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The Role and Mechanism of Action of Regdanvimab in the Treatment of COVID-19

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Abstract: The neutralizing antibody can be one of the promising treatments to fight the COVID-19 pandemic, based on the previous coronavirus outbreak. Regdanvimab (CT-P59) is a new monoclonal antibody developed by Celltrion that targets the receptor-binding domain (RBD) in the spike protein of SARS-CoV-2. The purpose of this literature review is to explore the various features of regdanvimab, inclusing chemical structural, mechanism of action, pharmacokinetics and efficacy. After the previous monoclonal antibodies (mAbs) approved by WHO, casirivimab, and imdevimab, regdanvimab has now received its first approval as the COVID-19 treatment in elderly patients aged >50 years old or at least one medical condition, including obesity, cardiovascular disease, chronic lung disease, diabetes, and ongoing immunosuppressive agents, and adult patients with moderate symptoms in South Korea. The attachment of regdanvimab to the RBD directly covers the SARS-CoV-2 binding surface area to the ACE2, which eventually inhibits the virus recognition and entry into the host cell. Therefore, regdanvimab can be used to reduce the viral titer in combination with the present antiviral therapies. The clinical trials of regdanvimab reported that a single intravenous administration of regdanvimab is associated with a shorter recovery time and a lower hospital admission and oxygen therapy requirement than the placebo. These studies signify the important role of regdanvimab as an anviral of patients infected with SARS-CoV-2.

Keywords: regdanvimab, CT-P59, monoclonal antibody, COVID-19 therapy.

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Introduction

The novel coronavirus disease 2019 (COVID-19) was reported first in late December 2019 in Wuhan (Tillett et al., 2021). The viral isolation and genomic identification were revealed to be closely related to the severe acute respiratory syndrome coronavirus (SARS-CoV) and thus named SARS-CoV-2 (Lu et al., 2020). Similar to patients infected by SARS-CoV in 2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, individuals who SARS-CoV-2 infected showed several symptoms including fever, dry cough headache, dyspnoea, and pneumonia (Liu et al., 2020). However, the SARS-CoV-2 has spread much more rapidly than SARS-CoV and MERS-CoV, eventually leading to a pandemic declaration on March 11, 2020 (Li et al., 2020). As of 12 October 2023, WHO recorded over 771 million confirmed cases and 6 million deaths worldwide (WHO 2023). COVID-19 not only has caused a spike in morbidities and mortalities but also severely

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affects the global economy due to the strict measures made to restrain the spread of the disease (Nicola et al., 2020). Therefore, the scientist has been conducting numerous researches to identify the most appropriate treatment to ease the burden of the pandemic.

Based on the previous coronavirus outbreak data, one of the treatment options that was found promising was passive immunization. The neutralizing antibody found in the convalescent plasma was considered best suited for reducing viral load in combination with antiviral therapy due to its mechanism of action. However, studies have reported inconsistent mortality and clinical benefit (Snow et al., 2021; Kloypan et al., 2021) and other limitations (Zhao et al., 2020) of convalescent plasma therapy. Therefore, monoclonal antibodies (mAbs) are an excellent alternative to meet neutralizing antibodies' medical demands.

A combination of two mAbs, casirivimab and imdevimab, has now been approved by WHO as the treatment option for COVID-19 for non-severe patients (the condition being high risk of severe disease) and the severe and critically ill patients (the condition being seronegative status) (WHO 2021). A novel mAb, regdanvimab (CT-P59), is found to be effective against various SARS-CoV-2 variants, including the D614G. Regdanvimab binds to the receptor-binding domain (RBD) of the SARS-CoV-2, interrupting the binding of the virus to its cellular receptor, angiotensin-converting enzyme 2 (ACE2). The binding orientation of regdanvimab is reported to be different from the previous neutralizing mAbs targeting SARS-CoV-2 RBD, suggesting that regdanvimab can be a new promising neutralizing antibody option for COVID-19 (Kim et al., 2021). This review describes recent evidence of regdanvimab from the basic biological activity, the molecular properties and focus on the role of regdanvimab as part of the pharmachotherapy modality in treatment of COVID-19.

