Annals of Biomedical Research
An open access journal
ISSN 2817-2094
eSciRes
Research Article
ABR-1-104

Efficacy and Tolerability of Oral Budesonide in Crohn's Disease Patients with Attenuated Response to Anti TNF-α Antibody Drug- a Single Institutional Study

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Abstract

Background: Budesonide is a glucocorticoid approved as an oral medication for mild to moderate active Crohn's disease (CD) in 2016. The objective of this study was to clarify the efficacy, side effects, and other details regarding use of budesonide in CD patients with attenuated response to anti-tumor necrosis factor (TNF)-α antibody. **Methods**: Our clinical records of six patients with CD who had been administered budesonide were retrospectively examined. Anti-TNF-α antibody drugs in double volumes had been administered to all cases; mesalazine had also been administered to all cases. Budesonide was administered at 3 capsules (total, 9 mg) per day for the first 8 weeks and 2 capsules (6 mg) for the subsequent week. The subjective symptoms and objective findings, especially the frequency of bowel movements, C-reactive protein [CRP] and Crohn's Disease Activity Index (CDAI) before, during and after the budesonide administration period were examined. **Results:** In five cases (83%) budesonide was administered for the full 63 days; in 1 case (17%) it was stopped at 45 days because of Grade 1 edema. Improvement of subjective symptoms was seen in all cases. The frequency of bowel movements tended to decrease after the beginning of budesonide administration. The average values of CDAI tended to decrease and were kept under 150 during and after budesonide administration. CRP values tended to decrease during the administration period but were elevated after the completion of 9-week budesonide. Overall there were no statistically significant data, but some cases showed evident decreases. **Conclusion**: Oral budesonide was effective in subjective symptom improvement, and well tolerated in CD patients with attenuated response to anti TNF-α antibody drug.

Keywords: Crohn's disease; Budesonide; Clinical disease activity index (CDAI); C-reactive protein (CRP); Anti TNF-α antibody

Abbreviations

CD: Crohn's Disease; AE: Adverse Events; FBM: Frequency of Bowel Movements; CRP: C-reactive Protein; CDAI: Clinical Disease Activity Index

Introduction

Crohn's disease (CD) is a chronic inflammatory disease characterized by transmural inflammation and recurrent episodes of abdominal pain and diarrhea [1]. CD can occur anywhere in the gastrointestinal tract but has a predilection for the proximal colon and terminal ileum [2]. CD is commonly diagnosed in the second or third decade of life, and most patients require long-term medical therapy. Information from 2013 showed that approximately 40,000 patients in Japan received registered treatment for CD in that year [3]. Updated in 2011, The treatment guidelines for CD in Japan describe 5-aminosalicylic acid as the first-line treatment for mild-to-moderate disease, and oral steroids as a treatment for moderate-to-severe disease [2].

A variety of therapeutic agents for CD are currently available in clinical practice in Japan. The locally acting oral steroid budesonide, which is characterized by a high local anti-inflammatory activity and a low systemic bioavailability, has recently become an important drug for CD treatment [4,5].

Budesonide for internal use (Zentakort™, Zeria Pharmaceutical Co. Ltd., Tokyo, Japan) is a glucocorticoid with limited systemic effect because of its rapid first pass effect. The oral capsule allows time-dependent, targeted elimination of the drug in the ileum and ascending colon. These features limit systemic effects. In corticosteroid-dependent patients, budesonide may be substituted for conventional corticosteroid therapy without loss of response and with less risk for toxicity, but its long-term efficacy requires further evaluation [6]. In Japan, budesonide was approved for induction of remission in patients with mild to moderately active CD in September 2016. Bonovas et al.

identified and synthesized evidence from 31 trials about budesonide, but none of the trials included anti-TNF-α antibody use cases [7].

In the present study, we sought to clarify the efficacy, side effects, and other details regarding the use of budesonide in CD patients with attenuated response to anti-TNF-α antibody.

