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CLINICAL PEARL UPDATE

April 2021

Johnson & Johnson (J&J/Janssen) COVID-19 Vaccine Pause

An abridged summary of events chronicling J&J COVID-19 Vaccine status, following the FDA/CDC recommended pause for review of safety data on Thrombosis-Thrombocytopenia Syndrome (TTS) [A]

To share this information with patients and residents, PharMerica encourages use of the attached CDC Posters!

FDA/CDC Issue Joint Recommendation to Suspend J&J Vaccine Administration

April 13th

The U.S. Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) issue a joint recommendation to pause administration of the J&J Vaccine, citing concern over 6 reported cases of **cerebral venous sinus thrombosis (CVST)** seen across >6.8 million doses administered in the U.S.

This statement notes that the 6 cases all occurred in women aged 18-48 years, with symptom onset between 6-13 days post vaccination. The FDA/CDC recognize that these adverse events appear to be extremely rare; however, out of an abundance of caution, recommend pausing administration to allow thorough review of safety data by the Advisory Committee on Immunization Practices (ACIP). This pause would allow for data aggregation and assessment, further subpopulation breakdown and for clinicians to be educated on this unique coagulopathy that requires treatment deviating from typical approaches.[1]

CDC Convenes ACIP to Review Findings

Emergency Meetings Held During Pause on April 14th and April 23rd

On April 14th, ACIP holds its first meeting to review post-authorization safety data for TTS after receipt of the J&J Vaccine. This inaugural meeting concludes with the voting members declining to change the current "pause" recommendation, citing a need for more complete evidence. Some members also stress concern that an indefinite pause could hurt the equitable vaccine rollout effort.[2]

During the meetings' interim, a dedicated ACIP subcommittee, dubbed the COVID-19 Vaccines Work Group (comprised of relevant experts in subjects such as infectious diseases, vaccinology and public health), reviews a risk-benefit assessment of TTS post-vaccination. The risk-benefit analysis includes an assessment of both population- and individual-level risks and benefits. A summary of these findings are presented again to ACIP during the second emergency meeting on April 23rd. The CDC's MMWR on this topic states that "The summary of evidence showed that the single-dose Janssen COVID-19 Vaccine is a highly effective and flexible (e.g., stored at refrigerator temperatures) prevention tool that can be useful in communities with increasing COVID-19 incidence and emerging variants of SARS-CoV-2, the virus that causes COVID-19. Limiting vaccine use to specific populations (i.e., by age or sex) could reduce numbers of TTS cases but could also challenge public health implementation, limit personal choice, and disproportionately affect populations with barriers to vaccine access or who have difficulty returning for a second dose. If the Janssen COVID-19 Vaccine were no longer available, excess COVID-19 cases and deaths could occur."[3]

On April 23rd, ACIP votes 10–4 in favor of **reaffirming its interim recommendation for use of the J&J COVID-19 Vaccine in all persons aged ≥18 years under the FDA's EUA**. Post-vote follow up reveals ACIP members who voted "no" would have preferred stronger language regarding the risk for TTS among women aged 18–49 years. All ACIP members agree that provider and patient education regarding the risk for TTS after vaccination among women aged 18–49 years and awareness of other COVID-19 vaccine options are critical as J&J COVID-19 vaccination resumes.[3]

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FDA/CDC Lift Recommended Pause following Thorough Safety Review

April 23rd

A press announcement for immediate release is jointly published stating, "Following a thorough safety review, including two meetings of the CDC's Advisory Committee on Immunization Practices, the U.S. Food and Drug Administration and the U.S. Centers for Disease Control and Prevention have determined that **the recommended pause regarding the use of the Johnson & Johnson (Janssen) COVID-19 Vaccine in the U.S. should be lifted and use of the vaccine should resume**."[4]

Summary of FDA/CDC Findings following ACIP Review [4]

