with failure to achieve treatment response or those with partial erythroid response (50% reduction in transfusion need) after at least 8 weeks of regular treatment, dose increment was performed. In patients who failed to achieve sufficient treatment response despite the maximum dose of ESA, treatment was discontinued at 16-24th weeks. Cross-over was not allowed in accordance with local regulations. Patients with low serum ferritin levels under treatment received iron supplementation therapy.

Statistical analysis

Statistical analysis was made using MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013) Cochran's Q test and post Hoc McNemar test with Bonferroni corrections were used for the comparison of categorical data, while numeric data were analyzed using Student-t test and Mann-Whitney u test for variables with normal distribution and for non-normally distributed variables, respectively. Change over time was analyzed via repeated measures ANOVA with Bonferroni corrections. Data were expressed as "mean±standard deviation (SD)", minimum-maximum and percent (%) where appropriate. $p<0.05$ was considered statistically significant.

Results

Baseline characteristics

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No significant difference was noted between treatment groups in terms of baseline characteristics (Table 1).

Hemoglobin levels

In both epoetin alfa and darbepoetin alfa groups, hemoglobin levels were significantly higher at 12th month compared to pre-treatment levels ($p<0.001$ for each). Hemoglobin levels at later visits (24-, 36- and 48-month visits) showed no significant change from the baseline hemoglobin levels (Table 2).

Epoetin alfa vs. darbepoetin alfa yielded significantly higher hemoglobin levels at 36-month ($p=0.025$) and 48-month ($p=0.022$) visits, (Table 2, Fig 1)

Hemoglobin levels were significantly higher in low risk vs. intermediate-1 risk group at pre-treatment period and at each follow up visit (p ranged 0.014 to <0.001) (Table 3, Fig 1)

In each risk group, hemoglobin levels were significantly increased from baseline at 12th week visit, regardless of the gender (Table 3).

Transfusion-need

A significant decrease in the transfusion-need from baseline was evident at each follow up visit in the epoetin alfa group ($p <0.001$ for each) and in low-risk group (p ranged <0.01 to <0.001). In the darbepoetin alfa and intermediate-1 risk groups, there was no significant change from baseline in the transfusion need during follow up visits (Table 4).

Transfusion-need was significantly lower in epoetin alfa vs. darbepoetin alfa groups at 24-month ($p=0.012$), and in low risk vs. intermediate risk groups at 24-month ($p=0.018$), 36-month ($p=0.025$) and 48-month ($p<0.001$) visits (Table 4).

Percentage of patients with treatment response (≥1.5 g/dL increase in hemoglobin)

The 24-month, 36-month and 48-month treatment response rates in epoetin alfa (43.0, 33.6 and 27.1%), darbepoetin alfa (29.9, 22.7 and 16.5%), low risk (39.3, 30.0 and 26.0 %) and intermediate risk (29.6, 24.1 and 11.1%) groups were lower than 12-month response rates, while the decrease was significant only at 36-month and 48-month visits (p values range, <0.05 to <0.001). The lowest response rates were achieved at 48-month in darbepoetin alfa and intermediate risk groups ($p<0.05$ for each) (Table 5).

Discussion

This real-life long-term ESA extension study revealed the treatment efficacy to reach plateau starting from the 24th month of therapy with a continuing decrease in treatment response rates, regardless of treatment type, risk status or gender. Nonetheless, hemoglobin levels were significantly higher along with more prominent improvement in transfusion dependency and a slower decrease in treatment response rates from baseline in the epoetin-treated vs. darbepoetin-treated groups as well as in the low risk vs. intermediate risk groups during the long-term follow up.

In the current study, the treatment response rates at 24-month, 36-month and 48-month visits in epoetin alfa (43.0, 33.6 and 27.1%) and darbepoetin alfa (29.9, 22.7 and 16.5%) groups were lower than the 12-month response rates in each group (44.9% and 46.4%, respectively). These findings seem consistent with overall response rates (range, 20-40%) and duration of response (range, 10 to 24 months) reported in previous studies on ESAs, and consideration of refractoriness rate for ESAs to be approximately 40-50% after 2 years of treatment (6,10,11). Specifically, multicenter studies in epoetin-treated MDS patients revealed the response rates of approximately 30-50%, with a duration of 12-24 months (1,6,15-21), while single-arm darbepoetin alfa studies reported duration of response ranging from 1 to 36 months (17,22-24). The prospective observational studies also revealed similar response rates for patients treated with epoetin alfa and darbepoetin alfa, despite the differences in median response duration obtained with epoetin alfa (7.5-15 months) and darbepoetin alfa (9.7 months) (1,25-27).

