Chapter

Applications of Corticosteroid Therapy in Inflammatory Rheumatic Diseases

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Abstract

Corticosteroids still remain the anchor drugs in therapy strategies for patients with inflammatory rheumatic diseases even though new drugs such as biologic or targeted synthetic molecules have emerged in the past years, being the most commonly prescribed medicines in the world due to their powerful immune-modulating properties. In this chapter, we aim to discuss the main characteristics of the glucocorticoids, their mechanism of action and effects on the immune system given the fact that they reduce the activation, proliferation, differentiation and survival of inflammatory cells such as macrophages and lymphocytes. Nevertheless, of great importance are the indications and tapering regimens, but also the adverse effects and various methods of monitoring the corticosteroid therapy.

Keywords: corticosteroids, immune system, regimens, adverse effects

1. Introduction

The adrenal glands are composed of the medulla which secretes cathecolamines (adrenaline and noradrenaline) and the adrenal cortex which produces glucocorticoids (cortisol), mineralocorticoids such as aldosterone and andogens (dehydropiandrosterone) [1].

In the 1930s, steroidal hormones were isolated from the adrenal cortex and synthesized a years later. Several of these structures have potent anti-inflammatory properties, but they can also have important side effects. Chemical analogues with improved activity and less side effects have been discovered and are being used for the treatment of numerous inflammatory and autoimmune diseases [2].

Although glucocorticoid (GC) is the preferred classification when using exogenous agents therapeutically, corticosteroids encompass both glucocorticoid and mineralocorticoid hormones, the term corticosteroid (CS) is considered synonymous to glucocorticoid. Commercially available synthetic GC formulations come in a number of chemical compositions, potencies and half-lives.

Glucocorticoids are hormones that regulate a variety of cellular functions, including growth, homeostasis, metabolism, cognition, and inflammation. GCs are one of the most commonly prescribed medicines in the world due to their powerful immune-modulating properties [3].

2. History of corticosteroid discovery and development

Thomas Addison first described the disease named after him in 1855 in London, in which postmortem examination of patients indicated adrenal gland atrophy. The following year, in Paris, Charles Edouard Brown-Se'quard demonstrated that surgical removal of the adrenals in small animals caused muscle fatigue, respiratory insufficiency, cardiac problems and death within 12 hours [4, 5].

The Mayo Clinic's Edward C. Kendall (1886–1972) and Zurich's Tadeus Reichstein (1897–1996) continued their research. Edward Calvin Kendall isolated four steroidal compounds from adrenal extracts in 1946. He labeled them A, B, E, and F. Later that year, Sarett synthesized compound E, known as cortisone nowadays. Rheumatologist Philip Hench discovered the compound's therapeutic potential in a patient with RA [6].

On April 13, 1949, the Mayo Clinic's Proceedings of Staff Meetings confirmed the first therapeutic use of cortisone. The first patient, a 29-year-old married woman in her fourth year of rheumatoid arthritis (RA), had been chosen by Philip S. Hench (1896–1965), chief of the Rheumatology Section [7, 8]. Before September 1948, when she received the first twice daily intramuscular injections of 50 mg of cortisone, the patient had been seen at the Mayo Clinic and had received multiple prescriptions on many occasions. Subjective improvement was recorded after the second injection. Although cortisone dosage was fluctuating between 50 mg and 100 mg per day, depressive and aggressive ideation became more prevalent, despite the improving of rheumatoid symptoms by 50% [9, 10].

Thus in 1950, Hench and Kendall, along with Tadeus Reichstein, were awarded the Nobel Prize for Medicine and Physiology for isolating with success several steroid hormones from the adrenals [11].

3. Mechanisms of action

The CS exercise their effect following the passive diffusion through cellular membranes, attachment to specific intracellular receptors and the formation of a complex that will be translocated intra-nuclear and will interact directly with certain specific DNA sequences or with other transcription factors [12, 13].

CS can exercise their effect by genomic or nongenomic mechanisms. It takes at least 30 minutes for the clinical effects of a GC to appear while operating by genomic mechanisms. Nongenomic mechanisms, by which GCs function within minutes, only occur when large doses are administered, such as in pulse therapy [14].

3.1 Genomic mechanisms

The majority of glucocorticoid effects are mediated by genomic pathways, such as binding to the GC receptor in the target cells' cytoplasm. Since GCs are lipophilic and their molecular mass is low, they can easily transit through the cell membrane [15, 16].

The balance of the intracellular enzyme 11-hydroxysteroid dehydrogenase (11–HSDs) possibly influences the sensitivity of specific tissues to GCs, in addition to the tissue-specific intracellular density of GC receptors. Only the isoform of the GC receptor, which is widely distributed in all target tissues, binds to GCs. The GC receptor–GC complex is activated and subsequently transported into the nucleus. As a dimer, it binds to sites in DNA which respond to GC, thus being able to control the transcription of targeted genes. This process is termed transactivation [17].

As monomers, activated GC receptor – GC complexes interact with transcriptional factors (such as activator protein (AP)-1, interferon regulatory factor (IRF)-3, and nuclear factor-κB (NF-κB)). These transcriptional factors are prevented from binding to their consensus sites in DNA. Transrepression is a process that results in the downregulation of predominantly pro-inflammatory protein synthesis [18].

The hypothesis has been proposed that side effects of GCs may be based predominantly on transactivation, whereas the anti-inflammatory effects can be attributed to transrepression.

The binding of GC to specific sites at the DNA level, can cause suppression or stimulation of gene transcription and numerous effects on the inflammatory process such as:

- attachment at the level of promoter sites of the pro-inflammatory genes and their inhibition (interleukin (IL)-1α, IL-1β);

- recruitment of transcription factors of gene promoter domains which encode the production of anti-inflammatory factors (IKBα-transcription inhibitor factor of NF-KB, IL-10, α-2 macroglobulin, IL-1R);

- suppression of the synthesis of most pro-inflammatory cytokines through the inhibition of NF-KB or AP-1, indispensable for the transcription of inflammation mediators [19].

Consequences of GC interference with the phenomenon of gene transcription consist of: stimulation of the synthesis of angiotensin conversion enzyme or endopeptidases which neutralizes bradykinin, a central vasodilator peptide involved in the onset angioedema. Another effect is the inhibition of the synthesis of pro-inflammatory factors by the phagocytic cells through stimulating lipocortin 1 synthesis and, subsequently, inhibition of phospholipase A2 which is responsible for the synthesis of arachidonic acid at the level of membrane phospholipid, prostaglandins, leukotrienes and free oxygen radicals. Nevertheless the inhibition of cyclooxygenase (COX)-2 synthesis, the inducible form of COX, responsible for production of prostaglandins (PG) at the inflammatory site is another consequence of the GC interference with gene transcription [20].

