GLUCOCORTICOIDS IN RHEUMATIC DISEASES. PART I

Glikokortykosteroidy w leczeniu chorób reumatycznych. Część I

Natalia Kostecka, Marta Jaworska, Katarzyna Rendaszka, Rafał Bilski, Robert Kruszewski, Witold Tłustochowicz

Military Institute of Medicine – National Research Institute, Department of Internal Medicine and Rheumatology, Poland

Natalia Kostecka – 0009-0009-6090-7484
Marta Jaworska – 0000-0003-4131-2281
Katarzyna Rendaszka – 0009-0003-0807-897X
Rafał Bilski – 0009-0004-1580-3807
Robert Kruszewski – 0000-0003-4214-2982
Witold Tłustochowicz – 0000-0002-7750-2901

Abstract

The discovery of glucocorticoids represented a crucial moment in the history of medicine, particularly in the treatment of rheumatic diseases. These powerful hormonal substances revolutionized therapeutic approaches, enabling effective management of severe diseases that previously resulted in disability or even death. Glucocorticoids remain an essential part of emergency treatment. The first section of this work presents the history of research on adrenal hormones, biochemical and pharmacological aspects of their action, as well as the general principles of glucocorticoid therapy in rheumatic diseases. The paper also discusses detailed expert recommendations and guidelines from recognized rheumatological organizations regarding the use of glucocorticoids in the treatment of arthritis and systemic connective tissue disorders. This review presents the current and systematic knowledge on the role of glucocorticoids in the therapy of rheumatic diseases, with particular emphasis on their use in daily clinical practice.

Streszczenie

Odkrycie glikokortykosteroidów stanowiło przełomowy moment w historii medycyny, zwłaszcza w leczeniu chorób reumatycznych. Substancje te, o silnym działaniu hormonalnym, zrewolucjonizowały możliwości terapeutyczne, pozwalając na skuteczne leczenie schorzeń o ciężkim przebiegu, które wcześniej prowadziły do niepełnosprawności lub nawet śmierci pacjentów. Glikokortykosteroidy nadal pozostają niezastąpione w stanach nagłych. W pierwszej części pracy przedstawiono historię badań nad hormonami nadnerczy, biochemiczne oraz farmakologiczne aspekty ich działania, a także ogólne zasady leczenia glikokortykosteroidami w chorobach reumatycznych. Omówione zostały również szczegółowe rekomendacje ekspertów oraz uznanych organizacji reumatologicznych dotyczące stosowania glikokortykosteroidów w leczeniu zapaleń stawów i chorób układowych tkanki łącznej. Opracowanie to ma na celu przedstawienie aktualnej i usystematyzowanej wiedzy na temat roli glikokortykosteroidów w terapii chorób reumatycznych, ze szczególnym uwzględnieniem wykorzystania ich w codziennej praktyce klinicznej.

Keywords: rheumatic diseases; pharmacotherapy; glucocorticoids

Słowa kluczowe: choroby reumatyczne; farmakoterapia; glikokortykosteroidy

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Corresponding author:
Robert Kruszewski
Military Institute of Medicine – National Research Institute, Department of Internal Medicine and Rheumatology, Warsaw
e-mail: rkruszewski@wim.mil.pl

Introduction

Despite the rapid advances in pharmacology over the past several decades, few classes of drugs have achieved such broad application in medicine as glucocorticoids (GCs). Their widespread use stems from their diverse effects on physiological and pathological processes, as well as the absence of therapeutic alternatives with comparable mechanisms of action. Today, GCs are used across nearly all fields of clinical medicine. Although decades of clinical experience with GCs have provided a thorough understanding of their pharmacological proper-

ties, further research is still needed. The development of optimal treatment regimens that balance therapeutic efficacy with the risk of adverse effects remains a major challenge.

Among the various effects of GCs, their ability to inhibit inflammatory and immune responses has been particularly valuable in the treatment of autoimmune disorders. For this reason, GCs hold a special place in rheumatology, and are frequently introduced as first-line therapy due to their relatively rapid therapeutic effects. Consequently, they are commonly used in remission-inducing protocols and, in selected cases, as part of maintenance therapy. In addition, their rapid action makes them valuable as emergency treatment in acute, life-threatening situations.

Our paper summarizes and compares current principles for the use of GCs in treating different rheumatic diseases, based on the latest recommendations and research data.

Historical outline

In 1929, Philip Showalter Hench, head of the Rheumatology Department at the Mayo Clinic, observed that symptoms of rheumatoid arthritis (RA) improved during jaundice or pregnancy. However, potential causes of this condition, such as hyperbilirubinemia or increased release of female hormones, do not occur simultaneously with pregnancy and jaundice. He therefore postulated that a naturally occurring, unidentified substance, later referred to as "Factor X" or "Substance X," was responsible for this symptomatic relief [1]. The temporary remission of RA symptoms observed in the postoperative period, together with knowledge of the adrenal response to surgical stress and the fatigue seen in Addison's disease, similar to that in RA, led Hench to consider the adrenal glands as a possible source of substance X. In 1935, he began cooperation with Edward Kendall, a professor of physiological chemistry at the Mayo Clinic, who had been the first to isolate crystalline thyroxine and, in 1930, had initiated research on the adrenal glands. At the same time, Tadeusz Reichstein, a Polish-born professor of organic chemistry conducting research in Switzerland, attempted to isolate adrenal hormones. By 1940, 28 substances had been isolated from the adrenal glands, four of which showed effects in animal testing. One of these was dehydrocorticosterone, referred to as 'Compound E' (cortin) by Kendall and 'Substance Fa' by Reichstein. Compound E appeared to have a life-saving effect in animals after adrenalectomy, leading Kendall and Hench to conclude that it might be the 'Substance X' they were seeking. At that time, however, isolating adrenal hormones was ineffective [2].

