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ORIGINAL RESEARCH



## Frequency and characteristics of infusion reactions during biosimilar infliximab treatment in inflammatory bowel diseases: results from Central European nationwide cohort

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### ABSTRACT

**Background:** Safety data of the ‘real life’ use of an infliximab biosimilar, CT-P13 in inflammatory bowel disease (IBD) are still lacking. Our **aim** was to assess the frequency and characteristics of infusion reactions during CT-P13 therapy in 13 Hungarian and 1 Czech IBD centres.

**Methods:** Clinical and safety data was registered at fixed appointments. Trough levels and anti-drug antibody (ADA) concentration were measured by ELISA. Association between demographic, clinical, laboratory parameters and infusion reaction rates were evaluated statistically.

**Results:** Three hundred and eighty-four IBD patients were included. Twenty-eight Hungarian IBD patients (9.6%) developed infusion reaction during the treatment, 64.3% of them was previously exposed to anti TNF therapy. No infusion reaction occurred in the Czech population. CT-P13 therapy had to be stopped in 17 patients who developed infusion reaction and was switched to adalimumab in 12 patients. However in 39.3% of patients developing infusion reaction CT-P13 therapy was continued with the use of premedication. Cumulative ADA positivity rates were 8.7%, 19.3%, and 28.0% at weeks 0, 14, and 30. Previous anti-TNF-alpha exposure (30% vs. 3.1%,  $p < 0.001$ , OR 6.3 (2.7–14.6)) and ADA positivity (32.6% vs. 4.1%,  $p < 0.001$ , OR 19(5–73)) during the induction therapy were predictive factors for infusion reactions.

**Conclusions:** Patients with previous exposure to anti-TNF-alpha and ADA positivity during the induction therapy were more likely to develop infusion reactions.

### ARTICLE HISTORY

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### KEYWORDS

Crohn’s disease; ulcerative colitis; infliximab; biosimilar; CT-P13; infusion reaction

## 1. Introduction

After some case series, a large, prospective Hungarian multicenter study has confirmed the efficacy of CT-P13, the first infliximab biosimilar, in inducing and maintaining remission in both Crohn’s disease (CD) and ulcerative colitis (UC) [1–5]. However, besides efficacy data, safety assessment is also very important when extrapolating indications for biosimilars. Immunological reactions including immunogenicity and infusion-related reactions are one of the main limiting factors of the originator infliximab (IFX), a chimeric mouse-human monoclonal antibody to TNF-alpha, and one of the most important concerns before the start of using

biosimilar IFX. Immediate infusion reactions, developing during the course of the infusion or within 1–2 h of its completion, are reported in 5–23% of IBD patients receiving originator IFX [6]. Patients who develop antibodies to IFX have been shown to have a 2-fold risk of acute infusion reactions and a 6-fold risk of serious acute infusion reactions [7]. In the two pivotal trials, Programme evaluating the Autoimmune disease in NESTIGATIONAL drug cT-p13 in rheumatoid arthritis (RA) patients (PLANETRA) and Programme evaluating the Autoimmune disease in NESTIGATIONAL drug cT-p13 in ankylosing spondylitis (AS) patients (PLANETAS), comparing CT-P13 with the reference IFX in patients with

rheumatoid arthritis and ankylosing spondylitis, rates of infusion reactions were 6.6% and 8.3% of rheumatoid arthritis patients and 3.9% and 4.9% of patients with ankylosing spondylitis for the IFX biosimilar, CT-P13 and for the originator IFX [8,9]. Despite these conclusive safety data, immunogenicity of monoclonal antibodies is a major safety concern for the biosimilars. The study published by Ben-Horin et al. in 2015 examined the presence of cross-immunogenicity of IFX biosimilar CT-P13 with the originator drug. Their findings indicated that antibodies to originator IFX developed during the previous exposure to the drug were also cross-reactive with the biosimilar IFX [10]. These data suggest a similar immunogenicity and shared immunodominant epitopes on these two IFX agents.

