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Clinical Applications of Raltegravir for HIV Therapy

CLINICAL APPLICATIONS OF RALTEGRAVIR

We are getting our first in-depth look at some of the research behind raltegravir, a powerful therapy for multidrug-resistant HIV infection already approved by the FDA. How is this raltegravir data impacting current clinical strategies for attacking the virus in multidrug-resistant patients. You are listening to ReachMD XM-157, The Channel for Medical Professionals. Welcome to the Clinician's Round Table. I am your host, Dr. Mark Nolan Hill, Professor of Surgery and practicing general surgeon and our guest is Dr. Roy Steigbigel, Professor of Medicine and Pathology, Molecular Genetics, Microbiology, and Pharmacologic Sciences and the founding director of the comprehensive AIDS Center at the State University of New York at Stony Brook. Dr. Steigbigel is the lead author of research on raltegravir published in the New England Journal of Medicine.

DR.HILL:

Welcome Dr. Steigbigel.

DR. STEIGBIGEL:

Well thank you.

DR.HILL:

We are discussing this clinical applications of raltegravir. Doctor for full disclosure you have served as an investigator for Merck, correct?

DR. STEIGBIGEL:

Yes.

DR.HILL:

Tell us a little bit about your background. How did you get involved with this research, with this drug in particular?

DR. STEIGBIGEL:

Well I have been involved in HIV research before HIV was discovered to be the cause of AIDS back in the early 80s when I was at the University of Rochester, so I have been involved in numerous studies fairly basic level and also at the clinical investigation level for new therapies and this is a compound that I have been involved with since it was first used in clinical trials, in fact, our center put the first patient in the world on this medication.

DR.HILL:

And how specifically did you think to use this medication an integrase inhibitor?

DR. STEIGBIGEL:

Well the advantage of this medication is as you state, it inhibits the integration step in the virus' replication cycle and we have not ever had a drug for that step in replication. That's an important point because the incidence of resistant to HIV in individuals who have been on therapy for years continues to increase. People do develop a resistant virus, especially if they are not taking their medications regularly. Additionally people who are newly acquiring virus, that is people who have never had therapy before are acquiring virus from other people that is resistant to current medications. So getting medications in a new class that is in a new step in replication is really quite a breakthrough and this drug raltegravir does represent that particular point.

DR.HILL:

In a very simplistic fashion and not thinking about the resistant patients, is this a better way to approach HIV as opposed to the standard antiretroviral treatment?

DR. STEIGBIGEL:

Well it is not necessarily better. It is not necessarily better, it is better for those people who have resistant virus because the chance of ever having virus resistant to it is very close to zero as there has been no integrase inhibitor out there ever. So viruses have not developed capacity to be resistant to raltegravir to this point. Of course, that does not mean that viruses will not become resistant to it and in fact, in the studies, a small number of people have already developed resistance to raltegravir.

DR.HILL:

Now you have studied for 48 weeks, I believe, the 2 clinical markers of HIV infection, correct?

DR. STEIGBIGEL:

That's correct.

DR.HILL:

And not the clinical efficacy.

DR. STEIGBIGEL:

That's right, the studies that were published in New England Journal of Medicine were not designed to look at clinical efficacy as the length of time, i.e. 48 weeks, would not likely be able to detect any clinical efficacy, so the design of the study, the proscribed design was to look at 2 aspects of HIV therapy which are clearly and unequivocally predictive of clinical outcome, i.e. the drop in the viral load, the amount of virus people have in their body and the increase in the CD4 cells, the cells that are normally damaged and eliminated and become dysfunctional because of HIV. So in the field of HIV research for new therapies, these 2 so-called surrogate markers are accepted as predictive efficacy by the research community and more importantly perhaps by the FDA.

DR.HILL:

To continue on this point, I am sure a lot of listeners are thinking, the FDA certainly is a very particular organization and how a drug can be approved without clinical studies is surprising, but I suppose it has to do with what you just said, right?

DR. STEIGBIGEL:

Yes, it is because of study after study after study and just basic information and knowledge about HIV indicates that the primary utility of a drug will depend on its ability to stop the virus from replicating. Unfortunately, none of the drugs we have cure. None eliminate virus, but they bring the viral load down to very low levels, levels that are often referred to as undetectable.

DR.HILL:

How do you think this is affecting clinical practice at this point?

DR. STEIGBIGEL:

Well I think this is a breakthrough, in that for people with highly resistant virus which was what this study was looking at, it offers an opportunity for people who had very few options who are really going to have major problems in the future, this offers a real turn for them to have periods of time, how long we don't know, but periods of time where their HIV can be well controlled. Many people think it is analogous to what happened around 95 when we had the new class of drugs, i.e. the protease inhibitors.

If you have just joined us, you are listening to The Clinician's Round Table on ReachMD XM-157. I am your host, Dr. Mark Nolan Hill and our guest is Dr. Roy Steigbigel, Professor of Medicine and Pathology, Molecular Genetics, Microbiology, and Pharmacologic Sciences and the Founding Director of the Comprehensive AIDS Center at the State University of New York at Stony Brook.

