with those in N-group, it seems plausible that the increased levels of those miRNAs can be a possible therapeutic biomarker for the induction therapy of IFX. Finally, we did not specify the source of serum miRNAs. Since miRNAs from different cell types seem to have different biological consequences for the development of CD,[22,44] simultaneous analyses of miRNAs expression levels using intestinal tissues and peripheral blood cells ought to be necessary. However, we believe that the present study could demonstrate important implications with regard to the therapeutic mechanisms of IFX because this is the first study that showed the distinctive expression patterns of the serum miRNAs according to the therapeutic efficacy by IFX.

In conclusion, our study demonstrated differences in serum expression of let-7d and let-7e according to the therapeutic efficacy by IFX. Although the other three miRNAs (miR-28-5p, miR-221, and miR-224) also showed increases in their expression during the induction therapy, the biological implication of those miRNAs remains unclear. The accumulation of studies focusing on biological and clinical roles of miRNAs may reveal further pathophysiological mechanisms in CD.

Acknowledgments

This study was supported by JSPS KAKENHI Grant Number 22590707. We appreciate the technical support from the Research Support Center, Graduate School of Medical Sciences, Kyushu University.

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Digestive Endoscopy 2014; **26**: 369–376 doi: 10.1111/den.12187

Original Article

Emergency endoscopy for acute gastrointestinal bleeding: Prognostic value of endoscopic hemostasis and the AIMS65 score in Japanese patients

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Background and Aim: To evaluate the prognostic factors, including risk scores (Glasgow-Blatchford score and AIMS65) in patients with acute upper or lower gastrointestinal bleeding.

Methods: The medical records of patients who had undergone emergency gastrointestinal endoscopy for suspected gastrointestinal bleeding during the past 5 years were retrospectively analyzed.

Results: A total of 232 endoscopies (130 esophagogastroduodenoscopies, 102 colonoscopies) for 192 patients met the inclusion criteria. Median age was 66 years, and 64% of patients were males. Endoscopy identified causes for bleeding in 173 patients (post-endoscopic interventions for neoplastic lesions in 36 cases, colonic diverticula in 34, gastroduodenal ulcers in 29, gastric erosions in 15, vascular ectasia in 14, post-biopsy bleeding in 13, malignant tumors in 10, inflammatory conditions in nine, esophagogastric varices in five, Mallory-Weiss tears in four, nasal bleeding in three, and injury by swallowed blister pack in one), whereas the source of bleeding remained obscure in 19 patients. Blood transfusion was given in 97 patients (51%), and 97 (51%) underwent endoscopic hemostasis. During the follow-up period, 49 patients (26%) experienced rebleeding, seven of whom were treated by interventional radiology. Thirty-nine patients (20%) died as a result of various diseases. The probabilities of overall survival (OS) after 3 and 5 years were 71% and 67%, respectively. Cox multivariate analysis revealed blood transfusion, co-existing malignancy, absence of endoscopic hemostasis, and high AIMS65 score to be independent prognostic factors for poor OS.

Conclusion: The AIMS65 score is useful for predicting the prognosis of patients with acute gastrointestinal bleeding.

Key words: AIMS65, emergency endoscopy, gastrointestinal bleeding, hemostasis, prognosis

INTRODUCTION

GASTROINTESTINAL (GI) BLEEDING is one of the most important disease presentations in the emergency department. The course of the disease ranges from a self-limiting process to a life-threatening condition that requires emergency intervention. Evaluation of severity and the need for endoscopic hemostasis are matters of immediate decision. In Western countries, several prognostic scoring systems have been used to predict outcomes of upper GI bleeding, such as the Rockall score,[1] Glasgow-Blatchford score (GBS),[2,3] and the AIMS65 score.[4,5] To date, however, the prognostic value of these scores has been evaluated in Japanese patients in one study only.[6] In addition, any prognostic scoring system for lower GI bleeding has not yet been established.

In the present study, we retrospectively analyzed the prognostic factors, including GBS and AIMS65 score, in Japanese patients with acute upper and/or lower GI bleeding who required emergency endoscopy.

METHODS

Patient selection

THE MEDICAL RECORDS of all patients who underwent emergency GI endoscopy at Kyushu University Hospital, Fukuoka, Japan, between 2008 and 2012 were retrospectively reviewed. During the study period, a total of

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Received 7 August 2013; accepted 6 September 2013.

31 199 GI endoscopic examinations were carried out; that is, 18 721 examinations by esophagogastroduodenoscopy (EGD), 11 337 by colonoscopy, and 1141 by small bowel endoscopy (balloon-assisted enteroscopy or capsule endoscopy). Among them, there were 232 emergency endoscopic examinations for acute GI bleeding in 192 patients. Those examinations included 130 EGD in 109 patients (upper GI group) and 102 colonoscopies in 83 patients (lower GI group). These 192 patients were included in the present study.

Data collection and evaluation

In all 192 patients, the following clinical and laboratory data were collected: age, sex, medical history, serum albumin level, international normalized ratio (INR) of prothrombin time, blood urea nitrogen, hemoglobin, systolic blood pressure, pulse rate, mental status, presence of melena or syncope, and medications including proton pump inhibitors (PPI), histamine H2 receptor antagonists (H2RA), nonsteroidal anti-inflammatory drugs (NSAIDs), antithrombotic agents including antiplatelet agents (low-dose aspirin, ticlopidine and/or clopidogrel) and/or anticoagulant agents (warfarin or dabigatran). The GBS (Table 1) and AIMS65 score (Table 2) at initial endoscopy were calculated in all patients. Hepatic disease was defined as known history, or clinical and laboratory evidence, of chronic or acute liver disease, whereas heart failure was defined as known history, or clinical and echocardiographic evidence, of cardiac failure.[2] Altered mental status was defined as Glasgow Coma Scale score <14 or physician-charted designation of disorientation, lethargy, stupor, or coma.[4,5] High-risk patients were defined as those with GBS ≥12, and those with AIMS65 ≥2.[5] Comorbid diseases, such as cardiovascular diseases, diabetes, malignancies or others were abstracted through medical chart review. Presence or absence of blood transfusion and endoscopic hemostasis were also recorded. Indication for blood transfusion was determined by the physician in charge of each patient and included conditions such as the presence or absence of altered mental status, tachycardia, changes of hemoglobin level and systolic blood pressure. *Helicobacter pylori* infection was investigated by serology, histology, rapid urease test, and/or ^{13}C urea breath test in 130 patients, of whom ^{13}C urea breath test was carried out in four patients at least 8 weeks after discontinuation of PPI.

Table 1 Glasgow-Blatchford score at initial endoscopy in patients undergoing emergency endoscopy for acute GI bleeding (n = 192)

Risk factors	Score	No. patients
Blood urea nitrogen (mg/dL)		
<18.2	0	65
≥18.2 to <22.4	2	27
≥22.4 to <28	3	16
≥28 to <70	4	60
≥70	6	24
Hemoglobin, men (g/dL)		
≥13	0	15
≥12 to <13	1	10
≥10 to <12	3	16
<10	6	81
Hemoglobin, women (g/dL)		
≥12	0	0
≥10 to <12	1	8
<10	6	62
Systolic blood pressure (mmHg)		
≥110	0	75
≥100 to <109	1	32
≥90 to <99	2	36
<90	3	49
Other markers		
Pulse rate ≥100 b.p.m.	1	61
Melena	1	152
Syncope	2	12
Hepatic disease†	2	15
Heart failure‡	2	54
Maximum score	23	

†Known history, or clinical and laboratory evidence, of chronic or acute liver disease.
‡Known history, or clinical and echocardiographic evidence, of cardiac failure.
GI, gastrointestinal.