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In addition, in an international pooled analysis of 1698 low risk MDS patients treated with ESAs, the authors reported that most responses occurred within 3 months, with a median duration of response of 17 months (28). Also, in a meta-analysis of 10 studies in 647 darbepoetin-treated patients on the efficacy and safety of darbepoetin, the erythroid response rate was reported to range from 38 to 72% (IWG 2000 criteria), while the response duration was noted to range from 12 month to more than 51 months (29).
Notably, in an epoetin extension study median response duration in epoetin alone and epoetin plus granulocyte colony stimulating factor (G-CSF) groups were reported to be 34 months and >20 months, respectively (9).
Overall, the meta-analyses and systematic reviews revealed no significant difference in pooled response rate for epoetin alfa and darbepoetin alfa and indicated a clinical benefit of ESAs, with benefits observed across key clinical outcomes (improved erythroid response rates and duration of response), as well as a reduction in the transfusion-need (1,30-32).
Likewise, our previous study on interim analysis of 12-month results indicated similar efficacy of epoetin alfa and darbepoetin alfa among low risk or intermediate-1 risk MDS patients with no difference in treatment response between treatment groups (12-month response rate: 58.1% for epoetin alfa and 41.9% for darbepoetin alfa), whereas a likelihood of earlier treatment response (within the first three months, 62.7%) and achievement of an earlier reduction in the transfusion need was noted in the epoetin alfa group (12). In the current extension study, while the two treatment groups also revealed similar efficacy in terms of rate and duration of treatment response up to 48 months of follow up, the epoetin-treated patients had a slower decrease in treatment response from baseline along with significantly higher hemoglobin levels accompanied with a greater reduction in transfusion-need from 24 to 48 months of follow up.
Notably, in a meta-analysis of 55 studies, the transfusion independence was concluded to be associated with decreased mortality (hazard ratio of 0.41; 95% confidence interval (CI): 0.29–0.56) (33). Hence, increased likelihood of transfusion independency with long-term epoetin treatment and lower-risk MDS in our cohort seem to be particularly notable given that the primary target of managing patients with lower-risk MDS in daily practice is to achieve transfusion independence, which is associated with improved survival (6,15,20,33-35).
Indeed, epoetin alfa treatment for patients with MDS is considered likely to achieve durable responses, thereby guaranteeing an improvement in the quality of life in these patients (10).
In a retrospective cohort study of 36 patients diagnosed with MDS and treated with epoetin alfa (30.000 to 60.000 IU per week), the authors reported a response rate of 80.5% with surprisingly prolonged response (range, 25 to 175 months) in 82.8% of patients who were also transfusion independent and having a favorable response stratification (10). The hemoglobin values were reported to increase significantly after 24 months and up to 175 months after the initiation of epoetin alfa treatment, and to remain over baseline values, while the overall survival rate was 51.64% after a median of 65 months of treatment along with a 43.5-month median event-free survival (10). The authors indicated the association of epoetin alfa with higher overall survival and event-free survival rates and longer response durations in their study than previously described in the literature, and emphasized the likelihood of sustained rates of erythroid response following the initiation of epoetin alfa treatment to also reflect the need for prolonged treatment to obtain the full clinical benefit (10).
The factors associated with treatment response in ESA-treated MDS patients have been reported to include certain clinical characteristics such as low serum EPO levels, a lack of transfusion dependence, and a low-risk stratification based on IPSS-R (5,29,32,36).
Particularly, the high-risk stratifications and transfusion dependence, in relation to their negative impact on event-free survival, are considered likely to be predictors of a poor response to epoetin alfa treatment (10). The association of epoetin alfa vs. darbepoetin alfa

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treatment as well as the low risk vs. intermediate risk status with significantly higher hemoglobin levels and greater decrease in transfusion dependency in the current study supports the reported data on lower rates and shorter durations of the response to epoetin treatment in high risk MDS patients and those with transfusion dependence (10,37). Indeed, treatment with ESAs has been associated with the delay in the transfusion-need along with a substantial increase the hemoglobin level for a longer period (10). The increased likelihood of erythroid response with a longer duration of ESA treatment (later responders) has also been suggested along with a potential benefit of continuing ESAs even after lack of treatment response within initial 8 to 12 weeks (7,36,38).

