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Infection risk in autoimmune hematological disorders with low-dose rituximab treatment

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Abstract

Background: Rituximab has been widely used in many autoimmune diseases.

Aim: To evaluate the infection risk of rituximab in autoimmune hematological disorders.

Methods: Retrospectively studied and compared the clinical data of 89 patients in our hospital who used low-dose rituximab (group R) or pulse cyclophosphamide (group C) for their refractory/relapsed autoimmune hematological diseases from January 2011 to January 2017. The kinds of their diseases included autoimmune hemolytic disease (AIHA), Evans syndrome, and idiopathic thrombocytopenic purpura (ITP). All patients chose either rituximab treatment or cyclophosphamide treatment on their own considerations.

Findings: The median follow-up time was six months in group R and four months in group C. After treatments, the patients in group R showed higher white blood cell (WBC) count and neutrophil count than group C ($P = .020$, $P = .037$). CD20-positive B cells in group R remained at a very low level after rituximab treatment and need about 15 months to return to normal level, which was longer than group C (six months). The incidence of infection in these two groups has no significant difference, which was 34.7% (17/30) in group R and 32.5% (13/28) in group C ($P = .976$). Tuberculosis infections after rituximab treatment were found in three patients for the first time.

Conclusion: The G-CSF, nadir WBC count, and IgA level were protective factors of infection during rituximab treatment. Low-dose rituximab therapy in autoimmune hematological diseases does not increase infection risk compared with cyclophosphamide.

KEYWORDS

autoimmune hematological diseases, cyclophosphamide, infection, risk factors, rituximab

Honglei Wang and Siyang Yan contributed equally to this manuscript.

1 | INTRODUCTION

As a chimeric murine/human monoclonal antibody, rituximab can completely deplete peripheral blood $CD20^+$ B cells for variable time periods. It has been widely used in various B cell–related diseases such as B-cell lymphoma, rheumatoid arthritis (RA), warm autoimmune hemolytic diseases (wAIHA), and idiopathic thrombocytopenic purpura (ITP), and has showed quite good and durable therapeutic response in these diseases.[1-3] As one coin has two sides, during B-cell depletion caused by rituximab, new vaccine responses would be impaired and risk of new infections exists theoretically.[4] Rituximab has been loaded in clinical over decade for a wide range of diseases, and infection is a major side effect for the clinicians when they use it. For hematological malignancies such as lymphoma, studies have been made and one Italian meta-analysis reported that adding rituximab to chemotherapy would not increase any infection risk.[5] But just at the same year, another study that was also in Italy showed that the non-Hodgkin lymphoma patients who received long-term rituximab therapy might have particular infection risk.[6] As for non-malignant diseases such as ITP and other autoimmune diseases, rituximab has been reported as the possible infection risk.[7,8] In 2013, Ishac Nazi et al claimed that rituximab in the treatment of ITP could damage the antibody responses for over six months and cellular immunity would also be reduced at the same time.[9] It answered the question about timing for vaccinations and the possible mechanisms for infections after the rituximab. However, in another study of 248 patients with ITP in France in 2014, Khellaf M et al found rituximab treatment had acceptable safety profile and it remained a valid option for ITP treatment.[3] The infection risk of rituximab seems still to be a controversial question.

For the treatments of other autoimmune hematological diseases, we have even less information about whether it would increase any infection risk or not. If rituximab does increase the risk, then how much it would increase compared with the traditional drugs? Could the low-dose regimen have less infection risk? And what are the factors that related to infections? We have made a study on the effect of low-dose rituximab in the treatment with refractory AIHA in our department last year [10]; to shed light on these questions and get some practical notes for clinical work, this study has been carried out.

2 | METHODS

2.1 | Patients

To have a better understanding about the infection risk of rituximab in autoimmune hematological diseases and make a comparison with relatively old second-line drugs, the patients with relapsed/refractory autoimmune hemolytic disease (AIHA), Evans syndrome, and idiopathic thrombocytopenic purpura (ITP) who received rituximab or traditional drugs such as cyclophosphamide were enrolled in our study. One hundred and one patients in Hematology Department of Tianjin Medical University General Hospital from January 2011 to January 2017 had been retrospectively studied. Twelve patients were excluded because of not finishing the complete course, and 89 patients were enrolled at last. The clinical diagnostic criteria of refractory AIHA and Evans syndrome refer to Chinese expert consensus on the diagnosis and treatment of autoimmune hemolytic anemia (2017).[11] The clinical diagnostic criteria of refractory ITP correspond to the 2009 International Working Group (IWG) definition of refractory ITP.[12] All these patients had already received steroids therapy but failed. According to their different major treatments, the patients were divided into two groups: rituximab group (group R) and cyclophosphamide group (group C). Clinical features of all the patients are shown in Table 1.

