Extension Study of Participants from the Trial of Early Aggressive Therapy in Juvenile Idiopathic Arthritis

Carol A. Wallace, Sarah Ringold, John Bohnsack, Steven J. Spalding, Hermine I. Brunner, Diana Milojevic, Laura E. Schanberg, Gloria C. Higgins, Kathleen M. O'Neil, Beth S. Gottlieb, Joyce Hsu, Marilynn G. Punaro, Yukiko Kimura, and Audrey Hendrickson

ABSTRACT. *Objective.* To follow children with juvenile idiopathic arthritis (JIA) who had completed at least 6 months of the TRial of Early Aggressive Therapy (TREAT) clinical study for an additional 2 years, describing safety of early aggressive treatment, disease activity, function, and duration of clinical inactive disease (CID) during followup.

Methods. Children were treated as per provider's discretion. Physician, patient/parent, and laboratory measures of disease status as well as safety information were collected at clinic visits every 3 months for up to 2 years.

Results. Forty-eight children were followed for a mean of 28 months (range 12-42) beyond the end of the TREAT study. Half of patients were in CID for > 50% of their followup time. Overall, 88% of patients achieved CID at > 1 study visit and 54% achieved clinical remission while taking medication. Six patients were in CID for the duration of the study, and, of those, 2 achieved a full year of clinical remission while not taking medication. Active disease was mild: mean physician's global assessment 2.4, active joint count 3.5, parent global evaluation 2.4, Childhood Health Assessment Questionnaire 0.32, erythrocyte sedimentation rate 19 mm/h, and morning stiffness 23 min. There were no serious adverse events or adverse events reported at grade 3 or higher of Common Terminology Criteria for Adverse Events.

Conclusion. Early aggressive therapy in this cohort of patients with polyarticular JIA who had high initial disease activity was associated with prolonged periods of CID in the majority of patients during followup. Those not in CID had low levels of disease activity. (First Release Sept 1 2014; J Rheumatol 2014;41:2459–65; doi:10.3899/jrheum.140347)

Key Indexing Terms:
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During the last 20 years, the development of biologic medications that directly inhibit proinflammatory mediators has revolutionized the treatment and expected outcome of juvenile idiopathic arthritis (JIA) such that extended periods of clinical inactive disease (CID) and periods of remission may be induced in a significant proportion of treated patients[1,2,3,4,5,6,7,8]. The polyarticular categories (both rheumatoid factor (RF)-positive and -negative) comprise nearly 30% of all patients with JIA[4,5,7,8,9,10]. The majority of these children continue to take medications for many years, and disease-free periods without medication longer than 1 year are uncommon[5,6,7,8,10,11,12]. The optimal timing

of aggressive treatment initiation and specific medication combinations most likely to result in CID and remission have yet to be determined.

The TRial of Early Aggressive Therapy (TREAT) study was a proof-of-concept study that randomized children with newly diagnosed polyarticular JIA (poly-JIA) early in their disease course to 1 of 2 aggressive treatment regimens[13]. This randomized, placebo-controlled clinical trial demonstrated that CID could be achieved in a large proportion of patients within 6 months of initiating treatment. Further, an early window of opportunity was evident; the likelihood of achieving CID increased for each month earlier that treatment was started following disease onset (OR 1.3).

While the TREAT study focused on achievement of CID at the 6-month visit and clinical remission while taking medication (CRM), the longer-term association between early aggressive treatment and disease activity remains unknown. This investigation followed patients from the original TREAT study prospectively for at least 2 additional years to describe the safety and longer-term effects of early aggressive therapy on CID, CRM, clinical remission (CR), functional outcomes, and disease activity.

MATERIALS AND METHODS

The original TREAT study was conducted by members of the Childhood Arthritis and Rheumatology Research Alliance (CARRA), and results have been published elsewhere[13].

Patients. Eighty-five patients aged 2 to 16 years diagnosed with clinically active poly-JIA (RF-positive or -negative) less than 12 months in duration were enrolled in the original TREAT study. At baseline, these patients had a significant burden of disease, with median physician global assessment of 7, median number of active joints 18, and 36% RF/anticyclic citrullinated peptide antibodies (anti-CCP)-positive. Patients who completed a minimum of 6 months in the TREAT study were eligible to enroll in the extension study regardless of response during the original trial and regardless of whether they continued to receive the same medications to which they were assigned during the initial trial.

