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Original Article

Beneficial influence of recombinant human erythropoietin therapy on the rate of progression of chronic renal failure in predialysis patients

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Abstract

Background. Partial correction of anaemia with recombinant human erythropoietin (rHuEpo) has been shown to markedly improve the general condition and quality of life of predialysis patients, but the effects of rHuEpo therapy on blood pressure and the rate of progression of chronic renal failure (CRF) are still disputed. In particular, no study evaluated the time duration until the start of maintenance dialysis in treated patients, compared to untreated predialysis patients.

Methods. We retrospectively evaluated the rate of decline of creatinine clearance (ΔCcr) and the duration of the predialysis period in 20 patients with advanced CRF treated with rHuEpo (Epo+ group), and in 43 patients with a similar degree of CRF but with less marked, asymptomatic anaemia, not requiring rHuEpo therapy (Epo− group). All patients were submitted to identical clinical and laboratory surveillance. All received similar oral supplementation with B_6, B_9, and B_{12} vitamins and oral iron supplementation. Maintenance dose of subcutaneous epoetin was 54.3 ± 16.5 U/kg/week (median dose 3300 U/week).

Results. Initial and final haemoglobin (Hb) levels were 8.8 ± 0.7 and 11.3 ± 0.9 g/dl in the Epo+ group, *vs* 10.9 ± 1.2 and 9.5 ± 0.9 g/dl in the Epo− group. In the Epo+ group, ΔCcr declined from 0.36 ± 0.16 during the preceding 24 months to 0.26 ± 0.15 ml/min/1.73 m^2/month after the start of rHuEpo therapy ($P < 0.05$). No significant variation was observed in the Epo− group. Time duration until the start of dialysis was 16.2 ± 11.9 in the Epo+ group, compared to 10.6 ± 6.1 months in the Epo− group ($P < 0.01$). Slowing of progression was observed in 10 Epo+ patients, whereas no significant variation in ΔCcr occurred in the other 10. There was no difference in previous ΔCcr rate, nor in Hb or blood pressure levels while on rHuEpo therapy between the two subgroups.

Conclusions. Our study affords conclusive evidence that rHuEpo therapy did not result in accelerated progression of CRF in any treated predialysis patients, nor deleterious increase in blood pressure, but instead resulted in significant slowing of progression and substantial retardation of maintenance dialysis. Such encouraging results remain to be validated in a large prospective, randomized study.

Keywords: chronic renal failure; predialysis; progression; recombinant erythropoietin; retardation of dialysis

Introduction

Following the dramatic improvement observed in the general condition of dialysis patients in whom anaemia was treated with recombinant erythropoietin (rHuEpo), this treatment was extended to chronic renal failure (CRF) patients not yet on dialysis. However, experimental studies in rats [1] have generated important concern regarding a potential adverse effect of correction of anaemia by epoetin treatment on the progression of CRF.

Initial clinical trials performed in the late 1980s were partially reassuring, as none noted any significant alternation in the rate of progression of renal disease, but they consistently reported a marked increase in blood pressure level [2]. In subsequent clinical studies using lower doses of rHuEpo, thus achieving a more progressive correction of anaemia, elevation of blood pressure was no longer observed and no acceleration of the progression of renal disease was noted [3–5]. Recently it has actually been claimed that correction of anaemia with epoetin may instead reduce the progression of renal failure in predialysis patients [6]. However, most published studies have included relatively small numbers of patients, and have had short follow-up periods. In addition, none of those studies evaluated the actual time until the start of

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dialysis, and therefore they could not evaluate whether epoetin therapy could delay the start of replacement therapy.

In a large cohort of predialysis CRF patients followed at our institution, we retrospectively evaluated the rate of decline of renal function, and the duration of the predialysis period, in patients treated with rHuEpo. We compared the results with those obtained in patients treated with the same degree of renal impairment but with a lesser degree of anaemia, thus not requiring rHuEpo therapy.

Subjects and methods

We studied 67 adult predialysis CRF patients (all Caucasian) with serum creatinine (Scr) $\geqslant 300$ μmol/l and/or creatinine clearance (Ccr) $\leqslant 15$ ml/min/1.73/m^2, followed at Necker Hospital between January 1990 and December 1999. All were managed until end-stage renal disease (ESRD) and start of dialysis therapy.

