Few alarms over cases of drug-resistant COVID

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Maha Farhat, assistant professor of biomedical informatics at HMS, said a recent study has found mutations in the gene that would cause remdesivir resistance … "are more rare than you would expect by chance." Credit: Rose Lincoln/Harvard Staff Photographer

As the latest coronavirus variant upends expectations about the

pandemic's coming months, drug manufacturers are working to expand treatment options to fight those stricken with severe disease. Even as new pills from Pfizer and Merck wind their way through the regulatory process, scientists last month detailed a case of resistance to remdesivir, one of the earliest drugs used to fight COVID-19. The case, in an immune-compromised patient who battled the illness for months, raised the specter of the virus opening a new front in the pandemic, one in which hard-won progress in devising new treatments is eroded by the fast-moving virus.

The Gazette spoke with Maha Farhat, assistant professor of biomedical informatics at Harvard Medical School and physician at Massachusetts General Hospital who researches drug resistance and pathogen evolution, about what the rise of remdesivir resistance means for the path of the pandemic. This interview was edited for length and clarity.

Q&A: Maha Farhat

GAZETTE: How concerning—or surprising—is it that at this stage of the pandemic, we're seeing resistance to one of these drugs?

FARHAT: It's not at all surprising. Considering how frequently viruses mutate, I actually expected to see it earlier. The risk of new mutations is also higher during a severe infection because there are many, many viruses in the body. That increases the chances that one of them will have the right mutation—the wrong mutation to us—that makes it resist the antiviral agent, in this case, remdesivir. But we hadn't actually seen much of it, and I don't think it's from lack of surveillance or effort.

GAZETTE: I was wondering how much we had been monitoring for it.

FARHAT: There has been a bit of literature on it. Specifically, what people have done is they've looked at mutations in the gene that is the target of remdesivir, RdRp, and we really haven't found many mutations there. The amount of sequencing that has been done of SARS-CoV-2 is pretty massive, at least in parts of the world where these drugs are being used at high volumes, so I would have expected to see more. We have recently done a study—it's not yet published—and found that mutations in the gene that would cause remdesivir resistance are selected against: They are more rare than you would expect by chance. We also found a negative association with disease severity with the mutation, meaning a virus that contains a mutation in the RdRp is less likely to cause severe COVID disease in a human. It might be because it's an essential protein for viral survival so if it mutates, the protein may not function as well.

GAZETTE: How concerning is it now that we've seen a case of this? Might there be more?

FARHAT: The bottom line is we don't know. There isn't enough data on the virus after treatment with remdesivir. But the fact that mutations in RdRp have been rare in the SARS-CoV-2 samples sequenced at diagnosis makes it less concerning. This is speculation, but not having observed mutations in RdRp in sequencing data may mean that even if resistance develops, it may be less likely to transmit to new patients. Also, the preliminary association between mutations in that gene and less-severe disease is reassuring, but does require confirmation in larger studies.

GAZETTE: Omicron is in the news, and there are all sorts of questions about what the many mutations do. How likely is it that drug resistance is one of the mutations for a variant like this?

FARHAT: There are no signs of remdesivir resistance in Omicron, based on the mutation data. At this point the major concern is the amount of variants in the spike protein itself, which is the target for vaccines, natural immunity, and monoclonal antibodies. And this is the reason the alarm bells have been rung. From the beginning of the pandemic, whenever a new variant comes out, the concern is that the vaccines are going to stop working. Omicron does have many more mutations in the spike protein than any of the other variants. Over the last two weeks, scientists around the world have rapidly shown that antibodies generated with vaccination are less neutralizing of Omicron. But the silver lining is that antibodies from individuals who have received the booster work better than those from patients who are vaccinated but have not yet received the booster. It is not yet clear what this means in our bodies as the data generated has mostly been from lab experiments. The clinical data is being actively collected. We will have to wait and see. The early indicators suggest that Omicron-related COVID is commonly mild, and severe outcomes will be delayed.

GAZETTE: Are there best practices from the past—the combination therapy we saw with HIV—that we should be using or at least aware of?

FARHAT: We're going to start to see the use of the new pills against COVID that have better activity than remdesivir. We have several drugs in our armamentarium now, which is a reason to be more reassured. The second intervention we can implement is that if patients don't seem to be responding to usual therapy, we may want to sequence or confirm whether or not they have resistance. Now that we're seeing some of it, it makes it much more worthwhile to consider testing for resistance, which we don't currently do. So it's the combination of reaching for additional drugs that are now available and testing and surveying for the presence of resistance mutations. This could be done for the individual patient

who may not be responding and on a population level, surveying for mutations similar to those reported in cases of remdesivir resistance, to see how many more we see.

GAZETTE: Is this an issue that's not going to go away? Are we locked in an arms race with this virus—in treatment as well as vaccination—that seems very adept at throwing a surprise at us every couple of months?

FARHAT: My personal view is that, in one sense, we lost the war; though in another sense, we won. We lost because it's likely that COVID's just going to be part of our lives moving forward, while we won because we were able to develop vaccines and therapies very early, and it has dramatically reduced the rate of severe disease.

Not only is the fact that Omicron is being observed now not surprising to me, but I suspect there are probably more variants that are undetected because we can't possibly sequence everything that's out there, especially in parts of the world that have limited access to vaccinations and to surveillance. Our task now is to double down on efforts to protect people around the world from developing severe disease by increasing access to preventatives and treatment.

GAZETTE: A year ago, we heard regularly that the more cases out there, the more likely there are going to be variants.

FARHAT: Vaccinating is essential for preventing severe disease. That's the No. 1 reason to vaccinate. It probably does lessen the emergence of variants, but I don't think it's going to eliminate it. I think that's too

optimistic a view. We're seeing asymptomatic and mild disease transmission among vaccinated individuals, and as long as the virus is around, it's going to mutate. So I don't think that stopping variants should necessarily be a goal. I expect that moving forward, we're going to need regular updating of the vaccine and regular vaccination, as we do for the flu. That's becoming more and more of a reality.

GAZETTE: So we're in this for the long haul.

FARHAT: Yes. Another thing to note about vaccination is that it can prevent resistance, because by preventing severe disease, you're preventing the need to use antivirals to begin with, and even the need to come into the hospital. That automatically reduces the risk of developing remdesivir resistance. Vaccination is a mantra that a lot of people have been pushing for bacterial resistance—develop vaccines for pneumonia, for example, the Pneumovax. That's definitely a strategy to tackle resistance emergence, and also the impact of resistance on health.

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