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BRIEF REPORT

Viral and Symptom Rebound Following Anti–Severe Acute Respiratory Syndrome Coronavirus 2 Monoclonal Antibody Therapy in a Randomized Placebo-Controlled Trial

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We explored viral and symptom rebound after coronavirus disease 2019 amubarvimab-romlusevimab monoclonal antibody therapy versus placebo in the randomized ACTIV-2/A5401 trial. Participants underwent nasal severe acute respiratory syndrome coronavirus 2 polymerase chain reaction testing at study days 3, 7, 14, and 28. Viral rebound was defined as RNA ≥3 and ≥0.5 $\log_{10}$ copies/mL increase from day 3 or 7, and symptom rebound as hospitalization or any moderate/severe symptom for ≥2 days after initial symptom improvement. There was no difference in viral rebound (~5%/arm) (analysis population n = 713) or symptom rebound among participants who initially improved (hazard ratio, 0.95 [95% confidence interval, .52–1.75]; analysis population n = 574); <1% had both viral/symptom rebound.

Keywords. SARS-CoV-2; COVID-19; monoclonal antibodies; nonhospitalized adults; viral rebound; symptom rebound.

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Viral and symptom rebound have been reported after coronavirus disease 2019 (COVID-19) treatment with ritonavir-boosted nirmatrelvir, molnupiravir, and VV116, short-acting direct antivirals [1–5], as well as in the natural history of untreated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [6, 7], but the risk of rebound with anti-SARS-CoV-2 monoclonal antibodies (mAbs) is unknown. We hypothesized that the longer half-life of mAbs would reduce risk for rebound and viral RNA (vRNA) dynamics with mAb treatment would further our understanding of mechanisms of rebound. We previously reported that the combination mAb amubarvimab-romlusevimab reduced risk of hospitalization or death by 79% and accelerated nasal viral clearance in the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)-2/A5401 trial in nonhospitalized adults with acute COVID-19 [8]. In this analysis, we assessed viral and symptom rebound with amubarvimab-romlusevimab compared to placebo.

METHODS

Study Design and Participants

ACTIV-2/A5401 was a multicenter randomized, controlled, phase 2/3 adaptive platform trial designed to evaluate the safety and efficacy of investigational agents for the treatment of nonhospitalized adults with mild-to-moderate COVID-19 (NCT04518410). The protocol was approved by a central institutional review board (Advarra Pro00045266) for United States (US) sites and by local ethics committees for non-US sites. All participants provided written informed consent.

The analysis included participants who initiated treatment in the double-blind phase 2/3 evaluation of amubarvimab-romlusevimab. Participants were nonhospitalized adults (≥18 years) at high risk of progression to severe COVID-19 and within 10 days of symptom onset [8]. Randomization was 1:1 to intravenous amubarvimab-romlusevimab or placebo administered on day 0, with stratification by days of symptoms at enrollment (≤5 or >5 days) [8]. Participant immunocompromised status was defined as described previously (Supplementary Material and [9]).

All participants self-collected anterior nasal swabs using standardized instructions on study days 0, 3, 7, 14, and 28. Quantitative SARS-CoV-2 RNA levels were measured centrally (lower limit of quantification [LLoQ] of 2 $\log_{10}$ copies/mL) [8] and next-generation sequencing was performed for variant determination (methods are shown in the Supplementary Material). All participants completed a daily symptom diary from day 0 through day 28 with each of 13 symptoms self-reported as "absent," "mild," "moderate," or "severe" (Supplementary Material). Participants were not expected to complete diaries or nasal swabs during hospitalization. Serum

anti-nucleocapsid and anti-spike antibodies were measured prior to intervention (Elecsys Anti-SARS-CoV-2, Roche Diagnostics).

Outcome Measures

For the primary prespecified comparison of viral rebound, rebound was defined as vRNA $\geq$3 $\log_{10}$ copies/mL at day 7, 14, or 28 that was $\geq$0.5 $\log_{10}$ copies/mL higher than day 3, or at day 14 or 28 that was $\geq$0.5 $\log_{10}$ copies/mL higher than day 7. This definition assumed that vRNA levels peaked by day 3. Participants included in the viral rebound analysis were required to have vRNA at day 3 and at least 1 subsequent time point. Considering the lack of a consensus definition of viral rebound, we explored definitions requiring thresholds of 4 and 5 $\log_{10}$ copies/mL (levels correlated with culture positivity and thus potential increased risk for infectiousness [3]), and requiring a 1 $\log_{10}$ copies/mL increase instead of 0.5. These definitions are similar to approaches used in other analyses of rebound in randomized controlled trials (RCTs) [10, 11]. RNA results below LLoQ were assigned the LLoQ when assessing differences between time points. Because nasal swabs were not required during hospitalization and vRNA rebound might have occurred during hospitalization, a sensitivity analysis was undertaken in which hospitalization occurring during days 7, 14, or 28 was also considered to be a viral rebound occurrence (requiring that no vRNA result was available on that visit day).

