Intra-articular Corticosteroid Treatment of Inflammatory Joint Diseases

3

Christopher L. Tracy and Jess D. Edison

Contents

C.L. Tracy • J.D. Edison (✉)
Walter Reed National Military Medical Center, 8901 Rockville Pike, Bethesda, MD 20889, USA
e-mail: Jess.d.edison.mil@health.mil

W.U. Kampen, M. Fischer (eds.), *Local Treatment of Inflammatory Joint Diseases: Benefits and Risks*, DOI 10.1007/978-3-319-16949-1_3

3.1 Introduction/History

On January 27, 1951, a study group led by Joseph Lee Hollander injected three rheumatoid arthritis patients with the first intra-articular hydrocortisone injections. These three patients showed clinical improvements in local inflammation. This group went on to inject 1,500 test patients with nearly 24,000 injections into the joints, bursae, and tendon sheaths. Fifty percent of these patients experienced clinically significant improvement of local inflammation [1]. Over the last 65 years, corticosteroid injections have become a valuable and efficacious treatment option in the management of inflammatory arthritis with an excellent safety record [2].

This chapter will provide an overview of the indications for use of corticosteroid injections, the specific agents used, the adverse effects of corticosteroid joint injections, corticosteroid effects on the synovium, and overall efficacy in select types of inflammatory arthropathies.

3.1.1 Indication

The most common indication for intra-articular injections in inflammatory joint disease is the presence of joint pain. Corticosteroids have been used successfully in a number of inflammatory arthritis conditions to include rheumatoid arthritis, crystalline arthropathies (gout and pseudogout), spondyloarthropathies (psoriatic arthritis, ankylosing spondylitis, reactive arthritis, inflammatory bowel disease-associated arthritis), other connective tissue disease-associated arthritis (systemic lupus erythematosus, mixed connective tissue disease, Sjogren's syndrome), and juvenile idiopathic arthritis. Although frequently used in clinical practice, there is little systematic evidence to guide corticosteroid selection for therapeutic injections.

3.1.2 Commonly Used Corticosteroids

Common corticosteroid preparations include topical, oral, and parenteral formulations. Only depot preparations are suitable for joint injections. Depot formulations remain at the injected site for a longer period of time and display mainly localized efficacy. Knowledge of the difference in potency and solubility of injectable corticosteroids is useful for clinical practice since the duration of action of the particular agent is inversely related to the solubility of the preparation – more soluble compounds are thought to have a shorter duration of action [3–5].

3.1.3 Solubility

Solubility is a key factor in efficacy because compounds with lower solubility maintain effective intra-articular therapeutic response longer and produce lower systemic levels of corticosteroid than would compounds of greater solubility. A lower

systemic level of corticosteroid is generally viewed as a favorable feature of intra-articular injections because of the potential to reduce systemic toxicity. To support this concept, in a comparison of two preparations with different solubilities, triamcinolone acetonide and triamcinolone hexacetonide, absorption rate was markedly different with the less soluble compound, triamcinolone hexacetonide, and resulted in lower corticosteroid peak plasma levels [6].

3.1.4 Duration of Action

Few controlled long-term studies assess pain relief after intra-articular corticosteroid injections in inflammatory arthritis, and the reported ranges of duration of action vary widely between corticosteroids. Data suggests that decreased solubility correlates with increased duration of action with many depot preparations. In one clinical trial, however, triamcinolone hexacetonide showed less of a clinical effect when injected into osteoarthritic knees than a more soluble compound, methylprednisolone acetate, suggesting that there may be a more complex explanation for duration of action in some disease states [3]. The most durable effect is achieved in the knee of patients with pauciarticular JIA with a mean duration of remission of 13.9 months. This is in contrast to osteoarthritis where the duration of symptom relief is only 3 weeks and function is not improved [4]. Overall, the duration of response has been found to vary according to the type of corticosteroid preparation used, dose, subtype of arthritis, duration of disease prior to the injection, specific joint injected, and accuracy of the injection [4, 7].

3.1.5 Frequency of Injections

Theoretical risks of cartilage loss and subsequent joint replacement are often cited when considering injection frequency. The optimal frequency remains controversial. Raynauld and colleagues showed relative safety with corticosteroid injections every 3 months in a patient population with osteoarthritis [8]. Patients with rheumatoid arthritis receiving up to ten injections in a year on a single joint failed to show significant increase in cartilage loss or need for joint replacement [8, 9]. In clinical practice, the inherent risk of cartilage loss and subsequent need for joint replacement in patients with active inflammation are well understood and often dictate frequency of injection.