TABLE 1 Clinical characteristics of patients before the treatments

Characteristics	Group R	Group C	*P* value
Total number	49	40	
Diseases			
ITP	30	11	
AIHA	14	22	
Evans	5	7	
Sex			
Female	29	26	.570
Male	20	14	
Age (y)			
14 ~ 17	3	0	
18 ~ 29	16	3	
30 ~ 39	6	8	
40 ~ 49	8	8	
50 ~ 59	7	17	
60 ~ 69	5	3	
70 ~ 79	3	0	
≥80	1	1	
Median	38	51	
Events during follow-up			
Autoimmune disease	10	6	.509
Malignant tumor	4	1	.489
Liver or kidney dysfunction	15	19	.103
CD 20 (%)	(n = 45)	(n = 33)	
Median (range)	17.66 (0.48 ~ 52.50)	18.97 (1.64 ~ 64.74)	.789
Follow-up time (months)			
Median (range)	6.0 (1 ~ 54)	4.0 (2 ~ 36)	.065

Abbreviations: AIHA, autoimmune hemolytic anemia; Group C, patients with treatments of cyclophosphamide; Group R, patients with treatments of low-dose rituximab; ITP, idiopathic thrombocytopenic purpura.

TABLE 2 Laboratory results after the treatments

	Group R		Group C	
	Before	**After**	**Before**	**After**
WBC ($\times 10^9$/L)				
Mean ± SD	9.02 ± 3.52	8.02 ± 2.94*	8.86 ± 4.04	6.65 ± 2.39*
Neutrophil absolute counts ($\times 10^9$/L)				
Mean ± SD	7.10 ± 3.30	6.48 ± 2.74**	6.72 ± 3.18	5.35 ± 2.20**
Hb (g/L)				
Mean ± SD	104.92 ± 35.23	114.53 ± 23.39	100.40 ± 28.44	113.10 ± 25.22
Immunoglobulin (g/L)	**(n = 44)**	**(n = 19)**	**(n = 33)**	**(n = 12)**
Ig G (Mean ± SD)	1597.43 ± 637.66Δ	1095.05 ± 321.94Δ	1345.88 ± 518.67Δ	895.50 ± 257.98Δ
Ig A (median (range))	198.5 (10.5 ~ 796)	127 (10.5 ~ 508)	208 (74.1 ~ 424)	148.5 (54.6 ~ 440)
Ig M (median (range))	127.5 (20 ~ 622.2)***	102 (12.3 ~ 396)	103 (29.2 ~ 267)***	122.5 (27.2 ~ 192)

Note: $^*P < .05$ (comparison between the two groups of the same time, $^*P = .020$, $^{**}P = .038$, $^{***}P = .010$). $^{\Delta}P < .05$ (comparison between before and after the treatments within the same group, $^{\Delta}P < .001$).

Abbreviations: Hb, hemoglobin; Ig A, immunoglobulin A; Ig G, immunoglobulin G; Ig M, immunoglobulin M; SD, standard deviation; WBC, white blood cell.

Clinical infection was defined as (a) infection adverse event above grade 3 (include grade 3) according to the American National Cancer Institute Common Terminology Criteria (NCICTC) v4.0; and (b) infection happened 2 days or more after the first rituximab or cyclophosphamide infusion.[13] Patients were considered at risk of infection once they received their first rituximab infusion until: (a) 545 days (18 months) after the treatment, or (b) the day they started a new treatment because of failure to respond to therapy, or (c) the day they died.[14] For subjects who received several courses of rituximab or cyclophosphamide, we used the data from the first course.