Table 2 AIMS65 score at initial endoscopy in patients undergoing emergency endoscopy for acute GI bleeding (n = 192)

Risk factors	Score	No. patients
Albumin <3.0 mg/dL	1	85
INR >1.5	1	30
Altered mental status	1	21
Systolic blood pressure <90 mmHg	1	49
Age >65 years	1	98
Maximum score	5	

GI, gastrointestinal; INR, international normalization ratio.

Prognostic factors and statistical analysis

Outcomes of patients were evaluated by rebleeding and overall survival (OS). Rebleeding was defined as a further episode of bleeding occurring since hospitalization after the initial bleeding had stopped, based on clinical evidence including recurrent hematemesis, melena, hematochezia or circulatory instability. OS was measured from the date of emergency endoscopy to death from any cause. The probabilities of OS were calculated by the Kaplan–Meier method,

and the values were compared using the log–rank test. Variables with probabilities (*P*-values) <0.1 were included in multivariate analyses using the Cox proportional hazards model. Other statistical differences were evaluated by Fisher's exact probability test, chi-squared test or Mann–Whitney *U*-test. Probabilities <0.05 were regarded as statistically significant.

The study protocol was approved by the ethics committee at Kyushu University Hospital, and the study was conducted in accordance with the Helsinki Declaration.

RESULTS

Patient characteristics and etiology for GI bleeding

CHARACTERISTICS OF PATIENTS are summarized in Table 3. Patients aged from 12 to 89 years (median, 66 years), and they consisted of 122 men (64%) and 70 women (36%). The most frequent cause for bleeding was post-endoscopic treatment (endoscopic mucosal resection [EMR] or endoscopic submucosal dissection [ESD]) for neoplastic lesions ($n = 36$), followed by diverticular disease ($n = 34$), gastroduodenal peptic ulcers ($n = 29$), gastroduodenal erosions ($n = 15$), vascular ectasia ($n = 14$), post-biopsy ($n = 13$), malignant neoplasia ($n = 10$), inflammatory conditions ($n = 9$), esophagogastric varices ($n = 5$), Mallory-Weiss tears ($n = 4$), nasal bleeding ($n = 3$), and injury by swallowed blister pack ($n = 1$). The source of bleeding remained obscure in 19 patients. The sites of bleeding origin were as follows: nasal cavity in three patients, esophagus in seven, stomach in 60, duodenum in 30, small bowel in nine, colon in 49, rectum in 12, ileal pouch in two, and anus in one; in the remaining 19 patients, the sites were undetermined. Among the nine patients with small bowel bleeding, the site of bleeding origin was diagnosed as the ileum by ileocolonoscopy in all six patients in the lower GI group, and as the jejunum by EGD in all three patients in upper GI group who had undergone total or subtotal gastrectomy. In the upper GI group, the most frequent cause was gastroduodenal ulcer (27%), whereas diverticular disease was the most frequent cause in the lower GI group (40%).

Comorbid diseases were found in 172 patients (90%); the most common was cardiovascular disease ($n = 86$), followed by malignant neoplasm ($n = 82$), and diabetes mellitus ($n = 51$). Others included renal disease ($n = 42$), neurological/mental disorder ($n = 36$), chronic inflammatory disease (including inflammatory bowel disease and rheumatic disease; $n = 32$), hepatic disease ($n = 15$) and immune thrombocytopenic purpura ($n = 2$). *Helicobacter pylori* infection was detected in 63 of 130 patients (48%) examined. Antithrombotic agents had been given in 70 patients (36%); single antiplatelet in 25, single anticoagulant in 24, antiplatelet plus anticoagulant in 13, and two antiplatelet agents in eight. NSAIDs other than aspirin were given in 39 patients (20%). Acid suppressants (PPI or H2RA) had been given in 87 patients (45%): 60 (31%) had PPI, whereas H2RA had been given in 27 patients (14%). No differences were observed between upper and lower GI groups in comorbid diseases or medication.

Treatment and prognostic factors

At emergency endoscopy, hemoglobin levels ranged from 2.9 to 16.0 g/dL (median, 7.9); the levels were significantly lower in patients who underwent EGD (upper GI group, median, 7.3 g/dL) than in those undergoing colonoscopy (lower GI group, median 8.8 g/dL, $P < 0.001$). Blood transfusion was given in 97 patients (51%), and endoscopic hemostasis was carried out in 97 patients (51%; Table 3), the methods of which included hemostatic clipping in 40 patients, electrocautery forceps with soft coagulation in 16, argon plasma coagulation in eight, hypertonic saline-epinephrine solution injection in seven, ethanol injection in five, band ligation in two, and a combination of these in 19.

The median follow-up period of all 192 patients after initial endoscopy was 11.4 months (range, 0–64.4 months). During the follow-up period, 49 patients (26%) developed rebleeding, of whom seven patients were treated by interventional radiology and two patients required surgical resection. Thirty-nine patients (20%) died as a result of various diseases (19 malignancies, eight serious infections, three bleeding events, three cardiac events, six others).

The median GBS value was 12 (range 0–20, maximum score 23), the value of which was significantly higher for the upper GI group (median 13) than the lower GI group (median 10, $P < 0.001$; Table 3). Figure 1 indicates the distribution of the number of patients with rebleeding and death, according to the GBS. Ninety-three patients (48%) had low-risk (score ≤11) GBS, and 99 patients (52%) were at high risk (score ≥12). Frequency of rebleeding was not different between high-risk ($n = 29$, 29%) and low-risk ($n = 20$, 22%) patients, whereas the mortality was significantly higher in high-risk patients (30%) than in low-risk patients (9.7%, $P < 0.001$). When we analyzed the lower-GI group only, the mortality was still higher in high-risk patients (27%) than in low-risk patients (6.0%; $P < 0.05$).

Distribution of patients according to AIMS65 score is shown in Figure 2. The median AIMS65 value was 1 (range 0–4, maximum score 5), which was significantly higher for the upper-GI group (median 2) than for the lower-GI group (median 1, $P < 0.005$). Ninety-eight patients (51%) had a low-risk (score of 0 or 1) AIMS65 score, and 94 patients (49%) were at high risk (score ≥3). Frequency of rebleeding

Table 3 Characteristics of patients undergoing emergency endoscopic examinations for acute GI bleeding (*n* = 192)