METHODS

There are several important questions need to be addressed. First, is there any potentional specific protein within the SARS-CoV-2 virus that can be targeted. Next, what will be the implication if the target can be succesfully identified and modulated. This will lead to another important question, is there any biological agent that can specifically targeted the virus protein. To address these questions, we explore the relevant studies from various platform including PubMed and Google Scholar by the following keywords: regdanvimab, CT-P59, monoclonal antibody, COVID-19 therapy. We, then, summarize the relevant studies as narrative review.

THE BIOLOGY OF SARS-COV-2

Spike Protein as Primary Target of Regdanvimab

SARS-CoV-2 is a non-segmented, single-stranded positive-sense RNA virus covered by an envelope made of crown-like spikes on the outer surface (Qamar et al., 2020). It belongs to the beta-coronaviruses group of the Coronavirinae subfamily and the Coronaviridae family (Pal et al., 2020). The genome of the SARS-CoV-2 was reported as over 80% identical to the previous SARS-CoV and 96% identical to the bat coronavirus RaTG13. Therefore, bats were thought to be the possible primary reservoir (Wu et al., 2020). SARS-CoV-2 consists of four main structural proteins and sixteen accessory proteins. The four structural proteins are the nucleocapsid (N) protein, spike (S) glycoprotein, small envelope (E) glycoprotein, and membrane (M) glycoprotein. The N protein forms a capsid outside the genome, whereas the other three make the envelope outside the capsid. The S protein is a transmembrane protein that forms homotrimers protruding on the viral outer surface and facilitates the binding of the virus to the receptor on the host cell. The M protein is the most structurally structured protein, which determines the shape of the virus envelope. And last, the E protein plays an essential role in virus production and maturation (Astuti & Ysrafil, 2020; Mohamadian et al., 2021).

Each S protein monomer consists of two functional subunits: receptor binding (S1) and cell membrane fusion (S2). The S1 subunit comprises the N-terminal domain (NTD) and the receptor-binding domain (RBD). The RBD plays an essential role in viral pathogenesis as it directly binds to the ACE2 receptors found in various organs, such as the lungs, heart, kidneys, and intestines. Both RBD and NTD are the most often used as the target of many monoclonal antibodies for COVID-19 therapy (Habli et al., 2021). The S2 subunit contains several peptides, such as fusion peptide (FP), heptad repeat 1 (HR1), central helix (CH), connector domain (CD), heptad repeat 2 (HR2), transmembrane domain (TM), and cytoplasmic tail (CT), that mediates the fusion of the virus and the host membranes (Wang et al., 2020). The border between S1 and S2 subunits is called S1/S2 protease cleavage site. This site will be cleaved by the host protease to activate the protein and start the fusion of the virus membrane with the host through irreversible conformational change (Walls et al., 2020; Wrapp et al., 2020). The cleavage of this site will only begin after the RBD binds to the N-terminal peptidase of ACE2 on the host cell (Yan et al., 2021).

The Complex of SARS-CoV-2 RBD and ACE2

RBD has two structural parts, which are the core and the extended insertion. The core domain, which is highly preserved, comprises five β strands (β1, β2, β3, β4, and β7) formed in an antiparallel manner with a disulfide bond between two strands. Between the β4 and β7 strands, there is an extended insertion consisting of the loops, α4 and α5 helices, and the short β5 and β6 strands. This extended insertion is called receptor-binding motif (RBM), which contains the most contacting RBD residues that bind to ACE2 (Wang et al., 2020, & Lan et al., 2020). The RBD has nine cysteine residues, eight of which form four pairs of disulfide bonds. Three of the disulfide bonds are in the core for stabilizing the β sheet structure, whereas the last one connects the loops in the distal end of RBM (Lan et al., 2020). The RBD constantly switches between an open state for receptor binding and a closed state position for immune evasion (Shang et al., 2020). In open conformation, RBM protrudes to the surface, facilitating the attachment of SARS-CoV-2 to its receptor on the surface of ACE2. On the other hand, all three RBDs are covered by the NTD, making it hard for the host immune system to recognize and kill the virus (Walls et al., 2020). The prefusion spike protein undergoes a structural transformation after binding to the ACE2 receptor to the post-fusion isoform, forming a long needle-like shape (Baral et al., 2021).

