Adverse Drug Reaction Gender Differences in Patients Treated with REGEN-COV (Casirivimab/Imdevimab) for Treatment of COVID-19

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ABSTRACT

Introduction

The FDA provided an emergency use authorization for the monoclonal antibody (mAb) REGEN-COV, which is casirivimab and imdevimab, administered together either intravenously or subcutaneously for the treatment of SARS-COV-2. NHIF retrospectively collected and analyzed data from the REGEN-COV patient charts. Data analysis showed that home infused REGEN-COV achieved comparable outcomes to other sites of care and provided improved access to treatment. For this study, NHIF conducted additional analysis of the REGEN-COV data to include gender-related factors. This study answered the question, "Does a significant difference exist between men and women and the rate of adverse drug reactions (ADRs) from REGEN-COV?" If a significant difference does exist, what variables might have caused the difference between the genders, such as patient age, infusion time, vaccination status, and the number of days between the onset of COVID-19 symptoms and the first dose of REGEN-COV?

Methodology

Home infusion providers participated in this study from July 2021 through October 2021, collecting the following REGEN-COV data; patient age and gender, date symptoms started, date of infusion, infusion time, vaccination status, 7-day follow-up, and adverse events. Analysis was conducted to determine if a significant difference (p=.05) existed between the mean age of the genders, rate of ADRs and genders, infusion time and genders, infusion time and rate of ADRs, vaccination rate and genders, and the mean number of days between the onset of COVID-19 symptoms and the first dose of REGEN-COV and genders. Descriptive statistics were used to analyze demographic data. An ANOVA was conducted to determine if the mean ages of the men and women in the study were significantly different. This statistic was also used to determine if the mean time between the onset of COVID-19 symptoms and the first dose of REGEN-COV was significantly different between the genders. Fisher's Exact Test was used to determine if a significant difference existed between gender and the occurrence of an ADR.

Results

There were 459 patient cases representing 5 home infusion providers. No significant difference (p=.615) was observed between the mean ages of the genders. Males had a significantly (p=.022) higher rate of reported ADRs when compared to females (6.94% versus 2.47%). This is contrary to previous gender and ADR studies which have shown that females have a higher rate of reported ADRs when various therapy types and illnesses are investigated. There was a significant difference (p=.009) in infusion times between the females and males. However, the infusion time that was predominantly for females, which was 20-minutes, was noted to have fewer overall ADRs. There was a significant difference (p=.001) between females and males in the number of days between the onset of COVID-19 symptoms and the first dose of REGEN-COV. Even so, there was no

significant difference (p=.078) between the overall mean number of days between the onset of COVID-19 symptoms and the first dose when cross tabulated by ADRs.

Discussion

Due to the possible confounding variables that might have caused the differences in the rate of ADRs among the genders, such as the potential difference in health status and the low rate of ADRs in the patients, the investigators are hesitant to conclude that gender and the infusion rate caused the difference in the rate of ADRs. It is recommended that future mAb studies should match genders by health status and compare various infusion times with the rate of ADRs.

Conclusion

As noted in the literature, females typically have a higher rate of ADRs than males. This study showed the opposite. When the rate of ADRs was compared by infusion time, the 20-minute time had a 0.42% ADR rate, while the 30-minute time had a 10.95% rate. Even though males had a higher rate of ADRs compared to females, more than half of the males (56.91%) had an infusion rate of 20 minutes. Of the reported ADRs, all but 1 was classified as mild. As recommended in previous ADR research, investigation of gender differences needs to be a standard protocol for all studies.