Methods

Study population

This report describes 6 patients who underwent budesonide therapy at our clinic. The Teikyo IBD Center has treated 110 CD patients since 1989. During the recent three years (2015-2017), 46% of the CD patients were treated with anti-TNF-α treatment. The clinical records of 6 patients with CD who were administered budesonide were retrospectively examined. The regimen comprised an 8-week treatment period, and a 1-week dose-tapering period. Budesonide was administered at 3 capsules per day (9 mg) for the first 8 weeks and 2 capsules per day (6 mg) for the 9th week. The frequency of bowel movements, C-reactive protein [CRP] and Crohn's Disease Activity Index (CDAI) before the beginning of budesonide administration were defined as pre-budesonide data.

According to the National Cooperative Crohn's Disease Study group, CDAI of 150 and below is associated with quiescent disease; 150<CDAI<220 is mildly active, 220 ≤ CDAI ≤ 450 is moderately active, and CDAI > 450 is extremely severe disease 1). Our study included two patients each with moderately active, mildly active and quiescent disease at baseline. During the budesonide administration period, patients visited the hospital every two weeks for a blood test and consultation.

The subjective symptoms, objective findings, frequency of bowel movements and CRP were recorded from the consultation. The lowest values for bowel movement frequency and CRP during budesonide medication were defined as "during budesonide" data. CDAI was calculated on the visit at the sixth week of budesonide administration, and was defined as "during budesonide" CDAI data. One month after the last medication day of budesonide, the frequency of bowel movements, CRP and CDAI were checked at a follow-up visit; these data were defined as "post-budesonide".

Safety assessments

The following safety variables were assessed: adverse events, laboratory variables (hematology, clinical chemistry and CRP levels, and urinalysis), vital signs (pulse, blood pressure, and body temperature), and physical examination findings.

Statistical analyses

Data between treatment groups were also compared by t-test using the JMP statistical package (SAS Institute, Vary, NC).

Results

These six patients correspond to all patients who underwent the budesonide therapy in the IBD center. A summary of baseline characteristics is given in Table 1. The patients comprised four males (67%) and two females (33%). The mean age at the time of administration of budesonide was 37 years. Four cases (67%) were small- and large-intestine type and 2 cases (33%) were colon type only. All cases were complicated by anal fistula.

Men, n(%)	4(67)
Mean age at budesonide intake, years (range)	37(29-49)
Disease duration, n(%)	
＜10 years	3(50)
≧10 years	3(50)
Disease location, n(%)	
Ileum and colon	4(67)
Colon only	2(33)
With anal fistula, n(%)	6(100)
Concomitant therapy, n(%)	
5-ASA	6(100)
Anti TNF-α, double amount	6(100)
Nutritional therapy	5(83)
Butyric acid bacterium	5(83)
Duration of budesonide administration, n(%)	
63 days	5(83)
45 days	1(17)
Improvements of subjective symptoms, n(%)	
Improvement of diarrhea	4(67)
Decrease of bowel movements	4(67)
Increased appetite	2(33)
Release of inflated abdomen	1(17)

Table 1: Summary of baseline characteristics.

Anti-TNF-α antibody drugs in double volumes had been administered to all cases; mesalazine had also been administered to all cases. Enteral nutrition and butyric acid bacterium were administered to 5 cases (83%). Past treatment history of each case was shown in Table 2.

In five cases (83%) budesonide was administered for 63 days, and in 1 case (17%) only for 45 days because of an adverse event, Grade 1 edema (Table 3). This was the only observed adverse event; no other budesonide-specific adverse events such as acne, rash, anemia, leukocytosis, Cushing's syndrome, hypertension, insomnia or hypokalemia were observed. Subjective improvement of symptoms was reported in all cases (Table 2). Improvement of diarrhea was confirmed in 4 cases (67%), decrease of bowel movements in 4 cases (67%), increased appetite in 2 cases (33%) and release of inflated abdomen in 1 case (17%); some of these improvements overlapped. Individual frequencies of bowel movements before, during and after budesonide

administration are shown in Table 2; average values are graphed in Figure 1. The frequency tended to decrease after the beginning of budesonide administration.

