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EFFECTIVENESS AND SAFETY OF INACTIVATED COVID-19 VACCINE IN PATIENTS WITH ULCERATIVE COLITIS RECEIVING ANTI-TNF COMPARED TO HEALTHY EGYPTIAN POPULATION

By
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Abstract

Ulcerative colitis (UC) has been proven to have an economic and physical burden upon patients, with an associated mortality of up to 2.9%. However, morbidity and mortality have peaked since the breakout Coronavirus disease 2019 (COVID-19) pandemic as result of direct relationship between Inflammatory bowel disease (IBD) severity and adverse outcome from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

This study evaluated the efficacy and safety of inactivated COVID 19 vaccine (e.g. Sinopharm) in UC patients receiving anti-tumor necrosis factor (TNF) as compared to normal hea lthy population receiving the same type of vaccine 3 months after the last dose of vaccination.

The results showed those twenty patients with ulcerative colitis and on Anti TNF treatment (GA), and 20 healthy controls (GB). In GA; the mean age was (31.65) years, included 12 females (60%) and 8 males (40%). While in GB; the mean age was (30.55) years, with 11 males (55%) and 9 females (45%) without significant difference between both as to age (P=0.459) or sex (P=0.619). In GA only 16 (80%) had positive anti-spike IgG versus 18 posit- ives in GB (90%) without significant difference. Anti-spike IgG titre after 3 months with median ranges of 33.5 (RU/ml) in IBD patients and 44.5 (RU/ml) in controls with significant difference between both (P=0.025). There was no significant difference between both groups as to pain at injection site, skin allergy and generalized symptoms (fatigue, fever, chills, headache, muscles and joints pain).

Keywords: Egypt, Patients, Ulcerative colitis, COVID-19, Vaccine, Anti-spike IgG.

Introduction

Ulcerative colitis has an economic and physical burden upon patients associated with mortality up to 2.9% (Sebastian *et al,* 2021).

COVID-19, the highly contagious viral illness caused by SARS-CoV-2, has had a catastrophic effect on the world's demographics resulted in more than 6 million deaths on March 2022, emerged as the most consequential global health crisis since the influenza pandemic era of 1918 (Cascella *et al,* 2023). COVID-19 virus colonized the gastrointestinal tract causing diarrhoea in 31% of patients with pneumonia, even after respiratory symptoms were resolved (Aydın and Taşdemir, 2021). This might due to the autoimmune response via molecular mimicry or angiotensin-converting enzyme 2(ACE-2) receptor (Venkatachalam and Nathan, 2021). Inflammatory cascade release was severe enough either to reactivate dormant UC or to generate a de novo autoimmune response in a genetically predisposed patient (Aydın and Taşdemir, 2021).

The available information about the safety of COVID-19 vaccines in patients with IBD is limited. But, the inactivated vaccinations were considered safe and recommended in IBD, whereas live vaccinations are contraindicated in the immunosuppressed patients (Siegel *et al,* 2020). Thus, the usual reason to test someone for SARS-CoV 2 antibodies must be confirmed prior to vaccination. The principal of SARS-CoV 2 virus antigens are the spike protein on the surface of virus particle and nucleoprotein that is internal (Plotkin, 2022). Separate use of antibody testing to confirm vaccination response since all

SARS-CoV 2 vaccines used spike protein to induce neutralizing antibodies; a serologic test for antibodies confirmed likelihood of immunity to infection (Dhama *et al,* 2020). To interpret antibody levels, one must know that antibody levels are predictive of protection against infection, but a completely protective level didn't exist. Besides, there is a great variation of SARS-2 strains, such that antibodies to the original Wuhan strain have limited value in predicting individual protection against newer variants such as omicron (Garcia-Beltran *et al,* 2021). Risk infection decreases in proportion to the antibody height of response, but without 100% protection (Mallano *et al,* 2021).

This is a single-center observational case control study to evaluate the efficacy and safety of inactivated COVID-19 vaccine (Sinopharm) in UC patients received anti-TNF as compared to normal healthy population received the same type of vaccine 3 months after the last dose.

