REGENERON

RECOMMENDATION

There is insufficient evidence to recommend the use of REGN-COV2 (casirivimab/imdevimab) as treatment for COVID-19 infection *(Low quality of evidence)*

Consensus Issues

The study included in this review is only an interim analysis of data from 275 non-severe COVID-19 patients. Complete results from ongoing studies are needed to better determine the effectiveness of regeneron as treatment for COVID-19 infection. The availability and cost of this intervention must also be considered. No mortality and only serious adverse events such as hypertension and hypoxia were reported.

EVIDENCE SUMMARY

Should regeneron (monoclonal antibody cocktail) be used in the treatment of COVID-19?

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Key Findings

Interim data from one ongoing RCT comparing REGN-COV2 monoclonal antibody cocktail (casirivimab and imdevimab) with placebo showed a significant reduction in viral load after 7 days of treatment with REGN-COV2 among non-hospitalized, non severe patients. Lesser COVID-19 related medically attended visits were noted in the treatment group, but this did not reach statistical significance. The incidence of adverse events was balanced between the treatment and the placebo groups. Due to very serious imprecision, the certainty of evidence regarding the effectiveness of Regeneron remains low. There are currently 6 ongoing clinical trials on the use of REGN-COV2 as treatment of COVID-19.

Introduction

COVID-19 hypoxemia has been theorized to be related to an immune hyperresponsiveness to viral infection. With recent studies showing high viral titers among hospitalized patients with hypoxemia, it is hypothesized that treatments that effectively reduce viral load could prevent complications and death resulting from COVID-19 infection [1-2]. One such treatment that has shown favorable effects from in vitro studies is Regeneron or REGN-COV2, an antibody cocktail containing two non-competing SARS-COV2-neutralizing human IgG1 antibodies (casirivimab [REGN10933], imdevimab [REGN10987]). By targeting the receptor-binding domain of the SARS-

CoV-2 spike protein, viral entry into human cells through the angiotensin-converting enzyme 2 (ACE2) receptor is prevented [3-4].

Review Methods

We performed a comprehensive systematic search of the literature from three electronic databases, Medline, CENTRAL and COVID-19 Living Evidence Database. We also searched for ongoing clinical trials using ClinicalTrials.gov and Clinicaltrialsregister.eu. We did freehand search using Google to check for other sources of information. Search was conducted using the following search terms: COVID-19, SARS-CoV-2, Regeneron monoclonal antibody, REGN-COV2, REGN10987, imdevimab, casirivimab, REGN10933. Potentially relevant articles were appraised for eligibility based on the following inclusion criteria:

Population	COVID-19 patients any severity, any age
Intervention/Exposure	Regeneron monoclonal antibody or REGN-COV2, REGN10987 or imdevimab or casirivimab or REGN10933
Comparison	Standard of Care or placebo
Outcomes	Mortality, clinical deterioration/ development of ARDS, need for mechanical ventilation, hospital length of stay, time to clinical improvement/ recovery, improvement in Chest CT Scan/ X-ray, virologic clearance by PCR test, adverse effects, cost
Methodological filter	Randomized controlled trials (RCT), observational, Clinical studies, systematic review and meta-analysis available, case series

Results

Characteristics of included studies

A total of 25 related articles were found using MEDLINE but only 1 article met our inclusion criteria. We found the same article using CENTRAL, which yielded 4 related articles. The same article was found in COVID-19 Living Evidence Database. The only included study was an interim analysis of data from 275 patients in the phase 1-2 portion of the ongoing multicenter, randomized, double blind, placebo controlled trial (NCT04425629). This RCT aims to recruit 6420 symptomatic or asymptomatic non-hospitalized COVID-19 patients who have received SARS-CoV-2 positive results no more than 72 hours before randomization, had onset of symptoms no more than 7 days before randomization, had ≥93% O_2 saturation on room air, and had not received any other putative COVID-19 therapies [5].

The study assessed the virologic efficacy, clinical efficacy, and safety and tolerability of REGN10933+REGN10987 combination therapy compared to placebo. Virologic efficacy was defined as the time-weighted average change of viral load through day 7 (log_{10} scale) measured through RT-PCR testing of nasopharyngeal swab samples, while clinical efficacy was measured through the proportion of patients with one or more medically attended visits.

Overall quality of evidence

The quality of evidence was assigned a GRADE rating of low due to very serious imprecision.

