

Predictors of Covid-19 vaccination acceptance in IBD patients: a prospective study

Anna Viola^a, Marco Muscianisi^a, Raffaele Li Voti^a, Giuseppe Costantino^a, Angela Alibrandi^b and Walter Fries^a

Background Adherence to vaccinations is unsatisfactory in the inflammatory diseases (IBD) population because of concerns regarding adverse events or low perception of infectious risk. The aim of this study was to maximise adherence to anti-Covid-19 vaccination in IBD patients.

Methods In the third trimester of 2020, all IBD patients were informed concerning the need for anti-Covid-19 vaccination and family physicians were advised to proceed with anti-Influenza and anti-pneumococcus vaccinations. Demographic data, disease-related data together with acceptance of vaccinations were recorded. From May 2021, vaccinations of IBD patients were directly arranged at our hospital. We registered performance, procrastination or denial of anti-Covid-19 vaccination, type of vaccine and adverse events.

Results Five hundred and twenty-three patients were included (Crohn's: 266, ulcerative colitis: 257; M/F 289/234; mean age 48 ± 17 years); 53 patients were excluded from analysis as they became infected with SARS-CoV-2 during the study period; overall adherence to vaccination was 400/470 (85%), procrastinators 44 (9%) and 27 patients (6%) refused. Compared with influenza (58%) and pneumococcus (65%) vaccinations, acceptance was higher for anti-Covid-19 vaccination ($P < 0.0001$, both). Mild adverse events occurred in 31% and two (0.5%) needed precautionary but uneventful hospitalization. On multiple stepwise regression analysis, factors positively associated with adherence to vaccination were age ($P < 0.039$; OR, 1.016, 95% CI: 1.001–1.031) and previous anti-influenza vaccination ($P < 0.008$; OR, 2.071, 95% CI: 1.210–3.545).

Conclusions Direct counselling and on-site administration were associated with a satisfactory acceptance of anti-Covid-19 vaccination, whereas vaccinations against influenza and pneumococcus remained below expected levels. Increased risk perception may account for the observed differences. *Eur J Gastroenterol Hepatol* 33: e1042–e1045
Copyright © 2021 Wolters Kluwer Health, Inc. All rights reserved.

Introduction

Although patients with chronic inflammatory diseases (IBD) seem not to have a higher risk for SARS-CoV-2 infection even if taking immunomodulators [1] or biologics [2,3], some variables like severely active disease, steroid treatment and, of course, age were associated with worse outcomes [4–6]. With the approval of several vaccines against Covid-19, immunization of IBD patients has become a major goal in the management of IBD patients, regardless of age.

In IBD patients, vaccinations against infectious diseases including influenza, pneumococcus pneumonia, hepatitis B, etc. belong to the standard of care [7] but, generally, adherence to vaccination programs is dissatisfying [8]. The aim of the present study was to obtain the highest possible adherence to anti-Covid-19 vaccinations by face-to-face counselling in an IBD population followed at our centre and to compare adherence with that of

anti-influenza vaccination and anti-pneumococcus vaccination. Moreover, adverse events due to anti-Covid-19 vaccinations were monitored together with the outcome of SARS-CoV-2 infections in our patients whether vaccinated or not.

Methods

Prospectively collected data of all consecutive IBD patients followed at our outpatient clinic from 1 October 2020 to 30 June 2021 were included in the present study. According to our standard protocol, patients were encouraged during the visits in 2020 to adhere to the national vaccination program against seasonal influenza and pneumococcus by a letter directed to their family physicians and, when available, to the anti-Covid19 vaccination. The national vaccination program against SARS-CoV-2 started in January 2021 but was initially limited to elderly people and to certain professional categories.

From 2 May 2021, the vaccination centre of our clinic was authorized to proceed with vaccinations for younger patients holding the national exemption code 009 for IBD. This new strategy was also extended to all other vaccination centres in Sicily.

At each visit, the patients were asked if he/she had already undergone any vaccination. For each patient, sex, age, type of IBD and disease characteristics were collected. Data on concomitant treatment (i.e. conventional or biologic therapies) for IBD and total months of follow-up at our centre were also collected for each patient.