	The record of treatments	Adverse events	FBM pre-BS	CRP pre-BS	CDAI when BS was started	Reason for which the responses to anti-TNF-α treatment was considered attenuated
1	Mesalazine, Prednisolone, Infliximab, Adalimumab	Infusion reaction by Infliximab	7	3.84	176	FBM,CRP and CDAI were increased.
2	Mesalazine, Infliximab, Adalimumab	None	10	0.23	181	FBM and CDAI were increased.
3	Mesalazine, Azathioprine, Infliximab, Adalimumab	Pancytopenia by Azathioprine	10	1.29	237	FBM,CRP and CDAI were increased.
4	Mesalazine, Infliximab, Adalimumab	None	1	2.09	94	CRP was increased. Anal fistula got worsen.
5	Mesalazine, Infliximab, Adalimumab	None	12	0.1	225	FBM and CDAI were increased.
6	Mesalazine, Infliximab	None	5	1.7	120	FBM and CRP were increased.
FBM: Frequency of Bowel Movements, CRP: C-reactive Protein, CDAI: Clinical Disease Activity Index						

Table 2: Past treatment history of each case.

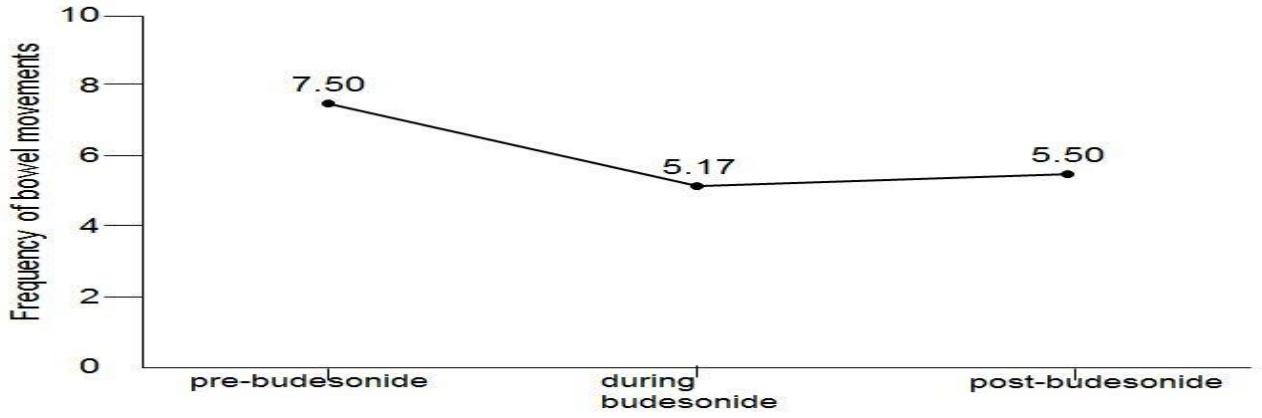

Figure 1: Average data of Frequency of bowel movements at pre-, during and post-budesonide administration.

	Age at CD onset	Age at BS intake	Sex	Duration of BS intake (days)	AE of BS	Improvemen-ts of subjective symptoms	FBM pre-BS	FBM during BS	FBM post-BS	CRP pre-BS	The minimum CRP during BS	CRP post-BS	CDAI pre-BS	CDAI during BS	CDAI post-BS
1	28	38	Female	63	None	IoD	7	7	7	3.84	0.64	1.75	176	175	159
2	20	39	Male	63	None	IoD, DoBM, RoIA	10	7	7	0.23	0.11	0.32	181	139	153

