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Original Article

Clinical, Laboratory, and Endoscopic Efficacy of Adalimumab and Infliximab in Inflammatory Bowel Disease

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Abstract

Objective: The aim of this study was to demonstrate the efficacy of the anti-tumor necrosis factor agents, adalimumab and infliximab, in patients with Crohn's disease and ulcerative colitis and to evaluate the efficacy duration and safety of remission maintenance in both diseases.

Methods: This is a case-controlled, cross-sectional study conducted on patients with Crohn's disease and ulcerative colitis followed up by the gastroenterology outpatient clinic. The clinical information, demographic data, laboratory values, and colonoscopy findings were analyzed prior to initiation and at 12 months after the use of infliximab and adalimumab. With these analyses, Crohn's Disease Activity Index score for Crohn's disease and Seo score for ulcerative colitis patients were calculated.

Results: The study included a total of 61 cases, 33 male (54.1%) and 28 female (45.9%) patients, who met the inclusion criteria, with a mean age of 36.44 ± 12.47 years. In this study, 37 (60.7%) Crohn's disease and 24 (39.3%) ulcerative colitis patients were included, 40 of whom use infliximab and 21 of whom use adalimumab. When the endoscopic scoring, laboratory data, and clinical scores (Crohn's Disease Activity Index $P=.002$ in infliximab users, SEO score $P=.001$; Crohn's Disease Activity Index $P=.001$ in adalimumab users, SEO score $P=.102$] at the start of anti-tumor necrosis factor therapy (month 0) and at month 12 of treatment were compared, infliximab and adalimumab treatments have been shown to be effective in remission.

Conclusion: According to our results, the initiation of anti-tumor necrosis factor therapy seems to be an effective approach when remission cannot be achieved with other conventional treatments in patients with Crohn's disease and ulcerative colitis.

Keywords: Adalimumab, Crohn's disease, inflammatory bowel disease, infliximab, ulcerative colitis

INTRODUCTION

In the pathogenesis of inflammatory bowel disease (IBD), it is known that inflammatory mediators, especially tumor necrosis factor-α (TNF-α), play an important role in intestinal inflammation. In recent years, biological agents, especially anti-TNF agents, have become the principal treatment for IBD. Infliximab (IFX), a chimeric monoclonal immunoglobulin G1 (IgG1) antibody developed against TNF-α, stops mucosal inflammation by preventing the interaction of TNF-α with cell receptors by binding to it.[1]

Sixty-five percent of active Crohn's disease (CD) patients refractory to glucocorticoid or mesalazine (5-ASA) treatment respond to IFX; one-third go into complete remission. Of these patients, 40% with an initial response maintain remission for at least 1 year with IFX therapy. Infliximab is also effective in CD patients with refractory perianal and enterocutaneous fistulas, with a response rate of 68% (50% reduction in fistula drainage) and a 50% complete remission rate.[2,3]

Adalimumab (ADA) is a recombinant IgG1 monoclonal antibody, which is developed against TNF-α containing only human peptide sequences. Like IFX, it is used in patients with steroid-resistant/steroid-dependent CD and ulcerative colitis (UC). It is also used in patients who cannot tolerate IFX treatment. It has proven beneficial in patients with fistulizing type CD, particularly in the treatment of perianal fistulas.[4]

The goals in the treatment of IBD are to achieve and maintain remission in the long term and to eliminate disease complications, hospitalizations, and the need for surgery. While planning the treatment in UC and CD cases, the duration of the disease, its localization, the presence of complications, and the response to previous treatments should be considered.

In this study, we aimed to demonstrate the efficacy of IFX and ADA treatments in patients with UC and CD followed up in our gastroenterology clinic.

METHODS

The study group consists of patients aged 18 years and older, who were admitted to the gastroenterology outpatient clinic of University of Health Sciences, Kartal Dr. Lütfi Kırdar City Hospital, between October 2017 and November 2018. Patients who were diagnosed with CD and UC endoscopically, pathologically or radiologically, who did not respond to mesalazine (5-ASA) and azathioprine (AZA) treatment, who had an active endoscopic appearance and who were subsequently started on IFX (every 8 weeks after week 0th, 2th, 6th; 5 mg/kg intravenously) or ADA (subcutaneously, 80 mg at week 0th; 40 mg every 2 week after two weeks) were included in this study. On the other hand, after the retrospective examination of the study group records, patients with a diagnosis of bowel disease other than IBD or with malignancy, who had undergone anti-TNF agent changes, and who did not come for follow-up after the anti-TNF agent was started were excluded from the study. Additionally, patients who had signs and symptoms of any active infection were excluded from the study at baseline and at 12 months of treatment.