Characteristics	All patients (*n* = 192)	Upper GI (*n* = 109)	Lower GI (*n* = 83)
Age			
Median (range, years)	66 (12–89)	67 (12–87)	65 (12–89)
Sex			
Male (%)	122 (64)	70 (64)	52 (63)
Endoscopic findings, *n* (%)			
Post-EMR/ESD ulcer	36 (19)	20 (18)	16 (19)
Diverticular disease	34 (18)	1 (0.9)	33 (40)
Gastroduodenal ulcer	29 (15)	29 (27)	0
Erosions	15 (7.8)	7 (6.4)	8 (10)
Vascular ectasia	14 (7.3)	12 (11)	2 (2.4)
Post-biopsy hemorrhage	13 (6.8)	8 (7.3)	5 (6.0)
Malignant neoplasia	10 (5.2)	10 (9.1)	0
Inflammation	9 (4.7)	4 (3.7)	5 (6.0)
Varices	5 (2.6)	5 (4.6)	0
Mallory-Weiss tear	4 (2.1)	4 (3.7)	0
Nasal bleeding	3 (1.6)	3 (2.8)	0
Injury by blister pack	1 (0.5)	0	1 (1.2)
Unknown	19 (10)	6 (5.5)	13 (16)
Comorbidity, *n* (%)			
Cardiovascular disease	86 (45)	50 (46)	36 (43)
Malignancy	82 (43)	49 (45)	33 (40)
Diabetes	51 (27)	34 (31)	17 (20)
Renal disease	42 (22)	24 (22)	18 (22)
Neurological/mental disease	36 (19)	21 (19)	15 (18)
Chronic inflammatory disease	32 (17)	14 (13)	18 (22)
Hepatic disease	15 (7.8)	10 (9.2)	5 (6.0)
ITP	2 (1.0)	2 (1.8)	0
None	20 (10)	7 (6.4)	13 (16)
Helicobacter pylori infection			
Positivity/examined case (%)	63/130 (48)	44/87 (51)	19/43 (44)
Medications, *n* (%)			
Antithrombotic agents	70 (36)	39 (36)	31 (37)
NSAIDs	38 (20)	19 (17)	19 (23)
Acid suppressants (PPI/H2RA)	87 (45)	58 (53)	29 (35)
Treatment, *n* (%)			
Blood transfusion	97 (51)	66 (61)	31 (37)
Endoscopic hemostasis	97 (51)	67 (61)	30 (36)
Interventional radiology	7 (3.6)	4 (3.7)	3 (3.6)
Surgery	2 (1.0)	0	2 (2.4)
Outcomes, *n* (%)			
Median hospital stay (range, days)	15 (1–111)	15 (1–111)	13 (1–83)
Rebleeding	49 (26)	31 (28)	18 (22)
Mortality	39 (20)	27 (25)	12 (14)
Score values, median (range)			
GBS	12 (0–20)	13 (0–20)	10 (1–19)
AIMS65	1 (0–4)	2 (0–4)	1 (0–4)

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; GBS, Glasgow-Blatchford score; GI, gastrointestinal; H2RA, H2 receptor antagonist; ITP, immune thrombocytopenic purpura; NSAIDs, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

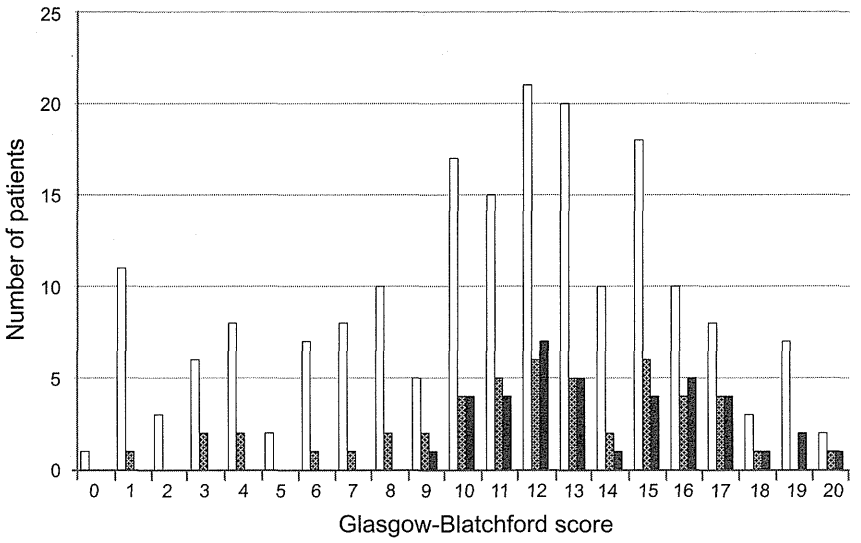

Figure 1 Distribution of total number of patients, rebleeding and death, according to the Glasgow-Blatchford score. □, total number of patients; ▩, patients with rebleeding; ■, patients who died.

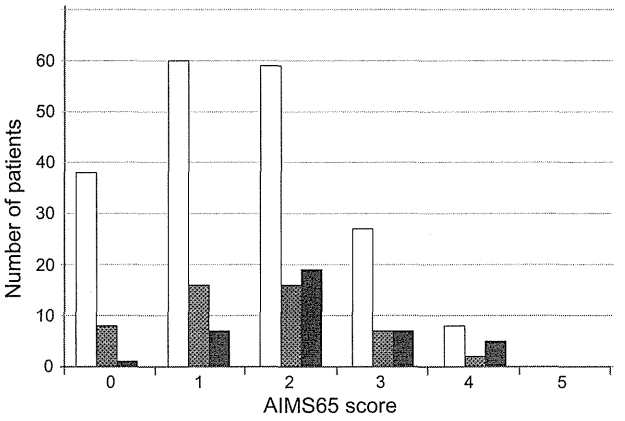

Figure 2 Distribution of total number of patients, rebleeding and death, according to the AIMS65 score. □, total number of patients; ▩, patients with rebleeding; ■, patients who died.

was not different between high-risk (27%) and low-risk (25%) patients, whereas the mortality was significantly higher in high-risk patients (33%) than in low-risk patients (8.1%, $P < 0.0001$). When we analyzed the lower-GI group only, the mortality was still higher in high-risk patients (28%) than in low-risk patients (5.9%; $P < 0.05$).

Probabilities of overall survival (OS) in all 192 patients after 1 and 3 years were 83% and 71%, respectively (Fig. 3a). As shown in Table 4, univariate analyses for OS revealed GBS, AIMS65 score, blood transfusion, combined malignancy and endoscopic hemostasis to be significant factors. Figure 3b shows the OS curves as stratified by AIMS65 score; the 3-year OS probability in high-risk (score ≥2) patients (51%) was significantly lower than in low-risk patients (88%; $P < 0.001$). Probability of OS after 3 years tended to be lower in patients with upper GI bleeding (66%) than in those with lower GI bleeding (83%), but the difference was not statistically significant ($P = 0.099$). By Cox multivariate analysis, need for blood transfusion, combined malignancy, absence of endoscopic hemostasis, and high AIMS65 score were determined to be independent prognostic factors for adverse OS (Table 4).

DISCUSSION

IN THE PRESENT study, we found the utility of both GBS and AIMS65 score in predicting the survival of Japanese patients with acute GI bleeding who required emergency endoscopy. Both risk scores were useful not only in patients with upper GI bleeding, but also in those with lower GI bleeding.

The usefulness of GBS has been reported mostly from European countries, USA, Australia, and a few Asian countries.[1–3,5–12] It has been shown that GBS was consistently similar or superior to the Rockall score for predicting outcomes in patients with upper GI bleeding.[3,7–9] However, GBS has not been widely adopted in routine clinical practice, because it is weighed and it assigns points to several elements in the patients' medical history and laboratory data, some of which lack a clear definition (Table 1).[5]

The AIMS65 score is a newly proposed scoring system that is quite simple and can be used in clinical practice without difficulty (Table 2).[4,5] In their retrospective study, Hyett *et al.* reported that the AIMS65 score was superior to GBS in predicting inpatient mortality.[5] In our multivariate analysis, the AIMS65 score, but not GBS, was determined to

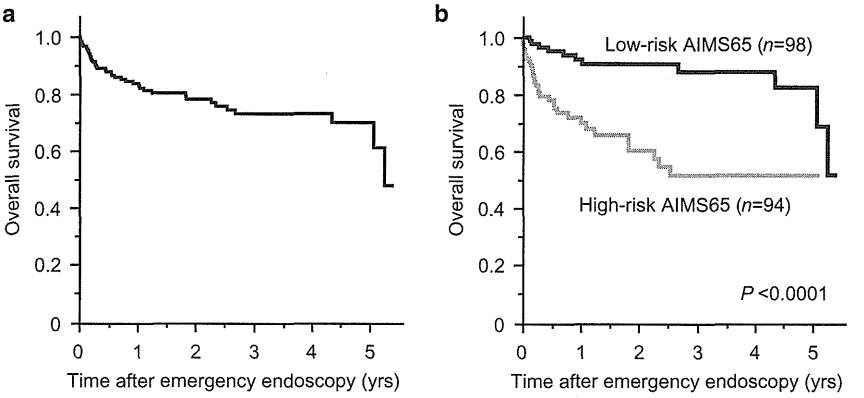

Figure 3 Overall survival (OS) curves of 192 patients who underwent emergency endoscopy for acute gastrointestinal bleeding. (a) Probabilities of OS in all 192 patients after 1 and 3 years were 83% and 71%, respectively. (b) OS curves as stratified by the AIMS65 score ($P < 0.0001$).

