Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/10811
DOI URL: http://dx.doi.org/10.21474/IJAR01/10811

RESEARCH ARTICLE

REMDESIVIR AND COVID-19

Suranjith L Seneviratne[1,3], Roshan Niloofa[2], Ishan De Zoysa[1], Sanjay de Mel[3] and Visula Abeysuriya[3]

1. Department of Surgery, Faculty of Medicine, University of Colombo, Sri Lanka.
2. Department of Zoology and Environment Sciences, Faculty of Science, University of Colombo, Sri Lanka.
3. Nawaloka Hospital Research and Education Foundation, Nawaloka Hospitals, Colombo, Sri Lanka.

Manuscript Info

Manuscript History
Received: 12 February 2020
Final Accepted: 14 March 2020
Published: April 2020

Key words:-
SARS-Cov-2, Covid-19, Remdesivir, Drugs

Abstract

The SARS-CoV-2 virus was first encountered in Wuhan, China in December 2019. At the present time, coronavirus disease 2019 (Covid-19) affects more than 170 countries. Several groups are carrying out intense research on drugs and vaccines to treat or prevent Covid-19. We have outlined aspects relating to Remdesivir, in treating RNA viral infections and its potential role in controlling SARS-Cov-2 infections.

Introduction:-

The SARS-CoV-2 virus, an RNA virus emerged in Wuhan, China in December 2019 and has now spread to all parts of the world (Wu and McGoogan, 2020). As of 10th April 2020, over 1.5 million cases have been reported with over 100,000 deaths. Intense research on both drugs and vaccines to treat or prevent Covid-19 is being pursued by different research groups. We have outlined aspects relating to the mechanism of action of one of these drugs, Remdesivir, in treating RNA viral infections and its potential role in controlling SARS-CoV-2 infections.

Ramdesivir (GS-5734) is a nucleoside analogue that inhibits RNA-dependent RNA polymerase (RdRP), an enzyme used by many RNA viruses to replicate (Siegel et al., 2017). When incorporated into a new strand of viral RNA, it causes chain termination. The monophosphate form is a prodrug, and it is metabolised to an active triphosphate form within the host. Remdesivir, has a broad spectrum of *in vitro* activity against RNA viruses belonging to the Filoviridae (Ebola and Marburg viruses), Paramyxoviridae (Nipah and Hendra viruses), Pneumoviridae and Coronaviridae families (Lo et al., 2017; Brown et al., 2019). Viral resistance is uncommon, as the drug is able to outpace proof-reading activity and thus retain its antiviral activity (Agostini et al., 2018). It comes as an intravenous preparation, and as it has a long half-life, it could be given once daily. Following its use in clinical trials in Ebola viral infections (in around 400 patients so far), it has been known to be generally safe in humans. In recent weeks, both the World Health Organisation and several world leaders have shown enthusiasm for using this medicine in Covid-19 patients. Recently, the company rescinded a FDA Orphan drug designation status for Remdesivir. Such a designation, would have allowed market exclusivity by the company for seven years.

Remdesivir has been found to have therapeutic efficacy in non-human primate models of lethal Ebola and Nipah virus infection. In a rhesus macaque model of Ebola virus infection, administration of Remdesivir for twelve days suppressed viral replication and protected all infected animals (Warren et al., 2016). However, in a subsequent randomised controlled clinical trial of four experimental treatments for human Ebola virus disease, Remdesivir had a higher mortality rate than two other therapies [Mab114 (a monoclonal antibody) and REGN-EB3 (a triple monoclonal antibody)] (Mulangu et al., 2019). A total of 175 patients received Remdesivir in this trial and the safety profile for this drug was found to be acceptable.

Corresponding Author:- Prof Suranjith L Seneviratne
Address:-Department of Surgery, Faculty of Medicine, University of Colombo, Sri Lanka.

