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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

What You Need to Know About Influenza Pathways & Novel Mechanisms of Action

Dr. Russell:
There is a new flu fighter in town, and it's not a neuraminidase inhibitor. It's called and endonuclease inhibitor. But how does this new inhibitor work? And is it for everyone? These are just some of the burning questions we'll be answering today as we explore what role this new treatment could have in the fight against flu epidemics.

This is CME on ReachMD, and I'm Dr. John Russell. Joining me today to discuss the pathophysiology of the influenza virus, its replication process, and how antiviral agents can stem viral load and reduce viral shedding is Dr. Michael Ison, Professor of Medicine and Surgery at Northwestern University Feinberg School of Medicine in Chicago, Illinois.

Dr. Ison, welcome to the program.

Dr. Ison:
Hello, how are you?

Dr. Russell:
So, before we get into how this new inhibitor works, let's start with a quick recap. Influenza control begins with vaccination, yet vaccination rates are quite low. And even when patients are vaccinated, we still see significant failure rates of the vaccine. So, what does this tell us about recognizing influenza quickly and initiating treatment earlier?

Dr. Ison:
So, unfortunately, although the current recommendations are that everyone greater than 6 months of age, irrespective of whether they have underlying medical conditions or not, should get their flu vaccine. Despite this, only a little less than half of patients get the flu vaccine, so this still leaves a very large proportion of the population still at risk for getting influenza. Additionally, the vaccines aren't universally effective. We learned that 2 years ago the greatest where the vaccine efficacy was relatively poor. And there's significant variability in the vaccine efficacy. Despite the fact that the vaccine may not be entirely effective in preventing influenza, it still, even if you've gotten the flu vaccine and still get sick from flu, reduces the likelihood that you're going to get very sick, require hospitalization or even die from influenza. And so, despite the challenges with the flu vaccine, there is still benefit to patients that have gotten the vaccine even if they still get sick themselves. But it's important to recognize, because of the low rate of vaccination and the risk that there is an imperfect match between circulating strains and the viruses that are infecting the patients, we always

need to be vigilant about influenza, and so, whether a patient has gotten the flu vaccine or not doesn't rule out them getting influenza, and if the patient is presenting with very classic symptoms of flu—fever, myalgias, cough being kind of hallmark symptoms with a very rapid onset—you need to be thinking about flu whether they have gotten the vaccine or not, because the use of antivirals can help the patients get better much more quickly.

Thankfully, we have some newer drugs, but the key message for all of them is the same. The earlier you get the medication started, the better the outcome in terms of speed of recovery from the infection.

Dr. Russell:
Now, viral load and viral shedding are 2 terms that are commonly used when discussing influenza treatment, but what is the significance of these terms regarding our understanding and approach to treating influenza?

Dr. Ison:
Well, viral shedding is just being able to detect virus that's coming out of the nose or other secretions, and that usually means that the virus can be transmitted from one person to another, and so that's what we are really most concerned with. Viral load is a more technical term that relates to how much virus is being shed at a particular time. The higher the viral load, the more virus there is, and so likely that it's much easier to transmit the virus from the infected person to an uninfected individual. Nonetheless, how high that viral load is relative to the risk of transmission hasn't been worked out super well other than to know that if you're able to culture the virus, you're likely able to infect another person.

Dr. Russell:
So, Dr. Ison, thank you for breaking down those terms for us. Now let's watch a brief video on the replication of influenza virus and the mechanisms of the actions of the antivirals.

3d MOA Video

There are 5 stages of the viral life cycle: viral entry; uncoating, viral replication, assembly and budding, and viral release.

The life cycle starts when the influenza virus enters the host through the respiratory tract. The main targets of the influenza virus are the columnar epithelial cells of the respiratory tract, where viral hemagglutinin is required for binding to the surface of the host cell.

As the virus passes through the cell membrane, the viral membrane fuses with the endosomal membrane, and the M2 ion channel facilitates the release of viral RNA into the nucleus for transcription and translation.

