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Impact of SARS-CoV-2 vaccination in inflammatory bowel disease patients with different biological agents: a systematic review and meta-analysis

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ABSTRACT

Background: there are concerns regarding the effect of biological agents on SARS-CoV-2 vaccination in patients with inflammatory bowel disease (IBD). A systematic review and meta-analysis was performed about the serological responses,

breakthrough infections and clinical relapse of IBD patients treated with biological agents following SARS-CoV-2 vaccination.

Methods: electronic databases were searched to identify relevant studies. Primary outcomes were the pooled seroconversion rates, breakthrough infection rates and clinical relapse rates after SARS-CoV-2 vaccination in IBD patients treated with biological agents. Secondary outcomes were the comparison of seroconversion rates, breakthrough infection rates and clinical relapse rates in IBD patients treated with biological agents and control cohort after SARS-CoV-2 vaccination.

Results: thirty-five studies were included in this meta-analysis. A high percentage of seroconversion (96.6 %, 99 % and 99.2 %) was achieved in IBD patients treated with anti-TNF-α therapy, vedolizumab and ustekinumab after SARS-CoV-2 vaccination, respectively. The pooled breakthrough infection rate was 2.5 % and 3.9 % in IBD patients treated with anti-TNF-α therapy and vedolizumab, respectively. The breakthrough infection rate in IBD patients treated with anti-TNF-α therapy was significantly lower than in the control cohort (RR 0.178, 95 % CI: 0.084-0.378). The pooled clinical relapse rate in IBD patients treated with anti-TNF-α therapy, vedolizumab and ustekinumab was 6.9 %, 5.4 % and 5.3 %, respectively.

Conclusion: the overall seroconversion rate after SARS-CoV-2 vaccination in IBD patients treated with biological agents is high. The overall breakthrough infection rate and clinical relapse rate in IBD patients treated with biological agents were low.

Keywords: COVID-19. SARS-CoV-2. Inflammatory bowel disease. Anti-TNF-α therapy. Vedolizumab. Ustekinumab.

INTRODUCTION

Coronavirus disease 19 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been associated with more than six million deaths worldwide and 500 million infections, as well as significant economic and social upheavals. One of the most effective measures to reduce COVID-19 infections is the development of the SARS-CoV-2 vaccination. Some studies found that various vaccinations have shown to be efficacious in reducing COVID-19 infection rates (1).

However, these studies excluded patients with comorbidities including immune-mediated inflammatory diseases such as inflammatory bowel disease (IBD) (2).

IBD are chronic inflammatory diseases of the intestinal tract with two major phenotypes including ulcerative colitis (UC) and Crohn's disease (CD), which is increasing in incidence and prevalence worldwide (3). IBD may be associated with immune dysfunction, related either to the underlying disease or the use of immune-modulating drugs such as biological agents (4). Guidelines currently recommend that IBD patients should be vaccinated against SARS-CoV-2 due to the ongoing pandemic and the risk of COVID-19 infection (5-8). However, there were concerns regarding a possible heightened risk of COVID-19 infection and worse clinical outcomes in IBD patients treated with biological agents.

There is a concern that IBD or the use of biological agents could attenuate responses to SARS-CoV-2 vaccination (9). The development of these responses and their persistence or decay over time may determine the future need for booster dosing schedules. The messenger RNA (mRNA) and adenoviral vector (AVV) based technologies used in SARS-CoV-2 vaccination development are relatively new and the impact of IBD and biological agents on serological responses, breakthrough infections and clinical relapse is uncertain. In view of these uncertainties, a systematic review and meta-analysis was performed to evaluate the antibody response, breakthrough infections and clinical relapse following SARS-CoV-2 vaccination in IBD patients treated with biological agents (anti-tumor necrosis factor alpha [anti-TNF-α] agents, vedolizumab [VDZ] and ustekinumab [UST]).

METHODS

Search strategy

PubMed, Ovid Embase, Medline and Cochrane CENTRAL were systematically searched since inception until September 2022. Search terms were "COVID-19", "SARS-CoV-2", "2019-nCoV", "2019 novel coronavirus", "novel coronavirus pneumonia", "Vaccine", "Vaccination", "Inflammatory bowel disease", "IBD", "Ulcerative colitis", "UC", "Crohn's disease", "CD", "Infliximab", "IFX", "Adalimumab", "ADA", "Vedolizumab", "VDZ", "Ustekinumab" and "UST".

Inclusion criteria and exclusion criteria

Studies which met the following criteria were included: a) all randomized control trials (RCTs) or prospective studies or retrospective studies or cohort studies of IBD patients treated with biological agents undergoing SARS-CoV-2 vaccination; b) all studies describing the seroconversion, breakthrough infection and clinical relapse after SARS-CoV-2 vaccination in IBD patients treated with biological agents; c) all studies with information available to evaluate the seroconversion rate, breakthrough infection rate and clinical relapse rate after SARS-CoV-2 vaccination; and d) full text. The exclusion criteria were as follows: a) studies published as reviews, letters, case reports, editorials, comments and conference abstracts; and b) studies did not include any of the outcomes of the interest.

Selection of studies

Two investigators (Zi-yuan Dong and Yi-nuo Wang) reviewed and selected the included studies. In cases of disagreement, a consensus was reached by consultation with the senior reviewer (Yu-Hong Huang).

Data extraction

Information was extracted from each study, including baseline characteristics such as author name, year of publication, country, study design, sample size, biological agents, age, sex, type of SARS-CoV-2 vaccination, dose, follow up duration, the seroconversion rate, breakthrough infection rate and clinical relapse rate. Primary outcomes were the pooled seroconversion rates, breakthrough infection rates and clinical relapse rates after SARS-CoV-2 vaccination in IBD patients treated with biological agents. Secondary outcomes were the comparison of seroconversion rates, breakthrough infection rates and clinical relapse rates in IBD patients treated with biological agents and control cohort (non-IBD population).

Statistical analysis

The data was analyzed by Stata SE 15.1. The proportion and 95 % confidence interval

(CI) were used to calculate the seroconversion rate, breakthrough infection rate and clinical relapse rate. Forest plots were used to present data visually. Heterogeneity was evaluated using the Cochran's Q test and I^2 statistics; p value < 0.10 or I^2 > 50 % means the heterogeneity was significant. The random-effects model was used if heterogeneity was significant; otherwise, the fixed-effects model was adopted. Publication bias was assessed with funnel plots and Egger's test. Relative risk (RR), 95 % CI and p value were computed to compare the difference. A p value < 0.05 meant that the difference between groups was statistically significant.