TREAT study design and treatments. TREAT was a prospective, randomized, double-blind, placebo-controlled study that compared the efficacy of 2 aggressive treatment arms to induce CID within 6 months of therapy initiation (primary endpoint), and an open-label phase that patients could enter if they failed to achieve either an American College of Rheumatology Pediatric 70 (ACR Pedi 70) at 4 months or CID at 6 months. Patients were randomized 1:1 to 1 of 2 aggressive treatment arms. Treatment Arm 1 (MEP) consisted of open-label subcutaneously administered methotrexate (MTX) at a dose of 0.5 mg/kg/wk (max of 40 mg/wk), blinded etanercept (ETN) administered subcutaneously at a dose of 0.8 mg/kg/wk (max of 50 mg), and oral blinded prednisolone daily at 0.5 mg/kg/d (max 60 mg/d) tapered to 0 over 4 months. Treatment Arm 2 (MTX) medications included open-label subcutaneously administered MTX as in the MEP arm, blinded placebo ETN administered subcutaneously every week, and daily blinded placebo oral prednisolone tapered to 0 over 4 months. Patients in each arm received oral folic acid 1 mg daily and were allowed a single nonsteroidal antiinflammatory drug (NSAID) as concomitant therapy. Up to 2 intraarticular corticosteroid injections within 2 weeks after the baseline visit were allowed. No other antiinflammatory or antirheumatic therapies were allowed during the study period.

Study visits occurred at screening, baseline, and months 1, 2, 4, 5, 6, 7, 8, 10, and 12. All joint examinations conducted over the duration of the study were done by certified joint assessors blinded to the treatment the patient was receiving (blinded joint assessment). At the 4-month visit, patients were assessed to determine whether they had achieved an ACR Pedi 70 score. Children who failed to achieve this level of response by 4 months were switched to open-label MEP medications. Patients who achieved an ACR Pedi 70 but did not achieve CID at the 6-month visit were treated with open-label MEP medications. Patients were assessed for CID at each visit except baseline.

Extension study procedures. Eligible patients at participating sites were enrolled as soon after completing the TREAT study as possible. Institutional review board approval was obtained at all participating sites. Patients were treated as per standard of care at clinic visits every 3 months for up to 2 years. The following examinations were done and these data collected: general examination, full joint examination, physician global assessment of disease activity (MD global), parent global assessment of overall well-being, Childhood Health Assessment Questionnaire (CHAQ), erythrocyte sedimentation rate (ESR), parent report of morning stiffness, and safety information. Adverse events of Common Terminology Criteria for Adverse Events (CTCAE) grade 3 and higher as well as infections requiring systemic therapy were reported.

Some patients were not enrolled immediately following TREAT study participation owing to delay in funding for the extension study; thus, data regarding disease status and safety during the time period between the end of the TREAT study and the start of the extension study were collected retrospectively by chart review. Information is reported from 3 time periods: from the extension study alone; from the end of the TREAT study through the end of the extension study (followup period); and from the start of the TREAT study (combined TREAT and followup period).

CID was defined as (1) no joints with active arthritis; (2) no fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA; (3) no active uveitis; (4) ESR in the normal range in the laboratory where tested; (5) physician's global assessment of disease activity score of 0; and (6) < 15 min of morning stiffness[14]. CRM was defined as CID for a period of 6 consecutive months while taking medications; and CR was defined as CID while taking no medication for a period of 12 consecutive months.

Statistical considerations. Descriptive statistics, including mean, median, and range were used to describe patient outcomes, and Wilcoxon rank-sum and Wilcoxon signed-rank tests were used for comparisons. Analyses were performed using Stata statistical software, version 12.1.

The cumulative time in CID was calculated as the time difference (in months) between the date of the visit at which the patient was observed to be in CID until the date at which he/she was observed not to be in CID, or completed the study. Information was gathered at extra visits if a flare occurred between visits. If no information was entered into the database, and a patient was in CID at 2 consecutive visits, we assumed there were no periods of flare between study visits. If a patient was found to be in CID at a visit but was not in CID at the next visit, they were counted as being in CID until observed to have active disease.

