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Background and Aims: No reports have described the immunogenicity and boosting effect of the quadrivalent inactivated influenza vaccine (QIV) in adults with inflammatory bowel disease.

Methods: Adults with Crohn's disease or ulcerative colitis were randomly assigned to a single vaccination group or booster group, and a QIV was administered subcutaneously. Serum samples were collected before vaccination, 4 weeks after vaccination, and after the influenza season in the single vaccination group. In the booster group, serum samples were taken before vaccination, 4 weeks after the first vaccination, 4 weeks after the second vaccination, and after the influenza season. We measured hemagglutination inhibition antibody (HAI) titer and calculated the geometric mean titer ratio (GMTR), seroprotection rate, and seroconversion rate.

Results: In total, 132 patients were enrolled. Twenty-two patients received immunomodulatory monotherapy and 16 received anti-tumor necrosis factor-α (anti-TNF-α) single-agent therapy. Fifteen patients received combination therapy comprising an immunosuppressant and anti-TNF-α agent. Each vaccine strain showed immunogenicity satisfying the European Medicines Agency criteria with a single inoculation. The booster influenza vaccination did not induce additional response. In patients administered infliximab, the seroprotection rate and seroconversion rate tended to be lower in patients who maintained blood concentrations [seroprotection rate: H1N1: OR, 0.37 (95% CI, 0.11–1.21); H3N2: 0.22 (0.07–0.68); seroconversion rate: H1N1: 0.23 (0.06–0.91); H3N2: 0.19 (0.06–0.56)].

Conclusion: Single dose QIV showed sufficient immunogenicity in patients with inflammatory bowel disease, and a boost in immunization by additional vaccination was not obtained. Additionally, immunogenicity was low in patients receiving infliximab therapy.

Key Words: ulcerative colitis, Crohn's disease, vaccination

INTRODUCTION

Several guidelines recommend influenza vaccination for patients receiving immunosuppressive therapy.[1,2] Patients with inflammatory bowel disease (IBD) associated with ulcerative colitis (UC) and Crohn's disease (CD) are included in this group. In particular, patients undergoing immunosuppressive therapy with agents such as azathioprine, 6-mercaptopurine, and anti-tumor necrosis factor-α (anti-TNF-α) might have more severe influenza symptoms than those who have not received immunosuppressive therapy.[3–5]

Influenza is a common infection. According to a report by the National Institute of Infectious Diseases, patients with influenza in Japan in the 2014–2015 season were estimated at about 15 million and influenza-related deaths were estimated at about 5000.[3] Additionally, in the United States, 8000 deaths occurred due to influenza and influenza-related deaths were estimated to number > 50,000.[4] The death rate of influenza A (H1N1), which caused a pandemic in 2009, is high.[5] Patients receiving immunosuppressive therapy also are at increased risk of opportunistic infections,[6] and the risk of influenza morbidity and severity is reportedly high.[7] Because patients with IBD often require immunosuppressive therapy to maintain remission, determination of how to prevent infections such as influenza is important.

Several studies have evaluated the immunogenicity of other vaccines such as influenza vaccine, pneumococcal vaccine, and hepatitis B vaccine in patients with IBD. Many reports have described difficulty increasing the antibody titer in patients

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receiving immunosuppressive therapy.[8–14] Infliximab (IFX) can reportedly inhibit the immune response to influenza vaccines.[15] It is generally accepted that a single inactivated influenza vaccine has a sufficient effect in healthy adults and that no further increase in immunogenicity due to booster vaccinations occurs.[16, 17] The booster effect of the trivalent influenza vaccine in patients with IBD receiving immunosuppressive therapy has also been investigated, and although single vaccination was shown to be effective,[18] research on immunogenicity by treatment status is insufficient.

The quadrivalent inactivated influenza vaccine (QIV) was introduced in Japan in the 2015–2016 season. Because QIV include 2 strains of type B, mismatch between vaccine strain and epidemic strain of type B is expected to be reduced.[19] Influenza type B particularly affects children and high-risk patients; thus, evaluating immunogenicity of QIV among high-risk groups is needed. However, no reports have described the immunogenicity of QIV in patients with IBD.