European Journal of Gastroenterology & Hepatology 2021, 33:e1042–e1045

Keywords: Crohn's disease, SARS-CoV-2 infection, ulcerative colitis

^aIBD-Unit, Department of Clinical and Experimental Medicine and ^bDepartment of Economics, Unit of Statistical and Mathematical Sciences, University of Messina, Messina, Italy

Correspondence and reprint requests to Anna Viola, MD, Clinical Unit for Chronic Bowel Disorders, Dept. of Clinical and Experimental Medicine, University of Messina, Messina, Italy

Tel: +390902212387; e-mail: annaviola88@gmail.com

Received 19 July 2021 **Accepted** 1 November 2021

Patients were prospectively stratified into three categories: (1) 'vaccinated', patients who had received at least one dose of vaccine or accepted the booking at our vaccination centre within the study period, (2) 'procrastinators', patients who temporarily did not want to get vaccinated because of concerns about potential adverse events and (3) 'strongly opposed', patients who did not want to get vaccinated in any circumstances. Adherence to the vaccination program and predictors for acceptance were sought as primary outcomes.

We also investigated adverse events (AE) that occurred in the days following vaccination considering therapy at the time of vaccination.

Together with data on anti-Covid19 vaccination, we collected data on influenza vaccination administered in the last three months of 2020 and on pneumococcus vaccinations (at least 1 administration of the 13-valent vaccine in the preceding 24 months).

Patients reporting a SARS-CoV2 infection during the study period were excluded from statistical analysis, as well as patients with <10 months of follow-up at our centre concerning the comparison between the three vaccinations, as they had not received a written notice from their family doctors for influenza and pneumococcus vaccination.

The study was approved by the local Ethics Committee protocol. no. 98/21.

Statistical analysis was carried out using SPSS version 22.0 software for Windows. Descriptive statistics included the calculation of mean values with SD or median with their range, for all continuous variables. Categorical variables were summarized using absolute frequencies and percentages.

Rate of anti-Covid19 vaccination was compared with influenza and pneumococcus vaccinations by means of the proportion test, and multiple stepwise regression analysis was performed to assess factors associated with adherence to anti-Covid19 vaccination. Comparison of AE between different groups was performed with Chi-square test. *P* values <0.05 were considered statistically significant.

Results

Five hundred and twenty-three patients were included in the study. Characteristics of patients are summarized in Table 1. Concerning demographic and disease-related characteristics at baseline, no significant differences were found between vaccinated and not vaccinated patients. Patients with anti-Covid19 vaccination had a higher rate of influenza and pneumococcus vaccinations (*P* = 0.001 and *P* = 0.04, respectively). Adherence to vaccination was very high, reaching 85% in our patients. Only a small percentage of patients, despite being informed of the risks associated with coronavirus infection, refused vaccination (6%) or preferred to delay vaccine administration (9%).

The vast majority (91%) was vaccinated with the BNT162b2 vaccine, only few patients (2%) received the ChAdOx1 nCoV-19 vaccine (no patient on thiopurines and no patient on biologic therapies) and only 7% of patients underwent vaccination with the mRNA-1273 vaccine.

In order to identify predictive factors associated with greater propensity to undergo vaccination, the following

variables were selected and included in the stepwise regression analysis: age, sex, months of follow-up, concomitant therapy with steroids, biologics or conventional treatment, previous vaccinations against influenza and pneumococcus.

Factors positively associated with adherence to vaccination were age (*P* < 0.039; OR, 1.016, 95% CI: 1.001–1.031) and having undergone anti-influenza vaccination in 2020 (*P* < 0.008; OR, 2.071, 95% CI: 1.210–3.545).

Anti-influenza and anti-pneumococcus vaccinations reached 58% (243/417) of adherence for the former and 65% (271/417) for the latter. When compared with Covid-19 vaccination, adherence was significantly lower for the latter vaccinations (*P* < 0.0001, both). Patients with previous Sars-Cov-2 infection and patients with short follow-up were excluded from comparison.

