Experimed 2022; 12(3): 160-7

ORIGINAL ARTICLE

DOI: 10.26650/experimed.1183920

Evaluating the Long-Term Outcomes of Medical and Surgical Treatments in Fibrostenotic Crohn's Disease Patients Treated with Anti-TNF/Biologic Therapy

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Cite this article as: Ak C, Sayar S, Kahraman R, Ozdil K. Evaluating the long-term outcomes of medical and surgical treatments in fibrostenotic Crohn's disease patients treated with anti-TNF/biologic therapy. Experimed 2022; 12(3): 160-7.

ABSTRACT

Objective: This study analyzed the follow-up findings on hospitalization requirements and clinical activities for fibrostenotic Crohn's disease (CD) patients who received biological/anti-TNF treatment without undergoing surgery as well as CD patients who were treated medically and surgically.

Materials and Methods: This study compared the Harvey-Bradshaw scores, control colonoscopy results, and hospitalization times regarding the long-term follow-ups for fibrostenotic CD patients who've undergone surgery and for those who only received medical treatment. In addition, the study analyzed the factors associated with disease activation.

Results: The study was consisted of 117 patients receiving anti-TNF therapy. Patients who underwent surgery for stenotic CD had a lower one year Harvey-Bradshaw score and shorter hospitalization regarding their long-term follow-up compared to those who did not undergo surgery. Patients who underwent surgery had a lower albumin level ($p < 0.001$) and developed perianal CD ($p = 0.046$) less than those who had not undergone surgery. C-reactive protein elevation ($p = 0.024$) and smoking ($p < 0.001$) have been associated with disease activity, and the absence of granuloma ($p = 0.003$) and neural plexitis ($p = 0.006$) on the surgical specimen was found to be associated with disease activation.

Conclusion: Surgical treatment is seen to improve the quality of life and result in fewer hospitalizations for fibrostenotic CD patients. Also, hypoalbuminemia may be a marker indicating a surgical decision.

Keywords: Crohn's disease, anti-TNF therapy, surgical therapy, disease activation

INTRODUCTION

Crohn's disease (CD) is a highly heterogeneous inflammatory bowel disease with different disease phenotypes, including perianal disease, fistulas, and strictures (1). CD is a chronic recurrent disease characterized by a decrease in the quality of life as a result of symptoms and a global health problem posing a significant financial burden for both patients and healthcare systems (2). One of CD's common complications is intestinal strictures, which occur in one-third of patients within 10 years. CD strictures are classified as inflammatory, fibrotic, or mixed, but all symptomatic inflammatory strictures have some components of fibrosis (3). Many challenges still remain regarding treatment selection and management for patients with fibrostenotic CD. Medical therapy for inflammatory strictures is considered as the first-line therapy, with anti-TNF agents being one of the most important therapeutic agents used for this purpose. However, medical treatment is ineffective against strictures with a fibrotic component, with some

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Submitted: 05.10.2022 **Revision Requested:** 31.10.2022 **Last Revision Received:** 30.11.2022 **Accepted:** 02.12.2022 **Published Online:** 29.12.2022

further studies suggesting anti-TNF agents to possibly increase the development of stenosis. A high proportion of patients on anti-TNF therapy will require surgery. In addition, although radiological imaging methods (magnetic resonance enterography (MRE), computed tomography enterography, ultrasonography and inflammatory indicators (C-reactive protein (CRP) and fecal calprotectin) can be useful in detecting the presence of the inflammatory component, these examination methods have limitations and low specificity. Therefore, predicting the success of a patient's response to medical therapy can be difficult. Meanwhile, the literature data on which medical and surgical treatment options might be more beneficial in terms of the effects of the natural course of the disease and its clinical outcomes are also unclear (4, 5). This study aimed to analyze and compare the follow-up findings in terms of hospitalization requirements, clinical activities, and laboratory findings for fibrostenotic CD patients who've received biological treatment as a medical treatment without undergoing surgery compared to patients who received medicine in addition to surgical therapy. In addition, the study analyzed the factors associated with disease activation in patients who were followed up with the biological/anti-TNF therapy in their long-term follow-up.