In the present study we investigated the immunogenicity of the QIV in the 2015–2016 season in patients with IBD and examined the effects of booster immunity and immunosuppressive therapy, particularly the influence of the blood concentration of IFX.

METHODS

Study Design

We conducted a prospective, randomized, parallel-group comparison study from October 2015 to August 2016 in the Department of Gastroenterology of Saga University Hospital. The study protocol was approved by the Ethics Committee of Saga University Hospital and registered at the University Hospital Medical Information Network Clinical Trial Registry in advance (UMIN000018975).

Patients with IBD either receiving or not receiving immunosuppressive therapy, immunomodulators, and/or anti-TNF-α agents were enrolled. The exclusion criteria were as follows:[1] previous administration of the 2015 QIV,[2] a history of influenza infection within the last 6 months, and[3] a history of anaphylactic reaction to a previous influenza vaccine or an acute febrile illness or signs of severe acute illness at the time of vaccination. All participants provided written informed consent after receiving an explanation of the study design and possible risks. The patients were randomized into a single vaccination group and a booster vaccination group. The participants whose birthdays were on even days were assigned to the single vaccination group, and those whose birthdays were on odd days to the booster vaccination group.

From October 20, 2015 to December 24,2015, we administered a single influenza vaccination to 83 patients and booster vaccination to 49 patients. We followed- up all 132 patients until August 2016.

In addition, the 27 healthy controls were randomized into a single influenza vaccination to 12 individuals and booster vaccination to 15.

Patient Information

We collected the following clinical information from the medical records of all patients with IBD: age, sex, diagnosis (UC or CD), current therapy [azathioprine, 6-mercaptopurine, IFX, or adalimumab (ADA)], disease activity (UC: partial Mayo score,[8] CD: Harvey–Bradshaw index[9]), and endoscopic findings (UC: Mayo endoscopic score, CD: SES-CD). A partial Mayo score of ≤2 for UC and Harvey–Bradshaw index of ≤4 for CD were defined as remission.

We examined each patient's history, including vaccinations, and allergies at the time of inoculation by self-administered questionnaires.

Vaccination

Patients and controls received a single dose or double doses (as a booster) of the 2015–2016 seasonal QIV (Lot: HK24C Biken, Osaka, Japan) subcutaneously.

The vaccine strains were A/California/7/2009(H1N1) pdm09, A/Switzerland/9715293/2013(NIB-88)(H3N2), B/Phuket/3073/2013(B/P), and B/Texas/2/2013(B/T). A standard vaccine dose was 0.5 ml and contained 15 μg of the hemagglutinin antigen of each strain. In the booster vaccination group, the second vaccination was performed 4 weeks after the first vaccination.

Whole-body reactions such as fever after vaccination and localized reactions such as swelling of the inoculation site were observed in each patient for at least 1 week, and each patient's condition was described in the questionnaire.

Measurement of Antibody Titers

Serum antibody titers were measured. The serum samples were collected at 4 time points in the booster vaccination group: before vaccination (S0), 4 weeks after the first vaccination (S1), 4 weeks after the second vaccination (S2), and after the influenza season post May 2016 (S3). The serum samples were collected at 3 time points in the single vaccination group: before vaccination (S0), 4 weeks after the first vaccination (S1), and after the influenza season post May 2016 (S3). All serum specimens were stored at −80ºC until they were tested for hemagglutination inhibition (HI) antibody titers. The antibody titer of each specimen was measured at the Research Foundation for Microbial Disease of Osaka University, which conducts joint research. HI antibody was measured with the same antigen as the vaccine using a standard microtiter HI method. Immunogenicity was evaluated based on the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA). The EMA required a seroconversion rate (SC%) of > 40%, mean geometric increase of > 2.5, or seroprotection rate (SP%)

of > 70% in adults aged 18 to 60 years.[10] The FDA required the lower limit of the 95% confidence interval of SC% to exceed 40% and the lower limit of the 95% confidence interval of SP% to exceed 70%.[11] The serum ADA concentration was assessed by means of ELISA kit (Shikari®Q-ADA Matriks Biotek, Ankara, Turkey).

