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□ ORIGINAL ARTICLE □

Effects of Biologic Agents in Patients with Rheumatoid Arthritis and Amyloidosis Treated with Hemodialysis

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Abstract

Objective Our objective was to examine the safety and effects of therapy with biologics on the prognosis of rheumatoid arthritis (RA) patients with reactive amyloid A (AA) amyloidosis on hemodialysis (HD).

Methods Twenty-eight patients with an established diagnosis of reactive AA amyloidosis participated in the study. The survival was calculated from the date of HD initiation until the time of death, or up to end of June 2015 for the patients who were still alive. HD initiation was according to the program of HD initiation for systemic amyloidosis patients associated with RA.

Results Ten patients had been treated with biologics before HD initiation for a mean of 28.2 months (biologic group), while 18 had not (non-biologic group). HD was initiated in patients with similar characteristics except for the tender joint count, swollen joint count, and disease activity score (DAS)28-C-reactive protein (CRP). History of biologics showed that etanercept was frequently used for 8 patients as the first biologic. There was no significant difference in the mortality rate according to a Kaplan-Meier analysis (p=0.939) and or associated risk of death in an age-adjusted Cox proportional hazards model (p=0.758) between both groups. Infections were significantly more frequent causes of death in the biologic group than in the non-biologic group (p=0.021). However, treatment with biologics improved the DAS28-CRP score (p=0.004).

Conclusion Under the limited conditions of AA amyloidosis treated with HD, the use of biologics might affect infection and thus may not improve the prognosis. Strict infection control is necessary for the use of biologics with HD to improve the prognosis.

Key words: rheumatoid arthritis, reactive amyloidosis, biologics, prognosis, hemodialysis

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Introduction

Reactive amyloid A (AA) amyloidosis is a serious and life-threatening systemic complication of rheumatoid arthritis (RA) that arises from chronic, systemic and long-lasting inflammation, with elevated levels of serum amyloid A (SAA) protein (1-3). AA fibrils are insoluble and can be deposited in systemic organs, including the kidneys, heart, or gastrointestinal (GI) tract, due to the overproduction of SAA under such inflammatory conditions (2-4). The frequency of AA amyloidosis associated with RA ranges from 7-26% (5-9), although the prevalence of clinically symptomatic amyloidosis is reportedly lower (10, 11). Many amyloidosis patients ultimately develop end-stage renal disease (ESRD) and are started on hemodialysis (HD). The patient's status is difficult to maintain, thus many patients die at the time of HD initiation. It is quite important to manage the conditions of this state. Additionally, the prognosis of patients treated with HD has been quite poor.

Recently, therapy with biologic agents such as anti-tumor necrosis factor (TNF) and anti-interleukin (IL)-6 receptor

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antibodies has developed against a foundation of increased understanding of the pathogenesis of RA, representing a tremendous advance in the management of RA. Such biologic agents produce reliable effects in RA patients who are resistant to conventional disease-modifying anti-rheumatic drugs (DMARDs). Treatment with biologics has emerged as a highly effective approach for inducing rapid and sustained clinical remission of RA (12, 13). Furthermore, these biologics dramatically reduce the systemic inflammatory response. Recently, many rheumatologists have focused on therapy with biologics, not only to control RA disease activity, but also as potential agents for the treatment of reactive AA amyloidosis. These biologics show strong suppression of acute-phase reactants such as SAA. A retrospective study and several case reports have previously indicated that such agents are effective against AA amyloidosis (14, 15). We also revealed rapid resolution of amyloid deposits from GI tissue treated with biologics (16, 17). Clinical experience with anti-TNF and anti-IL-6 therapy in AA amyloidosis has gradually increased, and recent reports have revealed the short-term effects of these treatments. A reduction in urinary protein or improvement of pathological findings in a series of GI biopsies has been frequently reported (15, 16). We have also demonstrated both clinical and pathological improvements in 14 amyloidosis patients who were treated with biologics (17). Additionally, we revealed that the use of biologic agents can reduce the risk of death and the use of biologics may influence the HD-free survival rate (18). The purpose of the present study was to examine the safety and prognosis of anti-TNF and anti-IL-6 therapy in RA patients with reactive AA amyloidosis by following their clinical course in comparison to AA amyloidosis patients who did not receive such therapy. In general, amyloidosis patients have a hard time continuing HD therapy because congestive heart failure, infections, and hypotension can disturb HD therapy and lead to elevated mortality. It is also necessary to clarify important points of the management of HD patients who are treated with biologics.