3.2 Nongenomic mechanisms

In addition to genomic effects, GCs exert their effects through nongenomic pathways, represented by the interaction with selective membrane receptors (specific nongenomic effects) or directly on the biological membranes (nonspecific nongenomic effects).

Nongenomic effects at high doses of GCs occur much faster than genomic effects—within minutes. Membrane-bound GC receptors are one mechanism. Nongenomic actions which do not include GC receptors change cell function by physicochemical interactions with biologic membranes [21].

4. Effects on the immune system

One of the main function of GCs is the inhibition of the activation, proliferation, differentiation and survival of macrophages and T lymphocytes as well as other inflammatory cells. GCs also promote apoptosis mainly of immature and activated T cells. Changes in cytokine synthesis and secretion are primarily responsible for this activity.

B lymphocytes and neutrophils, on the other hand, are less responsive to glucocorticoids, and glucocorticoid treatment can improve their survival [22].

4.1 Leukocytes and fibroblasts

The administration of GC has an effect on the circulating neutrophil granulocytes, increasing their number in the peripheral blood. This results in decreased myelopoiesis and bone marrow release. The effects also apply to the T cells, resulting in their redistribution. The redistribution of lymphocytes has no clinical implications. This effect occurs after 4 to 6 hours of a single dose of prednisone and returns to normal within 24 hours. The activity of B cells and the synthesis of immunoglobulin are unaffected. However, the susceptibility to infection is increased due to the effects of GCs on monocytes and macrophages. These effects lead to a decrease in the expression of class II major histocompatibility complex (MHC) molecules and Fc receptors. The administration of GC also affects the fibroblasts, leading to reduced proliferation and synthesis of fibronectin and prostaglandins [23].

4.2 Cytokines

One of the most important effects of GC therapy in chronic inflammatory disorders is on cytokine synthesis and action. A wide range of cytokines are inhibited by GC administration. GCs inhibit most Th1 pro-inflammatory cytokines such as interleukins (IL-1, IL-2, IL-3, IL-6, IL-17), but also tumor necrosis factor (TNF), interferon-γ and GM-CSF. These cytokines are thought to be responsible for synovial proliferation, cartilage damage and bone deterioration in people with RA [24]. GCs have controversial effects on Th2 cytokines such as IL-4, IL-10 and IL-13, either by stimulating or having no effect on their development [25].

4.3 Pro-inflammatory enzymes

Arachidonic acid metabolism is an essential part of the inflammatory cascade. An essential part of the cascade of inflammation is the development of prostaglandins and leukotrienes, the majority of which are highly pro-inflammatory. GCs also have an effect on the inhibition of the development of COX-2 and phospholipase A2, induced by cytokines. This process is located in monocytes/macrophages, fibroblasts and endothelial cells. Furthermore, in vitro and in vivo, glucocorticoids promote the inhibition of the metalloproteinases, especially collagenase and stromelysin. These metalloproteinases are considered the key effectors of cartilage degradation induced by IL-1 and TNF [26].

4.4 Adhesion molecules and permeability factors

Pharmacologic doses of GCs significantly reduce plasma exudation and leukocyte recruitment into inflammatory sites. Adhesion molecules regulate the migration of inflammatory cells into the sites of inflammation, which is essential in chronic inflammatory diseases.

GCs also exert their effect by stimulating the expression of adhesion molecules such as intercellular adhesion molecule-1 and E-selectin through the inhibition of pro-inflammatory cytokines. GC also have an effect on the inhibition of chemotactic cytokines such as IL-8 and macrophage chemoattractant proteins which attract immune cells to the inflammatory site. The production of nitric oxide is increased in the sites with active inflammation by the pro-inflammatory cytokines, leading

to an increase in blood flow, exudation and likely activation of the inflammatory response. GCs effectively inhibit the inducible form of nitric oxide synthase induced by cytokines [27].

5. Pharmacology

After administration, both orally and parenterally, absorption is rapid and subsequently CS bind to 90% of plasma proteins. The binding is mainly done by specific globulin (CBG-corticosteroid binding globulin or transcortin) and in a reduced percentage by albumin. The biologically active form is the free cortisol (10%), which achieves high concentrations in most tissues. Metabolism takes place in the liver and excretion is urinary.

Medicinal products included in this class are similar in absorption rate, with differences in half-life and intensity of anti-inflammatory effect. Depending on the duration of action, GC can be classified into short-, medium- or long-term.

The route of administration can be:

- parenteral - intravenous pulse therapy in doses of 1–2 g, in the activity periods of the disease, in patients with RA, systemic lupus erythematosus (SLE) vasculitis, or intramuscular;
- oral - usually in the case of chronic GC therapy;
- intra-articular with depot preparations with local action;
- topical with variable absorption rates [28].

Systemic administration of GC therapy can be done in high doses, for a short period, in acute situations, or chronically, with periodic dose adjustment, depending on the therapeutic response and adverse effects. Discontinuation of therapy is considered either when the maximum therapeutic effect has been reached or in case of inefficiency or severe adverse effects without response to the specific therapy [29].

The main pharmacological characteristics of GCs are illustrated in **Table 1**.

	Equivalent GC dose	Relative GC activity	Protein binding	Half-life in plasma (hours)	Biologic half-life (hours)
Short-acting					
Cortisone	25	0.8	No	0.5	8–12
Cortisol	20	1	Yes	1.5–2	8–12
Intermediate-acting					
Methylprednisolone	4	5	No	>3.5	18–36
Prednisolone	5	4	Yes	2.1–3.5	18–36
Prednisone	5	4	Yes	3.4–3.8	18–36
Triamcinolone	4	5	Yes	2–5	18–36
Long-acting					
Dexamethasone	0.75	20–30	Yes	3–4.5	36–54
Betamethasone	0.6	20–30	Yes	3–5	36–54

Table 1.
Characteristics of main GCs.

6. Indications and dosing

Glucocorticoid therapy is indicated in multiple rheumatic diseases. In pathologies such as inflammatory myopathies, polymyalgia rheumatic, but also in systemic vasculitis, GCs are considered the focal point of the therapeutic strategy.

