Do Corticosteroid Injections for the Treatment of Pain Influence the Efficacy of Adenovirus Vector-Based COVID-19 Vaccines?

Haewon Lee, MD1; Jennifer A. Punt, A.B., VMD, PhD2; Jaymin Patel, MD3; Milan P. Stojanovic, MD4; Belinda Duszynski, BS5; and Zachary L. McCormick, MD6, on behalf of the Spine Intervention Society’s Patient Safety Committee

1 University of California, San Diego, Department of Orthopedic Surgery, San Diego, California, USA
2 University of Pennsylvania School of Veterinary Medicine, Philadelphia, Pennsylvania, USA
3 Emory University, Department of Orthopaedics, Atlanta, Georgia, USA
4 Anesthesiology, Critical Care and Pain Medicine Service, VA Boston Healthcare System, Harvard Medical School, Boston, Massachusetts, USA
5 Spine Intervention Society, Hinsdale, Illinois, USA
6 University of Utah, Division of Physical Medicine and Rehabilitation, Salt Lake City, Utah, USA

Myth: Corticosteroid injection for the treatment of pain is known to decrease the efficacy of the adenovirus vector-based vaccines for COVID-19.

Fact: There is currently no direct evidence to suggest that a corticosteroid injection before or after the administration of an adenovirus vector-based COVID-19 vaccine decreases the efficacy of the vaccine.

• However, based on the known timeline of hypothalamic-pituitary-adrenal (HPA) axis suppression following epidural and intraarticular corticosteroid injections, and the timeline of the reported peak efficacy of the Janssen and AstraZeneca vaccines, physicians should consider timing an elective corticosteroid injection such that it is administered no less than two weeks prior to and no less than two weeks following a COVID-19 adenovirus vector-based vaccine dose, whenever possible.

• We emphasize the importance of risk/benefit analysis and shared decision-making in determining the timing of corticosteroid injections for pain indications in relation to receipt of a COVID-19 vaccine given that patient-specific factors will vary.

Introduction

In the midst of the ongoing COVID-19 pandemic, the Janssen (a.k.a., Johnson & Johnson) COVID-19 vaccine (Ad26.COV2.S) recently received the United States Food and Drug Administration’s approval for emergency use authorization [1] and the AstraZeneca-Oxford University vaccine (AZD1222) has been in use worldwide since early 2021. The Janssen vaccine is a recombinant vector vaccine that uses a human adenovirus (Ad26) to express the entire length of the SARS-CoV-2 spike protein. The AstraZeneca vaccine is a chimpanzee adenoviral vectored vaccine with full length SARS-CoV-2 spike insert [2]. In contrast to the current mRNA vaccine options, which require two doses to achieve optimal efficacy, the Janssen COVID-19 vaccine is administered as a single dose [1]. Despite mechanistic properties similar to the Janssen vaccine, the AstraZeneca vaccine requires two doses to achieve optimal efficacy [2]. Additionally, as adenovirus vector-based agents, the Janssen and AstraZeneca COVID-19 vaccines remain stable at normal refrigerator temperatures between 2°C to 8°C (36°F to 46°F) allowing ease of storage [3,4]. They do not require reconstitution, which provides ease of preparation and administration compared to the mRNA based COVID-19 vaccines currently available [4,5]. The purpose of this FactFinder is to examine the potential influence of corticosteroid injection for pain on the efficacy of the Janssen and AstraZeneca COVID-19 vaccines, and to delineate the optimal timing of corticosteroid injections before and after vaccine administration.
DO CORTICOSTEROID INJECTIONS FOR THE TREATMENT OF PAIN INFLUENCE THE EFFICACY OF ADENOVIRUS VECTOR-BASED COVID-19 VACCINES?

SPINE INTERVENTION SOCIETY
FACTFINDERS FOR PATIENT SAFETY

Adenovirus Vector-Based Vaccines

Adenoviruses contain a single linear double-stranded DNA genome of approximately 26-45 kb [6,7]. This relatively small genome size lends the adenovirus to easy manipulation for therapeutic integrative purposes. Additionally, the genome can be altered to prevent viral replication. These characteristics make adenoviruses ideal candidates for the transfer of foreign material. Most adenoviruses cause only mild disease in immunocompetent humans. They can be grown to high titers in tissue culture. Their relative thermostability lends to ease of clinical use in transport, storage, and administration [7].

