Original Article

A comparison of haemoglobin levels and doses in haemodialysis patients treated with subcutaneous or intravenous darbepoetin alfa: a German prospective, randomized, multicentre study

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Abstract

Background. The different efficacy of subcutaneous and intravenous rHuEPO results in higher doses and costs in intravenously treated patients. Darbepoetin alfa has a different pharmacokinetic profile compared to rHuEPO, and previous clinical experience suggests that subcutaneous and intravenous darbepoetin alfa may have similar efficacy.

Objective. The aim of this study was to compare the efficacy of intravenous and subcutaneous darbepoetin alfa regarding haemoglobin levels and doses.

Methods. Patients treated with subcutaneous darbepoetin alfa for at least 6 months were randomized 1:1 to continue with subcutaneous treatment of darbepoetin alfa or to switch to the intravenous administration route. The application frequency was not altered. Darbepoetin alfa dose as well as haemoglobin concentrations were evaluated as per patient average at baseline (Week −3 ± 1), Week 24 ± 3 and Week 48 ± 3.

Results. One hundred fourteen patients in 9 German dialysis centres were included. Fifty-three patients were treated intravenously and 61 patients continued the subcutaneous therapy. Mean haemoglobin levels and mean weekly darbepoetin alfa dose did not change significantly in either treatment group.

Conclusions. Our data suggest that the darbepoetin alfa dose can be kept constant if patients are switched from subcutaneous to intravenous treatment.

Keywords: anaemia; darbepoetin alfa; haemodialysis; intravenous; subcutaneous

Introduction

Renal anaemia treatment with erythropoiesis-stimulating agents (ESAs) has improved the quality of life of haemodialysis (HD) patients considerably and resulted in observational studies in lower morbidity and mortality [1–4]. The ESA treatment can be administered subcutaneously or intravenously according to the patient characteristics. However, it was shown that intravenous administration of rHuEPO maintains the haemoglobin level in the desired target range with a significantly higher weekly dose compared to subcutaneous administration [5]. Similar results were found in other studies [6–10]. Furthermore, a meta-analysis demonstrated that the cost of rHuEPO is reduced considerably when rHuEPO is administered subcutaneously in comparison to the intravenous administration route [11].

Darbepoetin alfa is an ESA that contains two additional carbohydrate sites compared to rHuEPO and a higher sialic acid content. With the higher sialic acid content, darbepoetin alfa has longer terminal half-life and a greater in vivo biologic activity compared to rHuEPO [12–15].

As a consequence of the longer half-life and the greater in vivo activity, darbepoetin alfa can be administered with a reduced dosing frequency [16,17]. Furthermore, clinical experience and secondary analyses suggest that the pharmacokinetic properties of darbepoetin alfa allow a similar efficacy of intravenous and subcutaneous treatment [18]. These characteristics can be advantageous in HD patients as intravenous therapy may be more convenient for this patient group than subcutaneous application. If it could be proven that efficacy of intravenous and subcutaneous treatment is similar for both administration routes, subcutaneous administration would become unnecessary in most HD patients.

The presented prospective, randomized, multicentre study had the objective to investigate the efficacy of the subcutaneous and intravenous administration routes for darbepoetin alfa.
Methods and patients

This study was an open, controlled, prospective, randomized, multicentre study. It was conducted from February 2002 until September 2005 in nine German dialysis centres. The study was conducted in accordance with the declaration of Helsinki, the ICH-GCP guidelines and the German drug law. The protocol was approved by the Ethics Committee of the Medical University Hospital Heidelberg and the local ethics committee at every participating site, if required. Patients were requested to give written informed consent before participation.

