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Mini Review

A New and Effective Drug (Simnotrelvir) As A Treatment For COVID-19

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Introduction

(Figure 1) Simnotrelvir is an oral 3-chymotrypsin-–like protease inhibitor that has in vitro activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and potential efficacy in a phase II-III trial.

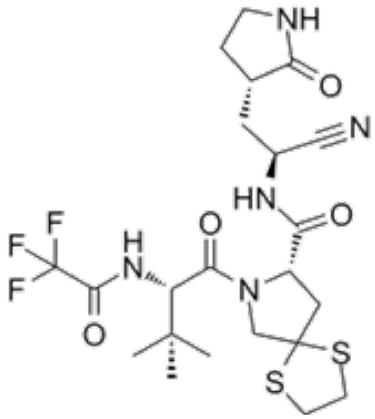

Figure 1: Simnotrelvir structure.

"Oral Simnotrelvir for Adult Patients with Mild to Moderate COVID-19" was published in The New England Journal of Medicine on January 18, 2024. The outcomes of these phase II-III clinical trials offer a fresh prospect for individuals of average means who are searching for alleviation from COVID-19. Administering simnotrelvir to individuals has demonstrated the ability to accelerate the recuperation process from mild to moderate illness by approximately 1.5 days. The drug Simnotrelvir (also known as SSD8432 or SIM0417) has been introduced into the market in China under the brand name XIANNUOXINTM. It is combined with ritonavir to treat adult patients with mild-to-moderate cases of COVID-19 [1].

The experimental study revealed that simnotrelvir, when ingested in oral tablets, exhibits a rapid onset of action, promptly alleviating symptoms such as fever, cough, and rhinorrhea. During the initial stages of the pandemic, antiviral medications were primarily evaluated in individuals who were at a heightened risk of experiencing severe symptoms of COVID-19. Currently, the World Health Organization advises that antiviral medications like Paxlovid, which is widely used to treat COVID-19 in the United States and other countries, should only be taken by individuals in high-risk categories. SARS-CoV-2 has now become a common respiratory virus among the general population. The researchers synergistically combined simnotrelvir with ritonavir, a constituent of Paxlovid, to inhibit the enzymatic degradation of simnotrelvir. The researchers conducted trials on over 600 individuals, with a median age of 35. Approximately half of the participants had at least one risk factor, such as obesity, that could lead to severe illness. None of the participants experienced severe cases of COVID-19. On the fifth day post-treatment, the levels of SARS-CoV-2 in participants who received simontrelvir decreased approximately 30 times more than those who received a placebo. Simnotrelvir's

capacity to enhance the pace of recovery in individuals with a standard risk profile resembles ensitrelvir, an antiviral medication that received conditional approval in Japan in November 2022. The drawbacks of simontrelvir closely resemble those of Paxlovid, encompassing an infamously unpleasant flavor and incompatibility with a variety of commonly used medications. Furthermore, the researchers requested that trial participants commence treatment within three days of the onset of symptoms.

The Concept Underlying the Novel Pharmaceutical

Coronaviruses possess similar components that present potential targets for therapeutic interventions, including spike glycoprotein, RNA-dependent RNA polymerase (RdRp), and 3C-like protease (3CLpro)1. 3CLpro and PLpro enzymes are accountable for splitting two viral polyproteins (pp1a and pp1ab) formed when host ribosomes translate the viral genomic RNA. This process produces nonstructural proteins crucial for viral replication. 11 cleavage sites for the 3CLpro enzyme exist within the polyproteins. Hence, 3CLpro is commonly known as the main protease (Mpro). The 3CLpro enzyme can identify specific substrates and cleave them adjacent to glutamine (Leu-Gln↓(Ser, Ala, Asn, Gly)). This ability sets coronavirus 3CLpro apart from similar human proteases, serving as a built-in mechanism to reduce the negative consequences of inhibiting 3CLpro. In contrast to the spike glycoprotein, which is susceptible to mutations, the structure of 3CLpro, especially the substrate binding cavity, remains highly conserved among various pathogenic coronaviruses, including SARS-CoV, Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2 and its variants of concern (VOCs) [2].