2.2 | Treatment

The patients in group R received low-dose rituximab (100 mg as an intravenous infusion on days 7, 14, 21, and 28 along) combined with steroid therapy (prednisone, 1 mg/kg × d for 14 days, 0.5 mg/kg × d for 14 days). The patients in group C received intermittent intravenous cyclophosphamide (1 g as an intravenous infusion on day 10, 20, 30 along) combined with steroid therapy (prednisone, 1 mg/kg × d for 14 days, 0.5 mg/kg × d for 14 days). The different treatments for the patients were based on their own will, mainly according to their demands for giving a birth and their economic conditions. All the patients were treated with intravenous immunoglobulin (10 g as intravenous drop infusion, twice a week for 28 days) simultaneously to help reduce the adverse reactions caused by the possible impairment of immunity. There was no infection or hepatitis before treatment.

Clinical data, including hemoglobin (Hb), white blood cell (WBC), neutrophils, immunoglobulin level before and after treatment, WBC and neutrophils, nadir level during treatment, were analyzed in our study. $CD20^+$ cell percentage was tested by flow cytometry.

2.3 | Statistical analysis

Descriptive statistics included mean ± SD or median (range) as appropriate for continuous variables and frequency (percentage) for categorical variables. Univariate analysis involved the chi-squared test or Fisher exact test as appropriate to compare categorical variables, and Student's t test with Satterthwaite method or nonparametric tests were used to analyze continuous variables.

Variables were extracted for analysis by regression analysis of factors related to the occurrence of infection during rituximab therapy. The binary variables were male = 1 and female = 2 for gender, not administered = 0, and administered = 1 for medications administered for granulocyte colony-stimulating factor (G-CSF) and intravenous immunoglobulin (IVIG). Five of the variables [age, use of G-CSF, IgA level before rituximab therapy, nadir white blood cell count, and nadir neutrophil count] were tested by forward selection. Then, logistic regression analysis was used on these variables. All *P* values were two-sided, and those below .05 were considered statistically significant. All the analyses were performed with the software SPSS, version 23.

3 | RESULTS

3.1 | Clinical characteristics and Laboratory examinations

Clinical characteristics of patients in two groups are shown in Table 1, in which there was no significant difference between two groups, such as disease, age, and sex.

As about the complete blood count before treatments, we also did not found significant difference in two groups, such as white blood cell (WBC) accounts, hemoglobin (Hb) levels, and absolute neutrophils.

Forty-four patients in group R and 31 patients in group C had performed the immunoglobulin level test before they start the treatments. Comparing the two groups, no difference exits except IgM levels, in which group R showed a statistic significant higher level than group C.

According to our data, CD20-positive B cells in group R kept staying at a very low level after rituximab treatment and it took about 15 months to come back to normal. In group C, the CD20-positive B cells also showed a remarkable decrease, while it only took about six months for them to return to normal level. Both groups had no difference at the baseline.

As the results shows, differences on WBC level and neutrophil granulocyte level of the two groups appeared after the treatments (Table 2). After treatments, group R showed higher WBC accounts and neutrophil accounts than group C ($P = .020$, $P = .037$). The hemoglobin level and immunoglobulin level showed no difference after the treatments.

As for the change in laboratory test results after patients taking treatments of each group, there is a significant decrease in IgG level in both groups ($P < .001$).

3.2 | Infections

According to our static results, there was no significant difference in overall infection risk in both groups. Bacterial infection took the major role of all the infections (Table 3).

According to different infected sites, the main infections were respiratory infections, and most of them were lung infections. Among all the 42 respiratory infections, there were three cases of tuberculosis in group R and they all were males. The median age was 28 years (17-79). The median time that was found to have tuberculosis after rituximab course was 120 days (2-360days). Both of the young patients never infected with tuberculosis before, and they got recovery quickly after receiving the antituberculosis therapies. They have very good prognosis in the end. The 79-year-old patient had a history of intestinal tuberculosis and performed partial intestinal resection 20 years ago, he died of respiratory failure (detail is mentioned later). No tuberculosis was found in group C.

Both the two groups had eight cases of non-respiratory infections, which include skin and soft tissue infection, gastrointestinal infection, central nervous system infection, and bacteremia. We did not find any urinary tract infection in these two groups. The two central nervous system infections in group C were happened on the same 52-year-old female patient. The first time happened about three months after the CTX course and *Listeria Monocytogenes* was detected in her cerebrospinal fluid culture, no specific bacteria were found on the second time. The interval of the two infections was about four months. After receiving timely anti-infection treatment, the AIHA patient got good recovery and kept quite stable blood cell counts.