According to the current central regulation, in Hungary, IFX biosimilar has to be used in every new patient and is allowed to be introduced in patients who previously responded to the reference drug and at least one year elapsed after stopping the originator IFX. Therefore, data on frequency and predictors of infusion reactions developed during the administration of CT-P13 from the clinical practice would be very important when assessing the start of IFX biosimilar. This study **aimed** to assess the frequency, characteristics and predictors of infusion reactions during CT-P13 therapy.

## 2. Patients and methods

### 2.1. Patient population

This was a prospective, observational, multicenter study carried out in 13 Hungarian and 1 Czech IBD tertiary centers between June 2014 and September 2015. Consecutive IBD patients treated with CT-P13 IFX biosimilar were prospectively enrolled in the study (Inflixtra®, Hospira was used in Hungary, Remsima®, Celltrion was used in the Czech Republic). Eligible patients were older than 18 years and were diagnosed with CD or UC defined by the European Crohn's and Colitis Organisation (ECCO) Consensus Report [11,12]. None of the enrolled patients received originator IFX within 12 months before initiation of CT-P13. Clinical data were collected according to a predefined monitoring strategy. CT-P13 5 mg/kg was given as an intravenous infusion at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks except for one Czech patient receiving 10 mg/kg induction dose for acute, severe disease. Demographic data including history of previous anti-TNF-alpha administration and concomitant medications were collected. Clinical data were recorded, disease activity was evaluated by activity scores and blood samples were collected for the measurement of serum inflammatory parameters (namely, C-reactive protein, leukocyte, hematocrit, thrombocyte, albumin), CT-P13 and anti-drug antibody (ADA) levels during the visits. Clinical response was estimated at fixed appointments throughout the treatment period: at week 2, 4, 6, 14 and then at every 8 weeks.

CT-P13 trough levels and presence of ADA were assessed by ELISA (LISA TRACKER, Theradiag, France in Hungary and SHIKARI Q-Inflixix, Q-ATI, Matriks Biotek, Turkey in the Czech Republic) at baseline, at weeks 14, 30, and 54 right before anti-TNF administration.

The detection cut-off value of CT-P13 trough level was 0.1 µg/ml, while 3–7 µg/ml was defined as therapeutic. The

standard cut-off value of ADA level was 10 ng/ml. ADA positivity was defined above the cut-off value of ADA level. ADA formation was defined as positive when a patient tested positive for antibody during follow-up on more than two consecutive time points. Association between infusion reactions, demographic and clinical characteristics of patients such as age, gender, smoking habits, type of IBD, extent of disease, perianal involvement, disease activity, previous anti-TNF-alpha, previous and concomitant azathioprine/5-aminosalicylates (5-ASA)/corticosteroid use, and ADA positivity were statistically analyzed. Therapy (reduction of the infusion rate, or administration of iv. antihistamine and/or iv. steroid) and outcomes of infusion reactions were prospectively evaluated.

### 2.2. Statistics

Data were analyzed with the use of SPSS 20.0 software. Descriptive statistics were used to characterize patients' demographics and infusion reactions. ADA positivity rates were compared between IFX-exposed and naive patients by Chi<sup>2</sup> test or Fisher's Exact test.  $p < 0.05$  was considered statistically significant.

## 3. Results

### 3.1. Patient population

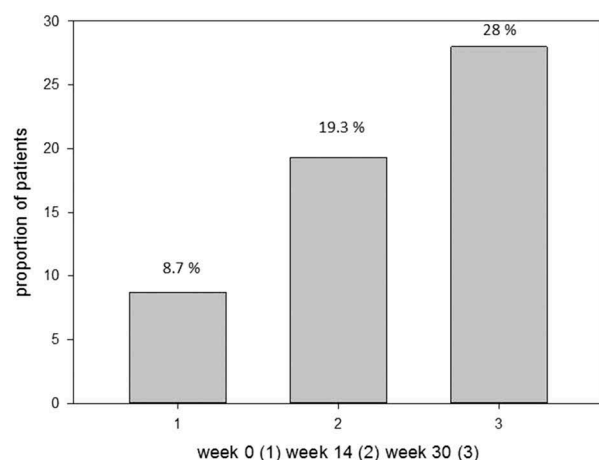
Three hundred and eighty-four consecutive IBD patients (253 CD patients and 131 UC patients; 291 Hungarian, 93 Czech) were included in the present cohort. Forty-five CD patients and 15 UC patients had received previous anti-TNF-alpha therapy in the Hungarian cohort, and none of the patients in the Czech IBD population. 2.7% of CD and 4.6% of UC patients received originator IFX and adalimumab treatment and 21.8% of CD and 9.4% of UC patients received only originator IFX prior CT-P13 therapy. Concomitant azathioprine therapy was administered in 146 CD and 62 UC patients at inclusion (Table 1). Mean CT-P13 trough levels were 20.1, 14.7, and 5 µg/ml at weeks 2, 6, and 14 ( $n = 124, 86$  and 174). ADA measurements were available in 229, 192, and 143 IBD patients at baseline and at 14, 30 weeks. Cumulative ADA positivity rates were 8.7%, 19.3%, and 28.0% in patients at weeks 0, 14, and 30 (Figure 1).