In fact, the dose-dependency of ESA efficacy has also been emphasized with consideration of epoetin 60 000 U/week and darbepoetin 300 µg/week doses to be superior to lower doses (11,35,39), while more frequent dosing and a prolonged treatment are also considered to be necessary to obtain the full clinical benefit (29,35,38). In addition, the implementation of the stringent IWG 2006 criteria (1.5 g/dl hemoglobin increase maintained for 8 weeks, even in patients with low transfusion burden) is considered likely to yield a lower-than-expected clinical benefit rate (35). The increase in observed response rates with ESAs was reported with relaxing the strict interpretation of IWG 2006 criteria, from 15% to 24% in ARCADE and from 32% to 46% in EPOANE3021 studies (1,18,35), as well as in other ESA studies using other erythroid response criteria (1,40,41). Moreover, early dose reduction in patients with a rapid hemoglobin rise who were still anemic is also suggested to hamper the achievement of sustained hemoglobin responses and thus to lower the erythroid response rate (1). Nonetheless, the recently proposed revised IWG criteria for assessment of hematologic response considers a requirement for duration of hematologic improvement to last 16 weeks (vs 8 weeks) among other recommendations (11,42).

Importantly, given the occurrence of functional changes in hormonal receptors upon chronic exposure to agonists and that the ESAs are used for the long-term treatment of anemia, gradual decrease in response to ESAs after 24 months could also be a result of the down-regulation of erythropoietin receptors (EPORs) after prolonged exposure to ESAs or may be related to the disease progression (43-45).

Study limitations

Certain limitations to this study should be considered. First, due to the retrospective design, establishing temporality between the cause and effect is not possible. Second, lack of data on timing of ESA initiation and patient reported outcome measures related to quality of life is another limitation, which would otherwise extend the knowledge achieved in the current study.

Conclusion

In conclusion, this real-life long-term ESA extension study investigated the clinical efficacy of epoetin alfa and darbepoetin alfa for up to 48 months, revealed the treatment efficacy to reach plateau starting from the 24th month of therapy with a continuing decrease in treatment response rates, regardless of treatment type, risk status or gender. Nonetheless, significantly higher hemoglobin levels and marked improvement in transfusion need was noted in the epoetin-treated vs. darbepoetin-treated groups and in the low risk vs. intermediate risk groups. This seems to emphasize the likelihood of long-term epoetin treatment to achieve a durable reduction in transfusion-need and a substantial increase in the hemoglobin level for a longer period by delaying the need for transfusion, and thereby increasing the probability of an improved quality of life and prolonged survival in low risk MDS patients.

Ethics

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Ethics Committee Approval: This study was approved by Zonguldak Bulent Ecevit University Clinical Research Ethics Committee (Date of Approval: 01/12/2021; Reference Number/Protocol No: 2021/23)

Informed consent: Written informed consent was obtained from each subject.

Authorship contributions:

Conceptualization: M.A.A., S.E.; Data curation: M.A.A., A.G., I.H.A, C.S; Formal analysis: M.G.P., I.H.A., C.S.; Investigation: M.A.A., A.G., I.H.A., M.G.P., C.S., A.Z.B., T.H., B.G., S.E.; Methodology: M.A.A., A.Z.B.B.G.,S.E.; Project administration: M.A.A., A.G., I.H.A., M.G.P., C.S., A.Z.B., T.H., B.G., S.E.; Resources: M.A.A., A.G., I.H.A, M.G.P., C.S., T.H.; Supervision: M.A.A., T.H.; Validation: A.Z.B., B.G., T.H.; Visualization: M.A.A, S.E.; Roles/Writing - original draft: M.A.A., A.Z.B., B.G.; Writing - review & editing: S.E., A.Z.B., B.G.

Conflict of Interest

No conflict of interest was declared by the authors.