The symptom rebound analysis included only participants who met sustained symptom improvement as defined for the primary trial, the first of 2 consecutive days where all 13 targeted COVID-19 symptoms in the study diary improved in severity from entry (symptoms initially reported as moderate or severe were required to be mild or absent, and symptoms reported as mild or absent were required to be absent) [8]. Symptom rebound was defined as the first occurrence of hospitalization or any moderate/severe symptom lasting for $\geq$2 consecutive diary entries, after achieving sustained symptom improvement.

Statistical Analysis

The analysis population consisted of all participants who were randomized and received amubarvimab-romlusevimab or placebo in the trial and met criteria for inclusion as above. Due to concerns about data integrity, data from 6 sites were excluded from analyses. Comparisons were based on treatment received (a small number of participants received a different treatment from their randomized assignment). Analyses were performed using all available data as of 28 September 2023 (data freeze). The proportion of participants with viral rebound was compared between arms using Fisher exact test. Characteristics of participants with and without rebound were compared using Fisher exact, Wilcoxon rank-sum, or χ^2 tests. Risk of symptom rebound was assessed using hazard ratios from Cox models with time of symptom improvement as the time origin, adjusting for day 0 total symptom score (see Supplementary Material for score calculation). Participants with a hospitalization that occurred prior to symptom improvement were assumed not to have met the symptom improvement outcome during hospitalization. Missing data prior to symptom improvement were imputed using the more severe of the immediately preceding and succeeding symptom report. Missing diary entries after improvement were ignored when determining rebound. No adjustments were made for multiple comparisons for this exploratory analysis. All analyses used a 2-sided 5% significance level. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Eight hundred and seven participants were randomized from January to July 2021 (prior to emergence of Omicron variants) from sites in the US, Argentina, Brazil, Mexico, Philippines, and South Africa; 713 were included in the viral rebound analysis (370 amubarvimab-romlusevimab, 343 placebo, of which 6 amubarvimab-romlusevimab and 17 placebo arm participants were hospitalized within 28 days of follow-up) and 574 in the symptom rebound analysis (292 amubarvimab-romlusevimab, 282 placebo) (Supplementary Figure 1). Characteristics were similar between arms (Supplementary Table 1). Median age was 48 years, with 52% female sex, 72% White, 18% Black/African American, and 49% Hispanic/Latino. The median number of days of symptoms prior to treatment was 6, and 9% had received at least 1 COVID-19 vaccine dose.

Viral Rebound

Viral rebound ($\geq$0.5 $\log_{10}$ copies/mL increase to a level of $\geq$3 $\log_{10}$ copies/mL) occurred in 4.6% (17/370) and 5.0% (17/343) in the amubarvimab-romlusevimab and placebo arms, respectively ($P = .86$). The proportion of participants with rebound decreased successively when requiring a higher vRNA threshold at rebound, with 1.6% and 2.0% in the amubarvimab-romlusevimab and placebo arms having rebound to $\geq$5 $\log_{10}$ copies/mL (Figure 1*A*). Rebound was transient and nearly all participants with rebound had vRNA <LLoQ on study day 28 (Supplementary Figure 2). All amubarvimab-romlusevimab–treated participants had evidence of viral decline prior to rebound and none with rebound were hospitalized. For 3 placebo participants, vRNA levels were on an upward trajectory between day 0 and day 3 with "rebound" occurring on day 7. Two of these 3 participants were hospitalized for COVID-19–related reasons. One additional placebo recipient was hospitalized after viral rebound. In the sensitivity analysis treating hospitalization as viral rebound, rebound occurred in 5.1% in the amubarvimab-romlusevimab arm versus 6.7% in the placebo arm (Supplementary Table 2).