3	27	35	Female	45	Edema (Grade 1)	IoD, DoBM	10	7	6	1.29	2.7	1.85	237	213	213
4	24	32	Male	63	None	IA	1	1	1	2.09	1.5	4.48	94	91	95
5	27	49	Male	63	None	DoBM	12	7	10	0.1	0.4	0.1	225	155	189
6	22	29	Male	63	None	IoD, DoBM, IA	5	2	2	1.7	0.04	0.08	120	78	66
CD: Crohn's Disease, BS: Budesonide, AE: Adverse Events, Iod: Improvement Of Diarrhea, Dobm: Decrease Of Bowel Movements, Roia: Release Of Inflamed Abdomen, IA: I Ncreased Appetite, FBM: Frequency Of Bowel Movements, CRP: C-Reactive Protein, CDAI: Clinical Disease Activity Index															

Table 3: Characteristics of each case.

As for CDAI, the average pre-budesonide value was 172, corresponding to mildly active disease; the average values during and after budesonide administration tended to show decrease and were under 150, corresponding to quiescent disease (Figure 2a). Individual investigation showed two cases who transitioned from moderately active to mild disease (Figure 2b, Cases 3 and 5). Two mildly active cases did not transition to quiescence (Figure 2b, Cases 1 and 2), but they showed decreased CDAI values. Likewise, the two quiescent disease cases (Figure 2b, Cases 4 and 6) showed decreased CDAI values decreased. In all, two cases (33%) improved their disease classification with budesonide treatment. Though not statistically significant, all cases showed decreased CDAI after starting budesonide; however, three cases showed increased CDAI from the 6th week to the post-budesonide follow-up (Figure 2b, Cases 2, 4 and 5).