Twenty-four patients received rHuEpo therapy for a haemoglobin (Hb) level <9 g/dl (13 cases) or between 9 and 10 g/dl with poorly tolerated anaemia (11 cases). Among them, four patients who started rHuEpo therapy at a very advanced stage of CRF and actually had reached ESRD were excluded from data analysis. The other 20 were treated with rHuEpo at a less advanced stage of CRF and were included in the study. They constituted the treated group (Epo+). Forty-three patients with less marked and asymptomatic anaemia who did not require rHuEpo therapy until the start of dialysis constituted the control group (Epo−).

All patients, rHuEpo-treated or not, were followed as outpatients at a single nephrology clinic and received identical care. All were submitted to moderate protein restriction (0.7–0.8 g/kg/day) and received oral supplementation with vitamins B_1 and B_6 (250 mg each, twice weekly), vitamin B_{12} (1 mg once weekly), folic acid (5 mg thrice weekly), and oral iron supplementation (80–200 mg elemental iron daily) from the time when Ccr dropped below 25–30 ml/min/1.73 m^2.

Recombinant human erythropoietin (epoetin alpha, Eprex®) was administrated subcutaneously. Starting doses were 2000–4000 units per week in two injections, in order that the increase in Hb level did not exceed 1 g/dl/month. Maintenance dose ranged from 1000 to 4000 U/week, aimed at a target Hb level of 11.5 ± 0.5 g/dl. Vitamin and iron supplementation were continued at the same dose during follow-up, with folic acid augmented to 5 mg every day in rHuEpo-treated patients.

Clinical and laboratory monitoring was performed every 3 months before the start of rHuEpo, and monthly thereafter in both groups. Scr was determined at each visit, together with Hb level, body weight and blood pressure. Ccr was calculated according to the Cockcroft–Gault formula.

In both groups, the rate of decline in Ccr (ΔCcr, expressed as ml/min/1.73 m^2/month) was determined over the 24 months preceding the start of follow-up (T_0). T_0 was defined as the time of starting rHuEpo in the Epo+ group, and as the time when Ccr had a similar value as in the Epo+ group, in the Epo− group patients.

Results are presented as mean ± SD. Inter-group comparisons used ANOVA and the χ^2 test of Pearson. P value <0.05 was considered as significant.

Results

Characteristics of patients at start of follow-up in the Epo+ and Epo− groups are given in Table 1. The proportion of women was significantly higher, as was the mean age of patients, in the Epo+ than in the Epo− group. There was no significant difference with respect to the distribution of primary renal diseases, except that there was no diabetic patient in the Epo+ group, *vs* five among the 43 Epo− patients. The proportion of patients with polycystic kidney disease was similar in both groups. Scr and Ccr values, as well as systolic blood pressure (SBP) and diastolic blood pressure (DBP) did not differ between the two groups. Notably, the proportion of patients treated with angiotensin-converting enzyme inhibitors (ACEI) was also similar in both groups.

The mean duration of nephrological follow-up prior to T_0 was 22.8 ± 3.5 months in the Epo+ group and 22.9 ± 5.9 months in the Epo− group. In the treated group, starting dose of rHuEpo was 59.2 ± 16.3 U/kg/week (median 3600 U/week) and maintenance dose was 54.3 ± 16.5 U/kg/week (median 3300 U/week). Hb level was 11.5 ± 0.7 g/dl 3 months after the start of rHuEpo, with a final value before initiation of dialysis of 11.3 ± 0.9 g/dl in the Epo+ group, compared to 10.8 ± 1.1 and 9.5 ± 0.9 g/dl respectively, in the Epo− group.