3.1.6 Local Anesthetics

Local anesthetics to include lidocaine 1 % and bupivacaine 0.25–0.5 % are commonly mixed with the corticosteroid depot preparation to provide temporary analgesia and dilute the crystalline suspension for improved diffusion within the injection site. Local anesthesia can also be used to diagnostically confirm the

correct placement of the preparation by improving pain in the local area with its quick onset of action. Manufactures advise against mixing corticosteroid preparations with lidocaine because of the risk of clumping and precipitation of steroid crystals; however, in clinical practice, lidocaine is a useful diluent. Patients rarely experience side effects directly related to the anesthetic. These side effects occur within 30 min of the injection and include flushing, hives, and chest or abdominal discomfort [5].

3.1.7 Corticosteroid Preparations

The major depot preparations include methylprednisolone acetate, triamcinolone hexacetonide, triamcinolone acetonide, betamethasone acetate/betamethasone sodium phosphate, and betamethasone dipropionate/betamethasone sodium phosphate. All dissolve slower than earlier depot preparations such as hydrocortisone acetate in order to achieve a prolonged local effect [4].

Potency of corticosteroids is measured against that of hydrocortisone and ranges from low-potency short-acting agents to high-potency, long-acting agents.

Hydrocortisone acetate (hydrocortisone acetate, 25 mg/ml) has the shortest duration of action of steroids mentioned in this chapter and is dosed at 10–25 mg for small-joint injections and 50 mg for large-joint injections. It is very soluble and has limited utility in joint injections given its low potency and short duration of action [8].

Methylprednisolone acetate (methylprednisolone acetate 40 mg/ml – concentrated) has intermediate potency and duration of action. It is dosed at 2–10 mg for small-joint injections and 10–80 mg for large-joint injections [8, 9].

Triamcinolone acetonide (triamcinolone acetonide 40 mg/ml – concentrated) has intermediate potency and duration of action and is very similar to methylprednisolone in structure and activity and is dosed similar to methylprednisolone for small- and large-joint injections [8, 9].

Betamethasone sodium phosphate and acetate (betamethasone sodium phosphate and acetate 6 mg/ml) has high potency. This formulation combines a soluble ester (sodium phosphate) to provide prompt activity with a much less soluble betamethasone acetate to obtain sustained duration of activity. It is dosed at 2–6 mg for large joints and 1–3 mg for small joints [8, 9] (Table 3.1).

Table 3.1 Corticosteroid agents by relative potencies [8, 9]

Steroid	Potency	Solubility	Relative anti-inflammatory potency
Hydrocortisone acetate	Low	Soluble	1
Methylprednisolone acetate	Intermediate	Soluble	5
Triamcinolone acetonide	Intermediate	Relatively insoluble	5
Betamethasone sodium phosphate and acetate	High	Combination	25

Table 3.2 Adverse effects following intra-articular corticosteroid injections [3, 4, 20]

Adverse effect	Estimated rate/frequency
Infection	Rare 1:1,000–1:50,000
Capsular calcification	Common 25–50 %
Cutaneous atrophy	Uncommon <1 %
Flushing	Relatively common 1–15 %
Post-injection flare	Relatively common 1–10 %
Tendon rupture	Uncommon <1 %
Osteonecrosis	Uncommon, reported cases

3.1.8 Adverse Events

Although animal studies have suggested that corticosteroid injections may have damaging effects on articular cartilage, human studies have not shown similar results [11, 12]. Intra-articular corticosteroid injections have an excellent safety record, and its safe use is supported by a large body of clinical data. The American College of Rheumatology has endorsed corticosteroid injections as safe and effective when administered by experienced physicians [2]. Despite their relative safe use, known side effects exist. Table 3.2 lists common and uncommon local adverse effects of intra-articular corticosteroids.

The most common reported side effects following corticosteroid injections are post-injection flair, facial flushing, and cutaneous atrophy [13].

3.1.9 Post-injection Flare

Pain in the injected joint or at the site of injection can occur within the first 24 h after injection in up to 10 % of patients. Localized tissue damage resulting from needle puncture may be a partial cause for injection site reactions. More often, though, it is the crystalline structure of the particular corticosteroid agent used that results in a localized synovitis [14].