Outcomes

The results showed a significant reduction in viral load in the combined low- and high-dose group with -0.41 log_{10} copies per milliliter (95% CI, -0.71 to -0.10) and high dose REGN-COV2 -0.56 log_{10} copies per milliliter (95% CI, -0.91 to -0.21) compared to placebo. There was also a trend of reduction in viral load in the low-dose group with -0.25 log_{10} copies per milliliter (95% CI, -0.60 to 0.10) however this did not reach statistical significance. The proportion of patients who had medically attended visits was lower in the REGN-COV2 group compared to the placebo group (6/182 or 3% vs. 6/93 or 6%; absolute difference = 3%; 95% CI -16 to 9%), but this difference did not reach statistical significance.

Both low and high doses for REGN-COV2 were associated with fewer number of adverse effects, which were mainly low-grade toxic effects. The incidence of serious adverse events and adverse events of special interest (i.e. scientific and medical concern specific to the sponsor's product or program) that occurred or worsened during the observation period were comparable for the combined REGN-COV2 dose groups and the placebo group. Serious adverse events were reported in two (1 hypertension and 1 hypoxia) of 93 patients (2%) in the placebo group, two (1 vomiting and 1 nausea) of 88 patients (2%) in the low dose REGN-COV2 group, and none in the high dose group. Adverse events of special interest were noted in five (vomiting, nausea, rash, dizziness and headache) of 93 (5%) patients in the placebo group and five (abdominal pain, pruritus, urticaria, chills and flushing) of 88 (6%) in the high dose REGN-COV2 group and none in the low dose group.

Recommendations from Other Groups

The IDSA (2 March 2021) suggests bamlanivimab/etesevimab rather than no bamlanivimab/etesevimab for ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease [6]. IDSA further added bamlanivimab monotherapy or casirivimab/imdevimab may have similar clinical benefit, but data are more limited [6].

The European Medicines Agency (26 February 2021) states that REGN-COV2 can be used for the treatment of confirmed COVID-19 in patients who do not require supplemental oxygen and who are at high risk in progressing to severe COVID-19 [7].

There were no recommendations from the World Health Organization on the use of REGN-COV2 in the treatment of COVID-19.

Research Gaps

There are currently 5 ongoing randomized clinical trials on REGN-COV2 as treatment for COVID-19 (Appendix 3).

References

[1] Blanco-Melo D, Nilsson-Payant BE, Liu WC, et al. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. Cell 2020;181(5):1036-1045.e9.

[2] Wölfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. Nature 2020;581:465-9.

[3] Baum A, Fulton BO, Wloga E, et al. Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies. Science 2020;369:1014-8.

[4] Hansen J, Baum A, Pascal KE, et al. Studies in humanized mice and convales- cent humans yield a SARS-CoV-2 antibody cocktail. Science 2020;369:1010-4.

[5] Weinrich D, Sivapalasingam S. et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with COVID-19. NEJM 2021; 384(3): 238-51

[6] Bhimraj A, Morgan R. et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. www.idsociety.org/COVID19guidelines [Accessed March 5, 2021]

[7] European Medicines Agency. EMA issues advice on use of REGN-COV2 antibody combination (casirivimab / imdevimab). https://www.ema.europa.eu/en/news/ema-issues-advice-use-regn-cov2-antibody-combination-casirivimab-imdevimab [Accessed April 4, 2021]

Appendix 1: Characteristics of Included Studies

Author, Year	Patients (n)	Intervention	Comparator	Outcomes	Study Design
Weinreich 2021	Ambulatory confirmed COVID-19 patients (n=275)	REGN-COV2 MAB Cocktail (Casirivmab and Imdevimab)	Placebo	Virologic efficacy Clinical efficacy Adverse effects	RCT

Appendix 2: GRADE Evidence Profile

Author(s): Antonio L. Faltado Jr. MD, Anna Angelica Macalalad-Josue, MD
Question: REGN-COV2 (MAB Cocktail) compared to Placebo for COVID-19
Setting:
Bibliography: Weinrich D, Sivapalasingam S. et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with COVID-19. NEJM 2021; 384(3): 238-51

