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Research Article

Efficacy of Early Adalimumab or Immunomodulator on Postoperative Remission Maintenance in Patients with Crohn's Disease: Randomized study

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ABSTRACT

Background and Aim: This study aim was to clarify the efficacy of early adalimumab (ADA) and azathioprine (AZA) in Postoperative recurrence of Crohn's disease (CD).

Methods: In a 78-week single-center prospective study, patients with bowel resection were randomly assigned to ADA 160-80-40 mg subcutaneously (SC) or AZA 0.5-1.5 mg/kg/day. The primary endpoint was endoscopic remission at 18 months (Rutgeerts i0, i1 and Simple endoscopic score for CD (SES-CD) ≤ 4).

Results: A total of 47 patients (median age 39.0 years, disease duration 9.5 years, 19.1% smokers, 44.6% previous resections) were recruited, 39 patients were received the study drugs. Endoscopic remission was confirmed in 5/16 patients in the AZA group (31.2%) and 7/12 patients in the ADA group (58.3%) (p=0.24) in the intention-to-treat population. In the per-protocol population (19 patients with evaluable images), remission was recorded in 3/9 (33.3%) patients in the AZA and 7/10 (70.0%) in the ADA group (p=0.17). Re-surgery rate was trend to higher in the AZA group (21.1%) than in the ADA group (0%) (p=0.10). Treatment was discontinued due to adverse events in 6 patients (15.3%), severe adverse events were significantly more frequent in the AZA group than in the ADA group (AZA, 25.0% vs ADA, 0%; p=0.04).

Conclusions: Early ADA did not show statistically better efficacy than AZA for postoperative CD recurrence in this study, although safety profile of ADA is better. (UMIN000032485).

Keywords: *Crohn's disease; Endoscopy; Adalimumab (ADA); Azathioprine (AZA)*

INTRODUCTION

Crohn's disease (CD) is known in its various forms as regional enteritis, granulomatous ileitis and colitis. Clinical and endoscopic recurrence are common after CD surgery, and a substantial proportion of patients require multiple surgeries [1]. Despite increasing evidence for CD postoperative outcome and drug therapies, therapy for prevention of postoperative recurrence (POR) remains the subject of debate. Thiopurines and anti-TNF-α agents are more effective than placebo for preventing POR [2]. Direct comparison of efficacy ADA or AZA for POR is not sufficient, and this study was conducted.

MATERIALS AND METHODS

Study design and patients

The Study was 78-week, single-center, prospective randomized study. The study was approved by the Institutional Review Board of the coordinating center (Sakura medical center, Toho university: and confirmed by the local ethics committees) (UMIN000032485). The study period ranged from January 2015 to December 2018. Patients aged 20-70 years with a confirmed diagnosis of CD based on the criteria determined by the Japanese Ministry of Health, Labor and Welfare, and who were candidates for clinically indicated intestinal resection, were approached to obtain their informed consent before surgery. Patients with stoma creation or perianal

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surgery were excluded. The usual contraindications to azathioprine and anti-TNF therapy were also exclusion criteria.

Randomization and procedures

This study randomization was based on a pre-generated block randomization list stratified by Toho university Sakura medical center. Patients were assigned (1:1) to receive AZA or ADA. Allocation was concealed by means of a computer-generated randomization schedule with stratification or block allocation (previous ADA or AZA use). Therapy was initiated at the postoperative hospital discharge, and drugs were administered AZA 0.5 - 1.5 mg/kg/day or ADA 160 mg subcutaneously (SC), then 80 mg SC at Week 2, or 40 mg SC, at Week 4 and every 2 weeks thereafter.