DR.HILL:

We are discussing the clinical applications of raltegravir. Doctor, are we seeing a significant group of patients that develop resistance directly to raltegravir?

DR. STEIGBIGEL:

There was a small group of people who on the raltegravir, the study began just, was looking at people who received raltegravir plus optimized treatment background versus placebo plus optimized treatment background and in some there were a small number of people in the raltegravir group who did develop resistant virus. They were people who had very few other active drugs, so that as a single agent raltegravir and as any other single agent will not be working very well. It needs to be taken in combination with some other medications that have effect on the virus.

DR.HILL:

Now when we speak about only 1 genetic mutation is needed to develop the resistance, what does that exactly mean?

DR. STEIGBIGEL:

Well, with raltegravir actually, its one major one plus minor ones. So it is more than 1, what that means is in the enzyme which is blocked by raltegravir, in this case integrase, the change in amino acids in that enzyme can lead to the inability of the drug to block the integrase function. For some medications, there is a requirement of virus to have multiple amino acid changes and for others fewer. So raltegravir it seems at this point a single mutation, a major mutation plus some other mutations along with it can lead to resistance.

DR.HILL:

Is this problem of continuing resistance, is this going to affect raltegravir and just continue on and also require more medications, different medications in the future?

DR. STEIGBIGEL:

Most likely, while this is a breakthrough, it is not a panacea for the resistance problem with HIV and that is why continuing look for additional medications that act at other steps of viral replication inhibition are needed. In fact, there are another class of drugs also recently approved which operate in another step in the virus' replication cycle and they block what is called CCR5 which is one of the places that the virus heads to latch on to the host cell. So we do have these 2 truly new medications that have come out in the last 6 to 8 months which represents really a breakthrough.

DR.HILL:

A general question, is there any way to combat the problem of resistance?

DR. STEIGBIGEL:

Well the most important thing clinically is for us to encourage our patients to take their medications very regularly, unlikely other medications for infectious diseases, a skipped dose can lead to resistance quite quickly.

DR.HILL:

Why is that?

DR. STEIGBIGEL:

Probably because the virus has the great ability to mutate and additionally because we haven't cured the infection, the virus levels can come up quite quickly and then resistance will occur. So HIV is a difficult virus for many, many reasons, but among those reasons is the necessity for keeping the viral load very, very, very low in which case the chance for resistance is diminished, but never totally eliminated.

DR.HILL:

You have mentioned several times about being able to cure the disease with this treatment. Will we be able to cure the disease at all in the future?

DR. STEIGBIGEL:

Currently there is no way that we understand that this can be cured, because in addition to the replicating virus, at a high level there is virus replicating at a very low level or not replicating at all in resting cells and none of the medications can get at that group of viruses or cells currently. There have been methods that have been attempted to rid the body of all virus, but so far they have all failed. So in the near future and may be unfortunate longer term future, cure of HIV is not on the horizon.

DR.HILL:

Are there any patients who must stay away from raltegravir?

DR. STEIGBIGEL:

Well currently there is no identification of people who have had any side effects or allergic reactions, but whether that will occur when it gets to use in thousands of patients is unknown, but so far that has not been seen.

DR.HILL:

Do you think that we eventually will see this as a first line HIV therapy in nonresistant patients?

DR. STEIGBIGEL:

That's definitely something that is going to be looked at. In fact, there are ongoing studies comparing it to other so-called first line therapies to see if it as good or better than other first line therapies. So those studies are ongoing.

DR.HILL:

Finally doctor, if you could look into your crystal ball, 5 to 10 to 15 years down the way, tell us what you see in terms of therapy for HIV.

DR. STEIGBIGEL:

Well I think what we have seen is a continuum of more medications and better medications and simplified regimens. So while I have been in this field since the early 80s, people were taking 15 to 20 to 25 medicine pills a day. We now have some regimens where people are taking 1 pill a day which is combination therapy of several medicines. So I think we continue to simplify and fortunately developing new medications for people who have resistant virus. Hopefully that will continue, but at the same time, it is likely that the virus will also continue to find ways to become resistant, so we have to develop new medicines and of course the most important thing we would all like to see is prevention with either vaccine which does not seem to be in the near horizon, but also remembering that we do know how this virus is transmitted and so methods to educate the human race about preventing transmission is also very important.

DR.HILL:

I want to thank our guests Dr. Roy Steigbigel. We have been discussing the clinical applications of raltegravir. I am Dr. Mark Nolan Hill and you have been listening to The Clinician's Round Table on ReachMD XM-157, the Channel for Medical Professionals. Be sure to visit our website at www.reachmd.com featuring on-demand pod casts of our entire library. For comments and questions, please call us toll-free at 888-MD-XM157 and thank you for listening.

This is Dr. Aron Karol, Director of the Center of Health Policy and Professionalism Research in Indianapolis, Indiana and you are listening to ReachMD XM-157, The Channel for Medical Professionals.