3.1.10 Facial Flushing

Facial flushing occurs within a few hours post injection in up to 15 % of patients and is particularly common in women. Although benign, symptoms may linger for up to 3–4 days [15].

3.1.11 Cutaneous Atrophy

Skin or fat atrophy following corticosteroid injections usually develops within 1–4 months. It occurs more commonly in patient with juvenile idiopathic arthritis and is reported in up to 8 % of injections [16]. Overall it is thought to occur at a rate of less than 1 % and may be accompanied with depigmentation of the

skin [13]. The atrophy and depigmentation is due to the leakage of the injected steroids into the skin and may improve over a few months. It is more likely to occur following the small-joint injections where the accuracy of injection is not guaranteed, the subcutaneous tissue is thinner, and a larger volume of corticosteroids are injected. Less soluble agents are also more likely to cause these cutaneous adverse effects [3, 4].

3.1.12 Capsular Calcification

Capsular calcification is the most common local adverse reaction following an intra-articular corticosteroid injection and occurs in up to 25–50 % of patients but is rarely clinically significant [17]. Pericapsular or intracapsular calcifications are noted within 2 months to 1 year following the injection and are usually asymptomatic. The location of the calcification is related to the site of the needle injection and is composed of hydroxyapatite [4].

3.1.13 Tendon Ruptures

Ruptured tendons occur uncommonly and have been reported in patients following intra-articular corticosteroid injections that have been placed directly within a tendon and may occur following a single injection in nearly 25 % of reported cases. Achilles tendon ruptures make up 50 % of reported cases followed by patellar tendon and biceps tendon ruptures in 19 and 8 % of cases respectively [18]. Great care should be used to avoid inadvertent injections within tendons.

3.1.14 Infections

The risk of causing a joint infection is one of the greatest concerns with the use of intra-articular corticosteroid injections, but it is one of the least common reported side effects. Pal B and Morris J reported the perceived risks of joint infection following intra-articular corticosteroid injections between 1 in 1,000 and 1 in 25,000 among rheumatologists surveyed [19]. The reported incidences in another study following knee injections ranged from 1 in 3,000 to 1 in 50,000 [20].

Systemic side effects on intra-articular injections are generally milder than with oral or intravenous formulations and often of unclear significance when present. Reported systemic side effects of systemic glucocorticoids include weight gain and fat redistribution, osteoporosis and fracture, osteonecrosis, ocular complications, hyperglycemia and diabetes, cardiovascular effects, infection, gastrointestinal complications, steroid-induced myopathy, hypothalamic-pituitary-adrenal axis suppression, and psychiatric complications. Table 3.3 lists drug-referenced side effects of glucocorticoids

Table 3.3 Adverse reactions of glucocorticoids for systemic therapy reported from manufacturers prescribing information

	Adverse reactions
CNS	Euphoria, insomnia, psychotic behavior, pseudotumor cerebri, vertigo, headache, paresthesia, seizures
Cardiovascular	Heart failure, hypertension, edema, arrhythmias, thromboembolism
EENT	Cataracts, glaucoma
GI	Peptic ulceration, GI irritation, increased appetite, pancreatitis, nausea, vomiting
GU	Menstrual irregularities
Hepatic	Liver dysfunction
Metabolic	Hypokalemia, hyperglycemia, carbohydrate intolerance, hypocalcemia
Musculoskeletal	Muscle weakness, osteoporosis
Skin	Delayed wound healing, acne, various skin eruptions, hirsutism
Other	Cushingoid state, immunocompromise, growth suppression in children, acute adrenal insufficiency

3.1.15 Hypothalamic-Pituitary-Adrenal Axis Suppression

Suppression of the hypothalamic-pituitary-adrenal axis following intra-articular injections is well-documented and usually mild and transient [3]. An average of 21.5 % reduction in serum cortisol levels returning to baseline after 72 h has been reported. Less commonly, prolonged HPA axis suppression lasting 5–7 weeks has also been reported [21].

3.1.16 Glucose Intolerance

Increased hepatic glucose synthesis and decreased insulin sensitivity have been shown to occur following corticosteroid therapy [22]. Intra-articular corticosteroid injections cause a transient increase in blood glucose levels; however no changes in fasting or predinner blood glucose readings were identified over a 2-week time period in a report of diabetic patients who received a methylprednisolone acetate injection for rheumatic complaints [23].

