Sandra Fryhofer, MD, on lifting of J&J/Janssen vaccine pause

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In today’s COVID-19 Update, Sandra Fryhofer, MD, AMA liaison to the CDC’s Advisory Committee on Immunization Practices (ACIP), discusses the committee’s recommendation to lift the pause on the Johnson & Johnson/Janssen COVID-19 vaccine and what physicians need to know to help address patients' concerns.

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Speaker

- Sandra Fryhofer, MD, physician, AMA trustee and AMA liaison to CDC’s Advisory Committee on Immunization Practices

Transcript

Unger: Hello, this is the American Medical Association’s COVID-19 Update. Today, we’re discussing the decision to lift the pause on Johnson & Johnson’s COVID-19 vaccine. I'm joined today by Dr. Sandra Fryhofer, an internal medicine physician, adjunct associate professor of medicine at Emory University School of Medicine and an AMA trustee in Atlanta. Dr. Fryhofer is the AMA's liaison to the CDC’s Advisory Committee on Immunization Practices, or ACIP, and serves as the AMA's representative on the COVID-19 Vaccine Work Group. I'm Todd Unger, AMA's chief experience officer in Chicago. Well, Dr. Fryhofer, we spoke about 10 days ago when the decision had just been made to pause distribution of the Janssen vaccine—Janssen being the pharmaceutical arm of Johnson & Johnson. Last Friday, ACIP recommended lifting the pause. You were there, can you tell us more about this?
Dr. Fryhofer: That's right, Todd, I was there. The pause has been lifted, ACIP voted, and now it's official. Janssen's vaccine is back. It's back as an option for those 18 and older, but with an amended EUA, emergency use authorization. The official announcement came Friday night, April 23, just hours after ACIP finished its daylong deliberations. FDA has updated its Janssen EUA with an additional warranty. The bottom line, women under 50 should be made aware of a rare risk of blood clots and low platelets following vaccination. They also need to know there are other COVID vaccines out there that don't pose this small risk. This empowers patient choice. It also means vaccination sites and clinics should make clear which vaccine or vaccines are being offered and when. CDC and FDA also have coined a new name for this rare but serious combinations of blood clots and low platelets, TTS, thrombosis with thrombocytopenia syndrome.

Unger: Is it a surprise that the ACIP committee wasn't unanimous? It appeared that 10 people voted in favor and there were four against with an abstention? How does that work?

Dr. Fryhofer: Well after the vote, ACIP members had a chance to explain the why of how they voted. Pretty much all of them were in favor of resuming Janssen administration. The difference was where the warning should appear. The majority voted to keep the recommendation language simple. Recommend for those 18 and older under FDA's EUA; and for them, having warning details in the EUA was sufficient, especially when CDC verified plans to amplify messaging through additional education and outreach to both physicians and the public. The minority wanted the warning in the actual recommendation, which could be discouraging and add confusion. And comments from several other liaisons from other organizations also supported keeping the recommendation language simple for clarity and to avoid confusion.

Unger: Along those lines of the clarity and simplicity, how much detail is in that EUA from the FDA?

Dr. Fryhofer: There's a lot of detail, and it's in the warnings and precautions section. It's Section 5.2, lots of detail. It warns of increased risk of thrombosis combined with thrombocytopenia occurring one to two weeks after Janssen vaccination. The blood vessels involved include cerebral venous sinuses and other sites, including but not limited to large blood vessels in the abdomen, as well as veins in the lower extremities. It specifies that most cases were in females 18 to 49, and that some of them died. It gives warning signs patients should look for. Patients who’ve had the Janssen vaccine should seek immediate medical attention if they develop shortness of breath, chest pain, leg swelling, persistent abdominal pain, neurological symptoms, including severe or persistent headache or blurred vision, or petechiae beyond the site of where they got the vaccination.

It also urges health care professionals to be on the alert. So if you see a patient with blood clots or low platelets, you need to ask about recent COVID vaccination and consider this syndrome. The EUA also includes specific nuances about treatment and how the clinical course is similar to HIT, auto-immune heparin induced thrombocytopenia. Using heparin to treat these clots could be harmful. Alternative treatments may be needed. The EUA stopped short of specifically recommending platelet factor-4 HIT.
antibody testing to look for platelet and activating antibodies. For diagnosis and treatment, it does reference ASH, the American Society of Hematology, and actually links to the ASH website. Consulting a hematologist is advised. Patient and health care provider sheets have also been updated and now include this vital information.