RESULTS

Twelve of the 15 original TREAT study sites participated in the 24-month extension study, enrolling 52 of 63 eligible patients (83%). The 9 patients who did not participate moved, were lost to followup, or declined participation in our study. The 3 sites that did not participate lacked coordinator or investigator time, or the funding needed to participate. Forty-eight patients returned for followup visits and are the basis of our report. Baseline demographic and disease characteristics in the initial TREAT study, as well as disease state at the end of the TREAT study, did not differ between those who participated in the extension study and those who did not (data not shown). Twenty-seven of the 48

patients in the extension study had been in the MEP arm and 21 had been in the MTX arm.

Disease activity. Thirty patients (63%) entered the extension study in CID, while 18 patients (37%) had active disease. Patients were followed for a mean of 21.4 months in the extension study (range 9–24) and the majority of patients (56%) were in CID more than 50% of their followup time (Figure 1). Patients were followed for a mean of 28 months (range 12–42) past the end of the TREAT study. Overall, 88% of patients achieved CID at ≥ 1 study visit during the extension study and 26 patients (54%) achieved CRM. Six of 48 patients (13%) were in CID for the duration of the
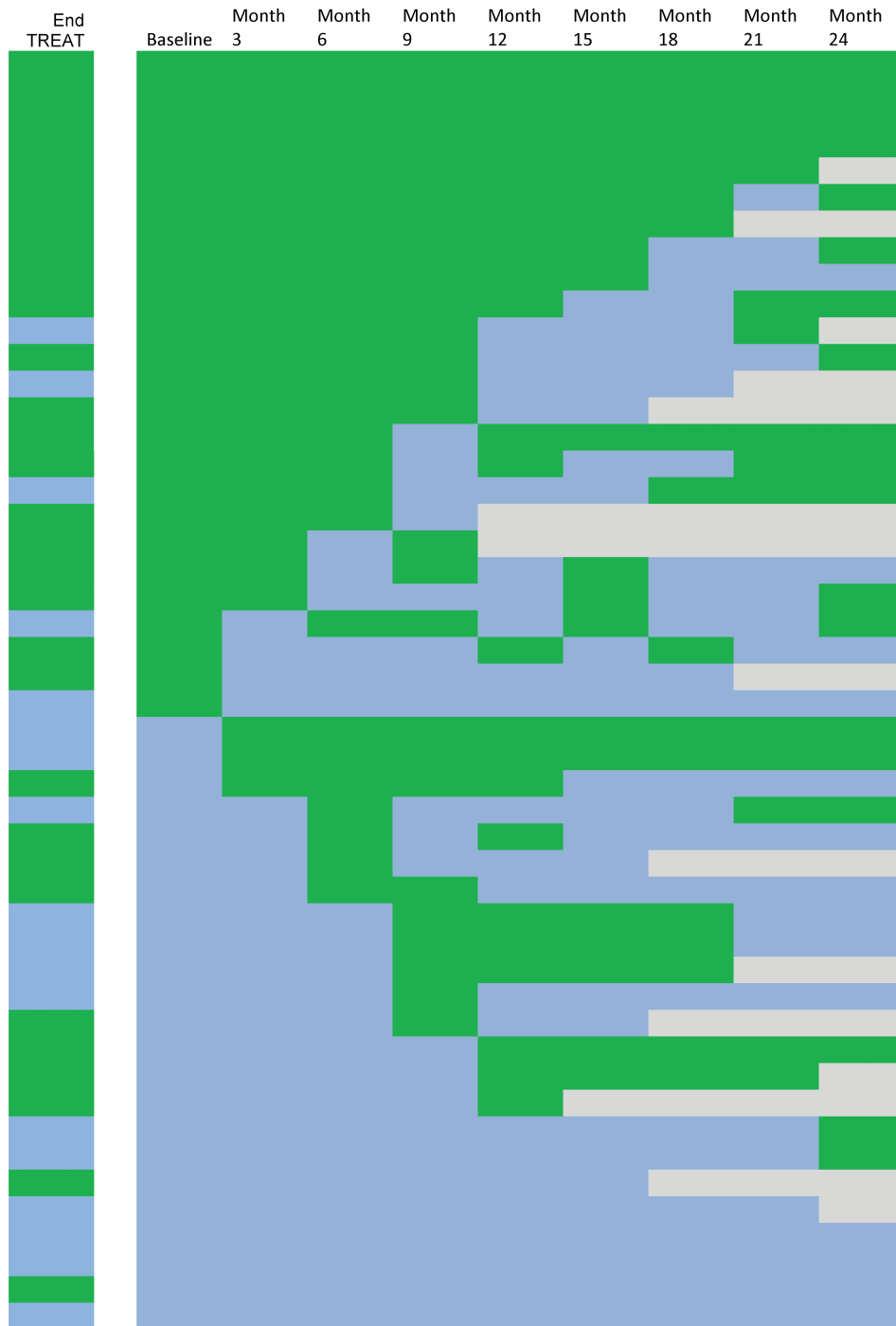