During World War II, reports surfaced that German scientists had isolated an adrenal hormone, which enhanced combat pilots' tolerance to low oxygen levels and was used in treating post-traumatic shock. In 1941, the progression of the war led the National Research Council, a U.S. government organization, to fund three initiatives: the development of antimalarial medications, the production of penicillin, and isolation and synthesis of cortin, with the latter one given highest priority.

In 1942, Lewis Sarett of Merck Pharmaceuticals completed a research fellowship at the Mayo Clinic and began close collaboration with Edward Kendall. By December 1944, Sarett had synthesized Compound E from ox bile, and by November 1948, with Kendall's assistance, he had improved a 37-step process for producing the hormone, making commercial use possible [3].

The first recipient of Compound E was a 29-year-old woman with severe RA unresponsive to treatment for four and a half years. She was admitted to the Mayo Clinic on July 26, 1948, with complaints of stiffness, pain, and oedema involving multiple joints. Imaging revealed destructive joint changes and elevated erythrocyte sedimentation rate (ESR) of 109 mm/h. Oral lactoferrin produced neither jaundice nor clinical improvement. The patient's symptoms worsened over hospital stay, making the patient bedridden. On September 21, 1948, the first intramuscular injection of 100 mg of compound E was administered. Gradual improvement was initially observed, but morning stiffness had nearly resolved by day 3, allowing the patient to walk. Joint pain and oedema decreased after a week of receiving compound E. At 8 days, the dose was reduced to 50 mg/day for 4 days, followed by 25 mg/day for 10 days. However, the symptoms recurred, accompanied by a further increase in ESR. Since the fall of 1948, compound E had been administered to 14 patients with moderate to severe disease. Two of these patients also received adrenocorticotropic hormone (ACTH). A water-based cholesterol solution was used as a control, administered either in place of or several days before compound E. Both patients and researchers were blinded to the timing of its replacement with compound E. Compared to the control solution, all patients treated with the active substance showed significant improvement in joint stiffness and pain, as well as increased mobility, and a lower ESR. Some patients experienced first adverse reactions. On June 1, 1949, Hench and his team published a paper reporting the efficacy of compound E and ACTH in treating RA [1].

In 1950, Edward Calvin Kendall, Tadeusz Reichstein, and Philip Showalter Hench were jointly awarded the Nobel Prize in Physiology or Medicine "for their discoveries relating to the hormones of the adrenal cortex, their structure and biological effects".

Endogenous synthesis of steroid hormones

The adrenal gland is made up of medulla, which releases catecholamines, and cortex, which is histologically and endocrinologically divided into three layers. The outer layer (zona glomerulosa) secretes aldosterone, the middle layer (zona fasciculata) releases cortisol, and the inner layer (zona reticularis) secretes a sex hormone precursor - dehydroepiandrosterone (DHEA) and its derivative, dehydroepiandrosterone sulfate. Each layer releases hormones upon stimulation by ACTH, whose release is regulated by hypothalamic corticotropin-releasing hormone (CRH). The outer layer secretes aldosterone, whose primarily role is to regulate water and electrolyte balance. In addition to ACTH stimulation, its secretion is also mediated by extracellular potassium levels and angiotensin II. Therefore, this layer does not undergo atrophy in the absence of ACTH stimulation. The two inner layers of the

adrenal cortex, however, are more dependent on ACTH. Increased levels of this hormone cause their hypertrophy and up-regulate the secretion of GCs and androgen precursors, whereas decreased ACTH levels result in their hypotrophy.

At the cellular level, ACTH binds to the MC2 receptor (MC2R), activating the adenylate cyclase pathway and promoting the translation of multiple enzymes required for steroid hormone synthesis in the adrenal cortex [4].

The effects of corticosteroids on the body

The adrenal cortex synthesizes two classes of steroid hormones: corticosteroids (glucocorticoids and mineralocorticoids), which have 21 carbon atoms, and androgens, which have 19 carbon atoms. Corticosteroids affect the metabolism of carbohydrates, proteins, and lipids. They also play a role in regulating the immune, cardiovascular, excretory, nervous, musculoskeletal, and endocrine systems. They help the body cope with stressors such as trauma, infections, and extreme temperatures. Corticosteroids are classified into mineralocorticoids and glucocorticoids, based on their roles in regulating water, electrolyte, and carbohydrate metabolism. Their effects on glucose metabolism typically correlate with anti-inflammatory properties, without significantly influencing sodium retention. This results from stimulation of different target sites and variations in ligand selectivity [4].