- Use of the Janssen COVID-19 Vaccine should be resumed in the United States.
- The FDA and CDC have confidence that this vaccine is safe and effective in preventing COVID-19.
- The FDA has determined that the available data show that the vaccine's known and potential benefits outweigh its known and potential risks in individuals 18 years of age and older.
- At this time, the available data suggest that the chance of TTS occurring is very low, but the FDA and CDC will remain vigilant in continuing to investigate this risk.
- Health care providers administering the vaccine and vaccine recipients or caregivers should review the Janssen COVID-19 Vaccine Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) and Fact Sheet for Recipients and Caregivers, which have been **revised** to include information about the risk of this syndrome, which has occurred in a very small number of people who have received the Janssen COVID-19 Vaccine.

Summary of Revisions made to the J&J COVID-19 Vaccine EUA Fact Sheet for Vaccination Providers[5]

WARNINGS AND PRECAUTIONS

Subsection **5.2 'Thrombosis with Thrombocytopenia'** including the information below was added to this section:

- Reports of adverse events following use of the Janssen COVID-19 Vaccine under emergency use authorization suggest an increased risk of thrombosis involving the cerebral venous sinuses and other sites (including but not limited to the large blood vessels of the abdomen and the veins of the lower extremities) combined with thrombocytopenia and with onset of symptoms approximately one to two weeks after vaccination.
- Most cases of thrombosis with thrombocytopenia reported following the Janssen COVID-19 Vaccine have occurred in females ages 18 through 49 years; some have been fatal.
- Specific risk factors for thrombosis with thrombocytopenia following the Janssen COVID-19 Vaccine and the level of potential excess risk due to vaccination are under investigation.
- Based on currently available evidence, a causal relationship between thrombosis with thrombocytopenia and the Janssen COVID-19 Vaccine is plausible.
- Healthcare professionals should be alert to the signs and symptoms of thrombosis with thrombocytopenia in individuals who receive the Janssen COVID-19 Vaccine.
- The clinical course shares features with autoimmune heparin-induced thrombocytopenia.
- In individuals with suspected thrombosis with thrombocytopenia following the Janssen COVID-19 Vaccine, the use of heparin may be harmful and alternative treatments may be needed.
- Consultation with hematology specialists is strongly recommended.
- The American Society of Hematology has published **considerations** relevant to the diagnosis and treatment of thrombosis with thrombocytopenia following the Janssen COVID-19 Vaccine.

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- Recipients of Janssen COVID-19 Vaccine should be instructed to seek immediate medical attention if they develop shortness of breath, chest pain, leg swelling, persistent abdominal pain, neurological symptoms (including severe or persistent headaches or blurred vision), or petechiae beyond the site of vaccination.

OVERALL SAFETY SUMMARY

The following information was added to this section:

- Thrombosis involving large blood vessels, including the cerebral venous sinuses, portal vein, lower extremity veins, and pulmonary artery, with thrombocytopenia have been reported following the Janssen COVID-19 Vaccine.

CLINICAL TRIALS EXPERIENCE, SERIOUS ADVERSE EVENTS (SAES) AND OTHER EVENTS OF INTEREST

- Information was added to convey that the case of transverse sinus thrombosis observed in study COV3001 (J&J's Phase 3 Clinical Trial, AKA "Ensemble") also included thrombocytopenia and that onset of symptoms was 8 days post-vaccination.
- Clarification was made to state that for adverse events for which imbalances were observed in vaccine recipients compared to placebo recipients, a causal relationship with the Janssen COVID-19 Vaccine could not be determined based on study COV3001.
- The following information was also added:
    - However, taking into consideration post-authorization experience, a causal relationship with Janssen COVID-19 Vaccine is plausible for thrombosis with thrombocytopenia.

POST AUTHORIZATION EXPERIENCE

Subsection **6.2 'Post Authorization Experience"** including the information below was added:

- The following adverse reactions have been identified during post-authorization use of the Janssen COVID-19 Vaccine. Thrombosis involving large blood vessels, including the cerebral venous sinuses, portal vein, lower extremity veins, and pulmonary artery, combined with thrombocytopenia.