Primary endpoint

The primary endpoint was the rate of remission of CD in the endoscopy performed at Week 78, the evidence based on the Rutgeerts score. The Rutgeerts score was calculated [3] as follows: i0, no lesions; i1, ≤ 5 aphthous lesions; i2>5 aphthous ulcers or larger areas of skip lesions; i3, diffuse aphthous ileitis with diffusely inflamed mucosa; and i4, any combination of large ulcers, nodules, and/or narrowing. Grades i0 and i1 were considered indicative of endoscopic remission. We also calculated endoscopic disease activity: the Simple Endoscopic Score for Crohn's Disease (SES-CD) [4]. Remission defined as SES-CD ≤ 4.

Secondary endpoints

The secondary endpoints included the percentages of clinical remission (Crohn's Disease Activity Index; CDAI ≤ 150) after 78 weeks of therapy, as well as negative titer in activity markers such as fecal calprotectin ≤ 300 mg/g, serum C-reactive protein ≤ 0.3 mg/dl at Weeks 78. Adverse events and surgical requirements were evaluated until Weeks 78.

Statistical analysis

We analyzed the outcome based on the intention-to-treat (ITT) population or the per-protocol (PP) population defined as the following. ITT population, which included all consenting patients who were randomized and received at least one dose included all patients who received at least one dose of the study of the study medications, and the PP population, which included all patients who received at least one dose of the study medications and in whom the primary endpoint was assessed at the end of study. or at premature withdrawal. Patients lost to follow-up were consider -ed the exclusion of outcome analysis.

Analysis was undertaken using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0, Vienna, Austria). We used bivariate analysis to assess differences between study groups. Certain values are presented as the median (interquartile range: IQR) and compared by Wilcoxon-Mann-Whitney test. Categorical variables are represented as number (%) and compared by the Fisher's exact test. p-value of <0.05 was significant difference. Statisticians were not involved in patient care and were blinded to the study groups.

Ethical considerations

This study was approved by the ethics committee of the Toho University Sakura Medical Center. Written informed consent was obtained from all participating patients after explaining the purpose of the study and the nature of the procedures involved. Further, the investigations were conducted with strict adherence to the Helsinki Declaration at all times.

RESULTS

A total 47 patients were entered into the study (Figure1). Eight patients (17.1%) were excluded during screening (five did not fulfill the selection criteria, and three patients were lost to follow-up), leaving 39 eligible patients; 20 patients were randomized to the AZA group and 19 to the ADA group. (ITT population) There were no statistical difference between groups regarding baseline including smoking status, previous resections, CD phenotype, previous perianal disease, and previous drug exposure (Table 1). All 39 eligible patients received at least one dose of the study drug and were included in the analysis (AZA, 20 patients; ADA, 19 patients). A total of 22 patients completed the study (AZA, 9 patients; ADA, 13 patients). There were 11 withdraw in the AZA group (five adverse events, two clinical deteriorations, three protocol violation and one lost to follow-up) and 6 in the ADA group (one pregnancy, two clinical deteriorations and three protocol violation).

Table 1: Baseline characteristics of patients (intention-to-treat population).

	Azathioprine (N=20)	Adalimumab (N=19)	p value
Age, yr. (median, IQR)	36.0 (30.5–45.2)	40.0 (35.7–43.5)	0.38
Female gender, N (%)	2 (10.0)	4 (21.1)	0.40
Duration of disease, yrs.	8.5	15.1	0.09
CD Location, N (%)			
-L1 ileal	7 (35.0)	6 (31.6)	1.00
-L2 colon	1 (5.0)	0 (0)	
-L3 ileum +colon	12 (60.0)	13 (68.4)	
-L4 upper	3 (15.0)	5 (26.3)	0.45
Behavior, N (%)			
-B2	9 (45.0)	7 (36.8)	0.74
-B3	11 (55.0)	12 (63.2)	
-Perianal	13 (65.0)	16 (84.2)	0.27
Previous resection,N (%)	12 (60.0)	9 (47.4)	0.52
Current smoker, N (%)	4 (20.0)	5 (26.3)	0.71
Medication at entry, N (%)			
5 Aminosalicylic acid	17(85.0)	16(84.2)	1.00
-corticosteroid	6 (30.0)	5 (26.3)	1.00
-IM (current)	7 (35.0%)	5 (26.3%)	
(previous use)	2 (10.0)	5 (26.3%)	0.44%
-Anti-TNF- α	15 (75.0)	15 (78.9)	1.00