Statistical Analysis

Baseline characteristics were compared using the chi-square test or Fisher's exact test. The geometric mean antibody titer (GMT) was defined as 5 if HI antibody titer was less than 10. The GMT ratio (GMTR) was calculated as the ratio of S1 or S2 to S0. The significance of the GMT and GMTR within each category was evaluated using the Wilcoxon signed rank test. Categories also were compared using the Wilcoxon rank sum test.

We calculated the proportion of SP% (HI titer of ≥1:40) and SC% (ratio of patients in whom the HI titer after vaccination increased by more than 4 times that before vaccination, or ratio of patients with a HI titer of ≥1:40 aftervaccination with an HI antibody titer of < 1:10 before vaccination with an HI antibody titer of < 1:10). Patients in whom the antibody titer post influenza season increased by more than 4 times that after the final vaccination were excluded from the analysis because they were considered to be infected with influenza. We examined the odds ratios and 95% confidence intervals of SP and SC in the multivariate logistic analysis of the vaccination (single or booster) and IFX blood concentrations with prevaccination antibody titers as confounding factors. All tests were 2-sided, and the significance level was set at 5%. SAS Ver. 9.3 (SAS Institute, Cary, NC) was used for statistical analysis.

RESULTS

Baseline Characteristics of IBD Patients

One hundred thirty-two patients with IBD (44 with CD and 88 with UC) were enrolled. The patients' baseline characteristics showed no significant difference between the single vaccination group and booster vaccination group after randomization (Table 1). There also were no significant differences in immunosuppressive therapies (immunosuppressant monotherapy, anti-TNF-α monotherapy, and combination therapy), disease activity, and endoscopic findings between the 2 groups.

Immunogenicity in Each Strain

There was no significant difference in seroprotection rates between all IBD patients and healthy controls (see Table, Supplemental Digital Content 1, which shows the immunogenicity of healthy controls).

Several patients were diagnosed as serologically infected with influenza and excluded from the analysis after the end of the season (H1N1: 6 patients, H3N2: 2 patients, B/P: 1 patient, and B/T: 2 patients). Immunogenicity of QIV was shown in Table 2. There was no significant difference in the GMT after vaccination and after the end of the season between S1 in the single vaccination group and S2 in the booster vaccination group (after vaccination: H1N1, $P = 0.81$; H3N2, $P = 0.79$; B/P, $P = 0.82$; B/T, $P = 0.84$; after the end of the season: H1N1, $P = 0.39$; H3N2, $P = 0.74$; B/P, $P = 0.62$; B/T, $P = 0.98$) (Table 2). There was no significant difference in the rate of seroprotection after vaccination and after the influenza season in both groups (after vaccination: H1N1, $P = 0.72$; H3N2, $P = 0.33$; B/P, $P = 0.56$; B/T, $P = 0.49$; after the influenza season: H1N1, $P = 0.29$; H3N2, $P = 0.83$; B/P, $P = 0.12$; B/T, $P = 0.88$). In both vaccination groups, the seroprotection rate after vaccination (S1 for single group or S2 for booster group) was less than 70% in the H1N1 strain [SP% (95%CI): H1N1, 66% (55%–76%) (S1) and 63% (48%–77%) (S2); H3N2, 77% (67%–87%) (S1) and 80% (66%–90%) (S2); B/P, 80% (69%–88%) (S1) and 86% (73%–94%) (S2); and B/T, 84% (75%–91%) (S1) and 82% (68%–91%) (S2)]. Additionally, the seroconversion rate after vaccination (S1 for single group or S2 for booster group) was only < 40% in the H1N1 strain [SC% (95%CI): H1N1, 36% (26%–47%) (S1) and 33% (20%–48%) (S2); H3N2, 58% (46%–69%) (S1) and 67% (52%–80%) (S2);

TABLE 1: Baseline Characteristics of the Study Subjects[a]

Characteristics	Study Subjects	Single Group	Booster Group	
n	132	83	49	*P*
Gender				
Male	76	49	27	
Female	56	34	22	0.80
Age at vaccination	42.5	42.6	42.3	0.51
Disease				
UC	88	53	35	
CD	44	30	14	0.48
Disease activity				
Partial Mayo Score	1.65	1.64	1.66	0.75
Harvey Bradshaw Index	2.52	2.70	2.14	0.26
Endoscopic score				
Endoscopic Mayo Score	1.2	1.3	1.0	0.09
SES-CD	5.2	4.9	4.6	0.96
Therapy				
5-ASA	116	71	45	0.89
Immunosuppressive therapy				
AZA	22	15	7	0.81
anti TNF-α	16	11	5	0.85
AZA + anti TNF-α	15	11	4	0.60

[a]Based on X2 test, or Fisher's exact test.

