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CLINICAL TRIAL

A longitudinal study of FDG-PET in Crohn disease patients receiving granulocyte/monocyte apheresis therapy

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Abstract

Background aims. Endoscopy is the gold standard for the diagnosis and follow-up of patients with Crohn disease (CD). However, a less invasive approach is now being sought for the management of these patients. The objective of this study was to examine whether ^{18}F–fluorodeoxyglucose (FDG)-positron emission tomography (PET) might be relevant for monitoring the disease activity in CD patients undergoing granulocyte/monocyte apheresis (GMA). *Methods.* This study was conducted in 12 patients with CD who were receiving treatment with 10 once-a-week GMA sessions with the Adacolumn. The response to treatment was monitored by measuring standard laboratory variables, Crohn's Disease Activity Index (CDAI) score, International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) score, and regional and global bowel uptakes on FDG-PET. *Results.* In 6 of the 12 patients, significant improvement of the CDAI was observed after the final session of GMA. The patients who showed clinical response to GMA had a decrease in the regional and global bowel uptakes on FDG-PET, whereas those who did not respond showed no change. In the patients who responded to the GMA, the decrease in regional bowel uptake on FDG-PET in each disease area of the same patient varied in parallel. There was a significant correlation between decrease in the global bowel uptake on FDG-PET and improvement of the CDAI and IOIBD scores. *Conclusions.* The longitudinal changes in FDG-PET uptakes are of potential clinical interest for assessing the regional and global bowel disease activity in CD patients undergoing GMA therapy.

Key Words: *Crohn disease, FDG, granulocyte/monocyte apheresis, PET*

Introduction

Crohn disease (CD) is a chronic inflammatory disorder involving the gastrointestinal tract. While the precise cause remains unknown at present, leukocyte infiltration throughout the intestinal wall is a hallmark of this disorder [1]. During active disease, leukocytes migrating from the circulation are activated by intestinal lumen antigens to release various pro-inflammatory molecules including cytokines, chemokines and free radicals, causing intestinal inflammation and tissue damage [2–8].

Evaluation of the disease activity is a critical part of effective patient care in CD management. Radioimaging techniques, such as contrast enema and small bowel follow-through, have been applied for monitoring CD patients but carry a high risk of radiation exposure. Systemic inflammation markers like serum C-reactive protein are of limited value because these are non-specific reactions. The value of fecal calprotectin still needs to be established [9]. Thus, endoscopic evaluation remains an essential procedure for the diagnosis and follow-up of CD patients.

Endoscopy is the gold standard to determine disease activity and the extent of disease, define the

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disease type, and institute appropriate therapy in CD patients. However, there are certain problems with this approach as well. First, serial endoscopy, which is an invasive procedure, is uncomfortable for the patients. Second, colonoscopic examination is often challenging because of the presence of strictures and unreachable segments. Third, the disease characteristically affects the deeper parts of the intestinal wall and may thus be invisible from the luminal side. Therefore, a less invasive approach useful for assessing inflammation across the entire thickness of the intestinal wall is desirable as an adjunctive modality in the management of CD patients.

^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) is a molecular imaging modality that relies on the accumulation of the radioisotope in metabolically active cells. This modality fulfills the criteria of being less invasive and painless, with a low radiation exposure of 3–7 mSv (range of natural exposure/year). Because of the increased glycolytic metabolism in inflammatory cells, inflammation as well as neoplasms show elevated FDG uptake. Accordingly, an increase in FDG uptake has been shown clinically in patients with inflammatory disorders, including rheumatoid arthritis, fibrosing alveolitis and sarcoidosis [10–12]. Recent studies have shown that FDG-PET has the potential to detect and characterize the anatomic location and the disease activity in the bowel in CD patients at the time of diagnosis. Reflecting these characteristics, the sensitivity of FDG-PET for the detection of active disease in patients with CD has been reported to be 81.3% [13,14]. However, many questions remain with regard to the usefulness of FDG-PET in patients with CD. In particular, there are limited data about the longitudinal changes in the FDG-PET findings during medical therapy of CD patients [15].