In *in vitro* cell based assays, Remdesivir has been found to be active against SARS-CoV and MERS-CoV.For example, studies on human airway epithelial cells showed Remdesivir to inhibit the replication of many coronaviruses including MERS (Sheahan et al., 2017). Remdesivir has also shown encouraging results in animals infected with the Severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronaviruses. Prophylactic Remdesivir treatment prevented MERS-CoV-induced clinical disease and lung lesions in Rhesus macaques injected with MERS-CoV. In addition, therapeutic Remdesivir was also found to provide a clear clinical benefit in this study (deWit et al., 2020). In a mouse model of MERS, Sheahan et al (Sheahan et al., 2020), found both prophylactic and therapeutic Remdesivir to improve pulmonary function and reduce lung viral loads and severe lung pathology.

Wang et al (Wang et al., 2020), studied the impact of several antiviral agents against a clinical isolate of SARS-Cov-2 *in vitro* using Vero V6 cells. Remdesivir [half maximal effective concentration (EC50) = 0.77microM, half cytotoxic concentration (CC50) > 100microM and selectivity index (SI) >129.87] and chloroquine potently blocked virus infection at low concentrations.

Remdesivir was given to the first US Covid-19 patient (Holshue et al., 2020). Here a 35 five year old male, who returned to the US from Wuhan, was hospitalised at the Providence Regional Medical Centre in Washington with Covid-19 infection. He received Remdesivir on day 7 of the illness and symptomatic improvement was noted the next day. No adverse effects were observed. In a cohort of hospitalised severe Covid-19 patients who were treated with compassionate-use Remdesivir, clinical improvement was observed in 36 (68%) of 53 patients (Grein et al, 2020). Initially patients were able to obtain the drug on a compassionate basis or by registering in a clinical trial. Compassionate use allows patients to gain access to an investigational drug outside of a clinical trial, when no alternative effective therapies are available. However, some patients may not be able to enter a trial as they do not satisfy all entry criteria and some may reside in a location that makes it not possible for them to travel to a trial site. As initial demand was very high, emergency access was temporarily halted except for pregnant women and children younger than 18 years with severe Covid-19. Subsequently, a modified expanded access programme has been designed for widespread treatment use instead of an individual patient pathway. Here, Gilead allows physicians, hospitals and medical professionals to make requests for multiple patients at a time. Additionally, the EMA has recommended compassionate use of Remdesivir as treatment for severely ill Covid-19 patients.

At present, several clinical trials on the use of Remdesivir in Covid-19 patients are ongoing, and results of some of these trials should be released in the coming weeks. The two earliest trials were commenced in Wuhan, China.The severe Covid-19 trial (NCT04257656) is a Phase 3, randomised double blind, placebo controlled multicentre study evaluating the efficacy and safety of Remdesivir in hospitalised adult patients (18 years or older) with severe Covid-19. The study started on 6th Feb 2020 and four hundred and fifty three patients have been enrolled. They were allowed to enter the study up to 12 days from onset of Covid-19 symptoms.Improvement of symptoms within 28 days was assessed using a six point scoring system. To be classed as a responder, there has to be an improvement of at least two points. The second study (NCT04252664), started on 12th Feb 2020, and is on hospitalised adult patients with mild-moderate Covid-19. Doses of Remdesivir used in both studies are: Day1 - 200mg IV and Days 2 to 10: 100mg IV.

The National Institute of Allergy and Infectious Diseases (NIAID) study (NCT04280705) has recruited patients from multiple US sites and several countries. It is a randomised double blind, placebo controlled study. Adult patients (18 years or older) receive Remdesivir (Day 1: 200mg IV; Days 2 to10: 100mg IV) or placebo and a seven category, clinical severity scale is used to evaluate outcomes. Blood tests and nose and throat swabs are taken every two days to track the amount of virus in their bodies. The first patient to volunteer for this study was a passenger who tested positive whilst aboard the Diamond Princess.

