

## LITERATURE REVIEW

# The systemic immunosuppressive effects of peripheral corticosteroid injections: A narrative review of the evidence in the context of COVID-19

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**Abstract**

**Introduction:** Injected glucocorticoid's (corticosteroids) are commonly used in musculoskeletal practice. The current global COVID-19 pandemic has increased attention on the potential for locally injected corticosteroids to exert a systemic immunosuppressive effect and the implications this may have in relation to COVID-19 infection and vaccination.

**Aim:** This narrative review summarises the evidence regarding the potential systemic immunosuppressive effects of peripheral corticosteroid injections in relation to the ongoing COVID-19 pandemic.

**Method:** A narrative review was selected to allow inclusion of evidence related to a diverse range of topics relevant to this subject in order to provide the most comprehensive and clinically relevant guidance for clinicians.

**Results/discussion:** Current evidence demonstrates that cytotoxic, phagocytic and antigen presenting cells involved in both the innate and adaptive immune responses are suppressed for 48 h post-injection and messenger cytokines that are integral to immune function are suppressed for over 96 h post-injection. This potentially reduces an individual's ability to prevent viral infection, limit early viral replication, and delays activation of adaptive immune mechanisms (T and B lymphocytes) and subsequent viral clearance and elimination. The hypothalamic–pituitary–adrenal (HPA) axis can be suppressed for 2–4 weeks or longer following peripheral corticosteroid injections. The role of the HPA axis in immune function is not fully understood, however this could potentially indicate longer lasting immunosuppression.

**Conclusions:** This review found evidence of suppression of immune cell numbers for the first 48 h post-injection, cytokines for over 96 h post-injection and HPA axis suppression lasting for 2–4 weeks or longer. There is currently no evidence that these physiological changes translate into a clinically meaningful increased risk of COVID-19 infection or related morbidity or mortality, but there is also no persuasive evidence that they do not. This review discusses the implications of the current evidence in relation to shared decision making, informed consent, risk management and COVID-19 vaccination to provide clinicians with a pragmatic guide to help navigate the current uncertainty regarding the potential immunosuppressive effects of peripheral corticosteroid injections.

**KEYWORDS**

corticosteroids, COVID-19, immune, immunosuppression, injections, musculoskeletal, vaccination

## 1 | INTRODUCTION

Injection of exogenous glucocorticoids (commonly termed corticosteroids) has been part of musculoskeletal and rheumatological practice for over 50 years (Cole & Schumacher, 2005). It is well established that oral corticosteroids exert a systemic immunosuppressive effect (Hoes et al., 2009; Stuck et al., 1989; Youseff et al., 2016), and that locally injected corticosteroids can exert a local immunosuppressive effect (Kaspar & De Beer, 2005; Marsland et al., 2014; McIntosh et al., 2006). However, the systemic immunosuppressive effects of locally injected corticosteroids are less clear. The declaration of a global COVID-19 pandemic in March 2020 (World Health Organization, 2020) led to new guidance advocating a more cautious approach to corticosteroid injections in musculoskeletal practice based on this uncertainty (British Society of Rheumatology, 2020; British Society of Skeletal Radiology, 2020; Faculty of Pain Medicine of the Royal College of Anaesthetists, 2020; National Health Service, 2020). This prompted a widespread reduction or suspension in the use of corticosteroid injections in musculoskeletal services across the United Kingdom (Amani et al., 2020; Little et al., 2020). Current multi-professional guidance advocates the judicious use of corticosteroid injections within a shared decision making framework (British Orthopaedic Association, 2020). This requires clinicians and patients to make decisions based upon the best available evidence regarding the risks and benefits of corticosteroid injections including the possibility of systemic immunosuppression (Elwyn et al., 2010). This narrative review is designed to summarise the current evidence regarding the potential systemic immunosuppressive effects of peripheral intra-articular and soft tissue corticosteroid injections in order to provide a pragmatic guide for healthcare professionals. This is intended to promote shared decision making, facilitate informed consent, and inform risk management related to the use of peripheral musculoskeletal corticosteroid injections in the context of the ongoing COVID-19 pandemic.