RESULTS

Study selection and baseline characteristics

We initially retrieved 845 unique citations from PubMed, Ovid Embase, Medline and Cochrane CENTRAL. Two hundred and twenty-one studies were excluded in the first screening because of duplication. After reading the titles, abstracts and full-text of citations, 589 literatures were excluded and 35 studies were included (Fig. 1). These included 13 cohort studies, 12 prospective studies, nine retrospective studies and one case-control study. The PRISMA Flow chart is shown in figure 1. The study details are shown in table 1 (4,9-30). In this meta-analysis, the time span of case collection was from 2019 to 2022. The median age of patients ranged from 14.5 to 55.7 years.

Seroconversion rate after SARS-CoV-2 vaccination

Twenty-three studies were included to analyze the pooled seroconversion rate after SARS-CoV-2 vaccination in IBD patients treated with biological agents. The pooled seroconversion rate in IBD patients treated with anti-TNF-α therapy was 96.6 % (95 % CI: 0.945-0.988) (Fig. 2). There was significant heterogeneity in the analysis (I^2 = 76 %). The pooled seroconversion rate in IBD patients treated with anti-TNF-α combination therapy (anti-TNF-α therapy and immunosuppressive drugs [IMM]) was 94.4 % (95 % CI: 0.909-0.981) (Fig. 3). There was significant heterogeneity in the analysis (I^2 = 77 %). The pooled seroconversion rate in IBD patients treated with VDZ was 99 % (95 % CI: 0.985-0.994) (Fig. 4). There was no significant heterogeneity in the analysis (I^2 = 41.5 %). The pooled seroconversion rate in IBD patients treated with

UST was 99.2 % (95 % CI: 0.981-1) (Fig. 5). There was no significant heterogeneity in the analysis (I^2 = 0 %).

Breakthrough infection rate after SARS-CoV-2 vaccination

Five studies were included to analyze the breakthrough infection after SARS-CoV-2 vaccination in IBD patients treated with biological agents. Two hundred and seventy-one breakthrough infections were reported in 5,824 IBD patients. The pooled breakthrough infection rate in IBD patients treated with anti-TNF-α therapy was 2.5 % (95 % CI: -0.009-0.059). There was significant heterogeneity in the analysis (I^2 = 96.8 %). Only one study by Frey found that the breakthrough infection rate in IBD patients treated with anti-TNF-α combination therapy (anti-TNF-α therapy and IMM) was 0 % (0/38). The pooled breakthrough infection rate in IBD patients treated with VDZ was 3.9 % (95 % CI: 0.030-0.049). There was no significant heterogeneity in the analysis (I^2 = 0 %). Only one study by Frey found that the breakthrough infection rate in IBD patients treated with UST was 0 % (0/17). The meta-analysis revealed that the breakthrough infection rate in IBD patients treated with anti-TNF-α therapy was significantly lower than in the control cohort after SARS-CoV-2 vaccination (RR 0.178, 95 % CI: 0.084-0.378; $p < 0.05$). There was no significant heterogeneity in the analysis (I^2 = 48.6 %).

Clinical relapse rate after SARS-CoV-2 vaccination

Eight studies were included to analyze the clinical relapse after SARS-CoV-2 vaccination in IBD patients treated with biological agents. Four hundred and twenty patients with clinical relapse were reported in 4,622 IBD patients. The pooled incidence rate of clinical relapse in IBD patients treated with anti-TNF-α therapy after SARS-CoV-2 vaccination was 6.9 % (95 % CI: 0.039-0.098). There was significant heterogeneity in the analysis (I^2 = 98.4 %). The pooled incidence rate of clinical relapse in IBD patients treated with VDZ after SARS-CoV-2 vaccination was 5.4 % (95 % CI: 0.019-0.088). There was significant heterogeneity in the analysis (I^2 = 95.2 %). The pooled incidence rate of clinical relapse in IBD patients treated with UST therapy after SARS-CoV-2 vaccination was 5.3 % (95 % CI: 0.014-0.091). There was

significant heterogeneity in the analysis (I^2 = 92.1 %).

Publication bias

A funnel plot was performed to assess the publication bias. The Deeks' test revealed no evidence of publication bias (seroconversion rate in IBD patients treated with anti-TNF-α therapy: p = 0.27; anti-TNF-α therapy + IMM: p = 0.565; VDZ: p = 0.143; UST: p = 0.542) (breakthrough infection rate in IBD patients treated with anti-TNF-α therapy: p = 0.821) (clinical relapse rate in IBD patients treated with anti-TNF-α therapy: p = 0.088; VDZ: p = 0.192; UST: p = 0.181).

DISCUSSION

The IBD patient population is theoretically at a higher risk for COVID-19 infection due to immune dysfunction and the frequent use of immune-modulating drugs such as biological agents. Therefore, some guidelines have recommended SARS-CoV-2 vaccination in the IBD population (8). There have been numerous studies and two meta-analyses reporting the antibody response of the SARS-CoV-2 vaccination in the IBD population (4,11,12,14,15,17,23,24,26-29). However, some studies found that some biological agents such as infliximab may result in a lower efficacy of protection from SARS-CoV-2 vaccination (9,15). In patients with other autoimmune diseases using rituximab, the seroconversion rate after SARS-CoV-2 vaccination was significantly lower than that in the control group (31-33). In contrast, our meta-analysis showed that a high percentage of seroconversion (96.6 %, 99 % and 99.2 %) was achieved in IBD patients treated with anti-TNF-α therapy, VDZ and UST after SARS-CoV-2 vaccination, respectively. Some studies found that the risk of severe COVID-19 infection was higher in IBD patients receiving steroids and 5-ASA treatment (14), thus, vaccination for IBD patients taking biological agents is highly suggested. Our findings supported SARS-CoV-2 vaccination in IBD patients treated with biological agents as recommended by the professional societies. Our findings also indicated that the antibody response to the SARS-CoV-2 vaccines was not attenuated in IBD patients treated with VDZ and UST. The seroconversion rates did not significantly differ between VDZ and UST. However, the seroconversion rates in

IBD patients treated with anti-TNF-α therapy was lower than that in IBD patients treated with VDZ and UST. Interestingly, our analysis demonstrated the decreased seroconversion with the use of combination of anti-TNF agents with IMM as compared with anti-TNF agents alone. Further studies will be important to evaluate the impact of a booster dose on seroconversion of IBD patients treated with anti-TNF-α therapy.