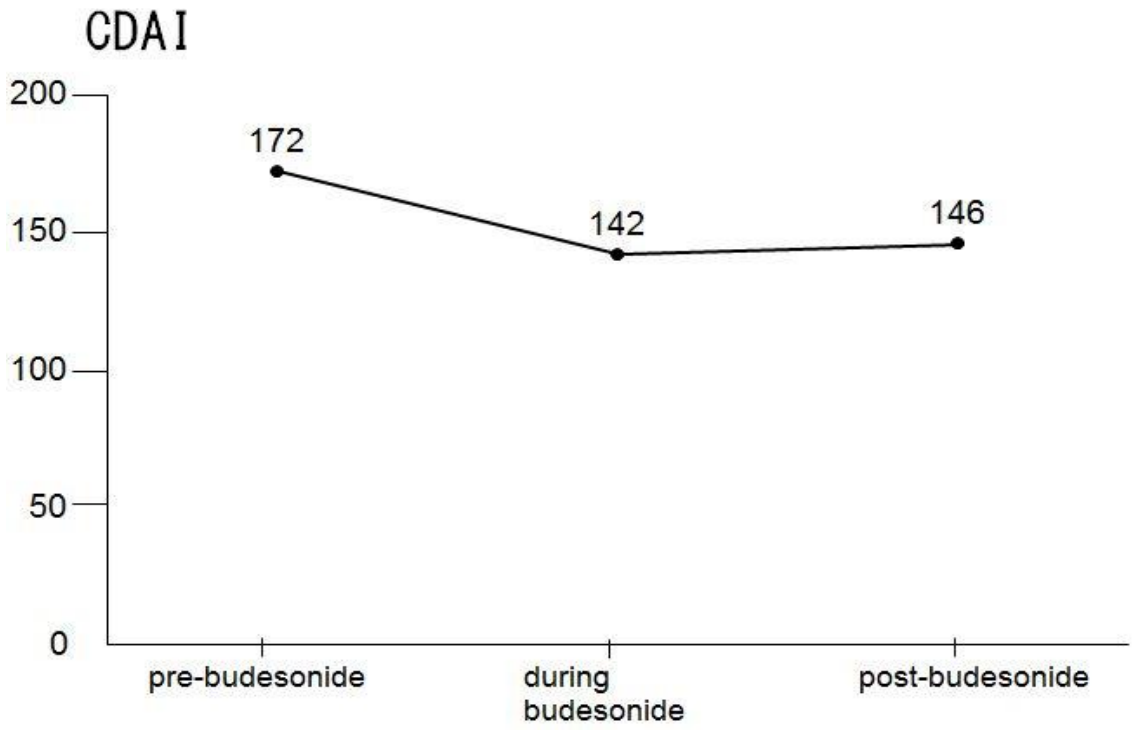

Figure 2a: Average data of CDAI at pre-, during and post-budesonide administration.

As for CRP, the average pre-budesonide value was above 1 mg/dl; that value decreased, but not significantly, to less than 1 during budesonide administration (Figure 3a) and increased post-budesonide to 1.43 mg/dl. Individual investigation showed there were 4 cases with CRP greater than 1 mg/dl at pre-budesonide, 2 during budesonide, and 3 at post-budesonide (Figure 3b). In 4 cases CRP declined from before to during budesonide administration (Figure 3b, Cases 1, 2, 4 and 6). But in 2 of these CRP was elevated at post-budesonide (Figure 3b, Cases 2 and 4). There were no significant differences in the frequency of bowel movements, CDAI or CRP among the data before, during and after budesonide administration.

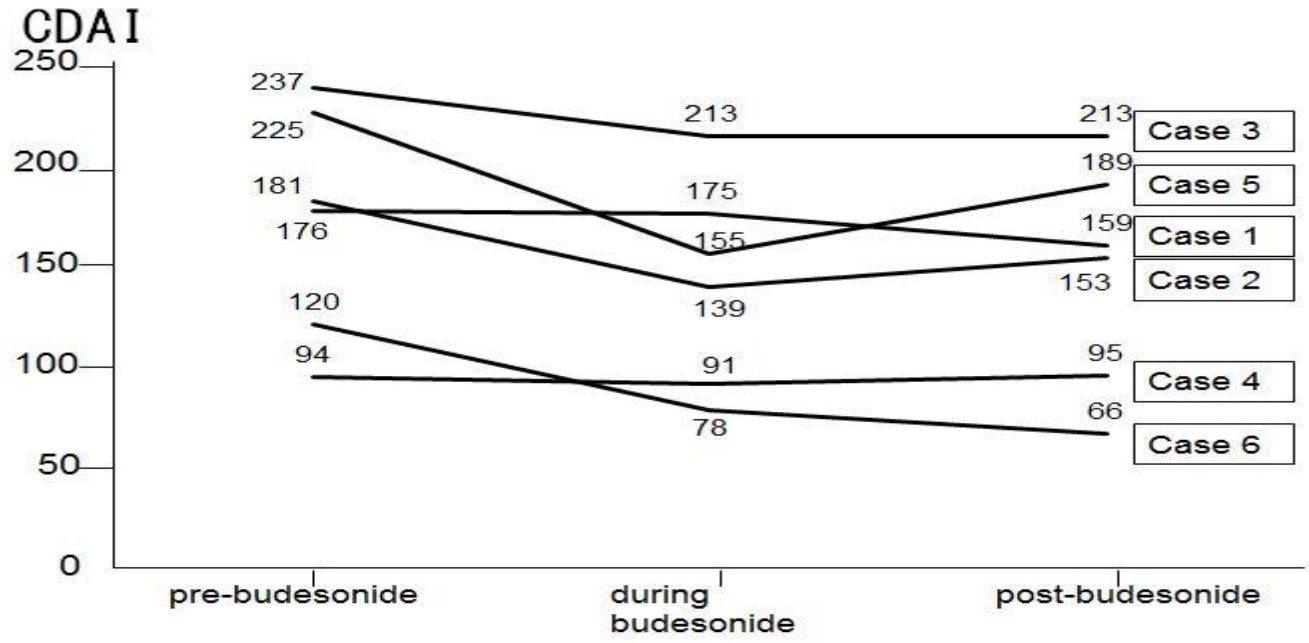

Figure 2b: Individual data of CDAI at pre-, during and post-budesonide administration.