ACE2 physiologically plays an essential role in regulating body fluid and blood pressure via the renin-angiotensin-aldosterone system pathway. Studies reported that RBD SARS-CoV-2 has a solid affinity for ACE2 receptors in humans, cats, ferrets, and other mammals with homologous receptors (Mohamadian et al., 2021). In humans, ACE2 is highly expressed in the lower respiratory tract, such as type II alveolar cells (AT2) of the lungs, upper esophagus, and stratified epithelial cells, and other cells such as myocardial cells, cholangiocytes, absorptive enterocytes from the ileum and colon, kidney proximal tubule cells, and urothelial bladder cells. Therefore, COVID-19 patients might experience not only respiratory symptoms, but also heart, kidney, and intestinal symptoms (Xu et al., 2020). SARS-CoV-2 RBD binds the ACE2 on its N-terminal peptidase. This N-terminal peptidase has two lobes, forming a peptide substrate binding site between the two lobes (Lan et al., 2020). The surface of RBM shapes concave to attach perfectly to the claw-like N-terminal peptidase on the outer surface of ACE2 (Shang et al., 2020). Despite having similarities, the SARS-CoV-2 RBD-ACE2 complex has a higher affinity than the complex of previously SARS-CoV RBD and ACE2. This probably explains why COVID-19 appears to be more contagious than the previous SARS-CoV outbreak (Lan et al., 2020).

REGDANVIMAB

Regdanvimab (Regkirona™) developed by Celltrion Inc., is a new recombinant human monoclonal antibody targeted against the SARS-CoV-2. Regdanvimab is reported to have an antiviral effect against SARS-CoV-2 in vitro, in vivo, and in clinical studies. It is associated with decreased disease progression regarding hospitalization and oxygen requirements (Baral et al., 2021). Through Emergency Use Authorization (EUA) in July 2021, the Indonesia Food and Drug Administration (BPOM) has permitted the emergency use of regdanvimab to treat adult patients confirmed with COVID-19 who do not require oxygen supplementation but are at high risk for progressing to a severe symptom (BPOM 2021). On September 17, 2021, regdanvimab received its first approval by the Korean Ministry of Food and Drug Safety (MFDS) as a treatment for COVID-19 in elderly patients aged >50 years old or at least one medical condition (obesity, cardiovascular disease, chronic lung disease, chronic kidney disease, diabetes, chronic liver disease, and ongoing immunosuppressive agent treatment) with mild symptoms of COVID-19 and adult patients with moderate symptoms of COVID-19 (MFDS 2021). Its recommended dosage is 40 mg/kg, administered in a single intravenous infusion within 60 minutes (Celltrion 2020).

Screening

Regdanvimab was identified by screening the antibody library from the sera of South Korean convalescent patients and selecting those with the highest affinity to SARS-CoV-2 RBD. Regdanvimab was assessed in vitro plaque reduction neutralization test (PRNT) for its neutralization potency against the wild SARS-CoV-2 and D614G variant. Regdanvimab was reported to considerably inhibit viral replication with a low half-maximal inhibitory concentration (IC50) at 8.4 ng/ml. Interestingly, regdanvimab could inhibit D614G variant replication in an even lower IC50 at 5.7 ng/ml. A competitive binding assay using biolayer interferometry (BLI) reported that regdanvimab inhibited the binding between SARS-CoV-2 RBD and ACE2 completely. Further investigation on the new SARS-CoV-2 mutant variants revealed that regdanvimab still competitively inhibits the attachment of their RBD to the ACE2 on the host cell (Zhang et al., 2021). The binding of regdanvimab to other coronaviruses, including SARS-CoV, HCoV-HKU1, and MERS-CoV, was also evaluated using BLI. This investigation indicated that regdanvimab binds specifically to SARS-CoV-2. In addition, regdanvimab was reported to have a high

affinity with SARS-CoV-2 RBD, with a KD value of 27 pM (European Medicines Agency 2021).