GCs bind to receptors in specific tissues, altering the expression of target genes and, consequently, affecting the production of specific proteins. The genomic response is delayed, becoming apparent after at least 30 minutes, usually several hours. Glucocorticoid receptors (GCRs or GRs) are members of the nuclear transcription factor family. In the cytoplasm, they remain inactive, bound to other proteins. Binding to corticosteroids activates the receptor and translocates it to the nucleus, where it interacts with specific DNA sequences called glucocorticoid response elements (GREs), which confer specificity in gene transcription. Genes can be activated or suppressed in this way, thereby altering protein production. A key mechanism by which GCs exert their ant-inflammatory action is by inducing the production of lipocortin 1, which inhibits phospholipase A2, affecting the arachidonic acid cascade and reducing the synthesis of inflammatory mediators. GCs also reduce the synthesis of various cytokines, including TNF-alpha and interleukins 2 and 6 (IL-2, IL-6). Some inhibitory effects of GCs, such as reduced expression of genes encoding cytokines, collagenases, and metalloproteinases, are mediated by protein-protein interactions between GRs and other transcription factors (e.g., NF-kB and AP-1). GCs also influence mRNA stability, translation, and secretion. For example, they can limit the production of cyclooxygenase-2 mRNA, which is normally stimulated by interleukin 1 (IL-1). Furthermore, GCs have rapid, not fully understood non-genomic effects on specific cell membrane receptors. A possible physicochemical mechanism has also been described, whereby GCs directly affect membrane channel activity, thereby interfering with lymphocyte activation induced by elevated intracellular calcium. Summarising, the genomic effects of GCs develop gradually at low doses, while non-genomic effects appear almost immediately but require much higher doses [4, 5].

Molecules used in rheumatology

For therapeutic use, synthetic GCs with high anti-inflammatory activity and minimal or no mineralocorticoid effects are preferred. The anti-inflammatory potency of different preparations is expressed in milligrams of prednisone-equivalent dose. Prednisone is used as a reference for historical reasons, being the first synthetic, pharmacologically relevant glucocorticoid introduced into clinical practice. This conversion applies when equivalent doses do not exceed 100 mg of prednisone, as genomic effects predominate at these levels. At higher doses, non-genomic effects emerge, and the relative potency of different GCs may vary [6].

To achieve a rapid therapeutic effect during rheumatic disease exacerbations, intravenous methylprednisolone is often preferred over prednisone. While both agents share similar genomic effects, methylprednisolone exhibits more than three times the non-genomic effect [6]. The therapeutic effect and the risk of adverse effects are directly proportional to both the dose and the duration of GC therapy. This is due to GCR saturation and the enhanced non-genomic effects at high doses. It was proposed in 2002 that daily glucocorticoid doses be divided into:

- low: ≤7.5 mg prednisone equivalent;
- medium: >7.5 mg but ≤30 mg prednisone equivalent;
- high: >30 mg but ≤100 mg prednisone equivalent;
- very high >100 mg prednisone equivalent.

Another treatment approach, referred to as 'pulse therapy', involves intravenous doses of ≥250 mg prednisone equivalent per day administered for up to five days [6].

General principles of GC treatment in rheumatology

In 2007, the European League Against Rheumatism (EULAR), renamed the European Alliance of Associations for Rheumatology in 2021, issued recommendations for the use of GCs in rheumatic diseases [7]. Initial dose, dose reduction and long-term dosing depend on the underlying rheumatic disease, its activity, risk factors, and the patient's individual responsiveness. The timing of GC administration can also affect their effectiveness, as symptoms (such as morning stiffness in RA) and pro-inflammatory cytokine levels follow a circadian rhythm, peaking in the morning. The lowest effective dose should be used due to the pharmacodynamic properties of GCs. The therapy should be tapered or discontinued during remission or low disease activity. Before starting treatment, risk factors for adverse effects need to be assessed, and comorbidities such as glaucoma, diabetes mellitus, and hypertension should be taken into account, implementing appropriate prophylaxis and treatment where needed. Potential adverse effects should be discussed with patients, and the benefits of therapy should be clearly explained.

During treatment, regular patient monitoring is recommended, including body weight, blood pressure, and relevant laboratory parameters, along with lifestyle guidance

to prevent undesirable metabolic changes [7]. Vitamin D and calcium supplementation is recommended for patients receiving prednisone at ≥7.5 mg/day for more than three months to prevent secondary osteoporosis. Indications for antiresorptive therapy are based on risk factors, including bone mineral density measurements. When GCs and nonsteroidal anti-inflammatory drugs (NSAIDs) are used concurrently, co-administration with a proton pump inhibitor (PPI), misoprostol (synthetic analogue of prostaglandin E1), or a selective COX-2 inhibitor is recommended. Conventional NSAIDs combined with PPIs are less likely to cause dyspepsia than selective NSAIDs alone [7].

Patients on corticosteroids for longer than 1 month, who will undergo surgery, need perioperative management with adequate GC replacement to overcome potential adrenal insufficiency. For minor procedures, 100 mg of hydrocortisone is recommended preoperatively. For major surgery, supplementation should continue postoperatively with four doses given every 8 hours, followed by a gradual taper over the subsequent days [7].

GC therapy poses no additional risks to the pregnant woman or foetus, but it may increase the risk of pregnancy-related conditions such as hypertension, diabetes, and osteoporosis. Dexamethasone may be used when a glucocorticoid effect in foetal tissues is required, as it is poorly metabolized by the placenta. Prednisone, prednisolone, or methylprednisolone are a preferred option in pregnant women with exacerbations of chronic diseases, since only about 10% of the administered dose reaches the foetus. Prednisone and methylprednisolone are classified as FDA Category B, as there is no evidence of teratogenicity in humans. Exposure to GCs in utero does not increase the risk of neonatal infection. Breastfeeding by women on low-dose GC therapy is not contradicted, but it should be avoided during the first 4 h after GC intake. Children receiving GCs should be monitored for linear growth and considered for growth-hormone replacement if necessary. In rheumatology, disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, azathioprine, and cyclosporine A are commonly used to shorten GC therapy and reduce patient exposure to adverse effects [7, 8].