Patients

Patients ≥18 years of age with anaemia and under maintenance HD for >1 year for terminal renal insufficiency were eligible for inclusion into the study. Inclusion criteria were treatment with subcutaneous darbepoetin alfa once weekly or every 2 weeks for at least 6 months. Before inclusion, the darbepoetin dosage had to be constant for at least 8 weeks (defined as ±25% dosage change). Further, a haemoglobin level between 10.0 g/dl and 13.0 g/dl and a serum ferritin ≥200 µg/l were required. Patients were excluded from the study given they met one of the following reasons: grand mal epilepsy during the last 6 months before inclusion, congestive heart failure (NYHA III and IV), uncontrolled arterial hypertension (diastolic RR ≥110 mmHg at 2 days before inclusion), uncontrolled hyperparathyroidism (iPTH >1500 pg/ml during the last 12 months), major surgery during the last 3 months, ALT and AST above the double normal values, blood transfusions and/or androgen treatment during the last 12 weeks and systemic haematological diseases such as sickle cell anaemia, myelodysplasia, haematological malignancies, chronic inflammatory status, infections, haemolytic anaemia, pregnancy, breast feeding, psychiatric diseases, participation in any other study during 30 days before inclusion and expected transplantation from a living donor.

Randomization and treatment

Patients with stable haemoglobin values were randomized centrally by a separate random figure table for each centre (to account for potential differences among the centres) either to continue the treatment with subcutaneous darbepoetin alfa or to switch to intravenous darbepoetin alfa without altering the application frequency and dose. In both treatment groups (subcutaneous and intravenous route), darbepoetin alfa was administered with prefilled syringes containing one of the following fixed doses: 10 µg, 15 µg, 20 µg, 30 µg, 40 µg, 50 µg, 60 µg, 80 µg, 100 µg and 150 µg. The patients were treated for 52 weeks.

It was recommended to keep the haemoglobin levels constant at least in the range between 10 g/dl and 13 g/dl. As routine haemoglobin assessments were scheduled at least every 4 weeks, measurements had to be repeated within 1 week if the haemoglobin value was or tended to be outside the target range.

If two consecutive haemoglobin measurements were outside the target range, the darbepoetin alfa dose had to be adjusted. In the case of two haemoglobin values >13 g/dl, the dose had to be reduced to the next lower fixed darbepoetin alfa dosage whereas two values <10 g/dl resulted in an increase to the next higher fixed darbepoetin alfa dose. If patients at the lowest darbepoetin alfa dose (10 µg), however, presented a haemoglobin value >13 g/dl at two consecutive measurements, application frequency was reduced. If patients at the highest darbepoetin alfa dosage (150 µg) presented with a haemoglobin value less than 10 g/dl at two consecutive measurements application frequency was increased. In patients with haemoglobin values >14 g/dl, darbepoetin alfa treatment was stopped until the haemoglobin decreased to the target range. After dose adjustments, the haemoglobin level was controlled every 1–2 weeks as required by the European Best Practice Guidelines [19].

Concomitant therapies including blood transfusions were applied at the discretion of the physicians. In patients with iron deficiency (serum ferritin <200 µg/l) iron was substituted, predominantly intravenously, otherwise orally.

Clinical assessment

After informed consent had been obtained, the patients entered the screening examination (Week -4 to -2) that consisted of medical history including aetiology of the end-stage renal disease, concomitant diseases and the time on dialysis, physical examination, blood pressure measurement (before and after dialysis) and laboratory parameters such as haemoglobin, haematocrit, urea, creatinine, albumin, ALT, γ-GT and serum ferritin. Furthermore, treatment with antihypertensive drugs (name of the drug, dosage, and application mode and frequency) and/or iron (oral, intravenous, dose and application frequency) were recorded.

At baseline (Week -2 until randomization) iron treatment, two haemoglobin and haematocrit measurements within maximal 2 weeks as well as leukocyte and platelet counts were documented. During the treatment period until the final examination (Week 48 ± 3), iron substitution, blood pressure (before and after dialysis) as well as haemoglobin and haematocrit values were recorded at least every 4 weeks. The treatment with antihypertensive drugs was recorded at the beginning and at the end of the study period.

Serum ferritin, electrolytes, calcium, phosphate, urea, creatinine, AST and γ-GT were determined every 3 months. Furthermore, one measurement of iPTH was required. It was recommended to take all blood samples before dialysis at a constant day of the week and at least 1 week (better 2 weeks) after the last intravenous iron substitution. All blood transfusions were recorded.

Safety

All adverse events (AEs) were recorded beginning after the application of the first dose of the study drug until the evaluation after treatment termination, given there was a possible causal relationship with the treatment. The severity of any AE, possible relationship to treatment, action taken and
outcome were also recorded. A serious adverse event (SAE) was defined as one resulting in death, a life-threatening event, hospitalization or prolongation of existing hospitalization, or any condition causing persisting or significant disability (incapacity). In the case of an SAE, the SAE documentation was forwarded within two working days to the principal investigator or his substitute.