Table 4 Prognostic factors for adverse overall survival as determined by univariate and multivariate analyses

Factors	Kaplan–Meier	Cox multivariate analysis	
	P-value	Hazard ratio (95% CI)	*P*-value
Age (≥66 years)	0.773	NE	
Sex (male)	0.511	NE	
Upper GI *vs* lower GI	0.099	1.36 (0.68–2.86)	0.388
GBS (score ≥12)	<0.001	1.52 (0.69–3.64)	0.304
AIMS65 (score ≥2)	<0.001	2.36 (1.06–5.67)	0.034
Cardiovascular disease	0.604	NE	
Diabetes mellitus	0.131	NE	
Malignancy	0.099	2.02 (1.08–3.81)	0.028
Helicobacter pylori	0.122	NE	
Antithrombotic agents	0.759	NE	
NSAIDs	0.147	NE	
Acid suppressant	0.419	NE	
Blood transfusion	<0.001	3.28 (1.39–8.79)	0.005
Endoscopic hemostasis	0.027	2.55 (1.29–5.26)	0.006

CI, confidence interval; GBS, Glasgow-Blatchford score; GI, gastrointestinal; NE, not evaluated; NSAIDs, non-steroidal anti-inflammatory drugs.

be an independent prognostic factor for OS. We thus consider that AIMS65 is the best in predicting the prognosis of patients with acute GI bleeding.[13] Reasons for the difference between the two scoring systems are uncertain. Nonetheless, all of the five parameters in the AIMS65 score seem more appropriate as prognostic factors, compared to those in the GBS. We speculate that older age (>65 years) or low levels of albumin (<3.0 mg/dL) might have directly affected the mortality of patients.

It should be noted that both GBS and AIMS65 score values were significantly higher for the upper-GI group than for the lower-GI group (Table 3). Whereas age of patients, levels of systolic blood pressure, frequencies of hepatic disease, heart failure or melena did not differ between the two groups, hemoglobin levels were significantly lower in the upper-GI group (median 7.3 g/dL) than in the lower-GI group (median 8.8 g/dL). In addition, patients with elevated levels of blood urea nitrogen (78% *vs* 51%), decreased levels of albumin (53% *vs* 33%), tachycardia (39% *vs* 23%), and altered mental status (17% *vs* 4%) were more frequent in the upper-GI group than in the lower-GI group (detailed data not shown). The latter observations were considered to have affected the differences in both scores. Thus, the general condition in patients with upper GI bleeding seemed more serious than in those with lower GI bleeding, although OS of patients did not statistically differ in our study ($P = 0.099$, Table 4).

In our current study, the most frequent cause for upper GI bleeding was gastroduodenal (peptic) ulcer (27%), which is compatible with previous studies.[1,3,5–7,10,12] The most frequent cause for lower GI bleeding was diverticular disease (40%), which is also concordant with previous reports.[13–15] It should

be noted that post-EMR/ESD ulcer was the second-most frequent cause for both upper (18%) and lower (19%) groups (Table 3). In a large population-based study from the USA,[16] post-polypectomy bleeding was found in 262 of 29 988 patients (0.87%); the frequency was significantly higher than for screening colonoscopy (0.21%). Another large study from Canada also reported similar results.[17] Recently, the occurrence of post-ESD bleeding has increased as a result of the widespread use of ESD for not only gastric, but also for colorectal neoplastic, lesions.[18]

Various methods for endoscopic hemostasis have been described. In our hospital, clipping was most frequently used (40 patients). In the lower-GI group, 27 of 30 patients (90%) who underwent endoscopic hemostasis were treated only by clipping (data not shown). Hemoclip is useful not only for post-EMR/ESD ulcers, but also for hemorrhagic diverticula.[19] Recently, efficacy of endoscopic band ligation for diverticular hemorrhage has been reported.[13,20] In the upper-GI group, electrocautery forceps with soft coagulation was the most frequently used. Of 67 patients who underwent endoscopic hemostasis, 26 (39%) were treated by coagulation forceps, 10 of whom whose treatment was combined with other methods. This method has become the most useful hemostatic method for peptic ulcer disease and artificial ulcers after EMR/ESD.[21]

There are some limitations in the present study. The retrospective nature seems to have been a source of selection biases and the number of study patients was small. Various methods were used for endoscopic hemostasis and the choice of method depended on the endoscopist. Despite these shortfalls, we believe that our results, especially the prognostic value of the AIMS65 score, will be useful for readers.

In conclusion, the AIMS65 score is useful for predicting the prognosis of patients with acute upper and lower GI bleeding. Prospective validation and comparisons of this score with other prognostic systems are awaited.

CONFLICT OF INTERESTS

AUTHORS DECLARE NO conflict of interests for this article.

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Original Paper

Patients' Assessment of Adalimumab Self-Injection for Crohn's Disease: A Multicenter Questionnaire Survey (The PEARL Survey)

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Key Words: adalimumab, self-injection, Crohn's disease, patient reported outcomes, adherence

Abbreviations: ADA:adalimumab,CD:Crohn's disease,QOL: quality of life, IFX:infliximab, CZP:certolizumab pegol, ECCO:European Crohn's and Colitis Organization, IBD:inflammatory bowel disease

ABSTRACT

Background/aims: Adalimumab (ADA) is a self-injectable anti-tumor necrosis factor-α antibody used for treating Crohn's disease (CD). Although self-injecting ADA may be convenient for patients, few reports have assessed patients receiving ADA self-injection therapy. **Methodology:** We conducted a questionnaire survey involving outpatients on ADA self-injection therapy at four university hospitals. We analyzed the degree of satisfaction with and adherence to the self-injection therapy and performed sub-analyses. **Results:** Responses were obtained from 124 patients. Before treatment initiation, 38% patients replied that they were unwilling to accept the self-injection therapy. However, after treatment initiation, 75% patients were satisfied with the treatment. 66 patients previously treated with infliximab (IFX), the degree of treatment satisfaction was significantly higher in patients who felt burdened to the time required for IFX infusion than in those who had not felt burdened ($P < 0.05$). Patient adherence to ADA was high (85%). Multivariate analysis regarding adherence revealed that duration of disease (OR, 0.99), degree of treatment efficacy satisfaction (OR, 13.42), and schedule registration (OR, 7.95) were significant. Safety assessment results were within the range of those already reported. **Conclusions:** ADA self-injection was thought to have good adherence and a safe administration method according to patients' assessments.

INTRODUCTION

Crohn's disease (CD) is an inflammatory bowel disease associated with chronic inflammation of the gastrointestinal tract, for which no radical treatment is currently available and patient quality of life (QOL) is impaired.(1) Autoimmunity is involved in the pathology of CD, with excessively expressed cytokine tumor necrosis factor-α (TNF-α) being an important factor.(2) Anti-TNF-α antibodies are known to be highly effective for inducing(3,4) and maintaining remission([illegible] in CD and are currently considered the most effective therapy for CD.7 Adalimumab (ADA), one of the anti-TNF-α antibodies, is a fully human monoclonal antibody, available as a self-injectable subcutaneous injection. Such injections are easily administered, convenient to use, and well accepted by patients.(8) However, few reports have assessed patients receiving ADA self-injection therapy. Specifically, concerns have been raised regarding adherence to therapy.(9) The efficacy of ADA for inducing and maintaining remission, as well as CD treatment safety, has been confirmed in Japan(10); since October 2010, the drug has been used to treat patients with moderate-to-severe CD that is resistant to other therapies. We conducted a multicenter questionnaire survey (the PEARL survey: Patients assessment of Humira [adalimumab] self-injection) to evaluate the efficacy, safety and problems associated with ADA self-injection therapy.