MATERIALS AND METHODS

The study involved 542 CD patients who visited the University of Health Sciences Gastroenterology Clinic of the Umraniye Training and Research Hospital between January 2010-June 2021. This study analyzed the patients who'd been diagnosed with CD based on clinical, laboratory, radiological, endoscopic, and histopathological findings and were followed up both through electronic files and the inflammatory bowel disease (IBD) outpatient clinic file. The study retrospectively recorded the data (clinical, laboratory, radiological, endoscopic data, operation epicrisis, hospitalization data) gathered during the diagnosis and follow-up of 64 patients with fibrostenotic CD who were monitored regularly at least twice a year and of 117 patients undergoing anti-TNF therapy. Figure 1 shows the inclusion and exclusion criteria of patients.

The study has also recorded the patients' demographic characteristics, age at disease onset, disease involvement (according to the Montreal classification), duration of biological treatment and medication (e.g., adalimumab, infliximab, vedolizumab), drug switching, and use of immunomodulatory drugs (azathioprine). MRE was used to measure stenosis in cm. The termination and onset of anti-TNF therapy were recorded for patients who'd developed ileocecal valve resection due to stenosis. The study also made use of the records pertained to the postoperative follow-up period; the Harvey Bradshaw scores before the operation and for the third, sixth, ninth, and twelfth months after the operation; and the Rutgeerts score at the 12th-month control colonoscopy for patients who'd undergone surgery. Records were also used regarding the initial, third, sixth, ninth, and twelfth month Harvey Bradshaw scores as well as the simple endoscopic score for Crohn's disease (SES-CD) during the 12th-month control colonoscopy for the

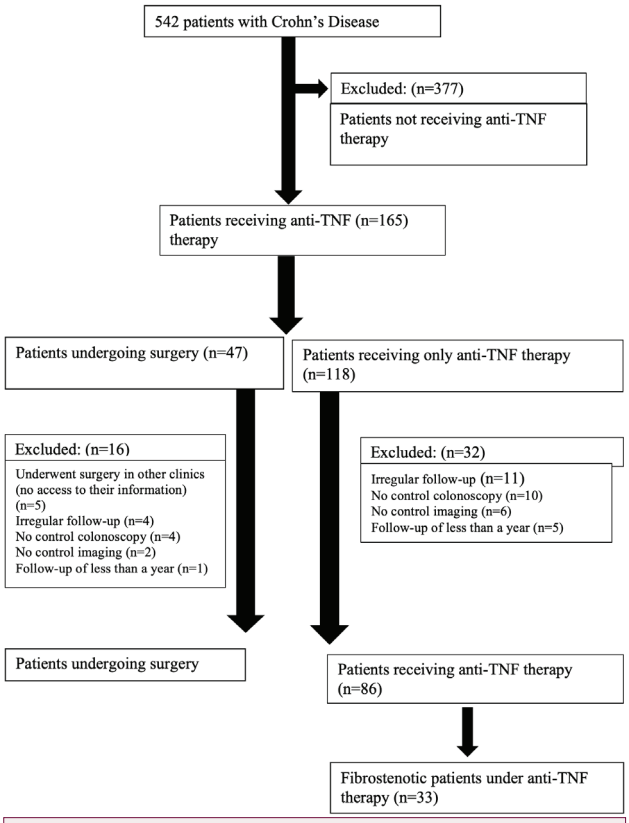

Figure 1. Inclusion and exclusion criteria of patients.

patients who were followed up with medical therapy. Albumin, sedimentation, CRP levels, tobacco use status, perianal CD, fistulas, abscess development, and the number and length of hospitalizations during long-term follow-up (after the onset of anti-TNF therapy) were recorded for all patients upon starting anti-TNF therapy. A Rutgeerts score of < 2 and an SES-CD score of < 6 in the control colonoscopy indicates endoscopic remission. Non-operated patients who were hospitalized for stenosis at least once and whose stenosis was documented through control imaging and/or endoscopically were defined as stenotic non-operated patients. Non-operated and non-stenotic patients receiving anti-TNF therapy were defined as non-operated non-stenotic patients. Perianal CD, abscesses, fistula development, and/or stenosis detection endoscopically during the long-term follow-up after the treatment or operation were considered as indicators of disease activation. The Harvey Bradshaw scores and length of hospitalization stays in the long-term follow-up were compared in terms of the patients who'd been operated on for fibrostenotic stenosis and the patients who were only followed up through medical treatment. In addition, the study has analyzed the associations with disease activation in the long-term follow-up for all patients receiving biologic and anti-TNF therapy.