Data analysis and statistics

Data were analysed at three time periods: baseline, Week 24 and Week 48. For baseline, the mean or median of the per patient average during Weeks −3 to +1 was calculated. In the 24-week period and 48-week period the per patient averages during Weeks 24 ± 3 respectively Weeks 48 ± 3 were used.

The primary study endpoint was the weekly mean darbepoetin alfa dose necessary to maintain the haemoglobin value in the target range of 10–13 g/dl during the treatment period of 52 weeks. Data were analysed by comparing the means and medians of the per patient average haemoglobin and darbepoetin dose at baseline (Week −3 to +1) and the evaluation periods at 24 ± 3 weeks and 48 ± 3 weeks. Secondary objectives included the changes in the haemoglobin level in the individual patients by comparing average haemoglobin levels at baseline (Weeks −3 to +1) and Week 24 ± 3 and Week 48 ± 3, the changes in the required darbepoetin dose in the individual patients between baseline and the evaluation periods (Week 24 ± 3 and Week 48 ± 3) and the requirement of blood transfusions. The safety was checked by documentation of AEs.

Statistical comparisons between the randomized patient groups were performed using the t-test for independent observations in the case of haemoglobin and the Wilcoxon–Mann–Whitney test for ESA dosages. For within-group comparisons of haemoglobin measurements between different time points, the paired versions of the t-test and the Wilcoxon test procedures were applied. A probability level <0.05 was considered as significant. Baseline characteristics were compared using Fisher’s exact test, the $\chi^2$ test and the Wilcoxon test, respectively, according to the type of the parameter distribution. All P-values provided are two sided.

Results

A total of 126 patients at nine German dialysis centres were randomized. Twelve patients were not eligible or had to be excluded from the analysis for various reasons, such as patient’s consent was withdrawn (2 patients), baseline data did not fully agree with the inclusion criteria (5 patients), violation of protocol (3 patients), transplantation (1 patient) and decision of the local nephrologists (1 patient) (Figure 1). From 114 patients, matching all required preconditions of the study, complete baseline values were obtained. Fifty-three (46%) were male and 61 (54%) female. Females and males were distributed equally in both treatment groups; body weight was similar and the mean age of the intravenous group was 62.3 ± 14.1 years compared to 62.4 ± 15.3 years in the subcutaneous group. Fifty-three (46%) patients received intravenous treatment, 61 (54%) were on subcutaneous therapy (for more details see Table 1). Clinical characteristics such as time on dialysis, primary cause of end-stage renal disease, concomitant diseases (hypertension and diabetes) and laboratory values (except haemoglobin) did not differ considerably at baseline. Further details about clinical characteristics are presented in Table 1.

During the study 8 patients died [cardiac death (2 patients s.c. and 2 patients i.v.), septicaemia (2 patients s.c. and...
1 patient i.v.) cerebral bleeding (1 patient s.c.), 4 patients received a kidney transplant (1 patient s.c., 3 patients i.v.), and 1 patient was withdrawn after decision of the local physician (Figure 1).

**Haemoglobin**

Despite randomization, slight but significant differences in terms of haemoglobin levels within the two treatment groups were observed (i.v.: 11.6 ± 1.0 g/dl; s.c.: 12.0 ± 0.8 g/dl; *P* = 0.01). After 24 weeks, the mean haemoglobin level reached 11.9 ± 1.0 in both groups. At the end of the study (Week 48) intravenous darbepoetin alfa therapy resulted in a mean haemoglobin concentration of 11.6 ± 1.0 compared to 11.7 ± 0.8 g/dl in patients treated subcutaneously. For the haemoglobin levels after 24 and 48 weeks of treatment, no statistical differences could be detected. The difference of the haemoglobin values between baseline and Week 24 (mean of the differences Week 24 − baseline) for i.v. versus s.c. was +0.46 g/dl [range 0.04 − 0.88, *P* = 0.034 (t-test)], and between baseline and Week 48 (Week 48 − baseline) was +0.36 g/dl [range −0.04 − 0.76, *P* = 0.073 (t-test)] (Figure 2).