### 3.2. Infusion reactions

Twenty-eight patients (9.6%, 18 CD, 10 UC) developed infusion reaction during the induction and maintenance treatment. Infusion reactions occurred most frequently during the 2nd and 3rd infusion. The most common symptoms of infusion reactions were flushing in 39.3%, dyspnea and chest pain in 25% and 14.3%, coughing in 17.8%, palpitation and tachycardia in 10.7%, swelling of the throat in 10.7% and headache in 7.1%. All of the infusion reactions were mild to moderate. They could be controlled by the reduction of the rate of infusion, or administration of iv. antihistamine or iv. steroid. None of the patients with infusion reaction required to be admitted to intensive care unit. Clinical data of patients who developed infusion reaction are summarized in Table 2. Notably, no significant difference was observed in disease location and

**Table 1.** Demographic and clinical data of the Hungarian and Czech IBD patients enrolled in the study.

	Hungarian cohort		Czech cohort		Total	
	CD	UC	CD	UC	CD	UC
Patient number	184	107	69	24	253	131
Mean age at diagnosis (years)	23	28	28.3	29.8	25.5	28.9
Previous anti-TNF-alpha therapy (No.)	45	15	0	0	45	15
Concomitant azathioprine therapy (No.)	111	55	35	7	146	62
Ileal location (No.)	31	0	14	0	45	0
Colonic location (No.)	60	0	16	0	76	0
Ileocolonic location (No.)	90	0	28	0	118	0
Upper GI location (No.)	3	0	11	0	14	0
Stricturing/penetrating behavior (No.)	76	0	36	0	112	0
Perianal disease (No.)	64	0	21	0	85	0
Previous surgery (No.)	41	0	21	0	62	0
Proctitis (No.)	0	9	0	1	0	10
Left-sided UC (No.)	0	35	0	9	0	44
Extensive colitis (No.)	0	63	0	14	0	77
Patients with ADA positivity	21	19	3	0	24	19

**Figure 1.** Cumulative ADA positivity rates in enrolled patients at week 0, 14 and 30**Figure 1.** Cumulative ADA positivity rates in enrolled patients (8.7%, 19.3% and 28%;  $n = 229, 192$  and  $143$ ) at weeks 0, 14, and 30.

behavior between patient groups with and without developing infusion reactions.

In CD patients with infusion reaction, prior to biological therapy with CT-P13 therapy, 15 patients received 5-ASA, 14 corticosteroid and 9 patients immunomodulator therapy ever during the disease course. Thirteen CD patients with infusion reaction received previous anti-TNF-alpha treatment; every patient was treated with originator IFX. Regarding UC patients who developed infusion reaction, prior to CT-P13 therapy 8 patients was treated with 5-ASA, 7 with corticosteroid and 5 with immunomodulator therapy during their whole disease course. Five UC patients with infusion reaction were previously treated anti-TNF-alpha drug; three of them with originator IFX, and 2 patients with adalimumab. Overall, infusion reactions occurred in 10 of 231 anti-TNF-alpha naive patients (4.3%). ADA positivity was detected in 10 CD and 4 UC patients (8 CD and 3 UC patients were previously treated with anti-TNF-alpha therapy) of 28 patients who developed infusion reaction (Figure 2). Concomitant corticosteroid and azathioprine were given for 7 and 9 CD and for 3 and 5 UC patients developing infusion reaction during the CT-P13 therapy, respectively. Dose escalation of CT-P13 from 5 mg/bwkg to 10 mg /bwkg

was necessary in two patients (one CD, one UC) with infusion reaction during maintenance therapy.