Mechanism of Action

An in vitro study was conducted to investigate the crystal structure of the regdanvimab-RBD complex using X-ray crystallography at 2.7 Å resolution. The structure shows that regdanvimab interacts with SARS-CoV-2 RBD at its RBM (Figure 1a). The attachment angle of regdanvimab to the RBD is different from the previously reported neutralizing antibodies targeting RBD, which indicates that the epitopes of regdanvimab might differ from the other antibodies (Figure 1b). Further analysis reveals that the binding of regdanvimab and RBD is mediated by all three complementary determining regions (CDRs) of the heavy chain. In total, 16 residues from the heavy chain of regdanvimab bind to 19 residues of the RBD. The CDR H3 forms eight hydrogen bonds and hydrophobic interactions in the middle of the ACE2-binding surface that play a crucial role in the regdanvimab-RBD complex attachment. On another side, the light chain shows marginal interaction with RBD where only three residues of CDR L1 and L2 attach with four residues of RBD (Kim et al., 2021).

The blocking RBD and ACE2 interaction by regdanvimab is then further analyzed by making a superimposed regdanvimab-RBD complex on the RBD-ACE2 complex. This superposition structure shows that the heavy chain of regdanvimab completely overlaps the ACE2 protein, whereas the light chain overlaps partially with the receptor. Consistent with this structure, there are considerable overlaps between the regdanvimab and ACE2-binding surface area to the SARS-CoV-2 RBD. Twelve of 21 contacting RBD residues to the ACE2 are also involved in interacting with regdanvimab (Kim et al., 2021). In conclusion, the bond between regdanvimab and RBD SARS-CoV-2 covers the opened-state RBD by directly closing the SARS-CoV-2 binding surface area to the ACE2 and thus preventing the virus recognition and entry into the host cell (European Medicines Agency 2021). This antiviral activity also appears to be found on the new SARS-CoV-2 variants, D614G and other variants, associated with higher transmissibility, immune evasion, and increased mortality (Kim et al., 2021).

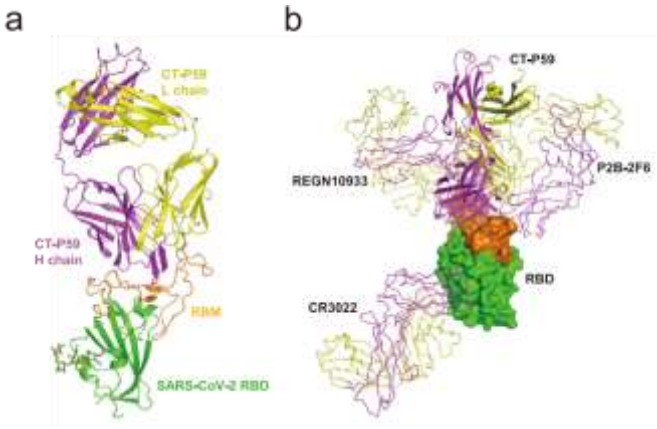

Figure 1. **a**. The overall structure of the regdanvimab-RBD complex. The RBD core subdomain is green, while the RBM subdomain is orange. The heavy and light chains of regdanvimab are respectively magenta and yellow. **b**. Several neutralizing antibodies in complex with RBD. The RBD is shown in a surface model. Regdanvimab is in a cartoon, while the others are in ribbon models. [From Kim C, Ryu D-K, Lee J, Kim Y-I, Seo J-M, Kim Y-G, et al. A therapeutic neutralizing antibody targeting receptor binding domain of SARS-CoV-2 spike protein. Nat Commun. 2021 Dec;12(1):288]

Pharmacokinetics

The pharmacokinetics of regdanvimab were assessed through all three clinical studies. Over a dose range of 20-80 mg/kg, regdanvimab reported dose-proportional pharmacokinetics with maximum plasma concentration increasing in a more significant than the dose-proportional manner (Kim et al., 2021). Regdanvimab is reported to have low clearance, small volume distribution, and 12 days terminal half-life. Regdanvimab is likely eliminated through the normal immunoglobulin degradation pathway, and the clearance is not expected to be dependent on renal or hepatic function. And therefore, it is expected to have minimal or no interaction with other drugs. The incidence of the drug hypersensitivity reaction is also reported to be low (Park et al., 2022).

