FACTFINDERS FOR PATIENT SAFETY

Do Corticosteroid Injections for the Treatment of Pain Influence the Efficacy of mRNA COVID-19 Vaccines?

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Myth: Corticosteroid injection for the treatment of pain and inflammation is known to decrease the efficacy of the messenger ribonucleic acid (mRNA)-vaccines for COVID-19.

Fact: There is currently no direct evidence to suggest that a corticosteroid injection before or after the administration of an mRNA 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 Pfizer-BioNTech and Moderna vaccines, physicians should consider timing an elective corticosteroid injection such that it is administered no less than two weeks prior to a COVID-19 mRNA vaccine dose and no less than one week following a COVID-19 mRNA vaccine dose, whenever possible.**

Introduction

Currently, there are two FDA-approved mRNA vaccines that demonstrate efficacy against COVID-19. They are the Pfizer-BioNTech COVID-19 Vaccine (previously "BNT162b2"), and the Moderna COVID-19 Vaccine (previously "mRNA-1273").

While the mRNA platform facilitated the rapid development of vaccines against COVID-19, the potential effects of therapeutic injected corticosteroid for the treatment of pain and inflammation on the ability of these mRNA vaccines to produce immunological memory and protection from COVID-19 have not been described. Given the effort to provide rapid and widespread access to these vaccines in order to curtail the COVID-19 pandemic, the effect of injected corticosteroid treatment on mRNA vaccine efficacy is unknown.

Here, we discuss the current state of evidence that provides guidance regarding the following two clinical questions:

1. Does corticosteroid injection *before* mRNA COVID-19 vaccine administration influence immunological memory and subsequent vaccine efficacy and during what window of time?
2. Does corticosteroid injection *after* mRNA COVID-19 vaccine administration influence immunological memory and subsequent vaccine efficacy and during what window of time?

Mechanisms and Time Course of Immunological Memory Formed by the Adaptive Immune System

Various cells and molecules of the innate and adaptive immune systems work together to create an integrated defense system against pathogens. The portion of a pathogen or other 'non-self' agent capable of engaging the immune system is known as an antigen. The innate immune system is the first line of defense, which mounts an immediate, but non-antigen-specific response over hours or days to try and eliminate the foreign invader and prevent the establishment of an infection. Once the level of antigen surpasses a certain threshold, the more specific adaptive immune system, consisting of both a humoral immunity (antibody-mediated) and cellular immunity (involving T and B lymphocytes), is engaged. Adaptive immunity requires several days to weeks to fully mature, but

ultimately helps provide specific, long-lasting protection once immunological memory has been established [2].

To initiate an adaptive immune response, specialized receptors on lymphocytes detect either native circulating antigen, in the case of B cells, or through engagement with antigen-presenting cells, such as dendritic cells and macrophages, which present antigen fragments directly to T cells. This engagement with antigen causes activation of lymphocytes and differentiation into distinct subsets with specialized effector functions. During the first seven days of the initial exposure to antigen, the primary immune response is set into motion. Antigen presenting cells traffic to secondary lymphoid organs, present antigen and activate antigen-specific T cells. During the four to five days of rapid cell division that follow, these activated T cells proliferate and differentiate into specialized subsets that can help B cells to generate antigen specific antibodies, help other T cells to develop into killers of infected cells, and activate other immune subsets by the release of immune mediators such as interferon or tumor necrosis factors (TNFs) [3]. All subsets of T and B cells also form long-lived memory cells that are responsible for protection against subsequent infection.

The role of T cells in directing and amplifying an immune response is important. While activated B cells initially produce lower-affinity IgM antibody with a short half-life (one to two days), T-cell-dependent B cell development improves the antibody quality, which facilitates the switch to higher affinity IgG isotypes with an approximate three-week half-life [4]. T-cell-dependent B cell development also amplifies the antibody response and induces differentiation towards memory B cells [4]. By two to three weeks after initial exposure to a pathogen, the primary immune response calms as the threat is contained [2]. Circulating antibody titers decrease and most effector cells die off, except those that differentiated into long-lived memory cells [2]. Immunological memory is responsible for the secondary immune response, a more rapid and robust response that results in

higher titers of antibodies and more immediately active T cells in an individual that has been previously exposed. Although this more efficient and effective secondary response does not always prevent reinfection, it protects the host and dramatically reduces reinfection via neutralizing antibodies and cytotoxic T cells, thus preventing illness [3].