At the time of analysis, 23 (6%) patients had received 1 dose and 348 (87%) had received both doses, of either the BNT162b2 or ChAdOx1 vaccine and 29 patients (7%) had the single dose of mRNA-1273.

Adverse events (Table 2) were reported by 125 (31%) patients and were generally mild, being limited to pain at the injection site limited to 2 or 3 days (21%), fever (14%), muscle pain on the following day (11%), asthenia (10%), headache (6%) or other (6%), such as vertigo (two patients), sore throat, insomnia, backpain, cough and vomiting in one patient. A lower percentage of patients reported diarrhoea with abdominal discomfort (1%). Two patients needed precautionary hospitalization but were dismissed shortly thereafter (1 patient with urticaria and 1 patient collapsed); unfortunately, adverse events to influenza vaccine (Vaxigrip tetra) or to pneumococcus vaccine (13- or 23-valent) were not registered in our charts. No concomitant therapies (mesalazine, steroids, immunomodulators, anti-TNF or other biologic therapies) were associated with more frequent AEs. Younger patients (<50 years of age) experienced AEs more frequently than those over 50 years of age (63% vs. 37%, *P* < 0.001). No difference was found between sex and type of disease.

During the study period from October 2020 to the end of June 2021, 53 patients became infected with SARS-CoV-2, with 1 coronavirus-related fatality of an 82-year-old man with Crohn's disease.

Discussion

To our knowledge, this is the first report on the effective adherence to SARS-CoV-2 vaccination in a cohort of IBD patients. We showed a very high acceptance rate of 85% in our patient cohort, achieved by face-to-face counselling and, starting from May 2021 through June 2021, by direct booking of vaccination at our vaccination centre.

Previous reports dealing with willingness to receive SARS-CoV-2 vaccination in IBD patients, mainly collected through questionnaires, reported 54% acceptance in France [9], 58.8% in Germany [10], 54% in Italy [11] and 80.9% in a local cohort in the USA while the same paper reported only a 60% potential adherence in a cohort recruited through social media [12]. The highest data on adherence were reported in an Italian centre with direct counselling achieving 96.4% adherence but the study population was rather small [13]. This latter paper, together with the present one, demonstrates that personal

Table 1. Baseline patients characteristics

| N = 470 | Vaccinated (n = 400) | Not vaccinated (n = 70) | P value |
|---|-------------------------|----------------------------|---------|
| Age; years mean ± SD | 48 ± 18 | 49 ± 18 | |
| Sex, male; n (%) | 221 (55) | 44 (63) | 0.23 |
| Disease activity; n (%) | 308 (73) | 45 (64) | 0.30 |
| Remission | 73 (18) | 12 (17) | |
| Mild | 14 (3) | 4 (6) | |
| Moderate | 1 (0.3) | - | |
| Severe | Missing data: 4 | Missing data:9 | |
| Montreal classification CD ^a ; n (%) | n = 203 | n = 39 | 0.96 |
| | L1: 115 (57) | L1: 21 (54) | |
| | L2: 25 (12) | L2: 5 (13) | |
| | L3: 61 (32) | L3: 12 (31) | |
| | L4: 3 (1) ^b | L4: 1 (3) ^b | |
| Montreal classification UC ^a ; n (%) | n = 197 | n = 31 | 0.61 |
| | E1: 32 (16) | E1: 4 (16) | |
| | E2: 88 (45) | E2: 17 (45) | |
| | E3: 74 (38) | E3: 10 (38) | |
| | Missing data: 3 | | |
| Concomitant therapy; n (%)§ | 15 (4) | 1 (1) | 0.33 |
| No treatment | 206 (52) | 15 (21) | |
| 5-ASA | 20 (5) | 4 (6) | |
| Steroids | 51 (13) | 6 (9) | |
| IMM | | | |
| Biologic therapy | | | |
| Anti-TNF | 163 (41) | 22 (31) | 0.07 |
| Vedolizumab | 61 (15) | 6 (9) | |
| Ustekinumab | 46 (12) | 13 (19) | |
| Tofacitinib | 2 (0.5) | 1 (1) | |
| Guselkumab | 1 (0.3) | - | |
| | Missing data: 3 | | |
| Seasonal influenza vaccination in 2020; n (%) | 230/398 (58) | 26/69 (38) | 0.001 |
| Former pneumococcus vaccination; n (%) | 246/397 (62) | 34/69 (49) | 0.04 |

Data are expressed as numbers (percentages) or mean (SD).