An important measure of the effectiveness of SARS-CoV-2 vaccination is the incidence of breakthrough infection after SARS-CoV-2 vaccination. Our meta-analysis showed that the breakthrough infection rate was 2.5 % and 3.9 % in IBD patients treated with anti-TNF-α therapy and VDZ after SARS-CoV-2 vaccine, respectively. The breakthrough infection rate in IBD patients treated with UST was 0 %. Furthermore, the breakthrough infection rate in IBD patients treated with anti-TNF-α therapy was significantly lower than in the control cohort after SARS-CoV-2 vaccination. Therefore, breakthrough infections in IBD patients treated with biological agents after SARS-CoV-2 vaccination could occur, but the overall frequency was low. In addition, the included studies demonstrated that the majority of breakthrough infections did not require hospitalization.

Fear of the flare of disease activity remains a major concern in IBD patients after SARS-CoV-2 vaccination. Our previous study revealed that fear of negative impact on the course of IBD was seen in 88.06 % of IBD patients who did not receive SARS-CoV-2 vaccination (34). To address this, we found a flare of disease activity in IBD patients treated with anti-TNF-α therapy, VDZ and UST following SARS-CoV-2 vaccination was seen in extremely small numbers. The data confirmed the fact that biological agents have minimal impact on the course of disease in IBD patients following SARS-CoV-2 vaccination.

The strength of this study is the large number of IBD patients treated with biological agents included in the meta-analysis across a high number of prospective, well-designed studies. This is the first study to pool seroconversion rate, breakthrough infection rate and clinical relapse rate in IBD patients treated with different biological agents following SARS-CoV-2 vaccination. At the same time, there were limitations in our meta-analysis. First, some factors that impact the seroconversion

and breakthrough infections could be responsible for the high heterogeneity: differences in populations (type of IBD, age, sex, disease activity, and severity), type of vaccine (AAV, mRNA, or both) and booster dose, previous COVID-19 exposure history, definition or assessment of seroconversion and breakthrough infections, the different assays to assess for the antibodies against SARS-CoV-2, and the timing of determination of outcomes (time from vaccination to the estimation of antibody responses, time of follow-up for breakthrough infections). Second, there could be an overlap in certain definitions such as gastrointestinal symptoms and clinical relapse. We have used the definitions exactly as provided in the included studies. For example, some studies considered clinical relapse as a component of gastrointestinal symptoms while others considered these as separate entities, such as C reactive protein (CRP) and fecal calprotectin (FC) elevation. Third, there is small number of studies for some of the analysis (comparison of seroconversion and breakthrough infections with healthy control subjects) in this meta-analysis.

In conclusion, this systematic review and meta-analysis showed that the overall seroconversion rate after SARS-CoV-2 vaccination in IBD patients treated with biological agents is high. However, the seroconversion rates in IBD patients treated with anti-TNF-α therapy was lower than that in IBD patients treated with VDZ and UST. The rates of breakthrough infection and clinical relapse in IBD patients treated with biological agents after SARS-CoV-2 vaccination were low. Further studies are needed to accurately determine this risk and the related mechanisms.

REFERENCES

1. Francis AI, Ghany S, Gilkes T, et al. Review of COVID-19 vaccine subtypes, efficacy and geographical distributions. Postgrad Med J 2022;98(1159):389-94. DOI: 10.1136/postgradmedj-2021-140654

2. Jena A, Mishra S, Deepak P, et al. Response to SARS-CoV-2 vaccination in immune mediated inflammatory diseases: systematic review and meta-analysis. Autoimmun Rev 2022;21(1):102927. DOI: 10.1016/j.autrev.2021.102927

3. Kaplan GG, Windsor JW. The four epidemiological stages in the global evolution of inflammatory bowel disease. Nat Rev Gastroenterol Hepatol 2021;18(1):56-66.

DOI: 10.1038/s41575-020-00360-x

4. Alexander JL, Kennedy NA, Ibraheim H, et al. COVID-19 vaccine-induced antibody responses in immunosuppressed patients with inflammatory bowel disease (VIP): a multicentre, prospective, case-control study. Lancet Gastroenterol Hepatol 2022;7(4):342-52. DOI: 10.1016/S2468-1253(22)00005-X

5. Queiroz NSF, Teixeira FV, Freire CCF, et al. Brazilian IBD Study Group Position Statement on SARS-CoV-2 Vaccination. Arq Gastroenterol 2021;58(1):1-4. DOI: 10.1590/s0004-2803.202100000-02

6. Alexander JL, Moran GW, Gaya DR, et al. SARS-CoV-2 vaccination for patients with inflammatory bowel disease: a British Society of Gastroenterology Inflammatory Bowel Disease section and IBD Clinical Research Group position statement. Lancet Gastroenterol Hepatol 2021;6(3):218-24. DOI: 10.1016/S2468-1253(21)00024-8

7. Eder P, Lodyga M, Dobrowolska A, et al. Position statement of the Polish Society of Gastroenterology and the National Gastroenterology Consultant on vaccination against COVID-19 among patients with inflammatory bowel diseases. Prz Gastroenterol 2021;16(1):2-4. DOI: 10.5114/pg.2021.103666

8. Siegel CA, Melmed GY, McGovern DP, et al. SARS-CoV-2 vaccination for patients with inflammatory bowel diseases: recommendations from an international consensus meeting. Gut 2021;70(4):635-40. DOI: 10.1136/gutjnl-2020-324000

9. Kennedy NA, Lin S, Goodhand JR, et al. Infliximab is associated with attenuated immunogenicity to BNT162b2 and ChAdOx1 nCoV-19 SARS-CoV-2 vaccines in patients with IBD. Gut 2021;70(10):1884-93. DOI: 10.1136/gutjnl-2021-324789

10. Ben-Tov A, Banon T, Chodick G, et al. BNT162b2 messenger RNA COVID-19 vaccine effectiveness in patients with inflammatory bowel disease: preliminary real-world data during mass vaccination campaign. Gastroenterology 2021;161(5):1715-7. DOI: 10.1053/j.gastro.2021.06.076