Statistical Analyses

This study accepted statistical significance level as $p < 0.05$ and used the program SPSS (ver. 25) to perform the analysis and the

Kolmogorov-Smirnov test for normality testing. The study used means and standard deviations for the normally distributed data, while medians and interquartile range methods (IQR) were used for the non-normally distributed data. The study analyzed the normally distributed data using the independent t-test and the non-normally distributed data using the Mann-Whitney U test. The chi-square test has been used for evaluating the categorical data.

RESULTS

The patients (n = 542) had a mean age of 41.4 ± 11.4 years, and more than half the patients were men (56.4%). Table 1 shows the patients' general characteristics, treatments, complication rates, tobacco use status, and laboratory findings during the follow-up. Of the patients, 31 underwent ileocecal resection (26.5%), two of whom underwent surgery again due to having developed stenosis during the long-term follow-up (6.5%). Of all the patients, 33 were non-operated stenotic patients (28.2%). Table 2 shows these patients' general characteristics, treatments, clinical and endoscopic scores, and complication rates during the long-term follow-up. Patients were monitored for an average of 69.1 ± 37.4 months in total. Table 3 shows the analysis of the activity-related factors during the long-term follow-up.

DISCUSSION

Fibrostenotic CD is a prevalent and compelling clinical phenomenon. A considerable number of patients may require surgical intervention due to medical treatment being unlikely to reverse intestinal damage and fibrosis. Surgical treatment due to the absence of anti-fibrotic therapy depends on the location and length of the disease, concomitant complications, and patient preference (6). Although anti-TNF therapy has been proven effective in inducing and maintaining successful treatment of moderate-to-severe active CD patients, long-term bowel resection is inevitable in most patients (7). CD patients have a cumulative surgical risk of 16.3% in the first, 33.3% in the fifth, and 46.6% in the tenth year (8). Riss et al. (9) also reported an 8.6% recurrence rate for required surgery after an average follow-up of more than eight years. The current study has found 31 patients (26.5%) to have undergone surgery and two (6.5%) to have undergone a second surgery due to relapse. These rates were slightly lower when compared with the other study, possibly due to the fact that all patients who underwent surgery had also undergone anti-TNF therapy.

Research has also revealed postoperative treatment with an anti-TNF agent to decrease the risk of both clinical and endoscopic recurrence (10-12). Schwartz et al. (13) found the risk of perianal CD to be 55% at a median of 4.8 years post-diagnosis. Fistulizing CD is likely to develop in 35% of patients, 46% of which are non-perianal (14). The rate of perianal CD decreases with the increased use of thiopurine and anti-TNF therapy (15). The present study found the perianal CD and non-perianal fistulizing CD rates to respectively be 24.8% and 18.8% during the long-term follow-up under anti-TNF therapy with and without thiopurine treatment. These lower rates of perianal CD and fistulizing CD compared to previous studies may possibly be related to the fact that all patients had received the anti-TNF therapy, either with or without the thiopurine treatment. The European Crohn's and Colitis Organization

Table 1. General characteristics, treatments, complication rates, tobacco use status, and laboratory findings during follow-up.

Parameters	
Age (year)	41.4±11.4
Female	51 (43.6%)
Male	66 (56.4%)
Disease type L1/ L2/ L3	37 (31.6%) / 9 (7.7%) / 71 (60.7%)
Operated stenotic patients	31 (26.5%)
Non-operated stenotic patients	33 (28.2%)
Non-operated non-stenotic patients	53 (45.3%)
Follow-up time (month)	69.1±37.4
Treatment	
Infliximab	60 (51.3%)
Adalimumab	52 (44.4%)
Vedolizumab	5 (4.3%)
Azathioprine	79 (67.5%)
Drug switching	12 (10.3%)
Activation	36 (30.8%)
Fistula	22 (18.8%)
Enterocutaneous	14 (63.6%)
Enteroenteric	5 (22.7%)
Enterovesican	2 (9.1%)
Enterovaginal	1 (4.5%)
Perianal Disease	29 (24.8%)
Abscess	14 (12.0%)
Smoking	22 (18.8%)
Albumin (g/dL)	3.66±0.44
ESR (mm /hour)	26.74±11.55
CRP (mg/dL)	3.10±2.54

L1: Ileal, L2: Colonic, L3: Ileocolonic, ESR: Erythrocyte Sedimentation Rate, CRP: C-reactive protein. Otherwise not mentioned, the values indicate (mean±SD) of the groups or number of individuals (percentages) in mentioned groups.