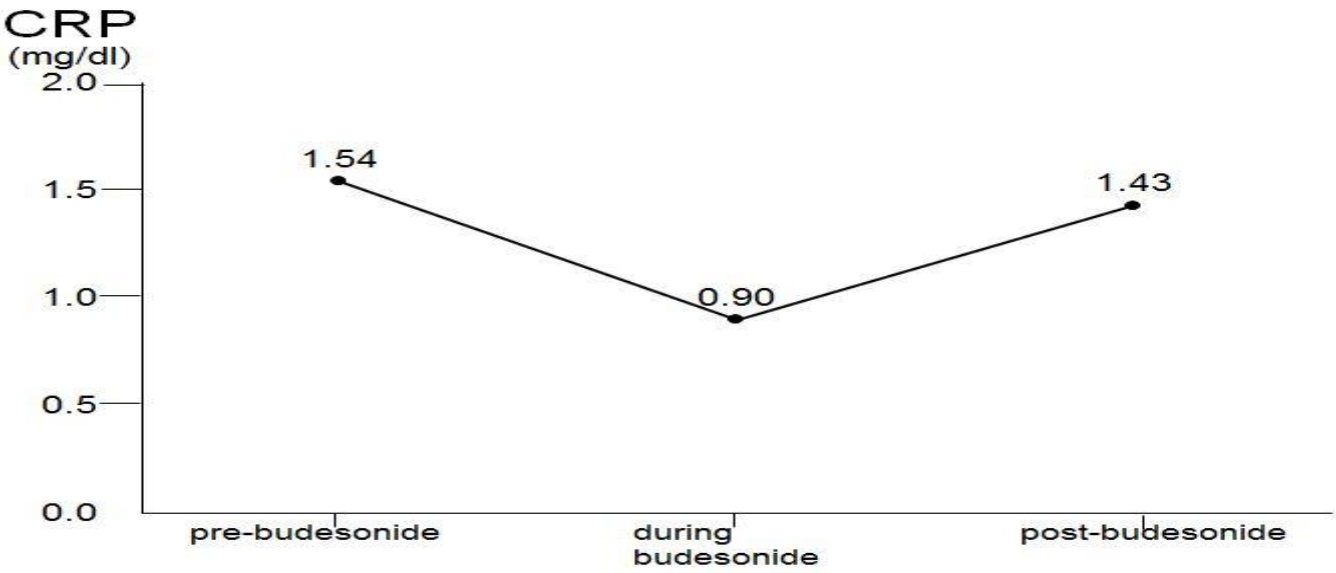

Figure 3a: Average data of CRP at pre-, during and post-budesonide administration.