Figure 1. Disease status of each patient at visits in the TRial of Early Aggressive Therapy extension study. Colors indicate disease status: blue = active disease, green = clinical inactive disease, and grey = end of study.

study and 2 of them achieved a full year of CR. No TREAT baseline clinical characteristics were significantly associated with CRM during the followup period, including antinuclear antibody (ANA), RF or anti-CCP status, age, duration of disease prior to treatment, ESR, active joint count (AJC), global assessment of overall well-being, MD global, and CHAQ. Treatment arm did not predict CRM or length of CID. As at the end of the TREAT study, of the 48 patients enrolled into the extension study, 43 were taking MTX and ETN; only 5 were taking MTX alone. Additionally, medications that the patients attaining CRM received were similar in distribution to those patients not achieving CRM (MTX/ETN 42% vs 45%; ETN 15% vs 10%; MTX 31% vs 23%). Of note, age at enrollment in TREAT, TREAT baseline AJC, and duration of symptoms prior to treatment did not correlate with proportion of time in CID during the observation period.

When the time in the active TREAT study is combined with the followup period (time to the extension study plus time in the extension study), the mean period of prospective observation for these 48 patients was 39 months (range 24–54) from the start of treatment in TREAT until last followup visit, with a mean of 17.4 months in CID (range 0–49 months). Treatment arm assignment in the original TREAT study did not affect the proportion of time in CID during the total observation period, because 43 of the 48 patients were taking MTX and ETN by the end of the TREAT study; only 5 continued taking MTX alone. Likewise, ANA status did not correlate with proportion of total time in CID. In contrast, patients who were RF-negative tended to have a larger proportion of total time in CID than did RF-positive patients, but this difference was not statistically significant (Table 1). Those patients who achieved an ACR Pedi 70 at 4 months, CID at 6 months, CID at 12 months, or CRM in the original TREAT study were in CID overall a significantly larger proportion of time than were those who did not achieve those levels (Table 1). Starting the original TREAT study prior to 90 days of disease symptoms or prior to 120 days of disease symptoms did not predict sustainability of CID in the followup period.

There was no difference in the number of missed visits for those patients who were in CID > 50% of their time compared to those who were in CID < 50% of their time (median 1–2 for both).

Six of the 48 patients (12%) never achieved CID at any time during the entire followup period. All of the patients not achieving CID were ANA+; 3 were RF+ (and anti-CCP+), and 3 had normal ESR. The median active joint count was 26 and they were 3.8–15.6 years old (median 12.0) at the baseline TREAT study visit. All except 1 were treated after 4 months of symptoms. Of these patients, 4 did not achieve ACR Pedi 70 at 4 months and 5 did not achieve CID during the original TREAT study.

Measures of disease activity during periods of active disease in the extension study tended to be low. Patients who were in a period of active disease had mean MD global 2.4 (baseline 7), AJC 3.5 (baseline 22), parent global assessment of overall well-being 2.4 (baseline 5.4), CHAQ 0.32 (baseline 1.2), ESR 19 mm/h (baseline 28), and morning stiffness of 23 min. Core set measures of disease activity at the end of the extension study were dramatically improved from the baseline TREAT visit (p < 0.0001; Table 2). Of note, 20 patients had a CHAQ of 0 at the end of the followup period, and an additional 11 had a score of 0.125, indicating excellent function.