Keywords: *COVID, REGEN-COV, gender-differences, home infusion, infusion rate, ADR*

Introduction

The first case of COVID-19 in the U.S. was reported on January 21, 2020. Since then, there have been over 92 million reported cases and 1 million deaths.[1] A combination of the high mortality rate and the debilitating effects of the virus has led to the development of various treatment options, including monoclonal antibodies (mAbs). The first mAb, muromonab-CD3 (OKT3), was produced in 1975 and fully licensed in 1986. Today, more than 100 mAbs have been approved by the U.S. Food and Drug Administration (FDA) and are used in treating various diseases and conditions, including cancer, chronic inflammatory diseases, transplant rejection, infectious diseases, and cardiovascular diseases.[2] When used to treat COVID-19, mAbs assist in preventing viral progression in patients at risk for serious outcomes,[3] especially those 65 and older with underlying comorbidities such as cardiovascular disease, obesity, diabetes, chronic kidney disease, and chronic lung disease.[4] As reported by the National Institutes of Health (NIH), the major benefit from mAb therapy in the treatment of COVID-19 appears to be a reduction in the viral load, subsequently preventing hospitalizations and death.[3] The NIH further states that the benefit of this type of therapy is that it is well-tolerated with minimal risks, with the most reported adverse events being injection site reactions and infusion-related reactions.[3]

On November 21, 2020, the FDA provided an emergency use authorization (EUA) for the mAbs REGEN-COV, which is casirivimab and imdevimab, administered together either intravenously or subcutaneously.[5] This therapy was used for patients who tested positive for COVID-19 and were at high risk for progressing to severe COVID-19, hospitalization, or both, and had mild-to-moderate COVID-19 symptoms.[5] A phase 3 adaptive trial was conducted on REGEN-COV and showed that COVID-19 related hospitalizations or death from any cause occurred in 18 of 1,355 (1.3%) patients in the REGEN-COV group compared to 62 of 1,341 (4.6%) patients in the placebo group.[6] The trial concluded that REGEN-COV reduced the risk of COVID-19-related hospitalizations or death from any cause, resolved symptoms, reduced the SARS-CoV-2 viral load more rapidly than placebo.[6]

To ease access to treatment and due to the contagious nature of COVID-19, many patients and care takers gravitated to home health care. Furthermore, with changes in the Centers for Medicare and Medicaid Services (CMS) reimbursement for home COVID-19 treatment, home infusion providers could administer REGEN-COV in the home. As a novel COVID-19 treatment, the National Home Infusion Foundation (NHIF) retrospectively collected and analyzed data from the REGEN-COV patient charts. From the results of this analysis, it was reported that home infused REGEN-COV achieved comparable outcomes to other sites of care and provided improved access to treatment for SARS-COV-2 infection.[7] Furthermore, it was concluded that home infusion providers played an essential role in reducing exposure, saving lives, and reducing hospitalizations.[7]

NHIF decided to conduct additional analysis of the REGEN-COV data after noting the adverse drug reaction (ADR) recommendation in the medical literature that advocated for reporting systems to expand their focus to include gender-related factors to understand, prevent, or reduce the occurrence of ADRs in all people.[8] Without these reporting systems, ADRs that are more common among certain groups, such as women, may remain undetected for years, increasing the possibility of unanticipated risks.[8] It was further stated that research is needed to identify the relationships between gender-related factors in the occurrence and reporting of ADRs to adequately detect and prevent ADRs.[8] Subsequently, this study aimed to answer the research question, "Does a significant difference exist between men and women and the rate of ADRs from REGEN-COV?" If a significant difference does exist, what confounding variables might have caused the difference between the genders, such as patient age, infusion time, vaccination status, and the number of days between the onset of COVID-19 symptoms and the first dose of REGEN-COV.