Intra-articular corticosteroid injections may be considered for aseptic arthritis, although their local mechanism of action remains unclear. Possible mechanisms include reduced permeability of periarticular vessels and synovial membrane blood flow, decreased synovial fluid volume and synovial membrane size, increased pain threshold, and lower joint temperature. Additionally, removing excess synovial fluid during arthrocentesis can be therapeutic by eliminating leukocytes and crystals and improving joint mobility. Indications include mono- or oligoarthritis and cases where systemic therapy is ineffective or contraindicated. GCs can also be injected into other synovial spaces, such as bursae and tendon sheaths [9].

Arthritis

In rheumatoid arthritis, GCs are used to rapidly control symptoms before DMARDs start to take effect. As set out in the 2022 EULAR recommendations, short-term GCs should be considered when initiating or changing DMARDs. When starting GCs, it is important to plan for a gradual tapering as soon as possible, aiming for complete discontinuation, ideally within three months. The need to continue GC therapy beyond four months should be considered a sign of DMARD inefficacy and prompt treatment modification [10].

The American College of Rheumatology (ACR) recommends initiating RA therapy without routine GCs, both short-term (<3 months) or long-term (≥3 months), in treatment-naïve patients with moderate-to-high disease activity. Short-term GCs are acceptable if symptom relief is needed before DMARDs take effect. GC therapy can only be continued if the maximum DMARD dose has been already reached or DMARD type switch fails to produce satisfactory outcome [11]. A systematic review by Bergstra et al., which evaluated a two-year follow-up of high-dose GCs in combination with DMARDs in early RA, found that clinical improvement and radiographic progression at moderate doses (≤30 mg/day) were comparable to those achieved with higher doses (60 mg/day) [12]. The Steroid Elimination in Rheumatoid Arthritis (SEMIRA) study investigated the effects of GC discontinuation in RA patients [12]. In patients with stable, low disease activity receiving tocilizumab (a monoclonal antibody targeting the IL-6 receptor, used in the treatment of arthritis and other rheumatic diseases) prednisone dose reduction was associated with an increase in Disease Activity Score 28 (DAS28) and a lower likelihood of maintaining remission. No increase in disease activity was observed in patients who continued prednisone at 5 mg/day [12].

In psoriatic arthritis (PsA), GCs can be used as initial supportive therapy, either as local injections or systemically at the lowest effective dose [13]. They are also used as first-line treatment for limited disease (mono- or oligoarthritis) and enthesitis. Systemic GCs should not be used in axial PsA. The risk of psoriasis exacerbation should be evaluated when systemic GCs are used. In ankylosing spondylitis (AS), involvement may extend beyond the axial skeleton to peripheral joints, tendon attachments, and the uvea. The 2022 joint recommendations of the Assessment of Spondyloarthritis International Society (ASAS) and EULAR permit the use of local GC injections into inflamed musculoskeletal sites, despite limited clear scientific evidence [14]. Few studies confirm the benefits of GC injections into the sacroiliac joints (SIJ), particularly under ultrasound guidance, which provides pain relief with a low risk of adverse reactions [14]. The authors of the recommendations advise against long-term systemic GC therapy solely for axial disease, due to insufficient evidence of its efficacy. However, some data suggest that moderate benefit may be achieved with short-term systemic therapy at 50–60 mg/day, tapered over six months [14].

According to ACR recommendations, intra-articular GCs are more effective than NSAID monotherapy in patients with isolated sacroiliac arthritis. Systemic GCs are not recommended for AS [15]. Local GCs are also recommended for patients with controlled axial disease but active inflammation in peripheral joints or entheses. However, injections into the Achilles tendon, patellar

ligament, and quadriceps tendon should generally be avoided, as these structures are at high risk of rupture, a potential complication of GC treatment [15].

GCs also play an important role in treating uveitis, which often accompanies AS. In such cases, topical GCs are used to control acute inflammation. Delaying treatment increases the risk of a chronic, corticosteroid-resistant disease. Prompt GC administration also reduces the risk of posterior synechiae [15]. In the absence of poor prognostic factors, such as prior visual impairment, ocular hypotony, glaucoma, cataracts, macular oedema, or vitreous tortuosity, intensive topical treatment should be initiated, administering 1% prednisolone acetate drops every 1–2 hours. If, however, these factors are present, systemic prednisone should be added at an initial dose of 1 mg/kg/day, gradually tapered, and limited to no more than three months. Periocular injections of methylprednisolone acetate or triamcinolone acetate may also be used. If symptoms persist beyond three months or the patient's condition worsens, DMARDs should be added to the local corticosteroid therapy [16].

GCs are also used for inflammatory bowel disease (IBD) and its extraintestinal manifestations. Local injections are preferred for the involvement of individual peripheral joints. However, the few available publications do not specify doses. GCs are generally not effective for axial arthritis and enthesitis in IBD [17].

Intra-articular GC injections should be considered for oligoarticular reactive arthritis [18]. In more severe cases with multiple joint involvement, short-term oral prednisone at 30–40 mg/day, which is further gradually tapered, may be used. Some symptoms of reactive arthropathies, such as uveitis, may require topical GCs in the form of eye drops [18]. According to EULAR recommendations, intra-articular (IA) corticosteroid injections should be considered for early undifferentiated arthritis to control local inflammation. Limited literature data prevent precise determination of doses and systemic treatment strategies. Nevertheless, systemic treatment is considered safe when used at the lowest effective dose for the shortest duration (up to six months) and can effectively relieve symptoms and limit disease progression [19]. It is also emphasized that GCs should always be used alongside DMARDs, never as monotherapy, in patients with early undifferentiated arthritis. This is particularly important because GCs alone may mask disease activity, leading to misdiagnosis, inadequate treatment, or a more challenging prognosis [19].