11. Boland BS, Goodwin B, Zhang Z, et al. Preserved SARS-CoV-2 vaccine cell-mediated immunogenicity in inflammatory bowel disease patients on immune-modulating therapies. Clin Transl Gastroenterol 2022;13(4):e00484. DOI: 10.14309/ctg.0000000000000484

12. Caldera F, Knutson KL, Saha S, et al. Humoral immunogenicity of mRNA COVID-19 vaccines among patients with inflammatory bowel disease and healthy controls. Am J Gastroenterol 2021;117(1):176-9. DOI: 10.14309/ajg.0000000000001570

13. Cannatelli R, Ferretti F, Carmagnola S, et al. Risk of adverse events and reported clinical relapse after COVID-19 vaccination in patients with IBD. Gut 2022;71(9):1926-8. DOI: 10.1136/gutjnl-2021-326237

14. Cerna K, Duricova D, Lukas M, et al. Anti-SARS-CoV-2 vaccination and antibody response in patients with inflammatory bowel disease on immune-modifying therapy: prospective single-tertiary study. Inflamm Bowel Dis 2022;28(10):1506-12. DOI: 10.1093/ibd/izab301

15. Chanchlani N, Lin S, Chee D, et al. Adalimumab and infliximab impair SARS-CoV-2 antibody responses: results from a therapeutic drug monitoring study in 11422 biologic-treated patients. J Crohns Colitis 2022;16(3):389-97. DOI: 10.1093/ecco-jcc/jjab153

16. Charilaou P, Tricarico C, Battat R, et al. Impact of inflammatory bowel disease therapies on durability of humoral response to SARS-CoV-2 vaccination. Clin Gastroenterol Hepatol 2022;20(6):e1493-9. DOI: 10.1016/j.cgh.2021.12.007

17. Dailey J, Kozhaya L, Dogan M, et al. Antibody responses to SARS-CoV-2 after infection or vaccination in children and young adults with inflammatory bowel disease. Inflamm Bowel Dis 2021;2021.06.12.21258810.

18. Deepak P, Kim W, Paley MA, et al. Effect of immunosuppression on the immunogenicity of mRNA vaccines to SARS-CoV-2: a prospective cohort study. Ann Intern Med 2021;174(11):1572-85. DOI: 10.7326/M21-1757

19. Edelman-Klapper H, Zittan E, Bar-Gil Shitrit A, et al. Lower serologic response to COVID-19 mRNA vaccine in patients with inflammatory bowel diseases treated with anti-TNF-alpha. Gastroenterology 2022;162(2):454-67. DOI: 10.1053/j.gastro.2021.10.029

20. Frey S, Chowdhury R, Connolly CM, et al. Antibody response six months after SARS-CoV-2 mRNA vaccination in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2022;20(7):1609-12.e1. DOI: 10.1016/j.cgh.2021.12.045

21. Garrido I, Lopes S, Macedo G. Safety of COVID-19 vaccination in inflammatory bowel disease patients on biologic therapy. J Crohns Colitis 2022;16(4):687-8. DOI: 10.1093/ecco-jcc/jjab189

22. Hadi YB, Thakkar S, Shah-Khan SM, et al. COVID-19 vaccination is safe and effective in patients with inflammatory bowel disease: analysis of a large multi-institutional research network in the United States. Gastroenterology 2021;161(4):1336-9.e1333. DOI: 10.1053/j.gastro.2021.06.014

23. Kennedy NA, Goodhand JR, Bewshea C, et al. Anti-SARS-CoV-2 antibody responses are attenuated in patients with IBD treated with infliximab. Gut 2021;70(5):865-75. DOI: 10.1136/gutjnl-2021-324388

24. Khan N, Mahmud N. Effectiveness of SARS-CoV-2 vaccination in a veterans affairs cohort of patients with inflammatory bowel disease with diverse exposure to immunosuppressive medications. Gastroenterology 2021;161(3):827-36. DOI: 10.1053/j.gastro.2021.05.044

25. Lev-Tzion R, Focht G, Lujan R, et al. COVID-19 vaccine is effective in inflammatory bowel disease patients and is not associated with disease exacerbation. Clin Gastroenterol Hepatol 2022;20(6):e1263-82. DOI: 10.1016/j.cgh.2021.12.026

26. Lin S, Kennedy NA, Saifuddin A, et al. Antibody decay, T cell immunity and breakthrough infections following two SARS-CoV-2 vaccine doses in inflammatory bowel disease patients treated with infliximab and vedolizumab. Nat Commun 2022;13(1):1379. DOI: 10.1038/s41467-022-28517-z

27. Shehab M, Zurba Y, Al Abdulsalam A, et al. COVID-19 vaccine hesitancy among patients with inflammatory bowel disease receiving biologic therapies in Kuwait: a cross-sectional study. Vaccines (Basel) 2021;10(1). DOI: 10.3390/vaccines10010055

28. Shire ZJ, Reicherz F, Lawrence S, et al. Antibody response to the BNT162b2 SARS-CoV-2 vaccine in paediatric patients with inflammatory bowel disease treated with anti-TNF therapy. Gut 2022;71(9):1922-4. DOI: 10.1136/gutjnl-2021-326196

29. Weaver KN, Zhang X, Dai X, et al. Impact of SARS-CoV-2 vaccination on inflammatory bowel disease activity and development of vaccine-related adverse events: results from PREVENT-COVID. Inflamm Bowel Dis 2022.

