Research Article

Pharmacovigilance of ChAdOx1 nCoV-19 (COVISHIELD) Vaccine after first and second dose in volunteers in Punjab, India

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Abstract

COVID-19 infection is still an ongoing pandemic and it emerged in December 2019, in Wuhan, China. The research indicate that coronavirus is a beta-coronavirus belonging to the subtypes as SARS virus leading to the pandemic and life-threatening infection. There is no antiviral available for this infection so vaccination is the best method for providing immunity against this virus. **Objective:** To generate the pharmacovigilance data of Covishield vaccine in subjects given both doses of this vaccine. **Methods:** This was an observational, retrospective, non-interventional, passive surveillance safety study with no formal sample size. The study was based on spontaneous reporting of ADEs following Covishield vaccination in subjects with consent for vaccination. The Covishield vaccination was given at medical institute Sri Guru Ram Das Institute of Medical Sciences and Research (SGRDIMSAR), Amritsar, Punjab, India in dosage of 0.5 ml and with a gap of 12 to 16 weeks. The subjects were informed to report solicited and unsolicited ADEs within 7 days from vaccination by personal interaction, telephonic reporting, and even by reporting at pharmacovigilance cell, SGRDIMSAR. The solicited and unsolicited reactions after vaccination till 7 days were noted on the proforma designed as per the literature provided by the Serum Institute of India, Pune, Maharashtra, India. **Results:** The results indicate that 1364 and 1340 subjects were given first and second doses of Covishield vaccine, the most common age group being >50 years. After first dose, out of the total 1119 ADEs, 1078 (96.3%) were solicited and 41 (3.6%) were unsolicited ADEs while 559 (97.2%) were solicited while 16 (2.7%) were unsolicited ADEs after second dose and most common ADEs reported was pain and fever at injection site. The severity of ADEs after second dose was much lesser in terms of percentage in comparison to first dose and There was no serious ADEs leading to death, prolonged hospitalization, any event requiring hospitalization or visit to emergency department of the hospital. **Conclusion:** The results of this study indicate that Covishield is safe and effective vaccine. The ADEs after second dose are lesser in comparison to first dose and similarly in high-risk patients the vaccine was found to be tolerated effectively.

Keywords: Coronavirus, SARS-CoV-2, Covishield, Pharmacovigilance.

Introduction

COVID-19 infection was emerged in December 2019, when a group of patients presented with pneumonia of unknown cause in Wuhan, China. COVID-19 is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARSCoV-2 infection may be asymptomatic or it may cause a wide spectrum of symptoms, such as mild symptoms of upper respiratory tract infection and life-threatening sepsis. Coronaviruses (CoV) are a family of viruses called Coronaviridae. These viruses are zoonotic, that is, they are transmitted between animals and humans. The SARS-CoV-2 virus belongs to the family of RNA viruses and the genomic sequence ranges from 125 nm or 0.125μm. Corona virus is a single stranded, enveloped RNA in shape having a positive sense RNA genome also known as (+ssRNA) with a 5′-cap structure and 3′-poly-A tail (Chen et al., 2019). There are four essential structural proteins required to regulate the function and viral structure of the virus; which are (E) the envelope protein, (M) the membrane protein, (S) the spike protein, and (N) the nucleocapsid protein (Schoeman et al., 2019). The genome sequencing based research revealed that the coronavirus is a beta-coronavirus belonging to the subtypes