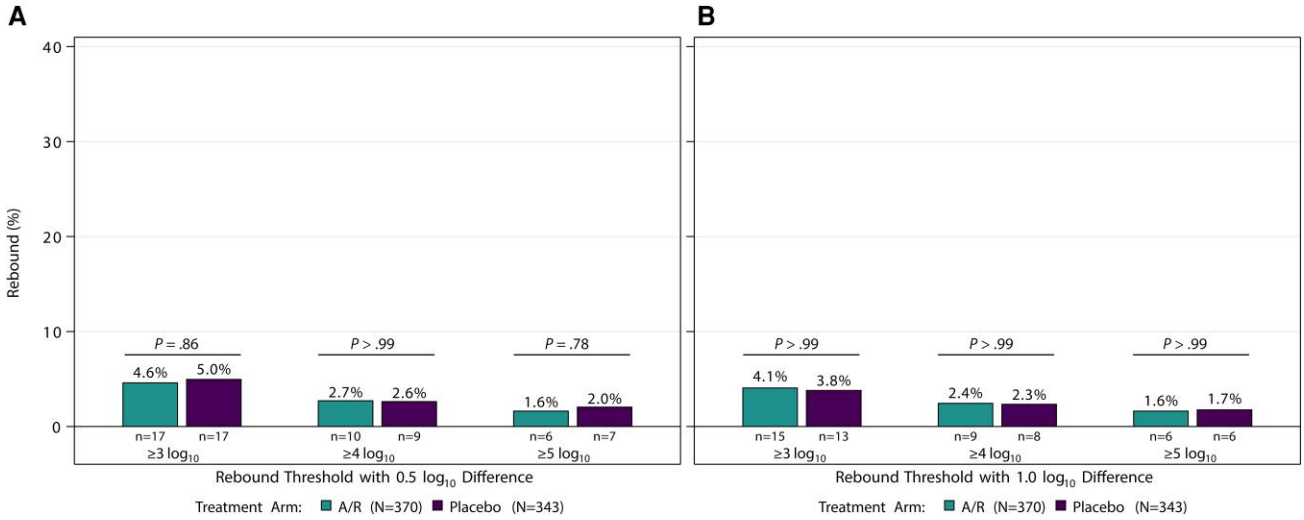

Figure 1. Percentage of participants with viral rebound by treatment arm and rebound definition. *A*, Viral rebound definition requiring at least 0.5 $\log_{10}$ increase in nasal viral RNA level and reaching at least 3, 4, or 5 $\log_{10}$ copies/mL. *B*, Viral rebound definition requiring at least 1 $\log_{10}$ increase in nasal viral RNA level and reaching at least 3, 4, or 5 $\log_{10}$ copies/mL. *P* values by Fisher exact test for between-arm difference in rebound frequency. Abbreviation: A/R, amubarvimab-romlusevimab.

Requiring a ≥1 $\log_{10}$ copies/mL increase in vRNA (to ≥3 $\log_{10}$ copies/mL), 4.1% (15/370) versus 3.8% (13/343) had rebound in the amubarvimab-romlusevimab and placebo arms, respectively ($P > .99$) (Figure 1*B*).

As characteristics of participants with and without viral rebound were similar between treatment arms (Supplementary Table 3), data were combined across arms for comparisons of risk factors for rebound (Table 1). Day 0 vRNA levels were higher among participants with versus without rebound (median: 4.8 vs 3.7 $\log_{10}$ copies/mL, $P = .013$), and days from positive SARS-CoV-2 test to randomization was shorter (median: 1 vs 3 days, $P = .001$). Participants with rebound were less likely to be seropositive (15% vs 51%, $P < .001$). There was no difference in Delta versus non-Delta variant frequency (29% vs 25%, $P = .68$) or in having any immunocompromising condition (32% vs 24%, $P = .29$, participants with vs without rebound). However, participants with rebound to at least 5 $\log_{10}$ copies/mL were more likely to have an immunocompromising condition (62% vs 24%, $P = .005$) (Supplementary Table 4).

Symptom Rebound

Seventy-five percent (292/390) of participants in the amubarvimab-romlusevimab arm and 72% (282/390) in the placebo arm achieved sustained symptom improvement. Among participants who had symptom improvement, symptom rebound occurred in 22 of 292 (7.5%) amubarvimab-romlusevimab and 20 of 282 (7.1%) placebo recipients (Supplementary Table 5). There was no difference in risk of symptom rebound by treatment arm (hazard ratio, 0.95 [95% confidence interval, .52–1.75]; $P = .87$; Supplementary Figure 3). Individual participant symptom rebound experiences are summarized in Supplementary Figure 4. Three participants (2 amubarvimab-romlusevimab, 1 placebo) were hospitalized after achieving symptom improvement—both of the amubarvimab-romlusevimab participants for non-COVID-19–related reasons, and the placebo participant for worsening COVID-19.