30. Wetwittayakhlang P, Albader F, Golovics PA, et al. Clinical outcomes of COVID-19 and impact on disease course in patients with inflammatory bowel disease. Can J Gastroenterol Hepatol 2021;2021:7591141. DOI: 10.1155/2021/7591141

31. Magliulo D, Wade SD, Kyttaris VC. Immunogenicity of SARS-CoV-2 vaccination in rituximab-treated patients: effect of timing and immunologic parameters. Clin Immunol 2022;234:108897. DOI: 10.1016/j.clim.2021.108897

32. Boyarsky BJ, Ruddy JA, Connolly CM, et al. Antibody response to a single dose of SARS-CoV-2 mRNA vaccine in patients with rheumatic and musculoskeletal diseases. Ann Rheum Dis 2021;80(8):1098-9. DOI: 10.1136/annrheumdis-2021-220289

33. Spiera R, Jinich S, Jannat-Khah D. Rituximab, but not other antirheumatic therapies, is associated with impaired serological response to SARS-CoV-2 vaccination in patients with rheumatic diseases. Ann Rheum Dis 2021;80(10):1357-9. DOI: 10.1136/annrheumdis-2021-220604

34. Dai C, Jiang M, Huang YH. COVID-19 vaccination in patients with inflammatory bowel disease: a survey from China. Dig Dis Sci 2022;67(7):3468-70. DOI: 10.1007/s10620-021-07169-x

Table 1. Characteristics of the included studies about patients with inflammatory bowel disease treated with biological agents after SARS-CoV-2 vaccination

Study	*Year*	*Country*	*Study design*	*Study inclusion criteria*	*Vaccine*	*Dose*	*Mean age*	*Female*	*Biological agents*	*Number*		*Follow-up duration*
										UC	CD	
Alexander J	2022	UK	Cohort study	NA	ChAdOx1n, BNT 162b2 and mRNA-1273 vaccine	2	NA	NA	Anti-TNF, VDZ, UST	NA	NA	NA
Ben-Tov A	2021	Israel	Multicenter retrospective cohort study	Age ≥ 16 years with diagnosis of IBD based on the registry	BNT 162b2 vaccine	2	NA	NA	NA	NA	NA	NA
Boland BS	2022	USA	Cohort study	NA	mRNA-1273 and BNT 162b2 vaccine	2	37 (28-56)	15	Anti-TNF, VDZ	10	19	2 months
Caldera F	2022	USA	Prospective cohort	NA	mRNA-1273 and BNT 162b2	2	NA	NA	NA	NA	NA	2 months

study vaccine

Cannatelli R	2021	Italy	Prospective cohort study Prospective study	NA	mRNA-1273 and BNT 162b2 vaccine mRNA-1273 and BNT 162b2 vaccine	2	55.3 (14.4)	270	Anti-TNF, VDZ, UST	246	233	NA
Cerna K	2021	Czech Republic	Single center prospective cohort study	IBD patients on steroids were excluded	BNT 162b2 CX-024414 and ChAdOx1n vaccine	1	NA	NA	NA	NA	NA	6 months
Classen JM	2021	Germany	Retrospective observational study	NA	NA	1	48.4 (15.2)	38	Anti-TNF, VDZ, UST	32	40	NA
Charilaou P	2021	USA	Single center prospective	NA	BNT 162b2, mRNA-1273 and JNJ-78436735	2	NA	NA	NA	NA	NA	7 months

cohort vaccine

study

					BNT 162b2, mRNA-1273 and JNJ-78436735 vaccine							
Chanchlani N	2021	UK	Retrospective cohort study	NA	BNT 162b2 and ChAdOx1nCoV-19 vaccine	1	36.77 (25.53-51.48)	5,324	Anti-TNF, VDZ, UST	NA	NA	15 months
Dailey J	2021	USA	Prospective longitudinal cohort study	NA	mRNA-1273 and BNT 162b2 vaccine	2	NA	NA	NA	NA	NA	6 months
Deepak P	2021	USA	Longitudinal prospective observational study	NA	mRNA-1273 and BNT 162b2 vaccine	2	45.5 (16.0)	32	Anti-TNF, VDZ, UST	18	22	4 months
Edelman-Klapper H	2022	Israel	Multicenter prospective	NA	BNT 162b2 vaccine	1	38.1 (14.3)	73	Anti-TNF, VDZ, UST	53	122	30 days

			observational study								
Frey S	2022	USA	Cohort study	Age ≥ 18 years with diagnosis of IBD	mRNA-1273 and BNT 162b2 vaccine	2	45 (38-58)	55	Anti-TNF, VDZ, UST	NA	NA	6 months
Garrido I	2021	Portugal	Single center longitudinal cohort study	NA	mRNA-1273 and BNT 162b2 vaccine	1	NA	NA	Anti-TNF, VDZ, UST	NA	NA	NA
Hadi YB	2021	USA	Multicenter retrospective cohort study	Age ≥ 16 years with diagnosis of IBD based on ICD-9-CM and ICD-10-CM codes with an IBD-specific medication	mRNA-1273 and BNT 162b2 vaccine	2	NA	NA	NA	NA	NA	NA

Kennedy NA	2021	UK	Multicenter prospective observational cohort study	Age 5 years and over with diagnosis of IBD and current treatment with IFX or VDZ for 6 weeks or more	BNT 162b2 and ChAdOx1n vaccine	1	NA	NA	Anti-TNF, VDZ	NA	NA	NA
Knezevic T	2022	Serbia	Cohort study	NA	BNT 162b2, Vero cell vaccine and SPUTNIK V Gam-COVID-Vac	1	55.7 ± 15.1	152	Anti-TNF, VDZ	125	202	NA
Khan N	2021	USA	Multicenter retrospective cohort study	Age ≥ 18 years with IBD and no prior CoV-19 infection and	mRNA-1273 and BNT 162b2 vaccine	2	NA	NA	NA	NA	NA	5 months

				taking IBD medication							
Kappelman MD	2021	USA	Prospective observational cohort study	Age ≥ 16 years with diagnosis of IBD	mRNA-1273 and BNT 162b2 vaccine	2	NA	NA	NA	NA	NA	18 months
Lev-Tzion R	2021	Israel	Retrospective cohort study	NA	BNT 162b2 vaccine	2	NA	NA	NA	NA	NA	7 months
López Marte P	2022	Puerto Rico	Cohort study	NA	mRNA-1273 and BNT 162b2 vaccine	1	NA	NA	Anti-TNF, VDZ, UST	NA	NA	6 weeks
Levine I	2021	USA	Single-center retrospective study	NA	mRNA-1273 and BNT 162b2 vaccine	2	NA	NA	NA	NA	NA	NA
Lin S	2022	UK	Cohort	NA	mRNA and AAV	2	39.8	118	Anti-TNF,	NA	NA	10 weeks