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	REGN-COV2 (MAB Cocktail)	Placebo	Relative (95% CI)	Absolute (95% CI)		
At least one COVID-19-realted Medically Attended visit within 29 days (follow up: 29 days)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	6/182 (3.3%)	6/93 (6.5%)	**RR 0.51** (0.17 to 1.54)	**32 fewer per 1,000** (from 54 fewer to 35 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Time-weighted average change in viral load from day 1 through day 7 (follow up: 7 days)												
1	randomised trials	not serious	not serious	serious [b]	not serious	none	143	78	-	MD **0.41 log10 copies/ml lower** (0.71 lower to 0.1 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT
Adverse Events												
1	randomised trials	not serious	not serious	not serious	very serious [a,c]	none	2/176 (1.1%)	2/93 (2.2%)	**RR 0.53** (0.08 to 3.69)	**10 fewer per 1,000** (from 20 fewer to 58 more)	⨁⨁◯◯ LOW	IMPORTANT
Serious Adverse Events												
1	randomised trials	not serious	not serious	not serious	very serious [a,c]	none	1/176 (0.6%)	2/93 (2.2%)	**RR 0.26** (0.02 to 2.88)	**16 fewer per 1,000** (from 21 fewer to 40 more)	⨁⨁◯◯ LOW	IMPORTANT
Adverse Events of Special Interest												
1	randomised trials	not serious	not serious	not serious	very serious [a,c]	none	5/176 (2.8%)	5/93 (5.4%)	**RR 0.53** (0.16 to 1.78)	**25 fewer per 1,000** (from 45 fewer to 42 more)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. The confidence interval includes potential benefit and harm
b. Measure of viral clearance is a surrogate outcome for hospital admission, need for intensive care, intubation, and death.
c. Few events suggest the fragility of estimates

Appendix 2: Table of Ongoing Studies

Clinical Trial Identifier/Title	Study Design	Country	Population	Intervention	Outcome	Estimated Date of Completion
NCT04790786 Evaluation of Monoclonal Antibodies in COVID 19	Prospective Cohort	USA	COVID-19 positive patients	Lilly Bamlanivimab vs Regeneron Casivirimab+ Imdevimab Vs Lilly Bamlanivimab + Etesevimab	Alive and free from hospitalization	Feb 20, 2022
NCT04425629 Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for the Treatment of Ambulatory Adult and Pediatric Patients With COVID-19	Randomized controlled trial	USA	COVID-19 positive patients ≥93% o2 saturation on room air	Regeneron single dose vs placebo	Serious adverse events, time weighted average change from baseline in viral load, cumulative incidence of hospital visit and all cause death	April 10, 2021
NCT04426695 Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for Hospitalized Adult Patients With COVID-19	Randomized controlled trial	USA	COVID-19 positive patients, symptoms compatible with COVID-19, hospitalized less than 72 hrs, with or without oxygen requirement	Regeneron single dose vs placebo		April 16, 2021

NCT04666441 COVID-19 Study Assessing the Virologic Efficacy of REGN10933+REGN10987 Across Different Dose Regimens in Adult Outpatients With SARS-CoV-2 Infection	Randomized controlled trial	USA	COVID-19 positive patients, low risk	Regeneron vs placebo	Time-weighted average daily change from baseline in viral load	Aug 13, 2021
NCT04519437 Study Assessing the Safety, Tolerability, Pharmacokinetics, and Immunogenicity of Repeated Subcutaneous Doses of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies (REGN10933+REGN10987) in Adult Volunteers as Related to COVID-19	Randomized controlled trial	USA	Healthy individuals with no COVID-19	Regeneron vs placebo	Adverse events of special interests	October 25, 2021
NCT04452318 COVID-19 Study Assessing the Efficacy and Safety of Anti-	Randomized controlled trial	USA	Asymptomatic patients RT PCR negative at baseline with household contact	Regeneron vs placebo	Proportion of participants who have a positive SARS-CoV-2 RT-qPCR (based	June 15, 2021

Spike SARS CoV-2 Monoclonal Antibodies for Prevention of SARS CoV-2Infection Asymptomatic in Healthy Adults and Adolescents Who Are Household Contacts to an Individual with a Positive SARS-CoV-2 RT-PCR Assay			exposure to a known COVID-19 confirmed patients.		on central lab test) and signs and symptoms (strict-term) of SARS-CoV-2 infection during the Efficacy assessment period (EAP) Proportion of participants who have a RT-qPCR confirmed SARS-CoV-2 infection (either symptomatic or asymptomatic) during the EAP Incidence and severity of treatment-emergent adverse events (TEAEs)	