Abbreviations: IQR: Interquartile Range; CDAI: Crohn's Disease Activity Index; IM: Immunomodulator; anti-TNF-: anti-tumor necrosis factor- agent

Primary endpoint: endoscopic remission

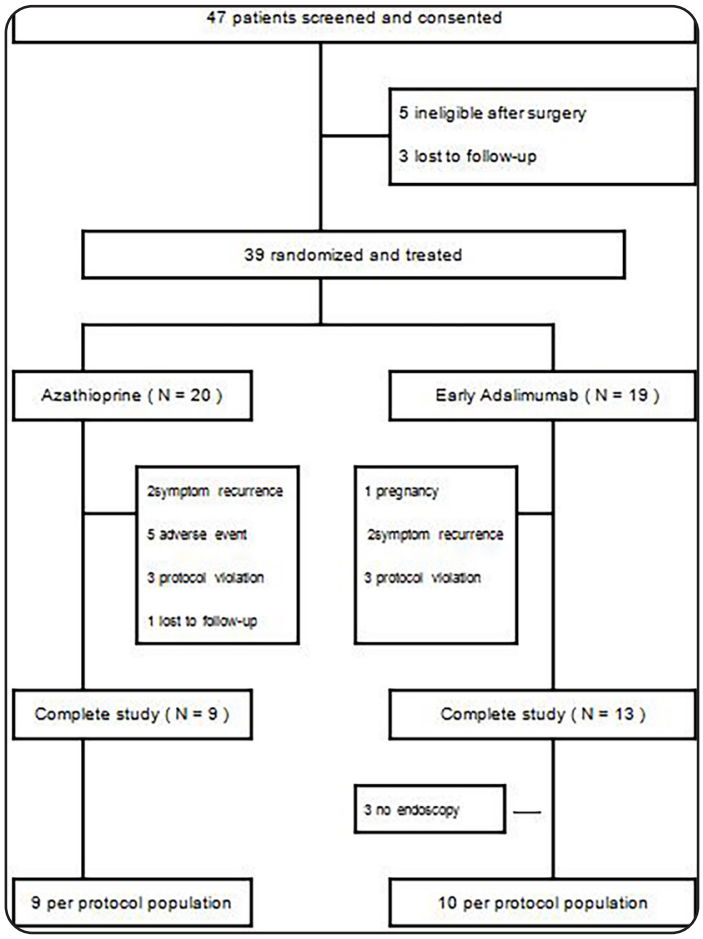

Figure 1: Flow diagram of the progress of patients through the study..

At weeks 78. In the ITT population, mucosal healing were achieved in 5/16 patients in the AZA group and in 7/12 patients in the ADA group (31.2% and 58.2%, respectively; p=0.24). The PP population revealed endoscopic remission patients in the AZA group and 7/10 patients in the ADA group (33.3% and 70.0%, respectively; p=0.17) (Figure 2).

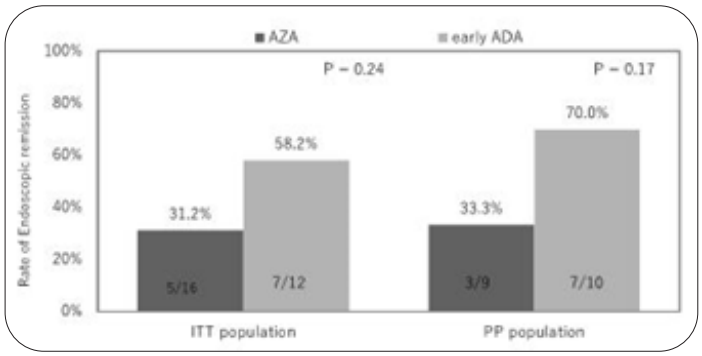

Figure 2: Primary endpoint. The rate of patients with endoscopic remission in the endoscopy at Weeks 78 are shown for azathioprine and adalimumab in intention-to-treat (ITT) population and per-protocol (PP) population. The Rutgeerts endoscopic grades i0, i1, and simple endoscopic score for Crohn's disease (SES-CD) ≤ 4 were considered indicative of endoscopic remission..