Table 2. Operated and non-operated stenotic patients' general characteristics, treatments, clinical and endoscopic scores, and complication rates during the long-term follow-up.

Parameters	Operated Patients (n=31)	Non-Operated Stenotic Patients (n=33)	p
Age (year)	42.3 ± 12.4	39.8 ± 10.7	0.390*
Female	11 (35.5%)	12 (36.4%)	0.942†
Male	20 (64.5%)	21 (63.6%)	
Disease type			
L1	13 (41.9%)	12 (36.4%)	0.900†
L2	0 (0.0%)	1 (1.6%)	
L3	18 (58.1%)	20 (59.4%)	
Diagnosis Time (month)	86 (Median) 69 (IQR)	52 (Median) 26 (IQR)	**0.017**‡
Medicated follow-up period (month)	50.1 ± 24.3	50.8 ± 27.4	0.902*
Preoperative medication (month)	20.2 ± 9.2		
Number of patients hospitalized	5 (16.1%)	17 (51.5%)	**0.011**†
Hospital (day)	8.40 ± 6.77	7.65 ± 6.74	0.829*
Medication			
Infliximab	15 (48.4%)	16 (48.5%)	-
Adalimumab	16 (51.6%)	16 (48.5%)	-
Vedolizumab	0 (%0)	1 (%3)	-
Azathioprine	17 (54.8%)	23 (69.7%)	0.343†
Drug switching	6 (19.4%)	3 (9.1%)	0.317†
Activity	8 (25.8%)	14 (42.4%)	0.201†
Fistula	7 (22.6%)	8 (24.2%)	0.796†
Perianal Disease	4 (12.9%)	12 (36.4%)	**0.046**†
Abscess	5 (16.1%)	7 (21.2%)	0.546†
Smoking	6 (19.4%)	9 (27.3%)	0.439†
Endoscopic Remission	26 (83.9%)	21 (63.6%)	0.466†
	Median(IQR)	**Median(IQR)**	
Harvey Bradshaw (month 0)	9 (3)	10 (2)	0.176‡
Harvey Bradshaw (month 3)	7 (3)	9 (2)	**0.013**‡
Harvey Bradshaw (month 6)	4 (3)	7 (3)	**0.000**‡
Harvey Bradshaw (month 9)	4 (1)	6 (2)	**0.000**‡
Harvey Bradshaw (month 12)	3 (2)	5 (3)	**0.000**‡
Stenosis length (cm)	11 (4)	8 (4)	**0.011**‡
Albumin (gr/dL)	3.3 (0.6)	3.8 (0.3)	**0.000**‡
ESR (mm /hour)	31.2 ± 9.7	30.6 ± 12.5	0.826*
CRP (mg/dL)	4.1 (4)	3.1 (2.9)	0.350‡

*: Independent t test., †: Chi-Square test, ‡: Man-Whitney U test, L1: Ileal, L2: Colonic, L3: Ileocolonic, ESR: Erythrocyte Sedimentation Rate, CRP: C-reactive protein. Otherwise not mentioned, the values indicate (mean ± SD) of the groups or number of individuals (percentages) in mentioned groups.

Table 3. Analysis of activity-related factors during the long-term follow-up.