## 2 | INJECTED CORTICOSTEROIDS AND THE IMMUNE RESPONSE

The innate immune response is the body's rapid but non-specific first line of defence against all invading pathogens including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Innate immune processes are activated within a few hours of viral infection and play a critical role in preventing the initial stages of infection and slowing or inhibiting viral replication and transfer between cells (Sette & Crotty, 2021). Innate immune cells employ various complicated pathways and pattern recognition molecules to detect invading viruses. This triggers the release of messengers known as cytokines.

Cytokines have numerous functions at multiple stages of the immune response. There are two types of interferon (IFN) induced upon viral infection (Samuel, 2001). Type one IFNs are secreted from infected cells and include IFN $\alpha$  and IFN $\beta$  (McNab et al., 2015). Their functions include induction of cell-intrinsic antiviral states in infected and neighbouring cells which limits the spread of viruses. They also support antigen presentation and activation of the adaptive immune response and promote Natural Killer (NK) cell functions whilst restraining pro-inflammatory pathways and cytokine production (Ivashkiv & Donlin, 2014). NK cells are a type of lymphoid cell that play an essential role in the innate immune response against viral infections. They express both inhibitory and activating or stimulatory receptors that regulate their cytotoxicity. Hence, NK cells are able to kill virally infected and stressed cells via various pathways (Cervenka & Lanier, 2001; Duev-Cohen et al., 2016; Glasner et al., 2012). Recent studies demonstrate a reduction in NK cell cytotoxicity in severe COVID-19 (Wilk et al., 2020; Zheng et al., 2020). Type two IFNs include IFN $\gamma$  which is mainly produced by T lymphocytes and NK cells (McNab et al., 2015). IFN $\gamma$  activates innate responses by augmenting inflammatory cytokine and chemokine production, microbial killing by phagocytic monocytes such as macrophages, and antigen presentation by dendritic cells (Hu & Ivashkiv, 2009). Other important cytokines, include tumour necrosis factor alpha (TNF- $\alpha$ ) and interleukins (IL), particularly IL-1, IL-6 and IL-18. Together they induce antiviral programs in target cells and potentiate the adaptive immune response (Vabret et al., 2020). Cytokines present a major barrier to viral infection and replication. Consequently many viruses including SARS-CoV-2 have evolved various complex mechanisms to evade and inhibit induction and signalling of IFNs and other cytokines (Vabret et al., 2020; Cameron et al., 2012; Blanco-Melo et al., 2020).

The adaptive immune response is slower but more sophisticated than the innate immune response and is specific to the invading pathogen. It can take up to 6–20 days after priming to generate sufficient adaptive immune cell numbers to control viral infections such as COVID-19 (Sette & Crotty, 2021). Adaptive immune mechanisms are primarily responsible for viral clearance and elimination. T lymphocytes play a pivotal role in the adaptive immune response to viral infections. CD4 T lymphocytes orchestrate the response of other immune cells and provide B lymphocytes with the required help to produce immunoglobulins (antibodies) which help neutralise viruses. CD8 T lymphocytes kill virally infected cells to reduce the burden and spread of viruses. In response to SARS-CoV-2 infection both CD4 and CD8 T lymphocytes have been found to be reduced in patients with moderate and severe COVID-19 (Blanco-Melo et al., 2020; Chen et al., 2020; Diao et al., 2020; Liu et al., 2020; Zhou et al., 2020). This is most notable with respect to CD8 T lymphocytes in patients with severe COVID-19 that required admission to intensive care, which may correlate with COVID-19-associated

disease severity and mortality (Wang et al., 2021). Prolonged use of oral corticosteroids affects both the innate and adaptive immune responses to infection (Pivonello et al., 2016). All the main components of the innate immune response are reduced including NK cells cytotoxic action on virally infected cells as well as other phagocytic and antigen-presenting monocytes and granulocytes (Guarnotta et al., 2020). Similar effects have been described in relation to the adaptive immune response (Strehl et al., 2019).

There is limited evidence investigating whether injected corticosteroids have similar immunosuppressive effects. Steer et al. (1998) measured peripheral blood leucocyte counts and TNF- $\alpha$  release by peripheral blood monocytes for 96 h following intra-articular injection of methylprednisolone acetate into 1–5 large joints (total dose 40–240 mg) in six patients with rheumatoid arthritis. The results demonstrated a significant fall in mononuclear leucocytes (lymphocytes and monocytes) in peripheral blood 4 h post-injection. Lymphocyte numbers fell by a mean of 42% with peak suppression occurring 8 h post-injection, whereas monocyte numbers fell by a mean of 16% with peak suppression occurring 12 h post-injection. Both lymphocyte and monocyte numbers remained significantly suppressed 24 h post-injection but had returned to pre-injection levels after 48 h. A reduction in cytotoxic lymphocytes including NK cells and phagocytic monocytes is likely to impair an individual's ability to prevent viral infection, limit early viral replication, and reduce killing of virally infected cells. A reduction in antigen presenting monocytes like dendritic cells may also delay activation of adaptive immune mechanisms.