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Figure 1. Marginal cut-off values for hemoglobin according to treatment type and risk groups

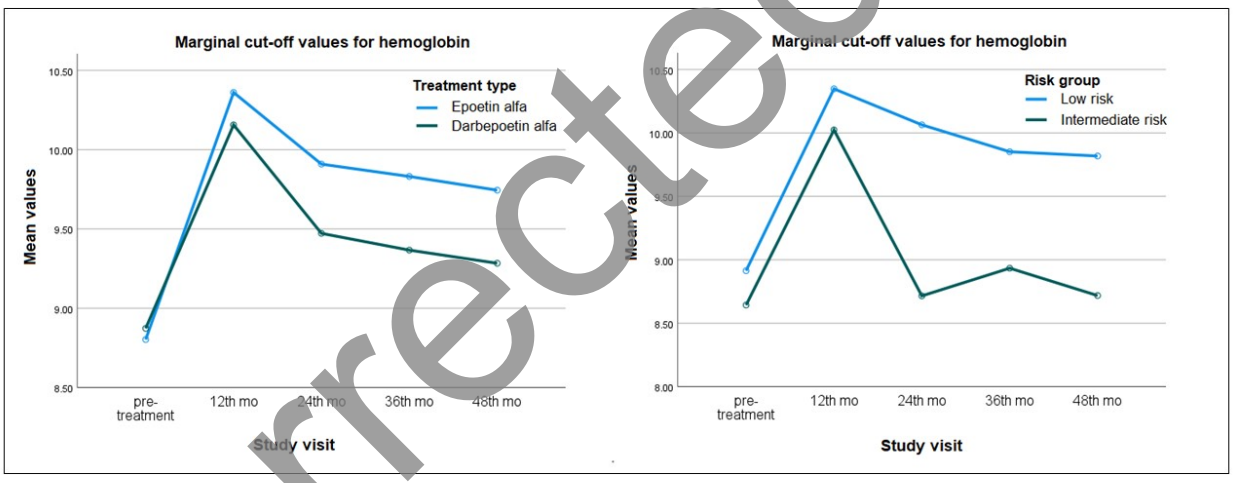


Table 1. Baseline characteristics					
		Total (n=204)	**Epoetin alfa (n=116)**	**Darbepoetin alfa (n=88)**	**p value**
Age (year)	mean±SD	72.0±10.0	71.6±10.6	72.5±10.3	0.415[1]
	median (min-max)	72.0 (35.0-95.0)	72 (39-93)	73.5 (35-95)	
Gender, n(%)					
Female		119(58.3)	71 (61.2)	48 (54.5)	0.390[2]
Male		85(41.7)	45 (38.8)	40 (45.5)	
Risk group, n(%)					
Low		170(83.3)	99 (85.3)	71 (80.7)	0.449[2]

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Intermediate		34(16.7)	17 (14.7)	17 (19.3)	
Transfusion need, n(%)					
Yes		80(39.2)	49 (42.2)	31 (35.2)	0.316[2]
No		124(60.8)	67 (57.8)	57 (64.8)	
Hemoglobin level (g/dL),	mean±SD	8.74±1.04	8.7±1	8.8±1.1	0.275[1]
	median (min-max)	8.8 (5.1-11.0)	8.7 (5.9-10.9)	9.05 (5.1-11)	
[1]Mann-Whitney U test, [2]χ^2 test					

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Table 2. Hemoglobin levels according to treatment and gender									
		Hemoglobin levels (g/dL)					**p value[a]**		
Treatment groups		**Pre-treatment**	**12th month**	**24th month**	**36th month**	**48th month**	**p[1]**	**p[2]**	**p[3]**
Epoetin alfa	Mean ±SD	8.8±0.9	10.4±1.4*	9.9±1.4	9.8± 1.3	9.7±1.1	**<0.001**	0.052	0.131
	Median (min-max)	8.8 (6.5-10.9)	10.4 (5.7-13.1)	10.1 (7.1-12.2)	9.9 (7.0-12.8)	9.8 (7.2-13.7)			
Darbepoetin alfa	Mean ±SD	8.9±1.0	10.2±1.5	9.5±1.6	9.4±1.2	9.3±1.1			
	Median (min-max)	8.9 (5.5-11.0)	10.6 (6.1-12.9)*	9.4 (6.4-13)	9.3 (5.8-12.9)	9.4 (6.4-12)			
	p value	0.254[b]	0.811[b]	0.086[b]	**0.025[c]**	**0.022[c]**			
Gender in treatment groups		**Pre-treatment**	**12th month**	**24th month**	**36th month**	**48th month**	**p[1]**	**p[2]**	**p[3]**
Epoetin alfa									
Female	Mean ±SD	8.8±1.0	10.1±1.5*	10.1±1.5	10.0±1.4	9.9±1.2	**<0.001**	0.491	**0.008**
	Median (min-max)	8.8 (6.5-10.9)	10.4 (5.7-12.4)	10.3 (7.2-12.2)	10.3 (7-12.8)	10 (7.5-13.7)			
Male	Mean ±SD	8.8±0.8	10.7±1.2*	9.7±1.2	9.6±1.1	9.5±0.9			
	Median (min-max)	8.7 (7.7-10.3)	10.9 (7.7-13.1)	9.5 (7.1-12)	9.5 (7.3-12.3)	9.8 (7.2-11.1)			
	p value[b]	0.786	0.191	0.153	0.081	0.138			
Darbepoetin alfa									
Female	Mean ±SD	8.8±1.3	10.3±1.4*	9.8±1.6	9.5±1.2	9.6±0.9	**<0.001**	0.105	0.235
	Median (min-max)	8.9 (5.5-11)	10.8 (7-12.8)	9.6 (7-13)	9.3(8-12.9)	9.5(7.9-12)			
Male	Mean ±SD	8.9±0.8	10±1.6*	9.2±1.6	9.2±1.3	9±1.1			
	Median (min-	8.9 (7.4-10.4)	10.6 (6.1-12.9)	9 (6.4-12)	9.3 (5.8-11.2)	9.2 (6.4-10.			