ACR recommendations for the treatment of juvenile idiopathic arthritis (JIA) base the approach on predominant clinical symptoms. Eight disease subtypes have been distinguished according to these symptoms [20–22]:

- oligoarthritis;
- polyarthritis;
- sacroiliitis;
- enthesitis;
- temporomandibular joint inflammation;
- active systemic JIA with or without macrophage activation syndrome (MAS);
- inactive systemic JIA with or without MAS;
- uveitis.

Due to the risk of impaired bone growth in children, GC treatment should be given at the lowest effective dose, for the shortest possible duration, and in combination with DMARD [20, 21]. Treatment of active oligoarthritis (involving ≤ 4 joints, without systemic symptoms) includes, among others, intra-articular GC injections [20]. Systemic GCs are not recommended for initial therapy. However, they may be used when intra-articular treatment is not possible, symptoms are severe and need rapid relief, or when conventional DMARDs are ineffective. IA corticosteroids may be used in polyarthritis to achieve faster disease control, particularly when arthritis causes patient's dysfunction. However, frequent or multiple IA injections can be burdensome for children. In such cases, systemic therapy may be less likely to cause unpleasant treatment-related experiences [21].

Oral corticosteroids may be used when starting DMARD therapy or during flares. Treatment with intra-articular GCs may be intensified in polyarthritis with low disease activity (JADAS ≤ 2.5) but exacerbation in at least one joint that limits daily activities [21]. Oral corticosteroid therapy is recommended for up to three months, either at disease onset or during flares in JIA with active sacroiliac arthritis unresponsive to NSAIDs. This approach may be useful when high disease activity is difficult to control (severe symptoms, limited mobility). Injections directly into the sacroiliac joints may also be considered, although supporting research is limited [21].

For enthesitis unresponsive to NSAIDs and associated with high, mobility-limiting disease activity, short-term (<3 months) systemic GCs at the lowest effective dose are recommended. IA glucocorticoids are used in addition to NSAIDs in JIA with temporomandibular joint involvement. However, injections should be reserved for the most severe cases due to the risk of complications, heterotopic ossification and growth disturbances in particular. Routine oral GCs are not recommended, and if necessary, the dose should be minimized [20].

In most cases, oral GCs should not be used as monotherapy in patients with systemic JIA without MAS. Systemic treatment may be considered when access to other therapies, such as biological DMARDs, is limited, in the initial stages of treatment or in cases of severe joint symptoms. Corticosteroids are an important component of initial therapy in JIA with MAS. The benefits of corticosteroids outweigh the risks, even in infection-induced MAS. High-dose systemic corticosteroids are warranted to control severe symptoms, although no exact dosing has been specified in the recommendations [20]. Regardless of MAS, once JIA remission is achieved, gradual GC tapering aiming at complete discontinuation is recommended, as the risks of long-term use (even at low doses) outweigh the risk of flare [20].

Prednisolone acetate 1% (1–2 drops daily) or an equivalent corticosteroid is the first-line treatment for chronic anterior uveitis (CAU). Prompt initiation is crucial to prevent complications such as cataracts, glaucoma, elevated intraocular pressure (IOP), infections, and vision loss. It is essential to exclude other causes of elevated IOP or cataracts and to ensure regular, close ophthalmologic monitoring before initiating prednisolone monotherapy [22].

If CAU flares despite systemic treatment, the dose of 1% prednisolone acetate should be added or increased to a maximum of three drops daily. If topical treatment is used alongside systemic therapy for more than three months without improvement, the systemic strategy should be modified, and the topical treatment gradually tapered to discontinuation [22]. Acute anterior uveitis (AAU) is associated with the HLA-B27 antigen and may occur in children with enthesitis or psoriatic arthritis. In these cases, topical GC drops are usually sufficient, without modifying the primary JIA therapy [22].

Systemic connective tissue diseases

According to the 2023 update of EULAR recommendations for the management of systemic lupus erythematosus (SLE), GCs should be used for flares and tapered as quickly as possible, while still allowing for maintenance therapy. Dosage depends on the type and severity of organ involvement. The recommended maintenance dose is up to 5 mg/day of prednisone equivalent [23]. Available data indicate it is relatively safe to use GCs at this dose. Patients at cardiovascular risk, in whom doses of 5–10 mg/day carry an uncertain risk, while doses above 10 mg/day significantly increase the risk of adverse effects, are an exception [24].

The initial oral dose depends on disease activity. Moderate to severe SLE may require intravenous methylprednisolone pulses at 125–1000 mg/day for 1–3 days. Specific indications include severe active neuropsychiatric involvement, lupus nephritis, and severe thrombocytopenia. Topical and systemic corticosteroids are a first-line treatment for cutaneous lupus erythematosus (CLE), and should be discontinued as soon as possible. Pharmacotherapy is discontinued once sustained remission is achieved, which is more easily reached when DMARDs are added [23].

The 2019 EULAR recommendations for antiphospholipid syndrome (APS) limit corticosteroid use to catastrophic or obstetric cases. Low-dose prednisolone may be used in obstetric APS, particularly in the first trimester for women experiencing recurrent pregnancy complications despite first-line therapy [25].