3.1.17 Steroid-Induced Myopathy

Steroid-induced myopathy is a known consequence of corticosteroid therapy and is more common with fluorinated corticosteroids (triamcinolone, dexamethasone) than with the non-fluorinated corticosteroids (hydrocortisone and methylprednisolone). It has not been reported following intra-articular injections [24].

3.1.18 Osteonecrosis

Osteonecrosis occurs in 5–40 % of patients treated with oral glucocorticoids with increased incidence at higher doses and longer duration. It is reported rarely in oral doses less than 20 mg/day and has been reported following multiple joint injections within days to months.

3.1.19 Osteoporosis

Osteoporosis is a known side effect of systemic glucocorticoid use. Observational studies report the development of fracture-related bone loss in as high as 40 % of patients with systemic glucocorticoid use [25]. In contrast, no net effect on bone resorption and only a transient effect on bone formation were found in a study following single intra-articular triamcinolone acetonide injections [26]. A theoretic benefit of increased mobility following intra-articular injections may also counteract osteoporotic effects.

3.2 Effects of CSI on Synovium

The rationale for using corticosteroids in the treatment of arthritis is to suppress inflammation, suppress inflammatory flares, and disrupt the inflammatory damage-repair-damage cycle. While the clinical efficacy of intra-articular glucocorticoids is well described, there is very limited data on the effects on human synovial tissue in inflammatory arthritis. The systemic effects of glucocorticoids are well described and mediated by receptor antagonism of nuclear factor kappa beta (NF-kB). NF-kB antagonism results in decreased transcription of several genes involved in the immune inflammatory response. It has also been shown to destabilize mRNA. These effects result in a dramatic reduction in cytokine production yielding pleotropic results to include effects on endothelial cells, cell migration, monocytes, macrophages, neutrophils, eosinophils, lymphocytes, fibroblasts, bone, cartilage, muscle, and the synovial tissue [27]. An in vivo study examining the synovial biopsy tissue of 31 patients with inflammatory arthritis, mostly RA, sheds some light on what happens in the synovium. Synovial protein expression of tumor necrosis factor (TNF), interleukin (IL)-1 beta, extranuclear high-mobility group box protein (HMGB)-1, vascular endothelial growth factor (VEGF), and ICAM-1 was reduced but without significant effects on vascularity [28]. Notably, macrophage infiltration and proinflammatory endothelial cytokine expression were not reduced, possibly explaining the transient nature of improvements with intra-articular corticosteroids. In this study, all patients demonstrated clinical improvements, although it should be noted that many patients were on other DMARDs or systemic corticosteroids [28]. More recently, synovial citrullinated protein has been correlated with the degree of local inflammation. Treatment with intra-articular corticosteroids has been shown to alter the expression of the synovial citrullinated proteins in the inflamed joint.

This downregulation has been correlated with glucocorticoid effects on a specific protein, peptidylarginine deiminase 4 (PAD4). PAD4 activation, induction, and signaling pathway is dependent on NF-kB suggesting glucocorticoids may affect citrullination through PAD4 downregulation in an NF-kB-dependent pathway [29, 30]. A summary of the described cellular effects following glucocorticoids is listed in Table 3.4.

Table 3.4 Cellular effects following glucocorticoid administration [27]

Endothelial cells and cell migration	Inhibits MHC class II antigen, ICAM-1, ELAM-1, E-selectin, TNF-α, IL-1, IL-6, and COX-2 expression; inhibits nitric oxide, arachidonic acid metabolites, complement proteins, and angiogenesis. Blocks endothelin receptor expression, stabilizes vascular permeability, upregulates lipocortin 1
Monocytes, macrophages, and neutrophils	Inhibit neutrophil functions of superoxide generation, chemotaxis, adhesion, apoptosis, and phagocytosis; inhibit arachidonic acid metabolites
	Decrease migration to sites of inflammation
	Induce lipocortin 1, lipomodulin, macrocortin
	Inhibit macrophage antigen presentation to T lymphocytes
	Suppress NF-kB and COX-2
	Inhibit production of cytokines (e.g. IL-1, TNF, IL-6)
	Decrease monocyte Fc receptors
	Decrease Fc receptors on phagocytes
Eosinophils	Decrease migration to sites of inflammation
Lymphocytes	Induce lymphopenia due to redistribution (e.g., in the bone marrow) of lymphoctyes
	Decrease IL-2 and IFNγ production and signal transduction
	Regulate thymopoiesis, primarily via apoptosis
	Inhibit T cell function and natural killer cell activity
	Suppress T cell function and natural killer cell activity
Fibroblast	Decrease proliferation and protein synthesis
	Decrease synthesis and metalloproteinases (e.g., stromelysin and collagenase)
	Inhibit IL-6, IL-8, and GM-CSF
Bone	Inhibit bone formation, inhibit osteoblast function, increase osteoclast life span and function
Cartilage (chondrocytes)	Increase glycosaminoglycan and DNA synthesis
Muscle	Induce atrophy
Synovium	Decrease expression of collagenase, TIMP, PIIINP, TNF, IL-8, E-selectin, ICAM-1, hyaluronate, CCP