Patients and Methods

The study was conducted on UC patients visited IBD study group clinic in Tropical Medicine Department, Ain Shams University Hospitals from March 2022 to the end of February 2023. They were 130 patients, of who 20 patients (15%) met the inclusion criteria (GA), as compared to 20 healthy adults (GB). Cases were all above 18 years olds collected by convenience sampling (A type of non-probability sampling method was taken from them easy to contact or to find) from patients presented to IBD clinic, already diagnosed clinically, endoscopic and histopathological and received anti-TNF.

Inclusion criteria: GA: All patients with confirmed diagnosis of UC based on clinical history, laboratory and endoscopic result according to ECCO 2017 & 2021 Guidelines (Magro *et al,* 2017; Raine *et* ***al,*** 2021) in remission on anti-TNF and received two doses of inactivated COVID 19 vaccine in centres allocated by the Egyptian Ministry of Health & Population according to their nearby location of homes. GB: Control samples from healthy Egyptian subjects; age and sex matched with GA and received two doses of inactivated COVID 19 vaccine in centres.

Exclusion criteria: 1- UC Patients in activity at time of vaccination, 2- Subjects already received a single dose of COVID 19 vaccine, 3- Subjects received any dose other than inactivated COVID 19 vaccines, & 4- Subjects confirmed or suspected to have COVID 19 infection three months before or during the study.

All patients (GA) were subjected to: 1- History taking with focus on basal demographic data, smoking, lower gastrointestinal symptoms (bleeding per rectum, bloody stool, frequency and consistency), extra-intestinal ones (uveitis, episcleritis, arthritis, skin lesions as pyoderma gangrenosum and primary sclerosing cholangitis) and respiratory symptoms (cough, chest pain, shortness of breath, hemoptysis). 2- Clinical general and local abdominal examinations. 3- Review of received therapy whether medical or surgical. 4- Assessment of Aisease severity was assessed due to Truelove and Witts' severity index. 5- Anti-spike IgG titre three months after full vaccination by two doses of inactivated COVID 19 the governmental MOH vaccine.

Interpretation of results, according to the manufacturer: 1- negative results those with titers <8 RU/mL (Relative units/millilitre), 2- borderline results ranged between 8 to < 11 RU/ml., 3- positive results with titres ≥11 RU/ml, & 4- vaccine side effects were monitored on receiving two doses of vaccine and throughout 3months post full vaccination.

Controls (GB) were subjected to: 1- History taking to exclude any disease, 2. Anti-spike IgG-titre three months after full vaccination by two doses of inactivated COVID 19 vaccine, & 3- Vaccine side effects were monitored on receiving two doses of vaccine and via 3months post full vaccination.

Statistical analysis: Data were coded, tabulated and analysed using statistical package for Social Science (26). In descriptive analysis mean, standard deviation (±SD) and range for parametric numerical data; median &

interquartile range (IQR), for non-parametric numerical data and frequency for non-numerical percentage. Student T test assessed significant means difference between two groups. Mann Whitney test (U) assessed significant difference of a non-parametric variable between two groups. Chi-square test examined relation between two qualitative variables, and Fisher's exact test examined relation between two qualitative variables if the expected count was less than 5 in more than 20% of cells. Paired t-test assessed significant difference between two means measured twice in one group. Wilcoxon rank test assessed difference of the ordinal variable (score) measured twice for same group, and marginal homogeneity test assessed significant difference of a variable with multiple categories twice for same group.

Ethics approval: The study was approved by the Ethics Committee, Faculty of Medicine (Assurance No. FWA 000017585), which was adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000. All participants signed an informed consent after explaining the study purpose.

Results

The study found that the mean age of patients (GA) and control (GB) was 31.65 (±7) years versus 30.55(±5.67) respectively. In cases females were 12 (60%) & males were 8 (40%), in control females were 9 (45%) and males 11 were (55%), without significant difference as to age and sex, with significant difference only in smoking; none in GA and five in GB (25%) with P =0.047.