IMM, immunomodulators.

^aDisease location is expressed according to Montreal Classification.

^bL4 was present with concomitant other disease locations.

[§]Combined treatments not specified. Data for influenza and pneumococcus vaccinations were given excluding patients with short follow-up.

Table 2. Adherence to anti-Covid-19 vaccinations, adverse events and Sars-CoV-2 infection during study period

| | IBD population N = 470 |
|--|---------------------------|
| Anti Covid-19 vaccination; n (%) | |
| Administered | 400 (85) |
| Procrastinators | 44 (9) |
| Refusal | 27 (6) |
| Type of vaccine; n (%) | |
| BNT162b2 | 362 (91) |
| ChAdOx1 | 9 (2) |
| mRNA-1273 | 29 (7) |
| Adverse events; no. of patients (%) | 125 (31) |
| Pain at the injection site | 84 (21) |
| Fever | 55 (14) |
| Muscle pain | 43 (11) |
| Asthenia | 42 (11) |
| Headache | 23 (6) |
| Diarrhoea and abdominal discomfort | 4 (1) |
| Other | 7 (2) |
| Hospitalization | 2 (0.5) |
| COVID Infection during study period; n (%) | 53 (10) |

Data are expressed as numbers (percentages). Percentages for adverse events do not sum up to 100% as more than one AE could have been present in the same patient.

contact and on-site vaccination are more efficacious than anonymous counselling.

Compared to the vaccination status of the total population in Sicily by the end of July with 59% vaccinated with at least one dose [14], our IBD population showed a much higher vaccination status but still, 15% remained without vaccine administration. This may indicate that with

our direct vaccination booking indolent patients may be convinced but not those afraid of or against vaccinations. Unfortunately, among our patients, an in-depth investigation concerning the reasons for vaccination refusal or procrastination was not recorded.

When investigated, a positive association with former influenza vaccinations and the willingness to receive SARS-CoV-2 vaccination [10,11], was reported and this finding was confirmed in the present study.

Acceptance rates in terms of willingness in the general non-IBD population among different European countries roughly resembled those of IBD patients investigated through questionnaires, ranging from a low 47% (France, Hungary) to intermediate acceptance (Germany 60%, Italy 60%, Sweden 61%) to highest acceptance in Denmark 83% and UK 73% [15].

Concerning vaccination-related AEs, in the present study, one or more mild AEs occurred in 31% of our patients. A former report on a smaller cohort of IBD patients found a frequency of 39% of AEs after vaccination with mRNA vaccines with an additional finding that they were less common with major IBD-related therapies and in patients aged over 50 years [16]. In the present study, we can only confirm an increased frequency in younger patients but not for disease type, sex or therapy.

Conclusion

In the present study, we found a high acceptance rate among our IBD patients to anti-Covid-19 vaccination

through direct counselling and direct vaccination delivery. Increasing age was positively associated with vaccination uptake most likely by a combination of direct counselling and high-risk perception. Having accepted seasonal influenza vaccination in the preceding year represents another positively associated cofactor for acceptance. A combination of trusting in prescribing physicians, age, risk perception, general propensity with regard to vaccines together with user-friendly facilities may represent the best base for a positive vaccination uptake.

Acknowledgements

A.V., M.M and W.F. designed the study. A.A. helped with statistics. M.M., R.L.V. and G.C helped with patient' visits and data collection. A.V. and W.F drafted the manuscript. A.V, W.F, G.C and M.M. critically reviewed the manuscript.

Conflicts of interest

There are no conflicts of interest.