Effect of Corticosteroid on the Adaptive Immune Response

All immune cells express glucocorticoid receptors, so all steps of the immune response may be influenced by exogenous corticosteroids [5]. In the context of a vaccine response, it is most important to focus on two main events: (1) the generation of the memory response and (2) the response of immune cells (and other cells) to subsequent infection/invasion. Corticosteroids are known to suppress the ability of antigen presenting cells to process antigen and impair naïve T cell activation [5]. Given that the ability of antigen presenting cells to activate naïve T cells is vital to initiating the adaptive immune response, the presence of corticosteroids could impair this process. Even though memory T and B cells may start forming early in the response, they continue to differentiate and proliferate over several weeks [6,7,8]. Corticosteroids may also affect memory cells once they are generated. Although it is possible that some memory cells are more resistant to such insult, recent data suggest that CD8+ T cell memory may be more sensitive [9,10]. Importantly, these effects are dependent on corticosteroid half-life. For example, if the half-life of a long-acting corticosteroid is (at most) three days, its levels will be reduced 1000-fold, four weeks after administration (and close to 100-fold, two to three weeks after). This will reduce the effects on immune response dramatically. Table 1 shows the duration of action of various corticosteroids used in clinical settings [11].

Table 1: Corticosteroid Dose Equivalents

AGENT	CORTICOSTEROID DOSE EQUIVALENTS*	EPIDURAL DOSE LOW (mg)	EPIDURAL DOSE HIGH (mg)	TRIAMCINOLONE EQUIVALENTS (mg)
Betamethasone	12	6	12	36-80
Dexamethasone	15	4	16	21-85
Methylprednisolone	80	40	80	20-120
Triamcinolone	80	20	100	20-100
Prednisone	100			

*Adapted from https://emedicine.medscape.com/article/2172042-overview

mRNA Vaccines

Vaccines capitalize on the process of adaptive immunity, and in the absence of pathogenic infection, elicit a robust immune response through B- and T-cell dependent mechanisms to effectively establish immunological memory. As is the case between a primary and secondary immune response, both affinity and amount of antibody increase with repeated immunizations [2,4].

It is important to recognize that the mRNA vaccines are more akin to subunit (or killed) vaccines, similar to most influenza vaccines. Both the Pfizer-BioNTech and Moderna COVID-19 vaccines deliver mRNA encoding for the COVID-19 spike protein that is enclosed in a lipid particle. Once injected, the lipid particles are taken up by various cells, including antigen presenting cells. The mRNA will not be a permanent fixture of any cell, but it will last long enough inside the cytoplasm

to be translated into spike proteins that can be expressed, secreted and processed into peptides to be presented by major histocompatibility complex (MHC) and recognized by T cells. Antigen presenting cells and the secreted protein make their way to draining lymph nodes relatively quickly. Although our understanding of the precise kinetics of T- and B-cell responses to the mRNA vaccines is still incomplete, published data show that neutralizing (anti-spike protein) antibodies develop within two weeks after immunization [12,13]. This timing is consistent with our general understanding of the kinetics of immune responses to vaccination – it takes several days for antigen specific T and B cells to mount a useful response [8,14]; time is needed for B- and T-cell activation and proliferation, and, in the case of B cells, to generate the high affinity antibodies that will be most effective in a response.