Recently, granulocyte/monocyte apheresis (GMA) with an Adacolumn has been recognized as a safe and effective therapy to reduce the disease activity and improve the quality of life of patients with CD, ulcerative colitis (UC) and generalized pustular psoriasis [16–21]. GMA is a non-pharmacological method designed to remove activated leukocytes from the peripheral circulation. The adsorptive carriers in the apheresis column removes about 65% of the granulocytes, 55% of the monocytes and less than 2% of the lymphocytes from the blood, which passes through the column. As a result, the production of pro-inflammatory molecules is markedly reduced, which leads to recovery from the intestinal inflammation [22,23].

In this pilot study, we were interested in studying, for the first time, whether serial FDG-PET might be relevant for monitoring the CD activity during GMA therapy of CD patients. In addition, the clinical efficacy of GMA on CD was also assessed.

Methods

Patients

Twelve patients with CD recruited from Kurume University Hospital between 2009 and 2010 were included in this follow-up study. Patients were initially included if (i) they had been clinically and histologically diagnosed as having CD, (ii) their CD was refractory or the patient was intolerant to conventional drugs for CD and (iii) their mucosal status represented an active disease stage. Patients who were pregnant, had blood sugar >200 mg/dL (hyperglycemia interferes with FDG uptake) and those with short bowel syndrome were excluded.

Study design

The patients were treated with 10 consecutive GMA sessions, at one session per week. All baseline anti-inflammatory therapies, including 5-aminosalicylic acid, prednisolone, immunomodulators or anti-tumor necrosis factor (TNF)-α, could be continued throughout the study without change in the dosage. Likewise, no dietary modification was made after the patients entered into the study.

Disease activity was monitored by measuring routine laboratory variables, the Crohn's Disease Activity Index (CDAI) [24], the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) score [25] and the uptakes on FDG-PET at baseline and at the 5th and 10th GMA sessions. Response to GMA was considered clinical remission when the CDAI fell to <150 and as partial response when the CDAI score decreased by >70 points relative to baseline.

GMA

GMA was done with the Adacolumn as previously described. Briefly, the Adacolumn is filled with specially designed cellulose acetate beads, which serve as the column adsorptive leukocytapheresis carriers. Enrolled patients received weekly GMA sessions according to a pre-determined schedule, described later. The duration of each GMA session was 60 min at 30 mL/min. An optimal dose of sodium heparin (2000 units/session) was administered during the GMA session as an anticoagulant. Use of nafamostat mesilate, a commonly used anticoagulant during Leukocytapheresis, was avoided because this substance often elicits allergic reactions. During the GMA therapy, no additional therapy was started, and the dosages of the currently used drugs were maintained at the same level.

FDG–PET

An integrated full-ring PET/computed tomography (CT) scanner (Gemini-GXL 16; Philips Medical Systems) was used for data acquisition. The dimen-

sions of the individual Gd2SiO5 crystals were $4 \times 6 \times 30$ mm^3, and the system's National Electrical Manufacturers Association 2001 transverse spatial resolution at 1 cm was 5.3 mm. Before the FDG injection, the patients were instructed to fast for 4 h. Intake of liquids not containing sugar was permitted. Before the examination, each patient drank 500 mL of water to accelerate the renal elimination of FDG. The patients were administered a mean of 5.92 mCi (range 4.79–9.17; 254 MBq [0.12 mCi /kg]) of FDG via the antecubital vein. All patients rested quietly for approximately 60 min after the FDG injection, and then whole-body imaging was performed. Patients were examined in the supine position. Initially, a non-contrast full-dose CT scan was acquired, starting from the level of the head and using the following settings: 200 mAs, 120 kV, 0.75 s/tube rotation, 3-mm slice thickness, 940-mm scan length, and 40-s data acquisition time. The CT scan was acquired during breath holding in the normal expiratory position. The CT data were used for attenuation correction and lesion localization. PET emission scans of the areas from the level of the auditory meatus to the mid-thigh were acquired with a time of 2 min 30 s per cradle position, using the three-dimensional acquisition mode. The 8–9 cradle positions starting from the head and continuing to the mid-thigh resulted in an acquisition time of approximately 30 min. After both the transmission and emission images were obtained, the images were reconstructed using the standard NORMAL reconstruction protocol based on the three-dimensional line-of-response row-action maximum likelihood algorithm, with which the PET/CT scanner was equipped [26].

