BRAC UNIVERSITY
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PHARMA HIGHLIGHTS

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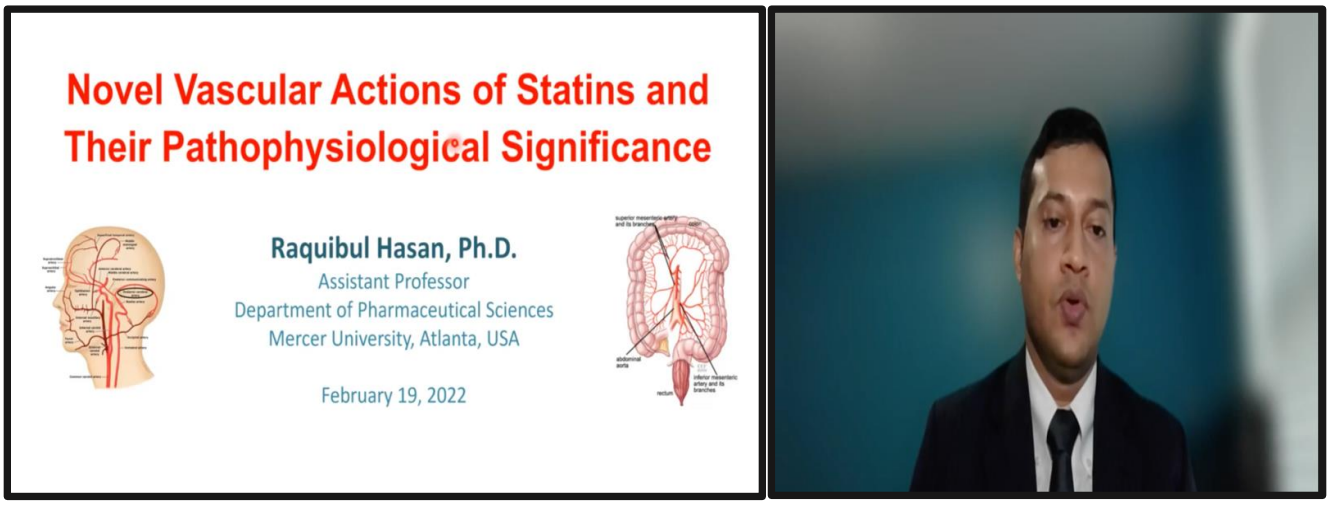
Webinar on 'Novel Vascular Actions of Statins and Their Pathophysiological Significance'



Statins are the world's most prescribed class of cholesterol-lowering medications which also possess beneficial vascular effects. According to the conventional view, these beneficial vascular effects are mediated by the inhibition of cholesterol or mevalonate production, a process that requires months to years of treatment. However, whether statins could directly act on a novel molecular target to rapidly modify blood vessel diameter remained unknown.

The distinguished speaker of the webinar was Dr. Raquibul Hasan, whose lab recently identified two unconventional targets of statin action in brain and gut arteries that have immense pathophysiological significance. Dr. Raquibul Hasan obtained his Bachelor of Pharmacy degree in 2005 and MS in Pharmaceutical Sciences degree in 2006 from Jahangirnagar University in Bangladesh. He joined the Department of Pharmacy, Brac University as a lecturer in 2010 and later on went on to pursue his doctoral studies in pharmacology at the University of Cambridge in the UK, investigating the molecular modulation of TRP ion channel trafficking in neurons. Following his PhD, Dr. Hasan was awarded an American Heart Association grant in 2016 to study vascular physiology as a postdoctoral fellow at the University of Tennessee, USA. In 2018, he established his own independent research laboratory as an Assistant Professor at the Department of Pharmaceutical Sciences in Mercer University, in Atlanta, USA. Currently, his laboratory is mainly focused on the molecular pharmacology of ion channels and G-protein-coupled receptors (GPCRs) to discover new drug molecules and/or repurpose pre-existing drugs to improve vascular dysfunction in cardiovascular disease. Dr. Hasan also teaches different areas of pharmacology to PharmD students and supervises PhD, PharmD and Master's students, as well as hosts postdoctoral trainees in his lab. Dr. Hasan has recently been awarded a competitive NIH research grant of $425,000 from NIH's Heart, Lung and Blood Institute to study novel vascular effects of statins in the body.

During the webinar Dr. Hasan shed light on the molecular mechanisms of the novel vascular actions of statins. He described step by step how he formulated his research questions and performed cutting-edge experiments to address those using state-of-the-art equipment, eventually arriving at his novel findings. Dr.Hasan gave students a close insight into modern pharmacological research and also encouraged them to pursue research in their higher studies.The attendees asked excellent questions which reflected their enthusiasm towards the topic and were highly appreciated by Dr. Hasan.