Each group had one patient died of fatal infection. The unlucky patient in group R was a 79-year-old man with AIHA. The patient had fever 2 days after the first rituximab finished, accompanied by central nervous system symptoms, liver function, and coagulation abnormalities. The chest CT showed diffuse miliary nodules with a likely diagnosis of acute disseminated miliary tuberculosis. Then, he died of respiratory failure. The patient in group C who died of diffuse pulmonary interstitial fibrosis was a 66-year-old woman with Evans syndrome. She had fever and dyspnea forty-five days after the first CTX finished. *Enterobacter Cloacae* and *Stenotrophomonas Maltophilia* were detected in the culture of the patient's sputum. Blood test of virus showed CMV IgM was positive. Chest CT scan showed diffuse shadow of both lungs and lower permeability than before. Both of the two patients were died of respiratory failure, which was caused by the fatal pulmonary infection.

TABLE 3 Infections after the treatments in two groups

	Group R (N = 49)	Group C (N = 40)	*P* value
Infected patients	17	13	.976
Infected cases	30	28	–
Death cases	1	1	1.000
Etiology			
Bacterial	17	11	.186
Tuberculosis	3	0	
Fungal	4	7	.257
Viral	0	2	–
Concurrent	9	8	.905
Infected sites			
Respiratory	22	20	.871
Upper	0	1	
Lung	22	19	
Other sites	8	8	–
Skin and soft tissue	2	4	.608
Gastrointestinal	2	0	–
Central nervous system	1	2	1.000
Urinary tract	0	0	–
Bacteremia	3	2	1.000

Abbreviations: Group C, patients with treatments of cyclophosphamide; Group R, patients with treatments of low-dose rituximab.

3.3 | Risk factors

To measure out the potential infection risk factors in rituximab treatment, we made comparisons on the clinic characteristics of infected patients and non-infected patients in group R (Table 4). Then, according to the results, variables were extracted for analysis by regression analysis of factors related to the occurrence of infections during rituximab treatment.

The results showed that administration of G-CSF (odds ratio [OR] = 0.090, 95% confidence interval [95%CI] = 0.017-0.480; $P = .005$), nadir WBC count during treatment (OR = 0.625, CI = 0.405-0.965; $P = .034$), and IgA level before rituximab therapy

TABLE 4 Univariate analysis of the possible infection risk factors in group R

Factors	Infected	Non-infected	*P* value
Number	17	32	–
Sex (Female/Male)	9/8	20/12	.517
Age (y)			
Median (Range)	50.0 (16 ~ 80)	30.5 (14 ~ 66)	.056
Numbers of R courses			
(One/More than one)	16/1	28/4	.816
G-CSF (Yes/No)	7/10	2/30	.009*
IVIG (Yes/No)	13/4	19/13	.231
WBC before R ($\times 10^9$/L)			
Mean ± SD	9.11 ± 3.70	8.98 ± 3.47	.900
WBC after R ($\times 10^9$/L)			
Mean ± SD	7.58 ± 2.88	8.25 ± 3.00	.450
Neutrophils absolute counts before R ($\times 10^9$/L)			
Mean ± SD	7.79 ± 3.25	6.74 ± 3.32	.290
Neutrophils absolute counts after R ($\times 10^9$/L)			
Mean ± SD	6.32 ± 2.43	6.56 ± 2.92	.770
WBC nadir ($\times 10^9$/L)			
Median (Range)	4.53 (0.84 ~ 13.90)	6.60 (3.70 ~ 10.00)	$P < .001$*
Neutrophils absolute counts nadir ($\times 10^9$/L)			
Median (Range)	3.23 (0.74 ~ 10.10)	4.99 (2.19 ~ 8.28)	.002*
Immunoglobulin before R (g/L)	**(n = 14)**	**(n = 30)**	
IgG			
Mean ± SD	1554.93 ± 602.10	1617 ± 662.66	.768
IgA			
Median (Range)	177 (62 ~ 317)	208 (10.5 ~ 796)	.147
IgM			
Median (Range)	119 (20 ~ 622)	129 (40.9 ~ 458)	.960
Immunoglobulin after R (g/L)	**(n = 9)**	**(n = 10)**	
IgG			
Mean ± SD	1008.11 ± 245.75	1173.30 ± 373.16	.276
IgA			
Median (Range)	108 (51.9 ~ 220)	162 (10.5 ~ 508)	.468
IgM			
Median (Range)	83.7 (12.3 ~ 394)	153 (42 ~ 396)	.498