Co-occurrence of Viral and Symptom Rebound

Less than 1% of participants in each arm experienced both symptom and viral rebound (Supplementary Table 6).

DISCUSSION

In this analysis of viral and symptom rebound following treatment with blinded combination anti-SARS-CoV-2 mAbs amubarvimab-romlusevimab versus placebo, we found no difference in viral rebound rates (4.6% vs 5.0%) when examining available vRNA levels or when imputing hospitalization as viral rebound (5.1% vs 6.7%). This contrasts with the greater risk of viral rebound with nirmatrelvir-ritonavir compared to no treatment that has been reported in observational cohorts [3, 12, 13] and post hoc analyses of RCTs (although generally no statistically significant difference in rebound has been identified with nirmatrelvir-ritonavir vs placebo across most comparisons from RCTs) [10, 11]. The lack of increase in viral rebound may be explained by the longer half-life of amubarvimab-romlusevimab (~17 days vs ~6 hours for nirmatrelvir-ritonavir) [8, 14].

Viral rebound rates were influenced by the rebound definition, particularly level of vRNA at rebound, more than degree of increase in vRNA. Given this, that 0.5 $\log_{10}$ increase represents a substantial increase in viral replication, and that little difference was observed in rebound rates when requiring

Table 1. Participant Characteristics by Viral Rebound Status in Primary Analysis Population

Characteristic	Participants With Rebound (n = 34)	Participants Without Rebound (n = 679)	*P* Value[a]
Age, y	48 (39, 61)	48 (39, 58)	.74
Sex			
Female	16 (47)	353 (52)	.60
Male	18 (53)	326 (48)	
Race			
Asian	0 (0)	32 (5)	.42
Black or African American	4 (12)	127 (19)	
Multiple	0 (0)	5 (1)	
Native Hawaiian or other Pacific Islander	0 (0)	1 (<1)	
Other	3 (9)	26 (4)	
White	27 (79)	488 (72)	
Ethnicity			
Hispanic or Latino	22 (65)	329 (48)	.08
Not Hispanic or Latino	12 (35)	350 (52)	
Body mass index, kg/m^2	29.6 (24.8, 36.8)	29.8 (26.0, 35.7)	.75
BMI ≥30 kg/m^2	16 (47)	325 (48)	
Missing	0	8	
Comorbidities			
Hypertension	14 (41)	263 (39)	
Diabetes	8 (24)	100 (15)	
Cardiovascular disease	1 (3)	35 (5)	
Chronic lung disease (asthma or other)	6 (18)	92 (14)	
Malignancy	0 (0)	9 (1)	
Cirrhosis	0 (0)	3 (<0.5)	
Chronic kidney disease	0 (0)	2 (<0.5)	
Immunocompromised status			
None	23 (68)	513 (76)	.26
Mild	7 (21)	125 (18)	
Moderate	4 (12)	32 (5)	
Severe	0 (0)	9 (1)	
Any immunocompromising condition (mild or worse)	11 (32)	166 (24)	.31
Current smoking (cigarette)	9 (27)	194 (29)	.37
Days from symptom onset to randomization	4 (3, 7)	6 (4, 7)	.11
≤5	20 (59)	333 (49)	.29
>5	14 (41)	346 (51)	
Days from positive SARS-CoV-2 test to randomization	1 (1, 3)	3 (1, 5)	**.001**
History of SARS-CoV-2 vaccination	2 (6)	63 (9)	.76
Variant			
Delta	10 (29)	128 (25)	.68
Non-Delta	24 (71)	377 (75)	
Missing	0	174	
Serum anti-N antibody	0.08 (0.07, 0.11)	0.10 (0.07, 3.69)	**.002**
Negative	30 (94)	434 (69)	**.002**
Positive	2 (6)	193 (31)	
Missing	2	52	
Serum anti-S antibody	0.3 (0.3, 0.3)	0.3 (0.3, 74.6)	**<.001**
Negative	29 (88)	347 (55)	**<.001**
Positive	4 (12)	281 (45)	
Missing	1	51	
Anti-N or anti-S antibody			
Negative	28 (85)	308 (49)	**<.001**
Positive	5 (15)	320 (51)	
Missing	1	51	
Day 0 total symptom score	10 (6, 15)	10 (6, 15)	.52
Day 0 viral RNA level (log_{10} copies/mL)	4.8 (3.8, 6.7)	3.7 (1.7, 5.7)	**.013**
Not detected	2 (6)	140 (22)	
Detected, <LLoQ	2 (6)	58 (9)	
≥ LLoQ	27 (87)	426 (68)	
Missing	3	55	
Viral RNA level at rebound (log_{10} copies/mL)	4.5 (3.5, 5.4)	NA	

