

ORIGINAL ARTICLE

## 한국의 염증성 장질환 환자에서의 예방접종

윤환식, 민양원, 장동경, 이풍렬, 김재준, 이종철, 김영호

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### Factors Associated with Vaccination among Inflammatory Bowel Disease Patients in Korea

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**Background/Aims:** Vaccinations are generally recommended in patients with inflammatory bowel disease (IBD). However, several studies showed low rates of vaccinations in IBD patients. Furthermore, vaccination rate among IBD patients in Korea has never been investigated. We investigated the vaccination rate among IBD patients in Korea and evaluated some factors that might affect the vaccination rate.

**Methods:** From November 2011 to February 2012, a total of 192 patients with IBD who visited Samsung Medical Center (Seoul, Korea) answered the IRB-approved questionnaire. The questionnaire included their sex, age, residence, past medical history, type of IBD, duration of illness, medications, history of vaccination about measles-mumps-rubella (MMR), varicella, tetanus-diphtheria (Td), influenza, hepatitis A and B, pneumococcus and human papilloma virus (HPV).

**Results:** One hundred twenty one (63.0%) male and 71 (37.0%) female answered the questionnaire. The mean age of the enrolled patients was 39.7 (18-76) years. Eighty four patients (43.8%) had ulcerative colitis and 108 patients (56.3%) had Crohn's disease (CD). The percentage of the patients who had got vaccination was 42.2% for MMR, 34.9% for varicella, 15.6% for Td, 37.5% for influenza, 15.6% for hepatitis A, 52.6% for hepatitis B, 6.3% for pneumococcus and 11.3% for HPV respectively. Not knowing the necessity or the existence were the common reasons for non-vaccination. Age less than 40 years, CD patients and duration of illness less than 10 years were associated with a higher vaccination rate ( $p=0.002$ , 0.015 and 0.020, respectively).

**Conclusions:** Immunization rates for recommended vaccinations were very low in patients with IBD. Efforts to improve vaccination rate are needed. (Korean J Gastroenterol 2013;61:203-208)

**Key Words:** Inflammatory bowel disease; Vaccination; Ulcerative colitis; Crohn's disease; Korea

### INTRODUCTION

Inflammatory bowel disease (IBD) including Crohn's disease (CD) and ulcerative colitis (UC), are chronic conditions seemed to be related with an abnormal immunologic response to normal bowel flora.<sup>1</sup> Because of this altered immunity, IBD patients are in endogenous immunosuppressive

state. Other than altered immunity, treatment of IBD often involves the use of immunosuppressive drugs including corticosteroids, antimetabolites, and biologic agents (such as infliximab or adalimumab). Although these drugs are effective for IBD, these medications increase the risk of opportunistic infections, several of which are vaccine-preventable. Many case reports of opportunistic infections in IBD patients are in

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the literature.<sup>2-5</sup> Because of these endogenous and exogenous immunocompromised states, IBD patients are vulnerable to opportunistic infections.

Furthermore, specific concerns about vaccination are that IBD patients may not be able to mount an immune response to a vaccine or vaccination itself might impact the clinical course of IBD. There is a report that IBD patients who had received infliximab and immunomodulators were more likely to have an inadequate response to vaccination.<sup>6</sup> However, studies showed that vaccinations induced slightly diminished immune response and did not impact the clinical course of IBD.<sup>7,8</sup> Therefore vaccination is generally recommended for IBD patients.<sup>9,10</sup> However, the vaccination rates in IBD patients have not been well investigated. Several studies about vaccination rates in IBD patients have been reported in western countries and have shown woefully inadequate results.<sup>11,12</sup> The clinical course and opportunistic infection of IBD could be quite different in Asian countries compared to western countries. However, the vaccination rates among IBD patients have not been studied in Asian countries including Korea. We aimed to evaluate the vaccination rates of IBD patients in Korea and find out any clinical factors that might affect the vaccination rates.

