Review Article
Open Access
CrossMark

Glucocorticoids in rheumatology: myths vs. reality

Summary

Glucocorticoids (GC) have been the mainstay of practicing rheumatologists since the Nobel Prize was awarded for the discovery of cortisone in 1950. It has been proven that GC have highly effective anti-inflammatory and immunosuppressive properties. Identification of genomic and non-genomic effects, which directly affect most pathogenetic processes in the course of rheumatic diseases, served as the basis for the implementation of GC in routine rheumatological therapy. The further widespread introduction of GC into rheumatology practice is due to low cost, high availability, quick onset of action, and activity aimed at preventing organ damage. The optimal choice for the use of GC in the treatment of rheumatic diseases is a specific and individual approach in dosage and routine monitoring. To date, there are no reliable tools for determining the toxicity of GC, which is associated with poor compliance, acute onset or chronic course of adverse events AE, variability in the duration of GC use, and the need for the different dosages to control diseases.

Keywords: glucocorticoids, osteoporosis, genomic effects, prednisolone, dose

Volume 16 Issue 1 - 2024

D Rekalov,[1] I Golovach,[2] I Briner,[3] T Tarasenko,[4] D Nikitina,[3] V Mospan,[3] V Krupko,[3] E Samofal[4]

[1]State Institution «National scientific center «Institute of Cardiology named after academician M.D. Strazhesko» National Academy of Medical Sciences of Ukraine, Ukraine
[2]Feofaniya Clinical Hospital, Ukraine,
[3]Rheumatology Clinic of Professor Rekalov, Zaporizhzhia, Ukraine
[4]Clinic of Rheumatology of Professor Rekalov, Ukraine

Correspondence: D Rekalov, State Institution «National scientific center «Institute of Cardiology named after academician M.D. Strazhesko» National Academy of Medical Sciences of Ukraine, Kyiv, Emial dmitryrekalo@gmail.com

Received: January 21, 2024 | **Published:** February 08, 2024

Introduction

Adrenal hormones differ in their relative glucocorticoid (regulates carbohydrate metabolism) and mineralocorticoid (regulates electrolyte balance) activities and have therefore historically been differentiated according to their relative efficacy in sodium retention, effects on carbohydrate metabolism and anti-inflammatory effects. For these reasons, the terms “glucocorticoids” or “glucocorticosteroids” are scientifically correct and appropriate to describe the use of these drugs for the treatment of rheumatic diseases (RD).[1] However, the term «glucocorticosteroids (GCS)» is not used very often, comparing to the term «glucocorticoids (GC)», which is more common in the professional environment.[2]

Cortisol (hydrocortisone) is the main human endogenous glucocorticoid. This steroid hormone is produced in a circadian rhythm (high in the morning before waking up and very low around midnight). Synthesis significantly increases during stressful conditions.[1,3] The synthetic GC most commonly used to treat systemic inflammation are structurally very similar to cortisol, with relatively modest modifications that affect the steroid’s ability to bind to the GC receptor and reduce or eliminate intrinsic mineralocorticoid activity.[4,5]

GC has been the most important support of practicing rheumatologists since the Nobel Prize for the discovery of cortisone was awarded in 1950 to E. Kendall, P. Hench and T. Reichstein.[6]

Approximately one in three patients with inflammatory RD is treated for a short or longer period with the use of GC.[7,8] The debate regarding the acceptable balance between efficacy and safety (often of low doses) of GC in the treatment of inflammatory RD is as old as the treatment itself.[1]

Dosage, time and route of administration

To unify the evaluation about the dose of various drugs, it is recommended to express it in mg of «prednisone equivalent», using information about the relative strength of classical genomic action.[4] This data roughly corresponds to the accepted values of therapeutically equivalent doses: prednisolone - 5 mg, methylprednisolone - 4 mg, triamcinolone - 4 mg, dexamethasone - 0.75 mg, betamethasone - 0.75 mg. The potency of prednisone and prednisone is simsilar, but the term «prednisone equivalent» is preferred for historical reasons: prednisone was the first synthetic GC implemented into clinical practice. So, today we can distinguish the following doses, equivalent to prednisone:

- **Low dose <7.5 mg prednisone equivalent per day**

When given at a low dose: less than 50% of receptors are bound, quite often the dose range is often used for chronic therapy, rare side effects

- **Average dose > 7.5 mg but < 30 mg prednisone equivalent per day**

GC in medium doses are prescribed for the treatment of moderate disease activity or for the initial treatment

- **High dose > 30 mg but < 100 mg prednisone equivalent per day**

High doses of GC are used as the initial treatment, in patients with severe activity, require optimal correction when a clinical and laboratory response is achieved

- **Very high dose > 100 mg prednisone equivalent per day**

Recently, it is used very rarely, for the management of severe manifestations of RD, as a treatment for patients who do not respond to standard therapy, with a threat to life or an unfavorable prognosis

- **Pulse therapy > 250 mg of prednisone equivalent per day for one or more days**

It is used for acute or life-threatening course of RD with the damage of kidneys, brain, etc.

It is known that the dose determines the strength of the effects and adverse events (AE). This is related to the saturation of GC receptors (the more receptors are bound, the stronger the effect is) and very likely to the appearance of additional non-genomic effects at higher doses.[1,9]

The route of administration is necessary for predicting the effectiveness of GC therapy: oral, intravenous, intramuscular or intra-articular.[10] It should be noted that intra-articular administration is more effective because, provided local therapeutic concentrations are reached, GC can exert both the most important genomic and non-genomic effects.[8] The range of GC available for intra-articular administration is greater than the range for systemic use. In addition, these intra-articular GC differ significantly in structure with important implications for their therapeutic effects.[1]

The prescribing time is extremely important, taking into account the circadian rhythm of endogenous cortisol production, which can be changed in various RD, as well as taking into account the daily change of symptoms, in particular, morning stiffness, which is inherent, in particular, in rheumatoid arthritis (RA). Therefore, the management of RD should be based on the earliest possible appointment of GC, for example, once between 6:00 and 8:00 in the morning.

In routine rheumatology practice we use some tools which can minimize the risks and emphasize the benefits of the adequate continuous GC management. The brilliant option, we think, are European Alliance of Associations for Rheumatology (EULAR) 2013 evidence-based and consensus-based recommendations on the management of medium to high-dose GC therapy in RD (Table 1).[11]

Table 1 The recommendations with strength of recommendation and level of evidence (Duru N et al)[13]

Proposition		SOR		
		VAS: mean (95% CI)	A+B %	LoE
Education and prevention				
1.	Discuss measures to mitigate such risks, including diet, regular exercise and appropriate wound care	75 (57 to 93)	75	III/IV
2.	Patients with, or at risk of, GC-induced osteoporosis should receive appropriate preventive/ therapeutic interventions	91 (84 to 99)	100	I-A
3.	Patients and the patients' treatment teams should receive appropriate, practical advice on how to manage with GC-induced hypothalamic-pituitary-adrenal axis suppression	84 (67 to 101)	92	IV
4.	Provide an accessible resource to promote best practice in the management of patients using medium/high-dose GCs to general practitioners	80 (69 to 91)	75	IV
Dosing/risk-benefit				
5.	Before starting medium/high-dose GC treatment consider comorbidities predisposing to AEs. These include diabetes, glucose intolerance, cardiovascular disease, peptic ulcer disease, recurrent infections, immunosuppression, (risk factors of) glaucoma and osteoporosis. Patients with these comorbidities require tight control to manage the risk/benefit ratio	85 (76 to 94)	83	IV
6.	Select the appropriate starting dose to achieve therapeutic response, taking into account the risk of undertreatment	85 (76 to 95)	92	I-A/IV
7.	Keep the requirement for continuing GC treatment under constant review, and titrate the dose against therapeutic response, risk of undertreatment and development of AEs	82 (72 to 94)	92	IV
8.	If long-term medium/high-dose GC therapy is anticipated to be necessary, actively consider GC-sparing therapy	REJECTED		
Monitoring				
9.	All patients should have appropriate monitoring for clinically significant AEs. The treating physician should be aware of the possible occurrence of diabetes, hypertension, weight gain, infections, osteoporotic fractures, osteonecrosis, myopathy, eye problems, skin problems and neuropsychological AEs	75		IV

A+B %, percentage of the task force members that strongly to fully recommended this proposition based on an A—E ordinal scale (A, fully recommended, B, strongly recommended); AEs, adverse effects; CI, confidence interval; GC, glucocorticoid; LoE, level of evidence (table 1); SOR, strength of recommendation; VAS, visual analogue scale (0–100 mm 0= not recommended at all, 100, fully recommended).