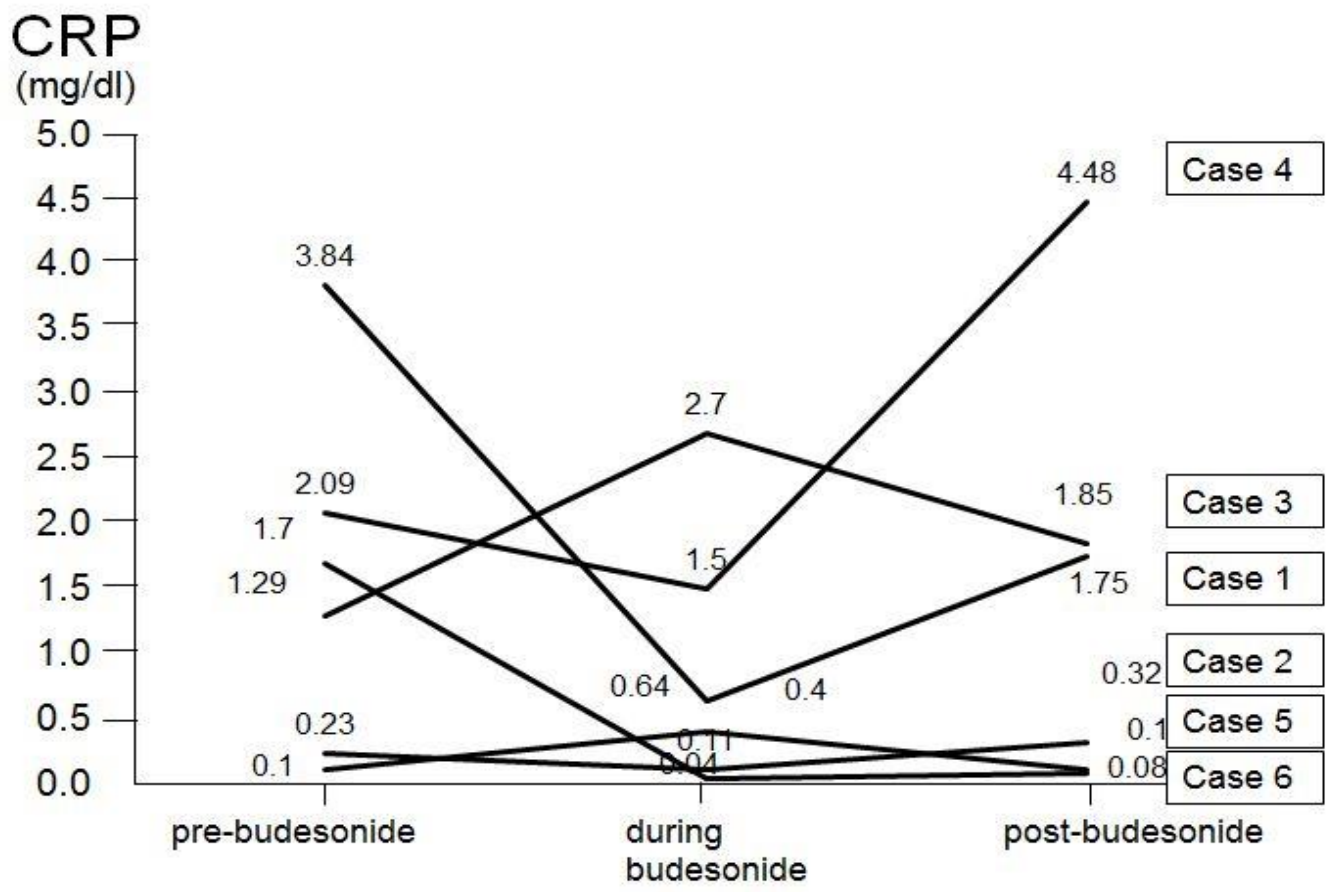

Figure 3b: Individual data of CRP at pre-, during and post-budesonide administration.

Discussion

Corticosteroids have been considered to be the most effective in inducing remission of active CD, but in 1994 budesonide was recognized as a drug with high efficacy and few side effects [8]. Single-dose administration of budesonide was first recommended as the simplest and safest therapeutic approach [9]. Later, oral budesonide formulations were developed that gradually release budesonide from the ileum around the ascending colon [3]. Compared to prednisolone, budesonide is considered to be taken up at high concentration in local tissues, and it is thought that some budesonide is fatty acid-esterified in the mucosal cells such that it is maintained at high concentrations locally [4]. According to the American College of Gastroenterology practice guideline, controlled-release oral budesonide formulations at a dose of 9 mg daily have been demonstrated to be more effective than placebo or oral mesalamine at 4 g daily, and have similar efficacy when compared with conventional oral corticosteroids for the treatment of disease in patients with mild to moderately active CD involving the distal ileum and/or right colon [10]. Thus, budesonide is recommended for use as the preferred primary therapy for patients with mild to moderately active CD who have disease localized to the ileum and/or right colon [10]. Bonovas et al. identified and synthesized evidence from 31 trials about budesonide, but none of the trials included cases with anti-TNF-α antibody use [7]. Suzuki et al. studied the efficacy and tolerability of oral budesonide for Japanese patients in a Phase II study and recommended 9 mg oral budesonide for up to 8 weeks for active CD treatment [11]. Yokoyama performed a Phase III study and showed the noninferiority of budesonide to mesalazine in patients with active CD [12]. Owing to the studies on budesonide including Suzuki et al. [11], budesonide for CD was officially covered by Japan's medical insurance in 2016. Our report is the first clinical report describing budesonide administration in cases in which anti-TNF-α antibody had already been used.