GCs are also effective for haemolytic anaemia and severe thrombocytopenia in APS patients. In such cases, intravenous methylprednisolone at 250–1000 mg/day for three days is recommended [26].

Polymyalgia rheumatica requires long-term GC therapy. According to the 2015 EULAR recommendations, treatment should last at least 12 months, starting with 12.5–25 mg of prednisone equivalent per day. Single daily dosing is preferred over divided doses except in cases of prominent night pain when tapering below 5 mg daily. Higher doses may be considered in patients at high risk of relapse, while lower doses are advisable in cases with comorbidities such as glaucoma, diabetes mellitus, or osteoporosis. Intramuscular methylprednisolone may be considered when cumulative dose reduction is desired. Dose tapering should be individualized, though the recommended regimen suggests reducing the oral dose to 10 mg daily within the first 4–8 weeks of therapy. In the event of a flare, the previous dose should be reinstated and then tapered over 4–8 weeks to the relapse level. Once remission is achieved, the prednisone dose should be reduced by 1 mg every four weeks. For a 10/7.5 mg every-other-day regimen, a 1.25 mg reduction is possible. Sustained remission allows for gradual tapering until treatment discontinuation [27].

The efficacy of corticosteroids in primary Sjögren's syndrome has not been confirmed due to the lack of randomized clinical trials. The 2019 EULAR recommendations include corticosteroids as a treatment option for active systemic Sjögren's syndrome. In severe cases, induction therapy includes methylprednisolone pulses, followed by prednisone at doses ≤0.5 mg/kg/day. Doses <0.5 mg/kg/day are used in mild to moderate cases. GCs should be discontinued once remission is achieved. If no remission is achieved, the dose should be maintained at 5 mg/day or lower, or additional immunosuppressants should be introduced. Detailed recommendations for tapering GCs in these patients have not yet been established. EULAR recommends GCs for patients with specific organ involvement in Sjögren's syndrome, including:

- acute involvement of salivary glands, after excluding infection and inefficacy of NSAIDs used for 3–5 days – prednisone 0.3 mg/kg/day;
- arthritis involving > 5 joints or simultaneous extensive, severe tenosynovitis if the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) is moderate or high – prednisone 0.5 mg/kg/day with hydroxychloroquine (HCQ);
- arthritis in fewer joints or limited tenosynovitis, moderate to high ESSDAI scores and no response to NSAIDs or HCQ – GCs 0.5 mg/kg/day in combination with hydroxychloroquine;
- cutaneous vasculitis with moderate ESSDAI scores and limited purpura – prednisone 0.3 mg/kg/day, high ESSDAI score, and diffuse purpura – GCs 0.5–1 mg/kg/day;
- limited annular erythema – local GCs, diffuse annular erythema – prednisone 0.3 mg/kg/day, in monotherapy or in combination with HCQ;
- bronchial involvement resistant to inhaled treatment with moderate ESSDAI score – prednisone 0.5 mg/kg/day;
- interstitial lung disease (ILD) with moderate ESSDAI score – prednisone 0.5 mg/kg/day; the dose should be increased to 0.5–1 mg/kg/day if there is no response to treatment;
- ILD with high ESSDAI score – prednisone from 0.5 to 1 mg/kg/day;
- glomerulonephritis or interstitial nephritis, after excluding SLE and the presence of anti-neutrophil cytoplasmic antibodies (ANCA), if the ESSDAI score is low and despite correction of metabolic acidosis and potassium levels, the symptoms have not subsided and if the ESSDAI score is moderate – prednisone 0.5 mg/kg/day; 0.5–1 mg/kg/day in patents unresponsive to treatment and with high ESSDAI score;
- peripheral neuropathy after exclusion of vasculitis unrelated to cryoglobulinemia and axonal polyneuropathy associated with vasculitis – prednisone 0.5–1 mg/kg/day as first-line treatment;
- central nervous system vasculitis, neuromyelitis optica, and lymphocytic meningitis unresponsive

to symptomatic treatment or with cerebral involvement – prednisone 0.5–1 mg/kg/day;
- neutropenia <500/mm^3 that does not respond to granulocyte colony-stimulating factor (G-CSF) – GKS 0.5–1 mg/kg/day;
- platelets <20,000/mm^3 or haemoglobin 8–10 g/dL – prednisone 0.5–1 mg/kg/day; no treatment response or haemoglobin <8 g/dL requires the inclusion of intravenous immunoglobulins.

Corticosteroids are not recommended for pharmacological stimulation in xerostomia. However, they may be used for dry eye treatment, but only in combination with artificial tears and lubricating ointments. Treatment duration should not exceed 2–4 weeks due to the risk of infection, cataract, and increased IOP. Fluorinated GCs are recommended for neonatal lupus (NL) with anti-Ro antibodies, depending on the degree of congenital heart block [28].

Dermatomyositis, polymyositis, necrotizing autoimmune myositis, and inclusion body myositis are considered the major types of idiopathic inflammatory myopathies (IIMs). According to the 2022 British Society for Rheumatology recommendations, high-dose GCs are advised as initial treatment for skeletal myositis, typically 0.5–1 mg/kg/day of oral prednisolone. Once clinical response is achieved, the dose should be gradually tapered. If a rapid therapeutic effect is needed, intravenous methylprednisolone pulses may be considered [29]. According to some authors, the initial prednisone dose of 1–2 mg/kg/day should be maintained for 4 weeks, followed by tapering to the lowest effective dose, with treatment continued for 6–12 months [30]. Specific indications for GC therapy include joint and skin involvement, dysphagia, and chronic progressive interstitial lung disease [29, 30].