On the other hand, in systemic scleroderma, GCs are contraindicated in high doses, due to the increased risk of scleroderma renal crisis. However, they can be of use when systemic sclerosis is complicated by myositis or interstitial lung disease. Glucocorticoids are used as an adjunctive treatment or not at all in the treatment of other diseases [30].

In RA, GCs exert their effects by complementing the disease-modifying antirheumatic drugs (DMARDs). GCs are helpful in reducing pain in osteoarthritis, although they are not administered on a regular basis, with the exception of intra-articular injections if there are symptoms of synovitis in an osteoarthritic joint.

GCs are used to treat a variety of rheumatic diseases in varying dosages. Standardization of dosing regimens has been suggested based on pathophysiologic and pharmacokinetic evidence:

- low dose - ≤ 7.5 mg prednisone equivalent per day;
- medium dose - >7.5 mg and ≤ 30 mg prednisone equivalent per day;
- high dose - > 30 mg and ≤ 100 mg prednisone equivalent per day;
- very high dose - >100 mg prednisone equivalent per day;
- pulse therapy - ≥250 mg prednisone equivalent per day for one or a few days [31].

7. Systemic adverse effects of glucocorticoid therapy

It is not surprising that glucocorticoids may have a wide range of side effects given their diverse pathways and sites of action. The majority of these side effects are unavoidable, but the risk of most complications is dose and time dependent and lowering GC dosage reduces the risk of complications [32].

7.1 Risk of infections

In vitro, glucocorticoids reduce neutrophil phagocytosis and bacterial destruction, but natural bactericidal and phagocytic activities are found in vivo. Monocytes are however more susceptible; bactericidal and fungicidal activity in vivo and in vitro is decreased during treatment with medium to large doses of glucocorticoids. These variables can have an impact on the risk of infection. Therapy with a daily dosage of less than 10 mg of prednisolone or its equivalent seems to have little or only a mild elevated risk of infection, while treatment with doses of 20 to 40 mg daily seems to have an increased risk of infection. However, if the dosage and duration of therapy is prolongued, the risk of infection also rises [33].

7.2 Cardiovascular adverse effects

Some glucocorticoids seem to have mineralocorticoid effects, such as decreased sodium and chloride excretion and increased potassium, calcium, and phosphate excretion. Edema, weight gain, high blood pressure and heart complications are

also possible side effects of this action. Reduced sodium and chloride excretion can result in heart failure.

Patients with inflammatory diseases have been linked to accelerated atherosclerosis and increased cardiovascular risk. Cardiovascular mortality is linked to the length of the disorder and the use of glucocorticoids. Because of their potentially harmful effects on lipids, glucose tolerance, insulin production and resistance, blood pressure and obesity, GCs can increase cardiovascular risk [34].

In vitro, GCs were found to suppress macrophage aggregation in damaged arterial walls, potentially reducing the local inflammatory response. Low-dose glucocorticoids can also improve inflammatory disease-related dyslipidemia. Low-dose GCs, on the other hand, are likely to have different effects on lipids and other cardiovascular risk factors in inflammatory disorders than medium and large doses of GCs.

Thus, in addition to conventional cardiovascular risk factors such as diabetes mellitus, length and level of inflammatory disease involvement, and co-therapies such as COX-2 selective NSAIDs, moderate and high glucocorticoid doses and long duration of therapy seem to be the most significant cardiovascular risk factors [35].

7.3 Osteoporosis

GC therapy directly influences osteoblasts, osteocytes and osteoclasts, reducing the process of bone formation and accelerating bone resorption.

Glucocorticoid receptors are located exclusively in osteoblasts, not in osteoclasts, the proliferation of the latter being the consequence of inhibition of osteoprotegerin synthesis (inhibitor of osteoclast differentiation in hematopoietic cells) and stimulation of RANK production, necessary for the osteoclastogenesis. High doses of GC also stimulate RANKL synthesis by osteoblast precursors, an event that activates osteoclast differentiation and the bone resorption process [36].

Other mechanisms involved are the decrease in the secretion of androgen and estrogen hormones, the increase in the serum level of parathormone (consequent to the decrease in intestinal calcium absorption and the increase in its renal elimination).

Suppression of the osteoformation process is mediated by accelerating the apoptosis of mature osteocytes and osteoblasts and the consequent inhibition of osteoblast proliferation. In addition, GC influences the physiological dynamics of parathormone secretion, antagonizes its anabolic action and inhibits the production of insuline-like growth factor (IGF)-1 and testosterone.

Loss of bone mass is evident from the first months of administration, especially in the first year, and mainly affects the trabecular bone, which associates a higher risk of fracture for the vertebral site. Fracture events can occur in 30–50% of patients and are directly related to dose, duration of administration of GCs and patient age.

The assessment of fracture risk in the first six months after initiation of therapy should include an assessment of risk factors and bone mineral density in selected cases and subsequently in accordance with current recommendations. Prevention of GC-induced osteoporosis is done by administering calcium (1000–2000 mg/day) and vitamin D (600–800 IU/day) [37].

7.4 Aseptic osteonecrosis

Aseptic osteonecrosis is the cause of high doses compared to the administration of small, long-term doses, and is rarely seen during prednisone therapy or equivalent of below 20 mg/day [38].

7.5 Myopathy

Cortisone myopathy can occur following the administration of any type of GC and is the consequence of the direct catabolic effect on skeletal muscles. It is clinically evident in the form of proximal muscle weakness, unaccompanied by myalgias or changes in the serum level of muscle enzymes [39].

7.6 Gastrointestinal adverse effects

Glucocorticoids are less toxic to the upper gastrointestinal tract than NSAIDs, but they do raise the risk of adverse gastrointestinal events like gastritis, ulcers and gastrointestinal bleeding. The effect of glucocorticoids on gastrointestinal events is very limited. In addition to evidence of upper gastrointestinal tract morbidity, GCs have been linked to cases of intestinal rupture, diverticular perforation and pancreatitis. In rheumatology, glucocorticoids are commonly used in conjunction with NSAIDs and the two drugs work together to increase the risk of GI side effects [40].

7.7 Ocular adverse effects

Posterior subcapsular cataracts is a well-known side effect of long-term GC therapy. There is no safe dosage for this complication and cataract formation has been documented even with inhaled GC preparations. The use of glucocorticoids has also been linked to cortical cataracts.

Patients taking glucocorticoids can develop cataracts as well as elevated intraocular pressure, which may cause vision problems. The occurrence of frank glaucoma, particularly with low-dose therapy, is uncommon and usually occurs in patients who are genetically predisposed [41].