Efficacy

In vivo antiviral efficacy was analyzed in three animal models: ferrets, hamsters, and monkeys. The ferret study was conducted through administration of intranasal and intratracheal, followed by intravenous regdanvimab at one day post-infection. The study reported a significantly reduced virus titer in the nasal wash, lung tissue, and rectal swab. This viral load reduction was consistent with improved clinical symptoms and lung pathology. Regdanvimab was further analyzed by comparing it with daily

administration of remdesivir for five consecutive days. Ferrets treated with remdesivir showed a slower viral clearance than the regdanvimab-treated ferrets. The hamster and monkey study reported a similar result. After a single administration of intraperitoneal and intravenous regdanvimab, no infectious virus was detected in the upper and lower respiratory tract (Kim et al., 2021). Additional mice studies involving Gamma and Delta variants reported symptom remission and viral elimination after a single intraperitoneal administration of regdanvimab (Ryu et al., 2021). Another study reported a viral titer reduction in ferrets infected with Beta variants in both nose and lung wash, consistent with no weight loss compared to placebo (Ryu et al., 2021).

Phase I trial of regdanvimab with a single ascending dose of 20, 40, and 80 mg/kg in adult COVID-19 patients with mild symptoms reported a reduction of viral titers in nasopharyngeal swabs up to day 14. Regdanvimab was also associated with a faster mean recovery time (3.39 days) than placebo (5.25 days) (30). Phase II/III trial was then conducted on adult COVID-19 patients confirmed with RT-PCR, with oxygen saturation >94% on room air and not requiring oxygen supplementation, and the onset of symptoms within 7 days before trial. Patients were randomly administered with 40 or 80 mg/kg regdanvimab as 90 minutes IV infusion, or placebo. The time recovery for regdanvimab treated patients (5.79 days) was significantly shorter than placebo (8.77 days). It was consistent with the decreased time needed for conversion to negative RT-PCR on patients treated with regdanvimab (5.96 days) compared to placebo (8.92 days). On 28 dpi, patients treated with regdanvimab were associated with a lower hospitalization and oxygen therapy requirement than placebo (Streinu-Cercel et al., 2021).

Apart from the clinical trials, a systematic review reported that regdanvimab with a 40 mg/kg dose decreased hospital admission and death in mild to moderate COVID-19 symptoms compared to placebo (Kreuzberger et al., 2021). In a retrospective cohort study in high-risk mild and moderate COVID-19 patients, regdanvimab treatment was associated with reducing disease aggravation, including death without increasing adverse reactions compared to no regdanvimab treatment. In addition, fewer patients treated with regdanvimab were treated with remdesivir, azithromycin, lopinavir/ritonavir, or corticosteroids (Heo et al., 2021).

Future Development

The Celltrion is currently developing a neutralizing antibody therapy with regdanvimab against the emerging SARS-CoV-2 variants. In collaboration with Inhalon Biopharma, Celltrion is also developing a nebulized form of regdanvimab using a muco-trapping antibody platform to treat COVID-19 patients at home. This new formulation antibody is expected to directly trap the virus in the air mucus and eventually prevent the local spread of the virus infection. The neutralized virus is then expected to be eliminated from the airway tract through the body's natural ability to clear mucus (Inhalon Biopharma 2021).

Conclusion

Regdanvimab is a new monoclonal antibody targeted against RBD in the spike protein of SARS-CoV-2. Regdanvimab can be used to reduce the viral load in combination with the present antiviral therapy. The attachment of regdanvimab to the RBD directly covers the SARS-CoV-2 binding surface area to the ACE2, which eventually inhibits the virus recognition and entry into the host cell. A single administration of regdanvimab is associated with shorter recovery time and a lower hospital admission and oxygen supplementation requirement in high risk mild and moderate symptoms of COVID-19 compared to placebo. Regdanvimab can be further developed as the treatment for the probable emerging SARS-CoV-2 variants as it is reported to have an antiviral activity to the current viral mutants. T

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