The rate of decline in Ccr did not change in the Epo− group, with a mean ΔCcr value of 0.55 ± 0.48 ml/min/1.73 m^2/month before *vs* 0.57 ± 0.44 ml/min /1.73 m^2/month after T_0 (difference not significant). In contrast, the progression of CRF was already slower before T_0 in the Epo+ group, with a mean ΔCcr value of 0.36 ± 0.16 ml/min/ 1.73 m^2/month, and decreased to 0.26 ± 0.15 ml/min/ 1.73 m^2/ month after T_0 ($P < 0.05$) (Table 2). The slope of ΔCcr was reduced by more than 50% in 10 of the Epo+ patients (decrease

Table 1. Characteristics of CRF patients treated with rHuEpo (Epo+) or not treated (Epo−) at start of follow-up

	Epo+ ($n=20$)	Epo− ($n=43$)	P value
Gender (M/F)	10/10	35/8	<0.01
Age (years)	67.1 ± 9.2	58.7 ± 13.4	<0.01
Renal disease			
Glomerular	6 (30%)	12 (23%)	NS
Interstitial	6 (30%)	9 (21%)	NS
PKD	4 (20%)	9 (21%)	NS
Vascular	4 (20%)	8 (19%)	NS
Diabetic	0	5 (12%)	<0.01
Scr (μmol/l)	525 ± 74	553 ± 77	NS
Ccr (ml/min/1.73 m^2)	10.2 ± 1.7	11.9 ± 2.4	NS
SBP (mmHg)	154 ± 12	155 ± 18	NS
DBP (mmHg)	83 ± 7	85 ± 7	NS
ACEI	30%	37%	NS
Hb (g/dl)	8.8 ± 0.7	10.9 ± 1.2	<0.01

Scr, serum creatinine; Ccr, creatinine clearance; PKD, polycystic kidney disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACEI, angiotensin-converting enzyme inhibitors; Hb, haemoglobin level.

Table 2. Variation of the rate of decline in Ccr (ΔCcr) and duration of predialysis time in Epo+ and Epo− groups, with respect to Hb, blood pressure, and Ccr levels at end of follow-up

	Epo+ ($n=20$)	Epo− ($n=43$)	P value
ΔCcr before T_0 (ml/min/1.73 m^2/month)	0.36 ± 0.16*	0.55 ± 0.48	< 0.01
ΔCcr after T_0 (ml/min/1.73 m^2/month)	0.26 ± 0.15*°	0.57 ± 0.44	< 0.01
Duration T_0—dialysis (months)	16.3 ± 12.7*	10.6 ± 6.1	< 0.01
Hb at end (g/dl)	11.3 ± 0.9*	9.5 ± 0.9	< 0.01
SBP at end (mmHg)	159 ± 17	150 ± 16	NS
DBP at end (mmHg)	82 ± 8	83 ± 7	NS
MAP at end (mmHg)	107 ± 10	105 ± 9	NS
Ccr at end (ml/min/1.73 m^2)	7.1 ± 1.1	7.7 ± 1.3	NS

*$P < 0.05$ between Epo+ and Epo−; °$P < 0.05$ between before and after T_0.
Hb, haemoglobin level; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; Ccr, creatinine clearance.

Table 3. Comparison of patients with slowed *vs* unchanged rate of progression on rHuEpo therapy

	Slowed progression ($n=10$)	Unchanged progression ($n=10$)	P value
Age at T_0 (years)	69.5 ± 7.9	64.6 ± 10.1	NS
Dose of Epo (U/kg/week)	54 ± 17	55 ± 16	NS
ΔCcr before T_0 (ml/min/1.73 m^2/month)	0.38 ± 0.17	0.34 ± 0.16	NS
Ccr at T_0 (ml/min/1.73 m^2)	9.9 ± 1.9	10.4 ± 1.6	NS
Ccr at end (ml/min/1.73 m^2)	7.2 ± 0.9	6.9 ± 1.2	NS
MAP at T_0 (mmHg)	104 ± 7.0	109 ± 7.0	NS
MAP at end (mmHg)	107 ± 8.0	108 ± 11	NS
Hb at T_0 (g/dl)	8.7 ± 0.6	8.9 ± 0.7	NS
Hb at end (g/dl)	11.6 ± 0.6	11.1 ± 1.0	NS
Primary renal disease			
Interstitial or vascular	7/10	3/10	
Glomerular or PKD	3/10	7/10	

Hb, haemoglobin level; MAP, mean arterial pressure; Ccr, creatinine clearance.

from 0.39 ± 0.06 to 0.18 ± 0.03 ml/min/1.73 m^2/month), whereas ΔCcr did not significantly change in the other 10 Epo+ patients (from 0.34 ± 0.05 to 0.33 ± 0.05 ml/min/1.73 m^2/month).