7.8 Endocrine and metabolic side effects

Exogenous hypercorticism (Cushing's syndrome) is the consequence of long-term high doses and determines the characteristic appearance by redistribution of adipose tissue in the chest, face ("moon facies") and neck ("buffalo bump"), trunk obesity, the appearance of hirsutism, acne, increased appetite, obesity and subsequently the complications represented by osteoporosis, edema, hypertension, growth retardation in children which require dose adjustment or alternative administration - every two days.

Adrenal insufficiency may result from suppression of the hypothalamic–pituitary axis and is directly proportional to dose and duration of administration. High-dose corticosteroids can block the suppression of ACTH release and the rapid onset of adrenal insufficiency in approximately 5 days, lasting up to 4–6 weeks, even at doses of 10–15 mg/day. Restoration of the hypothalamic–pituitary axis usually occurs after 9–12 months. In order to prevent hypercorticism, it is preferred to administer a single morning dose, the use alternative therapy every two days or gradual reduction of the dose.

Changes in glucose metabolism represented by increased blood sugar is a consequence of the stimulation of the process of hepatic neoglucogenesis, hepatic production and storage of glycogen and decreased peripheral glucose utilization. It may cause diabetes or imbalance of pre-existing diabetes. Although the "de novo" onset of diabetes in patients with previously normal glucose levels is relatively rare, the risk is increased in the presence of a family history of diabetes, old age or a history of gestational diabetes.

Changes in lipid metabolism consist in stimulating the lipolysis process and increasing the amount of free fatty acids. The increase in insulin secretion, due to hyperglycemia, will cause a stimulating effect on the lipid metabolism, so that the two concomitant processes, lipolysis/lipogenesis, will cause the reorganization of adipose tissue and the appearance of the characteristic appearance of "lemon on toothpicks".

Protein metabolism is inhibited, except for the hepatic site, with the occurrence of side effects, especially cutaneous, muscular or of the connective tissue [42].

7.9 Cutaneous adverse effects

The most common side effects, even at low doses, are represented by the appearance of bruises and skin atrophy, due to the the acceleration of protein catabolism. In addition, facial erythema, hair fragility, acne and hirsutism may be present [43].

7.10 Neuropsychiatric adverse effects

The spectrum of symptoms is dependent on the dose and duration of administration and may be represented by anxiety, depression, psychosis, delirium, confusion, disorientation, cognitive deficits, sleep disturbances, the appearance of akathisia, usually of mild or moderate intensity. Psychosis is associated with the administration of prednisone at a dose of more than 20 mg/day over a long period of time and may require specific therapy, even under conditions of dose reduction. Behavioral disorders can range from mild euphoria to anxiety or depression in the case of long-term therapy [44].

8. Glucocorticoid therapy in rheumatoid arthritis

In this era of targeted treatments, therapeutic strategies, and comorbidity management in patients with RA, the potential role of GCs in RA is important to consider. Despite the fact that GC therapy was a significant clinical breakthrough for RA in the 1950s, the current focus is on the treatment's drawbacks rather than its benefits.

The aim of RA therapies is to reduce disease activity and achieve clinical remission in the short term, but also to restrict or avoid structural damage and systemic manifestations in the medium term. In RA, GCs have a rather rapid onset of action, which allows time for the DMARDs exert their immunosuppressive effect. Furthermore, GCs are also considered to have a structural impact on the affected joints. However, clinicians tend to use them when in need of rapid symptomatic relief for their RA patients. Thus, the benefit-to-risk ratio of GCs is still uncertain, and their use in RA is still debatable [45].

The use of GCs therapy in RA is regulated by international rheumatology societies such as the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR). These societies have formulated recommendations regarding the indications of GC therapy in RA.

The 2015 ACR recommendations for early and established RA state that GC therapy should be used in conjunction with DMARDs at the lowest possible dose and for short periods of time, only in disease flares. Adding GCs when starting a csDMARD, contrary to EULAR guidelines, is dependent on disease activity [46].

The benefit of GCs therapy was emphasized more in recent revisions of the EULAR recommendations for the treatment of early arthritis and RA than in previous versions. Short-term GCs therapy can be taken into consideration in the initial treatment strategy or subsequently if the beneficial effects of the initial strategy

have not been considerable, as bridging therapy when a change in DMARD being taken into account. Long-term use of GCs should be discouraged and GCs should be progressively diminished and discontinued, normally by 3 months and only in rare cases by 6 months [47].

These international protocols, taken together, recommend the use of GCs for disease flares and likely at the beginning of a new conventional synthetic DMARD (csDMARD), although specific guidance on dose, duration and length of administration protocols is not yet standardized. A dosage of less than 10 mg/day is considered a low dose in the United States, and GCs could be tapered in less than 3 months, while the European threshold is 7.5 mg/day, and GCs may be administered in conjunction with csDMARDs for up to 6 months total, with the understanding that this duration is mostly expert-driven. Despite these discrepancies, international recommendations stress the effectiveness of GCs while also recommending that they be used at the lowest cumulative dose possible due to the widespread understanding of potential side effects. The doses of GCs are usually expressed in prednisone equivalents in recommendations and studies [48].

In the CareRA trial were included patients with early RA and no negative prognosis signs. Subsequently, they were randomly assigned to one of two treatment arms: Methotrexate associated with GCs in one arm (30 mg/day prednisone tapered to 5 mg/day in 6 weeks) and Methotrexate without the association of GCs in the other arm. At 16 weeks, the patients who received GCs reached Disease Activity Score in 28 Joints (DAS28) remission more compared to the Methotrexate group (65% vs. 47%, $p = 0.08$). The rates of remission in the Methotrexate and GCs arm were also higher than the Methotrexate-only arm at 1 and 2 years, but not substantially [49].

The results of the BARFOT trial at ten years have been released. The study included 250 patients with early RA. Therapy with csDMARDs alone was compared to csDMARDs plus 7.5 mg/day prednisolone over the course of two years. The patients who recieved GCs demonstrated imporved clinical results at all time points (3, 6, 12, 18, and 24 months). A four-year follow-up analysis showed no variations in the percentage of patients in remission between the two groups. The use of bDMARDs with and without GCs did not vary after ten years. Patients in the BARFOT cohort were included between 1995 and 1999, before the age of biologics, thus the proportion of patients who used a bDMARD was very limited (15% in either group) [50].