Baseline haemoglobin values had an impact on further haemoglobin level changes during the study course. The haemoglobin level of patients (based upon the entire population, i.v. and s.c. treated patients) with a baseline value <11.5 g/dl (*n* = 34) increased by 0.54 (median of differences) until Week 24 and by 0.58 until Week 48, whereas it did not change until Week 24 and decreased by 0.23 by Week 48 in patients with a baseline value between 11.5 and 12.4 g/dl (*n* = 36). In patients with a baseline haemoglobin level ≥12.5 g/dl (*n* = 31), the haemoglobin level decreased by 0.72 median of differences until Week 24 and by 0.95 by Week 48 (*P* < 0.0001, Kruskal–Wallis test).

**Darbepoetin alfa dose requirements**

According to the haemoglobin levels at baseline, starting doses of darbepoetin alfa after randomization differed slightly between the intravenous and the subcutaneous application group, but the difference was not significant [mean dosage of the i.v. group: 31.7 ± 20.9 µg/week versus mean dosage of the s.c. group 25.8 ± 17.0 µg/week, respectively; *P* = 0.11 (Wilcoxon test)]. After 24 weeks, the mean intravenous dose increased non-significantly by 1.5 µg/week to 33.2 ± 26.8 µg/week) whereas the mean subcutaneous dose decreased by 1.0 µg/week to 24.8 ± 17.8 µg/week (*P* = 0.16 Wilcoxon test). At the study end (Week 48), a mean weekly dose of 31.1 ± 22.8 µg/week in intravenously treated patients as compared to 26.9 ± 19.9 µg/week in subcutaneously treated patients (*P* = 0.38 (Wilcoxon test)) was observed (see Figure 2). The higher darbepoetin alfa dose administered in patients treated intravenously compared to subcutaneously treated patients did not reveal any relevant relative differences along the observation time of the study in view of the higher baseline dosage being taken into account.

For the darbepoetin doses after 24 and 48 weeks of treatment, no significant differences could be detected. The difference of the average per patient darbepoetin doses between baseline and Week 24 (mean of the differences Week 24 − baseline) for i.v. versus s.c. was +2.53 µg, *P* = 0.41 (t-test), and between baseline and Week 48 (Week 48 − baseline) was −1.25 µg, *P* = 0.67 (t-test).

The darbepoetin alfa baseline dose closely corresponded to the haemoglobin value. Patients who received darbepoetin alfa at randomization <30 µg/week had a mean baseline haemoglobin level of 11.9 ± 0.9 g/dl that changed to 11.8 ± 1.0 µg/week at Week 24 and 11.7 ± 0.8 µg/week at Week 48. In patients who received darbepoetin alfa at randomization ≥30 µg/week, the mean haemoglobin level at baseline was 11.7 ± 1.0 g/dl and changed to 12.1 ± 1.1 g/dl after 24 weeks and 11.6 ± 1.1 g/dl after 48 weeks.

**Erythropoietic resistance index**

Comparisons of the mean erythropoietic resistance index (darbepoetin alfa dose × 200)/(body weight × haemoglobin level) between baseline and Week 24 as well as Week 48 resulted in similar differences as the darbepoetin alfa doses. Intravenously treated patients had a higher baseline index (8.0 ± 5.4) compared to subcutaneously treated patients (6.2 ± 4.0) (*P* = 0.047, Wilcoxon test). After 24 and 48 weeks, the resistance index was 8.0 ± 6.6 and 7.7 ± 5.6 in patients with intravenous therapy and 6.3 ± 4.8 and 6.8 ± 5.1 in patients with subcutaneous application of darbepoetin alfa, respectively. The differences of the resistance index between baseline and Week 24 ± 3 or 48 ± 3 in i.v. versus s.c. patients were not significantly different (*P* = 0.65 or *P* = 0.17).

**Iron substitution, blood pressure and laboratory parameters**

Systolic and diastolic blood pressure and laboratory parameters were similar in both treatment groups. During the pre-study period, up to Week 1 of the study, serum ferritin in the i.v. group was 543 ± 223 pg/ml and the most recent level during the study was 502 ± 224 pg/ml. The corresponding ferritin levels in the s.c. group were 538 ± 193 and
556 ± 227 pg/ml. In the i.v. group, mean iPTH was 203 ± 141 pg/ml in the pre-study period and the mean of the most recent level was 258 ± 216.8 pg/ml. The corresponding iPTH levels in the s.c. group were 275 ± 236 and 286 ± 306 pg/ml. Only eight patients (four per group) received blood transfusions.