study	(30.9-49.7)	VDZ

			Cohort study				39.8 (30.9-49.7)		Anti-TNF, VDZ			
Melmed GY	2021	USA	Multicenter prospective cohort study	NA	BNT 162b2, mRNA-1273 and JNJ-78436735 vaccine	2	NA	NA	NA	NA	NA	7 months
Mayorga Ayala LF	2022	Spain	Cohort study	NA	mRNA	1	NA	NA	Anti-TNF	NA	NA	8 weeks
Quan J	2022	Canada	Cohort study	NA	mRNA-1273 and BNT 162b2 vaccine	1	49.9 (14.7)	249	Anti-TNF, VDZ, UST	128	336	18 weeks
Rodríguez-Martino E	2021	Puerto Rico	Cohort study	NA	mRNA	2	34 (22-59)	14	Anti-TNF	7	17	2 weeks
Shehab M	2021	Kuwait	Multicenter retrospective cohort study	All patients ≥ 18 years of age with diagnosis of IBD on IBD-related	BNT 162b2 vaccine	2	NA	NA	NA	NA	NA	2 months

medications

Shire ZJ	2021	Canada	Prospective study	All patients ≥ 18 years of age with diagnosis of IBD on IBD-related medications IBD patients with 12-17 years of age	BNT 162b2 vaccine	1	14.5 (14-16)	29	Anti-TNF	19	49	3 months
Spencer EA	2021	USA	Single center retrospective cohort study	All patients younger than 21 years of age	BNT 162b2, mRNA-1273 and JNJ-78436735 vaccine	2	NA	NA	NA	NA	NA	NA
Vollenberg R	2022	Germany	Cohort study	NA	mRNA-1273 and BNT 162b2 vaccine	1	46 (33-55)	45	Anti-TNF, VDZ, UST	35	60	6 months
Wong SY	2021	USA	Longitudina	NA	mRNA-1273 and	2	49.1 (20.2)	25	Anti-TNF,	25	23	85 days

l nested case-control study	BNT 162b2 vaccine	VDZ, UST

									Anti-TNF, VDZ, UST			
Weaver KN	2021	USA	Prospective observational cohort study	NA	mRNA-1273 and BNT 162b2 vaccine	2	43.7 (15.1)	2,378	Anti-TNF, VDZ, UST	NA	1,811	7 days
Wetwittayakhlang P	2021	Canada	Cohort study	NA	NA	2	39.0 (27.8-48.0)	41	Anti-TNF, VDZ, UST	NA	NA	14 months
Zhang E	2022	Australia	Cohort study	NA	BNT 162b2 vaccine and Oxford AstraZeneca	1	NA	NA	Anti-TNF, VDZ, UST	28	60	42 days

Anti-TNF: anti-tumor necrosis factor alpha; VDZ: vedolizumab; UST: ustekinumab; IBD: inflammatory bowel disease; IFX: infliximab.

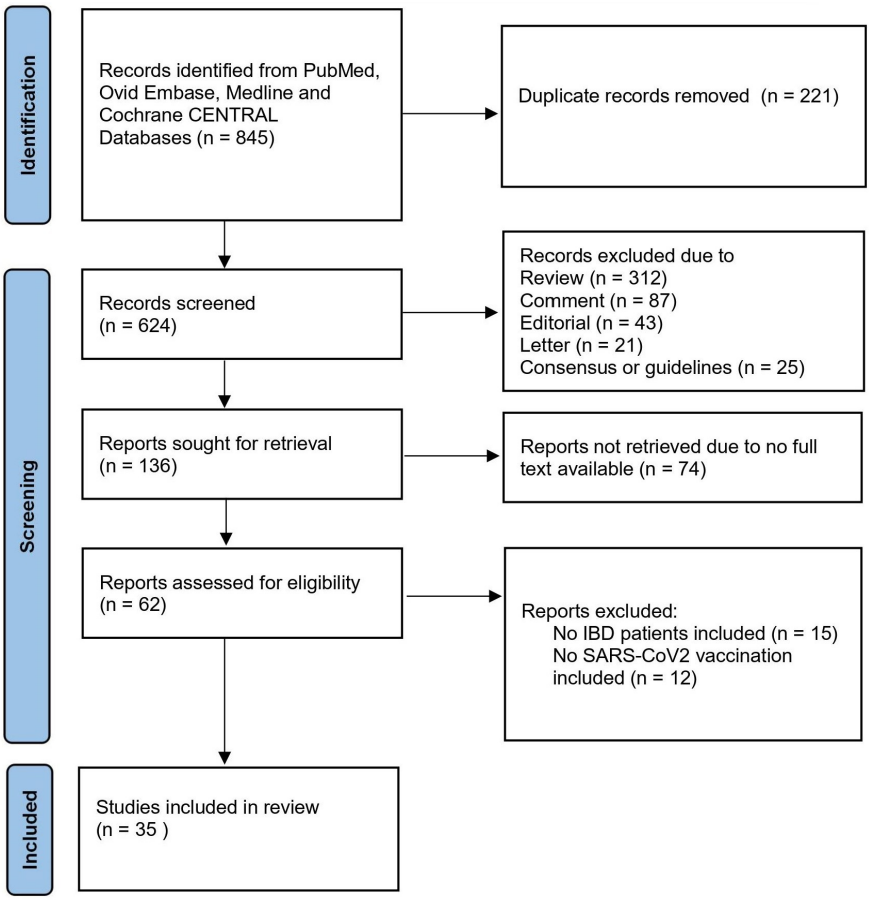

Fig. 1. A flow diagram of articles retrieved and inclusion progress through the stage of meta-analysis.