Secondary endpoints

The rate of CDAI clinical remission was calculated at Weeks 78, and no significant differences were observed between the

Table 2: Secondary clinical endpoints at weeks 78.

	Azathioprine (N=19)	Adalimumab (N=19)	Total (N=38)	p value
CDAI ≤ 150, N (%)				
ITT	10/19 (52.6)	11/19 (57.9)	21/38 (55.2)	1.00
PP	5/9 (55.6)	8/13 (61.5)	13/22 (59.0)	1.00
Fecal calprotectin negative ≤ 300 mg/g, N (%)				
ITT	1/2 (50.0)	No data	1/2 (50.0)	-
PP	0/1 (0)	No data	0/1 (0)	-
C-reactive protein negative ≤ 0.3 mg/ml, N (%)				
ITT	9/19 (47.4)	9/19 (47.4)	18/38 (47.3)	1.00
PP	4/9 (44.4)	7/13 (53.8)	11/22 (50.0)	1.00
Re-surgery rate, N (%)				
ITT	4/19 (21.1)	0/19 (0)	4/38 (10.5)	0.10
PP	2/9 (22.2)	0/13 (0)	2/22 (9.0)	0.14

Abbreviations: CDAI: Crohn's Disease Activity Index; ITT: Intention-To-Treat; PP: per-protocol

treatment groups for the percentage with CDAI<150 (ITT; p=1.00 and PP; p=1.00, respectively). For fecal calprotectin, it was difficult to compare because of missing data. No significant differences were found at Week 78 between the groups for C-reactive protein (Table 2). Re-Surgery was necessary in four patients in the AZA group (21.1%) and in no patient in the ADA group (0%), (p=0.10).

Safety and adverse events

Sixteen (41.0%) patients withdrew from the trial before the 78-month end point, although 4 (10.2%) of these patients withdrew only after clinical recurrence. The reasons for withdrawal are detailed in Table 3. A total of 12 adverse events were observed, the adverse event rates were similar across treatment groups (p=1.00). Six patients were withdrawn due to severe adverse events (AZA; 5, vs ADA; 0, p=0.04). The adverse events experienced in the patients treated with AZA were leukopenia (1 patient), lymphoproliferative disorder (1 patient), pneumonia (1 patient), thrombosis (1 patient), nausea (1 patient) and ileus (1 patient). Adverse events noted in patients receiving ADA were pregnancy (1 patient), leukopenia (1 patient), anemia (1 patient), pharyngitis (1 patient) and bowel obstruction (2 patients).

	Azathioprine (N=20)	Adalimumab (N=19)	p value
AEs, N (%)	6 (30.0)	6 (31.6)	1.00
SAEs related to the study drugs, N (%)	5 (25.0)	0 (0)	0.04
Withdraw, N (%)	11 (55.0)	6 (31.6)	0.20

Reason for the study drug discontinuation; N	leukopenia; 1	SAEs; 0	
	lymphoproliferative disorder;1		
	thrombosis;1	AEs; 1	Pregnancy; 1
	pneumonie;1		
	nausea; 1		
	Lost to follow-up,1	0	

Abbreviations: AEs: Adverse Events; SAEs: Severe Adverse Events

DISCUSSION

This study demonstrated that head-to-head comparison of ADA and AZA for prevention of post-operative Crohn's disease recurrence.

