Association between AZD7442 (tixagevimab-cilgavimab) administration and SARS-CoV-2 infection, hospitalization and mortality

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Abstract:

Background

Intramuscular AZD7442 (Tixagevimab–Cilgavimab, (Evusheld)) has been found effective among immunocompromised individuals (ICI) in reducing Sars-Cov-2 infection and severe disease in ICIs. We evaluated the association between AZD7442 administration and SARS-CoV-2 infection and severe disease (COVID-19 hospitalization and all-cause mortality) among selected ICIs, during a fifth Omicron-dominated wave of COVID-19 (Dec 2021-April 2022) in Israel.

Methods

ICIs aged 12 and over identified in the Maccabi HealthCare Services database were invited by SMS/email to receive AZD7442. Demographic information, comorbidities, coronavirus vaccination and prior SARS-CoV-2 infection and COVID-19 outcome data (infection, severe disease), were extracted from the database. Rates of infection and severe disease were compared between those administered AZD7442 and those who did not respond to the invitation, over a three-month period.

Results

Of all 825 ICIs administered AZD7442, 29 (3.5%) became infected with SARS-CoV-2 compared to 308 (7.2%) of 4299 ICIs not administered AZD7442 ($p<0.001$). After adjustment, the AZD7442 group were half as less likely to become infected with Sars-Cov-2 than the non-administered group (OR: 0.51, 95% CI: 0.30-0.84). One person in the AZD7442 group (0.1%) was hospitalized for COVID-19 compared to 27 (0.6%) in the non-administered group ($p=0.07$). No mortality was recorded among the AZD7442 group, compared to 40 deaths (0.9%) in the non-administered group ($p=0.005$). After adjustment, ICIs administered AZD7442 were 92% less likely to be hospitalized/die than those not administered AZD7442 (OR: 0.08, 95% CI: 0.01-0.54).

Conclusions

AZD7442 among ICI may protect against Omicron variant infection and severe disease, and should be considered for pre-exposure prophylactic AZD7442.

Key Words: COVID-19; Omicron; immunocompromised; tixagevimab-Cilgavimab; Evusheld

Background:

As in many countries, Israel has experienced numerous waves of SARS-CoV-2 infection, each spurred by new variants of COVID-19 disease. Israel was amongst the first countries to implement nationwide vaccination, primarily using BNT162b2.[1,2] Vaccination against COVID-19 was effective in both reducing infection and severe disease (hospitalization or death).[3-5] While the vaccine's effectiveness against infection is lower for the Omicron variant, it still reduced the risk of hospitalization and death.[6] However, even from the initial vaccine effectiveness studies, immunocompromised individuals (ICI) were found to have lower risk reduction rates for both infection and disease sequelae with first-line vaccination.[3-5] ICIs who are fully vaccinated against COVID-19 are more likely to have breakthrough infections than people without immune-suppressed systems[7] and express poor humoral response.[8-9] In the absence of an effective vaccine for ICIs, the scientific and medical community were anxious to find a prophylactic treatment that would reduce the risk of infection and severe disease among ICIs.

Two long-acting monoclonal antibodies, tixagevimab (AZD8895) and cilgavimab (AZD1061), found to bind to the SARS-CoV-2 spike-protein and neutralize the virus, were combined to produce AZD7442 (engineered and marketed by AstraZeneca as Evusheld®).[10] Two ongoing Phase III trials, PROVENT[10] and TACKLE,[11] are evaluating the safety and efficacy of AZD7442 for the prevention of SARS-CoV-2 infection (PROVENT) and COVID-19 severe disease (TACKLE). Data from the PROVENT trial demonstrated an 83% relative risk reduction in developing symptomatic COVID-19 compared to placebo at a median follow-up of 6 months. No safety concerns have arisen so far.[10] Initial findings from the TACKLE trial indicate a relative risk reduction of 51% for severe disease or death compared to placebo, in outpatients who had been symptomatic for seven days or less.[11]