## MATERIALS AND METHODS

### 1. Patient selection

From November 2011 to February 2012, a total of 192 patients with IBD who visited Samsung Medical Center (Seoul, Korea) answered a questionnaire. Only agreed patients were

enrolled in this study. The questionnaire was approved by Institutional Review Board at Samsung Medical Center. The questionnaire included sex, age, residence, past medical history, their type of IBD, duration of illness, medication, history of vaccination about measles-mumps-rubella (MMR), varicella, tetanus-diphtheria (Td), influenza, HAV, HBV, pneumococcus and human papilloma virus (HPV), and the reasons why they got vaccinated or not. Also their history of getting national vaccination program was asked. All the patients received an explanation of the survey and answered the questionnaire. The patients who could not remember their history of vaccination were considered as not vaccinated. The reasons why they got vaccinated or not vaccinated were asked as multiple-choice questions.

### 2. Statistics

Vaccination rates among IBD patients were checked and clinical factors that affected vaccination rate were analyzed. Chi-square test was used for univariate analysis and logistic regressions for multivariate analysis. The level of statistical significance was set at  $p=0.05$  (IBM SPSS Statistics 20.0; IBM Co., Armonk, NY, USA).

## RESULTS

### 1. Baseline characteristics and vaccination rates

Baseline demographic characteristics were evaluated (Table 1). Mean age of the respondents was 39.7 (18-76) years old. One hundred twenty one patients (63.0%) were male. One hundred eight patients (56.3%) had CD, and 84

**Table 1.** Baseline Demographic Characteristics of the Participants

Characteristic	Data (N=192)
Age (yr)	39.7 (18-76)
Sex (male : female)	121 : 71
Type of IBD (CD : UC)	108 : 84
Duration of illness (yr), < 10 : ≥ 10	129 : 63
Residence (Seoul : other than Seoul)	71 : 121
Completion of national immunization	97 (50.5)
Past history	
Diabetes mellitus	3 (1.6)
Hypertension	11 (5.7)
Chronic hepatitis B	4 (2.1)

Values are n, n (range), or n (%).

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis.

**Table 2.** Vaccination Rates for Each Vaccine among Inflammatory Bowel Disease Patients

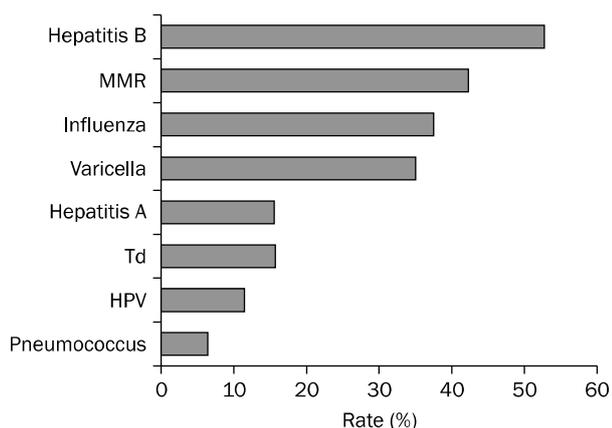
	CD (n=108)	UC (n=84)	Total (N=192)
MMR	55 (50.9)	26 (31.0)	81 (42.2)
Varicella	44 (40.7)	23 (27.4)	67 (34.9)
Hepatitis A	21 (19.4)	9 (10.7)	30 (15.6)
Hepatitis B	61 (56.5)	40 (47.6)	101 (52.6)
Td	23 (21.3)	7 (8.3)	30 (15.6)
Influenza	31 (28.7)	41 (48.8)	72 (37.5)
pneumococcus	6 (5.6)	6 (7.1)	12 (6.3)
HPV	5 (15.2) <sup>a</sup>	3 (7.9) <sup>a</sup>	8 (11.3) <sup>a</sup>

Values are presented as n (%).