MHC major histocompatibility complex, *ICAM-1* intercellular adhesion molecule 1, *ELAM-1* endothelial leukocyte adhesion molecule 1, *TNF* tumor necrosis factor, *IL-1* interleukin-1, *COX-2* cyclooxygenase 2, *NF-kB* nuclear factor kB, *IFNγ* interferon-γ. *GM-CSF* granulocyte-macrophage colony-stimulating factor, *TIMP* tissue inhibitor of metalloproteinase, *PIIINP* N-propeptide of type III procollagen

3.3 Efficacy

3.3.1 Rheumatoid Arthritis

Clinical results following intra-articular corticosteroid injections show immediate effect and demonstrate decreased synovial membrane volume within the first 24 h. Mean duration of improvement is up to 8-week duration following knee joint injection. Reduction in PMN leukocyte number and decrease in pannus size have been shown [4]. Following knee joint corticosteroid injections, patients show significant improvement in pain, morning stiffness of the injected knee, and decreased circumference of the knee and improved range of motion and walking distance when assessed at 1 and 3 months with no benefit with rest following injection [31].

The failure of IAGC to modulate disease, however, has also been noted in a small study evaluating the effects of IAGC with MRI and US. Intra-articular glucocorticoid injection into the wrist failed to arrest bone marrow edema or progression of erosions in rheumatoid arthritis when assessed by MRI and ultrasound at 4 weeks post injection; however, the patients enjoyed a significant clinical response [32].

3.3.2 Juvenile Idiopathic Arthritis (JIA)

Juvenile idiopathic arthritis is a heterogeneous group of disorders, and the use of intra-articular corticosteroids for treatment of joint inflammation can provide significant relief of pain and improved overall function in regard to walking velocity, joint movement, and gait pattern [33]. Patients who receive intra-articular corticosteroids as the primary therapy for oligoarticular JIA were less likely to experience localized growth disturbances versus NSAIDs alone [34]. Total remission has been shown in greater than 80 % of patients with a mean duration of nearly 15 months in patients with knee involvement [35]. Sustained remission has been found in patients with higher ESR and earlier treatment interventions. Shorter duration of efficacy has been found in patients with higher synovial fluid PMN% and + ANA status [36]. Unlike adult rheumatoid arthritis, there is evidence to support knee rest following intra-articular corticosteroid injections. MRI has shown long-lasting suppression of inflammation and pannus without evidence of cartilage destruction. Concern exists regarding the impact on growth in children exposed to corticosteroids, but there is currently no evidence to support any effect on statural growth with IAGC injections [37].

Multiple published reports have shown increased duration of efficacy with the use of less soluble corticosteroid preparations. The less soluble triamcinolone hexacetonide (THA) has shown to have superior efficacy to more soluble depot preparations, betamethasone and triamcinolone acetonide; however, increased rates of cutaneous/subcutaneous atrophy occurred with the less soluble depot formulation, THA, and ranged from 2.3 to 8.3 % [34, 38].