Based on these results, in December 2021, AstraZeneca received an Emergency Use Authorization (EUA) from the Food and Drug Administration (FDA) for the use of AZD7442 as pre-exposure prophylaxis against COVID-19. It is authorized for patients 12 years and older, weighing at least 40 kg, who have moderate to severe compromised immunity, or for whom vaccination is not recommended due to a history of severe adverse effects from prior vaccination. Using these guidelines as a framework, the Israel Ministry of Health (IMOH) defined a selected group of ICIs who were considered high-risk for SARS-CoV-2 infection and complication, for whom AZD7442 would be made available.[12]

Recent reviewed[13-15] and non-peer reviewed serology studies (Vanblargen et al., Dejinrattisai et al., manuscripts in preparation) have suggested that AZD7442 may be less effective against the Omicron variant. The current study aimed to test in a real-world setting whether AZD7442 administration among a selected group of ICIs during an Omicron-predominant COVID-19 infection outbreak[16] reduces the risk of SARS-CoV-2 infection and severe COVID-19 disease. The study was carried out in a large health maintenance organization (HMO) in Israel.

Methods:

The study was carried out among members of Maccabi HealthCare Services (MHS), the second largest HMO in Israel. MHS maintains a centralized database including demographic and comprehensive service utilization information for all members, including physician and nurse visits, diagnoses and procedures (community, outpatient and hospital), medication purchases, hospitalization data and laboratory results. Based on this data, the HMO has developed sophisticated disease registries for cardiovascular disease, diabetes, hypertension (HTN), cancer and chronic kidney disease (CKD). MHS also maintains a COVID-19 registry, based on laboratory results (including both tests carried out within the HMO and all external testing sites,

forwarded by IMOH). Similarly, COVID-19 vaccination data (number of doses received, type and date) are maintained in the MHS database.

AZD7442 administration in MHS:

From the middle of February 2022, AZD7442 (300 mg: 150 mg tixagevimab & 150mg cilgavimab) was offered to all members aged 12 and over, with a minimum weight of 40 kg, that did not have a positive test result (PCR or antigen) in the last month, were not vaccinated against COVID-19 in the last two weeks and had evidence of a severe immunosuppression, as defined by the IMOH (Table 1).

A database was developed and updated daily, that included any MHS member that met the above criteria for AZD7442 administration (herein referred to as the 'target population'). Automated systems were implemented, such that any member entering this database who had yet to receive AZD7442, received an SMS and an email advising that they were eligible for AZD7442 and inviting them to contact the MHS call center to make an appointment for vaccination. AZD7442 was offered free of charge. Attached to the SMS/email was a link providing information about AZD7442, its effectiveness, its target population and contra-indications. If no appointment was made within seven days, the SMS and email were sent again. Repeat SMS/emails were sent to for up to one month.

In addition to the target population who were actively outreached to receive AZD7442, physicians were able to prescribe AZD7442 for ICIs not in the target population deemed as likely to benefit. This group was not included in the present study.

Study Population:

The study population included all those in the target population who had been sent an SMS/email between 23.02.2022 (date of first SMS) and 02.05.2022, inviting the member to receive AZD7442. Of the target population, 81% were included in the study population; for the

remaining 19% either no SMS/email address was available or the member had indicated that they did not wish to receive SMS/emails from the HMO.

Date of first SMS/email was used to identify date of entry into study. The study population was divided into two groups: those administered AZD7442 and those not administered AZD7442 (did not open the SMS/email, were uninterested in receiving AZD7442 or were not averse to AZD7442 administration but did not take steps to make or attend appointment for whatever reason). AZD7442 administration was based on administration records from date of first SMS/email to 26.05.2022 (end of study period). Persons that died/left MHS or were found to have COVID-19 (see below) on the same day of the first SMS/email or date of AZD7442 administration were excluded from the analysis.

Study Design:

This retrospective observational study was based on data extracted from the MHS database. The primary study outcome was SARS-CoV-2 infection, defined as any person with a recorded positive polymerase chain reaction (PCR) or positive antigen test result in the follow-up period. The non-administered AZD7442 group were followed up between date of first SMS/email and end of study period. The AZD7442-administered group were followed up between date of AZD7442 administration and end of study period. The secondary study outcome was severe COVID-19 disease, defined as either COVID-19-related hospitalization and/or all-cause mortality, assessed in each group for the same time periods.