Steer et al. (1998) also demonstrated that TNF- $\alpha$  was maximally suppressed by 43% when measured 4–12 h post-injection, with suppression continuing beyond final follow up after 96 h. Reduced TNF- $\alpha$  release would decrease recruitment, maturation, activation and chemo-attraction of macrophages and NK cells, further diminishing an individual's ability to prevent early viral replication and delaying antigen presentation, T lymphocyte activation, and the adaptive immune response. Alex et al. (2007) documented a case report of a single patient with rheumatoid arthritis who underwent an intra-articular knee injection with 20 mg triamcinolone acetonide. The results showed a marked decrease in serum levels of seven key inflammatory and immune regulators (IL-2, IL-4, IL-6, IL-7, IL-17, TNF $\alpha$  and monocyte chemoattractant protein-1 [MCP-1]) when measured 3 h post-injection. The majority of these had returned to pre-injection levels by follow-up 2 months later; however, MCP-1 levels continued to decline suggesting a possible longer lasting inhibitory effect on cytokine-induced T lymphocyte function.

### 3 | INJECTED CORTICOSTEROIDS AND NEUROENDOCRINE FUNCTION

The body's endogenous glucocorticoid (cortisol) plays an essential but not fully understood role in modulating the immune system via the hypothalamic–pituitary–adrenal (HPA) axis. The HPA axis is activated by inflammatory stimuli that release pro-inflammatory

cytokines such as IL-1b and TNF $\alpha$ . This causes the release of cortisol which prevents further production of pro-inflammatory cytokines and thus exerts an anti-inflammatory effect. Continuous HPA axis activation following exogenous oral corticosteroid administration can lead to suppression of immune responses (McEwen et al., 1997; Sapolsky et al., 2000). Hypophysectomised animals (those with the pituitary gland surgically removed) have been shown to have impaired innate and adaptive immune responses (Gala, 1991). In such cases the function of the immune system can be restored following replacement of either prolactin and/or growth hormone (endogenous hormones produced by the anterior pituitary) demonstrating the pivotal role the HPA axis plays in immune function (Gala, 1991).

There are numerous studies investigating the effect of peripheral corticosteroid injections on HPA axis function. A detailed summary of these can be found in Table 1. Variations in the corticosteroid preparation and dosage administered, disease process studied, size and number of joints injected, follow-up times incorporated, and outcome measures utilised to assess HPA axis function makes comparisons between studies difficult. Combined with an incomplete understanding of the role of the HPA axis in immunomodulation, clinical interpretation of the results is challenging.

There is evidence of consistent transient HPA axis suppression following peripheral corticosteroid injection. Suppression is generally reported to last for up to 2–4 weeks although some studies using higher cumulative doses report suppression lasting 8 weeks or longer. There is significant individual variation reported. The implications of this related to immune function are less clear. However, considering the effects of prolonged oral steroid use (McEwen et al., 1997; Sapolsky et al., 2000) and hypophysectomy (Gala, 1991) on HPA axis and immunological function, a significant immunosuppressive effect cannot be excluded. HPA suppression following oral corticosteroids is associated with a variety of patient related risk factors including diabetes, depression, smoking, age, race and body mass index (Manson et al., 2009; Olivarius et al., 2011). Currently, there is no comparable evidence to support similar identifiable risk factors in relation to injected corticosteroid.