Demographic data such as age and gender were recorded. The age of diagnosis was noted as the age at which the patient's first symptoms started and received the diagnosis of CD or UC endoscopically, pathologically, or radiologically. After that, the disease duration was calculated as "years." The place of involvement and spread of the diseases (CD or UC) at the start of anti-TNF treatment (month 0); the presence of stricture, abscess, or fistula; stenosis and history of surgery; other conventional drugs (5-ASA, AZA, budesonide, methylprednisolone, sulfasalazine, and methotrexate) which were used before anti-TNF treatment; and the presence of extraintestinal involvement were recorded. In addition, methylprednisolone treatment was given as a maximum dose of 1 mg/kg, and it was gradually decreased and discontinued after 1 month.

In both disease groups, the efficacy of treatment was compared in 3 different categories, including clinical status, biochemical data, and endoscopic appearance of the patients. In clinical evaluation, the SEO clinical activity index was used for UC patients and the Crohn's Disease Activity Index (CDAI) was used for CD patients;[5,6] statistical evaluation was performed to compare with the data at baseline and 12th month of anti-TNF treatment.

For the laboratory evaluation, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), hemoglobin (Hb), and hematocrit (HCT) values were compared. When the retrospective data were scanned, it was observed that all IBD patients have iron deficiency anemia in our study group. We used oral iron preparations at the beginning and during the anti-TNF treatment to reach normal values of Hb.

The endoscopic appearance of the patients was described as active and in remission. According to the Mayo Endoscopic Score for UC (0, normal or inactive disease; 1, mild disease with erythema, decreased vascular pattern, and mild friability; 2, moderate disease with marked erythema, absent vascular pattern, friability, and erosions; and 3, severe disease with spontaneous bleeding and ulceration), scores 0–1 were considered remission and scores 2 and above were considered active. Selected endoscopic parameters (size of ulcers, ulcerated and affected surfaces, and stenosis) were scored from 0 to 3 for all colon segments with the Simple Endoscopic Score for Crohn's disease; scores 0–2 were considered remission and score 3 and above were considered active.[7,8]

Statistical Analysis

The Number CrunCHer Statistical System 2007 (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, SD, median, frequency, ratio, minimum, and maximum) were used for study data analysis. Student's *t*-test was used for 2-group comparisons of normally distributed quantitative data and Mann–Whitney *U*-test was used for the comparison of 2 groups of data that did not show normal distribution. Pearson's chi-square test, Fisher–Freeman–Halton exact test, and Fisher's exact test were used to compare qualitative data. Repeated measures test (analysis of variance in repeated measurements) and Bonferroni test were used to evaluate pairwise comparisons. Friedman test was used to evaluate the follow-up of variables that do not show normal distribution and Bonferroni Dunn test was used to evaluate pairwise comparisons. Significance was evaluated at the $P < .05$ level at least.

This study has been prepared in accordance with the "STARD 2015: An Updated List of Essential Items for Reporting Diagnostic Accuracy Studies" guideline, and there is no conflict of interest.[9]

RESULTS

Clinical Evaluation

The study was conducted with a total of 61 cases, of which 33 (54.1%) were men and 28 (45.9%) were women; there were 37 (60.7%) CD patients and 24 (39.3%) UC patients. Twenty (83.3%) of UC cases were using IFX and 4 (16.7%) of them were using ADA; 20 (54.1%) of CD patients were using IFX and 17 (45.9%) of them were using ADA.

Considering the demographic characteristics, the mean age of patients with CD was 35.62 ± 12.18 years; in patients with UC, it was 37.71 ± 13.07 years, with similar rates ($P = .528$). In terms of gender, the rates were similar, too ($P = .593$). The ages of diagnosis were similar (CD: 6.19 ± 4.56 years; UC: 8.63 ± 7.56 years, $P = .289$).