The use of GCs in scleroderma (also known as systemic sclerosis) remains controversial. According to the 2017 EULAR recommendations, they may be considered for interstitial lung disease or skin and musculoskeletal manifestations, despite limited supporting evidence. However, their use is associated with an increased risk of scleroderma renal crisis, which requires careful consideration [31].

In eosinophilic fasciitis, GC therapy is initiated with prednisone at 1 mg/kg/day, followed by gradual tapering. Higher doses may be needed if clinical symptoms or eosinophilia persist. In cases of inadequate response after 3 months of prednisone at 1.5 mg/kg/day, other immunosuppressive or immunomodulatory agents should be considered [32]. The optimal duration of treatment has not been established; therapy typically lasts from several months to several years. Observational data suggest that patients who initiate treatment with methylprednisolone pulses (0.5–1 g/day for three consecutive days) are more likely to achieve full remission and less likely to require additional immunosuppressive therapy [33].

The treatment of mixed connective tissue disease (MCTD), including corticosteroids, involves managing specific conditions that define its clinical picture. It should be noted that no specific treatment guidelines for MCTD have been established to date. GCs are used to manage symptoms such as refractory synovitis, myositis, myocarditis, pleurisy, aseptic meningitis, and oesophageal involvement. They also play a role in the initial management of thrombocytopenia and haemolytic anaemia [34].

According to the 2024 EULAR recommendations, systemic idiopathic arthritis (sJIA) and adult-onset Still's disease (AOSD) should be jointly referred to as "Still's disease". High-dose GCs (prednisone equivalent >1 mg/kg/day) are indicated in cases of severe disease, defined by symptoms such as high fever, VAS pain intensity score >6–7/10, pericarditis, and extensive inflammation involving multiple joints. The risk of MAS, which may present with elevated ferritin, triglycerides, and transaminases, along with decreased fibrinogen and thrombocytopenia, is another indication. Treatment is initiated intravenously and then continued orally, combined with an IL-1 or IL-6 inhibitor.

Medium- or low-dose GCs (≤0.1 mg/kg/day of prednisone), used either as monotherapy or in combination with IL-1 or IL-6 inhibitors, represent one of the treatment options for patients with lower disease activity. Dose tapering should be started as early as possible. The recommended regimen assumes resolution of clinical symptoms by month 3 of low-dose GC therapy, and complete discontinuation by month 6.

In MAS, intravenous pulses of methylprednisolone are recommended at doses of 15–30 mg/kg/day (maximum 1 g per infusion). In cases with CNS involvement, dexamethasone should be considered due to its superior ability to cross the blood–brain barrier (BBB). Nevertheless, current recommendations strongly emphasize the early initiation of IL-1 and IL-6 inhibitors, highlighting their role in reducing or even eliminating the need for GCs [35].

The principles of GC therapy can vary significantly depending on the disease entity and the goal of therapy, which should be remission or low disease activity. This is particularly important in cases that are refractory to treatment or pose a threat to health or life. It should be noted that the presented standards of practice do not preclude the use of GCs in other regimens, tailored to the individual patient's needs.

The principles of GC treatment discussed above apply to arthritis and collagenoses. The next part of the paper will summarize the recommendations and expert opinions on the use of GCs in vasculitis and other rheumatological conditions.

References

1. Hench PS, Kendall EC. The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone; compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis. Proc Staff Meet Mayo Clin, 1949; 24: 181–197
2. Lloyd M. Philip Showalter Hench, 1896–1965. Rheumatology (Oxford), 2002; 41: 582–584. doi: 10.1093/rheumatology/41.5.582
3. Burns CM. The history of cortisone discovery and development. Rheum Dis Clin North Am, 2016; 42: 1–14. doi: 10.1016/j.rdc.2015.08.001
4. Brunton LL, Hilal-Dandan R, Knollmann BC, eds. Goodman & Gilman's: The Pharmacological Basis of Therapeutics. 13th ed. New York: McGraw-Hill Education; 2017.