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as SARS (severe acute respiratory syndrome) virus having a variant group leading to the pandemic. The receptor- binding gene region appears to be very similar to that of the SARS-CoV and it is believed that the same receptor would be used for cell entry (Su et al., 2016). SARS-CoV-2 corona virus has a diameter of 60 to 140 nm and has characteristic spikes on the surface that range from 9 to 12 nm and so giving virions the appearance of a solar corona (Goldsmith et al., 2014). Coronaviruses can adapt to new appearances due to variation in its genetics and infect new hosts. Epidemiologic data have shown that droplets containing corona virus are expelled during face-to face exposure during coughing, talking, or sneezing and this can be the most common mode of transmission. The infected patient can spread the virus up to 6 feet when coughing for more than 15 minutes but the brief exposure of asymptomatic patients is less likely to spread infection in healthy population. The viral load is maximum in throat when the symptoms start and it has been seen that the viral shedding can occur 2 to 3 days before the symptoms appear. Thus, asymptomatic transmission of the virus is the major cause of spread of SARS-CoV-2. SARS covid virus can be detected up to 6 weeks in throat once the infection has started, however, many studies suggest that viral cultures are not seen in throat for SARS-CoV even 28 days after symptom onset (Wolfel et al., 2020). The most common signs of infection with COVID-19 include fever, dry cough, shortness of breath or difficulty in breathing, and tiredness or fatigue. Clinically many patients have mild symptoms and do not need hospitalization but approximately 20 % patients become seriously ill with breathlessness and multisystemic complications of coagulation system as clotting problems, heart disease like conduction abnormalities, brain like stroke, lung like acute respiratory failure, liver damage, kidney like acute kidney injury etc. COVID-19 can lead to myocarditis, cardiomyopathy, ventricular arrhythmias, and hemodynamic instability (Hendren et al., 2020). In addition to respiratory failure, hospitalized patients may develop acute kidney injury (9%), liver dysfunction (19%), bleeding and coagulation dysfunction (10 to 25%), and septic shock (6%) (Grasselli et al., 2020; Yang et al., 2020). Because of its pandemic nature, the National Institutes of Health (NIH) and pharmaceutical companies are involved in the development of COVID-19 vaccines. To end this pandemic best way is mass immunization against SARS-CoV virus. The vaccines are biological agents used to prevent infection, but sometimes even the vaccines can cause some AEFI (Adverse Events Following Immunization). The detection of adverse events after vaccination is an important step for prevention ADEs following vaccination. Thus, there is need for pharmacovigilance after vaccination. The aim of pharmacovigilance is the detection of ADEs given by some hypothesis or signals, related to probabilities. The early signal may not be known to us but a strong argumentation and indentation, must need further investigation. The overall goal of pharmacovigilance of COVID-19 vaccines is to protection and promotion of human well-being given drugs, vaccination, new procedures, blood products administration in the people globally. Many countries including India, have already taken necessary measures to contain the spread of COVID-19 infection using early diagnosis and treatment, however mass vaccination is the best way to build up the herd immunity in Indian population by improving immunity and containing the virus spread. The aim of vaccination is exposing the subjects to viral antigen and thus producing an immune response which can block viral multiplication in the person who is subsequently infected, without causing the disease. The different types of vaccines are as

a. **Viral-vector vaccines:** For the development of this vaccine, a virus (adenovirus or measles), is genetically engineered to producing a nonpathogenic coronavirus protein for administration. The two types of viral-vector vaccines manufactured by this technology are under development and these are replicating viral vector which is Replicable in the cells and non-replicating viral vector which is non replicable in cells (Ewen., 2020).

b. **Nucleic-acid vaccines:** here nucleic acid (DNA or RNA) is inserted into human cells which then produce the immune response after being infected. There are two types of nucleic-acid vaccines as DNA vaccine and RNA vaccine.

c. **Protein-based vaccines:** Here the virus protein fragments or protein shells are injected directly into the body for generating immunogenicity. The two types of protein-based vaccines being developed are the protein subunit vaccines and virus-like particle vaccines.

Indian COVID-19 vaccines under development or been marketed for use in human. The various vaccine available for use in India and theses are as (Product monograph including patient medication information 2020; Lombardi et al., 2019).

1. Covishield (Source: Chimpanzee Adenovirus) manufactured by Serum Institute of India, Pune in collaboration with Astra Zeneca.

2. Covaxin (Source: Inactivated Virus) manufactured by Bharat Biotech International Ltd, Hyderabad in collaboration with Indian Council of Medical Research, India.

3. Sputnik V (Source: Human Adenovirus vaccine) Trialled and manufactured in India by Dr. Reddy Lab located in Hyderabad, Telangana, India in collaboration with Gamaleya National Center, Russia.