CT-P13 therapy had to be stopped in 17 patients and was switched to adalimumab in 12 patients. However, in 11 (39.3%) patients, CT-P13 therapy was continued with the use of premedication (reduction of the rate of infusion, or administration of iv. antihistamine or iv. steroid). Four patients who continued CT-P13 therapy with the use of premedication presented ADA positivity.

Infusion reactions did not occur in the Czech population; moreover rate of infusion reaction was significantly higher in anti-TNF- $\alpha$  naïve Hungarian patient than in anti-TNF- $\alpha$  naïve Czech patients ( $p = 0.032$ ). Previous anti-TNF-alpha exposure (30% vs. 3.1%,  $p < 0.001$ , OR 6.3 (2.7–14.6)) and ADA positivity (32.6% vs. 4.1%,  $p < 0.001$ , OR 19 [5–73]) during the induction therapy were predictive to the development of infusion reactions (Figures 3 and 4). No association was shown between infusion reaction and gender, smoking status, type of disease, extent/location, perianal involvement, disease activity, concomitant or previous 5-ASA/steroids, and azathioprine therapy.

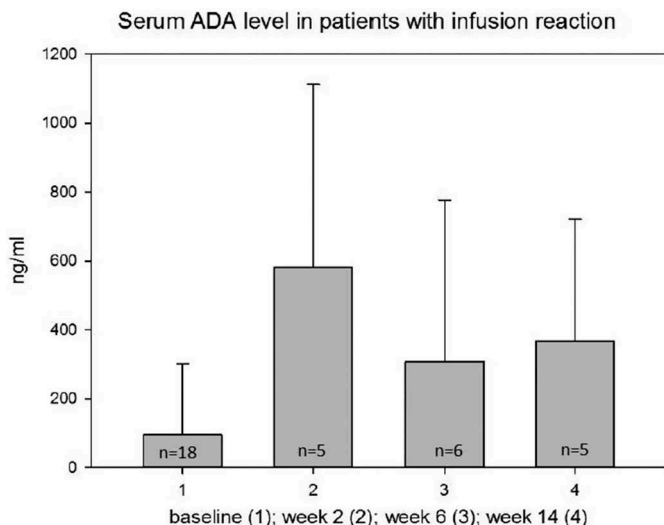
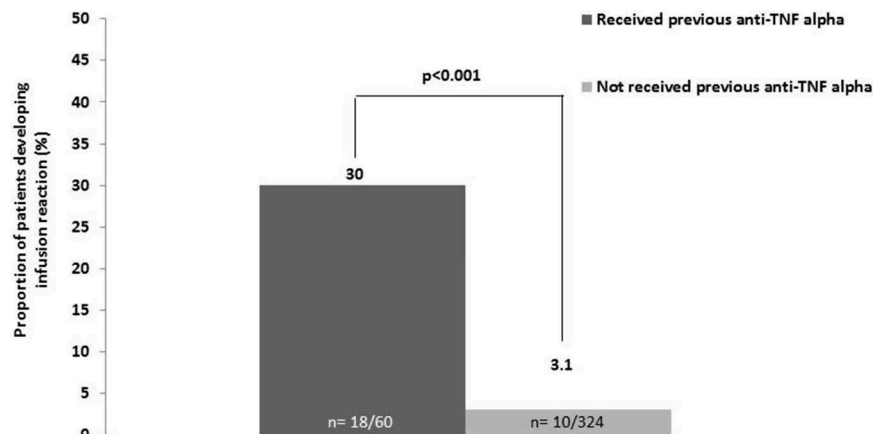
#### 4. Discussion

This multicenter, prospective study examined the rate, the characteristics, and the predictors of infusion reactions developed in CT-P13-treated Hungarian and Czech IBD patients. Infusion reactions occurred in 7.3% of all the enrolled patients. 35.7% of patients developing infusion reaction were anti-TNF naïve. Frequency rate of infusion reactions proved to be 9.6% of the Hungarian patients – in 64.3% of CD and 35.7% of UC patients. Anti-CT-P13 antibody was proved in 32.6% of patients with infusion reaction and 4.1% of subjects without any reaction during treatment. Infusion reactions occurred most frequently during the 2nd and 3rd infusions. The most common symptoms of infusion reactions included flushing, dyspnea, and chest discomfort. CT-P13 therapy had to be stopped in the majority of the patients after the development of an infusion reaction and switch to adalimumab was carried out in 43% of them. CT-P13 therapy was continued with the use of simple or combined premedication including reduction of the infusion rate or use of antihistamine or steroid in almost 40% of the patients.