Materials and Methods

Subjects

Twenty-eight patients with an established diagnosis of reactive AA amyloidosis participated in the study. Each patient satisfied the 1987 American Rheumatism Association criteria for RA (19). All patients were initiated on HD according to the program of HD initiation (20) from 2003 through 2013. The study protocol was approved by the institutional review board of Niigata University Medical and Dental Hospital and executed according to the Declaration of Helsinki. Written informed consent was obtained from all patients to participate in the study. The indications for the use of biologics were made by following the official Japanese guidelines (21). We recommended all patients that fulfilled these criteria to start biologic therapy. However, some of eligible patients opted out due to the high cost of therapy. Ten patients were treated with biologic agents (biologic group), while 18 patients were not (non-biologic group). In the non-biologic group, none of the patients had been treated with biologics during the treatment of RA. From this study population, the initial administration of a biologic was earlier than HD initiation.

Diagnosis of reactive AA amyloidosis

All patients underwent a renal biopsy and GI biopsy, which had confirmed the presence of reactive AA amyloidosis, before study entry. Upper GI endoscopy was performed on each patient, regardless of the presence or absence of GI symptoms, to obtain biopsy specimens. Biopsy specimens were stained with hematoxylin-eosin and Congo red. Amyloid deposits detected with Congo red showed green birefringence under polarization microscopy. These deposits were confirmed to be AA-type amyloid using two techniques: disappearance of Congo-red positivity after incubation with potassium permanganate and immunohistochemical analyses using anti-amyloid A antibody and anti-immunoglobulin light-chain (AL) antibody to exclude AL amyloidosis.

Assessment

Clinical data were assessed from the patient records at the time of the administration of biologics, 12 weeks after biologic therapy initiation and at the time of HD initiation. Laboratory indices at the time of HD initiation were assessed between the two groups and included creatinine clearance (Ccr). The disease activity score (DAS)28-C-reactive protein (CRP) was calculated using the formula described previously (22). The efficacy of biologics was measured from the initiation of biologics to 12 weeks after the treatment of biologics using the DAS28-CRP.

Hemodialysis initiation

The HD initiation protocol followed the program of HD initiation for systemic amyloidosis patients associated with RA (20). The summary of the protocol is the evaluation of serum creatinine (Cr) levels of 2.0 mg/dL when preparing the vascular access of HD. Patients with programmed initiation of HD started therapy when their Cr levels reached 2.5 mg/dL, whereas the equivalent Ccr level was about 10 mL/min/1.73 m^2 in patients with amyloidosis. Even if the Ccr levels were over 10 mL/min/1.73 m^2 and pleural effusion, pulmonary congestion and cardiomegaly were observed in these patients, HD was initiated. This study intended only for the cases that we initiated into HD by this program to avoid troubles at dialysis initiation.

Statistical analysis

Determination of the onset of the underlying disorder was made retrospectively by a review of the patients' charts after the diagnosis of amyloid had been confirmed. The clinical syndrome at presentation was presumed to be the main rea-

son for the clinician to seek a tissue biopsy to demonstrate amyloid deposits. All subjects were followed until the end of June 2015 and, for this study, the primary endpoint was death. The survival time was cumulated from the date of HD initiation. Fisher's exact test for dichotomous variables and Student's *t*-test for continuous variables were used to assess the clinical characteristics of amyloidosis patients. Survival curves were estimated using the Kaplan-Meier method and statistical differences between the two curves were analyzed by the log-rank test. Cox proportional hazards models were used to assess the effects of biologic therapy on the risk of each endpoint; age-adjusted models adjusting for age were used. All statistical analyses were performed using the SPSS ver. 13 for Windows software program (SPSS Inc., Chicago, USA). All tests were two-tailed, and differences at $p<0.05$ were considered to be significant.