While 59 (96.7%) of 61 cases were using the conventional medicine before anti-TNF treatment, it was observed that 52 (85.2%) of them continued to use these drugs together with anti-TNF treatment. The rates of using 5-ASA and methylprednisolone before anti-TNF treatment in UC cases were higher than in CD cases (5-ASA: 100% and 70.3%, respectively, $P = .002$ and $P < .01$, respectively; methylprednisolone: 95.8% and 48.6% respectively, $P = .001$ and $P < .01$, respectively).

While the rates of patients who continued to use AZA, methylprednisolone, sulfasalazine, and methotrexate during anti-TNF treatment among the diseases did not show a statistically significant difference ($P > .05$), the rate of those who continued to use mesalazine in cases with UC was higher than in cases with CD ($P = .001$; $P < .01$). While the number of patients who used IFX was higher in both diseases, the rate of using ADA was higher in CD patients than in UC patients (Table 1).

Laboratory Evaluation

Laboratory analysis was performed between IFX and ADA; however, no evaluation was made between UC and CD.

When drugs were analyzed separately, in the patients who used IFX, the increase in Hb and HCT measurements (Hb at baseline: 11.54 ± 2.41, Hb at month 12: 12.35 ± 2.40, $P = .007$, $P < .01$; HCT at

Table 1. Baseline Demographic and Clinical Features of Patients with CD and UC

		Disease		
		CD (n=37)	UC (n=24)	
		n (%)	n (%)	*P*
Age (years)	Minimum–maximum (median)	19-70 (35)	18-65 (37)	***.528***[a]
	Mean ± SD	35.62 ± 12.18	37.71 ± 13.07	
Gender	Male	19 (51.4)	14 (58.3)	***.593***[b]
	Female	18 (48.6)	10 (41.7)	
Age of diagnosis (years)	Minimum–maximum (median)	1-19 (5)	1-32 (6)	***.289***[c]
	Mean ± SD	6.19 ± 4.56	8.63 ± 7.56	
Drugs	Infliximab	20 (54.1)	20 (83.3)	***.019****[b]
	Adalimumab	17 (45.9)	4 (16.7)	
Steroid dependence	No	29 (78.4)	13 (54.2)	***.046****[b]
	Yes	8 (21.6)	11 (45.8)	
Prior used drugs	Azathioprine	31 (83.8)	18 (75)	***.513***[d]
	Mesalazine	26 (70.3)	24 (100)	***.002*****[d]
	Methylprednisolone	18 (48.6)	23 (95.8)	***.001*****[b]
	Sulfasalazine	6 (16.2)	1 (4.2)	***.229***[d]
	Budesonite	2 (5.4)	1 (4.2)	***1.000***[d]
	Methotrexate	4 (10.8)	0 (0)	***.147***[d]
Continuing drugs	Azathioprine	16 (43.2)	11 (45.8)	***.842***[b]
	Mesalazine	15 (40.5)	21 (87.5)	***.001*****[b]
	Methylprednisolone	3 (8,1)	1 (4,2)	1.000[d]
	Sulfasalazine	2 (5.4)	1 (4.2)	***1.000***[d]
	Methotrexate	1 (2.7)	0 (0)	***1.000***[d]
Extraintestinal involvement	No	23 (62.2)	19 (79.2)	***.161***[b]
	Yes	14 (37.8)	5 (20.8)	
	Uveitis	1 (2.7)	0 (0)	
	Sacroiliitis	3 (8.1)	2 (8.3)	
	Erythema nodosum	0 (0)	1 (4.2)	
	Arthritis	6 (16.2)	1 (4.2)	
	Uveitis+sacroiliitis	2 (5.4)	1 (4.2)	
	Uveitis+arthritis	2 (5.4)	0 (0)	

CD, Crohn's disease; UC, ulcerative colitis.
[a]Student's *t*-test; [b]Pearson's chi-square test; [c]Mann–Whitney *U*-test; [d]Fisher's exact test.
*P <.05; **P < .01.

baseline: 35.82 ± 6.46, HCT at month 12: 37.83 ± 6.43, P=.024) and the decrease in ESR and CRP (ESR at baseline: 49.58 ± 27.75; ESR at month 12: 28.13 ± 22.05, P=.001, P < .01; CRP at baseline: 49.39 ± 44.84; CRP at month 12: 17.48 ± 25.21, P=.001, P < .01) at month 12 compared to the baseline were found to be statistically significant.