4. ZyCoV-D (Source: DNA vaccine) manufactured by Cadila Healthcare Ltd, Ahmedabad (Zydus Cadila), in collaboration with Dept of Biotechnology, India

5. The Novavax COVID-19 vaccine (NVX-CoV2373), and also called SARS-CoV-2 rS (recombinant spike) protein nanoparticle containing Matrix - M1 adjuvant: It is a COVID-19 vaccine developed by Novavax in collaboration with Coalition for Epidemic Preparedness Innovations (CEPI). It is undergoing clinical trials in India under the brand name Covovax and is being manufactured by Serum Institute of India, Pune with brand name of Novavax.

6. Recombinant Protein Antigen based vaccine Dynavax Technologies Corporation (NASDAQ: DVAX), a US-based vaccine focused biopharmaceutical company, and Baylor College of Medicine manufactured by Biological E Ltd, Hyderabad.

7. HGCO 19 (a mRNA vaccine similar to Moderna and Pfizer in the USA). It is manufactured by Gennova, Pune in collaboration with Thomas Jefferson University, USA.

Since the phase III trials show the limited safety data of these vaccines so we need phase IV studies in large population i.e., pharmacovigilance. Pharmacovigilance aims to the science and activities relating to the detection, assessment, understanding, and prevention of adverse drug effects and other drug-related safety problems with an objective being to prevent harmful effects from drug administration in humans. The term vaccine pharmacovigilance defines "the science and activities related to the detection, assessment, understanding and communication of adverse events following immunization (AEFI) and other vaccine-related or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization (Vaccine Pharmacovigilance: CIOMS/WHO Working Group on Vaccine Pharmacovigilance. 2020)" Since 1965, the WHO has had a global program for International Drug Monitoring based at the Uppsala Monitoring Centre in Sweden. In 1999, the WHO established the Global Advisory Committee on Vaccine Safety (GACVS) to provide independent evidence-based responses to safety issues of global concern. GACVS established the Vaccine Safety Net which identifies and promotes websites on vaccine safety. Goal of Vaccine Pharmacovigilance is to early detection, appropriate and timely management of adverse events due to vaccine administration in population undergoing immunization. The success of the immunization system is reducing morbidity and mortality related to the vaccine. COVID-19 vaccines have received emergency approval and hence have limited safety data. Therefore, it is important to monitor the safety of covid19 vaccines when administered to a large population.

Materials and Methods

This was an observational, retrospective, noninterventional, passive surveillance safety study with no formal sample size. The study was based on spontaneous report following Covishield vaccination in subjects willing for Covishield vaccination. The Covishield vaccination was given by the Immunization Department, PSM (Preventive and Social Medicine) Department, Sri Guru Ram Das Hospital, a charitable hospital attached to the medical institute Sri Guru Ram Das Institute of Medical Sciences and Research (SGRDIMSAR), Amritsar, Punjab, India. The subjects willing for Covishield vaccination were given the vaccine, and following vaccination, subjects were observed for half an hour for any untoward event. The subjects after the consent were given a single dose of 0.5 ml of Covishield vaccine intramuscularly. The gap period was given of 12 to 16 weeks between two doses and this was as per the guidelines of Government of India (Summary of Product Characteristics 2020. and Health Ministry 2020). The following subjects were excluded from the study as immunocompromised subjects like taking any immunosuppressive drug, history of severe allergic reactions or anaphylaxis to previous vaccines or allergy to any components of the study vaccine, History of high-grade fever (axillar temperature ≥ 37.8º C) 72 hours before the vaccine. The participants were instructed to record any solicited local and systemic reactions within 7 days and all unsolicited events as been advised in proforma given within 42 days postvaccination. A diary card was given to improve the reporting, and subjects were advised to report any ADEs on WhatsApp group that has been created by the author. Afterward, the subjects were encouraged to report solicited and unsolicited ADEs within 7 days from vaccination by personal interaction, telephonic reporting, and even by reporting at pharmacovigilance cell, SGRDIMSAR, Amritsar, Punjab, India. The investigator observed, noted and transcribed the information in case report forms (CRFs) for the further analysis. The Covishield vaccine was provided by the Government of India (GOI) under the vaccination program. The vaccine was given at left arm, that is, left deltoid region after sterilization of the area and following the standard operating procedure of vaccine administration program. The dosage of Covishield™ vaccination course consists of two separate doses of 0.5 mL each. The second dose was given 12 to 16 weeks after the first dose. The solicited and unsolicited reactions after vaccination till 7 days were noted on the proforma designed as per the literature provided by the Serum Institute of India