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	max)								
	p value[b]	0.925	0.991	0.219	0.967	0.056			

[a]Mixed ANOVA: [1]between visits, [2]between EPO and DAPO (main group effect) and [3]EPO vs. DAPO during visits (measurement x group effect), [b] Mann Whitney u test, [c]Student t test

[*]p<0.001 compared to pre-treatment levels (Post hoc Bonferroni correction with p<0.005)

Table 3. Hemoglobin levels according to risk groups and gender

		Hemoglobin levels (g/dL)					**p value[a]**		
Risk groups		**Pre-treatment**	**12th month**	**24th month**	**36th month**	**48th month**	**p[1]**	**p[2]**	**p[3]**
Low risk	Mean ±SD	8.9±1.0	10.3±1.4**	10.1±1.4	9.9±1.2	9.8±1.0	**<0.001**	**<0.001**	**<0.001**
	Median (min-max)	9.0 (5.5-11.0)	10.5 (5.7-13.1)	10.2 (6.9-12.6)	9.8 (6.8-12.9)	9.8 (7.5-13.7)			
Intermediate-1 risk	Mean ±SD	8.6±0.7	10±1.5**	8.7±1.5	8.9±1.2	8.7±1			
	Median (min-max)	8.5 (7-9.9)	10.7 (6.1-11.9)	8.6 (6.4-13)	8.9 (5.8-11.4)	8.8 (6.4-10.7)			
	p value[b]	**0.014**	**0.043**	**<0.001**	**<0.001**	**<0.001**			
Gender in risk groups		**Pre-treatment**	**12th month**	**24th month**	**36th month**	**48th month**	**p[1]**	**p[2]**	**p[3]**
Low risk									
Female	Mean ±SD	8.9±1.1	10.2±1.5**	10.2±1.4	10±1.3	10±1.1	**<0.001**	0.505	**<0.001**
	Median (min-max)	8.9 (5.5-11.0)	10.4 (5.7-12.8)	10.3 (7.1-12.6)	10(7-12.9)	10(8.1-13.7)			
Male	Mean ±SD	8.9±0.9	10.6±1.3**4	9.9±1.3	9.7±1.1	9.6±0.9			
	Median (min-max)	9 (7.4-10.4)	10.9 (6.9-13.1)	10 (6.9-12)	9.7 (6.8-12.3)	9.8 (7.5-11.1)			
	p value[b]	0.879	0.059	0.376	0.221	0.115			
Intermediate-1 risk									
Female	Mean ±SD	8.5±0.8	10.3±1.4*	9.1±1.7	9.1±1.1	9.0±0.8	**<0.001**	0.179	0.304
	Median (min-	8.5 (7-9.8)	10.9 (7-11.9)	8.8 (7-13)	9 (7-11.4)	9.3(7.5-10.7)			

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	max)								
Male	Mean ±SD	8.8±0.6	9.8±1.6*	8.4±1.2	8.8±1.3	8.5±1.1			
	Median (min-max)	8.5 (7.9-9.9)	10 (6.1-11.8)	8.4 (6.4-10.7)	8.9 (5.8-10.9)	8.4 (6.4-10.2)			
	p value[b]	0.391	0.382	0.095	0.939	0.119			