The intensity of ^{18}F-FDG uptake was quantified by determining the standardized uptake value (SUV) corrected for the lean body mass. A region of interest was placed on transaxial images so that it totally surrounded the most intense area of ^{18}F-FDG uptake, and the SUV was calculated by using the maximum pixel activity value within the region of interest. The liver was chosen as a reference organ for the bowel because it was always in the field of view and not likely to be abnormal in CD patients. Two radiologists measured the SUV, and the measurements were averaged for each segment. The intra- and inter-observer variabilities of the SUV measurements were <5%. If multiple abnormal areas of ^{18}F-FDG uptake were found in one segment, they were recorded separately if they could be clearly distinguished from one another.

Ethical considerations

Approval was obtained from the Kurume University Research Ethics Board before commencement of the study. Before enrollment in the study, written informed consent was obtained from each patient after explaining the purpose of the study and the nature of the procedures involved. In case of an under-age patient, consent from one of the patient's parents was sought. Furthermore, the Principle of Good Clinical Practice and the Helsinki Declaration were adhered to at all times.

Statistical analysis

The data were analyzed by using the SPSS statistical software. Student's *t*-test, Mann-Whitney's *U*-test, Wilcoxon's signed-rank test, Pearson's correlation test, Spearman's correlation test and/or the χ^2 test were used as appropriate. For all comparisons, a P value <0.05 was considered as indicative of statistical significance.

Results

Patients' baseline demographic variable

The baseline demographic variables of the study patients are presented in Table I. There were 12 patients (5 male, and 7 female) with a mean age of 35.9 years. All 12 patients had active CD refractory to conventional medications.

Change in the CDAI

The longitudinal changes in the CDAI score during the GMA therapy are shown in Figure 1. The mean CDAI in the 12 patients of this study was 206.8, 158.9 and 149.8 at baseline and the 5th and 10th GMA sessions, respectively, reflecting a final decrease of 27.6%. Improvement of CDAI after the final session of GMA was observed in 6 of the 12 patients. The procedure

Table I. Baseline characteristics of the CD patients before the start of the GMA treatment.

Category	
Male/female, n	5/7
Age (years)	35.9 ± 11.6 (16–56)
Duration of disease (months)	78.8 ± 81.1 (1–250)
Location of lesions (ileitis/ileocolitis/colitis), n	1/10/1
Previous bowel resection	None
Ongoing medications, n	
Prednisolone	5
5-aminosalicylic acid	11
Azathioprine	1
Antibiotics	3
Anti-tumor necrosis factor	1
CDAI	206. 8 ± 81.1 (156–276)
IOIBD	3.3 ± 1.8 (1–7)
CRP (mg/dL)	3.77 ± 5.37 (0.04–16.11)
ESR (mm/ h)	32.9 ± 36.8 (3–117)

Mean ± SEM (range) unless noted.
CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

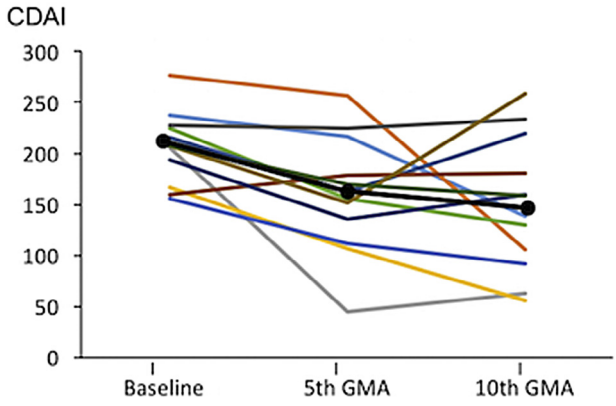

Figure 1. Longitudinal changes in the CDAI in the 12 patients with CD during GMA therapy. The black line with closed circles indicates the mean value at each time point.

was well tolerated in all patients. There were no significant differences in the baseline demographic features of the patient group in whom GMA was effective and those in whom it was not effective (Table II).