In the cases which used ADA, the decrease in the ESR measurements at month 12 compared to month 0 was found to be statistically significant (ESR at baseline: 35.95 ± 23.60; ESR at month 12:19.38 ± 14.96, P=.021). However, the change in Hb, HCT, and CRP levels at month 0 and month 12 was not statistically significant (Hb: P=.358; HCT: P=.294; CRP: P=.112) (Table 2).

As a result of the examination performed separately in patients diagnosed with CD who used IFX or ADA, the decrease in the month 12 CDAI score compared to the baseline (in the IFX arm: CDAI at baseline=160.62 ± 87.58, CDAI at month 12=110.36 ± 68.40, P=.002; P < .01; in the ADA arm: CDAI at baseline=154.18 ± 57.91, CDAI at month 12=85.34 ± 35.41, P=.001; P < .01) was found to be statistically significant (Table 3).

Table 2. Laboratory Parameters Before and After Anti-TNF Therapy

		Drugs	
		IFX	ADA
		n=40	n=21
Baseline Hb	Minimum–maximum (median)	7.6-15.6 (11.5)	7.3-15.1 (12.7)
	Mean ± SD	11.54 ± 2.41	12.20 ± 2.11
12-month Hb	Minimum–maximum (median)	7.3-16.3 (12.8)	9.9-15 (13.4)
	Mean ± SD	12.35 ± 2.40	12.92 ± 1.47
	p[a]	***.007*****	***.358***
Baseline HCT	Minimum–maximum (median)	24.7-47.8 (35.7)	20.3-43.8 (38.5)
	Mean ± SD	35.82 ± 6.46	36.71 ± 6.00
12-month HCT	Minimum–maximum (median)	23.8-49.6 (39.2)	32.5-44.6 (39.4)
	Mean ± SD	37.83 ± 6.43	38.95 ± 3.64
	p[a]	***.024****	***.294***
Baseline ESR	Minimum–maximum (median)	4-121 (50)	5-80 (35)
	Mean ± SD	49.58 ± 27.75	35.95 ± 23.60
12-month ESR	Minimum–maximum (median)	4-100 (20.5)	4-58 (14)
	Mean ± SD	28.13 ± 22.05	19.38 ± 14.96
	p[b]	***.001*****	***.021****
Baseline CRP	Minimum–maximum (median)	3-160 (40.4)	3-116 (9.2)
	Mean ± SD	49.39 ± 44.84	23.07 ± 29.95
12-month CRP	Minimum–maximum (median)	3-115 (6.9)	3-49.2 (3.2)
	Mean ± SD	17.48 ± 25.21	10.40 ± 11.94
	p[b]	***.001*****	***.112***

ADA, adalimumab; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; HCT, hematocrit; IFX, infliximab; TNF, tumor necrosis factor.
[a]Bonferroni test; [b]Bonferroni Dunn test.
*P < .05; **P < .01.

In the cases with UC which used IFX, a significant decrease was observed in the month 12 SEO score (175.67 ± 184.99) compared to the baseline SEO clinical activity score (203.67 ± 54.01) (P=.001); the change in the baseline SEO score (179.28 ± 52.64) and the month 12 SEO score (118.38 ± 33.20) of the cases which used ADA was not statistically significant (P=.102) (Table 4).

Table 3. CDAI Score in CD Before and After Anti-TNF Drugs

		Drugs	
		IFX	ADA
		n=20	n=17
Baseline CDAI	Minimum–maximum (median)	58.4-419 (150)	69.9-280.9 (162.3)
	Mean ± SD	160.62 ± 87.58	154.18 ± 57.91
12-month CDAI	Minimum–maximum (median)	49.1-273.4 (85.6)	31.5-176.6 (78.9)
	Mean ± SD	110.36 ± 68.40	85.34 ± 35.41
	p[a]	***.002*****	***.001*****

ADA, adalimumab; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; IFX, infliximab; TNF, tumor necrosis factor.
[a]Bonferroni Dunn test.
**P < .01.