Medications. At the end of the TREAT study, 43 of 48 patients were taking MTX and ETN; only 5 were taking MTX alone. At the start of the extension study, patients were taking the following medications: 21 MTX and ETN, 11 MTX, 6 ETN, and 7 no medications or NSAID. One each were taking prednisone; adalimumab and prednisone; and MTX and abatacept. During the extension study, 2 patients were taking no medications for over 24 months; 2 were taking NSAID only; 21 continued MTX and ETN; 13 were taking MTX alone; and 10 were taking other medications: adalimumab (n = 3), infliximab (IFX; n = 1), abatacept (n = 1), prednisone (n = 4), or a sequence of 4 biological therapies (n = 1). At the end of the extension study, 11 of 48 patients (23%) were taking no medications, with 7 of these in CID; the other 4 had active disease. For the other 37 patients, 10 (21%) were taking MTX alone, 8 (16%) ETN alone, 12 (25%) ETN and MTX, 2 MEP, and 2 abatacept, and 1 each taking adalimumab, IFX, and tocilizumab. Eleven patients had a median of 1 joint injected during Year 1 of the extension study (range 1–8) and 5 patients had a median of 1 joint injected during Year 2 (range 1–3).

Of 43 patients who achieved CID during the extension study, 28 patients (65%) did not maintain this level of disease control during the study. Of the 28 patients who lost CID, 7 had no change in medications; 16 tapered or discontinued all their medications; and 5 tapered/discontinued either MTX or their biologic, but not both. Thus, 75% of patients who lost CID did so during a time of medication taper.

Safety. There were no reported serious adverse events or adverse events of grade 3 (CTCAE) or higher. Four patients had 6 infections requiring systemic antibiotics: 2 episodes of sinusitis, and 1 episode each of pharyngitis, pharyngitis with ear infection, ear infection, and rash. One patient had 3 events at different times during the study while taking MTX monotherapy. No patient required hospitalization.

DISCUSSION

This is the first report, to our knowledge, on longterm followup of children with poly-JIA treated with early aggressive therapy. Our study presents the disease states of these patients for their entire course from initial treatment through followup, and is not simply a cross-sectional

Table 1. Combined TREAT study and followup period*.

	Proportion of Combined Time in CID, Mean; Median (range)	p**
ANA		
Positive, n = 37	0.43; 0.43 (0–0.97)	0.8733
Negative, n = 11	0.46; 0.42 (0.07–0.86)	
RF		
Positive, n = 15	0.37; 0.38 (0–0.74)	0.27
Negative, n = 33	0.47; 0.43 (0–0.97)	
TREAT Study, ACR Pedi 70 at 4 mos		
Yes, n = 28	0.50; 0.50 (0–0.97)	0.04
No, n = 20	0.35; 0.34 (0–0.76)	
TREAT Study, CID at 6 mos		
Yes, n = 16	0.61; 0.67 (0.29–0.97)	0.001
No, n = 32	0.35; 0.36 (0–0.75)	
TREAT Study, CID at 12 mos		
Yes, n = 28	0.55; 0.55 (0.21–0.97)	0.006
No, n = 20	0.28; 0.3 (0–0.76)	

*Time in TREAT study + time to extension study + time in extension study. **Comparison by Wilcoxon rank-sum test. TREAT: TRial of Early Aggressive Therapy; CID: clinical inactive disease; ANA: antinuclear antibody; RF: rheumatoid factor; ACR70: American College of Rheumatology Pediatric 70.

Table 2. Core measures at TREAT baseline and end of followup period.