References

- Meyer A, Semenzato L, Zureik M, Weill A, Carbonnel F, Dray-Spira R. Risk of severe COVID-19 in patients treated with IBD medications: a French nationwide study. *Aliment Pharmacol Ther* 2021; 54:160–166.
- Ardizzone S, Ferretti F, Monico MC, Carvalhas Gabrielli AM, Carmagnola S, Bezzio C, *et al.* Lower incidence of COVID-19 in patients with inflammatory bowel disease treated with non-gut selective biologic therapy. *J Gastroenterol Hepatol* 2021; 36:3050–3055.
- Khan N, Patel D, Xie D, Pernes T, Lewis J, Yang YX. Are patients with inflammatory bowel disease at an increased risk of developing SARS-CoV-2 than patients without inflammatory bowel disease? Results From a Nationwide Veterans' Affairs Cohort Study. *Am J Gastroenterol* 2021; 116:808–810.
- Macaluso FS, Orlando A. COVID-19 in patients with inflammatory bowel disease: a systematic review of clinical data. *Dig Liver Dis* 2020; 52:1222–1227.
- Lamb CA, Sebastian S, Kent AJ, Segal JP, Gonzalez HA, Brookes MJ, *et al.*; PREPARE-IBD Study Group. Letter: risk of severe COVID-19 outcomes associated with inflammatory bowel disease medications-reassuring insights from the United Kingdom PREPARE-IBD multicentre cohort study. *Aliment Pharmacol Ther* 2021; 53:1236–1240.
- Bezzio C, Saibeni S, Variola A, Allocca M, Massari A, Gerardi V, *et al.*; Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD). Outcomes of COVID-19 in 79 patients with IBD in Italy: an IG-IBD study. *Gut* 2020; 69:1213–1217.
- Kucharzik T, Ellul P, Greuter T, Rahier JF, Verstockt B, Abreu C, *et al.* ECCO Guidelines on the prevention, diagnosis, and management of infections in inflammatory bowel disease. *J Crohns Colitis* 2021; 15:879–913.
- Quera R, Simian D, Núñez P, Flores L, Figueroa C, Ibáñez P, *et al.* Are patients with inflammatory bowel disease receiving adequate immunisation? *Gastroenterol Hepatol* 2021; 44:198–205.
- Caron B, Neuville E, Peyrin-Biroulet L. Inflammatory bowel disease and COVID-19 vaccination: a patients' survey. *Dig Dis Sci* 2021; 12:1–7.
- Walldorf J, von Arnim U, Schmelz R, Riesner-Wehner A, Michl P, Grunert PC, *et al.* SARS-CoV-2 vaccination in patients with inflammatory bowel disease-fear and desire. *Inflamm Bowel Dis* 2021; 28:izab150.
- Crispino F, Brinch D, Carrozza L, Cappello M. Acceptance of SARS-CoV-2 vaccination among a cohort of IBD patients from Southern Italy: a cross-sectional survey. *Inflamm Bowel Dis* 2021; 5:izab133.
- Dalal RS, McClure E, Marcus J, Winter RW, Hamilton MJ, Allegretti JR, *et al.* COVID-19 vaccination intent and perceptions among patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2021; 4:S1542-3565(21)00105-1.
- Giannini EG, Demarzo MG, Bodini G. Elevated adherence to vaccination against SARS-CoV-2 among patients with Inflammatory Bowel Disease. *J Crohns Colitis* 2021; 5:jjab104.
- https://palermo.repubblica.it/cronaca/2021/08/01/news/covid_la_sicilia_dei_vaccini_ragusa_e_virtuosa_messina_maglia_nera-312595036. [Accessed October 04, 2021].
- Lindholt MF, Jørgensen F, Bor A, Petersen MB. Public acceptance of COVID-19 vaccines: cross-national evidence on levels and individual-level predictors using observational data. *BMJ Open* 2021; 11:e048172.
- Botwin GJ, Li D, Figueiredo J, Cheng S, Braun J, McGovern DPB, *et al.* Adverse events after SARS-CoV-2 mRNA vaccination among patients with inflammatory bowel disease. *Am J Gastroenterol* 2021; 31:2021.03.30.21254607.