METHODOLOGY

Study design

In this study, a questionnaire survey was conducted on patients with CD from February to August 2012 at four university hospitals in Japan. We did not perform statistical calculations to decide sample size; instead, we considered the state of ADA use at the 4 facilities and selected 100 patients as a feasible target number. The questionnaire survey of ADA self-injecting patients was conducted after obtaining informed consent following oral and written explanations of the study. Approval was obtained from the individual ethical committees of the four university hospitals before study initiation.

Hepato-Gastroenterology 2014; 61:1654-1660 doi 10.5754/hge 14471

This study was registered in the Clinical Trial Registry at UMIN.ac.jp (ID: UMIN000007197).

Questionnaire

We developed an original questionnaire for the purposes of this study. The questionnaire contents were as follows: (1) age; (2) gender; (3) disease duration; (4) employment status; (5) Travel time to the hospital; (6) ADA administration duration; (7) injection sites; (8) injecting person; (9) infliximab (IFX) treatment history; (10) concomitant drugs; (11) history of surgery; (12) willingness to accept self-injection therapy before treatment initiation (yes/no); (13) worries about self-injection therapy (1: no worries, 2: obscure, 3: a little worried, and 4: very worried); (14) reasons for self-injection therapy worries; (15) reasons for switching from IFX (loss of response/intolerance/convenience/other); (16) burden of time required for IFX infusion (1, not burdensome; 2, a little burdensome; 3, burdensome); (17) IFX infusion reactions (never/sometimes/always); (18) degree of satisfaction with self-injection therapy (1: very satisfied, 2: more or less satisfied, 3: obscure, 4: more or less unsatisfied; and 5: very unsatisfied); (19) merits of self-injection therapy (reduced treatment time/reduced frequency of hospital visits/no days off from work or school/other); (20) satisfaction with ADA treatment efficacy (1: very satisfied, 2: more or less satisfied, 3: obscure, 4: more or less unsatisfied, and 5: very unsatisfied); (21) degree of pain at the time of ADA injection (1: no pain, 2: weak pain that does not affect treatment continuation, 3: strong pain that does not affect treatment continuation, and 4: strong pain that affects treatment continuation); (22) measures to alleviate injection pain; (23) adverse events related to ADA self-injection (injection site reactions, adverse reactions, and injection failure), (24) adherence to ADA self-injection therapy (1: very good, 2: occasionally poor, 3: often poor, and 4: very poor/not injected); (25) schedule registration: entered the date of treatment in their calendars or schedule diaries, and registered the treatment date in the alarm of their mobile phones (yes/no); (26) willingness to continue ADA self-injection therapy (yes/no). To avoid bias as much as possible, each patient completed the questionnaire without a physician or nurse present.

Inclusion and exclusion criteria

Patients surveyed in this study were those who had started ADA treatment at least 4 weeks before the survey and were on maintenance therapy with self-injections of 40mg ADA every other week. All patients, regardless of age, gender, concomitant drugs, disease duration, disease type and severity, and other factors, except those from whom informed consent was not obtained, were surveyed and included in the analysis. Questions that were partially uncompleted were excluded only the questions from analysis. The completed questionnaires were serially numbered and controlled at the individual facilities to avoid compromise of personal information.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 20 (IBM Japan Ltd., Tokyo, Japan). Significance tests were performed using the chi-square test or Fisher's exact test for categorical data and Student's t-test or Mann Whitney U test for continuous variables. Logistic regression analysis was used for multivariate analyses. Differences were judged statistically significant when P was < 0.05.

RESULTS

Patient characteristics

The questionnaire was administered to all 124 eligible patients (except 1 patient who refused to participate in the survey) at the 4 hospitals during the study period. We surveyed a total of 124 patients after obtaining their informed consent. Baseline characteristics of the patients are shown in Table 1. Mean patient age was 36.3 ± 11.8 years; 86 patients (69.4%) were male, 66 patients (53.2%) were previously treated with IFX, and mean ADA treatment duration was 11.4 ± 10.6 months. For patients previously treated with IFX, the reasons for switching to ADA treatment were as follows: loss of response, 27 patients (40.9%); intolerance, 26 patients (39.4%); convenience, 6 patients (9.1%); and other, 7 patients (10.6%). Among the 66 patients previously treated with IFX, 45 patients (68.2%) felt that the time required for IFX drip infusion was burdensome.

Willingness to perform self-injections and worries before starting treatment

At the assessment before ADA treatment initiation, 46 (38.0%) of 121 patients were not willing to self-inject the drug. Only 28 (22.8%) of 123 patients replied that they were not worried about the self-injection, while 74 patients (60.2%) were worried about it (Figure 1). The most common reason for worry was "fear of injection" (40.0%); other reasons included "possible pain" (32.5%), "possible failure in injecting the drug" (24.2%), and "lack of confidence in dealing with adverse reactions" (33.3%).

Assessment after self-injection

Of the 120 patients, 90 (75.0%) were satisfied with the self-injection therapy (very satisfied: 40%, more or less satisfied: 35%). The satisfaction was no significant difference in comparison with the patients who were willing to accept self-injection and who were unwilling to accept before treatment initiation ($P = 0.380$; Figure 2a). Subgrouping of the patients previously treated with IFX, the satisfaction was significantly higher in patients who felt burdened by the time required for the IFX infusion than in those who had not felt burdened ($P = 0.012$; Figure 2b). The merits of self-injection therapy were replied "reduced treatment time" (48.0%), "reduced frequency of hospital visits" (39.0%), and "no days off from work or school" (24.4%). Of the 123 patients, 86 (69.9%) replied that they were satisfied with the ADA treatment efficacy (very satisfied: 27%, more or less satisfied: 43%). The degrees of satisfaction with the efficacy of ADA treatment were significantly different between those who were and those who were not previously treated with IFX ($P = 0.017$; Figure 3). Ultimately, 111 (93.3%) of 119 patients replied that they were willing to continue the ADA self-injection therapy.

Injection pain

Of the 120 patients, 30 (25.0%) said that they felt strong pain at the time of ADA injection; however, only two (1.7%) felt that the pain compromised their ability to continue treatment (Figure 4). To alleviate the pain, patients used measures such as "slow injection"

(90.8%), "using an adaptor (connector)" (63.3%), and "warming the drug solution with their palms" (54.2%).

Tolerability

With regard to ADA self-injection therapy-related adverse events, mild injection site reactions, such as swelling at the injection site, occurred frequently (33 of 123 patients; 26.8%). In addition, systemic adverse effects, such as urticaria, malaise, myalgia, and edema, occurred in 10.6% of the patients. Injection failures, such as leakage of drug solution, disconnection of the needle while injecting, and the needle failing to reach the subcutaneous area, occurred in 11.4% of patients.