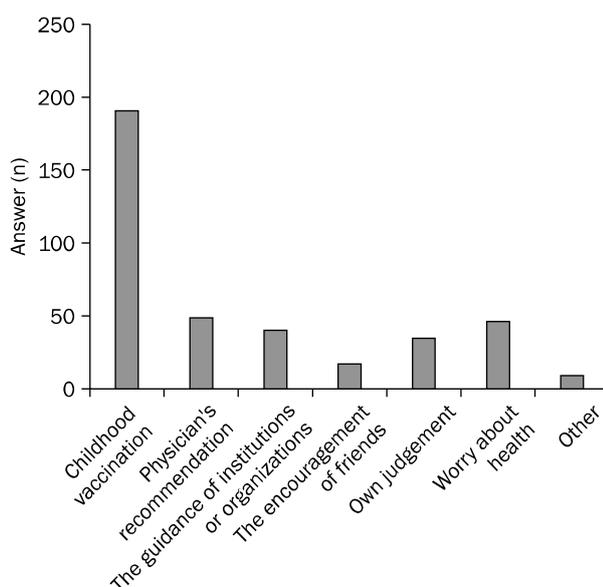
<sup>a</sup>Vaccination rate among women patients.

CD, Crohn's disease; UC, ulcerative colitis; MMR, measles-mumps-rubella; Td, tetanus-diphtheria; HPV, human papilloma virus.

patients (43.8%) had UC. Regarding the duration of illness, 129 patients (67.2%) had IBD less than 10 years. Seventy one respondents (37.0%) lived in Seoul, the capital city of South Korea, and 121 respondents (63.0%) lived out of Seoul. Among the respondents, the number of the patients who answered that he or she got national immunization was 97 (50.5%). Also their past medical histories were asked.



**Fig. 1.** Vaccination rates in regular order among inflammatory bowel disease patients in Korea. The rates of vaccinated patients were 52.6% for hepatitis B virus, 42.2% for measles-mumps-rubella (MMR), 37.5% for influenza, 34.9% for varicella, 15.6% for hepatitis A virus, 15.6% for tetanus-diphtheria (Td), 11.3% for human papilloma virus (HPV) and 6.3% for pneumococcus.



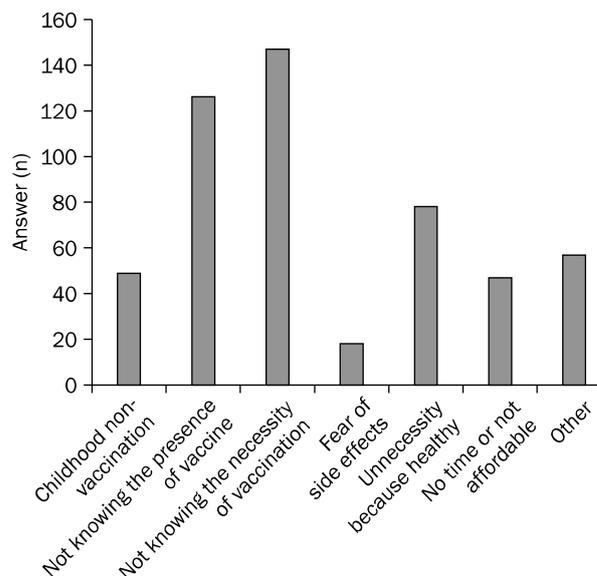
**Fig. 2.** The number of answers for the reasons of vaccination. The reasons for vaccination were childhood vaccination (191, 49.6%), physician's recommendation (48, 12.5%), patient's own worry about health (46, 11.9%), the guidance of institutions or organization (40, 10.4%), and etc.

Three patients (1.6%) had diabetes, 11 patients (5.7%) had hypertension and 4 patients (2.1%) had chronic B viral hepatitis.

Vaccination rates were investigated (Table 2, Fig. 1). Among CD patients (n=108), the respondents who got vaccinated for MMR, varicella, HAV, HBV, Td, influenza, pneumococcus and HPV were 55 (50.9%), 44 (40.7%), 21 (19.4%), 61 (56.5%), 23 (21.3%), 31 (28.7%), 6 (5.6%) and 5 (15.2%), respectively. Among UC patients (n=84), the numbers of the patients who got vaccinated were 26 (31.0%), 23 (27.4%), 9 (10.7%), 40 (47.6%), 7 (8.3%), 41 (48.8%), 6 (7.1%) and 3 (7.9%), respectively. The overall IBD patients who answered that they had got vaccination for MMR was 81 (42.2%), 67 (34.9%) for varicella, 30 (15.6%) for HAV, 101 (52.6%) for HBV, 30 (15.6%) for Td, 72 (37.5%) for influenza, 12 (6.3%) for pneumococcus and 8 (11.3%) for HPV.