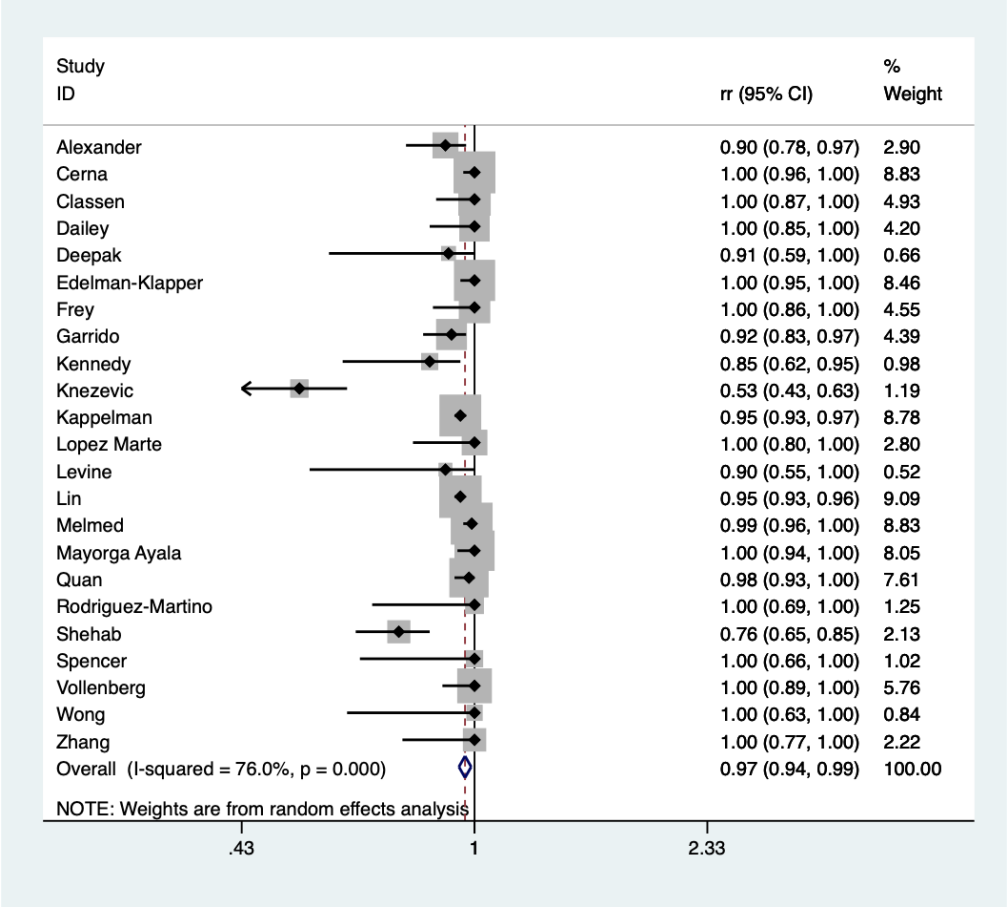

Fig. 2. Forest plot depicting the pooled seroconversion rate in IBD patients treated with anti-TNF-α therapy after SARS-CoV-2 vaccination.

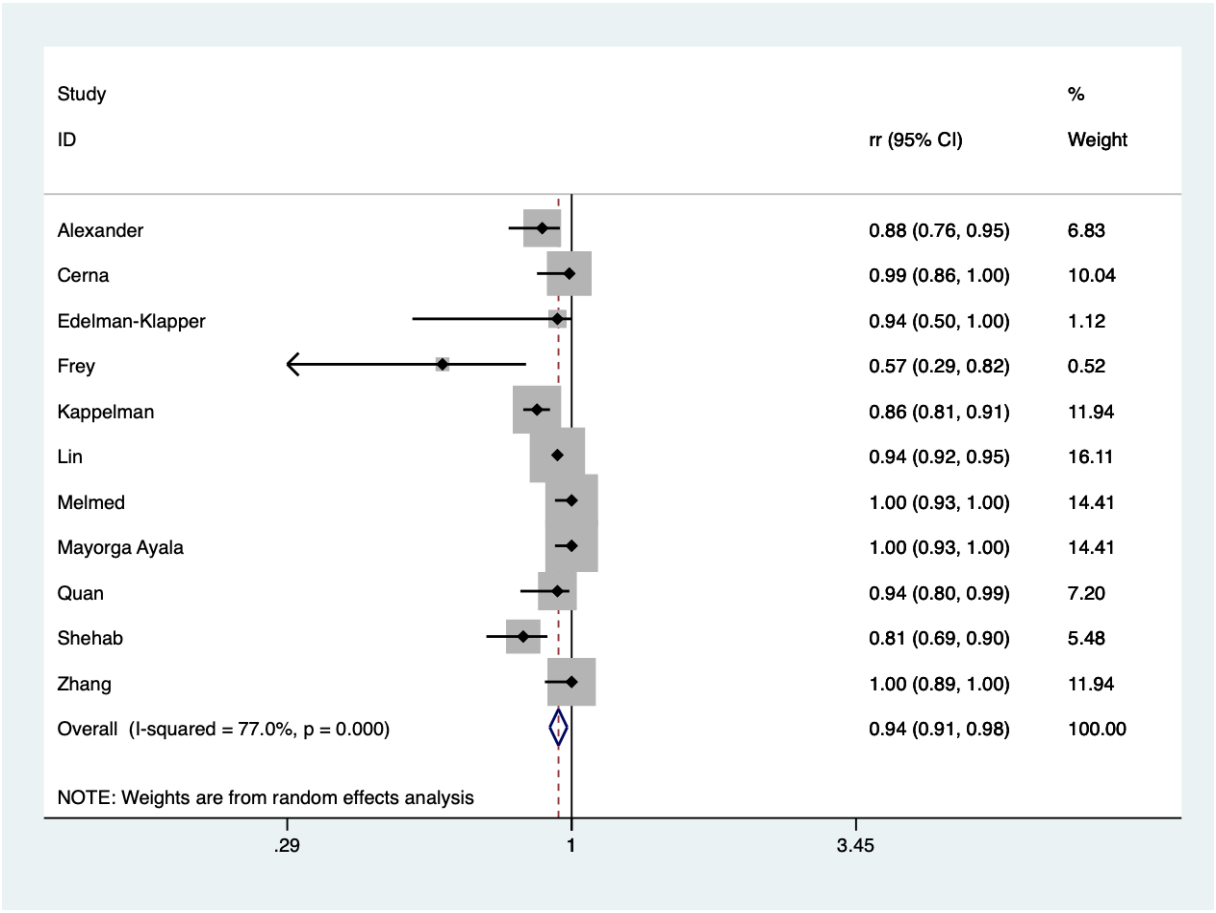

Fig. 3. Forest plot depicting the pooled seroconversion rate in IBD patients treated with anti-TNF-α combination therapy after SARS-CoV-2 vaccination.