Safety and tolerability

The darbepoetin alfa treatment was well tolerated in both treatment arms. A total of 18 AEs were documented in patients intravenously treated, whereas in patients treated subcutaneously 38 AEs were reported. The majority of AEs were slight or moderate. There were 6 SAEs in the intravenous group (three patients died) and 24 SAEs in the subcutaneous group (five patients died). Five AEs in the intravenous group and four in the subcutaneous group were classified as related to the darbepoetin alfa treatment by the investigators. None of the serious AEs with a fatal outcome was classified as related to the study treatment.

Discussion

This randomized clinical study demonstrated that switching from subcutaneous to intravenous administration of darbepoetin alfa can maintain haemoglobin in the defined range of 10–13 g/dl at the comparable dose requirements. Thus, for darbepoetin alfa the treatment of dialysis patients via the more convenient i.v. administration route does not result in economic disadvantages.

It was shown before that intravenous administration of rHuEPO in dialysis patients is associated with higher dose requirements than the subcutaneous route: Besarab et al. compared the effectiveness of different rHuEPO administration routes and dosing schedules in 36 patients and observed a 50% higher weekly rHuEPO dose requirement in patients treated intravenously compared to subcutaneous administration [20]. During the study period, the rHuEPO dose increased significantly in patients switched to i.v. treatment but not in the control group. Furthermore, Schaller et al. showed that during i.v. administration, on average 30% more rHuEPO was needed in anaemic dialysis patients compared to s.c. administration [9].

However, the easy access makes intravenous ESA treatment in HD patients more convenient. Due to the longer half-life of darbepoetin alfa, it was proposed that darbepoetin alfa might be intravenously administered without economic disadvantages or loss of efficacy. A first indication that this hypothesis might be correct was provided by the pooled data of clinical studies with darbepoetin alfa [21].

Recent studies provide additional data that suggest a clinical and economic equality of intravenous and subcutaneous darbepoetin alfa treatment in HD patients. Using the conversion factor 200 IU rHuEPO to 1 µg darbepoetin alfa, Summers et al. switched 82 chronic dialysis patients from subcutaneous rHuEPO to intravenous darbepoetin alfa [22]. After the switch, a haemoglobin increase was observed to be associated with a lower dose requirement. The authors concluded that intravenous darbepoetin alfa is at least as effective as subcutaneous rHuEPO and potentially a cost benefit can be obtained.

Using an initial dose conversion factor of 200:1 for the switch from rHuEPO to darbepoetin alfa, Locatelli et al. reported a trial in which 76 patients on rHuEPO i.v. were switched to darbepoetin alfa i.v., whereas 267 patients on rHuEPO s.c. were switched to darbepoetin alfa s.c. [23]. At evaluation phase, a dose reduction in the i.v. group was reported whereas constant dose requirements were faced in the s.c. group. However, the relative portion of patients on 1 × /week rHuEPO was higher in the i.v. group (36% in the i.v. group and 19% in the s.c. group; baseline haemoglobin levels were suboptimal in the s.c. group).

Vanrenterghem et al. randomized 522 European and Australian haemodialysis patients receiving stable intravenous or subcutaneous rHuEPO therapy open label to continue rHuEPO or to an equivalent dose of darbepoetin alfa at a reduced dosing frequency and titrated the doses to maintain haemoglobin close to the patient’s baseline level for up to 52 weeks [24]. During Weeks 21–24, 33–36 and 49–52, the ratios between s.c. and i.v. doses were 1.00, 1.05 and 1.11, respectively, which did not differ significantly from 1.0 for darbepoetin alfa. In the same interval, however, the corresponding ratios for s.c. rHuEPO doses were 0.81, 0.76 and 0.77, the latter ones being significantly different from 1.0. Dose requirements were 28% higher by intravenous administration compared to subcutaneous administration. All these studies suggested that intravenous darbepoetin alfa does not require higher doses than subcutaneous darbepoetin alfa in patients switched from rHuEPO to darbepoetin alfa.