Demographic and health factors were collected for both groups to allow comparison of outcome measures, adjusting for differences between the two groups. Demographic factors included age group, gender, socio-economic status and population group (based on census and national survey classifications applied to home address). Health factors included comorbidities (inclusion in registries described above), number of coronavirus vaccine doses received prior to first SMS,

prior SARS-CoV-2 infection (positive PCR or antigen test prior to first SMS/email). Specific condition/treatment on the basis of which each individual was included in the target population were also collected.

Statistical Analysis:

Demographic and health characteristics between the two groups, and the relationship between group and study outcomes were compared using Chi Square statistic or fisher exact test. Kaplan-Maier statistic was used to assess the relationship between AZD7442 administration status and outcome variables over time. Variables found to be associated with outcome variables were included in a logistic regression model. Analyses were carried out using SPSS software, version 24 (IBM©).

The study was approved by both the Maccabi internal review board and Helsinki committee (#0178-20-MHS), with exemption from informed consent.

Results:

Of 5,135 persons with selected immunosuppression conditions and invited to receive AZD7442, 11 (0.2%) tested positive for SARS-CoV-2 on the day of SMS/email receipt or day of administration, and therefore excluded from the study. Of the remaining 5124 persons that comprised the study population, most (90.4%) entered the study as the result of a single condition/treatment. The most prevalent conditions/treatments were lymphoma (39.5%), solid organ transplant (33.0%), anti-CD20 treatment (19.1%) and multiple myeloma (13.3%). The remaining entry conditions/treatments together represented 5.4% of the study population.

Of the study population, 825 (16.1%) were administered AZD7442. The AZD7442-administered group were more likely to be younger, male and from a higher socioeconomic level than those not administered AZD7442 (Table 2). The AZD7442 group were also more likely to have cardiovascular disease, diabetes, HTN and CKD, more likely to have been fully vaccinated

against COVID-19 (at least three doses) and less likely to have had a prior episode of COVID-19 than those not administered AZD7442 (Table 2). The AZD7442 group were more likely to have been included in the initial target population, as the result of a solid organ transplant, ant-CD20 treatment or multiple myeloma and were less likely to have lymphoma than the non-AZD7442 group (Table 2). Solid organ transplant patients were more likely to be male ($p<0.001$), thus explaining the higher proportion of males in the AZD7442 administered group. Median number of follow-up days for those receiving AZD7442 was shorter (53 days) than for those not receiving AZD7442 (73 days).

Risk of SARS-CoV-2 infection:

Of all 825 persons administered AZD7442, 29 (3.5%) were subsequently infected with SARS-CoV-2 compared to 308 (7.2%) of the 4299 persons not administered AZD7442 ($p<0.001$). This finding was consistent over time (Figure 1A). Factors found associated with SARS-CoV-2 infection (univariate analyses) were age, number of doses of COVID-19 vaccine received, prior COVID-19 illness, socioeconomic status and CKD (Supplementary data, Table S1). Gender and all other comorbidities were not found to be associated with SARS-CoV-2 infection in the univariate analyses. The odds of infection for the AZD7442 administered group, compared to the non-administered group was half (OR: 0.51, 95% CI: 0.30-0.84) (Table 3) after adjustment. Prior episode of infection also demonstrated a protective factor against SARS-CoV-2 infection.

When stratified by entry condition/treatment, patients treated with Anti-CD20 and patients after a solid organ transplant that were administered AZD7442 had lower rates of SARS-CoV-2 infection than those not administered AZD7442. A similar trend was observed by AZD7442 administration status for all other conditions/treatment groups (Table 4). However, given the small numbers, the findings for other groups did not achieve statistical significance.

Risk of severe disease (COVID-19 related hospitalization or death):

Only one person in the AZD7442-administered group (0.1%) was hospitalized for COVID-19 compared to 27 (0.6%) in the non-administered group (p=0.05). No deaths occurred in the AZD772-administered group during the study period, compared to 40 (0.9%) in the non-administered group (p=0.005). In all, only 0.1% of the AZD7442 group had evidence of severe disease compared to 1.5% of the non-administered group (p=0.001). This finding was consistent over time (Figure 1B). For univariate analyses, age and all comorbidities, with the exception of obesity, were associated with a severe disease outcome (Supplementary data, Table S1). COVID-19 vaccination status, socioeconomic status and prior COVID-19 illness were not associated with severe disease outcome. As the number of study participants with a severe disease outcome was small (64), a logistic regression analysis was carried out, including only age group and cardiovascular disease. After adjustment, the AZD7442 group odds of having severe disease were 0.08 (95% CI: 0.01-0.54) compared to those not administered AZD7442 (Table 5).