The duration from T_0 until the start of dialysis was 16.2 ± 11.9 months (range 7–53 months) in the Epo+ group, compared to 10.6 ± 6.1 months (range 6–23 months) in the Epo− group ($P < 0.001$), a gain in delay of renal replacement therapy of about 6 months. However, this effect was not observed uniformly in all of these patients. In 10 of them, the delay was substantial, with a mean T_0 to dialysis time of 21.4 ± 16.6 months, whereas in the other 10 patients, the predialysis period was only 11.1 ± 2.9 months, similar to that of 10.6 ± 6.1 months observed in the Epo− group. There was no significant difference in the SBP and DBP level at T_0 and during follow-up between the Epo+ and Epo− groups. However, antihypertensive treatment had to be augmented in five patients receiving Epo, with additional drugs prescribed in two and increase of the previous dosage in three. Similarly, the initial and final values of Ccr did not significantly differ between the two groups.

When comparing the 10 patients whose progression was slowed with the 10 patients whose progression was unchanged, there was no significant difference in terms of initial and final values of Hb, SBP, DBP, Scr, and slope of ΔCcr (Table 3). The only difference was the distribution of primary renal diseases between the two subgroups. Seven of the 10 patients with slowed progression suffered from vascular or interstitial nephropathies, whereas glomerular diseases or polycystic kidney disease were present in seven of the 10 patients with unchanged progression.

Discussion

Our study was aimed at evaluating the effects of partial correction of anaemia by rHuEpo in CRF patients with respect to the actual duration until the start of dialysis. Our data provide conclusive evidence that rHuEpo therapy was associated with a substantial extension of renal autonomy in rHuEpo-treated patients, when compared to untreated patients with a similar degree of renal failure.

The benefits of partial correction of anaemia with rHuEpo therapy in predialysis patients are well established in terms of improvement of physical ability, sense of well-being and quality of life. In addition, rHuEpo therapy has been shown to partially

protect against the development of left ventricular hypertrophy [7].

However, a major initial concern was that correction of anaemia with rHuEpo could result in deleterious effects on the rate of progression of renal failure in predialysis patients. Indeed, early animal experiments showed that raising haematocrit to the normal level (about 50%) in Munich–Wistar rats submitted to subtotal nephrectomy resulted in accelerated progression, higher proteinuria, and higher incidence of glomerular sclerotic lesions [1], when compared with rats not treated with rHuEpo (whose haematocrit was about 42%). In this model, micropuncture studies showed a marked increase in glomerular capillary pressure (P_{GC}) in rHuEpo-treated rats. Another study published by the same group in uninephrectomized DOCA salt-hypertensive rats led to similar conclusions [8]. However, in both studies, rHuEpo therapy was associated with a major increase in systemic blood pressure that appears to account for the development of glomerular hypertension and glomerulosclerosis. More recently Bellizzi *et al*. [9] in Sprague–Dawley rats submitted to subtotal nephrectomy, observed that despite increasing haematocrit as in the previous studies by Garcia *et al*. [1] and by Lafferty *et al*. [8], rHuEpo-treated rats did not develop more severe hypertension than untreated control rats, and had a similar incidence of glomerulosclerosis [9]. In their study, Epo-treated rats that were maintained at the same degree of anaemia as untreated animals by repeated phlebotomies had lower blood pressure and a slower progression than the other two groups, confirming the role of systemic hypertension in accelerated progression on one hand, and the lack of a direct 'nephrotoxic' effect of rHuEpo *per se* on the other [9]. In addition, Ruedin *et al*. [10], in Sprague–Dawley rats submitted to 3/4 surgical nephrectomy, provided evidence that antihypertensive treatment (not including ACEI) was able to prevent systemic hypertension in rHuEpo-treated animals (despite a rise in haematocrit to 53%) and to concomitantly prevent worsening of renal function [10].