using the following parameters as injection site pain / tenderness (>60%), headache, and or fatigue (>50%), myalgia and malaise (>40%), pyrexia and chills (>30%); arthralgia and nausea (>20%). The data collected from the subjects given Covishield vaccine were further analyzed for their appropriateness and suitability. The unsolicited adverse drug reactions (ADRs) were reported to the central pharmacovigilance center at PvPI, CDSCO, IPC, Ghaziabad, India, under the pharmacovigilance program of India. The end points of this trial for estimation were solicited or unsolicited ADEs, use of antipyretic or pain medication within 7 days after the receipt of each dose of vaccine. The adverse event data was monitored 14 weeks after the second dose. In this study represents the safety data / ADEs of all participants with informed consent given Covishield vaccine with two dosage regimens.

Study Objectives: The study was planned to document solicited and unsolicited AEs following immunization and hence to establish the safety of Covishield vaccination.

Rescue Medicine: Paracetamol 650 mg SOS, max up to four times a day as an analgesic agent, and domperidone 10 mg SOS, max 10 mg twice a day for nausea or vomiting, was given as a rescue drug. Severe reactions were managed according to the standard treatment guidelines of the diseases. All the participants were given an emergency 24-h telephone number to contact the investigators or on-call physician in emergency during the duration of the study for reporting any illnesses. Serious ADEs were recorded throughout the study and were reviewed at second dose, with causality assigned by the site investigator.

Statistical analysis

All data were anonymized, and analyses were performed on all the subjects who participated in the study. It was an observational, noninterventional study where vaccination with the consent of the participants was given. The number of the subjects experiencing an AE, SAE, or ADR, and the number experiencing solicited or unsolicited events in each category were analysed. The quantitative data were expressed in percentage for evaluation to show the relationships and comparisons between the category of responses. The data observed is presented in tables with number and percentages evaluation according to terms in the Medical Dictionary for Regulatory Activities (MedDRA), version 23.1, for each vaccine group (Brown et al., 1999).

Ethical approval

It was a prospective, observational, single center, single-arm, post-registration study done to assess the safety of the Covishield vaccine in subjects willing for covid19 vaccination with Covishield vaccine with ethical consent from the participants and authorities. This study is the subjective experience shared by the participants given Covishield vaccine in twice dosage schedule with an interval, been approved by Govt of India. The ethical standards in terms of confidentiality and informed consent were maintained.

Results

In our study, a total of 1364 and 1340 subjects were given first and second doses of Covishield vaccine respectively in dose of 0.5 ml per dose intramuscularly (Table 1). The 14 subjects did not report for the second dose of the vaccination and were not able to be contacted by telephone or by personal visit. After the first dose out of total 1364 subjects, 602 (44.1%) were males and 762 (55.9%) were females with male female ratio of 0.79/1 (Table 1). The most common age group given first dose of Covishield vaccine was in the age group >50 years as 465 (34.0%) while the number of subjects 340 (24.9%) was in age group 40-50 followed by 294 (21.5%) in 20-30 years and 265 (19.4%) in age group 30-40 years (Table 1). Similarly, after second dose it was observed that the total number of participants was 1340 and out of these 1340 subjects, 590 (44%) were males and 759 (55.9%) were females with male / female ratio of (M:F = 0.77/1). The most common age group who received second dose of Covishield vaccine was in the age group >50 years 460 (34.3%) followed by the 332 (24.7%) in age group of 40–50 years, 20-30 years given 289 (21.5%) and 259 (19.3%) in age group 30 - 40 years (Table 1).

ADEs after First dose: The total number of solicited and unsolicited ADEs observed after first dose of Covishield vaccine was 1119 in male and female subjects. Out of the total 1119 ADEs, 1078 (96.3%) were solicited and 41 (3.6%) were unsolicited ADEs. Out of all solicited 1078

Table 1. Total number of subjects in both groups by age & gender after both doses.