About loss of response (LOR) to anti TNF-α antibody, a review of 16 studies for CD reported LOR to infliximab at 13.1% per patient-year and LOR of 46% to adalimumab by 54 weeks [13,14]. Adverse events were found in approximately two thirds of Crohn's disease patients under anti-TNF therapy, and there were no significant differences between infliximab or adalimumab [15]. As anti TNF-α antibody is often administered to CD patient, LOR and adverse events should be taken care of.

Give our small population, there were no significant differences, but tendencies for decrease in the frequency of bowel movements, CDAI and CRP by budesonide administration were found. CRP increased post-budesonide, but CDAI did not. Of clinical importance, subjective symptoms improved in all cases. Only one adverse event,

Grade 1 edema of the limbs (Common Terminology Criteria for Adverse Events Version 5.0 from National Cancer Institute), was seen, but this occurred 45 days after beginning administration of budesonide and its relation to the budesonide administration is unclear.

Subjective symptoms were improved in all cases; however, no statistically significant effects such as lowering CDAI or CRP by budesonide administration were seen. In some individual cases budesonide was effective in lowering CDAI and lowering CRP. Further study is needed to predict in which cases budesonide will be effective and ineffective.

In Japan, budesonide is allowed to be administered for 9 weeks according to the medical insurance system. Long-time administration is not recommended. One budesonide-related adrenal insufficiency case was reported, but the drug had been administered to the patient for three years [16]. It is necessary to avoid abrupt discontinuation of long-standing corticosteroid treatment.

In conclusion, we show here that oral budesonide of 9 mg per day for 8 weeks and 6 mg per day for one week was effective in some cases and well tolerated in CD patients with attenuated response to anti TNF-α antibody drug. Budesonide was especially useful for improving subjective symptoms. The limitation was that the current study was retrospective, short-term and consisted of very few cases. It is necessary to perform long-term follow up and study the profiles of more patients.

Author's contributions

MK treated the patients, gathered the patient data and wrote the manuscript. OK, OY, MY, TM, FY, AT, HA, SR, HT, OK, TT, TJ, IH, NK, AH, IA, AK, KS, YT, KH and HY had a hand in the daily medical treatment for the cases. SY and KF were responsible for histopathological diagnosis. HY represented our surgical department and supervised the writing of the manuscript. All authors significantly contributed to this study and approved the final manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Received date: April 19, 2018; **Accepted date:** May 07, 2018; **Published date:** May 09, 2018

Citation: Matsuda K, Ohno K, Okada Y, Yagi T, Tsukamoto M, Fukushima Y, Akahane T, Horiuchi A, Shimada R, Ozawa T, Hayama T, Okamoto K, Tsuchiya T, Tamura J, Iinuma H, Nozawa K, Aoyagi H, Isono A, Abe K, Kodashima S, Yamamoto T, Kita H, Sasajima Y, Kondo F, Hashiguchi Y1,2 (2018) Efficacy and Tolerability of Oral Budesonide in Crohn's Disease Patients with Attenuated Response to Anti TNF-α Antibody Drug- a Single Institutional Study. *Ann Biomed Res* 1(1): 104.