Changes in the FDG-PET uptakes

Figure 2 shows the longitudinal changes in the regional bowel uptakes on FDG-PET at the sites of disease in the bowel during GMA therapy. At baseline, all 12 patients had multiple areas of active disease in the bowel, showing increased uptake on FDG-PET. In the six patients who responded to the GMA therapy, the regional bowel uptake on FDG-PET in each disease area decreased after treatment. In these patients, the decrease in the regional bowel uptake in each area of the same patient seemed to vary in parallel. In contrast, in the remaining six patients who did not respond to the GMA therapy, the regional bowel uptake on FDG-PET showed no change following the treatment.

Figure 3 shows the global bowel activity as determined by the uptake on FDG-PET, which represents the average uptake in all the regions in each patient. The global bowel uptake on FDG-PET was abnormal in all the 12 patients at baseline. The uptakes decreased significantly in the patients who responded to the GMA therapy, whereas no change was seen in the patients who did not respond to the GMA therapy. Figure 4 shows examples of the time course of changes in the uptakes on FDG/PET in one patient with CD who responded to the GMA therapy.

Correlation between the uptake on FDG-PET and the CDAI

As shown in Figure 5, there was a significant correlation between decrease in the regional bowel uptake on FDG-PET and improvement of the CDAI and IOIBD scores at the 5th and 10th GMA sessions, and the erythrocyte sedimentation rate at the 10th GMA session. A similar tendency was observed with respect to the serum C-reactive protein, although this relation did not reach statistical significance.

Discussion

There has been increasing awareness of the potential benefits of FDG-PET, a diagnostic and follow-up tool for patients with CD. In the present study, we evaluated, for the first time, the longitudinal changes in the uptakes on FDG-PET in patients with CD receiving GMA therapy.

We found that the GMA responders showed a marked decrease in the global bowel uptake on FDG-PET; in contrast, GMA non-responders showed no change in the uptake. The global bowel uptake on FDG-PET showed a significant correlation with the CDAI and IOIBD scores. These results suggest that the uptake patterns on FDG-PET could reflect the

Table II. A comparison of baseline characteristics of CD patients between GMA effective and non-effective groups.

Demographics	GMA effective group (n = 6)	GMA non-effective group (n = 6)	*P* value
Male/female, n	2/4	3/3	0.3173
Age (years)	34.2 ± 12.9 (16–56)	37.7 ± 11.1 (22–50)	0.6251
Duration of disease (months)	111.2 ± 98.8 (2–250)	46.3 ± 46.8 (1–125)	0.1896
Location of lesions (ileitis/ileocolitis/colitis), n	0/6/0	1/4/1	0.6726
Ongoing medications			
Prednisolone	4	1	0.0926
5-aminosalicylic acid	5	6	0.3173
Azathioprine	1	0	0.3173
Antibiotics	2	1	0.2690
Anti–TNF	1	0	0.3173
CDAI	211.3 ± 45.0 (156–276)	202.3 ± 23.5 (160–228)	0.6758
IOIBD	4.2 ± 2.4 (1–7)	3.8 ± 1.2 (2–5)	0.7687
CRP (mg/dL)	5.04 ± 6.9 (0.16–16.11)	2.49 ± 3.4 (0.04–9.23)	0.4439

Mean ± SEM (range) unless noted.
CRP, C-reactive protein.