Janssen COVID-19 Vaccine (Ad26.COV2.S)

The Janssen COVID-19 vaccine is a recombinant, replication-deficient adenovirus-based vector (Ad26), encoding a stabilized variant of the SARS-CoV-2 Spike (S) protein [8]. It is approved for use in individuals at least 18 years of age. The Phase 3 ENSEMBLE trial evaluated the efficacy and safety of the Janssen COVID-19 vaccine and was conducted in the United States, Latin America, and South Africa [7]. This trial demonstrated 72% efficacy in the United States, and 66% [95% Confidence Interval (CI): 59.9%-71.8%] efficacy overall at preventing moderate to severe COVID-19 infections ≥14 days after vaccination [8,9]. Efficacy against severe disease was observed to increase over time with no cases in vaccinated participants reported after day 49 [9]. Vaccine efficacy in preventing hospitalization ≥14 days after vaccination was 93.1% (95% CI: 71.1%-98.4%). No COVID-19-associated hospitalizations occurred ≥28 days after vaccination in the vaccine group, and 16 occurred in the placebo group (vaccine efficacy =100%; 95% CI: 74.3%-100.0%)[8].

An interim analysis of the Janssen vaccine phase 1-2a trial revealed strong evidence of cellular immunogenicity in the 18–55-year-old cohort, as well as both cellular and humoral immunogenicity in the 65 and older cohort as early as day 15. A humoral response was observed at day 29 in the younger cohort. In these phases of the vaccine trial, participants received a second dose of either low-dose, high-dose, or placebo vaccine 56 days after the first dose. In all groups, antibody titers either remained stable or increased and remained stable during 71 days of follow-up after the initial vaccine dose [10].

COVID-19 Vaccine AstraZeneca (AZD1222)

The AstraZeneca vaccine’s efficacy at preventing symptomatic COVID-19 occurring 15 days or more after receiving two doses given four weeks apart was 76% (95% CI: 68%-82%) overall, with vaccine efficacy of 85% (95% CI: 58%-95%) in adults 65 years and older. The vaccine demonstrated 100% efficacy in preventing severe or critical disease and hospitalization [11].

Effect of Single-Dose Corticosteroid on Immunogenicity and Hypothalamic-Pituitary Axis (HPA)

The literature on the effect of corticosteroid injections on vaccine immunogenicity is not well developed. It has been established that patients receiving chronic corticosteroid therapy for rheumatologic or pulmonary disorders generate an adequate antibody response to vaccines [12,13]. However, the effect of single corticosteroid injections on vaccine efficacy is not clear. There is one small retrospective study that suggests the efficacy of the influenza vaccine may be affected by the use of intraarticular corticosteroid injection [13]. This study reported that a single intraarticular corticosteroid injection was associated with increased risk of influenza infection in patients who had received the influenza vaccine [RR=1.52 (CI=1.2-1.93)], compared to a similar cohort who had not received a corticosteroid injection. While acknowledging the limitations of this study, the results suggest a relationship between intraarticular corticosteroid injections and increased risk of influenza infection in vaccinated individuals younger than age 65. Further studies are needed to confirm this finding.

The effect of corticosteroid injections on the HPA axis is better understood. As previously described, following a single intraarticular corticosteroid injection, the HPA axis and serum cortisol levels are suppressed for one to four weeks, and in some cases longer [14-16]. Even a relatively low-dose triamcinolone (20 mg) intraarticular injection influences the HPA-axis for one to two weeks. Epidural corticosteroid injections are known to have systemic endocrine effects similar to those of intraarticular corticosteroid injections [17-19].

It is not clear if effects on the adaptive immune response and immunological memory mirror the timing of hypothalamic-pituitary-adrenal (HPA) axis suppression following spinal and musculoskeletal corticosteroid injections. However, the known window of HPA axis suppression following such injections provides the ability for cautious extrapolation.
Corticosteroids in the Adenovirus Vector-based Vaccine Trials

The potential effect of corticosteroid below the immunosuppressive threshold on the efficacy of the Janssen COVID-19 vaccine has not been described. The Phase 3 ENSEMBLE trial excluded participants receiving chronic or recurrent doses of systemic corticosteroids within six months prior to the receipt of the study vaccine and also during the study period. An immunosuppressive steroid dose was considered to be ≥ two weeks of daily prednisone 20 mg equivalents. Similar to the mRNA vaccine trials, the study allowed steroids at non-immunosuppressive doses and permitted ocular, topical, and inhaled routes. However, there was no subanalysis examining whether participants who were exposed to corticosteroid before or after vaccination exhibited reduced efficacy compared to those who were not exposed to corticosteroid.

For comparison to the two-week limit of 280mg prednisone equivalents (20mg daily), a typical standard dose of corticosteroid used for pain indications amounts to approximately 67 mg of oral prednisone equivalents [20]. It must be noted that injected and oral corticosteroids are absorbed differently, dependent on corticosteroid type. Direct head-to-head comparison studies of the specific physiological and immunological effects at equivalent doses have not been performed.