Prior to conducting this investigation, literature on gender differences and ADRs was searched. A recent study that reviewed 33,147 patient charts with an ADR-related hospital admission between 2005 and 2017 determined that women accounted for 55.72% of ADR-related hospital admissions while men accounted for 44.28%.[9] It was also revealed a significant difference between the mean age of the men and women (Women = 72.1 years, Men = 71.3 years) and in the types of therapies that men and women were using. Both variables are known to skew the rate of ADRs in patients, evident by research that shows that the elderly are thought to be predisposed to ADRs.[10] Another ADR study that included 513,608 patients who were prescribed a newly marketed drug, concluded that women tend to have a 1.5-1.7 times higher risk of developing ADRs.[11] These results are in line with conclusions from other researchers.[12-14] The only study that addressed the rate of ADRs in home infused patients was a 2022 study by NHIF that had a sample size of 6,045 and concluded that the rate of ADRs that result in discontinuation from therapy is 0.33%.[15] Unfortunately, this study did not report the ADR rate by gender. Overall, the research on gender and ADRs concludes that women have a higher rate of ADRs than men, though most studies did not control for age and therapy differences between the genders.

Research Question

Does a significant difference ($p \leq .05$) exist between men and women and the rate of ADRs from intravenous infusion of REGEN-COV in the home setting? If a significant difference does exist, what other factors might have caused the difference between the genders, such as patient age, intravenous infusion rate, vaccination status, and the number of days between the onset of COVID-19 symptoms and first dose of REGEN-COV.

Methods

For the initial REGEN-COV study conducted and reported by NHIF in 2022, home infusion providers were given information about participation in the study, with those interested completing an online survey.[7] A unique data participation code was assigned to each selected location using a third-party to deidentify the provider and their data. Each location entered its patient data into a formatted Excel® file. No

patient identifiers were included in the Excel® file forwarded to NHIF. The variables collected included patient age and gender, date symptoms started, date of infusion, infusion time, vaccination status, 7-day follow-up, and adverse events. This study used the NHIF Standard Definition for an ADR, defined as an undesirable response, other than a known side effect, to the administration of an infused drug that compromises efficacy and/or enhances toxicity.[16] Known side effects include commonly reported mild and moderate reactions listed in the FDA-approved drug labeling or reported in published clinical studies.[5] Since the patient cases and provider locations were deidentified before being uploaded to NHIF's data depository; this study was exempt from IRB review.

The data collection was from July 2021 through October 2021. Each provider location was responsible for assessing patient eligibility per EUA, providing drugs and supplies for administration, coordinating nurses, and billing Medicare or commercial payers for administrations. After the study data was aggregated, differences in drug infusion times were noted. To gain insight into why the differences occurred, a follow-up survey was issued to each participating provider to better understand the intravenous administration protocols used for REGEN-COV. Survey results showed that intravenous infusion times for REGEN-COV were determined either by company protocol or based on patient clinical presentation, or both. Data collection for the infusion time was driven by either the physician order or the nurse documentation.

Data analysis

Descriptive statistics (means and standard deviations) were used to analyze demographic data. An ANOVA was conducted to determine if the mean ages of the men and women in the study were significantly different. This statistic was also used to determine if the mean time (days) between the onset of COVID-19 symptoms and the first dose of REGEN-COV was significantly different between the genders. In the initial study, ADRs were recorded by the type of ADR. This data was recoded as dichotomous data (yes, the patient had an ADR or no, that patient did not have an ADR) so that Fisher's Exact Test could be used to determine if a significant difference existed between gender and the occurrence of an ADR. This statistic was also used to determine if a significant difference existed between gender and infusion rate and gender and vaccination rate. SPSS (Statistical Package for Social Sciences) was used to analyze the data set.

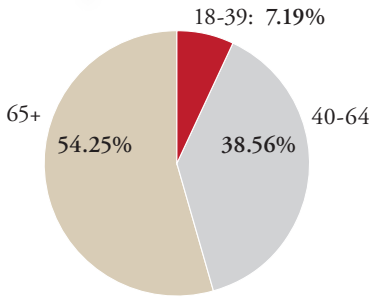
Results

This study had 464 patient cases representing 5 self-selected home infusion providers. Since the study focused on an adult population (18+ years of age), 4 patient cases were deleted from the original data set. It was also determined that only intravenous infusion rates of 20 and 30 minutes would be included, thus, the 1 patient case with a 50-minute infusion rate was deleted since it was deemed an outlier. The remaining 459 cases used in this study included patients 18 years of age and older with a REGEN-COV infusion rate of 20 or 30 minutes.