**Unger:** Well, I know that part of the pause was to look and see if there were more cases or more cases have been developed. Can you talk about the chain of events that has occurred since then?

**Dr. Fryhofer:** Well, more cases have been confirmed, but here's the timeline as a reminder. February 27, FDA authorized emergency use of Janssen's viral vector COVID vaccine for those 18 and older. And as of April 12, more than 6.8 million doses had been administered here in the U.S. Then on April 13, just six and a half weeks after it was authorized, FDA and CDC issued that joint statement calling for the pause in Janssen vaccine administration, and this is because of safety signal from VAERS. CDC's Vaccine Adverse Event Reporting System revealed six patients with the rare type of blood clot, cerebral venous sinus thrombosis, that's CVST, in combination with thrombocytopenia, really low platelets. Now, all six patients were women age 18 to 48. One of them died. All six patients had received Janssen's single dose viral vector vaccine within the previous two weeks. ACIP met on April 14. No vote was taken. ACIP said they needed more data and information. The pause continued. The pause gave time to increase public awareness and to alert the medical community of the unique treatment required for what CDC now calls TTS, thrombosis with thrombocytopenia syndrome. CDC issued a health alert notification with important treatment guidance. Platelet-activating antibodies seemed to play a role. So, again, you don't treat with heparin a less platelet factor-4 HIT testing is negative. Non heparin anti-coagulants and immune globulin may be needed. Now, meanwhile CDC and FDA did more digging and confirmed an additional nine cases. So now there's a total of 15 cases. ACIP met again on April 23, 10 days after the pause was initiated. And after reviewing all of the available data, it was determined the benefits of vaccination outweigh the risk. The pause was lifted. Janssen vaccine administration has now resumed.

**Unger:** Dr. Fryhofer, when they analyzed the data, were they able to identify any other risk factors that might predispose someone to developing TTS?

**Dr. Fryhofer:** Well, they're still working on that risk refinement. Specific risk factors are still under investigation, but here's what we know so far. We have a total of 15 confirmed cases of TTS. All occurred in women age 18 to 59, median age 37. All occurred between one and two weeks after Janssen vaccination. All were female. None were pregnant. None were postpartum. Two were taking oral contraceptives. Two had hypertension, two were hypothyroid, seven had obesity. None of them had previous coagulation disorders. So far, age under 50 and female gender are really all we have. All these post-authorization cases were in females. However, one case did occur in Janssen's phase three trial in a young male age 25. So it can occur in males. Similar cases with the AstraZeneca vaccine did include more males, so it's not just females who can be affected.
Unger: Does TTS seem to be a class effect of viral vector vaccines?

Dr. Fryhofer: Well, Todd, it's certainly looking that way. These case report findings were foreshadowed by European reports of unexpected blood clots in patients within weeks of receiving AstraZeneca viral vector vaccine. Janssen representatives were quick to point out the two vaccines are not the same, and although both use viral vectors, the viral vectors are different. AstraZeneca uses a chimpanzee adenovirus in its viral vector vaccine. AstraZeneca's vaccine does not yet been authorized in the U.S. Janssen uses a human adenovirus called Ad26. And Janssen says this TTS syndrome has not appeared in studies of its other vaccines using this same Ad26 adenovirus platform, including their Ebola vaccine, which has been approved in Europe.

Unger: Have they seen this syndrome, TTS, with other vaccines authorized here in the U.S.?

Dr. Fryhofer: No, not so far. There've been more than 180 million doses of mRNA vaccine administered and there have been no reports of cerebral venous sinus thrombosis combined with thrombocytopenia in patients who have received mRNA vaccines by Pfizer or Moderna. Now there have been three reports of CVST in patients who received the Moderna vaccine, but all three of these patients had normal platelets. And as FDA's Dr. Peter Marks explained in a recent AMA webinar, which was fabulous, it's not just the cerebral venous sinus thrombosis. It's not just the thrombocytopenia. It's the combination of them occurring together that makes a pattern. The combination of the two symptoms, both blood clots and low platelets, that's the red flag. We are so fortunate in the U.S. to have a choice of COVID vaccines using different platforms. And unlike some other countries, the United States has authorized two other highly effective COVID vaccines which use a completely different platform, two double-dose mRNA vaccines. One by Moderna, the other by Pfizer. And I repeat, this rare but deadly combination of blood clots and low platelets has not been seen with Pfizer and Moderna COVID vaccines.

Unger: I mean, as you point out, it is rare and there are other things that are going on. For instance, doesn't COVID increase the risk of blood clots in itself?