In 10 year follow-up of the BeSt study, published in 2016, 508 patients with early active RA were randomly assigned to one of four groups: a pre-determined maintenance care regimen starting with Methotrexate; a group in which sulfasalazine was added to Methotrexate in case of therapy failure; a group following the guidelines of the COBRA study (Sulfasalazine, Methotrexate, and GCs initially at 60 mg/day, then gradually tapered to 7.5 mg/day in 6 weeks) and a group of patients who were administered Methotrexate and Infliximab from the beginning. In the initial study, the protocol in the COBRA trial proved to be more efficient at three months. However, at the 10-year follow-up, almost 50% of patients were in remission regardless of their initial group of randomization, making it difficult to conclude on the long-term beneficial effect of the GC treatment administered in the beginning [51].

The CAPRA-2, the double-blind, placebo controlled trial results were published in 2012. The study included 350 patients with active RA who were randomly assigned 2:1 to receive either modified release (MR) prednisone 5 mg or placebo once daily in the evening in addition to their current RA DMARD therapy for 12 weeks. At week 12, the primary end point was to determine the number of patients who improved by 20% in RA signs and symptoms based on ACR guidelines, respectively the ACR20. Morning pain and stiffness, the 28-joint Disease Activity Score, and health-related quality of life were all evaluated. At week 12, the administration of MR prednisone in conjunction with DMARD therapy proved

higher response rates than the administration of placebo plus DMARD in the case of ACR20 (48% vs. 29%) and ACR50 (22% vs. 10%) scores. Overall, low-dose MR prednisone administered in concurrence with DMARD therapy lead to the improvement RA signs and symptoms more quickly and significantly [52].

Results from the SEMIRA trial which included 421 patients with RA divided into two groups: the first group (n = 128) were assigned to the continued prednisone regimen while the second group (n = 131) were assigned to the tapered prednisone regimen. All patients received Tocilizumab for 24 weeks with or without conventional synthetic DMARDs. In patients with low disease activity using Tocilizumab and treatment with GCs for at least 24 weeks, continuous glucocorticoid treatment at a dose of 5 mg per day for 24 weeks provided a safer and better solution than gradual reduction of glucocorticoids, although two-thirds of patients were able to safely reduce their GCs doses [53].

The CAMERA-II study's post-trial follow-up results were released in 2017. The study group included 236 patients with RA. CAMERA-II compared the administration of Methotrexate plus 10 mg/day prednisone for two years to a Methotrexate and placebo group. After two years of therapy, disease activity decreased more in the Methotrexate-GCs arm than in the Methotrexate-placebo arm on average, but the variations seen in the first months continued to fade with time. Patients in the Methotrexate-GCs group had initiated a biological DMARD slightly less often than those in the Methotrexate-placebo group (31% vs. 50%) during the follow-up analysis, with a median follow-up of about 6.6 years.

Given these findings, there is little question whether GCs will reduce disease activity in RA patients, at least in the short term. It's impossible to say if the therapeutic advantage of GCs will last in the short and long term. Because of their toxicity and limited structural impact, GCs should never be used alone and should always be combined with DMARDs [54].

9. Glucocorticoid therapy in connective tissue diseases

9.1 Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is one of the most severe autoimmune rheumatic diseases, with multisystemic involvement, with frequent flares and an increased risk of death. The treatment of SLE is guided by organ damage, but most often it is represented by a combination of hydroxychloroquine - the gold standard in SLE - and variable doses of corticosteroids depending on the severity of the visceral damage and often in combination with immunosuppressants agents. Early and aggressive treatment in SLE is essential for the prevention of organ damage, the 2019 EULAR recommendations for the treatment of SLE supporting both the prevention of organ damage and the improvement of patients' quality of life and their long-term survival [55]. Achieving remission or low disease activity is another important goal in SLE management. Complete remission, defined as the absence of disease activity in the absence of treatment with CS or immunosuppressant, is rare [56].

For the patients with active disease, CS in variable doses, in combination with hydroxychloroquine and sometimes with immunosuppressants agents, still represent the optimal management of SLE. Besides the anti-inflammatory and immunosuppressive effects, the side effects of CS are well known, most of them are time and dose dependent: osteoporosis, osteonecrosis, cataract, hyperglycemia or coronary heart disease. Although they produce a rapid reduction in symptoms and the recommendation is to reduce the doses ≤7.5 mg/day equivalent to prednisone, or discontinued therapy, some studies have shown adverse effects even at minimal

doses of cortisone [57]. Thus, it is recommended the administration of intravenous methylprednisolone pulse therapy (250–1000 mg/day for 3 consecutive days) depending on the body weight, during acute flares and also the early initiation of immunosuppressive agents, both having the role of initiating a lower oral dose, as well as a faster reduction of CS doses [58].

For skin damage, the first therapeutic line, in addition to avoiding exposure to UV radiation, is represented by topical CS. Oral CS can also be used, depending on the degree of skin damage [59].

Cardiovascular involvement in SLE is one of the main causes of death, due by both kidney damage, that can cause cardiovascular and cerebrovascular disorders, but also by the increased risk of developing atherosclerosis, a consequence of both chronic inflammation and the additional risk of CS [60]. In a study of a group of 175 women with SLE, Manzi et al. identified the presence of carotid plaques in 40% of them, which correlated with the cumulative dose of prednisone and with the duration of therapy. Similar results were recorded in other studies that showed the relationship between prednisone and weight gain, blood pressure or a high serum cholesterol, correlation with sudden death or demonstration of subclinical atheromatosis in 45% of a group of 78 Italian patients with SLE [61].

The risk of infections in SLE is caused by the activity of the disease, by severe leukopenia and by the administration of high doses of CS in association with immunosuppressants agents. The results of a 2009 case–control study showed that the risk of severe infections was higher in the group of patients with prednisone 7.5 mg/day vs. those who received a median dose of 2.5 mg/day thus demonstrating that the risk of developing infections increases by 12% for every mg/day.

In summary, CSs has an importnat role in SLE, but side effects, often dependent on dose and duration of administration, should not be overlooked. Therefore, intravenous pulsetherapy with methylprednisolone is preferred, with consequent faster reduction of oral doses, and also the combination of antimalarials and immunosuppressive agents in the therapeutic regimen [62].