### 4 | INJECTED CORTICOSTEROIDS AND COVID-19 INFECTION RISK

There are currently two studies investigating the possibility of increased COVID-19 infection risk following corticosteroid injection. McKean et al. (2020) conducted a retrospective review of 443 individuals (504 injections) in a single NHS trust in the United Kingdom between 1 February 2020 and 30 June 2020. The study included both image guided ( $n = 407$ ) and landmark guided ( $n = 97$ ) injections performed for both peripheral ( $n = 461$ ) and spinal ( $n = 43$ ) conditions. Doses for peripheral injections ranged from 10 to 80 mg (mean 37 mg). Electronic patient records were reviewed and participants were categorised as no COVID-19, classic/probable COVID-19, or indeterminate COVID-19 based on COVID-19 tests results and/or radiological findings. No participants tested positive for COVID-19

TABLE 1 A detailed summary of studies investigating HPA axis function following peripheral corticosteroid injection

Study	Design	N	Dx	Site(s)	Steroid	Dose	Follow up	Outcome	Definition of adrenal insufficiency	HPA suppression
Bird et al. (1979)	Double blind RCT (three different preparations)	30	RA	Knee	THA MPA PTBA	20–40 mg	6 weeks	Plasma cortisol	N/A	Maximal suppression after 2–4 days Suppression for <4 weeks after THA but >4 weeks after MPA and PTBA
Armstrong et al. (1981)	Observational	21	RA	Knee	MPA	40–80 mg	1 week	Plasma cortisol		Maximal suppression by 64%–81% after 24 h Suppression for 18/24 < 1 week; 3/24 > 1 week
Esselinckx et al. (1982) (part 1)	Observational	5	OA SRD SHS	Kneeshoulder	TA	40–120 mg	15 days	Urinary free cortisol	N/A	Suppression for >24 h after three-eighths injection sessions; 24–72 h after three-eighths injection sessions; >72 h after 2/8 injection sessions
Derendorf et al. (1986)	Observational	42	RA	Knee	THA TA BM	10–40 mg 20–40 mg 5.7 mg	3 weeks	Serum cortisol	N/A	Suppression for 1 week (dose dependent)
Lazarevic et al. (1995)	Observational (two groups IA v IM MPA)	21	RA PSA OA	Knee	MPA	40 mg	2 days	Serum cortisol	N/A	Maximal suppression after 24 h (average 21.5%) Suppression for >72 h in 4/21 participants
Furtado et al. (2005)	RCT (IA v IM THA)	69	RA	Elbow Wrist Knee Ankle MCPJ	THA	20–40 mg	24 weeks	Serum ACTH	N/A	No significant difference between IA and IM
Mader et al. (2005)	Observational	25	RA PSA SPA CPPD	Shoulder Knee Elbow Wrist	MPA	10–20 mg (small) 40–60 mg (medium) 80 mg (large)	4 weeks	Serum cortisol 1µg ACTH stimulation test	Cortisol levels >2SD below control mean (147 nmol/L) and/or peak response 30 min after ACTH test >2SD below control mean (396 nmol/L)	Adrenal insufficiency in 12% participants after 1 week; 8% after 2 weeks Cortisol abnormality more common after doses >80 mg

TABLE 1 (Continued)

Study	Design	N	Dx	Site(s)	Steroid	Dose	Follow up	Outcome	Definition of adrenal insufficiency	HPA suppression
Weitof and Ronnblom (2006)	RCT (24 h bedrest v normal activity)	20	RA	Subtalar	THA	20 mg	2 weeks	Serum cortisol	N/A	Maximal suppression after 24 h
				CMCJ				Serum ACTH	Suppression for 2 weeks in some individuals	
				PIPJ						
Duclos et al. (2007)	Observational	10	Trauma	Knee	Cortivazol	1.87–7 mg	2 weeks	Plasma cortisol	Serum cortisol <100 nmol/L and/or plasma cortisol <500 nmol/L 30 min after ACTH stimulation test and/or a change of <200 nmol/L on ACTH stimulation test	Adrenal insufficiency in 90% participants after 48 h; 20% after 1 week; 0% after 2 weeks (but 30% remained below reference range for normal adrenal function)
				Ankle	BM			1µg ACTH stimulation test		
				Wrist						
Habib et al. (2013)	Case controlled study	40	OA	Knee	BM	6mg	8 weeks	Serum cortisol	<7 µg/dl increase in serum cortisol level and absolute levels of <18 µg/dl 30 min after ACTH stimulation test	Adrenal insufficiency in one participant 3 weeks after injection
Habib, Jabbour et al. (2014)	RCT (IA MPA v IA NaH)	40	OA	Knee	MPA	80 mg	8 weeks	Serum cortisol	<7 µg/dl increase in serum cortisol level and absolute levels of <18 µg/dl 30 min after ACTH stimulation test	Adrenal insufficiency in 25% MPA group after 2–4 weeks
								1µg ACTH stimulation test	All participants returned to normal adrenal function after 8 weeks (no measurement week 4–8)	
Habib, Khazin et al. (2014)	Case controlled study	40	OA	Knee	MPA	160 mg	8 weeks	Serum cortisol	<7 µg/dl increase in serum cortisol level and absolute levels of <18 µg/dl 30 min after ACTH stimulation test	Adrenal insufficiency for >1 week in 40% participants; >4 weeks in 35%; >6 weeks in 20%; >8 weeks in 10%