Adherence

Of the 123 ADA self-injecting patients, 104 (84.6%) replied that they injected the drug without fail on the scheduled injection days (the good adherence group), 18 (14.6%) replied that they sometimes forgot or delayed the injection, and 1 (0.8%) had discontinued the injections (collectively, the poor adherence group). The main reason for non-adherence was that the patient forgot the administration day (i.e., unintentional delay). Intentional withdrawal or delay was observed in 2 patients (1.6%): due to apparent disease stability indicating lack of need for further injections in 1 patient, while the other patient simply chose to discontinue the injections. Of the 47 patients who entered "schedule registration" by putting the injection dates on their calendars or schedule dairies or by setting alarms on their mobile phones, 44 patients (93.6%) were good adherence. On univariate analyses, significant differences were observed in treatment efficacy satisfaction rates (P = .007) and the entry of "schedule registration" (P = .039) between the good adherence (n = 104) and poor adherence groups (n = 19). Furthermore, multivariate analyses allowed extraction of the following three factors related to good adherence: disease duration (months, odds ratio [OR]: 0.986, P = .007), treatment efficacy satisfaction (OR: 13.424, P = .004), and the entry of "schedule registration" (OR: 7.945, P = .017, Table 2).

DISCUSSION

Except for one previous report on ADA adherence(9), to our knowledge, this paper is the first survey report of ADA self-injection therapy by patients themselves. According to the European Crohn's and Colitis Organisation (ECCO) Guidelines, the efficacy and safety of the different anti-TNF-α drugs used for CD are similar, the choice of these drugs depending on the user, administration methods, patient preferences, costs, and individual country recommendations.(11) Three anti-TNF-α drugs—IFX, ADA, and certolizumab pegol (CZP)—have been approved for the treatment of CD. IFX is delivered via intravenous infusion, while ADA and CZP are delivered via subcutaneous injections. According to a report that investigated patient preferences, 36% of all patients preferred ADA, followed by CZP (28%) and IFX (25%), which indicates that many patients preferred subcutaneous injections because of the convenience and the shorter time required for these injections.(8) However, patient evaluations regarding the use of ADA or CZP are insufficient; in addition, a problem concerning adherence was previously suggested.(9) CZP has not been approved for use in Japan; so, we conducted a multicenter questionnaire survey of patients who were on ADA self-injection therapy.

In this study, we confirmed that many patients were initially worried about self-injection and were not willing to accept self-injection therapy. However, after experiencing self-injection therapy, many patients who were initially unwilling to self-injection realized that they were satisfied with the convenience of the therapy. It is important that physicians and nurses alleviate patients' worries, such as "fear of injection," "possible strong pain," and "possible failure of drug -injection," by providing self-injection explanations and training. Among the patients previously treated with IFX infusions, those who felt that the IFX drip infusion was burdensome were significantly more satisfied with the self-injection therapy. In other words, ADA was suitable for patients who felt burdened to the treatment time. This finding suggests the possibility that a particular anti-TNF-α antibody is more likely to be switched to another based on patient-specific factors, not only therapeutic factors such as intolerance or secondary failure. One report, however, warned that easy switching should be avoided12; therefore, further study is necessary regarding switching from IFX to ADA. The treatment efficacy of ADA was generally highly regarded; however, the degree of satisfaction with treatment efficacy in patients previously treated with IFX was significantly lower than that in patients not previously treated with IFX. Similar findings have also been reported in other publications.(13-16)

Although self-injection therapy is convenient, problems related to adherence and the measures to be taken at the time of adverse events are of concern. The non-adherence rate of IFX is reported to be 4–34.4%,(17,18)while good adherence is reported to be associated with lower medical costs, surgical rates and hospitalization rates.(19-21) One report from France stated an ADA treatment non-adherence rate of 45.4%(9); however, the rate in our study was clearly lower. Racial differences are reported to be involved in adherence in patients with inflammatory bowel disease (IBD)(22); therefore, this factor may have affected the results of both, the French and our study. The ADA treatment duration in our study was short (i.e., <1 year), which may have contributed to the higher adherence rate. Indeed, most cases of non-adherence in our study were unintentional (e.g., patients simply forgot to inject the drug), and there were very few cases of intentional non-adherence. It is possible that intentional non-adherence increases as the duration of symptom remission increases. A recent systematic review(23), about adherence to anti-TNF-α therapy in IBD, showed ADA pooled non-adherence excluded somewhat delay of injection was 16.9%. Although several methods were used to assess adherence, predictors for anti TNF-α non-adherence were female gender, smoking, constraints related to treatment, anxiety, and moodiness. Future studies, including long-term therapy with ADA should be conducted.

In this study, treatment efficacy, disease duration, and maintenance of an injection schedule were confirmed to be related to ADA adherence. The report from France(9) also suggested that most non-adherence factors may be avoidable; therefore, adherence can be improved by "schedule registration" and ensuring self-injection training. The adverse events encountered by our study subjects were within the range of those already reported.(24) No problems were identified regarding

self-injection-related adverse events or the measures to be taken if they occurred.

This study has some limitations. First the patients were already self-administering ADA, considering the number of eligible patients. As a result, the data could be biased to obtain more favorable results including recall bias for pre-ADA treatment assessment. Furthermore, the assessment includes patients with different ADA treatment duration. Second the original questionnaire that we used for the analysis was not validated, and we could not find similar examples. In addition, we did not assign a control group; therefore, further comparisons will not be possible. Third we did not assess disease activity in the questionnaire, which might have affected the results.

However, adherence and patients' preferences of anti-TNF-α antibodies are little known. Adherence and patients' preferences of ADA self-injection therapy have been generally good in the present study. Patients who felt burdened to IFX infusion time tended to be satisfied with ADA self-injection therapy. We were able to confirm these new insights from the present study.

In conclusion, despite a few limitations, this assessment of patients indicated that ADA self-injection therapy for CD was safe, with good treatment efficacy and patient adherence to therapy in Japan.

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Figure 1. Acceptance of self-injection before treatment initiation

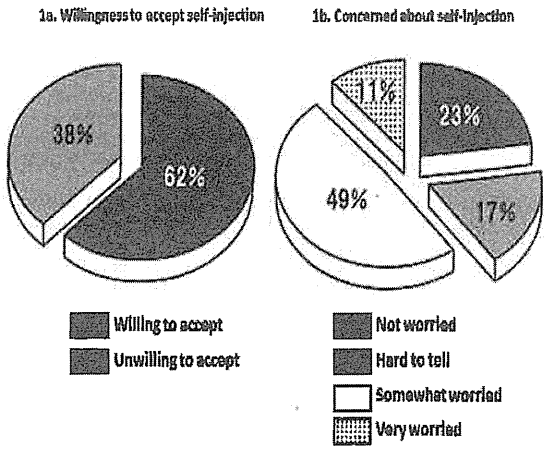

FIGURE 1. Acceptance of self-injection before treatment initiation. a) Patient willingness to accept self-injection before treatment initiation (yes/no, n = 121); b) Degree of patient concern about self-injection (n = 123) before treatment initiation.

Figure 2. Satisfaction with self-injection after treatment initiation

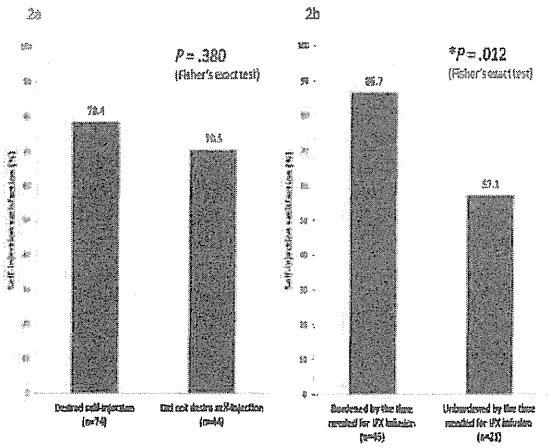

FIGURE 2. Satisfaction with self-injection after treatment initiation. a) Comparison of the rates of satisfaction (obtained by combining "very satisfied" and "more or less satisfied") with self-injection after treatment between 74 patients who were willing to accept self-injection and 44 patients who were unwilling to accept self-injection before treatment initiation. No significant difference was observed between the 2 groups (P = .380). b) Comparison of the rates of satisfaction with self-injection (obtained by combining "very satisfied" and "more or less satisfied") in 66 patients previously treated with IFX, consisting of 45 patients who felt burdened with the time required for the IFX drip infusion and 21 patients who did not feel burdened. A significant difference was observed between the 2 groups (P = .012).