Infusion reactions are one of the most common limiting factors of IFX therapy. Several possible mechanisms may be in

**Table 2.** Characteristics of patients developing infusion reaction.

	CD with infusion reaction (n = 18)	UC with infusion reaction (n = 10)
Gender (male/female)	6/12	5/5
Mean age at diagnosis (years)	22	27
Mean disease duration (years)	7	5
Previous therapy		
1. 5-ASA	15	8
2. Corticosteroid	14	7
3. Azathioprine	9	5
4. Anti-TNF-alpha	13	5
Concomitant therapy at the time of infusion reaction		
1. Corticosteroid	7	3
2. Azathioprine	9	5
3. ADA positivity	10	4
Mean value of ADA titer at infusion reaction (ng/ml)	655	743
Number of infusions at infusion reaction		
4. 2nd infusion	11	6
5. 3rd infusion	4	3
6. 4th infusion	2	1
7. 5th infusion	1	

**Figure 2.** Serum ADA level distribution in patients with infusion reaction at weeks 0, 2, 6 and 14.**Figure 3.** Proportion of patients developing infusion reaction regarding previous anti-TNF-alpha use.

the background of infusion reactions including cytokine release (immune cell hyperactivation, direct apoptosis, complement-mediated lysis, antibody-dependent cellular toxicity), IgE-mediated hypersensitivity reactions to IFX, IgG anaphylaxis, complement activation, or direct mast cell degranulation [13–15]. The most frequent symptoms of infusion reaction are pruritus, flushing, dyspnea, chest discomfort, hypertension, myalgia, nausea, urticaria, headache, rash, and dizziness [16]. Although there is no specific guideline for the treatment of IFX-related infusion reactions, according to therapeutic recommendations based on case reports and expert opinions, temporary attenuation of the infusion rate or temporary interruption of the infusion with the administration of medications for symptom control are usually eligible. Coadministration of immunomodulator or premedication with steroids and/or antihistamines is the most common interventions in the prevention of infusion reactions [6]. However, only a smaller proportion of patients may continue treatment with these premedications – in our study, almost 40% of the patients could maintain CT-P13 treatment with supplementary intervention and premedication.

Frequency rate of infusion reactions in CD patients seems to be different when comparing to the large randomized clinical trials conducted in CD patients receiving the originator IFX. The incidence of infusion reactions was 16% and 21% in ACCENT I and II studies, respectively [17,18]. The lowest incidence of infusion reactions occurred among patients receiving both steroids and immunosuppressives (8%) [17]. In our cohort, 9.8% of the CD patients developed infusion reaction, which is lower than that of the ACCENT trials. In ACT 1 and 2 infusion reactions occurred in 9.9% and 11.6% of UC patients receiving 5 mg of IFX [19]. These results are highly similar to our data where infusion reactions occurred in 9.3% of the UC patients. In ACT 1, 35.7% of patients with antibody positivity against IFX developed infusion reaction at week 54 [19].

Although the increasing data about the efficacy of IFX biosimilar confirmed that CT-P13 may be considered equivalent to its reference drug in IBD in practice, collection of immunogenicity data and immunological reactions in clinical practice is important to compare the safety profile of the biosimilar and the reference product especially if we only consider the 'Eprex