The generation of memory cells is the vital goal of vaccination. Although we continue to learn about the details of memory cell generation, it appears as if memory B and T cells can emerge early after vaccination and continue to develop and proliferate throughout the response. In both macaques [15] and humans [12], neutralizing antibodies develop within two to four weeks of COVID-19 mRNA vaccination and their levels are significantly enhanced two to four weeks after a second, boosting immunization. The boost seems particularly important for generating neutralizing antibodies in older individuals [12]. Of note, mRNA vaccines are effective at inducing two types of T-cell responses: T follicular helper cell (T_{FH}) responses, which enhance B cell activity and antibody production and T helper cell (T_H)1 responses, which enhance cytotoxic responses to intracellular pathogens [16,17]. mRNA vaccines do not seem to induce T_H2 responses, which may be fortunate, given that there is some evidence that T_H2 responses enhance lung disease caused by COVID-19 [16,18].

Effect of Corticosteroid Injection on Vaccine Efficacy

The general literature on how corticosteroids injections affect vaccine efficacy 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 [19,20]. However, the effect of single corticosteroid injections on vaccine efficacy is not clear. There is some evidence suggesting that the efficacy of the influenza vaccine is affected by the use of intraarticular corticosteroid injection [21]. An observational cohort study reported that a single intraarticular corticosteroid injection was associated with of 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 [22]. 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.

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. 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 [21,23,24]. Even a relatively low-dose triamcinolone (20 mg) intraarticular injection influences the HPA-axis for one to two weeks. No published study has examined the relationship between epidural corticosteroid injection and risk of infection among those vaccinated against influenza, although epidural corticosteroid injections are known to have systemic endocrine effects similar to those of intraarticular corticosteroid injections [25,26,27]. For example, one study demonstrated HPA axis suppression in 87% of participants seven days post-injection, 43% at day 14, and 7% at day 28 following epidural injection of 80 mg of

methylprednisolone [27]. Another study reported laboratory-confirmed suppression of adrenocorticotropic hormone (ACTH) and cortisol for one to four weeks and suppression of urinary free cortisol for more than twelve weeks following epidural injection with triamcinolone 80 mg [28]. Epidural corticosteroid injections have been shown to decrease cortisol production at three and six weeks following injection with methylprednisolone and triamcinolone [26,29]. However, notably, epidural injection with betamethasone or dexamethasone does not seem to significantly alter cortisol production when compared to patients who receive injection with lidocaine alone [26].

Effect of Corticosteroid on mRNA Vaccine Function

At the cellular level, glucocorticoids reduce inflammation by both direct and indirect mechanisms [30,31,32], classically by acting on glucocorticoid receptors involved in transactivation, DNA binding, and ligand binding [33,34,35,36]. Glucocorticoids also exert effects on post-transcription and translational phase mechanisms. For instance, it has been demonstrated that dexamethasone can suppress the synthesis of many ribosomal proteins and translation initiation factors [30,37]. This involves both transrepressive and transactivating functions of glucocorticoid receptors [30]. The clinical impact of corticosteroid administration on these varied and complex cellular mechanisms through which mRNA-based vaccines act is partially understood but not yet fully elucidated.

Corticosteroids in the Pfizer-BioNTech and Moderna COVID-19 Vaccine Trials

Corticosteroid Administration Prior to and Following Vaccine Administration:

The Pfizer-BioNTech protocol permitted localized injections of corticosteroids (intraarticular, bursal) during the study period at doses not exceeding 20 mg/day oral prednisone equivalents for more than 14 days either in the six months leading up to study enrollment or during the course of the study. The Moderna protocol did not specifically mention allowing local injections, but did have the same exclusion criteria for systemic corticosteroid use of excluding individuals receiving systemic corticosteroids greater than or equal to 20 mg/day oral prednisone equivalents for more than 14 days, or 280 mg of prednisone equivalent in total within six months prior to screening. For comparison, a typical standard dose of corticosteroid used for spinal or musculoskeletal pain indications amounts to approximately 67 mg of oral prednisone equivalent [38]. It must be noted that injected and oral corticosteroid 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.