Parameters	**Activated (*n* = 36) (30.8%)**	**Non-Activated (*n* = 81) (69.2%)**	***p***
Age (year)	39.5 ± 9.7	42.23 ± 12.1	0.237*
Gender			
Female	11 (30.6)	40 (49.4)	0.058†
Male	25 (69.4)	41 (50.6)	
Disease type			
L1	13 (36.1%)	24 (29.6%)	0.437†
L2	4 (11.1%)	5 (6.2%)	
L3	19 (52.8%)	52 (64.2%)	
	Median (IQR)	Median (IQR)	
Disease age (month)	56 - 63	53 – 59	0.571‡
Operated stenotic patients	8 (22.2%)	23 (28.4%)	0.231†
Non-operated stenotic patients	14 (38.9%)	19 (23.5%)	
Non-operated non-stenotic patients	14 (38.9%)	39 (48.1%)	
Medication			
Infliximab	18 (29.0%)	44 (71.0%)	0.666†
Adalimumab	18 (32.7%)	37 (67.3%)	
Azathiopirine	23 (63.9%)	56 (69.1%)	0.576†
Albumin (g/dL)	3.7 – 0.7 (IQR)	3.8 – 0.3 (IQR)	0.202‡
ESR (mm/hour)	28.0 ± 12.4	26.2 ± 11.2	0.425*
CRP (mg/dL)	3.7 – 3.5 (IQR)	2.2 – 2.2 (IQR)	**0.024**‡
Smoking	16 (44.4%)	6 (7.4%)	**0.000**†
Stenosis length (cm)	12.6 ± 4.1	9.0 ± 3.3	0.000*
Operated patients	***n* = 8 (25.8%)**	***n* = 23 (74.2%)**	
No granuloma	3 (15.8%)	16 (84.2%)	**0.003**†
No neural plexitis	6 (23.1%)	20 (76.9%)	**0.006**†
Medication termination day	19.7 ± 9.1	28.0 ± 19.8	0.335*
Medication onset day	80 ± 76.3	51.2 ± 25.8	0.327*

*: Independent t test, †: Chi-Square test, ‡: Mann-Whitney U test, L1: Ileitis CD, L2: Colonic CD, L3: Ileocolonic CD, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein. Otherwise not mentioned, the values indicate (mean ± SD) of the groups or number of individuals (percentages) in mentioned groups.

(ECCO) suggested that researchers perform studies comparing infliximab and surgery rates and stated, "Surgery is a sensible alternative for patients with disease refractory to conventional medical treatment and should also be discussed" (16). The present study observed the operated and non-operated patients who'd received stenotic anti-TNF therapy to have similar baseline clinical and demographic characteristics and Harvey Bradshaw scores. The operated patients had statistically lower Harvey Bradshaw scores compared to the non-operated patients during the one-year follow-up at three-month

intervals. In addition, only 16% of the operated patients had hospitalizations due to stenosis compared to 51.5% of the non-operated stenotic patients during the long-term follow-up ($p = 0.011$). In the 12th month, 83.9% of the operated patients were in endoscopic remission compared to 63.6% of the non-operated patients with strictures, but the difference is not statistically significant ($p = 0.466$). Ponsioen et al. (17) compared laparoscopic ileocaecal resection and infliximab for terminal ileitis in CD and found the early surgical and anti-TNF groups to have similar endoscopic remission rates at one year but the former to have a better general quality of life and lower medical costs than the latter. The current study has found no remarkable difference in sedimentation or CRP values between operated patients and non-operated patients with strictures. However, the operated and non-operated patients with strictures had respective albumin levels of 3.3 gr/dL (IRQ = 0.6) and 3.8 gr/dL (IRQ = 0.3; $p < 0.001$). Zhou et al. (18) found patients with albumin levels under 3.5 g/dL to have a higher rate of penetrating disease and emergency surgery compared to those with albumin levels over 3.5 g/dL. In CD, hypoalbuminemia is correlated with disease activation without no association to malnutrition, and low preoperative albumin is an independent risk factor for postoperative complications (19, 20). However, no data is found regarding the effect of hypoalbuminemia on surgery decisions. Significantly low albumin levels being detected in the operated group suggests that albumin levels may be a marker for decision to perform surgery; however, further studies are still needed on this subject.

No significant difference was found regarding fistula and abscess development in the long-term follow-up with regard to operated and non-operated patients ($p = 0.796$, $p = 0.546$, respectively). Operated patients and non-operated stenotic patients had similar disease involvement according to the Montreal classification, with perianal CD being more common in stenotic patients in the long-term follow-up compared to the non-operated patients ($p = 0.046$). This may be related to the transport of inflammatory cytokine load from the inflamed intestinal segment to the anal region by means of stool transport.