B/P, 52% (41%–63%) (S1) and 41% (27%–56%) (S2); and B/T, 51% (39%–62%) (S1) and 51% (34%–64%) (S2)].According to the EMA standards, good immunogenicity was observed in strains other than strain H1N1, but no strain met the criteria of the FDA standards.

Stratified Immunogenicity Analysis

We focused on the type of immunosuppressive treatment for 4 strains of influenza vaccine and compared the GMT and GMTR of the single vaccination and booster vaccination group (Table 3). Although some significant differences were observed in anti-TNF-α agents of the B strain, there was no significant difference in GMTR; thus, we could not conclude that booster immunity was obtained as a whole. However, after adjustment for the prevaccination titer and vaccine dose, the seroprotection rate against the H3N2 strain significantly decreased in patients whose serum levels of IFX were more than 0.1μg/ml compared with patients without biological therapy [Adjusted OR (95%CI): 0.22 (0.07%–0.68)]. Regarding seroconversion, adjusted ORs of H1N1 strain and H3N2 strain were significantly decreased in patients whose serum levels of IFX were more than 0.1μg/ml [Adjusted OR (95%CI): H1N1, 0.23 (0.06–0.91); H3N2, 0.19 (0.06–0.56)] (Table 4). Patients with a high ADA blood level had higher antibody titers; however, the number of patients

TABLE 2: Immunogenicity of the 4 Strains in the QIV During the Study

	Geometric Mean Titer[a]				Fold Rise[a]	Seroprotection Rate (≥1:40), %(95%CI)[b]				Seroconversion Rate, %(95%CI)[c]	
	Before vaccination	After vaccination		After season	S1/S0 for single	Before vaccination	After vaccination		After season	After vaccination	
	(S0)	(S1)	(S2)	(S3)	S2/S0 for booster	(S0)	(S1)	(S2)	(S3)	(S1)	(S2)
A/California/7/2009(H1N1) pdm09											
Single group (N = 83)	14	49	-	27	3.50	27 (18–39)	66 (55–76)	-	52 (41–63)	36 (26–47)	-
Booster group (N = 49)	13	47	35	23	2.69	18 (9–30)	69 (55–82)	63 (48–77)	49 (34–64)	43 (29–58)	33 (20–48)
P	0.81	0.81	NA	0.39	0.67	0.29	0.72	NA	0.29	0.44	NA
A/Switzerland/9715293/2013(NIB-88)(H3N2)											
Single group (N = 83)	13	67	-	40	5.15	17 (10–27)	77 (67–86)	-	59 (48–70)	58 (46–69)	-
Booster group (N = 49)	13	63	71	40	5.46	18 (9–30)	69 (55–82)	80 (66–90)	57 (42–71)	59 (45–73)	67 (52–80)
P	0.44	0.79	NA	0.74	0.35	0.82	0.33	NA	0.83	0.87	NA
B/ Phuket/3073/2013											
Single group (N = 83)	19	74	-	40	3.82	35 (25–46)	80 (69–88)	-	58 (46–69)	52 (41–63)	-
Booster group (N = 49)	22	76	73	45	3.38	35 (22–50)	84 (70–83)	86 (73–94)	71 (56–83)	41 (27–56)	41 (27–56)
P	0.34	0.82	NA	0.62	0.62	0.98	0.56	NA	0.12	0.22	NA
B/Texas/2/2013											
Single group (N = 83)	19	76	-	50	4.06	33 (23–44)	84 (75–91)	-	75 (64–84)	51 (39–62)	-
Booster group (N = 49)	20	77	72	50	3.67	39 (25–54)	80 (66–90)	82 (68–91)	73 (59–85)	43 (29–58)	51 (34–64)
P	0.6	0.84	NA	0.98	0.61	0.47	0.49	NA	0.88	0.39	NA

[a]Wilcoxon signed-rank test for intracategory comparisons, and either the Wilcoxon rank-sum test or the Kruskal-Wallis test for intercategory comparisons.
[b]χ^2 test or Fisher's exact test.
[c]Analysis excluding subclinically infected persons.