5. Buttgereit F, Wehling M, Burmester GR. A new hypothesis of modular glucocorticoid actions: steroid treatment of rheumatic diseases revisited. Arthritis Rheum, 1998; 41: 761–767. doi: 10.1002/1529-0131(199805)41:5<761::AID-ART2>3.0.CO;2-M
6. Buttgereit F, da Silva JA, Boers M, et al. Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology. Ann Rheum Dis, 2002; 61: 718–722. doi: 10.1136/ard.61.8.718
7. Hoes JN, Jacobs JW, Boers M, et al. EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. Ann Rheum Dis, 2007; 66: 1560–1567. doi: 10.1136/ard.2007.072157
8. Duru N, van der Goes MC, Jacobs JW, et al. EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases. Ann Rheum Dis, 2013; 72: 1905–1913. doi: 10.1136/annrheumdis-2013-203249
9. Uson J, Rodriguez-García SC, Castellanos-Moreira R, et al. EULAR recommendations for intra-articular therapies. Ann Rheum Dis, 2021; 80: 1299–1305. doi: 10.1136/annrheumdis-2021-220266
10. Smolen JS, Landewé RBM, Bergstra SA, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Dis, 2023; 82: 3–18. doi: 10.1136/ard-2022-223356. Erratum in: Ann Rheum Dis, 2023; 82: e76. doi: 10.1136/ard-2022-223356corr1
11. Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol, 2021; 73: 1108–1123. doi: 10.1002/art.41752
12. Bergstra SA, Sepriano A, Kerschbaumer A, et al. Efficacy, duration of use and safety of glucocorticoids: a systematic literature review informing the 2022 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis, 2023; 82: 81–94. doi: 10.1136/ard-2022-223358
13. Gossec L, Baraliakos X, Kerschbaumer A, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. Ann Rheum Dis, 2020; 79: 700–712. doi: 10.1136/annrheumdis-2020-217159
14. Ramiro S, Nikiphorou E, Sepriano A, et al. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. Ann Rheum Dis, 2023; 82: 19–34. doi: 10.1136/ard-2022-223296
15. Ward MM, Deodhar A, Akl EA, et al. American College of Rheumatology/ Spondylitis Association of America/ Spondyloarthritis Research and Treatment Network 2015 Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. Arthritis Rheumatol, 2016; 68: 282–298. doi: 10.1002/art.39298
16. Bachta A, Byszewska A, Kruszewski R, et al. Uveitis in rheumatic diseases – therapeutic management. Rheumatology Forum, 2023; 9: 112-118. doi: 10.5603/rf.95614
17. Rogler G, Singh A, Kavanaugh A, Rubin DT. Extraintestinal manifestations of inflammatory bowel disease: current concepts, treatment, and implications for disease management. Gastroenterology, 2021; 161: 1118–1132. doi: 10.1053/j.gastro.2021.07.042
18. Toivanen A. Managing reactive arthritis. Rheumatology (Oxford), 2000; 39: 117–119. doi: 10.1093/rheumatology/39.2.117
19. Combe B, Landewe R, Daien CI, et al. 2016 update of the EULAR recommendations for the management of early arthritis. Ann Rheum Dis, 2017; 76: 948–959. doi: 10.1136/annrheumdis-2016-210602
20. Onel KB, Horton DB, Lovell DJ, et al. 2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis: therapeutic approaches for oligoarthritis, temporomandibular joint arthritis, and systemic juvenile idiopathic arthritis. Arthritis Care Res (Hoboken), 2022; 74: 521–537. doi: 10.1002/acr.24853
21. Ringold S, Angeles-Han ST, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis. Arthritis Care Res (Hoboken), 2019; 71: 717–734. doi: 10.1002/acr.23870
22. Angeles-Han ST, Ringold S, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the screening, monitoring, and treatment of juvenile idiopathic arthritis-associated uveitis. Arthritis Care Res (Hoboken). 2019; 71: 703–716. doi: 10.1002/acr.23871
23. Fanouriakis A, Kostopoulou M, Andersen J, et al. EULAR recommendations for the management of systemic lupus erythematosus: 2023 update. Ann Rheum Dis, 2024; 83: 15–29. doi: 10.1136/ard-2023-224762
24. Strehl C, Bijlsma JW, de Wit M, et al. Defining conditions where long-term glucocorticoid treatment has an acceptably low level of harm to facilitate implementation of existing recommendations: viewpoints from an EULAR task force. Ann Rheum Dis, 2016; 75: 952–957. doi: 10.1136/annrheumdis-2015-208916
25. Tektonidou MG, Andreoli L, Limper M, et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. Ann Rheum Dis, 2019; 78: 1296–1304. doi: 10.1136/annrheumdis-2019-215213
26. Garcia D, Erkan D. Diagnosis and management of the antiphospholipid syndrome. N Engl J Med, 2018; 378: 2010–2021. doi: 10.1056/NEJMra1705454
27. Dejaco C, Singh YP, Perel P, et al. 2015 Recommendations for the management of polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. Ann Rheum Dis, 2015; 74: 1799–1807. doi: 10.1136/annrheumdis-2015-207492
28. Ramos-Casals M, Brito-Zerón P, Bombardieri S, et al. EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies. Ann Rheum Dis, 2020; 79: 3–18. doi: 10.1136/annrheumdis-2019-216114
29. Oldroyd AGS, Lilleker JB, Amin T, et al. British Society for Rheumatology guideline on management of paediatric, adolescent and adult patients with idiopathic inflammatory myopathy. Rheumatology (Oxford), 2022; 61: 1760–1768. doi: 10.1093/rheumatology/keac115
30. Cavagna L, Monti S, Caporali R, et al. How I treat idiopathic patients with inflammatory myopathies in the clinical practice. Autoimmun Rev, 2017; 16: 999–1007. doi: 10.1016/j.autrev.2017.07.016
31. Kowal-Bielecka O, Fransen J, Avouac J, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis, 2017; 76: 1327–1339. doi: 10.1136/annrheumdis-2016-209909

32. Mazilu D, Boltaşiu Tătaru LA, Mardale DA, et al. Eosinophilic fasciitis: Current and remaining challenges. Int J Mol Sci, 2023; 24: 1982. doi: 10.3390/ijms24031982
33. Lebeaux D, Francès C, Barete S, et al. Eosinophilic fasciitis (Shulman disease): new insights into the therapeutic management from a series of 34 patients. Rheumatology (Oxford), 2012; 51: 557–561. doi: 10.1093/rheumatology/ker366
34. Sapkota B, Al Khalili Y. Mixed connective tissue disease. In: StatPearls. Treasure Island (FL): StatPearls Publishing, 2024
35. Fautrel B, Mitrovic S, De Matteis A, et al. EULAR/PReS recommendations for the diagnosis and management of Still's disease, comprising systemic juvenile idiopathic arthritis and adult-onset Still's disease. Ann Rheum Dis, 2024; 83: 1614–1627. doi: 10.1136/ard-2024-225851