Early randomized clinical studies in the late 1980s were partially reassuring because they showed that the rise of haematocrit to about 38% did not result in a significant change in renal function, but a marked increase in blood pressure was observed in most patients [11]. Notably, very high doses of rHuEpo were used in these early studies, and the rise in haematocrit was rapid. Subsequent clinical studies using more moderate doses of rHuEpo with a slower correction of anaemia provided evidence that an increase in Hb up to 11–12 g/dl could be achieved without inducing untoward effects on blood pressure and no acceleration of the rate of progression of renal failure [3–5]. Even with a more marked rise haematocrit to nearly 40%, Hayashi *et al*. [12] observed no change in the rate of progression of renal failure in nine predialysis patients treated for 1 year.

Several recent studies in predialysis CRF patients not only confirmed the lack of deleterious effect of rHuEpo therapy on renal function but concluded that the rate of progression of CRF was slowed in at least some treated patients. Roth *et al*. [5], in a randomized study involving 83 patients followed for 48 weeks with serial determinations of GFR, reported a lower rate of progression in rHuEpo-treated patients than in controls. Lopez-Gomez *et al*. [13] compared 12 patients treated with rHuEpo with 15 other patients having the same degree of renal failure (Scr about 425 μmol/l), followed for 24 months before and 18 months after the start of the observation period. The slope of the inverse of Scr (1/cr) was lower in the rHuEpo-treated group, whereas it remained unchanged in the control group. Krmar *et al*. [14] also observed a reduction in the slope of 1/cr in 11 children treated for a mean of 31 months with rHuEpo, compared to the preceding period. The prospective, randomized study by Kuriyama *et al*. [6] involved 108 predialysis patients with an average Scr level of 250 μmol/l divided into three groups: 42 anaemic patients (haematocrit $< 30\%$) treated with rHuEpo, 31 with anaemia of similar degree left without rHuEpo therapy, and 35 non-anaemic patients followed for up to 36 weeks. Doubling of the baseline Scr was observed less frequently in the treated group (52%) and in non-anaemic patients (60%) than in untreated anaemic patients (84%). Accordingly, the cumulative renal survival curve was significantly better in treated patients than in untreated anaemic subjects. However, this study did not provide the actual duration of time from baseline until start of dialysis. Also, the dose of rHuEpo used was unexpectedly high (6000 U per week) and the route of administration (intravenous, once weekly) unusual for predialysis patients.

Our study confirms and extends the conclusions of these reports. With a moderate maintenance dose of rHuEpo, i.e. 50 U/kg/week, it was possible to achieve and sustain an Hb level at nearly 11.5 g/dl. Because the increase in Hb level was slow, no deleterious worsening of hypertension occurred and no patient had to stop rHuEpo for any adverse effect. In only five patients did we have to reinforce antihypertensive treatment. Of note, all of our patients had long received supplementation with hydrosoluble vitamins, especially vitamins B_1, B_6, B_{12} and folic acid, and received a regular iron supply. This may explain why only one-third of patients with a Ccr 10–15 ml/min/1.73 m^2 had an Hb level lower than 10 g/dl and needed rHuEpo therapy, whereas in the majority of patients, anaemia was of more moderate degree and well tolerated. The sustained, or even reinforced supplementation in vitamins, especially folic acid, and iron during rHuEpo therapy, and carefully monitored protein–calorie intake, may have contributed to the favourable results achieved by rHuEpo therapy. In particular, supplementation with folic acid was reinforced in treated patients. It has been shown that folic acid supplementation is needed to optimize the response

to rHuEpo [15], besides its favourable effect in reducing plasma total homocysteine levels [16].

The rate of decline in Ccr was significantly diminished in our rHuEpo-treated patients when compared with the previous 24-month period, whereas no alteration in the slope of ΔCcr was observed in non-treated patients. Of note, the previous rate of decline in renal function was already lower in patients who were subsequently treated with rHuEpo than in the Epo− group. One possible explanation is that a longer duration of the uraemic state allowed anaemia to reach a more marked degree in the former group. In addition, in the Epo-treated group, patients were older by 8.5 years, and the proportion of women, who are more subject to anaemia, was also higher than in the Epo− group. Of clinical relevance is the finding that initiation of renal replacement therapy was delayed by an average of about 6 months in the group of rHuEpo-treated patients, because this finding is based on follow-up until the ultimate stage of CRF and the start of dialysis of all patients, whether treated with rHuEpo or not.