Age in years	First Dose (n= 1364)			Second Dose (n= 1340)		
	Males	Females	Total	Males	Females	Total
20-30	107	187	294 (21.5%)	104	185	289 (21.5%)
30-40	142	123	265 (19.4%)	139	120	259 (19.3%)
40-50	157	183	340 (24.9%)	153	179	332 (24.7%)
>50	196	269	465 (34.0%)	194	266	460 (34.3%)
Total		**1364**			**1340**	

Table 2. Total Number of Solicited ADEs after Ist Dose (n = 1078, 96.3%)

Adverse Event	Number of subjects	% age	Mean Duration (Days)
Pain at site of injection	594	55.1	2
Mild Fever (Temperature ≤100.5°F)	201	18.6	2
Malaise	134	12.4	1
Injection site swelling	42	3.8	1
Headache	38	3.5	1
Myalgia	23	2.1	3
Chills	15	1.3	1
Rigor	12	1.1	1
Nausea	11	1.0	1
Joint Pains	04	NS	3
Influenza like illness	03	NS	1
Vomiting	01	NS	1

NS= % age < 1 or Zero value

Table 3. Total Number of Unsolicited ADEs after Ist Dose (n = 41, 3.6%)

Adverse Event	Number of subjects	% age	Mean duration in Days
Moderate to High Grade Fever (Temperature ≥100.6°F)	19	45.0	2
Decreased appetite	06	14.6	2
Dizziness	13	31.7	2
Pruritis	02	4.8	1
Increased Liver function Test	01	NS	3
Body Rash	Nil	NS	NS
Abdominal Pain	Nil	NS	NS
Hyperhidrosis	Nil	NS	NS
Injection Site Hematoma	Nil	NS	NS
Increased Kidney Function Test	Nil	NS	NS
Neurological Problem	Nil	NS	NS
Lymphadenopathy	Nil	NS	NS
Bleeding Problem	Nil	NS	NS

NS= % age < 1 or Zero value

ADEs, the most common solicited event reported was pain at injection site 594 (55.1%) for 2 days followed by mild fever (temperature ≤ 100.5°F) in 201 (18.6%) subjects for 2 days, malaise 134 (12.4%) for 1 day, injection site swelling 42 (3.8%) for 1 day, headache 38 (3.5%) for 1 day, myalgia 23 (2.1%) for 1 day, chills 15 (1.3%) for 1 day, rigors 12 (1%) for 1 day, nausea 11 (1%) for 1 day and with nonsignificant events with percentage <1 was seen as joint pains for 3 day, influenza like illness and vomiting for 1 day each (Table 2). Similarly, out of all unsolicited 41 (3.6%) AEs, the most common ADEs was high grade fever with Temperature ≥ 100.6°F 19 (45%) for 2 days followed by dizziness 13 (31.7%) for 2 days, decreased appetite 06 (14.6%) for 2 days, pruritus 02 (4.8%), 01 (NS) subject having impaired liver function test (slightly raised ALT/APT) remained for 3 days while no occurrence of body rash, abdominal pain, hyperhidrosis, hematoma at injection site, impaired kidney function test, neurological problem or lymphadenopathy occurred (Table 3). 604 out of 1119 (53.9%) subjects required paracetamol 650 mg for 1-2 days for the resolution of symptoms of fever / pain at injection site after first dose.

ADEs after Second dose: The total number of ADEs observed after second dose of Covishield vaccine was 575 in both males and female subjects. Out of all the ADEs, 559 (97.2%) were solicited while 16 (2.7%) were unsolicited ADEs. Out of all solicited 559 AEs, the most common ADEs reported was pain at injection site 362 (64.7%) for 2 days followed by 52 (9.3%) mild fever temperature ≤100.5°F for 2 days, 64 (11.4%) malaise for 1 day, 22 (3.9%) injection site swelling for 1 day, 18 (3.2%) headache for 1 day, 13 (2.3%) myalgia for 1 day, 11 (1.9%) chills for 1 day, 7 (1.2%) rigors for 1 day, 6 (1.0%) nausea and with nonsignificant ADEs with <1% seen as joint pains for 3 day, influenza like illness and vomiting for 1 day each (Table 3). Similarly, out of all unsolicited ADEs 16, the most common AEs was high grade fever with Temperature ≥100.6°F seen in 7 (43%) for 2 days followed by dizziness 5 (31%) for 2 days, decreased appetite 2 (12%) for 2 days, pruritus 1 (6%) for 3 days, only 1 (6.2%) subject reported of facial palsy which remained for 7 days and there was no report of impaired liver function test, body rash, abdominal pain, hyperhidrosis, hematoma at injection site, impaired kidney function test, neurological deficits or