Abbreviations: Hb, hemoglobin; Ig A, immunoglobulin A; Ig G, immunoglobulin G; Ig M, immunoglobulin M; SD, standard deviation; WBC, white blood cell.

*$P < .05$. For subjects who received several courses of rituximab or cyclophosphamide, we used the data from the first course.

(OR = 0.992, CI = 0.965-1.000; $P = .048$) were found to be protective factors of infection (OR < 1, protective factors; OR > 1, hazard factors)(Table 5).

4 | DISCUSSION

It is well known that rituximab might increase infection risk during and after the treatment. The possible mechanism is prolonged depletion of plasma cell precursors in rituximab therapy may reduce replenishment of mature plasma cells, which can lead to hypogammaglobulinemia and infection risk.[14] On the other hand, prolonged B-cell depletion can also impair T cell–mediated immunity as the memory T cells cannot make normal cytokine production when they formed without B cells.[15] So the infection risk of virus and fungi can be also increased.[16,17] In this study, virus was not found, and thus, infections of bacteria still took up the major part. This reminds us bacteria might be the first one to take into

TABLE 5 Results of logistic regression analysis for variables extracted by forward selection

Variable	Estimated value	Standard error	χ^2 value	*P* value	Odds ratio	CI of odds ratio	
						Lower 95%	Upper 95%
G-CSF	-2.412	0.856	7.934	.005*	0.090	0.017	0.480
Nadir WBC count ($\times 10^9$/L)	-0.470	0.222	4.499	.034*	0.625	0.405	0.965
Ig A level before R therapy (g/L)	-0.008	0.004	3.921	.048*	0.992	0.985	1.000

Abbreviations: CI, confidence interval; G-CSF, granulocyte colony-stimulating factor; Ig, immunoglobulin; R, rituximab; WBC, white blood cells.
*$P < .05$.

consideration when infections happen after rituximab. And antibacterials might be the first consideration as an infection happened. Reactivation of some virus such as hepatitis B virus (HBV) has been known related to rituximab,[18,19] so all the patients in our study who received rituximab treatment had been tested for HBV (HBsAg, HBsAb, HBeAg, HBeAb, and HBcAb) and HCV (anti-HCV antibodies), they all were negative.

As for the difference in age of the two groups, the reason was mainly that the patients all chose treatment on themselves. So for the relatively older patients who had children already, the reproductive toxicity is not as much important as that for the younger patients, thus leading to the difference in two groups. We speculate that the difference in IgM before treatments of two groups might also relate to this reason.

Infection complication can be frequent and potentially serve for rituximab in autoimmune diseases according to a French study, they also reported that age seems to be not the risk factor.[20] In our study, frequent infections did exist after rituximab treatment, but the infection frequency was not higher than that of cyclophosphamide treatment. Besides, prognosis for most of the infections was quite good. The crude infection rate was 34.7% in patients treated with low-dose rituximab, which was familiar with the 33.22% reported in previous meta-analysis on lymphoma [5,21] and the 40% reported in a multicenter randomized trial on ITP.[22] In another French study about the infections related the rituximab treatment, Tudesq et al had found that patients received an overall median number of five rituximab infusions. Infections occurred after 3.1 months after last rituximab infusion. Polymicrobial infection, monoclonal hematological disease, use of steroids over 10 mg/d within the last 2 weeks, and rituximab cumulative dose were the factors associated with mortality.[23]

According to our data, age was also not the infection risk factors of rituximab. In a study of patients with lymphoma, the infection risk factors of rituximab are reduction in IgM after administration of rituximab, duration of rituximab therapy, and G-CSF administration.[24] And in another study of patients with hematological malignancies, lymphocyte counts at nadir, graft-versus-host disease, HIV serostatus, and the type of malignancy are independently associated with the risk of infection.[13] However, in our study of patients with autoimmune blood diseases, we found the nadir WBC count during treatment, use of G-CSF, and IgA level before rituximab therapy were protective factors. The less the need of G-CSF, the higher the nadir WBC count after treatment, and the higher the IgA before treatment, the lower the risk of infection. Thus, it might suggest that some differences do exist about systemic autoimmune diseases, malignancy, and autoimmune blood diseases. On the other hand, rituximab has been used for a low dose and that may decrease its toxicity to some degree. In other studies, rituximab was used at an standard dose, which meant higher rituximab cumulative dose during the treatments.