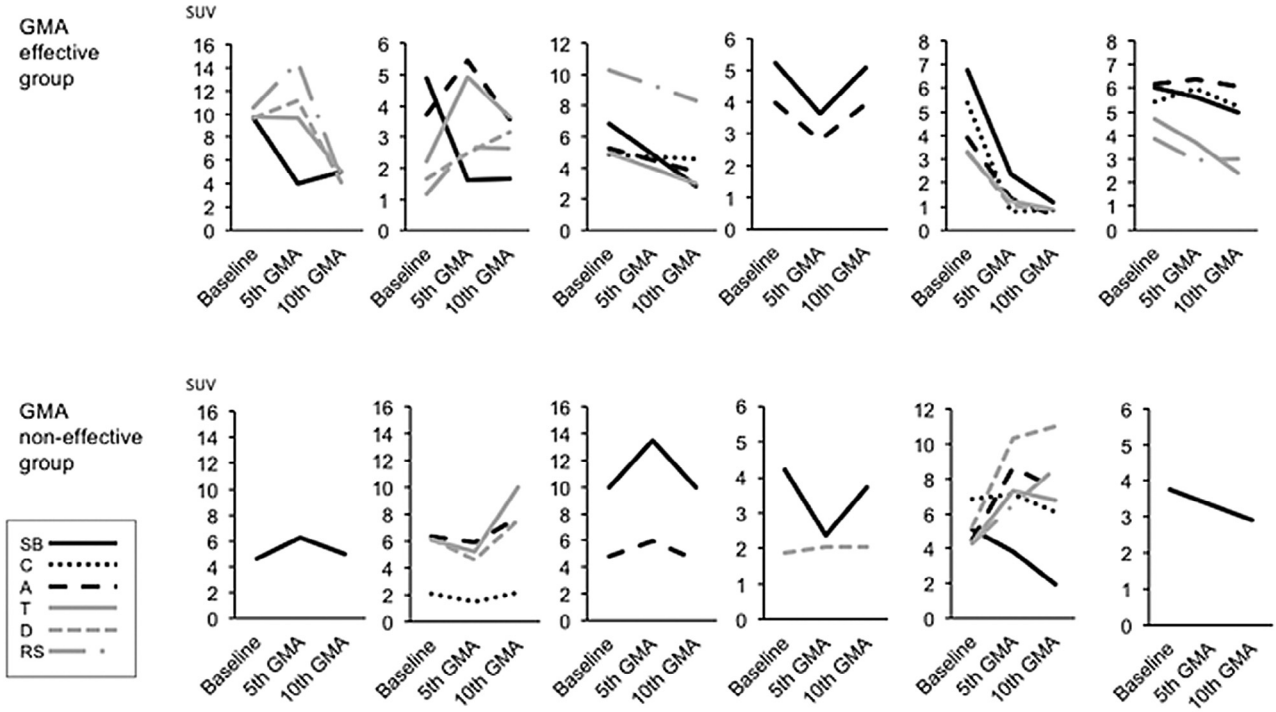

Figure 2. Longitudinal changes in the regional bowel uptake on FDG-PET in patients with CD who responded to GMA therapy (A) and those who did not respond to GMA therapy (B). The regional bowel uptake on FDG-PET at baseline, at the 5th GMA and at the 10th GMA sessions was determined quantitatively using the standardized uptake values (SUV) in each disease area and compared with the FDG uptake in the liver. A, ascending colon; C, cecum; D, descending colon; RS, rectosigmoid; SB, small bowel; T, transverse colon.

response to GMA therapy. However, a larger cohort of patients will be needed to reach a more solid conclusion.

One advantage of FDG-PET is its ability to map the distribution of the areas of active disease. In this study, we found that the regional bowel uptake on FDG-PET in all disease areas of the same patient varied in parallel after successful treatment. Previously, Matsui et al. reported that GMA was more effective for the treatment of CD with isolated colonic involvement than for CD with small bowel involvement [27]. Interestingly, our study showed that GMA could reduce the regional bowel uptake on FDG-PET in both the small bowel and the colonic lesions, suggesting that the therapeutic effect of GMA was distributed equally throughout the bowel.