Abbreviations: ACTH, adrenocorticotropic hormone; BM, betamethasone; CMCJ, carpometacarpal joint; CPPD, calcium pyrophosphate dehydrate crystal arthritis; IA, intra-articular; IM, intra-muscular; MCPJ, metacarpal phalangeal joint; min, minutes; MPA, methylprednisolone acetate; N/A, not applicable; NaH, sodium hyaluronate; OA, osteoarthritis; PIPJ, proximal interphalangeal joint; PSA, psoriatic arthritis; PTBA, prednisolone t-butyl acetate; RA, rheumatoid arthritis; RCT, randomised controlled trial; SD, standard deviation; SHS, shoulder hand syndrome; SRD, sympathetic reflex dystrophy; TA, triamcinolone acetate; THA, triamcinolone hexacetonide.

(viral detection) but two tested positive for COVID-19 IgG antibodies consistent with previous COVID-19 infection. Both were asymptomatic so the temporal relationship between COVID-19 infection and corticosteroid injection is unknown. An additional participant was judged to have indeterminate COVID-19 based on radiological findings. The authors conclude that this suggests a very low incidence of symptomatic COVID-19 in this cohort. However, patients deemed to be high risk of COVID-19 were not eligible for injection and the study was insufficiently powered to determine absolute risk and lacked a control group to calculate relative risk.

Chang et al. (2020) prospectively studied 71 individuals (of whom 66 completed follow-up) who underwent image-guided corticosteroid injections at two hospitals in Massachusetts, United States, between 15 April and 22 May 2020. The study included both peripheral ( $n = 43$ ) and spinal ( $n = 28$ ) injections. Triamcinolone acetonide was used for 54% of injections and betamethasone for 44% of injections. The dosages used are not stated. Participants were followed up for a minimum of 1 month post-injection by review of electronic medical records and telephone for evidence hospitalisation, emergency room, or clinic visits with symptoms of COVID-19 or COVID-19 test results (viral detection or antibody). Nine subjects had COVID-19 tests of which one 25-year-old male tested positive 21 days after an intra-articular ankle injection of 60 mg triamcinolone acetonide. No other subjects reported having symptoms of COVID-19. This equated to an incidence of COVID-19 of 1.52% (95% confidence interval 0.04%–8.2%) in the study population compared to 0.91% in the local community at the time of the study. There was no statistically significant difference between the two. However, the small sample size used may have lacked sufficient power to detect a difference between groups and produced wide confidence intervals reflecting the inherent uncertainty in the incidence reported. It should be noted that the general population in the local area was in lockdown at the time of the study which may have reduced the risk of exposure to infection and limits extrapolation to external populations not under similar restrictions.

## 5 | INJECTED CORTICOSTEROIDS AND COVID-19 VACCINATIONS

There are currently three vaccines for COVID-19 approved for emergency use in the United Kingdom by the Medicines and Healthcare products Regulatory Agency. The Pfizer-BioNTech and Moderna vaccines are nucleoside-modified messenger RNA (mRNA) vaccines that use viral mRNA to provide the genetic code to allow host cells to produce the SARS-CoV-2 viral spike protein (Amanat & Krammer, 2020; Pardi et al., 2018). The Oxford-AstraZeneca vaccine uses a replication deficient chimpanzee adenovirus vector to deliver the DNA sequence that codes for the SARS-CoV-2 viral spike protein to allow host cells to produce the viral spike protein (Van Doremalen et al., 2020). Production of the viral spike protein provides intracellular antigens that are subsequently expressed by antigen presenting cells (innate immune response) to activate T and B lymphocytes

(adaptive immune response). Activation of T and B lymphocytes provides long term immune memory (Ewer et al., 2021; Sahin et al., 2020). This facilitates a quicker and more effective immune response if an individual is subsequently exposed to SARS-CoV-2 infection.