Recently, Aarup et al. demonstrated that patients who switched from s.c. to i.v. darbepoetin alfa did not show dose penalties [18]. After a 3-week run-in period with darbepoetin alfa s.c. treatment and dose adjustments once weekly, Aarup et al. randomized 71 patients to a 20-week treatment with either darbepoetin alfa s.c. or i.v. and crossed them over to the other treatment modality for another 20 weeks. The mean darbepoetin alfa dose during intravenous administration was lower than that during subcutaneous administration (32.1 µg/week versus 34.1 µg/week; P = 0.036). Aarup et al. concluded that stable haemodialysis patients can be treated with intravenous darbepoetin alfa more effectively than with subcutaneous darbepoetin alfa.

In a further crossover study, Cervelli et al. treated 24 haemodialysis patients with i.v. or s.c. darbepoetin for 6 months [25]. The patients achieved a non-significantly higher haemoglobin (123 ± 376 versus 120.9 ± 4.42 g/l, P = 0.11) from a non-significantly lower darbepoetin dose (40.8 ± 10.7 versus 42.5 ± 11.0 µg/week; P = 0.23) with i.v. administration. This suggested a better efficiency of i.v. darbepoetin as compared to the s.c. administration route.

Our randomized study of over 1 year indicated a therapeutic equivalence of subcutaneous and intravenous darbepoetin alfa as well. We showed that darbepoetin alfa is efficacious irrespective of the administration route. Dose requirements were similar in both groups, and the switch from subcutaneous darbepoetin alfa treatment to intravenous therapy did not require dose adjustments.

Our study has some limitations. The study included only a limited number of patients, as all previous prospective
studies with that matter of evaluation did. By the central randomization, without knowledge of patients’ health and using a separate randomization table for each dialysate unit, we tried to avoid the selection bias and the effect of a different practice pattern in the centre. Even though the study protocol asked to keep the dialysis therapy unchanged during the study, we did not directly control the dialysis dose, e.g. by Kt/V measurement. Despite randomization, mean baseline haemoglobin levels were somewhat lower in intravenously treated patient group compared to subcutaneously treated patients. The different baseline haemoglobin levels may result from transient factors that can influence erythropoiesis like occult intermittent subacute infections, seasonal influenza, vascular problems with varying efficacy of dialysis or functional iron deficiency. During the treatment period, the differences decreased and at the evaluation periods after 24 ± 3 and 48 ± 3 weeks haemoglobin levels were similar in both treatment groups. Such transient influences may also explain the difference in the levels were similar in both treatment groups. Such tran-

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25.4 in the i.v. group and 25.4 ± 17.5 in the s.c. group. 

between baseline and Week 24 ± 3 or 48 ± 3 in i.v. versus s.c. patients was not significantly different, which agrees with a comparable efficacy of i.v. and s.c. darbepoetin. As compared to rHuEPO, darbepoetin alfa can be administered less frequently. In pilot studies, it has been applied up to only once a month for its long-lasting effect. As a consequence, carry-over effects may influence the results of short-term studies with darbepoetin alfa. Our long observation period of 1 year likely excludes a possible carry-over effect of the primary s.c. darbepoetin alfa treatment at the end of the study that has been faced in some trials with the 6-month observation period. In spite of the appropriate longer study period, our study cannot reach the detection power of equivalence of the efficacy of i.v. or s.c. darbepoetin. This can only be achieved by larger studies over 1 year or longer.

In the presented randomized clinical study, intravenous administration of darbepoetin alfa can be used in haemodialysis patients with the same cost/benefit ratio as subcutaneous darbepoetin alfa therapy that is also stated by the European Best Practice guidelines [19].

Conclusions

In contrast to the dose penalty of short-acting ESAs when switched from s.c. to i.v. administration, this has not been observed during our 1-year study. Therefore, when patients are switched from the s.c. to the i.v. route, i.v. darbepoetin alfa provides the same cost/benefit ratio as s.c. administration. Thus, from an economic point of view, patients can be treated by the easier and more convenient i.v. administration route.

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Conflict of interest statement. None declared.

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Efficacy of subcutaneous versus intravenous darbepoetin alfa

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