Discussion:

To our knowledge, this is the first real-world, observational study reporting lower rates of SARS-CoV-2 infection, COVID-19-related hospitalization and mortality among a heterogenous group of highly immunosuppressed patients that were administered AZD7442. After adjustment, AZD7442 reduced the odds of SARS-CoV-2 infection by half. These results are consistent with the randomized control trial (RCT) findings regarding AZD7442 efficacy for SARS-CoV-2 infection.[10] The RCT reported a relative risk reduction of 77% for a similar follow-up length period. They are also supported by findings in a study focusing exclusively on solid organ transplant patients, where AZD7442 administered patients exhibited a 5% infection rate compared to 14% in the control group.[17] Our study findings underscore the benefits of using AZD7442 among ICI under real-world conditions. Our study population only included persons with severely compromised immunity, where the majority had been fully vaccinated, a quarter

had a prior infection, and exposure risk was for the Omicron variant (predominantly BA1 between February and March 2022, with BA2 variant becoming the most prevalent from April 2022) In contrast, the randomized control trial (RCT)[10] also included those at high risk of exposure (eg: healthcare workers), excluded those had been vaccinated or had a prior infection and was carried out when other, more virulent variants of the COVID-19 disease were prevalent.

More recent studies have suggested that administration of monoclonal antibodies has a limited effect for immunocompromised patients at risk of Omicron infection. BOSCHI et al (2022)[18] found no neutralizing activity for the B.1.1.529 (original Omicron) variant for any of the following mAbs, irrespective of their combination: casirivimab, imdevimab, bamlanivimab and etesevimab. BENOTMANE et al (2022)[13], in a study of 63 kidney transplant patients with no prior SARS-CoV-2 infection that received tixagevimab-cligavimab antibodies, neutralizing capacity was observed in only 9% of patients within a median of 29 days. Stuver et al. (2022) found no evidence of neutralizing effect for hematologic patients administered AZD7742.[19] However, measures of neutralizing capacity in serum samples do not have a 1:1 correlation with actual infection outcome. Further, Benotmane et al's study (2022)[13] is based on a small, ICI-homogenous group (post-kidney transplant). The present study found evidence of a protective effect in a broad group of immunocompromised persons. Numbers, unfortunately, were too small to confirm if AZD7442 administration was effective for each group, after adjustment.

The TACKLE study[14] reported lower risk for severe disease among ICIs who had been infected with coronavirus that had been treated with AZD7442. In this study, lower odds for severe disease was found among those prophylactically administered AZD7442, compared to those not administered AZD7442. This finding remained significant, after adjustment for key variables. However, given the small numbers with severe disease, adjustment could not be made for all relevant variables and should be interpreted with caution.

Study limitations:

One of the major limitations of the present study is the potential for selection bias in the non-AZD7442 comparison group. It is unknown what proportion of this group never opened the SMS/email, what proportion did open the SMS/mail and decided not to receive AZD7442 and what proportion intended to receive AZD7442 but for whatever reasons, did not complete the process. Persons who refuse treatment and/or lack the motivation required to make/attend an appointment for treatment may be different regarding their healthcare practices from those presenting for treatment. While a large number of potential confounding factors were included in the study, data of this type are not available. It is also possible that those patients entering the study population for conditions requiring active treatment (eg. Anti-CD20) may have more regular contact with the healthcare setting and therefore, more opportunities to be offered AZD7442 (beyond the initial invitation to present).

Another major study limitation is the assumption made that all those who were positive for Sars-CoV-2 presented to MHS/outsourced services for testing. Given that the majority of those infected with the Omicron variant experienced mild illness and the availability of antigen home-testing kits, it is likely that not all those infected would test in the HMO/IMOH-appointed services, despite MOH directives. This would explain why in the present study, infection rates were lower in lower socioeconomic groups and the unvaccinated COVID groups, in contrast to the initial COVID-19 vaccination effectiveness studies.[3-5] Unvaccinated persons and lower socioeconomic bracket groups may have been less inclined to test. If we assume that there were more untested, positive COVID-19 cases among the non-administered group, the results here may under-estimate the effect of AZD7442 administration in preventing infection.