Table 4. SEO Clinical Activity Index in UC Before and After Anti-TNF Drugs

		Drugs	
		IFX	ADA
		n=20	n=4
Baseline SEO	Minimum–maximum (median)	105.9-289.3 (214.2)	106.8-232.8 (188.8)
	Mean ± SD	203.67 ± 54.01	179.28 ± 52.64
12-month SEO	Minimum–maximum (median)	54.7-938 (121.9)	92.7-165.8 (107.5)
	Mean ± SD	175.67 ± 184.99	118.38 ± 33.20
	***p*[a]**	***.001*[**]**	***.102***

ADA, adalimumab; IFX, infliximab; TCF, tumor necrosis factor; UC, ulcerative colitis.
[a]Bonferroni Dunn test.
[**]$P < .01$.

Endoscopic Evaluation

The month 12 endoscopic findings of the patients were evaluated according to the disease groups and the anti-TNF drugs; month 12 endoscopy results were obtained in the records of 45 out of 61 patients who participated in the study. Of the 45 patients, 25 had CD and 20 had UC; 31 patients were using IFX and 14 patients were using ADA. The initial endoscopic findings of all UC and CD patients were considered active according to endoscopic indices, and according to the endoscopic scoring of both diseases at the month 12 endoscopic evaluation, 30 (66.7%) of 45 patients were found to be in remission. There was no statistically significant difference between the 2 diseases in terms of remission ($P = .289$, $P > .05$).

In addition to that, patients with CD (n=25) and UC (n=20) whose endoscopic findings data were available at 12 months were statistically evaluated according to the anti-TNF drug (Table 5). When CD patients were examined among themselves, 15 (60%) of 25 patients were found to be in remission. It was observed that there was a significant difference in the first year of treatment according to the initial scores: 8 patients (57.1%) in remission were using IFX and 7 patients (63.3%) were using ADA. When 20 patients with UC were examined, 15 (75%) patients were found to be in remission endoscopically, and so the difference was statistically significant. Thirteen patients in remission were using IFX (76.4%), and 2 patients were using ADA (66.6%) (Table 6).

DISCUSSION

In our study, we aimed to show the efficacy of IFX and ADA treatment in UC and CD patients during a 1-year follow-up period. Infliximab and ADA are anti-TNF agents that have taken their place in the literature in recent years, and their efficacy and safety have been shown in most studies. In IBD, the goal is to suppress inflammation, achieve remission, and relieve symptoms. With the use of these agents, surgical risk, hospitalization, and complication rates are reduced.

Table 5. Endoscopic Findings According to Diseases at Month 12 of Treatment

		Disease			
		Total	CD	UC	
		n=45	n=25	n=20	***P***
Endoscopic findings	Remission	30 (66.7%)	15 (60.0)	15 (75.0)	***.289*[a]**
	Active	15 (33.3%)	10 (40.0)	5 (25.0)	

CD, Crohn's disease; UC, ulcerative colitis.
[a]Pearson's chi-square test.

Table 6. Endoscopic Findings According to Drugs at Month 12 of Treatment

		Drugs			
		Total	IFX	ADA	
		n (%)	n (%)	n (%)	***P***
CD endoscopic findings		25	14	11	
	Remission	15 (60%)	8 (57.1%)	7 (63.6%)	***.303*[a]**
	Active	10 (40%)	6 (42.9%)	4 (36.4%)	
UC endoscopic findings		20	17	3	
	Remission	15 (75%)	13 (76.4%)	2 (66.6%)	***.460*[a]**
	Active	5 (25%)	4 (23.6%)	1 (33.4%)	

ADA, adalimumab; CD, Crohn's disease; IFX, infliximab; UC, ulcerative colitis.
[a]Fisher's exact test.