There is no risk of developing COVID-19 from any licenced COVID-19 vaccine, even if immunocompromised, since none of them contain live organisms (Public Health England [PHE], 2020a). However, the effectiveness of all approved vaccines requires an effective T and B lymphocyte mediated immune response. Consequently immunodeficient individuals may mount an unsatisfactory immune response following vaccination which could reduce vaccine effectiveness. This could potentially be the case following peripheral corticosteroid injection. Reduced lymphocyte and monocyte numbers for 48 h and cytokine release for over 96 h post-injection is likely to delay or reduce stimulation, maturation, and chemo-attraction of B and T lymphocytes to the vaccination site which may diminish the immune response. HPA axis suppression for 2–4 weeks post-injection may confer longer lasting reduced effectiveness. Individual decisions to delay or withhold treatment should always be made on a case by case basis in conjunction with the patient and after careful consideration of the risks and benefits of doing so. In the context of corticosteroid injections and COVID-19 vaccination this should consider the comparable risk of delaying an injection in comparison to the risks of a suboptimal response to COVID-19 vaccination. A pragmatic approach based on the current evidence would therefore be to avoid peripheral corticosteroid injections where possible for at least 1 week preceding COVID-19 vaccination in healthy individuals and for up to 4 weeks in those that are at greater risk of increased severity or mortality related to COVID-19, those who have other forms of coexistent immunosuppression, or those who wish to take a more cautious approach given the current uncertainty.

The length of time corticosteroid injections should be avoided following COVID-19 vaccination is dependent of the temporal relationship between vaccination and the subsequent immune response that produces protective immunity. Current evidence suggests that the cellular (T lymphocyte) and humeral (B lymphocyte) responses to COVID-19 vaccination are comparable to those seen following COVID-19 infection. CD4 and CD8 lymphocytes are increased for the first 7–10 days following onset of COVID-19 symptoms and begin to return to normal at around day 20 (Poland et al., 2020; Thevarajan et al., 2020; Xu et al., 2020). IgM antibodies peak 10–12 days after symptom onset and start to reduce from day 18, whereas IgA antibodies peak after 20–22 days (Padoan et al., 2020). IgG antibodies are detectable 10 days after symptom onset and increase for the first 3 weeks before beginning to decrease after 8 weeks (Poland et al., 2020). Evidence from vaccine efficacy trials suggests that participants gain a substantial degree of immunity within 2–3 weeks following a single vaccination dose. The Pfizer-BioNTech vaccine demonstrates 89% vaccine efficacy 15–21 days after a single dose (PHE, 2020a). A single dose of the Oxford-AstraZeneca vaccine confers 76% efficacy after 21 days, with no participants in the vaccine group requiring hospitalisation due to



### **A plain English summary of the potential immunosuppressive effects of peripheral corticosteroid injections**

- Taking regular steroid tablets is known to reduce the body's ability to fight infections such as COVID-19.
- It is currently unknown if steroid injections reduce the body's ability to fight infections such as COVID-19 in the same way.

#### **What we know:**

- Steroid injections reduce the cells that help fight infection for 48 hours following steroid injection.
- Steroid injections reduce some of the messenger chemicals that help the body fight infection for over 96 hours following injection.
- Steroid injections affect other systems in the body which help control the body's ability to fight infection for 2 to 4 weeks following injection and possibly longer if larger doses are used.

#### **What we don't know:**

We currently do not know if steroid injections affect the body's ability to fight off the virus that causes COVID-19:

- We do not know if having a steroid injection makes you more likely to get COVID-19 if you are exposed to the virus that causes it.
- We do not know if having a steroid injection makes it more likely that you will get a more severe symptoms or more likely to be admitted to hospital or need help with your breathing if you get COVID-19.
- We do not know if having a steroid injection makes you more likely to die if you get COVID-19.