Summary of Revisions made to the J&J COVID-19 Vaccine EUA Fact Sheet for Recipients & Caregivers[5]

EUA Fact Sheet for Recipients and Caregivers has been updated to include the following information:

- The remote risk of blood clots involving blood vessels in the brain, abdomen, legs, along with low levels of platelets
- To note that most people who developed blood clots and low levels of platelets were females ages 18-49 years
- To note that for people who have developed blood clots and low levels of platelets following vaccination, symptoms began approximately one to two-weeks following vaccination
- To inform vaccine recipients that they should seek medical attention right away if they have any of the following symptoms after receiving Janssen COVID-19 Vaccine:
    - Shortness of breath
    - Chest pain
    - Leg swelling
    - Persistent abdominal pain
    - Severe or persistent headaches or blurred vision
    - Easy bruising or tiny blood spots under the skin beyond the site of the injection

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Glossary

A. **Thrombosis-Thrombocytopenia Syndrome (TTS)**: a rare syndrome that involves acute venous or arterial thrombosis and new onset thrombocytopenia in patients with no recent known exposure to heparin. This is a newly described syndrome; although the mechanism that causes TTS is not fully understood, TTS appears to be similar to heparin-induced thrombocytopenia, a rare reaction to heparin treatment. In the United States, 12 of 15 persons with TTS that occurred after Janssen COVID-19 vaccination had CVST with thrombocytopenia. The clinical presentation of the reported cases among recipients of the Janssen COVID-19 Vaccine (which is based on a human adenoviral vector) is similar to that of recently reported cases from Europe after receipt of the AstraZeneca COVID-19 Vaccine (which is based on a chimpanzee adenoviral vector), a vaccine that is not authorized for use in the United States. All post-authorization U.S. cases occurred among women; one case of CVST with thrombocytopenia occurred in a man, in the 18–49 years age group, during the Janssen Phase III clinical trial. No cases of CVST with thrombocytopenia have been reported after receipt of either of the two mRNA COVID-19 vaccines authorized for use in the United States (CDC, unpublished data, 2021).[3]

References

1. Marks P. US Food and Drug Administration. Joint CDC and FDA Statement on Johnson & Johnson COVID-19 Vaccine. 13 Apr 2021. Web. 30 Apr 2021. https://www.fda.gov/news-events/press-announcements/joint-cdc-and-fda-statement-johnson-johnson-covid-19-vaccine

2. Melillo G. American Journal of Managed Care. Pause of J&J Vaccine to Continue; ACIP to Reconvene After More Data Collected. 14 Apr 2021. Web. 30 Apr 2021. https://www.ajmc.com/view/pause-of-j-j-vaccine-to-continue-acip-to-reconvene-after-more-data-collected

3. MacNeil JR, Su JR, Broder KR, et al. Updated Recommendations from the Advisory Committee on Immunization Practices for Use of the Janssen (Johnson & Johnson) COVID-19 Vaccine After Reports of Thrombosis with Thrombocytopenia Syndrome Among Vaccine Recipients — United States, April 2021. MMWR Morb Mortal Wkly Rep 2021;70:651-656. DOI: http://dx.doi.org/10.15585/mmwr.mm7017e4

4. US Food and Drug Administration. FDA and CDC Lift Recommended Pause on Johnson & Johnson (Janssen) COVID-19 Vaccine Use Following Thorough Safety Review. 23 Apr 2021. Web. 30 Apr 2021. https://www.fda.gov/news-events/press-announcements/fda-and-cdc-lift-recommended-pause-johnson-johnson-janssen-covid-19-vaccine-use-following-thorough

5. Gruber M. Gruber m to Walawalkar R. 23 Apr 2021. EUA 27205 - EUA of Janssen COVID-19 Vaccine, Issued on February 27, 2021, Under Section 564 of the Federal Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. 360bbb-3) Multiple Amendments dated April 20, 2021 - April 23, 2021 to Update the Authorized Fact Sheet for Healthcare Providers Administering Vaccine, the Authorized Fact Sheet for Recipients and Caregivers. Last modified 23 Apr 2021. https://www.fda.gov/media/147865/download

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What do I need to know about
Johnson & Johnson's Janssen COVID-19 Vaccine (J&J/Janssen) now?