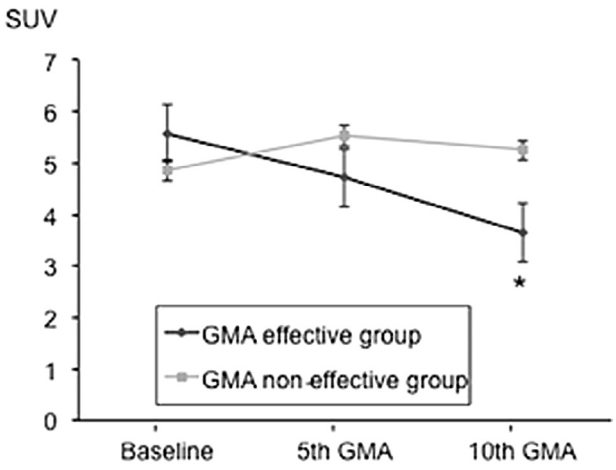

Figure 3. Comparison of global bowel uptake on FDG-PET in patients with CD who responded to GMA therapy (A) and those who did not respond to GMA therapy (B). The global bowel uptake on FDG-PET was calculated as the average of the standardized uptake values (SUV) in each disease area per patient. $*P = 0.0331$ versus the value at baseline.

Another advantage of FDG-PET is that it allows visualization of the entire bowel wall. This is particularly important in CD, because this disease often spreads to the deeper layers of the bowel wall. Although it is now well established that mucosal healing is associated with a better prognosis in CD patients, transmural inflammatory processes hidden by mucosal healing may not be noticeable by endoscopy. In particular, because FDG is not taken up by fibrotic tissue, FDG-PET might be valuable for distinguishing inflammatory from fibrostenotic lesions. A persistent increase of FDG uptake, even in endoscopically inactive areas, may have important therapeutic implications.

As for the cellular source of uptake, leukocytes activated by inflammatory stimuli may be responsible for the increased uptake on FDG-PET in the bowel in CD patients. In fact, an increase of FDG uptake

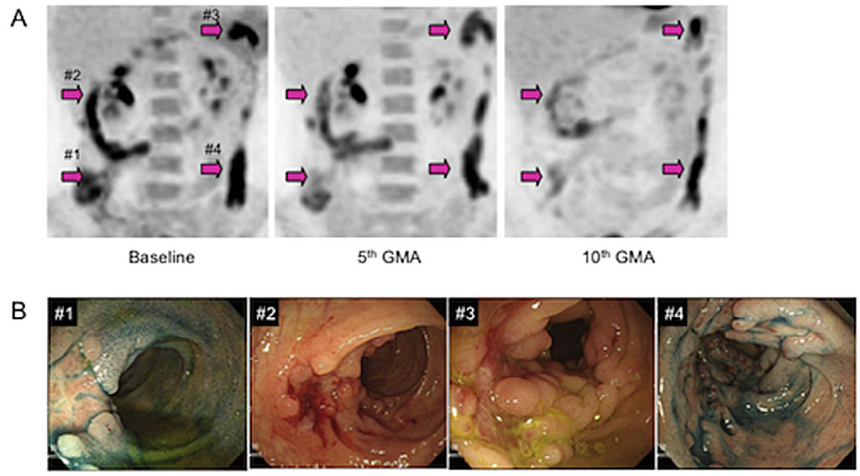

Figure 4. Anterior-view FDG-PET in a 22-year-old female CD patient with ileo-colonic inflammation who responded to GMA therapy. Note the patchy distribution with increased regional bowel uptake of FDG in the ileocecum (#1), hepatic flexure (#2), splenic flexure (#3) and descending colon (#4) at baseline. The presence of macroscopic inflammation in the same area (arrow) was confirmed by colonoscopy. The regional bowel uptake of FDG in each of the aforementioned areas decreased gradually after the treatment.

by the mucosal leukocytes has been demonstrated in animal models of intestinal inflammation, with the uptake being proportional to the disease activity [28–30]. *In vitro* studies have confirmed accumulation of FDG in leukocytes, including granulocytes, lymphocytes and macrophages [31,32]. After successful GMA therapy, mucosal leukocytes may show reduced FDG uptake, resulting in the overall decrease of FDG-PET uptake.