B-cell depletion can be achieved by the administration of rituximab. B cells are thought to be depleted via antibody-dependent cell-mediated cytotoxicity mode of clearance by natural killer cells.[25] Studies of protective immunity against *Mycobacterium tuberculosis* have focused mainly on T cells. Evidence suggests that B-cell and humoral immunity play important roles in shaping immune responses to *M tuberculosis*.[26] B cell–deficient mice display enhanced susceptibility to *M tuberculosis*.[27] So tuberculosis is a problem that cannot be ignored in the course of rituximab treatment. In our study, it appeared in three different patients. In my opinion, tuberculosis may relate to the immune deficiency due to rituximab. And as China is a developing country, contagious diseases such as tuberculosis still have relatively high morbidity in population. To our surprise, we also found bacteria such as tuberculosis could be reactivated after rituximab treatment and it can even be fatal. The old patient in group R who died had an extremely serious infection. The patient progressed rapidly, accompanied by central nervous system symptoms, liver function, and D-dimer abnormalities, the macrophage activation syndrome related to tuberculosis could not be excluded. Macrophage activation is also known to be influenced by the size of immune complexes, with both pro- and anti-inflammatory outcomes being possible.[28] The distinct outcomes of the three TB-infected patients could remind us the TB infections can be various according to different conditions of patients. For example, infections may be more potential fatal for old or debilitated patients than for the younger and relatively vigorous ones. So the clinicians should be more careful when treating with old patients and watching their symptoms and laboratory tests closer and changing the treatment on necessary.

In our study, tumors and autoimmune diseases appeared during follow-up. A single-institutional study of AIHA patients showed that an underlying condition could be found in 48% of patients at or preceding the diagnosis and in another 8% subsequently. The most common conditions were lymphoma or undefined lymphoproliferative disorder (54%) and autoimmune diseases (27%).[29] ITP has also been reported to predate tumors or autoimmune diseases.[30] Discovery of such conditions upfront and close follow-up may open the option of non–glucocorticoid-based therapies, improve the chance of response, and minimize relapses.

The limitations of this study include the missing laboratory data of some patients and incomplete randomization to choose about the two treatments. These missing laboratory data might have influence on our results of CD20 and immunoglobulin level of patients after rituximab to some degree. And the non-randomness might lead some bias in the study. The study would be a better one if it is a prospective multicenter randomized placebo-controlled trial. Besides, as a monocentric study, the number of enrolled patients in our study was relatively small, which might also cause some unpreventable bias in the research. This study comes up with two major points on the rituximab treatment in autoimmune hematological diseases. Firstly, rituximab therapy in autoimmune hematological diseases does not increase infection risk than traditional drugs such as cyclophosphamide. Secondly, for rituximab therapy in autoimmune hematological diseases, the infection protective factors probably are nadir WBC count during treatment, use of G-CSF, and IgA level before rituximab therapy.

To conclude, this study has shown us the safety in low-dose rituximab treatment for autoimmune blood diseases. What's more, it also revealed the three possible protective factors for infections after low-dose rituximab treatment, which can help clinicians observe patients and take necessary measures against infection more efficiently. As the efficacy of rituximab has been proven in autoimmune blood diseases, we can make rituximab give its best effect under close monitoring of the possible infection risk at the same time. In our country, rituximab and cyclophosphamide are commonly used for relapsed AIHA and ITP. The most common and dangerous side effect is infection, while we have not found any similar report about the infections events related to low-dose rituximab compared with cyclophosphamide in real-world evidence, this is the first study so far and may provide more supports to clinical decisions.

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INFORMED CONSENT

Informed consent was obtained from all patients for being included in the study.

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