The AstraZeneca study excluded patients who had been prescribed immunosuppressant medications within 6 months (≥ 20 mg per day of prednisone or its equivalent, given daily or on alternate days for ≥ 15 days within 30 days prior to administration of the vaccine). Topical/inhaled steroids and short-term oral steroids (course lasting ≤ 14 days) were permitted [21]. There were no reported data specifically examining corticosteroid exposure during the trial within participants who developed symptomatic COVID-19.

There is no direct evidence that corticosteroids within the range of doses for pain indications influence the immunogenicity of the adenovirus vector-based COVID-19 vaccines. There is low-quality evidence that corticosteroid injections may be linked to an increased risk of infection with the influenza vaccine. Therefore, clinicians must weigh the benefit of administering an adenovirus vector-based vaccine without unnecessary delay and potentially waiting to perform epidural or intraarticular corticosteroid injections. We recommend an evidence-informed, shared decision-making process. This must be carefully considered in immunocompromised patients.

Summary and Recommendations

Key Points:

- Synthesis of the best evidence related to HPA axis suppression indicates that there is attenuation of the immune response following a corticosteroid injection in the typical dose range for pain indications, greatest at one week, and to a lesser extent at two weeks following an injection.
- In early analysis of phase 1-2a and phase 3 trial data, the Janssen COVID-19 vaccine was found to elicit cellular and humoral immune responses and also confer clinical protection as early as day 14 following administration. The AstraZeneca study reported findings at 15 days after the second dose was administered, four weeks following a first dose.
- The Janssen phase 3 trial allowed corticosteroid use at or below the equivalent of prednisone 20 mg/day and permitted ocular, topical, and inhaled routes. Topical/inhaled steroids or short-term oral steroids (course lasting ≤ 14 days) were permitted in the AstraZeneca studies. However, no subanalyses were provided in either trial to determine whether participants who were exposed to corticosteroid before or after vaccination exhibited reduced efficacy compared to those who were not exposed to corticosteroid.
Recommendations:

- Given the known timeline of HPA axis suppression following epidural and intraarticular corticosteroid injections, and the timeline of the reported earliest efficacy of these vaccines (two weeks after administration of the Janssen vaccine and 15 days after the second dose of the AstraZeneca vaccine), physicians should consider timing an elective corticosteroid injection such that it is administered no less than two weeks prior to and no less than two weeks following a COVID-19 adenovirus vector-based vaccine dose, whenever possible.

- Notably, this timeframe is not identical to the window recommended for the timing of corticosteroid injections in relation to mRNA COVID-19 vaccines. While vaccine efficacy was demonstrated at seven days after the second mRNA COVID-19 vaccine dose in the Pfizer trial [22], there are no data on efficacy for the adenovirus COVID-19 vaccines at seven days post-injection. The earliest efficacy data reported for the adenovirus vaccines are at two weeks following final dose administration. However, for practical practice management, it may be reasonable to schedule corticosteroid injections no earlier than two weeks post-vaccination, regardless of vaccine type in order to simplify timing protocols.

- We emphasize the importance of shared decision-making between the patient and physician in determining the timing of corticosteroid injections for pain in relation to receipt of a COVID-19 vaccine. Individual circumstances may necessitate a corticosteroid injection outside the recommended window. We recommend patient-specific risk/benefit analysis and shared decision-making.

- These recommendations may change as more direct evidence regarding the effect of corticosteroid injection on COVID-19 adenovirus vector-based vaccine efficacy becomes available.

References

1. Food and Drug Administration. Janssen COVID-19 Vaccine Frequently Asked Questions. https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/janssen-covid-19-vaccine-frequently-asked-questions. [Accessed on March 29, 2021].

2. AZD1222 US Phase III Primary Analysis Confirms Safety and Efficacy. https://www.astrazeneca.com/content/astrazeneca/media-centre/press-releases/2021/azd1222-us-phase-iii-primary-analysis-confirms-safety-and-effficacy.html. [Accessed on March 29, 2021].

3. Food and Drug Administration. Fact Sheet For Healthcare Providers Administering Vaccine (Vaccination Providers) Emergency Use Authorization (EUA) of the Janssen Covid-19 Vaccine To Prevent Coronavirus Disease 2019 (Covid-19). https://www.fda.gov/media/146304/download. [Accessed on March 29, 2021].

4. Reg 174 Information for UK Healthcare Professionals: COVID-19 Vaccine AstraZeneca, solution for injection in multidose container COVID-19 Vaccine (ChAdOx1-S [recombinant]). https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/963838/AZD1222_Information_for_Healthcare_Professionals_-_22-02-2021.pdf. [Accessed on March 29, 2021].