It has been suggested that GMA is effective for reducing disease activity in CD. Although this pilot study was not designed to evaluate the efficacy of GMA, we found that the treatment reduced the disease activity in six of the 12 patients who had active CD refractory to available pharmacological treatment. Bresci et al. investigated the clinical efficacy of five sessions (once a week) of GMA in 16 patients with active CD and showed clinical remission in 63.3% of the patients at the end of GMA course, with the remission sustained in 53.3% and 40% at 6 and 12 months, respectively [33]. Fukuchi et al. evaluated the clinical efficacy of GMA (twice a week, 10 sessions) plus thiopurines in 22 steroid- and biologic-naive patients with active early-diagnosed CD. Clinical remission was observed in 81.8% of the patients and mucosal remission in 50% at the end of 52 weeks. However, a well-designed study is required to fully evaluate the efficacy of this non-pharmacological treatment intervention.

It is important to fully understand how the actions of GMA with the Adacolumn are translated into clinical efficacy in terms of disease remission. The Adacolumn is filled with cellulose acetate beads to which leucocytes that bear the FcγR and complement receptors adhere and are eliminated from the circulation [34]. Depletion of these myeloid lineage leukocytes as sources of inflammatory cytokines should potentially ameliorate inflammation. Accordingly, Yokoyama et al. [35] used this effect of GMA to treat a patient with CD and hepatitis B virus infection in whom anti-inflammatory drugs could reactivate the hepatitis B virus. However, removal of elevated myeloid leukocytes *per se* is unlikely to account for the full efficacy of GMA. Basic studies in inflammatory bowel disease (IBD) clinical settings by Yokoyama et al. [36] found a significant increase in the circulating levels of regulatory T cells, and more recently Ansary et al. [37] reported GMA-induced enhanced regulatory B-cell function. Furthermore, the leukocytes, which adsorb to the column carriers, undergo extensive release reaction [34]. Hanai et al. [38] found a significant increase in blood levels of soluble TNF-α receptors I and II post-GMA. Soluble TNF receptors are reported to neutralize TNF without invoking TNF-like actions [38]. In *in vitro* settings, Takeda et al. [39] reported a significant release of the interleukin (IL)-1 receptor antagonist (IL-1ra) and hepatocyte growth factor (HGF) from myeloid leukocytes on adsorption to the GMA carriers. IL-1ra is strongly anti-inflammatory, and HGF is known to promote epithelial cell regeneration and ulcer healing. In clinical settings, both IL-1ra and HGF reach patients' circulation via the GMA column outflow line to patients.

Studies in patients with UC have reported baseline demographic variables that potentially identify a patient as a responder or non-responder to GMA [34,40,41]. The best responders to GMA have been first-episode cases followed by steroid-naive patients, and applying GMA immediately after a clinical relapse is more likely to be effective than when active