3.3.3 Spondyloarthropathy

Inflammatory back pain and sacroiliitis are major clinical features of a heterogeneous group of inflammatory disorders: seronegative spondyloarthropathy. Conventional treatments which include nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs) are not completely effective. 3 NSAIDs and physiotherapy have been shown to be only partially effective as noted in a 1992 analysis in patients with ankylosing spondylitis [39]. In more recent studies, antitumor necrosis factor-α (TNF-α) agents have shown significant and sustained improvements in symptoms [40]. Many studies have shown efficacy with the use of intra-articular glucocorticoid treatments into the sacroiliac joint in the treatment of spondyloarthropathies. In one published review of 30 patients receiving CT-guided IACI at the sacroiliac joint using 40 mg of triamcinolone acetonide, 83 % had a significant reduction in back pain symptoms lasting greater than 8 months. Magnetic resonance imaging was completed to evaluate for inflammation and showed a mean duration of significant improvement of inflammation lasting 5.2 months [41]. In a meta-analysis, 58–90 % of patients showed greater than 6-month improvement of sacroiliitis following intra-articular corticosteroid injections [4]. Prevention of disease-related joint damage regardless of mode of therapy remains to be shown [42].

3.3.4 Crystalline Arthropathy

Crystalline arthropathies to include gout and pseudogout are inflammatory disorders characterized by the deposition of crystals in synovial fluid and other tissues resulting in exquisitely painful, inflammatory arthritis affecting one or more joints. Although the safety and efficacy of glucocorticoids has been established in other inflammatory arthropathies, there is little or no published evidence to support their safety and efficacy in this setting as noted in a 2013 systematic review [43]. Despite this lack of published evidence to establish efficacy, the use of intra-articular corticosteroid injections for acute gout remains an established therapeutic intervention and is deemed highly effective [44] (Table 3.5).

Table 3.5 Clinical efficacy following intra-articular injections [4, 44, 49]

Rheumatoid arthritis	
Knee	Improved pain and ROM for 1–3 months
Wrist	Improved tender joint score for 4 weeks
Juvenile idiopathic arthritis	
Knee	Remission in pauciarticular for >6 months
Seronegative spondyloarthritis	
Sacroiliac	Subjective improvements lasting up to 10 months
Crystalline arthritis (gout)	
Knee	Resolution of symptoms at 48 h with single injection

3.3.5 Musculoskeletal Ultrasound

Using physical exam techniques by palpating the surface anatomy, skilled orthopedic surgeons and rheumatologist have shown poor accuracy on proper needle placement for intra-articular corticosteroid treatments. Unintended non-intra-articular injection rates are as high as 50–60 % [45–47]. In contrast, sonographic image guidance has shown to improve accuracy with proper positioning of the needle in up to 96–100 % accuracy [47, 48]. Integration of image-guided procedures into clinical practice, however, has been slowed due to the limited evidence supporting improved outcomes using sonography relative to palpation techniques. In a more recently published review, 148 patients were randomized to IA triamcinolone acetonide injection by conventional palpation – versus sonographic image – guided technique. Relative to conventional palpation technique, sonographic needle guidance resulted in 43 % reduction in procedural pain, 58.5 % reduction in absolute pain scores at 2-week follow-up, 25 % increase in the responder rate, and 62 % decrease in the nonresponder rate. Sonography also increased the detection of effusion by 200 % and resulted in the increased volume of aspirated fluid by 337 % [47].

Conclusion

Intra-articular glucocorticoid injections have been used enthusiastically and successfully since 1951, but much remains to be understood regarding their optimal use in clinical practice. A large body of clinical trial data supports the efficacy of intra-articular corticosteroid injections. Used appropriately, injectable corticosteroids can improve pain and allow patients to regain mobility, but wide variability exists in their efficacy in any given disease state. IAGCs are generally safe with rare occurrences of serious adverse events such as infection or avascular necrosis. Despite their long history of use, questions remain concerning the comparative effectiveness and safety of different preparations in various conditions. Factors affecting the durability of treatment effects are also incompletely understood, and a better understanding may lead to more effective therapeutic agents in the future [3].

References

1. Hollander JL. The use of intra-articular hydrocortisone, its analogs, and its higher esters in arthritis. Ann N Y Acad Sci. 1955;61:511–6.
2. Guidelines, American College of Rheumatology Subcommittee on Rheumatoid Arthritis. Guidelines for the management of rheumatoid arthritis: 2002 update. Arthritis Rheum. 2002;46:328–46.
3. Cole BJ, Schumacher Jr HR. Injectable corticosteroids in modern practice. J Am Acad Orthop Surg. 2005;13:37–46.
4. Habib GS, Saliba W, Nashashibi M. Local effects of intra-articular corticosteroids. Clin Rheumatol. 2010;29:347–56.
5. Cordone DA, Tallia E. Joint and soft tissue injection. Am Fam Physician. 2002;66:283–8.
6. Derendorf H, et al. Pharmacokinetics and pharmacodynamics of glucocorticoid suspensions after intra-articular administration. Clin Pharmacol Ther. 1986;39:313–7.