## 2. The reasons for vaccination or non-vaccination

The participants were also asked about the reasons why they got vaccinated or not. There were seven examples for the reasons. The respondents chose 385 reasons that they got vaccinated and 509 reasons that they did not get vaccinated. Among the answers about the reasons for vaccination, the childhood vaccination was the most common (191, 49.6%)



**Fig. 3.** The number of answers for the reasons of non-vaccination. The reasons for non-vaccination were not knowing the necessity of the vaccination (144, 28.3%), not knowing the presence of the vaccine (124, 24.4%), no need because they are healthy (77, 15.0%), and etc.

**Table 3.** Univariate Analysis of Clinical and Demographic Factors Related with Higher Vaccination Rates

	Vaccination		p-value
	≥3	<3	
Age (yr)			0.002
< 40	48 (67.6)	54 (44.6)	
≥ 40	23 (32.4)	67 (55.4)	
Type of IBD			0.015
CD	48 (44.4)	60 (55.6)	
UC	23 (27.4)	61 (72.6)	
Sex			0.395
Male	42 (34.7)	79 (65.3)	
Female	29 (40.8)	42 (59.2)	
Residence			0.395
Seoul	29 (40.8)	42 (59.2)	
Other than Seoul	42 (34.7)	79 (65.3)	
Duration of illness (yr)			0.020
< 10	55 (42.6)	74 (57.4)	
≥ 10	16 (25.4)	47 (74.6)	
Medication			0.136
Other medication	32 (45.1)	68 (56.2)	
Immune modulators or biologics	39 (54.9)	53 (43.8)	

Values are presented as n (%).

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis.

(Fig. 2). Other than that, physician's recommendation (48, 12.5%), patient's own worry about health (46, 11.9%) and the guidance of institutions or organization (40, 10.4%) were the reasons for their vaccinations. On the other hand, not knowing the necessity of the vaccination (144, 28.3%) and not knowing the presence of the vaccine (124, 24.4%) were the most common reasons of non-vaccination (Fig. 3).

### 3. Higher vaccination rate related clinical factors

We evaluated clinical and demographic factors that were related with a higher vaccination rate (Table 3). Seventy one (37.0%) patients got three or more vaccinations among eight vaccines, and 121 (63.0%) patients got less than three vaccinations. Several factors were related with a higher vaccination rate in univariate analysis. Young patients less than 40 years got more vaccinations compared to older patients ( $p=0.002$ ). CD was related with a higher vaccination rates compared to UC ( $p=0.015$ ). Duration of illness less than 10 years ( $p=0.020$ ) was also related with a higher vaccination rate. On the other hand, sex, place of residence and medications of immune modulators or biologic agents were not re-

**Table 4.** Multivariate Analysis of Clinical and Demographic Factors Related with Higher Vaccination Rates

	OR	95% CI	p-value
Age (yr)			
< 40	1.850	0.952-3.595	0.061
≥ 40	1		
Gender			
Male	0.708	0.372-1.346	0.292
Female	1		
Type of IBD			
Crohn's disease	2.070	1.061-4.040	0.033
Ulcerative colitis	1		
Duration of illness (yr)			
< 10	1.930	0.940-3.965	0.073
≥ 10	1		

IBD, inflammatory bowel disease.

lated with higher vaccination rates. In multivariate analysis including age, sex, type of disease and duration of illness, only CD was related with a significantly higher vaccination rate (OR, 2.070; 95% CI, 1.061-4.040;  $p=0.033$ ) (Table 4).