Patient Demographics

The mean patient age was 64.21 years (SD=15.99), with slightly more than half (54.25%) of the patient cases in the 65+ age group, as shown in Figure 1.

FIGURE 1 | Patient Age Group (n=459)



Women and men accounted for 52.94% and 47.06%, respectively of the COVID-19 patients treated with REGEN-COV. There was no significant difference (p=.615) between the mean ages of the genders, which was 64.56 (SD=16.83) for women and 63.81 (SD=15.04) for men. Thus, age would not be considered a confounding variable that would skew the results when gender was cross tabulated by ADRs.

Intravenous Infusion Time

Fisher's Exact Test showed a significant difference (p=.009) between gender and intravenous infusion time (20 or 30 minutes), as shown in Figure 2. Females had a higher percentage of 20-minute infusions than males. Conversely, males had a higher rate of 30-minute infusions than females. As shown in Table 1, 10.95% of patients with an infusion time of 30 minutes had an ADR while only 0.42% of those with a 20-minute infusion time had an ADR. Fisher's Exact Test analysis showed a significant difference (p=<.001) between infusion time and adverse events.

FIGURE 2 | Infusion Time by Gender (n=373)

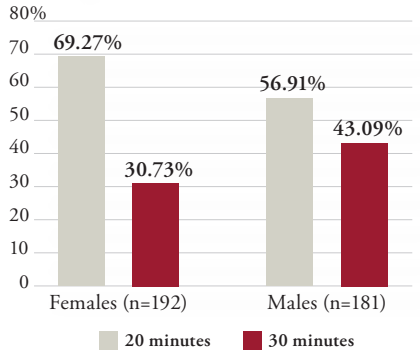


TABLE 1 | Infusion Time by Adverse Drug Reaction (Yes/No) (n=373)

			Infusion Time (minutes)		
			20	30	Total
Adverse Drug Reaction	No	Count	235	122	357
		%	99.58	89.05	95.71
	Yes	Count	1	15	16
		%	.42	10.95	4.29
Total		Count	236	137	373
		%	100.00	100.00	100.00

Gender and Vaccination Status

The vaccination rates were almost identical for females and males. No significant difference (p=1.0) was detected between the genders. Males' vaccination rate was 78.82%, while females were 78.65%. Additionally, there was no significant difference (p=.061) between overall vaccination status and the rate of ADRs.

Days Between Onset of Symptoms and First Dose

The mean number of days between the onset of COVID-19 symptoms and the first dose of REGEN-COV was significantly different (p=.001) between the females and males, with females having almost 1 day less time between symptoms and the first dose of REGEN-COV. The mean number of days for females was 5.61 (SD=2.652) and 6.50 (SD=2.699) for males. Furthermore, there was no significant difference (p=.078) between the mean number of days between the onset of COVID-19 symptoms, the first dose of REGEN-COV, and the rate of reported ADRs. The mean number of days for those with an ADR was 7.11 (SD=2.69), and those without, 5.98 (SD=2.70).

Gender and Adverse Drug Reactions (Yes or No)

Fisher's Exact Test shows a significant difference (p=.022) between gender and ADRs from REGEN-COV, as shown in Table 2. Females had a lower rate of reported ADR than males, with the overall rate being 4.58%. All but 1 of the ADRs reported in this study were classified as mild using the World Health Organization (WHO) rating scale, which defines a mild ADR as an experience that is usually transient and requires no special treatment or intervention.[17]

TABLE 2 | Gender by Adverse Drug Reaction (Yes or No) (n=459)

			Gender		
			Female	Male	Total
Adverse Drug Reaction	No	Count	237	201	438
		%	97.53	93.06	95.42
	Yes	Count	6	15	21
		%	2.47	6.94	4.58
Total		Count	243	216	459
		%	100.00	100.00	100.00

Gender and Post-infusion Outcome

Of the 391 patient cases with post-infusion outcome data, only 5 (1.28%) required hospitalization (3 females and 2 males), and 1 male patient expired. There was no significant difference (p=.546) between the genders and 7-day outcome, which showed that 200 (98.52%) of the females and 185 (98.40%) were not hospitalized or expired.