The speaker emphasized on the important role of health outcomes research in drug and medical device development. In addition, he also discussed the route students can take to pursue graduate studies in this emerging field in the US and its career prospects. The questions asked by the attendees were insightful and reflected their enthusiasm towards growing as competent professionals. The webinar was very interactive and the participants also shared their opinion on how the session will help them to focus on their goals.

Written by: School of Pharmacy

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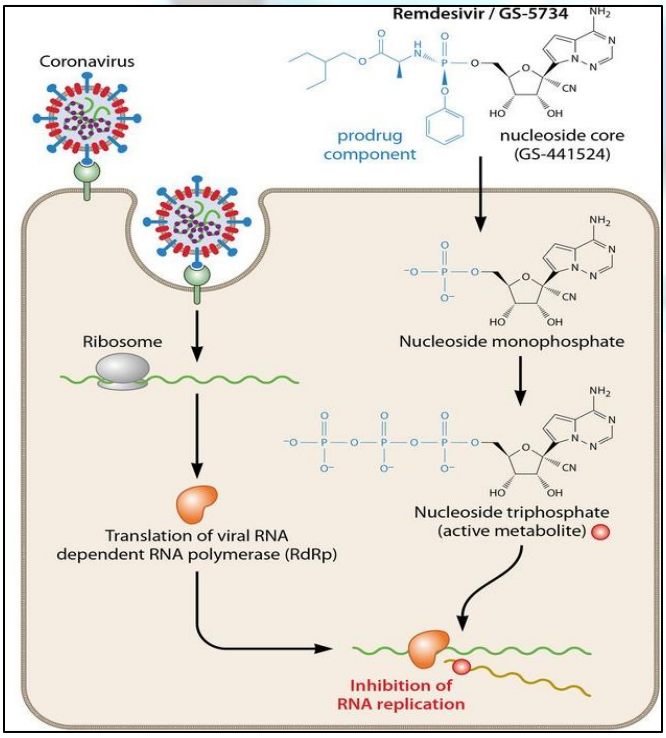
What Remdesivir Can Do Against COVID-19?

Remdesivir is an antiviral agent that works against a wide range of virus. It was synthesized and developed by Gilead Sciences in 2017 as a treatment for Ebola virus infection. Although the drug did not work well against that disease, it later showed promising results against SARS and MERS— illnesses caused by different coronaviruses — in animal studies in 2017, which is why researchers thought remdesivir might help fight COVID-19. With the emergence of COVID-19, we are in a need for an effective antiviral agent to be able to halt the current outbreak and remdesivir might be one for the therapy of patients with COVID-19.When coronavirus enters a human cell, it needs to replicate itself to increase in numbers so to win against the person's natural immune system. Since the genetic material of SARS-CoV-2 is a RNA, the genetic material is coped by using a RNA polymerase- a protein that acts as a copy machine if the genetic material is RNA.

During copying, using another protein of the virus called the exonuclease, the virus checks if the copying is being done correctly, or in other words 'proofreads' the growing strand of RNA. The "proofreader protein" or exonuclease that catches most of those errors, chops out the wrongly inserted chemical component and gives the polymerase another, generally successful, stab at inserting the proper chemical unit into the growing RNA sequence or strand.



Remdesivir disrupts this process of copying/replication and proofreading by obscuring the viralRNA polymerase and evading proofreading by the viral exonuclease. Rate of virus replicationthus is decreased as RNA strand production is decreased. How effective is remdesivir in combatting SARS-CoV-2? Remdesivir is very selective towards viral polymerase, hence has a low propensity to cause toxicity in human. Additionally, in animal cell model, it is seen to have a wide therapeutic index which means remdesivir might be safe to use over a wide range of doses in humans. This would reduce the chances of drug toxicity in humans that is usually caused by overdosing of drugs with narrow therapeutic window. However, a drawback of this drug is it doesn't block the body's overzealous immune system responses that cause additional damage for many severely ill COVID-19 patients. Beside this, remdesivir is most effective when given early — as soon as patients begin to show symptoms but giving the drug early in an infection is a challenge because it is administered to the patient over 10 days through an IV route. In a recent study, published by the New England Journal of Medicine, investigators used remdesivir on a compassionate-use basis to patients hospitalized with COVID-19. The authors concluded that remdesivir led to clinical improvement in 36 of 53 patients (68%) infected with Covid-19. However, adverse effects, most commonly- kidney failure, rash, diarrhea and low blood pressure, were reported by 60% of them during follow-up. 23% patients in the survey had grave adverse effects such as septic shock (a fatal condition that can be caused by foreign substances in blood), 8% had to terminate treatment prematurely where one had multiple organ failure.