We also reported that about a fifth of those eligible for vaccination were not sent an SMS/email, and therefore not included. This population group were younger and had lower rates of

comorbidity. Had their inclusion been possible, we suggest that the findings here may be somewhat attenuated.

The study did not take into account differences between the two groups regarding other antiviral treatments available, such as nirmatrelvir, that may also affect severe disease prevalence.[20] Finally, our outcome for severe disease included all-cause mortality and not COVID-related mortality; this may have inflated severe disease outcome for the non-administered group.

Conclusions:

AZD7442 administration among persons with severe immunosuppression appears to provide protection against Omicron variant infection and severe disease sequelae. These findings have broad implications on public health policy and health service provision for the immunocompromised individual, and encourage physicians to recommend AZD7442 for highly immunosuppressed patients.

Notes:

Contributions:

JK designed the study, analyzed the data and drafted the manuscript. SSBD, NEZ, NSS, LA and AS contributed to the design of the study and interpretation of results. KR contributed to the introduction of the manuscript. BH and AK contributed to the data analysis. SSBD, NEZ, LA, NSS, MMR & AS critically revised the manuscript. All authors read and approved the final manuscript.

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Potential conflict of interest:

SSBD and LA have both received funding for research from Pfizer. None of the authors have received funding for any purpose from Astra Zeneca (maker/supplier of AZD7442). No other conflicts of interest to report for all other authors. SSBD reports receiving payment from Pfizer for a lecture. LA reports payments made to the institution from Pfizer (Grant ID 65254759) for a study about Varencline.

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1 Table 1: Definition of conditions/treatments for AZD7442 administration

Condition/Treatment	Definition
Hypogammaglobulinemia	Diagnosis of chronic hypogammaglobulinemia AND purchase of intravenous immunoglobulin treatment (IVIg) in the past three months
Chronic lymphocytic leukemia (CLL)	Diagnosis of CLL AND purchase of immunosuppressant antineoplastic medications in the last three months OR purchase of anti-CD20 medications in the last six months
Anti-CD20 monoclonal antibody-mediated B cell depletion therapy	Purchase OR record of anti-CD20 treatment in last six months
Bone marrow transplant	Record of allogeneic bone marrow transplant in last year OR record of autologous bone marrow transplant in last six months
Chimeric antigen receptor T cell (CAR-T) therapy	Record of CAR-T treatment in last six months
Solid organ transplant	Record (ever) of solid organ transplant procedure
Aggressive lymphoma	Diagnosis of aggressive lymphoma
Multiple myeloma	Diagnosis of multiple myeloma undergoing active treatment

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Table 2: Demographic and health characteristics of the study population by AZD7442 administration status, Maccabi HealthCare Services, Feb-May 2022

Characteristic	Category	Administered AZD7442 N=825	Not administered AZD7442 N=4299	p value
Demographic:				
Age Group	12-39	4.1	13.9	<0.001
	40-59	29.9	32.4	
	60-69	28.6	22.6	
	70-79	30.5	21.3	
	80+	6.8	9.9	
Gender	% Male	62.1	53.3	<0.001
Socioeconomic status	Low	8.6	18.8	<0.001
	Middle	44.4	48.8	
	High	47.0	32.4	
Population group	General	95.8	89.6	<0.001
	Orthodox religious	2.5	3.6	
	Arab	1.7	6.8	
Health factors:				
Cardiovascular Disease	% in registry	32.6	28.1	0.008
Diabetes	% in registry	29.2	25.8	0.040
HTN	% in registry	58.8	49.4	<0.001
Cancer	% in registry	64.1	65.4	0.493
CKD	% in registry	61.9	49.4	<0.001
Obesity (BMI≥30)	% in registry	26.1	25.2	0.589
Number COVID vaccine doses	None	1.2	12.0	<0.001
	One-two	7.5	11.7	
	Three-four	91.3	76.3	
Prior COVID-19 episode	% with prior episode	20.7	25.9	0.002
Immunity compromised condition/treatment (Rx)*:				
Hypogammaglobulinemia	% with condition/Rx	0.7	0.4	0.153
CLL	% with condition/Rx	4.8	2.2	<0.001
Anti CD20 Rx in last 6 mth	% with condition/Rx	26.2	17.7	<0.001
Bone marrow transplant	% with condition/Rx	3.4	2.1	0.026
CAR-T Rx	% with condition/Rx	0.5	0.1	0.062
Solid organ transplant	% with condition/Rx	40.5	31.5	<0.001
Lymphoma	% with condition/Rx	24.6	42.4	<0.001
Multiple myeloma	% with condition/Rx	16.8	12.6	0.001