Table 4. Total Number of Solicited ADEs after IInd Dose (n = 559, 97.2%)

Adverse Event	Number of subjects	% age	Mean Duration in Days.
Pain at injection site	362	64.7	2
Mild Fever (Temperature ≤100.5°F)	52	9.3	2
Malaise	64	11.4	1
Injection site swelling	22	3.9	1
Headache	18	3.2	1
Myalgia	13	2.3	3
Chills	11	1.9	1
Rigor	7	1.2	1
Nausea	6	1.0	1
Arthralgia	2	NS	3
Influenza like illness	1	NS	1
Vomiting	1	NS	1

NS= % age < 1 or Zero value

Table 5. Total Number of Unsolicited ADEs after IInd Dose (n= 16, 2.7%)

Adverse Event	Number of subjects	% age	Mean duration in Days
Moderate to High Grade Fever (Temperature ≥100.6°F)	7	43	2
Decreased appetite	2	12	2
Dizziness	5	31	2
Pruritis	1	6	1
Facial Palsy	1	6	7
Increased Kidney Function Test	Nil	NS	NS
Neurological Problem	Nil	NS	NS
Abdominal Pain	Nil	NS	NS
Hyperhidrosis	Nil	NS	NS
Injection Site Hematoma	Nil	NS	NS
Increased Liver function Test	Nil	NS	NS
Body Rash	Nil	NS	NS
Lymphadenopathy	Nil	NS	NS

NS= % age < 1 or Zero value

lymphadenopathy (Table 5). All unsolicited ADEs resolved with or without symptomatic treatment and without any sequelae. There was no serious ADEs leading to death, prolonged hospitalization, any event requiring hospitalization or visit to emergency department of the hospital. Similarly, there was no new ADEs of neurological problems like optic neuritis, Guillain-Barré syndrome after 2 weeks of vaccine administration both after first or second dose. Paracetamol 650 mg was required in 198 out of 575 (34.4%) subjects for 1-2 days for the resolution of symptoms of fever / pain at injection site after first dose.

Discussion

Vaccine tolerability is an important feature for safety evaluation and hence its acceptance for future vaccine recipients before mass vaccination. The total number of subjects participated after first dose was 1364 and after second dose was 1340. Twenty-four subjects could not be traced and so the reasons of theirs non participation could not be established due their non-contactless either personally or by telephonically (Table 1). The total number of ADEs both solicited and unsolicited after first and second dose was 1119 and 575 respectively. However, the ratio of total number of ADEs/total number of subjects given Covishield vaccination after first dose was 1119/1364 (82%) and after second dose was only 575/1340 (42.9%), indicating a definitive fall in ADEs after second dose in comparison to first dose. The ratio of ratio of total number of solicited ADEs/total number of subjects after first dose was 1078/1364 (79.0%) and after second dose was 559/1340 (40.9%) respectively, showing a reduction solicited reactions after second dose (Table 2 and 4). Similarly, the ratio of ratio of total number of unsolicited ADEs / total number of subjects after first dose was 41/1364 (3.0%) and after second dose was 16/575 (2.7%) respectively, showing a reduction in unsolicited reactions after second dose (Table 3 and 5). Thus, it can be interpreted from the study that there was marked reduction in total number of ADEs (solicited and unsolicited) after second dose indicating that Covishield vaccine was better tolerated after second dose than after first dose. It was also observed that 22 ADEs were seen in males with comorbidities and 31 ADEs were seen in females with comorbidities after first dose. Similarly, it observed that 05 ADEs were seen in males with