Immunocompromised Patients:

Outside of the exclusion criteria of receiving systemic corticosteroids greater than or equal to 20 mg/day of prednisone equivalent for more than 14 days in the six months prior to study enrollment, the studies excluded immunocompromised patients. The Pfizer-BioNTech study excluded individuals with known infection with human immunodeficiency virus (HIV) (Phases 1 and 2 only) as well as immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination. The Moderna study excluded patients with immunosuppressive or immunodeficient state, asplenia, or recurrent severe infections. HIV-positive patients with CD4 count ≥350 cells/mm3 and an undetectable HIV viral load within the past year were permitted. Because of these exclusions, it is not possible to determine if the efficacy of the vaccine would have been reduced in the treatment

arm due to an immunocompromised state other than those described within prednisone equivalent dose limits.

Efficacy of mRNA COVID-19 Vaccines:

In the Pfizer-BioNTech safety and efficacy study with a total of 43,548 participants enrolled, eight cases of COVID-19 were observed among vaccine recipients and 162 cases among placebo recipients, leading to the conclusion that this vaccine is 95% (95% confidence interval, 90.3- 97.6) effective [39]. The two-dose regimen is administered 21 days apart, with reported efficacy data based on cases of COVID-19 with onset at least seven days after dose 2. At 12 days after dose 1, the vaccine was noted to have an efficacy of 52% (95% CI, 29.5-68.4) with 39 cases in the vaccine group, and 82 cases in the placebo group. While supplemental analyses indicated that vaccine efficacy among subgroups defined by age, sex, race, ethnicity, obesity, and presence of a coexisting condition was generally consistent with that observed in the overall population, there was no subgroup analysis of patients who may have received corticosteroid during the course of the trial.

The Moderna safety and efficacy trial enrolled 30,420 participants [40]. Eleven cases of COVID-19 were observed among vaccine recipients, and 185 cases among placebo recipients, leading to the conclusion that this vaccine is 94.1% (95% CI, 89.3-96.8%; $P<0.001$) effective in preventing COVID-19 in individuals who fit the trial criteria. The Moderna vaccine is also a two-dose regimen, with the second dose administered 28 days after dose 1. The reported efficacy rate is based on assessment at day 42, 14 days after dose 2 in the per-protocol analysis. In its modified intention-to-treat analysis, there were fewer incidences of COVID-19 onset in the vaccine group (two) compared to the placebo group (35) at 14 days after dose 1.

Notably, the Pfizer-BioNTech trial demonstrated peak vaccine efficacy one week following the second dose. Alternatively, the Moderna trial demonstrated peak vaccine efficacy two weeks following the second dose but did not measure efficacy at one week following the second dose. Given that both the Pfizer-BioNTech and Moderna vaccines result in production of viral spike protein via an mRNA mechanism, it is likely that the Moderna vaccine results in in peak efficacy by one week following the second dose, similar to the Pfizer-BioNTech vaccine. However, it must be recognized that the Moderna vaccine could possibly require a full two weeks to reach peak efficacy, pending further data.

Neither study reported if participants who contracted COVID-19 had received any amount of corticosteroid. Furthermore, the Pfizer-BioNTech study did not include a subgroup analysis of participants who may have received injectable corticosteroid during the course of the trial.

A single epidural or intraarticular corticosteroid injection amounts to a prednisone equivalent below the cutoff implemented in safety and efficacy trials. Intraarticular and bursal injections were permitted in the Pfizer-BioNTech protocol. However, questions remain as there is no subgroup data reported on the number of participants who may have received corticosteroid during the course of the trial in either study, and no subgroup analysis of patients who may have received injectable corticosteroid during the course of the Pfizer-BioNTech trial was reported.

With a prior study suggesting an increased incidence of influenza in vaccinated patients who received corticosteroids [22], there may be reason to expand the application of cautious administration of intraarticular and epidural corticosteroids to individuals receiving mRNA COVID-19 vaccines. Clinicians must weigh the benefit of administering the mRNA 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.