9.2 Systemic scleroderma

In systemic scleroderma, the use of CS is controversial, due to the lack of response of vasculopathy and fibrosis to CS, and due to the increased risk of developing scleroderma renal crisis. Itchy skin, arthralgia and myalgia in early and very early diffuse cutaneous systemic sclerosis have been shown to respond to low doses of CS, thus suggesting an inflammatory skin component in these stages, characterized by perivascular and tissue infiltrates with monocytes, macrophages and CD4 + lymphocytes. Thus, the effects of CS can be beneficial in these stages, before the appearance of irreversible fibrotic changes. Also, doses of CS can be used in interstitial lung disease related to systemic scleroderma. Asthenia in scleroderma may have a good response to CS administration, although there are no studies on this. Another benefit in patients with scleroderma is increased appetite, although it is well known that it is considered an adverse effect of corticosteroids, in patients with scleroderma it may be considered a benefit [63].

One of the most serious complications of systemic scleroderma is *scleroderma renal crisis* (SRC). Risk factors for its occurrence are: diffuse cutaneous forms, positivity of anti-RNA polymerase III antibodies and the use of CS. The mechanisms by which CS can trigger SRC are given in particular by vasoconstriction caused by the stimulation of endogenous and exogenous catecholamines by cortisol. Thus, there is a reduction in the production of prostaglandins by the endothelium, thus causing vasospasm. There is a decrease in juxtaglomerular perfusion by reducing the secretion of prostaglandin E2 (PGE2) with consecutive vasoconstriction of renal arterioles [64].

There are many studies that have shown that CS administration is a major risk factor for the development of SRC. Steen and Medsger in 1998 demonstrated in a case–control study that 36% of a group of 110 patients with SRC had received doses >15 mg/day equivalent of prednisone in the last 6 months [65]. Similar results were recorded in another studies in France - 60% of 50 patients with SRC had received CS with a mean duration of 2.65 months before the onset of SRC, respectively 59% of 64 patients with SRC in a study in UK [66, 67]. Montanelli et al. showed a 1.5% increased risk of developing SRC for each mg/day of prednisone administration [68]. The International Renal Crisis Survey has shown an increased risk of death of 4% for each mg/day of prednisone administration [69].

In contrast, there were open-label studies, but performed on a small number of patients with early difuse cutaneous systemic sclerosis, who not report SRC at low doses of CS.

CS are still ones of the most used therapies in *interstitial lung disease* in scleroderma. In 2018, EUSTAR showed that 60% of patients with interstitial lung disease were treated with CS, regardless of whether or not scleroderma was in the early stages of the disease [70].

For *cardiomyopathy* in scleroderma, doses of CS <15 mg/day of the equivalent of prednisone, alone or in combination with cyclophosphamide, have been shown to have beneficial effects.

In conclusion, GC can be indicated in the early and very early stages of systemic scerosis, when there is mainly inflammation, without fibrosis, indicated for skin or musculoskeletal damage, but should be used with caution, to very low-dose and a short time duration, to avoid CRS [71].

9.3 Inflammatory myopathies

CS are the first-line medication in polymiositis (PM) and dermatomyositis (DM). Patients with myositis and lung interstitial disease require high doses of CS, either 1 g methylprednisolone/day in pulse therapy - 3 consecutive days with subsequent oral follow-up or 60 mg/day for 3–4 months with monitoring clinical and biological parameters. Dose reduction is generally slow, usually with 5 mg/week. Some patients may relapse at dose reduction in these situation an immunosuppressive agent such as methotrexate or azathioprine may be associated; if muscle damage decreases with decreasing CS doses, but skin involvement persists, hydroxychloroquine may be associated [72]. High doses of CS, as well as long duration of administration, can cause glucocorticoid-induced myositis, so this condition must be differentiated by the relaps with pain and muscle weakness. If the increase in CS doses worsens the symptoms means it is glucocorticoid-induced myositis. Although some studies show that high-dose CS improves the prognosis in both PM and DM, another study has shown that mortality and morbidity in both poly- and dermatomyositis are elevated even at high doses of CS [73].

9.4 Sjőgren's syndrome

Sjőgren's syndrome is an autoimmune disease, characterized by the presence of anti-Ro and anti-La antibodies, a mononuclear focal infiltrate of the exocrine glands and whose main manifestations are xerostomia and xerophthalmia. Oral CS administration in primary Sjőgren syndrome has been shown to correlate with decreased proinflammatory cytokine levels, but with increased anti-Ro52 and anti-Ro-60 antibodies levels [74]. The same study did not show an increase in salivary volume after CS administration, in contrast to the study by Miyawaki et al. who demonstrated that there was a significant increase in salivary volume upon initiation of

CS treatment, but with a reduction after 48 months of follow-up. Haldorsen et al. showed in a study that neither the use of hydroxychloroquine nor CS influenced salivary production [75].

Regarding the effects of CS in lowering autoantibodies levels, a small study in a group of 20 patients with Sjőgren syndrome who received low-dose of CS had significantly reduced levels of both anti-Ro/SSA and anti- La/SSB antibodies, an effect that maintained a 48-month follow-up in 5 patients from the group, compared to the study of Reksten et al. which showed an increase in anti-Ro52 and anti-Ro-60 antibodies levels in patients with primary Sjogren syndrome treated with CS [76].

For *eye involvement* in Sjőgren syndrome, topical CS can also be used, but for a short period of time and with caution due to the increased risk of cataract, glaucoma or local infections especially during the exacerbation of sicca keratoconjunctivitis.

For *extraglandular involvement*, low doses of CS may be used in combination with hydroxychloroquine for musculoskeletal damage, arthralgias, myalgia or high doses or pulsetherapy of methylprednisolon in glomerulonephritis.

In *neurological impairment* in Sjőgren syndrome, such as acute transverse myelitis, the current treatment is an association of pulsetherapy of methylprednisolone with cyclophosphamide.

The role of CS alone or in combination with other immunosuppressive agents in the management of connective-tissue diseases is unquestionable, but it should be used with caution, in the lowest effective dose and for as short a period of time as possible to minimize the adverse effects [77].

10. Glucocorticoid therapy in systemic vasculitis

In the case active *large vessel vasculitis*, EULAR recommendations from 2018 are to initiate therapy with GCs in high doses (40–60 mg/day equivalent of prednisone), followed by tapering of the dose in 2–3 months to 15–20 mg/day, if the patients is in remission, and to 7.5–10 mg/day at 6 months. Subsequently, after more than 1 year of CS therapy, it is recommended to maintain a dose of ≤5 mg/day for giant cell arteritis and ≤ 10 mg/day for Takayasu arteritis and cease GCs therapy at 18–24 months. Therefore, for patients with no eye damage, the administration of 1 mg/kg/day of prednisone ≤60 mg/day causes a significant improvement in symptoms in 24–48 hours and a significant reduction of the inflammatory tests.