7. Dent PB, Walker N. Intra-articular corticosteroids in the treatment of juvenile rheumatoid arthritis. Curr Opin Rheumatol. 1998;10:475–80.
8. Saunders S, Longworth S. Injection techniques in musculoskeletal medicine. Edinburg: Churchill Livingstone; 2012.
9. Schumacher HR, Chen LX. Injectable corticosteroids in treatment of arthritis of the knee. Am J Med. 2005;118:1208–14.
10. Stephens M, Beutler A, O'Connor F. Musculoskeletal injections: a review of the evidence. Am Fam Physician. 2008;78:971–5.
11. Raynauld JP, Buckland-Wright C, Ward E, et al. Safety and efficacy of long-term intraarticular steroid injections in osteoarthritis of the knee: a randomized, double blind, placebo-controlled trial. Arthritis Rheum. 2003;48:370–7.
12. Roberts WN, Babcock EA, Breitbach SA, et al. Corticosteroid injection in rheumatoid arthritis does not increase rate of total joint arthroplasty. J Rheumatol. 1996;23:1001–4.
13. Kumar N, Newman RJ. Complications of intra- and peri-articular steroid injections. Br J Gen Pract. 1999;49:465–6.
14. Kahn CB, Hollander JL, Schumacher HR. Corticosteroid crystals in synovial fluid. JAMA. 1970;211:807–9.
15. Firetein GS, Panayi GS, Wollheim FA. Rheumatoid arthritis frontiers in pathogenesis and treatment. Oxford: Oxford University Press; 2000. p. 361–9.
16. Cassidy JT, Bole GG. Cutaneous atrophy secondary to intra-articular glucocorticoid administration. Ann Intern Med. 1966;65:1008–18.
17. Gilsanz V, Bernstein BH. Joint calcification following intra-articular corticosteroid therapy. Radiology. 1984;151:647–9.
18. Blanco I, Krahenbuhl S, Schlienger RG. Corticosteroid-associated tendinopathies: an analysis of the published literature and spontaneous pharmacovigilance data. Drug Saf. 2005;28: 633–43.
19. Pal B, Morris J. The perceived risks of joint injection following intra-articular corticosteroid injections: a survey of rheumatologists. Clin Rheumatol. 1999;18:264–5.
20. Charalambous CP, Tryfonidis S, Sadiq P, et al. Septic arthritis following intra-articular steroid injection of the knee: a survey of current practice regarding antiseptic technique used during intra-articular steroid injection of the knee. Clin Rheumatol. 2003;22:386–90.
21. Lazarevic MB, Skosey JL, Djordjevic-Denic G, et al. Reduction of cortisol levels after single-intra-articular and intramuscular steroid injection. Am J Med. 1995;99:370–3.
22. Godwin M, Dawes M. Intra-articular steroid injections for painful knees: systematic review with meta-analysis. Can Fam Physician. 2004;50:241–8.
23. Slotkoff AT, Clauw DJ, Nashel DJ. Effect of soft tissue corticosteroid injection on glucose control in diabetics. Arthritis Rheum. 1994;37:S347 (abstract).
24. Nesbitt LT. Minimizing complications from systemic glucocorticosteroid use. Clin Dermatol. 1995;13:925–39.
25. Gensler L. Glucocorticoids: complications to anticipate and prevent. Neurohospitalist. 2012; 3:92–7.
26. Emkey RD, Lindsay R, Lissy J, et al. The systemic effect of intraarticular administration of corticosteroid on markers of bone formation and bone formation and bone resorption in patients with rheumatoid arthritis. Arthritis Rheum. 1996;39:277–82.
27. Moreland L, O'Dell J. Glucocorticoids in rheumatoid arthritis. Arthritis Rheum. 2002;46: 2553–63.
28. afKlint E, Grundman C, Engström M, et al. Intra-articular glucocorticoid treatment reduces inflammation in synovial cell infiltrations more efficiently than in synovial cell infiltrations more efficiently than in synovial blood vessels. Arthritis Rheum. 2005;52:3880–9.
29. Neeli I, Khan SN, Radic M. Histone deimination as a response to inflammatory stimuli in neutrophils. J Immunol. 2008;180:1895–902.
30. Makrygiannakis D, Revu S, Engström M, et al. Local administration of glucocorticoids decreases synovial citrullination in rheumatoid arthritis. Arthritis Res Ther. 2012;14:1–9.
31. Chatham W, Williams G, Moreland L, et al. Intraarticular corticosteroid injections: should we rest the joints? Arthritis Care Res. 1989;2:70–4.