Figure 3. Rates of patient satisfaction with adalimumab (ADA) treatment efficacy in terms of previous infliximab (IFX) treatment status

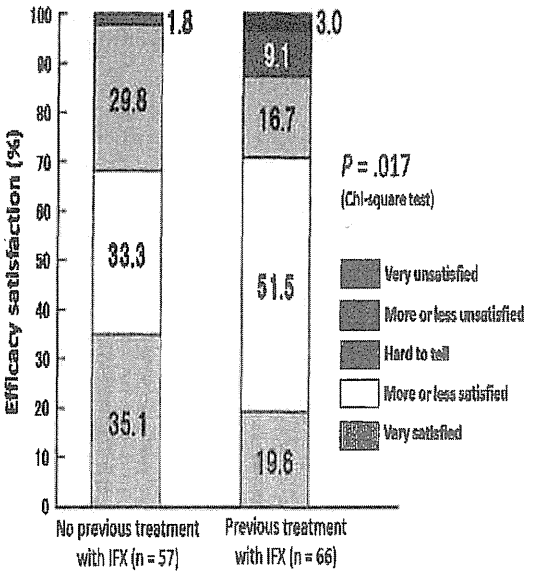

FIGURE 3. Rates of patient satisfaction with adalimumab (ADA) treatment efficacy in terms of previous infliximab (IFX) treatment status. Satisfaction rates of ADA treatment efficacy were compared between the 57 patients not previously treated with IFX and the 66 patients previously treated with IFX. A significant difference was observed between the 2 groups (P = .017).

Figure 4. Effect of adalimumab (ADA) subcutaneous injection pain on treatment continuation

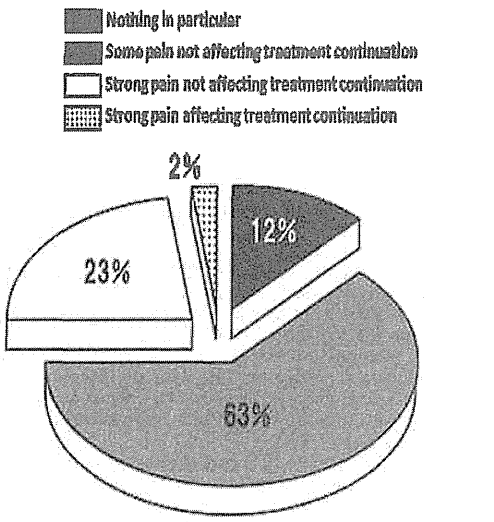

FIGURE 4. Effect of adalimumab (ADA) subcutaneous injection pain on treatment continuation in 120 evaluable patients.

TABLE 1. Baseline characteristics of the patients.

Patients (n)	124
Age (years; mean ± SD)	36.3 ± 11.8 (13–70)
Gender (male/female)	86/38
Disease duration (months; mean ± SD, range)	147.6 ± 109.4 (3–420)
History of surgery (yes)	79.2% (95/120)
Abdominal surgery	60.0% (72/120)
Perianal surgery	44.2% (53/120)
Travel time to the hospital (min; mean ± SD)	49.8 ± 32.4 (5–180)
Employment status	
Full time	52.0% (64/123)
Part time	9.5% (24/123)
Student	7.3% (9/123)
Housework helper	5.7% (7/123)
Unemployed	15.4% (19/123)
IFX experience (yes)	53.2% (66/124)
Reason for switching from IFX	
Loss of response	40.9% (27/66)
Intolerance	39.4% (26/66)
Convenience	9.1% (6/66)
Others	10.6% (7/66)
Concomitant medication	
Elemental diet	57.9% (70/121)
5-Aminosalicylate	61.2% (74/121)
Immunomodulator	33.1% (40/121)
Corticosteroid	5.8% (7/121)
ADA treatment duration (months; mean ± SD, range)	11.4 ± 10.6 (1–69)
Injection site	
Abdomen	94.2%(113/120)
Thigh	5.0%(6/120)
Arm	0.8%(1/120)
Injecting person	
Patient	99.2%(119/120)
Family	0.8%(1/120)

FX, infliximab; ADA, adalimumab

TABLE 2. Factors related to adalimumab adherence (multivariate analysis)

	Odds ratio (95% CI)	*P* value
Age (years)	1.074 (0.980–1.170)	.126
Gender (male)	0.534 (0.102–2.800)	.458
Disease duration (months)	0.986 (0.976–0.996)	*.007
Employed	0.727 (0.146–3.628)	.697
Satisfaction with self-injection	0.575 (0.110–3.004)	.512
Satisfaction with treatment efficacy	13.424 (2.249–80.117)	*.004
Schedule registration	7.945 (1.453–43.4)	*.017

Logistic regression analysis; $*P < .05$
Factors related to adalimumab (ADA) adherence (multivariate analysis)
Factors significantly related to good adherence and their odds ratios were identified using multivariate analysis of 104 patients with good adherence and 19 patients with poor adherence to therapy. Three factors—disease duration, satisfaction with treatment efficacy, and schedule registration— were identified as factors significantly related to good adherence.

J Gastroenterol (2014) 49:254–262
DOI 10.1007/s00535-013-0807-0

The Japanese Society of Gastroenterology

ORIGINAL ARTICLE—ALIMENTARY TRACT

C-reactive protein is an indicator of serum infliximab level in predicting loss of response in patients with Crohn's disease

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Received: 25 September 2012 / Accepted: 1 April 2013 / Published online: 20 April 2013

Abstract
Background The ability of serum infliximab level to predict clinical outcome in infliximab therapy in Crohn's disease is unclear. Here, we aimed to clarify the correlation between the timing of loss of response (LOR) to treatment and a decrease in serum infliximab level, and, in addition, to identify an indicator of infliximab level.
Methods The study used data from a previous clinical study of infliximab for Crohn's disease, in which infliximab was initially given at 0, 2, 6 weeks at 5 mg/kg, and then at 8-week intervals to 62 week-10 responders. Of these 62, here we analysed data from 57 in whom Crohn's disease activity index and serum infliximab level were evaluated at week 14.
Results Twelve patients showed a clinical response despite an infliximab level <1 μg/mL at week 14; of these, 8 (67 %) experienced LOR by week 54. A decrease in infliximab level preceded LOR in 6 (75 %). In receiver operating characteristic curve analysis, C-reactive protein (CRP) showed better performance in detecting an infliximab level <1 μg/mL. Infliximab level was <1 μg/mL in 60–80 % of patients with CRP >0.5 mg/dL. Time to LOR

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(median: 22.0 weeks) was significantly longer than that to a decrease in infliximab level to <1 μg/mL (14.0 weeks, $p < 0.05$) or to an increase in CRP to >0.5 mg/dL (14.0 weeks, $p < 0.01$).

Conclusions A decrease in serum infliximab level preceded LOR, and was easily detected by an increase in CRP. The CRP may be an indicator of serum infliximab level in predicting LOR.

Keywords Crohn's disease · Predicting loss of response · Serum infliximab trough level · C-reactive protein · Crohn's disease activity index

Introduction

Crohn's disease (CD) is a progressive disease, and patients often develop a stricturing or a perforating complication with repeated relapse and remission, eventually requiring surgery [1]. Repeated surgical procedures may result in intestinal dysfunction and decrease the quality of life of patients. These features emphasize the need for not only the early achievement of remission in the treatment of CD but also its long-term maintenance.