In the literature, it has been shown that the number of fistulas decreased significantly and the need for surgery decreased after the use of anti-TNF agents in treatment-resistant CD and fistulizing CD.[10-12] Previously, anti-TNF treatments were used in fistulizing CD; nowadays, they are also started in refractory luminal and fistulizing CD, steroid-dependent CD, chronic refractory UC, acute severe active UC, and cases of unresponsiveness to immunomodulatory treatment and intolerant to these drugs or in case of contraindications or extraintestinal involvement such as chronic uveitis, ankylosing spondylitis, and sacroiliitis. In our study, no further investigation was performed in the cases, and anti-TNF treatment was initiated in all cases resistant to conventional treatment.

C-reactive protein is used to monitor internal inflammation in patients who are clinically asymptomatic in IBD. C-reactive protein has been shown to correlate better with endoscopic and clinical findings in CD patients than in UC patients.[13] Rapid normalization of CRP levels in an IFX study by Jürgens et al, and in an ADA study by Kiss et al[14,15] was associated with a clinically prolonged response with IFX and ADA. Studies have shown that not only the decrease in CDAI score but also the decrease in CRP values is significant in terms of remission follow-up.[16] Sugimoto et al.[17] in their study on UC patients, showed that CRP levels started to decrease and Hb increased in the fourth week of ADA treatment. In our study, in line with the literature, it was found that disease activation scores and CRP levels decreased and Hb values increased. However, all patients were given iron replacement therapy, so that the relationship between the improvement in Hb level and the success of anti-TNF treatment could not be confirmed. Since there is no control group that does not use iron preparations, we cannot claim that anti-TNF drugs may positive effect on Hb levels.

In the study of Gavalas et al.[18] the effectiveness of IFX in UC patients was evaluated in terms of disease activity and clinical response with the SEO clinical activity index, and it was found that the SEO score improved significantly. Sugimoto et al also showed a significant decrease in clinical activity score after ADA use in UC patients.[14] In our study, consistent with the literature, a significant decrease in the SEO clinical activity index score at month 12 compared to the score at the beginning of the treatment was found in patients with UC who received IFX ($P < .01$). However, such a difference could not be observed in UC patients using ADA. We think that this is due to the low number of our UC patients, which may not have produced sufficient statistical results. In the following years, ADA effectiveness can be determined with studies with a large number of patients.

In the study of Armuzzi et al.[19,20] IFX monotherapy or combination therapy with AZA was effective in patients with steroid-dependent UC with

persistent active disease despite steroid treatment and shown to significantly increase steroid-free remission rate for up to 12 months. The clinical response of AZA+IFX combination therapy after 1 year was showed significantly superior to monotherapy in Crohn's patients in The Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease (SONIC) study and in UC patients in the UC-SUCCESS (NCT00537316, protocol number P04807)study.[21,22] In our study, 19 (31.1%) IBD patients had steroid dependence, and the number of steroid dependence (n=11) in UC patients was higher than in Crohn's patients (n=8). In the study, while 15 patients with CD continued to use 5-ASA and 16 patients with CD continued to use AZA after anti-TNF was started, 21 patients with UC continued to use 5-ASA and 11 patients with UC continued to use AZA. At the beginning of anti-TNF treatment in the patients included in our study, we were planning to form subgroups according to the use of 5-ASA and AZA and to determine its contribution to the treatment effectiveness, but this distinction could not be made due to the low number of subgroup patients.

In our study, it was aimed to demonstrate the efficacy of anti-TNF therapy by clinical scores and laboratory and endoscopic evaluations; consequently, the efficacy of both drugs was seen in the first year of the disease in UC and CD. According to our results, anti-TNF therapy should be started in patients who cannot maintain remission with conventional therapy, and in order to conclude that these treatments are effective and safe for the patient through the maintenance period, at least 1 year of follow-up should be made.

In conclusion, a new era has started with anti-TNF agents in the treatment of IBD. Despite the fact that this is a single-center retrospective study with a small number of patients and a short follow-up period, it reflects daily clinical practice and demonstrates the effectiveness of these drugs in the treatment of IBD. According to the results of our study, the efficacy of ADA and IFX in both diseases is similar and they seem to be effective in refractory IBD patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the University of Health Sciences, Kartal Dr. Lütfi Kırdar City Hospital Clinical Research Ethics Committee (Date: January 28, 2019, Decision No: 2019/514/146/6).

Informed Consent: This study was a designed, retrospective, and cross-sectional study.

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