Results Summary

This study investigated the gender differences in the reported rate of ADRs from REGEN-COV used to treat COVID-19 patients in the non-acute setting. Overall, a significant difference was observed between genders and the rate of reported ADRs, with females having a lower rate than males. Age was not a confounding factor since there was no significant difference between the mean age of the females and males. There was a significant difference between intravenous infusion time between females and males. However, the infusion time that was predominantly for females, which was 20 minutes, was noted to have fewer overall ADRs. There was a significant difference between females and males in the number of days between onset of COVID-19 symptoms and first dose of REGEN-COV. Even so, there was not a significant difference between the overall mean number of days between the onset of COVID-19 symptoms and the first dose when cross tabulated by ADRs, which was recoded as a dichotomous variable (Yes or No). Worth noting is that the mean number of days to treatment was 7.11 for the patients with a reported ADR versus 5.98 days for those without.

Study Limitations

Data regarding pre-COVID-19 patient health status was not collected and could bias the rate of ADRs. As reported by the CDC, there are underlying medical conditions that put people 18 years and older at higher risk of severe illness from COVID-19. These illnesses and risks could affect the rate of ADRs, hospitalization, and death. The males might have had more pre-COVID-19 medical conditions than females, which might have accounted for more of the reported ADRs. ADR data was self-reported by providers which could lead to reporting bias. There is also the possibility of gender bias in the reporting of ADRs. As noted, historically, females tend to have more reported ADRs than men. However, this study showed the opposite results, with males reporting more ADRs than females. Finally, a univariate analysis model was primarily used in this investigation which has the advantage of simplicity of interpretation but fails to account for the covariance/correlation in the data.

Discussion

The most notable finding in this study is that males had a significantly higher rate of reported ADRs when compared to females. This is contrary to previous gender and ADR studies which have shown that females have a higher rate of reported ADRs when various therapy types and illnesses are investigated. It is surmised that males might have had more underlying health conditions, which might have skewed the results. Future studies should control for pre-COVID-19 health conditions by matching genders on health status. Furthermore, fewer males than females had an infusion time of 20-minutes versus 30-minutes. This is notable because a significant difference (p=<.001) was found between infusion time and adverse events, with the 30-minute time demonstrating fewer reported ADRs than the 20-minute time.

Due to the possible confounding variables that might have caused the differences in the rate of ADRs among the genders, such as the potential difference in health status and the low rate of ADRs in the patients in this study, the investigators are hesitant to conclude that gender and/or the infusion rate caused the difference in the rate of ADRs. It is recommended that future mAb studies should match genders by health status and compare various infusion times with the rate of ADRs. A unique aspect of REGEN-COV was using different infusion times to administer the medication. Typically, mAbs approved by the FDA have 1 recommended infusion rate. This study provides a rare opportunity to collect outcome data from patients receiving treatment using different infusion times.

Conclusion

This investigation provides evidence that REGEN-COV administered in the home setting was generally well tolerated and produced similar outcomes compared to other studies, as noted by the ADR rate. In females and males, the rate of ADRs was 2.47% and 6.94%, respectively. As noted in the literature, females typically have a higher rate of ADRs than males. When the rate of ADRs was compared by infusion time, the 20-minute time had a 0.42% ADR rate, while the 30-minute time had a 10.95% rate. Even though males had a higher rate of ADRs when compared to females, more than half of the males (56.91%) had an infusion rate of 20-minutes. Of the reported ADRs, all but 1 was classified as mild. As recommended in previous ADR research, investigation of gender differences needs to be a standard protocol for all studies.

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