On April 29, 2020, the National Institute of Allergy and Infectious Diseases (NIAID), published preliminary results on the effect remdesivir (RVD) on COVID-19. The randomized, controlled trial that was initiated on February 21, 2020 involved 1063 patients from several countries including the US, UK, and Singapore.The preliminary result revealed that RVD helps to recover faster by 31% and may also reduce mortality, according to the US National Institutes of Health (NIH). The team carrying out the research in the UK expressed "cautious optimism" over the findings but stressed that other drugs would also be needed to show real progress, to attack the disease in a number of different ways. The team said the second stage of the trial will see patients given remdesivir in combination with another agent.

On April 29, 2020, Gilead revealed results from the last step of a simplified clinical trial (drug testing on humans)

evaluating 5-day and 10-day dosing durations of the investigational antiviral remdesivir in hospitalized patients with severe manifestations of COVID-19 disease. Inclusion criteria was pneumonia and reduced oxygen levels that did not require mechanical ventilation at the time of study. The study showed that patients who received a 10-day treatment course of remdesivir attained comparable improvement in clinical status compared with those taking a 5-day treatment course. Also, no unforeseen side effects were detected with the use of RDV across either treatment group.

On May 1, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of RDV for the treatment of hospitalized 2019 coronavirus disease (COVID-19) patients based on these trials/studies. For it to be a licensed therapeutic drug for COVID-19, the ongoing clinical trials have to be completed which would determine the ultimate clinical impact such as efficacy, safety profile etc of remdesivir on coronavirus.

As of now, since the experience of remdesivir application in the newly emerging COVID-19 is still limited, adverse drug effects need to be paid much attention to avoid fatal results in patients during emergency use.

There was preclinical (drug testing on animals) and early clinical data suggesting the drug would protect patients from Ebola, too, but results from that Phase 3 study(last step of the clinical trial) still disappointed. Hence, despite the evidence suggesting remdesivir could work, it's still an open question whether that potential will translate into real efficacy. It is just a matter of time we get that answer.

Written by: Rabeya Mollika (TA)

Truth About Patients with Penicillin Allergy

Penicillin allergy is an abnormal reaction of your immune system to the antibiotic drug penicillin. Penicillin is prescribed for treating various bacterial infections. Common signs and symptoms of penicillin allergy include hives, rash and itching. Severe reactions include anaphylaxis, a life-threatening condition that affects multiple body systems.

Hypersensitivity reactions are the major problem in the use of penicillin. True penicillin allergy is rare with the estimated frequency of anaphylaxis at 1-5 per 10 000 cases of penicillin therapy. Hypersensitivity is however, its most important adverse reaction resulting in nausea, vomiting, pruritus, urticaria, wheezing, laryngeal oedema and ultimately, cardiovascular collapse. Identification of patients who erroneously carry ß-lactam allergy leads to improved utilization of antibiotics and slows the spread of multiple drug-resistant bacteria. Cross-reactivity between penicillin and second and third generation cephalosporin is low and may be lower than the cross-reactivity between penicillin and unrelated antibiotics.

There are two clinical pictures that can result from penicillin allergy, namely acute and sub-acute reactions mediated by IgE and IgG antibodies respectively. The acute allergic reaction arises immediately or rapidly within minutes to an hour or two and includes sudden anaphylaxis with hypotension, bronchospasm, angioedema and urticaria. Acute reactions result from reaction with preformed IgE to penicillin as a result of previous exposure. The resulting release of histamine and other mediators from mast cells produce the signs and symptoms typical of a true anaphylactic reaction. A less dramatic picture may occur 7 to 10 days after penicillin treatment starts or 1–2 days after repeat therapy. In this setting the picture is sub-acute and can include urticaria, fever and arthralgias or arthritis. The sub-acute reaction is caused by preformed IgG to penicillin as a result of previous penicillin treatment. The IgG antibody results in the activation of the complement reactions producing inflammation resulting in the symptoms mentioned earlier.

Newsletter Editorial Board: Namara Mariam Chowdhury, Kazi Fatema Rahman and Farzana Islam

Penicillin skin sensitivity testing can help to confirm the safety of the drug and qualm fears of a dangerous drug reaction. A positive skin test indicates the presence of IgE antibodies to penicillin and immediately excludes the use of it and related ß-lactam antibiotics. For non-penicillin ß-lactams, the immunogenic determinants that are produced by degradation are unknown, and diagnostic skin testing is of limited value.

Clinicians commonly encounter patients with a history of allergy to penicillin and other ß-lactam antibiotics. However, it is known that about 90% of these patients are not truly allergic and could safely receive ß-lactam antibiotics. The seriousness of the problem posed by drug allergies is perhaps overblown in part because of the loose use of the word “allergy,” to refer to all immunologically mediated reactions. When assessing an allergy to penicillin the first issue is to establish whether or not a true allergic IgE mediated reaction has taken place. Instead, these patients are often treated unnecessarily with an alternate broad-spectrum antibiotic, which could increase costs and contribute to the development and spread of multiple drug-resistant bacteria.

Written by: Shafiqul Islam (TA)