Dr. Fryhofer: Yes, COVID is associated with blood clots. And in fact, at the ACIP meeting, ACIP showed a slide looking at hospitalized patients and the incidents of CVST two weeks after being diagnosed with COVID. It was 39 per million, which is a lot. They showed another summary slide that the risk of CVST after COVID, is five to six per million COVID infections. Now, in the safety presentation at ACIP for the Janssen vaccine, the overall TTS reporting rate so far is 15 confirmed cases and 7.98 million doses. So about 15 out of nearly 8 million doses. That translates to 1.9 cases per million people vaccinated. But if you look at it by age group, the reporting rate for females under 50 is higher, about 7 per million. The reporting rate was highest for women in their 30s at 11.8 per million. For females 50 and older, it's much lower, 0.9 per million, so less than one in a million. This is why younger women, those under 50, should be made aware of this rare risk of blood clots and low platelets following vaccination. There is risk, but we're in a pandemic and this vaccine is highly effective.
Unger: Lot of risk to weigh there, but the effectiveness of the vaccine is paramount. Can you talk a little bit more about the effectiveness of the Janssen vaccine?

Dr. Fryhofer: Well, in its phase three trial, Janssen's vaccine was 66.3% effective overall at preventing symptomatic COVID just 14 days after a single dose. It maintained at least 63% effectiveness across age sex, race and ethnic categories, and also for those with underlying medical conditions. The Janssen vaccine was 100% effective at preventing hospitalization from COVID by day 28 post-vaccination and there were no COVID associated deaths in those who were vaccinated. Right now, variants of interest and variants of concern are circulating here in the U.S. The Janssen vaccine was tested and was 52% effective in South Africa when the B.1.351 variant was dominant. So if you think about the risk of getting COVID, if you get it, you might be fine or not. You could transmit COVID to someone else who could die from it. And if you think about the long term effects of COVID, we're hearing about patients having the long-haul syndrome.

COVID disease can also damage the heart, the lungs, the brain. We've heard people talk about brain fog that they get after being infected with COVID. And yes, as we discussed, COVID disease itself can cause blood clots. And you'd never know until it happens if it's going to happen to you. Also, think of the risk of you or someone you love or care about being hospitalized or dying from COVID. So many people in this country have gone through this. The risk of hospitalization from COVID is 200 per million population. Death from COVID is 30 per million population. Now, granted the risk of hospitalization and death is higher in older patients. More older people than younger people have already been vaccinated because we started with the older people first, but we're seeing more and more variants, and variants could adversely affect severity of disease in younger patients. And that's a big concern.

Unger: And that is something we're reading a lot about in the news, but you follow that math that you're just going through there and there are a lot of great reasons to get vaccinated, obviously. But talk a little bit about why is it so important to have this vaccine. When we have two other vaccines that are highly effective, do we really need it?

Dr. Fryhofer: Todd, yes, we do need it, and here's why. Both of the mRNA vaccines require two doses. Janssen's vaccine is the only single dose vaccine option available. Its single dose regimen makes it a critical option for isolated, rural and transient populations, homebound patients, those experiencing homelessness, incarcerated persons, and also for migrant and seasonal workers who might not be in the same location when it comes time for that second vaccine dose. This one dose and you're done vaccine also means only one set of side effects, and that's certainly an added benefit, especially for those who can't miss work. And because it can be stored at normal refrigerator temperatures for up to three months, it doesn't require super freezers, this vaccine can reach places other vaccines cannot. It can be used to reach remote locations with mobile clinics. And remember, this is a global pandemic. These logistical advantages could greatly increase vaccination in other
countries.

**Unger:** I mean, all of those issues that you mentioned are so critical to access and access being so important right now in the phase that we're in. Dr. Fryhofer, this has been a great discussion. Do you want to sum it up?

**Dr. Fryhofer:** Well, I'm glad this one dose and you're done COVID vaccine is now back in action as an option, but please read the new EUA and make sure patients, especially women under 50, understand the warning. Vaccine safety surveillance for this and other signals will continue. Anyone can send a report to VAERS, CDC's Vaccine Adverse Event Reporting System. You do it online. It's not a HIPAA violation, and please encourage all your patients and everyone to get vaccinated. We must get vaccine into arms. That's the only way we're going to end this pandemic.

**Unger:** Absolutely. Well, thanks again for being here. That's it for today's COVID-19 Update. We'll be back with another segment shortly. For more information on COVID-19, visit AMA's resource center at ama-assn.org/COVID-19. Thanks for joining us. Please take care.

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