There is a risk of a rare but serious condition involving blood clots and low platelets in people after receiving the J&J/Janssen COVID-19 Vaccine. **This risk is very low.**

This problem is rare and happened in about 7 per 1 million vaccinated women between 18 and 49 years old.

For women 50 years and older and men of any age, this problem is even more rare.

This problem has not been linked to the other two COVID-19 vaccines (Pfizer-BioNTech and Moderna).

SHOULD I STILL GET VACCINATED with this or other vaccines to protect against COVID-19?

YES, experts agree that all COVID-19 vaccines help prevent COVID-19 disease, especially severe illness and death.

The known and potential benefits of all COVID-19 vaccines outweigh the known and potential risks. You need only one dose of the J&J/Janssen vaccine. You need two doses of the other two vaccines (Pfizer-BioNTech and Moderna).

What if I already got the J&J/Janssen COVID-19 Vaccine?

For three weeks after getting the J&J/Janssen vaccine, you should watch for possible symptoms of a blood clot with low platelets, like:

- Severe headache or blurred vision
- Shortness of breath
- Chest pain
- Leg swelling
- Gut pain that does not go away
- Easy bruising or tiny blood spots under the skin

Get medical care right away if you develop any of these symptoms.

Learn more by talking with your doctor, nurse, or pharmacist, or visit the CDC website: **www.cdc.gov**.

cdc.gov/coronavirus

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Effective April 23, 2021, CDC and FDA recommend that use of the Johnson & Johnson's Janssen (J&J/Janssen) COVID-19 Vaccine resume in the United States.

Your answers to patient questions matter. Your strong recommendation can help them make an informed decision and feel confident about getting vaccinated against COVID-19.

If your patient is **FEMALE AND UNDER 50 YEARS OLD**

- Discuss the **rare** risk of blood clots with low platelets after vaccination with J&J/Janssen vaccine. Data show the risk is about **7 in 1 million** women vaccinated between the ages of 18–49.
- Discuss the option to receive other COVID-19 vaccines (Pfizer-BioNTech, Moderna).
- Consider and discuss if the patient will be able and willing to complete the two-dose vaccine series.

Talking with patients

I STRONGLY ENCOURAGE YOU TO GET VACCINATED.

- » COVID-19 vaccine safety is a top priority for the federal government, and all reports of health problems following COVID-19 vaccination are taken very seriously.
- » What experts and I believe is that the known and potential benefits of the J&J/Janssen COVID-19 Vaccine **outweigh its known and potential risks.**
- » **I strongly encourage you to get a COVID-19 vaccine that we both feel comfortable with you receiving.**

Discuss risk with your patients:

There had been more than nearly 8 million doses of the J&J/Janssen COVID-19 Vaccine administered as of April 23, 2021. Since COVID-19 vaccines were first used in the United States, scientists and doctors have continuously and carefully reviewed all reports of vaccine side effects.

Data suggest the J&J/Janssen COVID-19 Vaccine is likely associated with a rare side effect that involves blood clots with low platelets.

Nearly all reports of this serious condition have been in adult women younger than 50 years old.

We know the safety systems are in place are working.

COVID-19 vaccines have undergone and will continue to undergo the most intensive safety monitoring in U.S. history.

Reports showed that symptoms of this side effect started between 6 and 15 days after vaccination.

These reports occurred in about 7 per 1 million vaccinations among women 18 through 49 years of age, and .9 per 1 million among women 50 years and older.

Summary: The available data show that the vaccine's known and potential benefits outweigh its known and potential risks.

More information: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/JJUpdate.html

cdc.gov/coronavirus

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