A patient's immunocompromised status or high-risk of severe illness from COVID-19 should not be cause to withhold the mRNA COVID-19 vaccine. According to UK National Health System guidelines, patients who are considered to be "clinically extremely vulnerable" and who are recommended to receive the vaccine include individuals treated with, or likely to be treated with, systemic corticosteroids for more than a month at a dose equivalent to prednisone 20 mg or more per day, at any age" [41]. Likewise, the US Centers for Disease Control & Prevention (CDC) advises immunization of immunocompromised individuals, noting that vaccines might be less effective during the period of altered immunocompetence [42]. A vaccine may be deferred during a period of altered immunocompetence due to a concern with effectiveness. Additionally, if an inactivated vaccine is administered during the period of altered immunocompetence, it might need to be repeated after immune function has improved [42].

Summary and Recommendations

Key Points:

- Synthesis of the best evidence indicates that there is a suspected immunosuppressive effect in the majority of individuals who receive a corticosteroid injection, greatest at one week, and to a lesser extent at two weeks following injection.

- Immunosuppressive effects may be less profound following dexamethasone or betamethasone injection compared to methylprednisolone and triamcinolone injection given less demonstrated effect on HPA axis suppression following epidural injection.
- The Pfizer-BioNTech COVID-19 mRNA vaccine is associated with 52% efficacy 12 days following dose 1 and 95% efficacy seven days following dose 2. In the Moderna COVID-19 mRNA vaccine trial, there were 35 cases of COVID-19 in the placebo group and two in the vaccine group two weeks after dose 1. The vaccine was reported to exhibit 95% efficacy at 14 days after dose 2. Notably, efficacy of the Moderna vaccine was not reported at one week following dose 2, but given the similarity to the Pfizer-BioNTech vaccine, it is likely that similar efficacy at week 1 following the second dose would have been observed.
- Both the Pfizer-BioNTech and Moderna COVID-19 vaccine trials allowed corticosteroid use under 20 mg/day oral prednisone equivalents for up to 14 days, or 280 mg of prednisone equivalent in total. However, no subanalysis was provided to inform whether participants who were exposed to corticosteroid before or after vaccination exhibited reduced efficacy compared to those who were not exposed to corticosteroid.

Recommendations:

- Based on the known timeline of HPA axis suppression following epidural and intraarticular corticosteroid injections as well as the timeline of the reported peak efficacy of the Pfizer-BioNTech and Moderna vaccines, physicians should consider timing an elective corticosteroid injection such that it is administered no less than two weeks prior to a COVID-19 mRNA vaccine dose and no less than one week following a COVID-19 mRNA vaccine dose, whenever possible.

- Physicians may consider the use of dexamethasone or betamethasone rather than triamcinolone or methylprednisolone when administering a corticosteroid injection in close temporal proximity as advised in recommendation 1. This recommendation is based on evidence of reduced HPA axis suppression associated with dexamethasone and betamethasone compared to triamcinolone or methylprednisolone. However, it must be acknowledged that the differential effects of these specific corticosteroids on adaptive immunity, immunological memory, and mRNA vaccine efficacy have not been studied.
- We recommend a shared decision-making process with each unique patient in the context of his or her indications for injection, as well as risk factors for a reduced adaptive immune response to vaccine exposure and risks for morbidity and mortality associated with COVID-19.
- These recommendations may change as more direct evidence regarding the effect of corticosteroid injection on COVID-19 mRNA vaccine efficacy becomes available.

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Table 1: Corticosteroid Dose Equivalents

AGENT	CORTICOSTEROID DOSE EQUIVALENTS*	EPIDURAL DOSE LOW (mg)	EPIDURAL DOSE HIGH (mg)	TRIAMCINOLONE EQUIVALENTS (mg)
Betamethasone	12	6	12	36-80
Dexamethasone	15	4	16	21-85
Methylprednisolone	80	40	80	20-120
Triamcinolone	80	20	100	20-100
Prednisone	100			

*Adapted from https://emedicine.medscape.com/article/2172042-overview