**FIGURE 1** A plain English summary of the potential immunosuppressive effects of peripheral corticosteroid injections

COVID-19 beyond this point (Voysey et al., 2021). The Moderna vaccine demonstrates 92.1% efficacy 15 days following a single dose (PHE, 2020b). However, emerging real-world effectiveness data supports a more cautious approach. A prospective study of 5.4 million people in Scotland, United Kingdom, of whom 35% had been vaccinated against COVID-19 using either the Pfizer-BioNTech or Oxford-AstraZeneca vaccines found that maximum vaccine effectiveness in preventing COVID-19-related hospitalisation was not reached after 28 days post-vaccination (Vasileiou et al., 2021). Current evidence therefore suggests that peripheral corticosteroid injections should be avoided where possible in all individuals for a minimum of 2 to 3 weeks following COVID-19 vaccination to ensure a satisfactory immune response. Administering corticosteroid injections between 2 and 4 weeks following vaccination is likely to reduce the effectiveness of the vaccine to some extent and should be avoided where possible and only considered in circumstances where it is felt that the benefits of corticosteroid injection outweigh the risks of a potential suboptimal response to vaccination. This should be avoided in those at greater risk of increased morbidity or mortality related to COVID-19, those with other forms of coexistent immunosuppression, and those wishing to prioritise or maximise vaccine effectiveness. It is possible that evidence of shorter timeframes related to subsequent vaccine doses may emerge but there is currently insufficient evidence to draw disparate conclusions.

There are currently no studies investigating whether peripheral corticosteroid injections have a detrimental effect on the immune response to vaccination or increase infection risk following COVID-19 vaccination. However, there is comparable evidence related to another RNA virus in influenza. Sytsma et al. (2018) studied the records of 58,304 individuals aged 50 years or older of which 43,236 were vaccinated against influenza and 15,068 underwent peripheral corticosteroid injection over 5 influenza seasons. The results demonstrated that 79 (1.64%) participants in the vaccinated group who had

corticosteroid injections developed influenza compared to 466 (1.08%) who had not had corticosteroid injections. In a multivariate analysis corticosteroid injection was the most important variable for developing influenza following vaccination. This provides practical evidence regarding the potential adverse effects of corticosteroid injection on the effectiveness of a vaccine for a comparable pathogen.

## **6 | CLINICAL APPLICATION OF THE EVIDENCE**

Clinicians are required to discuss the risks and benefits of treatments with patients to promote shared decision making and obtain informed consent (Turnham et al., 2020). The risks of administering a corticosteroid injection to an asymptomatic or pre-symptomatic individual with COVID-19 and the potential risks of nosocomial infection attending for an injection are currently unknown and likely to vary over time and between individuals (Bryan et al., 2020; Sokol & Dattani, 2020; Turnham et al., 2020). In such circumstances clinicians are obliged to discuss the potential risks including the inherent uncertainty involved (General Medical Council, 2020; Royal College of Surgeons England, 2020). It is currently unknown if peripheral corticosteroid injections have a clinically significant immunosuppressive effect. Current evidence suggests that there is suppression of cells and cytokines involved in the immune response for over 96 h post-injection. This may increase susceptibility to viral infection and reduce or delay the ability to prevent viral replication thus exposing individuals to increased viral loads. It may also delay maturation or activation of cells involved in the adaptive immune response and increase the severity or prolong the course of disease. Suppression of the HPA axis for 2–4 weeks or longer could potentially confer longer lasting immunosuppression. A plain English summary of the current evidence designed to assist with shared decision making and informed consent processes is outlined in Figure 1.

## **Risk management.**

### What preparation should I choose?

- There is evidence of lymphocyte, monocyte, and TNF- $\alpha$  suppression following injection of methylprednisolone acetate (Steer *et al.* 1998).
- There is evidence of cytokine (TNF- $\alpha$  and interleukins) suppression following injection of methylprednisolone acetate and triamcinolone acetonide (Steer *et al.* 1998; Alex *et al.* 2007).
- There are no studies comparing the effects of corticosteroids with different solubilities on immune cell or cytokine suppression.
- Freely soluble glucocorticoids (dexamethasone and betamethasone) elicit little or no HPA axis suppression whereas less soluble preparations (methylprednisolone and triamcinolone) have a marked and longer lasting effect (Derendorf *et al.*, 1986; Lazarevic *et al.*, 1995; Duclos *et al.*, 2007).
- There is no evidence of a significant difference in suppression between commonly used less soluble corticosteroids methylprednisolone acetate and triamcinolone acetonide (Bird *et al.*, 1979; Derendorf *et al.*, 1986; Mader *et al.*, 2005; Duclos *et al.*, 2007; Habib *et al.* 2014a; Habib *et al.* 2014b).