## DISCUSSION

As IBD patients are vulnerable to opportunistic infection, it is generally recommended to inject vaccinations for IBD patients. However, the vaccination rates in IBD patients are really low worldwide. Furthermore, the vaccination rates of IBD patients in Asia including Korea have not been studied as far as we know. This study was intended to check the vaccination rates among IBD patients in Korea. Through the brochure that explains recommended vaccines, we wanted to enlighten the necessity of the vaccinations in IBD patients. We also aimed that physicians take more interest in vaccination for IBD patients through this kind of study.

In the USA, the vaccination rates for Td, influenza and pneumococcus were only 45%, 28% and 9% respectively.<sup>11</sup> In our study, the vaccination rates for Td, influenza and pneumococcus were 15.6%, 37.5% and 6.3%, respectively, which were lower than the USA data for Td and pneumococcus. Another study in Spain, the effective vaccination rate for HBV in IBD patients was only 12%.<sup>12</sup> As Korea is an endemic area for HBV, it is recommended as a national vaccination program since 1991. The vaccination rate for HBV in our study showed a higher result (52.6%) than the Spain data. On the other hand, vaccination rates for hepatitis A, Td, HPV and

pneumococcus were very low that ranged from 6.3% to 15.6%. When considering the recent re-increase of hepatitis A in Korea,<sup>13</sup> we should pay more attention to hepatitis A vaccinations in IBD patients. Also, even though the development of uterine cervical cancers is still inconclusive,<sup>14</sup> the low vaccination rate of HPV (11.3%) is somewhat disappointing.

Among the vaccines that we investigated, MMR and HBV vaccines are usually injected in the childhood. And Td vaccines are recommended every 10 years. Therefore the respondents might not recall exactly whether they were vaccinated or not. Furthermore, we considered 'not knowing about the vaccination' as 'non-vaccination'. These factors probably underestimated the actual vaccination rates. However, the national immunization system has started in 1995 for HBV and in 2000 for MMR. Considering the age of the respondents, the recall bias would not affect much to the results.

In the multivariate analysis, only CD was related with higher vaccination rate. Several factors might lead the relation with CD and higher vaccination rate. The difference of the mean age between CD and UC (36.1 vs. 44.3,  $p < 0.000$ ) might be an important reason for higher vaccination. As CD patients are younger than UC patients, they are more vulnerable with internet information. Especially in South Korea, a lot of CD patients get information from several internet groups. These factors might affect higher vaccination rates in CD patients.

This is the first study that evaluated the vaccination rates of IBD patients in Korea. We also tried to find out some demographic or clinical factors that affected vaccination rates. The patients who were older than 40 years old and the duration of illness over 10 years were associated with lower vaccination rates. However, the actual needs for vaccinations and risks for opportunistic infections could be higher in those patients who were older and had a longer duration of illness. These contrary results imply that physicians and patients should be more concerned about the disease and vaccinations. Furthermore, the most common reasons for non-vaccinations were unawareness of the presence and necessity of the vaccination. Public efforts to increase vaccination rates are also needed.

Our study has several limitations. First, subjects were recruited from a referral center rather than a general population base. Patients might have more serious disease and

need more intensive medical treatments. Also in our study, 108 CD patients and 84 UC patients were enrolled. However the actual prevalence of UC is about 2.5 times more than CD.<sup>15</sup> These findings suggest that patients in this study could not represent the general IBD population of South Korea. Second, all of these patients were in follow-up of one doctor of the hospital, recommendations about their vaccinations by the physician were not different. Third, this study is based on patients' recall. Surveys relying on patient recall are prone to bias. However mean age of the patients was not that old (39.7, 18-76 years), recall bias could be minimized. Third, the difference of national immunization projects according to the respondents' age, the participants are heterogeneous for childhood vaccinations.

Despite these limitations, our study is the first data about vaccination rates among IBD patients in Korea, which were extremely low. Also some clinical factors that were related with lower vaccination rates turned out contrary to the medical needs. The reasons for non-vaccination indicated that the shortage of patients' knowledge about vaccinations is the main problem. Not only educations of the patients, but also public campaigns that enlighten IBD patients are needed.

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