Only patients 16/20 (80%) had positive anti-spike IgG versus 18 in control (90%) without significance. Anti-spike IgG-titre after 3 months, median ranges were 33.5 (RU/ml) in IBD patients and 44.5 in control with significant difference (P=0.025).

Complications by inactivated COVID-19 vaccine between groups didn't show significant difference as to pain at injection site, skin allergy and generalized symptoms (fatigue, fever, chills, headache, muscles and joints pain), without significant difference as to disease activity of ulcerative colitis according to truelove and Witt's in cases before and 3 months after 2 doses.

Details were given in tables (1, 2, 3 & 4).

Table 1: Comparison of demographic characteristics between cases and control groups (n=20)

Items		Cases (GA)	Controls (GB)	Test of significance	
		Mean ±SD No. (%)	Mean ± SD No. (%)	P value	Significant
Age		31.65 ± 7.01	30.55± 5.67	0.588(T)	NS
Sex	Male	8 (40%)	11 (55%)	0.342(C)	NS
	Female	12 (60%)	9 (45%)		
Smoking	No	20 (100%)	15 (75%)	0.047(C)	S
	Yes	0 (0%)	5 (25%)		

P > 0.05: Non significant; P < 0.05: Significant; P < 0.01: Highly significant, (T) Student t-test of significance, (C) Chi-Square test of significance.

Table 2: Comparison anti-spike IgG between both groups (n=20)

After 3 months		Cases (GA)	Controls (GB)	Significance test	
		No. (%)	No. (%)	P value	Sig.
Anti-spike IgG	Negative	4 (20%)	2 (10%)	0.661(F)	NS
	Positive	16 (80%)	18 (90%)		
Anti-spike IgG titre		Median (IQR) 33.5(22.5-43)	Median (IQR) 44.5(34-54.5)	0.025(M)	S

(F) Fisher's exact test of significance, (M) Mann-Whitney test of significance.

Table 3: Complications between both groups (n=20)

Complain	Result	Controls	Cases	Test of significance	
		No. (%)	No. (%)	P value	Sig.
Pain at injection site	No	6 (30%)	8 (40%)	0.507(C)	NS
	Yes	14 (70%)	12 (60%)		
Generalized symptom	No	7 (35%)	8 (40%)	0.744(C)	NS
	Yes	13 (65%)	12 (60%)		
Skin Allergy	No	17 (85%)	18 (90%)	1.00(F)	NS
	Yes	3 (15%)	2 (10%)		

Table 4: Disease activity before and 3 months after 2 doses of inactivated COVID 19 vaccine for cases

Variations		Median (IQR) No. (%)		Test of significance	
		Before	After	P value	Sig.
motions/day	1	9 (45%)	7 (35%)	0.683[(M)]	NS
	2	6 (30%)	8 (40%)		
	3	5 (25%)	5 (25%)		
Pulse (bpm)		76±7	76±7	0.888[(T)]	NS
Temperature (°C)		36.98±0.13	36.95±0.12	0.285[(T)]	NS
Haemoglobin (g/dl)		12.45±0.97	12.41±0.78	0.617[(T)]	NS
ESR (mm/h)		12±3	11±3	0.823[(T)]	NS
CRP (mg/L)		3 (2 - 4)	3 (2 - 4)	0.726[(W)]	NS

[(M)]Marginal Homogeneity test of significance, [(W)]Wilcoxon signed rank test of significance, [(T)] Paired t-test of significance.

Discussion

The present study showed the mean age of patients and control was 31.6±57years versus 30.55±5.67 respectively. This agreed with Pereira *et al.* (2023), who reported the IBD patients and control had a mean age of 34.6 & 36.3 years respectively. But, this disagreed with Doherty ***et al.*** (2022), and Garner-Spitzer *et al.* (2023)**,** they showed mean age of (45.1 & 40.6 years) in IBD groups & (53.5 & 34.8 years) respectively in control.