TABLE 3: Immunogenicity of the 4 Strains in the QIV Vaccine According to the Type of Immunosuppressive Treatment

	Geometric mean Titer[a]			Fold Rise[a]
	Before vaccination	After vaccination	After season	S1/S0 for single
	(S0)	(S1)/(S2)	(S3)	S2/S0 for booster
A/California/7/2009(H1N1) pdm09				
Azathioprine				
Single group (N = 15)	16	46	26	2.90
Booster group (N = 7)	8	38	18	4.54
P	0.27	0.88	0.95	0.14
Anti TNF-roup (N				
Single group (N = 11)	12	42	19	3.41
Booster group (N = 5)	15	37	23	2.52
P	0.15	0.44	0.18	0.55
AZA + Anti TNF-N = 5)(H1				
Single group (N = 11)	15	40	21	2.67
Booster group (N = 4)	9	49	20	5.38
P	0.34	0.67	1.00	0.50
A/Switzerland/9715293/2013(NIB-88)(H3N2)				
Azathioprine				
Single group (N = 15)	11	54	31	4.95
Booster group (N = 7)	10	66	27	6.62
P	0.33	0.09	0.86	0.036
Anti TNF-roup (N				
Single group (N = 11)	13	32	22	2.48
Booster group (N = 5)	7	23	15	3.17
P	0.30	0.51	0.39	0.44
AZA + Anti TNF-N = 5)93/				
Single group (N = 11)	11	34	21	3.00
Booster group (N = 4)	10	59	30	5.94
P	1.00	0.09	0.12	0.04
B/ Phuket/3073/2013				
Azathioprine				
Single group (N = 15)	25	78	47	3.15
Booster group (N = 7)	20	92	48	4.83
P	0.26	0.44	0.64	0.11
Anti TNF-roup (N				
Single group (N = 11)	24	68	39	2.83
Booster group (N = 5)	34	86	54	2.52
P	0.03	0.02	0.04	0.18
AZA + Anti TNF-N = 5)93/				
Single group (N = 11)	30	76	50	2.52
Booster group (N = 4)	27	90	59	4.49
P	0.29	0.35	0.50	0.61
B/Texas/2/2013				
Azathioprine				
Single group (N = 15)	21	66	48	3.15
Booster group (N = 7)	17	92	66	4.26
P	0.55	0.12	0.61	0.48

TABLE 3: (*Continued*)

	Geometric mean Titer[a]			Fold Rise[a]
	Before vaccination	After vaccination	After season	S1/S0 for single
	(S0)	(S1)/(S2)	(S3)	S2/S0 for booster
Anti TNF-roup (N				
Single group (N = 11)	22	57	37	2.61
Booster group (N = 5)	29	109	63	3.70
P	0.03	0.01	0.11	0.15
AZA + Anti TNF-N = 5)93/				
Single group (N = 11)	22	53	42	2.38
Booster group (N = 4)	20	131	88	6.56
P	0.92	0.06	0.09	0.22

[a]Wilcoxon signed-rank test for intracategory comparisons

receiving ADA was small, and the result was not statistically significant (Table 5).

Safety

No serious side effects such as anaphylactic shock accompanying vaccination occurred during this study.