Data are shown as median (1st and 3rd quartiles) or No. (%). Viral rebound was defined as viral RNA level ≥3 log_{10} copies/mL and ≥0.5 log_{10} copies/mL higher at day 7, 14, or 28 compared to day 3 or at day 14 or 28 compared to day 7.

Abbreviations: BMI, body mass index; LLoQ, lower limit of quantification; N, nucleocapsid; NA, not applicable; S, spike; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Characteristics were compared between participants with and without rebound using Wilcoxon rank-sum tests (continuous variables), χ^2 tests (variables with >2 categories), or Fisher exact tests (variables with 2 categories). Significant ($P < .05$) between-group differences are bolded.

rebound to 4 versus 5 log_{10} copies/mL (and vRNA levels to this degree are associated with culture positivity), we suggest that a reasonable, clinically meaningful definition of viral rebound would be at least 0.5 log_{10} increase in vRNA to at least 4 log_{10} copies/mL when using infrequent nasal sampling as in this trial.

We also found that viral rebound occurred in both the treated and untreated population and that risk factors for rebound were similar across these groups. The association of fewer days from test positivity, higher viral levels, and serostatus at entry with occurrence of viral rebound highlights the natural phenomenon of fluctuating vRNA levels in the first 10–14 days of acute COVID-19, likely reflecting the interaction between host immunologic response and virus prior to definitive immunologic control. That restricting to higher-level rebound enriched for immunocompromised persons in the rebound group further emphasizes the role of immune control in vRNA levels, independent of treatment.

We found that mAb therapy had no impact on risk of symptom rebound, and co-occurrence of both viral and symptom rebound in the same individual was rare. These data confirm prior reports that symptom fluctuations are common in the natural history of COVID-19 and may often be unlinked to viral detection and rebound [3, 6, 7, 13]. Symptom rebound rates were low, as reported with nirmatrelvir-ritonavir in the EPIC-HR trial [11]. Furthermore, the transience of the increased

vRNA levels and the rarity of co-occurring viral and symptom rebound raises questions as to the clinical significance of most viral rebound.

Strengths of this analysis include standardized, systematic collection of nasal swabs and randomized treatment comparison, providing a better estimate of both natural rates of viral rebound and treatment effects with minimized bias. Limitations include multiple comparisons, the rebound definition assuming vRNA levels peaked by day 3, and the analysis population being mostly unvaccinated and experiencing COVID-19 during the pre-Omicron period of the pandemic; it is uncertain if similar associations would be found in contemporary populations with higher rates of vaccination and if prior immunity from either vaccination or infection may affect viral and symptom rebound rates. The findings are, however, consistent with mechanisms of rebound suggested by the limited available reports of viral rebound with and without other antiviral therapies during Omicron.

This analysis demonstrates that, unlike short-acting direct antivirals, mAbs do not appear to confer any increased risk of viral rebound, viral and symptom fluctuations will occur with or without treatment, and lesser immunity/immunosuppression may increase risk of clinically relevant viral rebound.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Author contributions. K. W. C. and D. M. S.: Study design and analytic plan development, drafting of manuscript. B. M.: Analytic plan development and statistical analysis. C. M.: Study design, analytic plan development, statistical analysis, drafting of manuscript. J. Z. L., J. S. C., and J. J. E.: Study design and analytic plan development, manuscript edits. T. H. E., A. C. J., and D. M.: Parent study design, review of manuscript. J. R.: Parent study design, statistical analysis, drafting of manuscript. D. A. W. and E. S. D.: Parent study design, manuscript edits. M. D. H.: Study design, analytic plan development, statistical analysis, manuscript edits.

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Data sharing. The authors confirm that all data underlying the findings are fully available. Due to ethical restrictions the data are subject to restricted access. Access can be requested by submitting a data request at https://submit.mis.s-3.net/ and will require the written agreement of the ACTG and the manufacturer of the investigational product. Requests will be addressed as per ACTG standard operating procedures. Completion of an ACTG data use agreement may be required.

Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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