In the present study, females were in UC patients than in controls. This agreed with Pereira *et al*. (2023) and Cerna *et al.* (2022), who found patient females predominated in IBD, but disagreed with Vollenberg *et al.* (2022); Ferreira *et al.* (2023) and Jorgensen *et al.* (2023), who reported that patient males predominated in IBD. This discrepancy could be due to different human behaviors (e.g. smoking) between males and females, as well as genetic predisposition, immune deregulation or intestinal dysbiosis **(**Shah *et al,* 2018), or even due to unknown intake of hormone replacement therapy and oral combined pills (OCPS) that relatively increase risk for UC (Cornish *et al,* 2008). Again, the present smoking disagreed with Pereira *et al*. (2023), who didn't find association between smoking and ulcerative colitis but, have a protective effect on disease activity and overall outcome (Matsuoka *et al,* 2018).

In the present study, mean baseline C reactive protein (CRP) before vaccination was 3 mg/l, which were 2.5mg/l in Jorgensen *et al.* (2023) and 2 mg/l in Ferreira *et al.* (2023). Also, mean baseline of erythrocyte sedimentation rate (ESR) before vaccination was 12 mm/hr. but, Ferreira *et al.* (2023) reported 20mm/hr.

As to anti-spike IgG, the present results agreed with Jorgensen *et al.* (2023), they reported that after 3-5 weeks of complete vaccination had positive anti-spike IgG in IBD patients (80.6%) and controls (99.4%). Also, results were close to Doherty *et al.* (2022), who found that positive IgG anti-spike was in IBD patients (98.2%) and in all controls.

In the present study, anti-spike IgG titre after 3 months agreed with Doherty ***et al.*** (2022) and Jorgensen *et al.* (2023),who reported significant difference between UC patients and controls. Also, the present data partially agreed with Garner-Spitzer *et al.* (2023)**,** they found significant difference between BD patients on anti-TNF and control, when anti-spike IgG titre was measured after 6 months with types of mRNA vaccines with 22.5 (RU/ml) & 236.5 (RU/ml) in IBD patients and control respectively.

The present study didn't completely evaluated safety of COVID-19 vaccines among IBD patients. Botwin *et al.* (2021) first evaluated adverse effects (AEs) after the Pfizer and Moderna vaccines in 246 IBD patients, more events were after second dose (D2), patients (62%) didn't have event, 56% have local site reactions. The common systemic AEs were fatigue, malaise, headache, dizziness, fever, chills, and gastro-intestinal ones; increased frequency was among younger age and inversely associated with TNF, integrin antagonists, interleukin antagonists, & JAK inhibitors. Lev-Tzion *et al.* (2021) follow-up the IBD patients for about 12 weeks after the Pfizer vaccine D_2 didn't find differences in

flares in the first 40 days after vaccination. Weaver *et al.* (2021) reported that after the second dose with mRNA vaccines, younger age, female sex, TNF antagonists, and integrin antagonists were associated with severe systemic reactions, and the Moderna vaccine was associated with more severe systemic and local reactions than Pfizer one. Although 12%, 12%, & 11% of patients reported increased bowel frequency, extra-intestinal manifestations, and abdominal pain after vaccination but, patients 2.1% had an IBD flare (2.5% for Pfizer, 1.8% for Moderna, and 0.6% for Janssen). Edelman-Klapper *et al.* (2022) reported that IBD patients had AEs after the Pfizer vaccine with mild symptoms of headache, fatigue, muscle soreness, and shivering. They didn't find association between AEs and use of TNF antagonists, IBD patients' activity as before vaccination.

This study was limited by the relatively small participant size and not tested COVID 19 anti-spike IgG titre after complete vaccination directly.

Conclusion

Although inactivated COVID-19 vaccines are safe in UC patients receiving anti TNF, anti- spike antibody titre after 3 months was significantly reduced. A third primary or booster vaccine doses for UC patients was indicated.

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Authors' contributions: All authors equally contributed in theoretical and practical studies and approved the publication

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