Results

Clinical features of patients with amyloidosis

Twenty-eight patients with AA amyloidosis associated with RA were evaluated in this study. Ten patients were treated with biologics (biologic group), while 18 patients were not (non-biologic group). The total follow-up periods from the initiation of HD were 15.5 person-years for the biologic group and 34.3 person-years for the non-biologic group. During these follow-up periods, 8 out of 10 patients in the biologic group and 16 out of 18 patients in the non-biologic group died: the mean survival periods for non-survivors were 1.4±1.5 years and 2.0±2.6 years, respectively (p=0.547). Consequently, the mean follow-up periods and mortality rates were 1.6 years and 0.52/year for the biologic group and 1.9 years and 0.47/year for the non-biologic group. Table 1 shows the clinical characteristics and laboratory findings at the time of HD initiation in both groups. None of the patients were treated with methotrexate (MTX) during the course of HD. In the non-biologic group, patients were treated with conventional therapies for amyloidosis including modulating the dose of steroids or DMARDs (bucillamine and/or salazosulfapyridine) or immunosuppressants. However, none of the patients were treated with DMARDs or immunosuppressants in the biologic group. In the biologic group, prednisolone was used at an average dose of 5.9 mg daily, while the average dose was 6.8 mg in the non-biologic group; however, this difference was not significant. In addition, DMARDs, cyclophosphamide, azathioprine, and tacrolimus were used to treat arthritis and there was no change in the treatment before and after HD initiation, except for bucillamine use in one patient in the non-biologic group. No significant difference was observed for sex, mean onset age of RA, mean age of diagnosis of amyloidosis, duration of RA prior to the diagnosis of amyloidosis, duration between the diagnosis of amyloidosis and HD initiation, clinical stage, functional class serum creatinine or 24-hour Ccr at the time of HD initiation between the two groups. Only differences in the tender joint count, swollen joint count and DAS28-CRP were significant between the two groups.

History of treatment with biologic agents

Biologic agents had been administered to all of the patients in the biologics groups and to none of the patients in the non-biologic group. The profile of biologic usage is shown in Table 2. Etanercept was frequently used for 8 patients as the first biologic. The two survivors were treated with etanercept 25 mg per week. Two patients were treated with tocilizumab as the first biologic. Three patients were switched to tocilizumab because of loss of effectiveness. The mean duration of biologic treatment before HD was about 28 months.

Efficacy of biologics

The efficacy of biologics is shown in Fig. 1. The efficacy of biologics was measured from the initiation of biologics to 12 weeks after the treatment of biologics using the DAS28-CRP. The level of DAS28-CRP was significantly improved from the initiation of biologics (3.5) to 12 weeks after the treatment (2.0) (p=0.004). Additionally, seven out of 10 patients achieved DAS28-CRP remission.

Survival and causes of death

The survival of patients treated or untreated with biologics, determined according to the Kaplan-Meier method, is shown in Fig. 2. Of the 18 patients in the non-biologic group, 16 (88.9%) died. Similarly, among the 10 patients in the biologic group, 8 (80.0%) died. There was no significant difference in the survival between the biologic and non-biologic groups (p=0.939). The annual rate of mortality was 50.0% in the non-biologic group and 40.0% in the biologic group. The causes of death are shown in Table 3. In the non-biologic group, congestive heart failure was frequently observed, as reported previously (22). The frequency of infections were significantly higher in the biologic group than in the non-biologic group (p=0.021).

Cox proportional hazards models for mortality

Table 4 presents the results of Cox proportional hazards models for mortality. Biologic therapy was not significantly associated with a reduced risk of death in the age-adjusted model (p=0.758).

Discussion

The frequency of amyloidosis in RA has been reported to range from 5-13.3% in cases confirmed by a biopsy and from 14-26% in cases confirmed by an autopsy (8, 23). We recently evaluated the safety of therapy with anti-TNF and anti-IL-6 biologic agents in RA patients with reactive AA amyloidosis, with the prognosis and HD-free survival, in comparison with AA amyloidosis patients without such therapy (18). The results showed that patients with amyloidosis

Table 1. Clinical Characteristics and Laboratory Findings of 28 Amyloid-positive Patients Treated with Hemodialyis.