Treatment with infliximab, an anti-human tumor necrosis factor-α (TNF-α) monoclonal antibody, by intravenous administration of 5 mg/kg at weeks 0, 2, 6, and, thereafter, at 8-week intervals enables early remission and its maintenance in active CD [2, 3]. However, clinical response is lost in some patients during maintenance therapy [4]. One major cause of loss of response (LOR) to anti-TNF-α agents is considered to be the failure to maintain an effective serum level [5], and it is accordingly recommended that patients losing response be treated by a dose intensification, such as dose escalation or shortening of dosing interval [4–6].

We previously performed a clinical study in which dosing interval was shortened to 4 weeks in CD patients showing LOR during treatment with infliximab at 5 mg/kg at 8-week intervals [7]. The results indicated that: (1) clinical efficacy of infliximab correlated with its serum level; (2) a serum trough infliximab level of 1 μg/mL was the threshold for clinical efficacy; and (3) recovery of serum infliximab level in patients with LOR resulted in a high remission rate at week 54. Because this study defined LOR using the Crohn's disease activity index (CDAI) score, treatment could not be intensified until after the manifestation of symptoms. Instead, maintaining the quality of life and hindering disease progression would have been better achieved by intensifying treatment prior to the manifestation of symptoms.

Here, we hypothesized that a decrease in serum infliximab level precedes LOR as determined by CDAI score. To investigate this, we focused on the LOR caused by a decrease in infliximab level, and analyzed the timing of LOR and a decrease in trough infliximab level to below the effective level using data from the clinical study above. If confirmed, these findings would strongly support the benefit of monitoring serum infliximab level in the long-term maintenance of remission and help prevent the LOR caused by a decrease in infliximab level during maintenance infliximab treatment of 5 mg/kg at 8-week intervals. In addition, given that serum infliximab levels are not routinely monitored in daily practice, we also sought an indicator of a decrease in trough infliximab level below the effective level.

Methods

Patients and study design

This study was performed as a multicenter, open-label, controlled study. The study protocol was approved by each institutional review board and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. Written informed consent was obtained from all patients prior to registration. The study design, and criteria for patient registration, exclusion, and combination of nutritional and/or drug therapies have been described in detail in the previous report [7].

In brief, infliximab 5 mg/kg was administered at weeks 0, 2, and 6 to 64 patients with CD who had a CDAI score between 220 and 400 in spite of standard therapy. Maintenance therapy with infliximab 5 mg/kg at 8-week intervals was started in 62 patients who showed an improvement (decrease of ≥25 % and reduction of ≥70 points compared with baseline CDAI) by week 10 (week-10 responders). Patients meeting the criteria for LOR at weeks 14, 22, 30, 38, or 46 were administered infliximab at 5 mg/kg at 4-week intervals up to week 50.

Outcome measures

Outcome was evaluated by CDAI. Clinical response was defined as a decrease of ≥25 % and reduction of ≥70 points compared with baseline CDAI, and clinical remission as CDAI <150. The criteria for LOR were defined as

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follows: (1) CDAI ≥175; and (2) increase of ≥35 % and ≥70 points compared with the lowest CDAI up to week 10.

To assess serum levels of infliximab, blood samples were obtained before each treatment at weeks 0, 2, and 6, and then every 4 weeks until week 54. Serum infliximab levels were measured by an enzyme-linked immunosorbent assay using a monoclonal antibody against infliximab obtained from Janssen Biotech Inc. (Horsham, PA, USA) [8]. All measurements were performed by Mitsubishi Tanabe Pharma Corporation (Osaka, Japan). The detection limit was 0.1 μg/mL. In the present analysis, infliximab levels at trough were used, with the threshold trough level for clinical response set at 1 μg/mL based on the results of the previous study [7].

Among other laboratory tests, serum C-reactive protein (CRP) levels were determined by latex agglutination immunoassay (reference range ≤0.5 mg/dL); albumin by the bromocresol green method (reference range 3.8–5.3 g/dL); prealbumin and retinol-binding protein by nephelometry (reference range 22–40 and 2.9–7.9 mg/dL); and transferrin by turbidimetric immunoassay (reference range 190–320 mg/dL). Plasma levels of TNF-α and interleukin-6 (IL-6) were measured by chemiluminescence enzyme immunoassay. All measurements were performed by Mitsubishi Chemical Medience Corporation (Tokyo, Japan).

Statistical analysis

A marker for detecting serum trough infliximab levels of <1 μg/mL was explored in patients treated at 8-week intervals. Receiver operating characteristic (ROC) curve analysis was performed for the following clinical and laboratory parameters using a trough infliximab level of <1 μg/mL as positive. Clinical parameters (CDAI measurement items) were soft/liquid stool score, abdominal pain score, general well-being score, hematocrit (Hct) (male: 47-Hct, female: 42-Hct), and percent below standard body weight; while laboratory parameters were CRP, albumin, prealbumin, transferrin, retinol-binding protein, and IL-6. The TNF-α was excluded from the ROC curve analysis because levels cannot be accurately measured in the presence of infliximab.

Parameters with the highest area under the ROC curve (AUC) were analyzed with regard to accuracy, sensitivity, and specificity at an appropriate cut-off value. The correlation between infliximab level and the selected parameter was analyzed by Spearman's rank correlation coefficient. Fisher's exact test was used for analysis of statistical differences in patients with an infliximab level <1 and ≥1 μg/mL when stratified by cut-off value of the selected parameter.

Time to LOR, time to a decrease in trough infliximab level to <1 μg/mL, and time for the selected parameter to reach the cut-off value were compared in patients in whom response was lost and trough infliximab level decreased below 1 μg/mL. Statistical differences among respective parameters were analyzed using the Wilcoxon rank test.

Results

Patients

Baseline characteristics of patients included in the analyses are shown in Table 1. Of the 62 week-10 responders, 57

Table 1 Baseline patient characteristics

	Week-10 responders assessed for clinical response and serum trough infliximab level at week 14 ($n = 57$)
Gender (male:female)	43:14
Age (years), median (IQR)	29.0 (24.0–36.0)
Disease duration (years), median (range)	5.4 (0.5–27.0)
Disease location (ileum:colon:ileocolonic)	13:14:30
Previous surgery for Crohn's disease, *n* (%)	21 (36.8)
Resection:stricturoplasty	20:8
Smoker, *n* (%)	17 (29.8)
Concomitant medications, *n* (%)	
Corticosteroids	19 (33.3)
5-Aminosalicylates	55 (96.5)
Immunomodulators	8 (14.0)
Metronidazole/ciprofloxacin	9 (15.8)
Enteral nutrition	36 (63.2)
Crohn's disease activity index, median (IQR)	283.0 (248.0–329.0)
Inflammatory Bowel Disease Questionnaire, median (IQR)	148.0 (132.0–164.0)
Draining fistulas (none:1:2:3 or more)	50:3:3:1
C-reactive protein (mg/dL), median (IQR)	1.6 (0.7–4.0)
Albumin (g/dL), median (IQR)	3.8 (3.4–4.2)
Prealbumin (mg/dL), median (IQR)	21.0 (17.1–27.5)
Transferrin (mg/dL), median (IQR)	237.0 (193.0–270.0)
Retinol-binding protein (mg/dL), median (IQR)	2.6 (2.1–3.4)
Plasma tumor necrosis factor-α (pg/mL), median (IQR)	1.04 (0.74–1.59)
Plasma interleukin-6 (pg/mL), median (IQR)	6.40 (1.96–12.9)