* Patients could be assigned to more than one condition/treatment

Table 3: Factors associated with SARS-CoV-2 infection among selected ICIs, Logistic regression model, Maccabi HealthCare Services, Feb-May 2022

Characteristic	Category	N	OR	95% CI
AZD7442	Not administered	4299	-	
	Administered	825	0.51	0.30 – 0.84
Prior COVID-19 episode	No	3840	-	
	Yes	1284	0.17	0.11 – 0.28
Age group	12-79	4643	2.43	1.50 – 3.93
	80+	481	-	
Socioeconomic status	Low	879	-	
	Middle	2463	1.78	1.20 – 2.64
	High	1782	2.45	1.65 – 3.66
CKD	No	2488	-	
	Yes	2636	1.42	1.13 – 1.79
Number coronavirus vaccine	None	526	0.60	0.37 – 0.95
doses	One-two	564	0.79	0.49 –1.24
	Three-four	4034	-	
Number of follow-up days		5124	1.02	1.0 – 1.04

Table 4: Association between AZD7442 administration status and SARS-CoV-2 infection by study entry condition/treatment, Maccabi HealthCare Services, Feb-May 2022

Condition/Treatment	AZD7442 status				p value
	Administered		Not administered		
	N	% infected	N	% infected	
Anti-CD20 Rx in last 6 mth	65	9.2	913	23.0	0.010
Solid organ transplant	116	9.5	1574	20.5	0.004
Lymphoma	132	6.8	1892	10.3	0.204
Multiple myeloma	32	12.5	647	20.9	0.252
All other	17	11.8	252	30.2	0.111

Table 5: Factors associated with severe disease (COVID-19-related hospital infection or all-cause mortality) among ICIs, Logistic regression model, Maccabi HealthCare Services, Feb-May 2022

Characteristic	Category	N	OR	95% CI
AZD7442 status	Not administered	4299	-	
	Administered	825	0.08	0.01 - 0.54
Cardiovascular disease	No	3648	-	
	Yes	1476	2.38	1.43 - 3.98
Age group	12-99	3475	-	
	70+	1649	1.79	1.07 – 2.98

Figures 1A & 1B: Infection and severe disease rates over time by AZD7442 administration status, Kaplan Meier hazards ratios, Maccabi HealthCare Services, Feb-May 2022

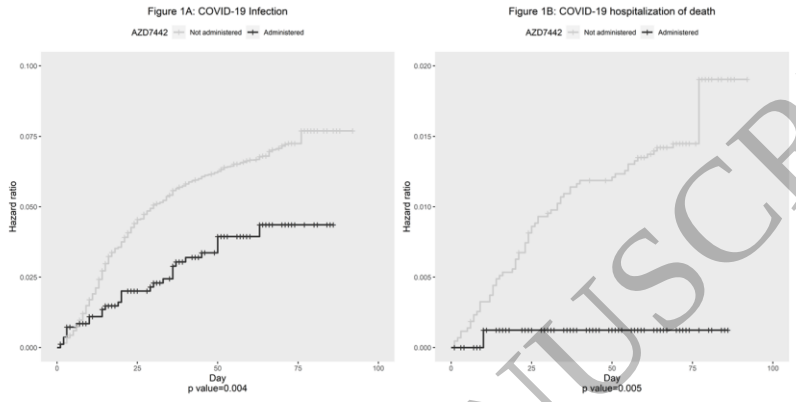

Figure 1
108x61 mm (.23 x DPI)