Characteristics	Number of patients with amyloidosis		
	Biologic group, n (%)	Non-biologic group, n (%)	p value
Sex Male/Female	4/6	3/15	0.21
Mean onset age of RA, years (SD) [range]	43.9 (13.9) [20-68]	48.2 (11.8) [26-75]	0.39
Mean age of diagnosis of amyloidosis, years (SD) [range]	60.2 (14.3) [28 -76]	62.3 (8.2) [47-75]	0.63
Duration of RA prior to diagnosis of amyloidosis, years (SD) [range]	18.5 (9.0) [8-34]	15.7 (9.1) [2-32]	0.44
Duration of diagnosis of amyloidosis to HD, years (SD) [range]	6.8 (5.3) [0-16]	4.4 (4.5) [0-15]	0.21
Duration of initiation of biologics to HD, months (SD) [range]	28.2 (27.0) [3.0-85.0]		
Stage, n (%)			
III	0 (0)	2 (11.1)	0.52
IV	10 (100.0)	16 (89.9)	
Class, n (%)			
2	6 (60.0)	8 (44.4)	0.70
3	4 (40.0)	10 (55.6)	
MTX therapy (yes/no)	0/9	0/15	
Laboratory findings	Mean (SD)	Mean (SD)	p value
Total protein, g/dL	5.69 (1.24)	5.35 (1.05)	0.45
Serum albumin, g/dL	2.68 (0.40)	2.81(0.67)	0.60
BUN, mg/dL	58.9 (17.8)	59.9 (28.0)	0.92
Cr, mg/dL	3.77 (1.39)	3.76 (2.09)	0.99
UA, mg/dL	7.93 (2.5)	6.99 (2.3)	0.34
CRP, mg/dL	0.81 (0.89)	2.62 (2.83)	0.06
ESR Westergren, mm/h	45.2 (40.6)	60.7 (34.6)	0.43
RF, IU/mL	54.5 (56.9)	101.0 (119.1)	0.31
Hematocrit, %	23.9 (6.6)	28.3 (5.7)	0.07
Creatinine clearance, mL/min/1.73 m^2	11.7 (4.9)	10.8 (5.9)	0.73
24-hour urinary protein, g/24 h	2.8 (2.4)	2.2 (2.0)	0.50
Cardiothoracic ratio, %	52.9 (10.0)	53.9 (14.4)	0.90
Tender joint count	1.7 (1.3)	5.3 (2.4)	0.00
Swollen joint count	1.1 (1.0)	2.8 (1.3)	0.00
DAS28-CRP	2.3 (0.5)	3.4 (0.7)	0.00

* Student's t-test and Fisher's exact test.

BUN: blood urea nitrogen, Cr: serum creatinine, UA: Uric acid, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, RF: rheumatoid factor, MTX: methotrexate, RA: rheumatoid arthritis, SD: Standard deviation, HD: hemodialysis, DAS: Disease activity score

Stage, Class, MTX therapy and Laboratory findings were at the time of hemodialysis initiation of amyloidosis patients.

Table 2. History of Biologics Therapy.

First	Second	Number of patients, Total (%)
ETA		5 (50.0)
ETA	TCZ	3 (30.0)
TCZ		2 (20.0)
Total		10 (100.0)

ETA: Etanercept, TCZ: Tocilizumab

have a higher mortality rate, however, the use of biologic agents can reduce the risk of death. Additionally, the use of biologics may influence the HD-free survival rate.

In the present retrospective cohort study, we evaluated the survival of 10 patients who were treated with HD and biologics (biologic group) and 18 who were treated with HD alone (non-biologic group). As shown in Table 1, no differences were observed between the two groups regarding sex, mean onset age of RA, mean age of the diagnosis of amyloidosis, duration between the diagnosis of amyloidosis and HD initiation, clinical stage, functional class or 24-hour Ccr. The patients in the biologic group were treated with biologics for more than 12 weeks and considered to have an ade-