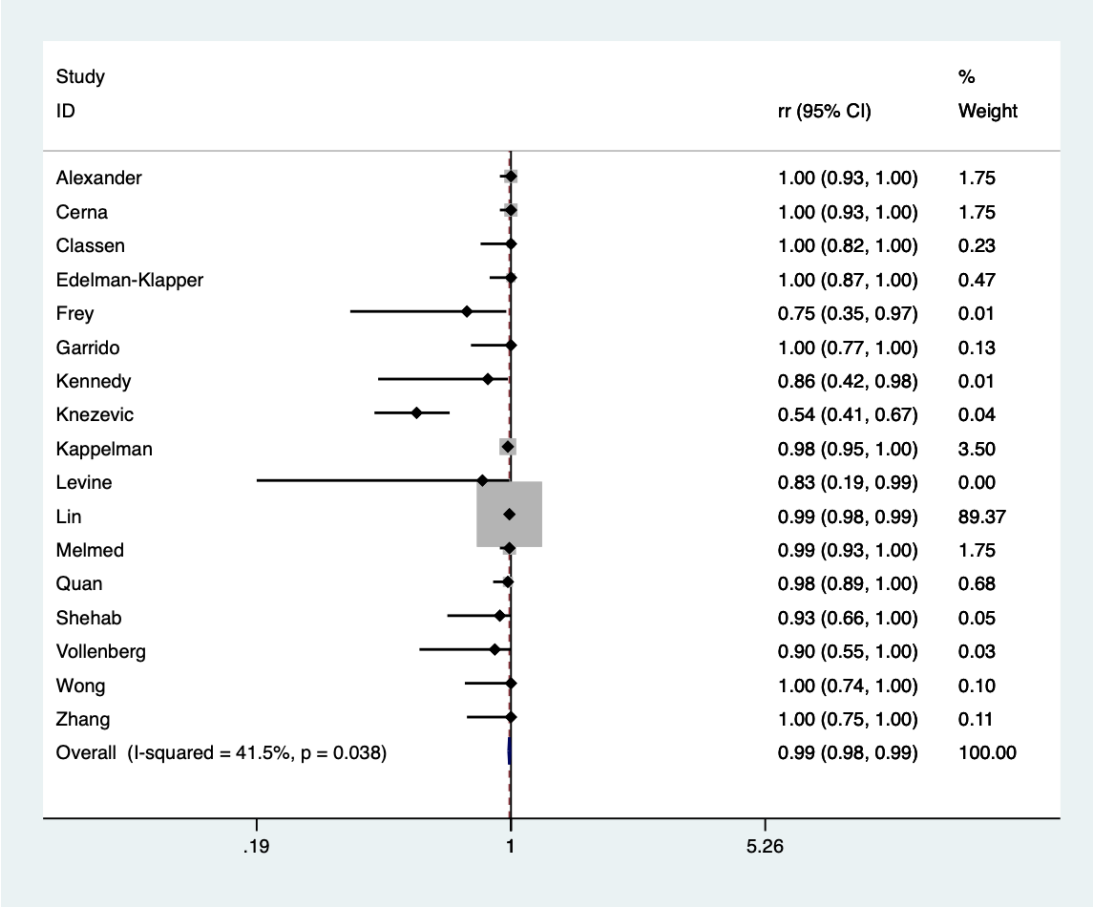

Fig. 4. Forest plot depicting the pooled seroconversion rate in IBD patients treated with VDZ after SARS-CoV-2 vaccination.

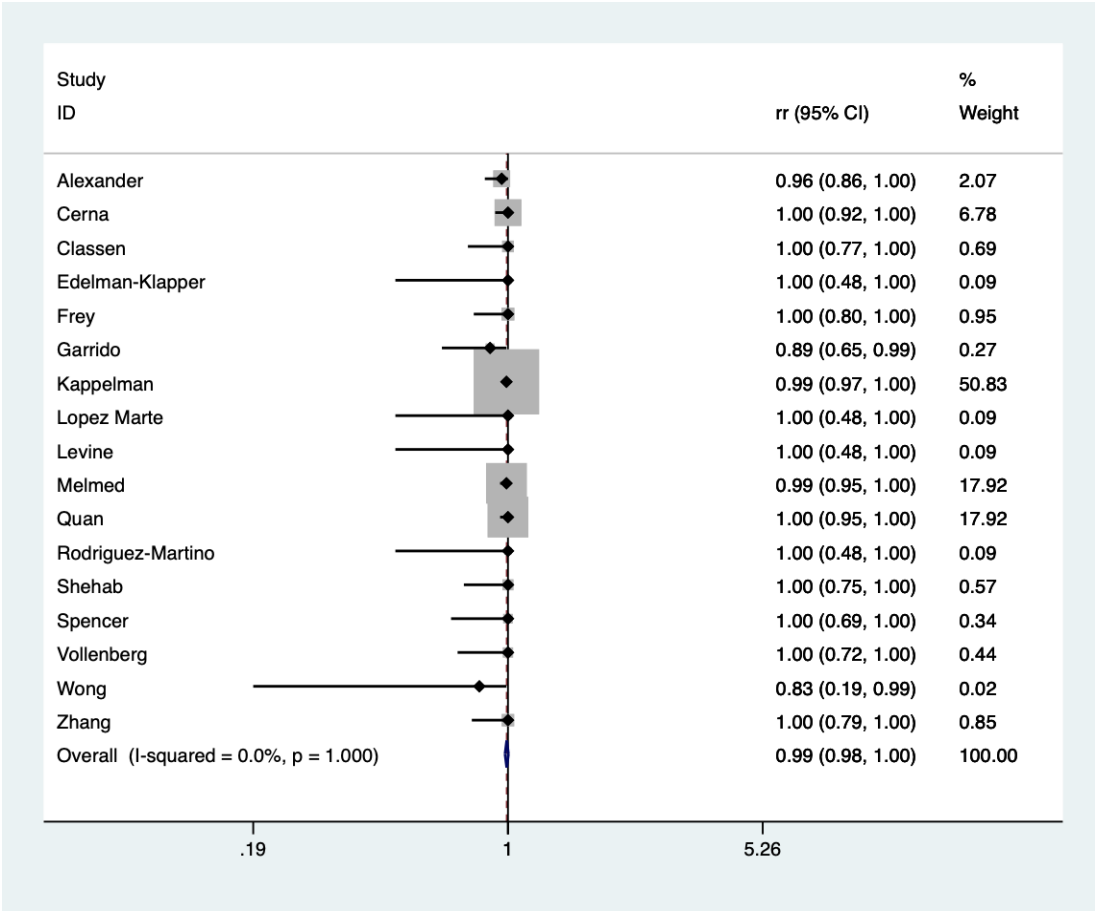

Fig. 5. Forest plot depicting the pooled seroconversion rate in IBD patients treated with UST after SARS-CoV-2 vaccination.