Decreases in dose reduction of corticosteroids are common in large vessel vasculitis, so in the case of minor relapses it is recommended to increase the dose of glucocorticoids to the last effective dose and in case of a major relapse it is recommended to increase the dose to 40–60 mg/day.

In case of acute blindness or amaurosis fugax in giant cell arteritis, it is recommended to administer pulse therapy with 500 mg - 1 g/day of intravenous methylprednisolone for 1–3 days followed by the administration of oral GCs, at a dose of 1 mg/kg/day, less than 60 mg/day, but the ocular damage is rarely reversible and loss of visual acuity may persist despite initiation of GC treatment in approximately 10% of patients [78].

The treatment of *polymyalgia rheumatica* is based on the 2015 EULAR/ACR recommendations. It is recommended to use the lowest effective GC dose of 12.5–25 mg/day equivalent of prednisone. It is necessary to individualize the dose reduction according to the clinical and biological profile of each patient. The following dose reduction principles are recommended:

- initial decrease - to 10 mg/day equivalent of prednisone in 4–8 weeks;

- relapse therapy - increasing the dose of glucocorticoids to the dose before relapse and gradually decreasing it in 4–8 weeks until the dose at which the relapse occurred;

- dose reduction in case of remission - the dose of prednisone is reduced by 1 mg every 4 weeks until discontinuation of therapy, as long as remission is maintained [79].

The therapeutic approach in *polyarteritis nodosa* patients with a five factor score (FFS) of 0 is the use of GCs in monotherapy. The doses used are pulse therapy with 500–1000 mg methylprednisolone/day for 3–5 days followed by 1 mg/kg/day of oral equivalent of prednisone in order to obtain remission, with the subsequent progressive decrease of doses. In the presence of severe organ damage, cyclophosphamide in combination with GCs is recommended in patients with FFS ≥ 1. The recommended doses are 2 mg/kgc/day orally or the administration of intravenous therapy of 600 mg/m^2 at intervals of 2–4 weeks, for 3–6 months [80].

In *ANCA-associated vasculitis*, the EULAR/ERA-EDTA recommendations state that GCs should be administered in doses of 1 mg/kg/day of equivalent of prednisone or in pulse therapy with methylprednisolone 1 g/day for 3 consecutive days to induce remission associated with cyclophosphamide or rituximab. The target is to reduce the dose to 7.5–10 mg/day equivalent of prednisone after 3 months of treatment. To induce remission in limited forms without severe organ damage, the use of methotrexate in doses of 20–25 mg/week or mycophenolate mofetil in doses of 2–3 g/day in combination with GCs is recommended [81].

In the case of *Behçet's disease*, the treatment is based on the EULAR recommendations of 2018. Thus, arterial lesions benefit from treatment with GCs in high doses, pulse therapy with 1 g/day methylprednisolone for 3 days, followed by of 1 mg/kg/day equivalent of prednisone and intravenous cyclophosphamide in monthly courses, if no surgery is required.

In the case of neurological manifestations, depending on the severity of the clinical manifestations, pulse therapy with GC in doses of 1 g/day is administered for 7 days, followed by oral prednisone at doses of 1 mg/kgc/day for one month and slow dose reduction by 5–10 mg every 10–15 days.

Ocular involvement benefits from topical treatment with GC or for the rapid suppression of episodes of acute inflammation of high doses of systemic GC. In the case of refractory cutaneous and mucosal manifestations, low doses of oral GC may be used [82].

11. Corticosteroids in local injections for inflammatory rheumatic disease

Injection therapy using corticosteroids in the local treatment of multiple musculoskeletal disorders has been used with success for already more than 70 years, nevertheless, only a few studies of its application in joint and periarticular lesions based on expert opinion and outcome measures in rheumatology define efficacy and compare local injection of corticosteroids with other treatments.

Several controversies regarding the local mechanism of action in rheumatic conditions, dosing regimen, volume, which type of steroid, injection technique, optimal schedule of injecting or for how long, blind or ultrasound guided placement of injection have arose as most of these aspects are non-standardized.

A decade after the first systemic use of steroid drugs, Hollander, in the USA reported the first documented use of hydrocortisone intra-articular injections for arthritis [83].

The rationale for injecting corticosteroids has become apparent after analyzing side effects generated by their systemic administration. Several mechanisms of action and pharmacological effects are proposed when injected into the joints and soft tissues, but the premise is that injecting insoluble corticosteroid suspensions in limited quantities, in contact with inflamed tissues will determine the up taking of the active drug by the synovial cells, before being absorbed in lesser amount in the blood and cleared, thus reducing the systemic effects [84].

The major effect when used in intra and periarticular injections is that of suppressing inflammation in inflammatory rheumatic diseases such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis or gout. As in systemic administration they exert these effects mostly by modulating the transcription of multiple genes, acting by binding on nuclear steroid receptors in order to regulate the rate of synthesis of mRNA and proteins, subsequently reducing the production of pro-inflammatory cytokines [85]. Administration of steroids can be done intra-articular, in the synovial sheath of tendons for tenosynovitis, for dactilitis, bursitis or entesitis.

Another indication for injecting local steroids is suppression of inflammatory flares in degenerative joint disease, although benefits over disadvantages are still subject of debate. The risk of infection, Charcot-like arthritis, aseptic osteonecrosis or cartilage loss through altered protein synthesis may overweight the favorable response of pain and inflammation. Still, studies sustain major improvement of pain and inflammation in osteoarthritis of the knee after local injection of corticosteroids (triamcinolone hexacetonide) compared to placebo, persistent for up to six weeks after administration. Improvement may be due also to the benefits of joint aspiration of pathological fluid. A review of intra-articular corticosteroid for knee osteoarthritis in terms of pain, physical function, quality of life and safety, that searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE (from inception to 3 February 2015), including 27 trials with 1767 participants identified that intra-articular corticosteroids appeared to be more beneficial in pain reduction than control interventions (SMD -0.40, 95% CI -0.58 to −0.22). In terms of follow up benefits were moderate at 1 to 2 weeks after end of treatment (SMD -0.48, 95% CI -0.70 to −0.27), small to moderate at 4 to 6 weeks (SMD -0.41, 95% CI -0.61 to −0.21), small at 13 weeks (SMD -0.22, 95% CI -0.44 to 0.00), and no evidence of an effect at 26 weeks (SMD -0.07, 95% CI -0.25 to 0.11). Corticosteroids have showed to be more effective also in function improvement than control interventions (SMD -0.33, 95% CI -0.56 to - 0.09), while no evidence has been proved of an effect of corticosteroids on quality of life compared to control (SMD -0.01, 95% CI -0.30 to 0.28, I2 = 0%). Patients with corticosteroid injections were 11% less likely to experience adverse events, 67% less likely to withdraw because of adverse events, and 27% less likely to experience any serious adverse event, but confidence intervals were wide and included the null effect.