Table 6. No of subjects having co-morbidities with ADEs after both doses

Parameters	ADEs after First Dose			ADEs after Second Dose		
	Total Subjects	No of subjects with comorbidities	No of ADEs	Total Subjects	No of subjects with comorbidities	No of ADEs
Males	602	08	22	590	06	05
Females	762	11	31	750	09	10
Total	1364	19	53 (3.8%)	1340	15	15 (1.1%)

Percentage expressed with total number of ADEs

comorbidities and only nine ADEs were seen in females with comorbidities after second dose. The ratio of total number of subjects with comorbidities with ADEs / Total number of subjects after first dose was 53/1364 (38%) and after second dose was 15 / 1340 (1.1%) (Table 6). Similarly, 804 (53.9%) subjects after first dose and 198 (34.4%) subjects after second dose required paracetamol 650 mg for resolution of symptoms as fever/pain at injection site indicating much lower percentage of subjects requiring paracetamol 650 mg and hence better tolerability of second dose of the vaccine. From this data, it can be interpreted that there was a marked reduction in total number of ADEs in subjects with comorbidities after second dose in comparison to first dos. This indicated that there was a better tolerability of Covishield vaccine after second dose in comparison to first dose of Covishield vaccine. As previously reported, systemic reactogenicity following Covishield vaccine was observed in 15 out of 52 (28.8%) subjects who reported pyrexia after vaccination. However, the booster dose (second dose) of Covishield vaccine in the same participants resulted in lower ADEs, with much lesser high-grade pyrexia than after first dose i.e., 19 vs 7. These results are consistent with multicentric, single-blind, randomized controlled trial done in UK of a chimpanzee adenovirus-vectored vaccine (ChAdOx1 nCoV-19) showing the acceptable safety profile in twice dosage regimen of 28-d interval (Folegatti et al., 2020). The results also showed the induction of both humoral and cellular immune responses in adult participants aged 18–55 years. In a study by Ramasamy et al., 2020, the safety and immunogenicity of the ChAdOx1 nCoV-19 (AZD1222) vaccine was evaluated in a controlled, single-blinded, randomized, phase 2/3 trial in healthy adults with age group 18-55 years, 56-69 years, and 70 years and older immunogenicity subgroups. The participants were randomly given intramuscularly either ChAdOx1 nCoV-19 or a control vaccine using block randomization. The Prime-booster regimens were given 28 days apart in the same study with an objective of assessing the safety and immunogenicity of a single-dose and two-dose schedule in adults older than 55 years. The results of the study indicates that ChAdOx1 nCoV-19 was better tolerated in older adults than in younger adults and had similar immunogenicity amongst all age groups after a boost dose. Similarly, the safety and efficacy of ChAdOx1 nCoV-19 vaccine against SARS-CoV-2 was evaluated in four randomized controlled trials in UK, Brazil and South Africa by Vosey et al., 2021. in subjects aged >18–55 years. The results of the all 4 studies indicated that the vaccine had a good safety profile. Serious adverse events occurred in 168 participants out of 23,848 participants and 79 of whom received ChAdOx1 nCoV-19 and 89 of whom received MenACWY (vaccine) or saline control. It was also observed that the ChAdOx1 nCoV-19 vaccine was well tolerated and that the side-effects were seen of lesser intensity and number in older adults and after the second dose. To conclude, the results of our observational pharmacovigilance study indicate that Covishield vaccine (0.5 ml dose given in twice dosage regimen with a gap period of 12 – 16 weeks apart) is safe and is devoid of any fatal or life threatening ADEs. The overall ADEs after the second dose was lower than after the first, and the pattern was consistent in subjects with comorbidities as well. No serious adverse events have occurred after first or second dose of the Covishield vaccine in our observational study. The study was not designed to assess the efficacy of a two-dose regimen and there was no intervention done in patients.

Conclusion

In conclusion it can be interpreted that Covishield vaccine is a safe, well tolerated vaccine. The ADEs after vaccination are seen lesser with second dose than after first dose indicating the better tolerability of the vaccine after second dose. Thus, all the patients who have taken first dose of the vaccine should take the second dose of the vaccine and should not be hesitant to take second dose as second dose in such patients is more tolerable.

Conflicts of interest: None

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