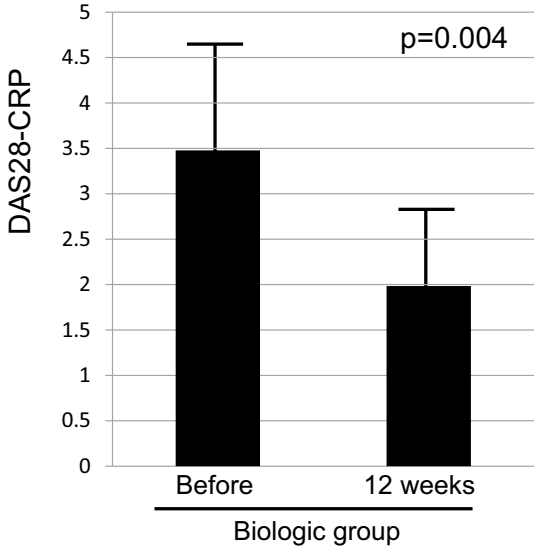

Figure 1. Clinical efficacy of biologics. The clinical efficacy of biologics was estimated using the DAS28-CRP. The levels of DAS28-CRP was 3.5 at biologic initiation to 2.0 at 12 weeks after the treatment (p=0.004).

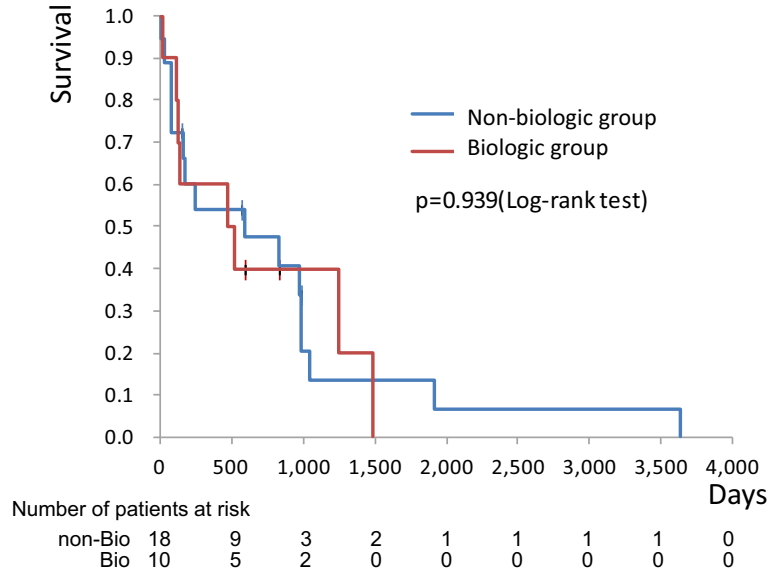

Figure 2. **Survival of patients receiving biologic or non-biologic therapy treated with hemodialysis. The survival of patients with or without biologic treatment according to the Kaplan-Meier method. Among 18 patients in the non-biologic group, 16 died and among 10 patients in the non-biologic group, 8 died. The survival was not significantly different between the two groups (p=0.939).**

Table 3. **Cause of Death in Patients with Amyloidosis with Hemodialysis in Patients with or without Biologics Therapy.**

Cause of death	Number of patients with amyloidosis			
	Biologic group, n (%)	Non-biologic group, n (%)	Total (%)	p value #
Congestive heart failure	1 (12.5)	8 (49.7)	9 (41.5)	0.178
Infections	5 (62.5)	2 (12.5)	7 (29.2)	0.021
Phlegmon	3 (37.5)	1 (6.3)	4 (16.7)	0.091
Pneumonia	1 (12.5)	0 (0)	1 (4.2)	0.333
Sepsis	1 (12.5)	1 (6.3)	1 (4.2)	1.000
Pulmonary hemorrhage	2 (25.0)	0 (0)	2 (8.3)	0.101
Acute pancreatitis	0 (0)	2 (12.5)	2 (8.3)	0.536
Intestinal perforation	0 (0)	1 (6.3)	1 (4.2)	1.000
Cerebral hemorrhage	0 (0)	1 (6.3)	1 (4.2)	1.000
Deep vein thrombosis	0 (0)	1 (6.3)	1 (4.2)	1.000
Shunt trouble	0 (0)	1 (6.3)	1 (4.2)	1.000
Total	8 (100)	16 (100)	24 (100)	

Fisher's exact test.