### Does dose matter?

- There is insufficient evidence to draw definitive conclusions as to whether suppression of immune cells or cytokines is dose dependent.
- Suppression of immune cell numbers is reported following injection of total doses ranging from 20mg to 240mg triamcinolone acetonide or methylprednisolone acetate (Steer *et al.* 1998; Alex *et al.* 2007).
- HPA axis suppression appears to be dose dependent with higher doses inducing greater and longer lasting suppression (Derendorf *et al.*, 1986; Mader *et al.*, 2005; Habib *et al.* 2014b).
- Studies incorporating doses of less than 80mg generally report HPA suppression lasting a maximum of 4 weeks (Armstrong *et al.*, 1981; Derendorf *et al.*, 1986; Lazarevic *et al.*, 1995; Weitof & Ronnblom, 2006).
- Some studies incorporating doses of 80mg or more report HPA suppression have reported lasting 8 weeks or longer (Habib *et al.* 2014a; Habib *et al.* 2014b)

### Should I inject more than one joint at a time?

- Increased HPA axis suppression has been reported when the same cumulative dose is split between two or more joints compared to a single joint (Armstrong *et al.*, 1981; Derendorf *et al.*, 1986).
- However other studies report that the number of joints injection does not affect HPA axis suppression (Mader *et al.*, 2005).

### How long should I leave between corticosteroid injections?

- Suppression of immune cells lasts for 48 hours and suppression of cytokines lasts for over 96 hours (Steer *et al.* 1998; Alex *et al.* 2007).
- HPA axis suppression generally reported to last for 2-4 weeks if doses of less than 80mg are used (Armstrong *et al.*, 1981; Derendorf *et al.*, 1986; Lazarevic *et al.*, 1995; Weitof & Ronnblom, 2006).
- Some studies using doses of cumulative doses of 80mg to 160mg report suppression lasting for 8 weeks or more (Habib *et al.* 2014a; Habib *et al.* 2014b)

**FIGURE 2** A summary of the current evidence related to risk management regarding administration of corticosteroid injections

The evidence presented in this review provides clinicians with a pragmatic guide to risk management. The potential immunosuppressive risks of corticosteroid injection may be mitigated to some extent by the choice of preparation, dose, number of injections performed simultaneously, and interval between injections. A review of the current evidence regarding risk management can be found in Figure 2.

## **7 | SUMMARY**

The systemic immunosuppressive effects of peripheral musculoskeletal corticosteroid injections are poorly understood. There is evidence of suppression of immune cell numbers for the first 48 h post-injection and cytokines for over 96 h post-injection. There is also

evidence of marked transient HPA axis suppression generally lasting for 2-4 weeks post-injection but with some reports of suppression lasting 8 weeks or longer. What remains less clear is what effect these physiological changes have on an individual's infection risk in relation to COVID-19. There is currently no evidence of increased risk of COVID-19 infection following peripheral corticosteroid injection. However, given the current limitations of the available evidence this should be interpreted as an absence of evidence rather than evidence of absence of effect. It is therefore currently unknown if peripheral corticosteroid injections have a clinically relevant immunosuppressive effect. Consequently it is unknown if they increase an individual's susceptibility to infection with the SARS-CoV-2 virus, make an individual more susceptible to developing symptomatic COVID-19, or ultimately increase the risk of greater morbidity or mortality associated with COVID-19.



## ACKNOWLEDGEMENTS

We would like to thank Dr Archana Herwadkar, consultant immunologist, who contributed to the planning and development of this review. No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

## ETHICS STATEMENT

Ethical approval was not required for this narrative review.

## AUTHOR CONTRIBUTIONS

Paul Regan was the lead author and was principally responsible for writing this manuscript. Shuayb Elkhalfifa and Paul Barratt have both made substantial contributions to conception and design interpretation of information contained within the review and have been involved in drafting the manuscript or revising it critically for important intellectual content and have approved the final version to be published.

## DATA AVAILABILITY STATEMENT

No data are associated with this article.

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**How to cite this article:** Regan, P., Elkhalfi, S., & Barratt, P. (2022). The systemic immunosuppressive effects of peripheral corticosteroid injections: A narrative review of the evidence in the context of COVID-19. *Musculoskeletal Care*, 20(3), 431–441. <https://doi.org/10.1002/msc.1603>