Core Measure	TREAT Baseline, Mean; Median (range), n = 48	End Followup, Mean; Median (range), n = 48	p*
Active joint count	21.9; 19 (6–55)	1.7; 0 (0–24)	< 0.0001
MD global assessment of disease activity	6.7; 7 (3–10)	1.5; 0 (0–9)	< 0.0001
Parent global assessment of overall well-being	5.1; 5 (0–10)	1.7; 1 (0–9), n = 43	< 0.0001
ESR	34.6; 28 (2–83)	12.3; 10 (1–40), n = 36	< 0.0001
Loss of motion	15.0; 12 (0–54)	2; 0 (0–28)	< 0.0001
CHAQ	1.1; 1 (0–2.6)	0.3; 0.125 (0–2.5), n = 47	< 0.0001

*Comparison by Wilcoxon signed-rank test. TREAT: TRial of Early Aggressive Therapy; ESR: erythrocyte sedimentation rate; CHAQ: Childhood Health Assessment Questionnaire.

analysis of their disease status at specific study timepoints. These children, with a high initial burden of disease and high proportion of RF positivity, were in CID for more than 50% of their followup time; with 88% achieving CID at ≥ 1 study visit, 54% achieving CRM, and 65% with excellent functional outcome. These impressive results highlight the importance of early aggressive therapy. While only 4% of the patients achieved CR (defined as CID while taking no medications for 12 months) during the study period, an additional 5 patients (10%) were in CID and taking no medications, but for less than 12 months by the end of the study period. This could suggest that more children might have achieved CR had longer followup been possible.

The percent of patients achieving CID and CRM in this cohort is higher than in previously reported longterm cohorts of poly-JIA[4,5,6] and the proportion of time in CID is significantly greater in this current cohort of patients treated early. Nearly all had received anti-tumor necrosis factor (TNF) therapy. In 2005, Wallace, et al, reported 17% median cumulative time in CID for patients with RF+ poly-JIA and 37% for patients with RF-negative disease[10]. In the era of biologic therapies, but without early treatment, previous reports document that 46–80% of patients with poly-JIA achieve CID with a median time to CID of 8–10 months[5,11].

The poly-JIA cohort report by Ringold, et al[11] most closely resembles the TREAT patients. This is a retrospective cohort study of 104 children with poly-JIA who were followed prospectively for a median of 27.4 months (range 6–77). Of the study subjects, 28% were RF-positive. While 80% of these patients achieved CID at a median time of 7.6 months after initiation of treatment, only 37% were

treated with anti-TNF therapy. Forty-seven percent of patients achieved CRM, none achieved CR, and 20% never achieved CID. Overall, these patients were in CID only a mean of 34% of their time followed.

Our current report highlights the importance of early therapy and the achievement of CID early in the disease course, because those patients who achieved CID at 6 and 12 months in the TREAT study were in CID a significantly greater proportion of time during their overall followup period when compared to those in the study by Ringold, *et al*[11]. However, the time to treatment did not correlate with overall proportion of time in CID in the followup period.

Similar to findings in patients with adult rheumatoid arthritis, early aggressive therapy appears to alter the trajectory of disease[15,16]. Patients with active disease in this TREAT Extension study tended to have low levels of disease activity despite their initial treatment condition. Further, 65% of children had excellent functional outcome with minimal or normal CHAQ scores.

While the proportion of patients achieving CID was excellent, many patients could not maintain CID beyond 6–12 months. This may be related to several factors such as a change in medications, because 75% of patients who lost CID during the study had a taper or discontinuation of medication. This has been documented previously for the majority of patients who discontinue MTX or anti-TNF therapy[8,12]. In addition, currently available medications do not appear to abolish inflammation in the long run in these patients. Another possibility that our data suggest is that the nature of poly-JIA requires patients to continue taking medications for many years, even with early aggressive therapy.

The current study has several limitations; most notably that only 48 of the 76 eligible patients from the TREAT study participated in the longer-term followup study. Additionally, patients in the TREAT study initially had a high burden of disease and may not be representative of all children with poly-JIA. It may have been that patients with more severe disease than average were enrolled into the TREAT study. If this selection bias is present, outcomes might actually be better for most children with poly-JIA with early aggressive treatment. Lastly, our study did not address the question of how important the early limited use of prednisone was, nor when or how to taper medications once CRM has been achieved.

Early aggressive therapy in this group of patients with poly-JIA with high initial disease activity and high proportion of RF positivity was associated with 90% of patients achieving CID and a majority of patients experiencing prolonged periods of CID. Those not in CID had low levels of disease activity. Loss of CID may be related to tapering or discontinuation of medications. Reporting the disease states of patients followed longitudinally over their course of disease provides a more accurate description of their disease and outcomes than do traditional cross-sectional reports.

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