The Allure of the Emerging Field of Chemistry

Based on the crystal structures and thermodynamic binding signature of SARS-CoV-2 3CLpro with inhibitors, a process was conducted to optimize the hit-to-lead-to-candidate by replacing the warhead, P1, P2, and P4 segments of boceprevir. These modifications enhance the effectiveness against SARS-CoV-2 3CLpro. The resulting simnotrelvir compound exerts its potent antiviral activity in enzymatic and cellular assays through a covalent mode of action. This new compound has a strong binding affinity to the SARS-CoV-2 3CLpro enzyme and acts as a covalent inhibitor. Simnotrelvir can be administrated orally as an absorbable inhibitor of the 3-chymotrypsin-like protease (3CLpro) of SARS-CoV-2. It has successfully undergone preclinical assessment, paving the way for clinical trials and the conditional approval of simnotrelvir, combined with ritonavir, for treating COVID-19. Simnotrelvir demonstrated significant potency as a pan-CoV 3CLpro inhibitor, targeting a large group of proteases with shared ancestry in coronaviruses. Simnotrelvir exhibits a strong affinity for its intended target and selectively avoids unintended targets. It has a wide-ranging inhibitory effect on SARS-CoV-2 and other CoV 3CLpros. It effectively hinders the replication of SARS-CoV-2 and its variants in both cells and mice. The specific way simnotrelvir binds, and its thermodynamic characteristics have been accurately identified. Simnotrelvir is safe and demonstrates significant oral plasma concentrations when given alone or in conjunction with ritonavir, giving potent antiviral effectiveness in living organisms. These advantages enable simnotrelvir to undergo both preclinical and clinical evaluations successfully. The preclinical studies of simnotrelvir exhibited greater antiviral efficacy than nirmatrelvir, a 3CLpro inhibitor currently used for COVID-19 treatment. This result emphasizes the potential of simnotrelvir as a candidate for developing COVID-19 therapy. Based on these findings, the initial investigation of simnotrelvir in humans was conducted to evaluate its safety, tolerability, and pharmacokinetics. This evaluation involved administering single and multiple doses of simnotrelvir alone or in combination with ritonavir [3]. The authorized utilization of simnotrelvir, in conjunction with ritonavir, as an oral therapy not only provides a productive and enduring treatment approach for COVID-19 and other coronavirus ailments but also broadens the clinical implementation and importance of covalent peptidomimetic inhibitors that target viral proteases. The compound demonstrates favorable pharmacokinetic and safety characteristics in both male and female rats and monkeys, resulting in oral solid effectiveness in a male mouse model of SARS-CoV-2 Delta infection. It dramatically decreases the lung virus and completely eradicates it from the brain. The identification of simnotrelvir underscores the value of the structure-based design of potent protease inhibitors to develop a small molecule therapy that efficiently targets human coronaviruses.

First Results: Clinical Trial Fase I

On September 30th, 2023, the European Journal of Pharmaceutical Sciences published online, "A first-in-human phase 1 study of simnotrelvir, a 3CL-like protease inhibitor for the treatment of COVID-19, in healthy adult subjects" [4]. This clinical trial evaluates the safety, tolerability, and pharmacokinetics of dose escalations of simnotrelvir alone or with ritonavir (simnotrelvir or simnotrelvir/ritonavir) in healthy subjects, as well as the food effect (ClinicalTrials.gov Identifier: NCT05339646). The study results showed that simnotrelvir had good tolerance and low incidence of adverse effects (Aes), similar to the safety profiles of nirmatrelvir. All AEs were mild, and no serious AE was observed. In addition, no apparent trend could be found between these AEs and the simnotrelvir dose levels. Both simnotrelvir and nirmatrelvir are the substrates of CYP3A and can use CYP3A inhibitor of ritonavir as the pharmacokinetic enhancer. The co-administration of ritonavir increased the steady-state AUC of simnotrelvir by 9.4 times after multiple doses, similar to nirmatrelvir [5]. This was because both simnotrelvir and nirmatrelvir were mainly metabolized by CYP3A (86.7 % for simnotrelvir and 99 % for nirmatrelvir). In addition, simnotrelvir and nirmatrelvir were substrates of efflux transporter P-gp, and ritonavir may further increase their exposures by inhibiting the P-gp transporter. Simnotrelvir was rapidly absorbed after administration, alone or in combination with ritonavir. Its pharmacokinetics exhibited linearity across the 250 750 mg dose range when co-administrated with ritonavir and less than dose-proportional increase if the dose levels exceeded the ranges above. The overall incidence of adverse events (AEs) was 22.2%

(17/72) and 6.3% (1/16) in intervention and placebo groups, respectively. The simnotrelvir apparent clearance was 135-369 L/h with simnotrelvir alone and decreased significantly to 19.5-29.8 L/h with simnotrelvir/ritonavir. All the above pharmacokinetic results provide a basis for selecting and optimizing the dose amount and interval in later clinical research. Food significantly increased the plasma exposure of simnotrelvir, and the influence on pharmacokinetics was comparable between a high-fat diet and a regular diet. This observation suggests that food status should be carefully considered in the future late-stage clinical treatment of simnotrelvir.

Conclusion

Simnotrelvir, a compound that inhibits the $3CL^{pro}$ enzyme, demonstrates excellent safety, tolerability, and favorable pharmacokinetic characteristics in clinical trial fase II-III study. These findings suggest that Simnotrelvir holds great potential for controlling COVID-19. All dosage levels administered to the subjects in the different studies were well tolerated, and no maximum tolerated dose was reached. Ritonavir has the ability to substantially enhance the concentration of simnotrelvir in the bloodstream, as simnotrelvir is a substrate of the enzyme CYP3A4. Consuming food, regardless of whether it is a normal or high-fat diet, can also enhance the plasma exposure of simnotrelvir. The pharmacokinetic data confirmed that the simnotrelvir/ritonavir combination, with a dosage of 750mg/100 mg twice daily without food, is the recommended treatment regimen for COVID-19.

Acknowledgements

None.

Conflict of Interest

None.

References

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