DISCUSSION

This study is the first to evaluate the immunogenicity of a QIV in patients with IBD. Overall, after a single vaccination, none of the strains met the FDA criteria, but all satisfied the EMA standards and good immunogenicity was obtained. The lack of further antibody elevation by booster vaccination suggests that a single vaccination is sufficient even in patients with IBD. Additionally, the GMT significantly decreased in patients receiving immunosuppressive therapy, especially those receiving treatment with an anti-TNF-α formulation, and no booster effect could be obtained. This result is similar to that obtained in studies of trivalent influenza vaccines to date.[9, 20, 21] With respect to the blood concentrations of IFX, SP% and SC% tended to be low, especially for the A strains in patients who maintained the blood levels of IFX. No association between the blood concentration of ADA and immunogenicity was found, but only 8 patients were evaluated, preventing a definitive conclusion. In terms of the achievement of a sufficient antibody titer despite the high blood level, the administration schedule of ADA varies depending on individual patients, in contrast to IFX; additionally, the time to vaccination may be affected. However, immunosuppressive therapy is a treatment often used in patients with IBD, and it is difficult to avoid. Therefore, vaccination before immunosuppressive therapy is considered necessary.[12] In this study, most patients receiving IFX were inoculated with the influenza vaccination just before IFX was administered. TNF-α has both pro-inflammatory and anti-inflammatory functions associated with influenza infection; in particular, soluble TNF-α regulates the magnitude of the immune response.[13] Therefore, if an anti-TNF-α preparation such as IFX is used, the immune response may not be sufficient and the GMT may decrease. It is necessary to consider the vaccination schedule according to the IFX administration schedule.

In previous reports, immunogenicity of type B was difficult to obtain,[9, 11, 22] but the seroprotection rate of B strains after vaccination were higher those of type A strains in the present study. It is considered that the proportion of patients with a prevaccination titer that was higher in type B than A affected the results.[14]

Although the risk of opportunistic infections increases in patients receiving anti-TNF-α formulation therapy, some reports have indicated that the risk of severe infection remains unchanged.[5, 23, 24] Additionally, some reports have indicated that the risk of hospitalization due to pneumonia in patients with IBD is higher than that in healthy people. Patients with IBD aged > 50 years are reportedly at high risk of opportunistic infection,[16] and immunity to diseases such as measles and whooping cough also is decreased.[17] In the present study, no patients required hospitalization or medication for opportunistic infections or influenza-related diseases during the study period. However, the immunogenicity of patients receiving anti-TNF-α preparations was low, raising the possibility that a sufficient protective effect cannot be obtained by vaccination. Standard prevention measures such as wearing masks are necessary to lower the risk of infectious disease in middle-aged and elderly patients.[20]

Although we used a QIV to examine the booster effect in the present study, no significant difference in the effect was observed compared with single inoculation.[18] However, some studies involving healthy individuals have revealed that the double-dose influenza vaccine (30μg) was significantly more immunogenic than the single-dose vaccine(15μg).[11, 25] Even in patients undergoing immunosuppressive therapy, it is necessary

TABLE 4: Factors Associated With a Sufficient Immune Response After Vaccination Among Patients With IBD