Once the viral RNA enters the nucleus, an influenza-specific polymerase acidic endonuclease cleaves a portion of the host's genetic code and replaces it with the viral RNA. This process of viral replication typically occurs within hours, producing numerous protein-based structures called virions that are then transported preferentially to the apical plasma membrane and released through a process called budding.

In an effort to get ahead of the sometimes severe influenza symptoms, there are several medications that target different stages of the viral life cycle. Let's rewind back to the Uncoating phase. M2 ion channel inhibitors, or adamantanes, block the viral life cycle during the uncoating stage. However, these medications are no longer recommended by the CDC due to high resistance.

Neuraminidase inhibitors, such as oseltamivir, on the other hand, target the last stage of the viral life cycle and prevent the replicated virus from spreading to nearby epithelial cells, while the antiviral medication baloxavir marboxil disrupts the viral life cycle during the viral replication stage by inhibiting the influenza-specific endonuclease that is required for viral replication.

Dr. Russell:
So, Dr. Ison, after watching that video, could you explain the clinical differences between the mechanisms of actions of the therapies we have available?

Dr. Ison:

So the main mechanisms basically result in differences in the outcome of the replication. In terms of oseltamivir, since you're blocking the virus at the stage of release, the virus is going through an entire round of replication. This can release cytokines or chemicals from the cells which makes people feel very sick. The virus stays glommed on, and so it can't infect other cells. Nonetheless, it still provides about a 1-day benefit if started within 48 hours after symptom onset but does cause a slower decline in viral titer compared to placebo or untreated patients. Baloxavir, on the other hand, basically blocks an earlier phase in the replication and really shuts off viral replication very quickly. As a result, the viral loads come down very, very quickly and likely to a level that makes it less likely to be transmitted from person to person, although we don't have strong clinical data yet to show that. Much like the neuraminidase inhibitors, if started within 48 hours, they provide about a 1-day clinical benefit to the patients despite this much more rapid decline in viral titer, which also likely correlates with more rapid reduction in cytokine production.

Dr. Russell:
So, Dr. Ison, now that we understand the pathophysiology of the disease and the mechanisms of actions of the 2 primary antiviral treatments, can you explain the benefits and limitations of these treatments?

Dr. Ison:
Yes. So the biggest benefit is that they both reduce the risk of developing complications from influenza and make the patient feel much better much more quickly when they take the medicine compared when they are untreated. To be effective though, they have to be given early, typically within the first 48 hours after symptoms begin, and they really improve the clinical outcome the earlier the medication is started. So there was a study of oseltamivir right after the drug was licensed about 20 years ago when the drug was given to some people very early, within 6 hours of symptom onset, and that gave a benefit of up to 4 days of clinical improvement compared to patients that were treated a little bit later, between 36 and 48 hours, where they only got about a day worth of benefit.

It's important to recognize that there are differences in how many pills have to be taken and how long they are given. In terms of oseltamivir, it's 1 pill twice a day for 5 days, which some people, especially when they start feeling better, may stop a little bit early, which could lead to rebound of the infection or other complications. In terms of baloxavir, it's a single dose, so they take the medication when it's prescribed and they are done. It stays in their system for a longer period of time and would improve compliance. In terms of safety and adverse event profiles, they are actually both very safe. Oseltamivir's most common side effect is a little bit of GI upset, which can be improved by giving the medication with food. Baloxavir generally is pretty well tolerated, and most of the side effects that were seen in clinical studies were at similar rates as what was seen in patients that received placebo, suggesting that what was seen in the studies was just what was coming from the flu itself.

Dr. Russell:
So, just to give our audience a bit of a background here, the Infectious Disease Society of America published new guidelines in December 2018. These updated guidelines included discussions of the importance of early treatment of patients at high risk for influenza complications. So, in light of what we've discussed today, how do you decide what to do if you suspect influenza in a high-risk patient? Do you initiate treatment anyway if you get a negative rapid molecular assay based on your clinical suspicion, and if so, what treatment would you recommend?