[a]Mixed ANOVA: [1]between visits in the same risk group, [2]between low and intermediate risk (main group effect) and [3]low vs. intermediate risk during visits (measurement x group effect), [b] Mann-Whitney U test **p<0.001 and *p=0.001 compared to pre-treatment levels (Post hoc Bonferroni correction with p<0.005)

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Table 4. Transfusion-need according to treatment and risk groups							
		Transfusion need, n(%)					
Treatment groups		**Pre-treatment**	**12th month**	**24th month**	**36th month**	**48th month**	**p value[1]**
Epoetin alfa	Yes	43(40.2)	15(16.1)**	14(13.5)**	13(14.3)**	9(11.8)**	**<0.001**
	No	64(59.8)	78(83.9)	90(86.5)	78(85.7)	67(88.2)	
Darbepoetin alfa	Yes	37(38.1)	17(18.7)	27(29)	19(22.9)	18(25)	**0.004**
	No	60(61.9)	74(81.3)	66(71)	64(77.1)	54(75)	
p value (epo vs. darbo)		0.765[2]	0.793[3]	**0.012[3]**	0.205[3]	0.063[3]	-
Risk groups		**Pre-treatment**	**12th month**	**24th month**	**36th month**	**48th month**	**p value[1]**
Low risk	Yes	51(34)	20(15.4)*	24(16.4)*	18(14.1)**	13(11.7)**	**<0.001**
	No	99(66)	110(84.6)	122(83.6)	110(85.9)	98(88.3)	
Intermediate-1 risk	Yes	29(53.7)	12(22.2)	17(33.3)	14(30.4)	14(37.8)	**0.005**
	No	25(46.3)	42(77.8)	34(66.7)	32(69.6)	23(62.2)	
p value (low vs. int-1 risk)		**0.011[2]**	0.368[3]	**0.018[3]**	**0.025[3]**	**<0.001[3]**	-

[1]Cochrans's Q test, [2]χ^2 test, [3]Contuinity Correction

*p<0.01 and **p<0.001 compared to baseline pre-treatment transfusion need (Mc Nemar test with Bonferroni correction p<0.005)

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Table 5. Treatment response (≥1.5 g/dL increase in hemoglobin) rates from baseline and from the previous visit during the long-term follow up									
	Percentage of patients with at least 1.5 g/dL increase in hemoglobin levels							**p value[1]**	
	12th month	**24th month**		**36th month**		**48th month**			
	vs. baseline	vs. baseline	vs. previous visit	vs. baseline	vs. previous visit	vs. baseline	vs. previous visit	vs. baseline	vs. previous visit
TREATMENT GROUPS									
Epoetin alfa	48 (44.9)	46 (43.0)	10 (9.3)	36 (33.6)***	6 (5.6)	29 (27.1)^{**,q}	4 (3.7)	**0.002**	0.229
Darbepoetin alfa	45 (46.4)	29 (29.9)	10 (10.3)	22 (22.7)	5 (5.2)	16 (16.5)***	1 (1.0)^{w}	**<0.001**	**0.017**
p value[2] (epo vs. darb)	0.826[2]	0.073[3]	1.00[3]	0.114[3]	1.00[3]	0.098[3]	0.372[4]		
RISK GROUPS									
Low risk	69 (46.0)	59 (39.3)	14 (9.3)	45 (30.0)**	9 (6.0)	39 (26.0)***	5 (3.3)	**<0.001**	0.096
Intermediate risk	24 (44.4)	16 (29.6)	6 (11.1)	13 (24.1)*	2 (3.7)	6 (11.1)^{***,q}	0(0.0)^{w}	**<0.001**	**0.030**
p value[2] (low vs. int)	0.184	0.270[3]	0.913[3]	0.513[3]	0.731[4]	**0.038[2]**	0.328[4]		

[1]Cochrans's Q test, [2]Chi-Square test, [3]Yates Continuity Correction, [4]Fisher Exact test
*p<0.05 and **p<0.001 compared to 12th month, ^{q}p<0.01 compared to 24th month, ^{w}p<0.05 compared to increase from previous visit at 24th month (Mc Nemar test with Bonferroni correction; p<0.05)

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