It did not show superiority of ADA to AZA (58.2% vs 31.2%, p=0.24), it is lower than originally expected remission rate (85% for ADA and 55% for AZA). One of the reasons was the impact of post-operative high risk population-young age, smoking, more than one surgery, perianal lesion and perforating disease-5) Most of our patients included one and more risk factors. AZA efficiency in the prevention of severe recurrence is not absolute; the result is largely supported by the evidence of RCTs or recent meta-analyses and systematic reviews for high risk populations [2-6].

Patients with previous intolerance to AZA and/or ADA or failure of either drug in the prevention of POR were excluded, but thiopurine was associated with a high rate of adverse events often leading to drug withdrawal (25.0%).

Recent study has reported that a non-synonymous SNP, nucleoside diphosphate-linked moiety X-type motif 15 (NUDT15) in Asian population, but not thiopurine S-methyltransferase (TPMT) mutations [7], is very strongly associated with thiopurine-induced severe leukopenia and alopecia [8]. By measuring the genotypes of NUDT15, we can predict thiopurine-induced leukopenia and alopecia development. A kit of NUDT15 genotyping be available clinically, it is expected for decreasing opportunities of adverse events.

There were several limitations, one was too small sample size, the other was less reliable study of single center. This could be a weakness of our study design, the difference in the proportion of endoscopic remission between treatment groups was estimated at 30% (85% for ADA and 55% for AZA), considering a type I error of 5%, a two-tailed contrast with Yates' continuity correction, 80% power, and an allocation ratio of 1:1. Therefore, 43 patients per treatment group would be needed. There was also a high dropout rate (40%), and sufficient detection power could not be obtained. Failure to conduct placebo-controlled study also reduce the design accuracy.

CONCLUSION

Our trial could not demonstrate the superior efficacy of ADA over AZA in the prevention of POR. ADA was well tolerated. Finally, the possibility remains that our results reflect a real equivalence of both drugs in this setting. Further head-to-head trials for postoperative CD including newly biologics are needed.

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CONFLICT OF INTEREST

Disclosure: AY has received honoraria from Abbvie, HI, HK, SO have declared no conflicts of interest. YS has received honoraria from Abbvie, Mitusbishi Tanabe Pharma, Zeria Pharma, Mochida Pharma, Kyorin Pharma, and Janssen Pharma, research funding from Abbvie, Mitsubishi Tanabe Pharma, EA Phama, JIMRO, Mochida Pharma and Kissei Pharma.

REFERENCES

1. Frolkis AD, Dykeman J, Negron ME. Risk of surgery for inflammatory bowel diseases has decreased over time: A systematic review and meta-analysis of population-based studies. J Gastroenterol. 2013;145:996-1006.
2. De Cruz P, Kamm MA, Hamilton AL. Crohn's disease management after intestinal resection: A randomised trial. Lancet. 2015;385:1406-1417.
3. Rutgeerts P, Geboes K, Vantrappen G. Predictability of the postoperative course of Crohn's disease. J Gastroenterology. 1990;99:956-963.
4. Daperno M, DHaens G, Van Assche G. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: The SES-CD. Gastrointest Endosc. 2004;60:505-512.
5. Nguyen GC, Loftus EV, Hirano I. American Gastroenterological Association Institute Guideline on the Management of Crohn's Disease After Surgical Resection. J Gastroenterol. 2017;152:271-275.
6. Singh S, Garg SK, Pardi DS. Comparative efficacy of pharmacologic interventions in preventing relapse of Crohn's disease after surgery: A systematic review and network meta-analysis. J Gastroenterol. 2015;148:64-76.
7. Yang SK, Hong M, Baek J. A common missense variant in NUDT15 confers susceptibility to thiopurine-induced leukopenia. Nat Genet. 2014;46:1017-1020.
8. Kakuta Y, Kawai Y, Okamoto. NUDT15 codon 139 is the best pharmacogenetic marker for predicting thiopurine-induced severe adverse events in Japanese patients with inflammatory bowel disease: A multicenter study. J Gastroenterol 2018;53:1065-1078.