Table 4. **Hazard Ratio of Death according to Treatment Status of Biologics.**

	HR	(95% CI)	p value
Crude	0.87	(0.35 – 2.13)	0.758
Age-adjusted	1.03	(0.43 – 2.48)	0.940

Crude and age-adjusted Cox proportional hazard models

quate clinical effect. The patients were gradually switched to biologics, as shown in Table 2, because of the loss of effectiveness. The European League Against Rheumatism (EULAR) recommendations for the use of biologics were recently published (24). In general, biologics were initially introduced as TNF inhibitors, and if this failed, other agents such as abatacept, rituximab or tocilizumab were considered. According to these recommendations, we routinely use a TNF inhibitor as a choice in our institution. However, previous studies on tocilizumab have demonstrated a dramatic reduction in the SAA level, with subsequent disappearance of the clinical symptoms of AA amyloidosis (15, 25). Considering these reports, we occasionally use tocilizumab as a first-line therapy.

MTX is now considered to be an anchor-drug for the treatment of RA. Several studies have indicated that MTX use is associated with a reduced risk of cardiovascular disease, cerebrovascular disease and atherosclerosis, and a reduction of mortality due to myocardial infarction and heart failure (26, 27). Previous studies have also suggested that control of inflammation with MTX may reduce mortality (28, 29). Because of ESRD, none of our patients in either group received MTX at the time of HD initiation. For

treatment with infliximab, a MTX dose greater than 6 mg per week is required; thus, none of the patients used infliximab. Recently, several reports have described that biologics can reduce mortality in RA patients (26, 27), however, it appears to be difficult to confirm a statistically significant effect. These reports described that biologic treatment did not worsen the prognosis of RA patients. Patients with amyloidosis showed a higher mortality rate than RA patients without amyloidosis, as we have already reported previously (30, 31). We revealed that the use of biologic agents can reduce the risk of death and the use of biologics may not significantly influence the HD-free survival rate (18). In this analysis, our data were not significant, however, the duration between amyloidosis and HD initiation might be more prolonged in the biologic group than in the non-biologic group.

The effects of biologics during HD therapy were unknown. The Kaplan-Meier survival curve analysis revealed that HD survival did not improve with biologic treatment (Fig. 2). In general, the initiation of HD for these patients was quite difficult because of sudden death at the time of HD initiation. Accordingly, it is necessary to apply the same program to initiate biologic treatment and HD. We advocated programmed HD initiation for these patients. None of the patients showed difficulty with treatment at initiation and the residual renal function was not different between the two groups at the time of HD initiation. The survival of patients treated or untreated with biologics, determined according to the Kaplan-Meier method, showed no significant difference between the two groups. Additionally, the age-matched Cox proportional hazards analysis confirmed that the use of biologics did not improve the prognosis of the patients in the biologic group. However, the disease activity was significantly reduced in the biologic group, which may indicate an improvement in the quality of life (QOL). Unfortunately, we did not evaluate the QOL in this analysis.

Infections were the predominant cause of death. While it is well established that a dysfunction in the immune system is induced by the uremic milieu, this disturbance has not been systematically studied as a potential contributing cause of premature deaths resulting in infections in ESRD patients. The immunosuppressive state induced by biologics and ESRD lead to such infections (32). Several studies have reported the effect of anti-TNF therapy for rapid removal and sustained disappearance of amyloid deposits in gastric mucosal tissue with amelioration of the renal function (17, 33). Therefore, we speculated that rapid removal of amyloid deposits from renal tissue might have resulted in amelioration of the renal function in addition to an improvement in the general condition and prognosis. However, our data suggested that biologic therapy for HD patients with amyloidosis could not reduce the mortality. In our study, the two survivors were treated with etanercept 25 mg per week and they did not experience severe infection. Therefore, low-dose biologic therapy might reduce the mortality of HD patients with amyloidosis. Further larger, prospective studies with a long-term follow-up are necessary to confirm these findings. For the use of biologics in the condition of HD, strict infection control is mandatory to improve the patient's prognosis.

In conclusion, our present study demonstrated that patients with amyloidosis on HD showed a higher mortality rate, and the use of biologics did not improve the survival rate. Infections were the predominant cause of death in the biologic group, suggesting that biologics and renal failure may influence the infection rate. However, in the biologic group, the disease activity was significantly reduced. Therefore, infection control is the most important strategy to improve the prognosis of patients who require biologic treatment under HD conditions.

The authors state that they have no Conflict of Interest (COI).

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