Domenech et al. (21) focused on the clinical outcomes of newly diagnosed CD patients before and after infliximab availability and found infliximab availability to have not reduced the need for surgery. The current study's results revealed fibrostenotic CD patients undergoing anti-TNF therapy to likely need surgery in the natural course of the disease, to have a better quality of life in the postoperative period, and to have experienced less disease-related hospitalization. Research studies have also reported better quality of life and less hospitalization during long-term follow-ups (17, 22).

The present study observed long-term disease activation in 36% of all patients undergoing anti-TNF therapy. Patients with the presence and absence of disease activation are also observed to have similar demographic and clinical characteristics and to have made similar treatment choices. Tobacco use was statistically higher in patients with disease activation ($p < 0.001$). Gracie and Ford's (23) systematic meta-analysis of 33 studies on the adverse effects of tobacco use on CD ($n = 11,000$) reported smokers to have 55%–85% higher rates of flare-up regarding disease activity compared to non-smokers. The present study found patients with disease activation to have higher CRP levels compared to those without disease activation ($p = 0.024$). Nevertheless, no remarkable difference was found regarding erythrocyte sedimentation rates between patients with and without disease activation ($p = 0.425$). Fagan et al. (24) found a correlation for disease activation with both CRP and erythrocyte sedimentation rate (ESR). However, they reported a more robust correlation between disease activation and CRP. Boschetti et al. (25) conducted a study on 86 CD patients who'd undergone ileocolonic resection and found a weak but significant difference in CRP concentrations between patients in endoscopic remission and those in recurrence. Earlier studies have also reported the effect of tobacco use and higher CRP levels on disease activation (24, 25). With regard to fibrostenotic CD, a surgical operation is performed on the refractory medical disease, with the most common procedure being bowel resection. Pathological evaluation of a resected bowel segment may also provide information about disease activation during long-term follow-up (26). Anseline et al. (27) found a significant association between granulomas and recurrence among patients who'd undergone surgery for CD ($n = 130$). Sokol et al. (28) also reported submucosal plexitis to be predictive of clinical recurrence ($n = 171$). The current study's results show the absence of granuloma in the surgical specimen ($p = 0.003$) and plexitis at the surgical margin ($p = 0.006$) to be correlated with no disease activation in the long-term follow-up. The time for termination and restart of anti-TNF therapy was also evaluated in terms of activation in operated patients during the long-term follow-up. Anti-TNF therapy was discontinued earlier for patients who experienced activation compared to those with no activation (19.7 ± 9.1 day vs. 28.0 ± 19.8 day). Anti-TNF therapy was initiated earlier in patients with activation compared to those with no activation (80 ± 76.3 day vs. 51.2 ± 25.8 day). The relationship between the discontinuation of preoperative anti-TNF therapy and postoperative onset time and postoperative disease activation remains unclear. Earlier termination and later initiation of anti-TNF therapy may be correlated with disease activation in long-term follow-up due to the loss of long-term anti-inflammatory pressure.

This study is one that compared the endoscopic and clinical long-term outcomes regarding the surgical and medical treatment of fibrostenotic CD and analyzed the factors related to activation during the long-term follow-up period. The study has two limitations: 1) it was conducted in only one center, and 2) it is a retrospective study.

CONCLUSION

Surgical treatment has been correlated with improved quality of life and fewer hospitalizations for fibrostenotic CD patients. Hypoalbuminemia may be a marker for a decision to perform surgery. Operated patients had no neural plexitis

and granuloma in their pathology specimen, which may be a marker for the lack of activation in long-term follow-up. Tobacco use and high CRP levels may predict disease activation during the long-term follow-up, with further comprehensive studies being needed in this regard.

Ethics Committee Approval: This study procedure was approved by the Istanbul Health Sciences University Umraniye Training and Research Hospital Clinical Research Ethics Committee (B.10.1.TKH.4.34.H.GP.0.01/230).

Peer-review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study - C.A.; Data Acquisition - R.K.; Data Analysis/Interpretation - C.A., R.K.; Supervision - S.S.; Drafting Manuscript - C.A.; Critical Revision of Manuscript - C.A., R.K., K.O.; Final Approval and Accountability – C.A., R.K., S.S., K.O.

Conflicts of Interest: The authors declare no conflict of interest.

Financial Disclosure: The authors declare that this study has received no financial support.

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