32. Boesen M, Boesen L, Jensen KE, et al. Clinical outcome and imaging changes after intraarticular (IA) application of etanercept or methylprednisolone in rheumatoid arthritis: magnetic resonance imaging and ultrasound-Doppler show no effect on IA injections in the wrist after 4 weeks. J Rheumatol. 2008;35:584–91.
33. Hertzberger-Ten RC, deVries-van der Vluge BLM, et al. Intra-articular steroids in pauciarticular juvenile chronic arthritis, type 1. Eur J Pediatr. 1991;150:170–2.
34. Bloom B, Alaria A, Miller L. Intra-articular corticosteroid therapy for juvenile idiopathic arthritis: report of an experiential cohort and literature review. Rheumatol Int. 2011;31: 749–56.
35. Beukelman T, Guevara JP, Albert DA. Optimal treatment of knee monoarthritis in juvenile idiopathic arthritis: a decision analysis. Arthritis Rheum. 2008;59:1580–8.
36. Lepore L, del Santo M, Malargio C, et al. Treatment of juvenile idiopathic arthritis with intraarticular triamcinolone hexacetonide: evaluation of clinical effectiveness correlated with ANA and T gamma/delta+ and B CD5+ lymphocyte populations of synovial fluid. Clin Exp Rheumatol. 2002;20:719–22.
37. Huppertz HI, Tschammler A, Horwitz AE, et al. Intraarticular corticosteroids for chronic arthritis in children: efficacy and effects on cartilage and growth. J Pediatr. 1995;127:317–21.
38. Zulian F, Martini G, Gobber D, et al. Triamcinolone acetonide and hexacetonide intraarticular treatment of symmetrical joints in juvenile idiopathic arthritis: a double blind trial. Rheumatology (Oxford). 2004;43:1288–91.
39. Gran JT, Husby G. Ankylosing spondylitis. Current drug treatment. Drugs. 1992;44: 585–603.
40. Gunaydin I, Pereira PL, Fritz J, et al. Magnetic resonance imaging guided corticosteroid injection of sacroiliac joints in patients with spondylarthropathy. Are multiple injections more beneficial? Rheumatol Int. 2006;26:396–400.
41. Braun J, van den Berg R, Baraliokos X, et al. Computed tomography guided corticosteroid injection of the sacroiliac joint in patients with spondyloarthropathy with sacroiliitis: clinical outcome and follow up by dynamic magnetic resonance imaging. J Rheumatol. 1996;23: 659–64.
42. Spies CM, Burmester GR, Buttgereit F. Analysis of similarities and differences in glucocorticoid therapy between rheumatoid arthritis and ankylosing spondylitis – a systemic comparison. Clin Exp Rheumat. 2009;27 Suppl 55:S152–8.
43. Wechalekar M, Vinik O, Schlesinger M, et al. Intra-articular glucocorticoids for acute gout. Cochrane Database Syst Rev. 2013;(4):1–16.
44. Richette P, Pardin T. Gout. Lancet. 2010;375(9711):318–28.
45. Koski JM. Ultrasound guided injection in rheumatology. J Rheumatol. 2000;27:2131–8.
46. Balint PV, Kane D, Hunter J, et al. Ultrasound guided versus conventional joint and soft tissue fluid aspiration in rheumatology practice: a pilot study. J Rheumatol. 2002;29:2209–13.
47. Sibbitt WL, Peisajovich A, Michael AA, et al. Does sonographic needle guidance affect the clinical outcome of intraarticular injections? J Rheumatol. 2009;36:1892–902.
48. Raza K, Lee CY, Pilling D, et al. Ultrasound guidance allows accurate needle placement and aspiration from small joints in patients with early inflammatory arthritis. Rheumatology. 2003;42:976–9.
49. Brostrom E, Hagelber S, Haglund-Akerlind Y. Effect of joint injections in children with juvenile idiopathic arthritis: evaluation by 3D-gait analysis. Acta Paediatr. 2004;93:906–10.