		Seroprotection (SP) rate (≥1:40), n (%)			Seroconversion (SC) rate, n (%)		
	N	After vaccination[a] (S1) or (S2)	OR (95%CI) for SP after vaccination	Adjusted[b] OR (95%CI) for SP after vaccination	After vaccination[a] (S1) or (S2)	OR (95%CI) for SC after vaccination	Adjusted[b] OR (95%CI) for SC after vaccination
A/California/7/ 2009(H1N1) pdm09							
Single group	83	55 (66)	1	1	30 (36)	1	1
Booster group	49	31 (63)	0.88 (0.42–1.83)	1.12 (0.48–2.59)	16 (33)	0.86 (0.41–1.81)	0.73 (0.31–1.75)
IBD without IFX	101	67 (66)	1	1	37 (37)	1	1
IBD with IFX < 0.1	7	6 (86)			4 (57)		
0.1 ≦	20	10 (50)	0.48 (0.18–1.26)	0.37 (0.11–1.21)	3 (15)	0.29 (0.08–1.05)	0.23 (0.06–0.91)
Prevaccination titer							
< 1:10	42	27 (64)	1	1	27 (64)	1	1
1:10–1:20	58	27 (47)	0.48 (0.21–1.09)	0.49 (0.21–1.14)	18 (31)	0.25 (0.11–0.58)	0.24 (0.10–0.59)
≦ 1:40	32	32 (100)	NA	NA	1 (3)	0.02 (0.00–0.15)	0.02 (0.00–0.14)
A/Switzerland/9715293/ 2013(NIB-88)(H3N2)							
Single group	83	64 (77)	1	1	48 (58)	1	1
Booster group	49	39 (80)	1.16 (0.49–2.74)	1.14 (0.42–3.09)	33 (67)	1.50 (0.72–3.15)	1.49 (0.66–3.35)
IBD without IFX	101	86 (85)	1	1	70 (69)	1	1
IBD with IFX < 0.1	7	4 (57)			3 (43)		
0.1 ≦	20	10 (50)	0.20 (0.07–0.55)	0.22 (0.07–0.68)	6 (30)	0.21 (0.07–0.58)	0.19 (0.06–0.56)
Prevaccination titer							
< 1:10	40	22 (55)	1	1	22 (55)	1	1
1:10–1:20	69	58 (84)	4.31 (1.76–10.57)	4.74 (1.81–12.40)	50 (73)	2.15 (0.95–4.87)	2.16 (0.90–5.19)
≦ 1:40	23	23 (100)	NA	NA	9 (39)	0.53 (0.19–1.49)	0.45 (0.15–1.37)
B/ Phuket/3073/2013							
Single group	83	66 (80)	1	1	43 (52)	1	1
Booster group	49	42 (86)	1.55 (0.59–4.04)	1.37 (0.47–3.96)	20 (41)	0.64 (0.31–1.31)	0.51 (0.23–1.15)
IBD without IFX	101	82 (81)	1	1	50 (50)	1	1
IBD with IFX < 0.1	7	7 (100)			5 (71)		
0.1 ≦	20	16 (80)	0.85 (0.26–2.84)	0.42 (0.10–1.72)	6 (30)	0.41 (0.15–1.56)	0.40 (0.13–1.25)
Prevaccination titer							
< 1:10	24	13 (54)	1	1	13 (54)	1	1
1:10–1:20	62	50 (81)	3.53 (1.27–9.78)	3.97 (1.34–11.8)	39 (63)	1.44 (0.55–3.73)	1.85 (0.68–5.05)
≦ 1:40	46	45 (98)	38.1 (4.49–323.0)	47.0 (5.20–424.5)	11 (24)	0.27 (0.09–0.76)	0.31 (0.11–0.90)
B/Texas/2/2013							
Single group	83	70 (84)	1	1	42 (51)	1	1
Booster group	49	40 (82)	0.83 (0.32–2.10)	0.65 (0.23–1.80)	24 (49)	0.94 (0.46–1.90)	0.88 (0.40–1.91)
IBD without IFX	101	85 (84)	1	1	54 (53)	1	1
IBD with IFX < 0.1	7	7 (100)			5 (71)		
0.1 ≦	20	15 (75)	0.52 (0.17–1.64)	0.50 (0.14–1.79)	6 (30)	0.36 (0.13–1.00)	0.37 (0.13–1.11)
Prevaccination titer							
< 1:10	26	20 (77)	1	1	20 (77)	1	1
1:10–1:20	60	44 (73)	0.83 (0.28–2.42)	0.72 (0.22–2.32)	33 (55)	0.37 (0.13–1.04)	0.36 (0.12–1.10)
≦ 1:40	46	46 (100)	NA	NA	13 (28)	0.12 (0.04–0.36)	0.11 (0.03–0.36)

[a]Seroprotection rate after vaccination (S1) for single group and seroprotection rate after vaccination (S2) for booster group.
[b]Adjusted for the variables listed in the Table.
NA: not applicable.

TABLE 5: Influenza Antibody Titer of Patients Who Received ADA

		A/California/7/2009(H1N1) pdm09				A/Switzerland/9715293/2013(NIB-88)(H3N2)			
		Antibody titer				Antibody titer			
CASE	Concentration (ng/ml)	Before vaccination (S0)	After vaccination (S1 or S2)	After season (S3)	GMTR	Before vaccination (S0)	After vaccination (S1 or S2)	After season (S3)	GMTR
1	1054.584	5	80	10	16	5	80	10	16
2	470.963	80	80	40	1	20	20	20	1
3	7956.484	5	320	40	64	20	160	40	8
4	6863.021	20	80	40	4	10	160	40	16
5	2098.500	5	5	5	1	20	20	40	1
6	5484.573	5	10	5	2	10	80	40	8
7	1096.834	20	40	20	2	80	640	640	8
8	9415.112	5	20	5	4	10	80	160	8
GMT(ADA)		10	40	14	4.00	15	87	52	5.66
GMT(IFX)		13	41	21	3.06	11	28	17	2.62
P		0.85	0.55	0.28	0.68	0.27	0.034	0.058	0.075
GMT(non immunosuppressive)		15	46	33	3.15	14	92	58	6.35
P		0.80	0.40	1.00	0.86	1.00	0.86	1.00	1.00