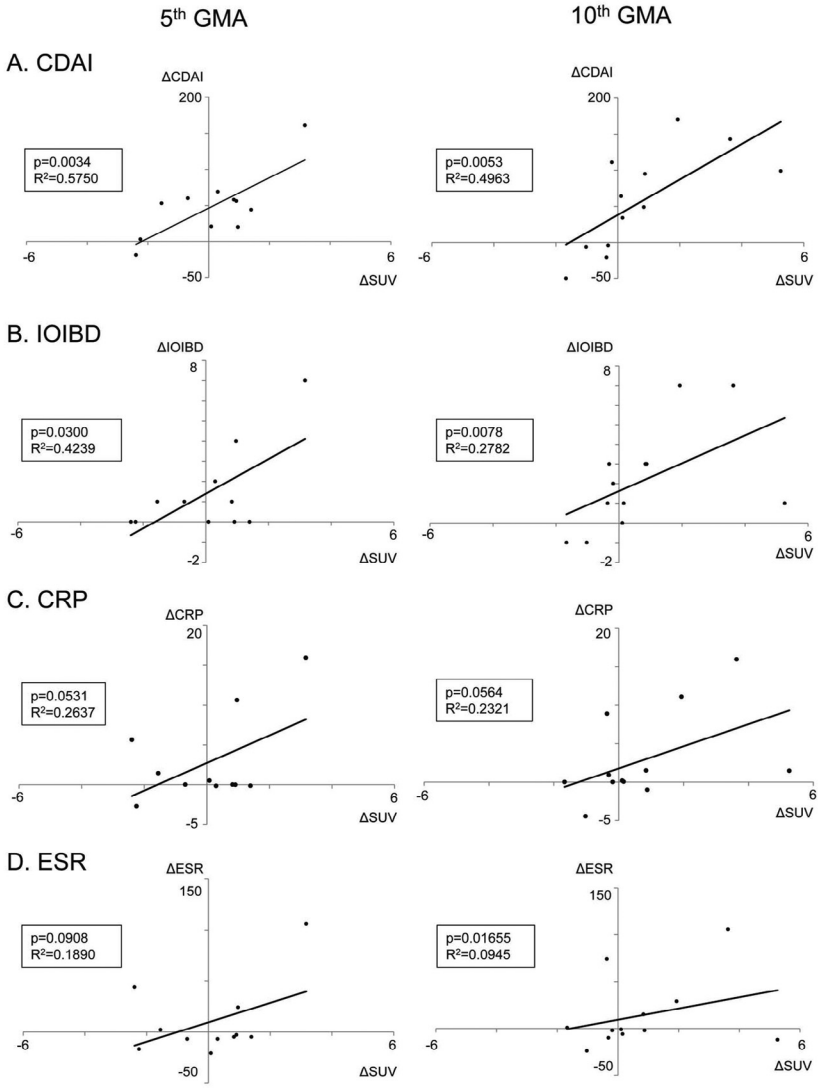

Figure 5. Correlations between the changes in the global bowel uptake on FDG-PET and the CDAI, the IOIBD, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). The changes in the global bowel uptake on FDG-PET (ΔSUV) and the CDAI (ΔCDAI), the IOIBD (ΔIOIBD), CRP (ΔCRP) and ESR (ΔESR) were calculated by subtracting the pre-treatment level from the post-treatment level. CDAI, Crohn's disease activity index; IOIBD, international organization for the study of inflammatory bowel diseases; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

disease has continued for some time. In line with this assertion, Yokoyama et al. [36] reported that patients with short-duration UC and low cumulative corticosteroid dose in the past respond well to GMA. However, the best responders in that study were patients who received GMA immediately after a clinical relapse. Similarly, Yamamoto et al. [42] found that patients who received Adacolumn GMA in the early days of their active IBD had a more favorable long-term clinical course by avoiding corticosteroids and other pharmacologics at an early stage of IBD. Patients in whom colonoscopy reveals deep ulcers and extensive loss of the mucosal tissue, together with those who have a long history of exposure to multiple pharmacologics to which the disease has become refractory, may not benefit from GMA [41,43].

Our study does have several limitations. First, this was a single-center investigation involving a limited number of patients. Second, assessment of efficacy was based on the CDAI and the IOIBD scores, which may not adequately factor in intestinal inflammation, but we hope that a future study with a larger patient cohort can consider endoscopic findings over a longer follow-up time. Third, patients were followed up for only 10 weeks after the initiation of GMA, but the full efficacy of GMA may take more than 10 weeks to be seen. Fourth, no conclusion could be made on the likely influence of the baseline conventional medications on

the FDG uptake. Nonetheless, the ability of FDG-PET to show reduced disease activity after successful treatment of a CD flare-up has important clinical implications, and a large-scale, long-term study is warranted to strengthen the findings of this study.

In conclusion, our study showed that observation of longitudinal changes in FDG-PET uptake in involved bowel areas is of potential clinical value for assessing both regional and global bowel disease activity in CD patients during GMA therapy. Although a large-scale study with an extended follow-up time is warranted to strengthen the findings of our study, the ability of FDG-PET to show reduced disease activity after successful treatment of a CD flare-up has many clinical implications.

Disclosure of interest: The authors have no commercial, proprietary, or financial interest in the products or companies described in this article.

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