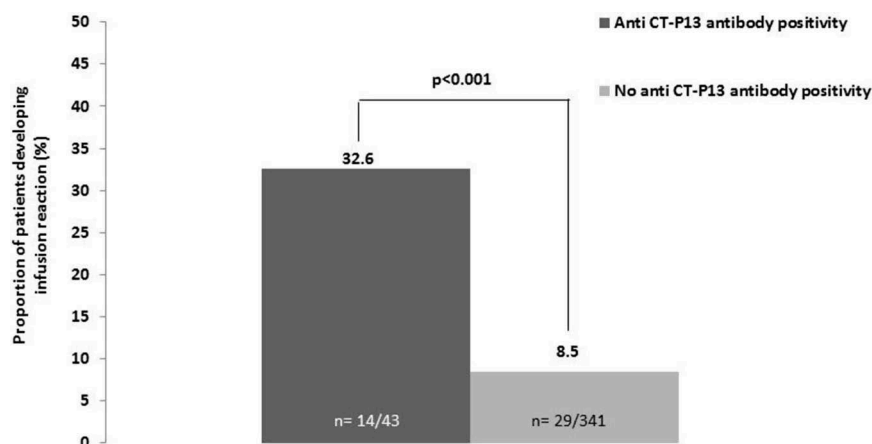


Figure 4. Proportion of patients developing infusion reaction regarding anti CT-P13, an IFX biosimilar antibody.

case,' when after a change in the formulation of epoetin-alfa, patients developed antibodies against both the administered epoetin and the endogenous erythropoietin, resulting in severe pure red cell aplasia [20]. However, no relevant differences were noted in the immunogenicity profiles of CT-P13 and reference IFX in the PLANETRA and PLATENAS studies from rheumatology [8,9]. In the Korean study by Kang et al., no serious adverse reaction occurred during CT-P13 therapy [3]. Yung et al. experienced adverse events in 6 UC patients (11.8%) including allergic (skin rash, scaling of palm) and infusion reaction in half of these patients [2].

In the Norwegian prospective study, one CD and one UC patients developed infusion reaction [1]. The UC patient with infusion reaction occurring at the second infusion was shown to have undetectable trough serum levels of CT-P13 and ADA positivity at week six. This patient had previously been treated with IFX in two periods [1]. None of these studies were powered enough to obtain predictive factors for infusion reactions. Infusion reaction did not occur in the Czech population, using Remsima. In September 2013, the EMA issued the marketing authorization of a biosimilar of Remicade, CT-P13, to 2 applicants, Celltrion Inc. (Incheon, South Korea) and Hospira Inc. (Lake Forest, IL) under the trade names Remsima and Inflectra [21,22]. However, Remsima and Inflectra can be considered as one product since they are both manufactured by Celltrion. Although considered to have no clinical impact, differences in impurities and break down products of the biosimilars can affect immunogenicity. According to the recent study by Gils et al., monoclonal antibodies raised against the originator product Remicade revealed a highly similar reactivity toward the biosimilars Remsima and Inflectra and with similar  $K_D$  values for both antibodies toward the different infliximab molecules [23]. In the present study, LISA TRACKER (Theradiag, France) and Matriks Biotek (Turkey) were used to measure IFX biosimilar trough level and ADA concentration. However, according to a recent Czech study, SHIKARI Q-Inflix (Matriks Biotek, Turkey), LISATracker Duo Infliximab (Theradiag, France), and RIDASCREEN IFX (R-Biopharm, Germany) assays were in perfect agreement in qualitative and quantitative results for the majority of the samples.

These observations suggested that substitution between the assay methods evaluated in the study is possible [24].

Our results showed that previous anti-TNF- $\alpha$  exposure and presence of antidrug antibody proved to predict the development of infusion reaction. Contrary to the Hungarian cohort, Czech population involved only anti-TNF- $\alpha$  naïve IBD patients. Considering these data, the absence of previous anti-TNF- $\alpha$  exposure and ADA positivity may be the reason for the lack of infusion reaction in the Czech cohort. However, this study has no power to assess differences regarding to immunogenicity between Inflectra and Remsima.

In conclusion, this large, multicenter study was the first that evaluated the immunogenicity profile of CT-P13 in IBD in the clinical practice, characterized infusion reactions in this population and revealed predictors for infusion reaction. Our results suppose a lower immunogenicity of the biosimilar in CD and similar rates and characteristics of infusion reaction with the originator. These data should be confirmed by other large studies with the consideration of potential differences in the characteristics of the patient population and the disease phenotype.

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## Declaration of interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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