Dr. Ison:
Well, the key take-home message from the updated IDSA guidelines is to start therapy as soon as possible, and so that's true for high-risk patients as well as if you decide to treat someone who's not a high-risk patient. The earlier you start the therapy, the better the benefit. In terms of testing for the patient, it really depends on a number of things. Do you think that the patient has the flu? If you are pretty confident that they do and you feel comfortable starting the therapy, you should just go ahead and prescribe the antiviral. If you have a patient that's a nursing home patient, an immunocompromised patient or someone who's being admitted to the hospital, you really should go ahead and test them. But even while you're waiting for the test to come back, you should start that therapy. It can always be discontinued if the test comes back negative. And the other thing is, is that we are—although having the availability of more rapid tests such as rapid PCRs, not all sites have them, so sometimes it still takes 6 to 12 hours to get that information back.

Even if you had a negative test, the one thing that you have to keep in mind is that the quality of the tests, particularly if you're using a PCR-type assay, are really dependent on the quality of the specimen, and if the nurse or physician that is collecting the specimen doesn't do a good job of collecting the specimen, which means getting back into the mid turbinates and getting some cells on the swab, you may get a false negative result. And so, if I had very strong suspicion, especially in someone of high risk of influenza, I would probably go ahead and treat them even if the PCR was negative. If I had collected the specimen and I knew it was a good quality specimen and it was negative or positive for a different virus, then I think using antivirals would be less important.

In terms of which drug to use, the current guidelines don't give preference to any one drug, so either oral oseltamivir, IV peramivir, inhaled zanamivir or oral baloxavir would be considered equally adequate. That being said, some of the data that will be coming out soon suggests that baloxavir may be better than oseltamivir for the treatment of influenza B, and so I think if I had a patient with influenza B, I would probably choose baloxavir. That's not what the guidelines say. That's just what I think.

Dr. Russell:
So Michael, Before the 2009 H1N1 influenza A pandemic, there were reports from 2007 through 2009 of resistance to the neuraminidase inhibitors, specifically oseltamivir. Given what we know about how these agents work, is there crossover resistance to a newer antiviral like baloxavir?

Dr. Ison:
I think the good news is, since baloxavir is a completely different mechanism of action to prevent the replication of the virus, cross-resistance isn't a problem, so if you are resistant to the neuraminidase inhibitors, you could easily use baloxavir. And likewise, if you had a virus that was resistant to baloxavir, you'd be able to use the neuraminidase inhibitors. It's important to note that the virus that emerged from 2007 to 2009 prior to the pandemic that was resistant to oseltamivir was still susceptible to zanamivir and was also at the time susceptible to the adamantanes, and so really, if there is broad circulation of a resistant virus, we'd have to get up-to-date guidance from experts, including the CDC, to see what drugs that they would recommend for the treatment of that infection.

Dr. Russell:
Well, this certainly has been a valuable discussion, and before we wrap up, Dr. Ison, is there one take-home message you'd like to leave our audience with today?

Dr. Ison:
Yes. I think that the key take-home message that I would say is that you need to start drug as early as possible, so don't wait until you get the test back if it's not going to be some very rapid result. If you think the patient has flu, you should start the therapy if those tests are negative. This is particularly important in high-risk patients where the drugs have been shown not only to speed recovery but reduce those complications that we dread the most. And again, as a provider that sees these types of patients, the fewer complications means fewer visits for the patients coming back, which not only is better for the patient, but during a busy winter season, keeps the flow of patients through our clinics more effective.

Dr. Russell:
Well, with that, I'd like to thank my guest, Dr. Michael Ison, for helping us better understand the mechanisms of actions of traditional neuraminidase inhibitors and a newer antiviral treatment for influenza and how these therapies can reduce viral load in the patient and, even more importantly, reduce the amount of virus that's spread out into the community. Dr. Ison, it was great speaking with you today.

Dr. Ison:
Great talking with you too.