Gilead Biosciences are also conducting two studies on moderate and severe Covid-19 patients from several countries (NCT04292899 and NCT04292730). Five and ten day courses of Remdesivir are being evaluated with respect to clinical status (assessed using a seven point ordinal scale) on day 14. The UK and EU arms of the study are referred to as the Adaptive Covid Treatment Trial (ACTT)-EU/UK study. In the UK the study is conducted across 15 clinical sites and was awarded an urgent public health research status by the Chief medical officer (CMO). Furthermore, the WHO sponsored Solidarity trial (NCT04315948) is an international trial to help find an effective treatment for Covid-19. Four treatment options are to be compared against standard of care. Remdesivir comprises one of the options, the others being Lopinavir/ritonavir alone, Lopinavir/ritonavir plus Interferon beta-1a and

Hydroxychloroquine. The US Department of defence affiliated personnel are able to access Remdesivir via an Expanded access treatment protocol (NCT0430766 and NCT04323761).

At present, the company has identified ways to accelerate production of this drug. Around 1.5 million individual doses (140,000 treatment courses) are available and expectations are for a million treatment courses by the end of the year. The results of studies that are being undertaken at present, would provide an important insight into the use of Remdesivir in the treatment of Covid-19.

References:-

1. Agostini, M.L., Andres, E.L., Sims, A.C., Graham, R.L., Sheahan. T.P., Lu, X. et al. (2018) Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease. mBio.,9
2. Brown, A.J., Won, J.J., Graham, R.L., Dinnon, K.H., Sims, A.C., Feng, J.Y. et al. (2019) Broad spectrum antiviral remdesivir inhibits human endemic and zoonotic deltacoronaviruses with a highly divergent RNA dependent RNA polymerase. Antiviral research.,169: 104541
3. de Wit, E., Feldmann, F., Cronin, J., Jordan, R., Okumura, A., Thomas, T. et al. (2020) Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. Proceedings of the National Academy of Sciences., 117: 6771 -76
4. Gordon, C.J., Tchesnokov, E.P., Feng, J.Y., Porter, D.P., Gotte, M,.(2020) The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. J. Biol. Chem,. April 10 (Epub ahead of print)
5. Grein, J., Ohmagari, N., Shin, D., Diaz, G., Asperges, E., Castagna, A. et al. (2020) Compassionate use of Reemdesivir for patients with severe Covid-19. N Engl J Med., April 10 (Epub ahead of print)
6. Holshue, M.L., DeBolt, C., Lindquist, S., Lofy, K.H., Wiesman, J., Bruce, H. et al. (2020) First case of 2019 novel coronavirus in the United States. N. Engl. J. Med., 382 (10): 929–936
7. Lo, M.K., Jordan, R., Arvey, A., Sudhamsu, J., Shrivastava-Ranjan, P., Hotard, A.L. et al. (2017) GS-5734 and its parent nucleoside analog inhibit Filo-, Pneumo-, and Paramyxoviruses. Scientific reports.,7: 43395
8. Mulangu.S., Dodd, L.E., Davey, R.T., TshianiMbaya, O., Proschan, M., Mukadi, D. et al. (2019) A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. The New England journal of medicine., 381: 2293-2303
9. Sheahan, T.P., Sims, A.C., Graham, R.L., Menachery, V.D., Gralinski, L.E., Case, J.B. et al. (2017) Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Science translational medicine.,9:396
10. Sheahan, T.P., Sims, A.C., Leist, S.R, Schafer, A., Won, J., Brown, A.J. et al. (2020) Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nature communications,. 11: 222
11. Siegel, D., Hui, H.C., Doerffler, E., Clarke, M.O., Chun, K., Zhang, L. et al. (2017) Discovery and Synthesis of a Phosphoramidate Prodrug of a Pyrrolo[2,1-f][triazin-4-amino] Adenine C-Nucleoside (GS-5734) for the Treatment of Ebola and Emerging Viruses. Journal of medicinal chemistry,.60: 1648-1661
12. Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M. et al. (2020) Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res,. 30 (3): 269–271.
13. Warren, T.K., Jordan, R., Lo, M.K, Ray, A.S, Mackman, R.L., Soloveva, V. et al.(2016) Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. Nature,. 531: 381-385
14. Wu, Z., McGoogan,J.M..(2020) Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA,.323: 1239-1242.