There is little evidence to support another rationale for using local corticosteroids such as the clivage of the inflammatory damage – repair – damage cycle that mentaines a continuous low-grade inflammatory response by inhibiting tissue repair and scarr formation in favor of adhesion formation [86].

Several studies support a direct protective effect on the cartilage metabolism through promotion of articular surfactant production and not related to the anti-inflammatory effect of corticosteroids [87].

Corticosteroids used for intra-articular injections differ in terms of potency and time of action, solubility playing an important role in choosing the best drug

according to indication. The most frequently used corticosteroid for local administration are illustrated in **Table 2**.

Local side effects of injectable corticosteroids may occur when injected too often or when the volume and dose are not adjusted to the anatomy of the joint, as well as when injecting the enthesis of the tendons with large quantities of corticosteroids.

Joint infection is one of the most severe local adverse effects that is most likely to occur between 4 days and 3 weeks after the procedure, usually in a immunocompromised patient or with high risk of infections such as diabetics, or patients with joint arthroplasties or intravenous lines [88]. After injecting periarticular soft tissues local infection and osteomyelitis may be suggested by increasing pain, local swelling, fever or systemic signs of infection.

Synovial and *subcutaneous tissue irritation* or *postinjection flare* usually happens after soft tissue injection and is caused by the rapid intracellular ingestion of the microcrystalline steroid ester, more frequent after methylprednisolone with pain and swelling that may mimic and should be differentiated from sepsis. Pain, swelling, limited range of motion and stiffness suggests transient synovitis after joint injection. Not only the steroid itself may cause a postinjection flare, but preservatives such as parabens may be incriminated in te appearance of a local irritative reaction [89].

Steroid arthropathy is mostly linked to frecquent number of corticosteroid injections with reports of Charcot-like joint distruction after osteoarthritic hip injection, with conflicting evidence over the risk due to corticosteroids or rather to the disease progression itself [90]. Most reports support the rather chondroprotective effect of steroids than chondrolitic, while repeating steroid injections no sooner than 3 months seems to be safe over a period of 2 years [91].

Prolonged bleedeng at the procedural site or *bruising* may occur in patients taking anticoagulants, vasodilators, aspirin or NSAIDs with significant antiplatelet activity. Anticoagulation within a therapeutical INR does not contraindicate joint injection of corticosteroids.

Skin depigmentation is mostly due to injecting superficial lesions or when drug refluates back through the needle tract after retraction, mostly in dark-skinned patients. Of more interest is *local atrophy* of skin and subcutaneous tissue that may appear as late as one to four months after injection bu. usually dissapears in six months to two years [92]. Also, *steroid "chalk" or "paste" deposits* after substance flocculation may be detected through surgery at the level of previously injected joints and tendons [93], as well as *soft tissue calcifications.*

Injecting corticosteroids into tendons associated with *tendon rupture or atrophy* is widely accepted although not well supported from studies [94]. Adjusting the dose and the volume injected, avoiding injecting enthesis or using peppering technique may minimise the risks (**Figure 1**).

Duration of action	Drug	Equivalent of prednisone
Short-acting	Hydrocortisone acetate	5 mg
Intermediate-acting	Methylprednisolone acetate	50 mg
	Triamcinolone acetonide	50 mg
	Triamcinolone hexacetonide	25 mg
Long-acting	Betamethasone sodium phosphate	50 mg

Table 2.
Corticosteroids frequently used for local administration.

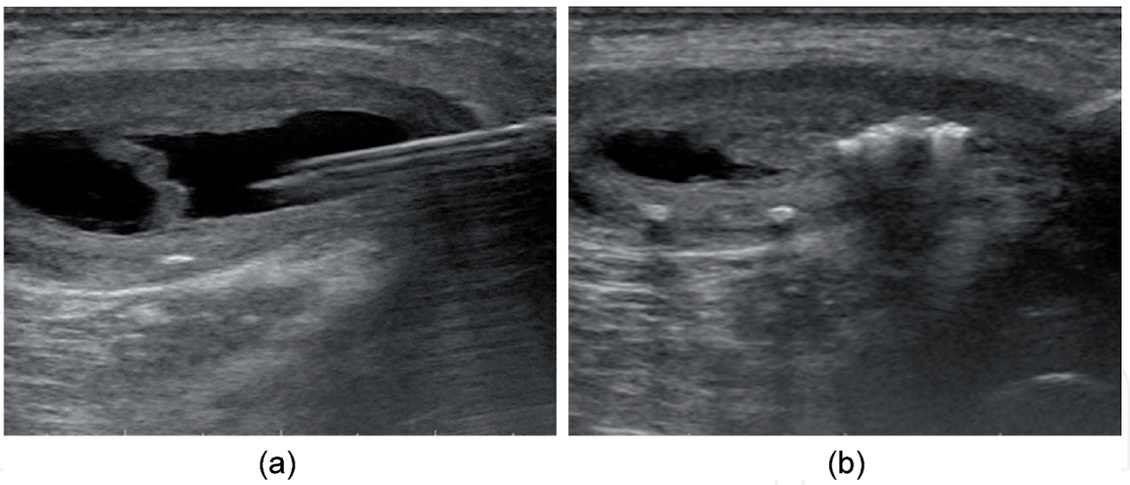

Figure 1.
(A) Aspiration of a Baker cyst guided by ultrasound. (B) Hyperechoic images consistant of steroid deposits after injection.

More rare side effects are linked mostly to the injecting technique or expertise, such as nerve damage when needling a nerve, transient paresis or needle fracture [95].

12. Conclusions

Corticosteroids still remain the anchor drugs in therapy strategies in inflammatory rheumatic diseases even though new drugs such as biologic or targeted synthetic molecules have emerged in the past years. In diseases such as systemic vasculitis, some of the connective tissue diseases such as SLE and poly/dermatomyositis GCs are considered the first-line therapy. Thus, it is of great importance to acknowledge the use of GCs in rheumatology.

Conflict of interest

The authors declare no conflict of interest.

DOI: http://dx.doi.org/10.5772/intechopen.98720

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