		B/ Phuket/3073/2013				B/Texas/2/2013			
		Antibody titer				Antibody titer			
CASE	Concentration (ng/ml)	Before vaccination (S0)	After vaccination (S1 or S2)	After Season (S3)	GMTR	Before vaccination (S0)	After vaccination (S1 or S2)	After season (S3)	GMTR
1	1054.584	5	160	20	32	5	320	160	64
2	470.963	160	160	160	1	20	80	40	4
3	7956.484	20	40	20	2	40	40	80	1
4	6863.021	20	160	160	8	40	160	160	4
5	2098.500	320	320	320	1	80	80	160	1
6	5484.573	40	80	80	2	10	20	10	2
7	1096.834	160	320	320	2	40	80	80	2
8	9415.112	10	40	20	4	10	80	20	8
GMT		40	123	80	3.08	22	80	62	3.67
GMT(IFX)		24	70	40	2.92	23	67	41	2.92
P		0.27	0.75	0.94	0.35	1.00	1.00	0.71	0.83
GMT(nonimmunosuppressive)		18	69	40	3.85	18	79	55	4.43
P		0.40	0.89	0.59	0.55	1.00	0.34	0.60	0.86

to consider whether double-dose administration of a QIV increases immunogenicity.

Vaccines with which to obtain more immunogenicity are currently being developed worldwide.[26] However, patients with IBD undergoing immunosuppressive therapy regardless of whether they have received the influenza vaccine cannot be inoculated with live vaccines[12]; at present, they may only be inoculated with inactivated vaccines. Inactivated vaccines used in Japan are split vaccines, but whole virion vaccines and adjuvant vaccines also are available. In one report, higher immunogenicity was obtained after administration of a whole virion vaccine and adjuvant vaccine than after a split vaccine in healthy people.[27–30] Therefore, it is necessary to develop an inactivated vaccine that is highly effective for patients undergoing immunosuppressive therapy.

The lack of severe side effects due to influenza vaccination and absence of exacerbation of the original disease in the present study are consistent with the findings of previous reports,[31, 32] and good tolerability was confirmed.

A limitation of this study is the small number of patients who received immunosuppressive therapy overall; this is a characteristic of our hospital. Additionally, we further investigated booster immunity, making the number of patients with each immunosuppressive therapy small. It is difficult to assess the effect of booster regimens. Although we were able to investigate the IFX concentration in the blood, we could not consider vaccination according to the administration schedule of the anti-TNF-α preparation. It is necessary to consider whether there is a difference in immunogenicity between inoculation immediately before versus 1 month after administration of IFX. Additionally, it is necessary to increase the number of patients who receive ADA, elucidate the administration schedule of ADA, and clarify the relationship between the blood concentration and administration schedule. As another limitation, we observed only 1 season in this study. Long-term follow-up is needed to assess if the lower seroprotection rates in IBD patients truly leads to higher rates of influenza infection. In this study, we did not assess whether the low seroprotection rate is related to the onset or severity of influenza because of the smalle number of patients. However, some reports regarding the immunogenicity of the institutionalized elderly and subjects with severe motor and intellectual disability revealed that a high prevalence of influenza infection was observed in subjects without seroprotective levels of antibody titer.[33, 34] Therefore, we presumed that IBD patients who did not reach seroprotective levels of antibody titer were susceptible to influenza infection.

CONCLUSIONS

In conclusion, although patients with IBD as a whole can obtain good immunogenicity that meets the EMA criteria, this study has shown that it is difficult to obtain immunogenicity in patients undergoing immunosuppressive therapy, especially those receiving IFX, even with a QIV.

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