In fact, this beneficial effect was not equally distributed among treated patients. Only 10 of them had a significant slowing of ΔCcr with a concomitantly significant delay in retarding dialysis of about 10 months when compared to non-rHuEpo-treated patients. The other 10 treated patients exhibited neither slowing of ΔCcr nor increasing duration of the predialysis phase, results similar to those in untreated patients.

This different response in the rate of progression of CRF to partial correction of anaemia by rHuEpo cannot be attributed to differences in the baseline or final level of anaemia and blood pressure, as similar Hb values were achieved and the control of hypertension was also similarly fair in both groups. The pre-rHuEpo rate of decline in Ccr was also similar in the two groups. However, the proportion of vascular or interstitial renal diseases, the course of which is spontaneously rather slow [17], was higher in the group of patients with slowed progression, whereas glomerular diseases and polycystic kidney diseases were predominant in the group with unchanged progression.

The extension of the predialysis phase observed in the rHuEpo-treated patients may have several explanations. A possible hypothesis could be that improved sense of well-being and nutritional status allowed patients to better tolerate uraemia and therefore delay the need for dialysis. However, as the final Ccr value did not differ between rHuEpo-treated and not-treated patients, one has to accept that the rate of decline in renal function was actually slowed. The reasons for this beneficial effect, observed in half of our patients, cannot be attributed to more frequent medical visits, as the clinical and laboratory surveillance schedule of Epo+ and Epo− patients was identical and performed by the same physician. Thus, Epo+ and Epo− patients received similar management, with the only difference being rHuEpo treatment. Although not stringent, blood pressure control was similar in both Epo+ and Epo− groups, with a mean arterial pressure of about 105 mmHg. The proportion of patients treated with ACEI was also similar in both groups, and the response to rHuEpo did not differ whether or not ACEI were used.

The possible mechanisms involved in the slowing of CRF progression in at least part of patients treated with rHuEpo are not fully elucidated. The increase in blood viscosity resulting from the rise in haematocrit should be expected to adversely affect glomerular haemodynamics, as observed in experimental animals [1]. However, the level of haematocrit achieved in our treated patients was far less than that of rHuEpo-treated rats. In fact, it was similar to the haematocrit level of control uraemic rats submitted to an iron-depleted diet or repeated bleeding. In parallel, systemic blood pressure did not increase in treated patients and was similar to the level observed in untreated patients.

Therefore, the beneficial effect of rHuEpo seems not to be attributable to altered glomerular haemodynamics, but rather to the alteration of tissue hypoxia. Indeed, hypoxia stimulates the development of interstitial fibrosis by stimulating the production of type I collagen by interstitial renal tubular cells [18]. Thus, partial correction of hypoxia may be expected to reduce the development of interstitial fibrosis which has been shown to be a major factor of progression of renal disease [19]. In addition, correction of anaemia reduces the oxidative stress associated with anaemia, and rHuEpo has been shown to exert a favourable mitogenic and chemotactic effect on endothelial functions in predialysis patients [20].

The substantial delay of dialysis in our Epo-treated patients, besides its evident benefits in terms of improved quality of life, also results in substantial savings, as the combined cost of rHuEpo and conservative treatment is far less than the cost of dialysis.

Our study suffers the limitations of a retrospective study. Since patients were followed at a single centre, some selection bias cannot be excluded. However, comparison between rHuEpo-treated and non-treated patients is probably meaningful, because both cohorts were contemporary and all patients were managed according to a homogeneous schedule. The beneficial effects observed in our patients suggest that starting rHuEpo at an earlier stage of CRF, with higher haematocrit and Ccr levels, should result in a longer predialysis state at the expense of low rHuEpo doses, thus affording patients the benefits of a better quality of life for a more prolonged period.

In conclusion, our study provides evidence that moderate doses of rHuEpo in predialysis CRF patients achieve effective and sustained correction of anaemia, without inducing worsening of blood pressure or adverse effects on renal function. On the contrary, rHuEpo therapy resulted in a substantial delay in the need for renal replacement therapy in half of our

patients. It remains to validate such results in a larger number of patients in a prospective, randomized protocol, with simultaneous serial evaluation of renal function, together with blood pressure, Hb level, left ventricular function, and quality of life, in order to determine the optimal indications of rHuEpo therapy in predialysis patients.

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