5. Centers for Disease Control and Prevention. Janssen COVID-19 Vaccine (Johnson & Johnson) Questions https://www.cdc.gov/vaccines/covid-19/info-by-product/janssen/janssen-faqs.html. [Accessed on March 29, 2021].

6. Davaison AJ, Benkő M, Harrach B. Genetic content and evolution of adenoviruses. J Gen Virol 2003;84(11):2895-2908.

7. Tatsis N, Ertl HC. Adenoviruses as vaccine vectors. Molecular Therapy 2004;10(4):616-629.

8. Centers for Disease Control and Prevention. Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Authorized in the United States. https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html. [Accessed on March 29, 2021].

9. Food and Drug Administration. Janssen COVID-19 Vaccine EUA FDA Review Memorandum. https://www.fda.gov/media/146338/download. [Accessed on March 29, 2021].

10. Sadoff J, Le Gars M, Shukarev G, Heerwegh D, Truyers C, de Groot AM, Stoop J, Tete S, Van Damme W, Leroux-Roels I, Berghmans PJ, Kimmel M, Van Damme P, de Hoon J, Smith W, Stephenson KE, De Rosa SC, Cohen KW, McElrath MJ, Cormier E, Scheper G, Barouch DH, Hendriks J, Struyf F, Douoguih M, Van Hoof J, Schuitemaker H. Interim Results of a Phase 1-2a Trial of Ad26.COV2.S Covid-19 Vaccine. N Engl J Med. 2021 Jan 13:NEJMoa2034201.

11. Kubiet MA, Gonzalez-Rothi RJ, Cottry R, Bender BS. Serum antibody response to influenza vaccine in pulmonary patients receiving corticosteroids. Chest 1996;110(2):367-70.

12. Herron A, Dettleff G, Hixon B, Brandwin L, Ortbals D, Hornick R, Hahn B. Influenza vaccination in patients with rheumatic diseases. Safety and efficacy. JAMA 1979;242(1):53-6.

13. Sytsma TT, Greenlund LK, Greenlund LS. Joint corticosteroid injection associated with increased influenza risk. Mayo Clin Proc Innov Qual Outcomes 2018;2(2):194-198.
14. Miller DC, Patel J, Gill J, Mattie R, Saffarian M, Schneider BJ, Popescu A, Babaria V, McCormick ZL. Corticosteroid injections and COVID-19 infection risk. Pain Med 2020;21(8):1703-1706.

15. Weitof T, Ronnblom L. Glucocorticoid resorption and influence on the hypothalamic-pituitary-adrenal axis after intra-articular treatment of the knee in resting and mobile patients. Ann Rheum Dis 2006;65:955-7.

16. Habib, GS. Systemic effects of intra-articular corticosteroids. Clin Rheumatol 2009;28:749-56.

17. Habib G, Jabbour A, Artul S, Hakim G. Intra-articular methylprednisolone acetate injection at the knee joint and the hypothalamic-pituitary-adrenal axis: a randomized controlled study. Clin Rheumatol 2014;33(1):99-103.

18. Friedly JL, Comstock BA, Heagerty PJ, Bauer Z, Rothman MS, Suri P, et al. Systemic effects of epidural steroid injection for spinal stenosis. Pain 2018;159:876-883.

19. Abdul AJ, Ghai B, Bansal D, Sachdeva N, Bhansali A, Dhatt SS. Hypothalamic pituitary adrenal cortical axis suppression following a single epidural injection of methylprednisolone acetate. Pain Physician 2017;20:E991-E1001.

20. GlobalRxPh. https://globalrph.com/medcalcs/corticosteroid-converter-based-on-anti-inflammatory-potency/. [Accessed on March 29, 2021].

21. A Phase III Randomized, Double-blind, Placebo-controlled Multicenter Study in Adults to Determine the Safety, Efficacy, and Immunogenicity of AZD1222, a Non-replicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19. https://s3.amazonaws.com/ctr-med-7111/D8110C00001/52bec400-80f6-4c1b-8791-0483923d0867/c8070a4e-6a9d-46f9-8c32-cece903592b9/D8110C00001_CSP-v2.pdf. [Accessed on March 29, 2021].

22. Lee H, Punt JA, Miller DC, Nagpal A, Smith CC, Sayeed Y, Patel J, Stojanovic MP, Popescu A, McCormick ZL; Spine Intervention Society’s Patient Safety Committee. Do corticosteroid injections for the treatment of pain influence the efficacy of mRNA COVID-19 vaccines? Pain Med 2021 Feb 19;pnab063. doi: 10.1093/pm/pnab063. [Epub ahead of print.]