These recommendations, as a guide for daily practice, are an attempt to promote safer use of GC in the management of RD. Important aspects of the guidelines are the broad participation of experts and patients, the use of research data, however limited, and the use of an evidence-based format. A significant body of textbooks and reviews focuses on the use of GC based on traditional clinical practice and common beliefs that developed before due attention was paid to the quality of the evidence base. This reflects changes in the approach to science-based rheumatology practice. It should be noted that systematic reviews and randomized clinical trials (RCTs) are considered the highest quality evidence, but these studies often focus on the effectiveness of treatment.[12] In the entire observational (ie, non-randomized) studies, the problem of bias/confounding by indication seriously impairs or excludes the ability to draw conclusions. Therefore, the greater the activity of inflammation, the higher the chance to start GC; however, due to the design, it is not possible to conclude a causal relationship between therapy and AE.

In addition, quite heterogeneous studies (eg, different diseases, ages, GC regimens and co-treatment) were pooled to obtain at least an overall impression of the occurrence of AEs. In these trials, almost all patients with most inflammatory RD received multiple drugs, which obviously prevents a separate study of the risk-benefit ratio of GCs. The presented recommendations relate to issues of GC therapy from a general point of view, that is, not a specific disease or patient. However, appropriate treatment varies considerably for different indications for such treatment, as discussed for initial doses in the guidelines.[7,8] It is clear that individual patient characteristics may require dosage adaptation or more frequent and longer monitoring for AEs.[5,7]

Clinical application of glucocorticoids

GCs have many therapeutic effects, ranging from pain relief to disease-modifying properties. Depending on the main disease and the

Citation: Rekalov D, Golovach I, Briner I, et al. Glucocorticoids in rheumatology: myths vs. reality. *MOJ Orthop Rheumatol.* 2024;16(1):17–23.
DOI: 10.15406/mojor.2024.16.00657

desired therapeutic goal (Table 2), the route of application, the type of GC, the dose and the duration of the selected therapy. All of the above determines the magnitude of the clinical effect and speed of action, but also the risk of developing side effects.

* initial doses: dose at the start of treatment will often decreased over time depending on disease activity; doses in prednisone equivalents a day: low, ≤7.5 mg, medium, >7.5 but ≤30 mg, high >30 mg but ≤100 mg, very high >100 mg

- indicates rare use; 1, infrequent use, for treatment-resistant disease, complications, severe flare, major exacerbation and for bridging the lag time of recently started treatment, 2, frequently added to|used as the basis therapeutic strategy; 3, basic part of the therapeutic strategy.

*CPP, calcium pyrophosphate

Table 2 General use og glucocorticoids in rheumatology, initial doses* (Bijlsma JW et al)[5]

	Oral			Intravenous
	Low*	**Medium***	**High***	**Very high dose|/pulse**
	-	2	2	-
Arthritides	-	1	1	-
Gouty arthritis				
Acute juvenile idiopathic arthritis	-	-	-	-
Osteoarthritis	-	-	-	-
Acute CPP* crystal arthritis				
Psoriatic arthritis	-	1	-	-
Reactive arthritis Rheumatic fever	-	-	-	-
Rheumatoid arthritis	-	1	1	-
	2	2	1	1
	-	-	3	1
	-	1	-	1
Collagen disorders				
Dermatomyositis, Polymyositis				
Mixed connective tissue disease				
Polymyalgia rheumatica Sjogren's syndrome, primary	-	3	-	1
Systemic lupus erythematosus	-	-	1	-
Systemic sclerosis	-	2	1	1
	-	1	-	-
Systemic vasculitides	-	-	3	1
In general				

According to existing practically-oriented recommendations, only a few nosologies require short-term appointment of GC in an average or even high dose. Among the most common are acute gouty arthritis, in which it is advisable to prescribe oral GC (30–35 mg/day of prednisone equivalent for 3–5 days), according to the recommendations of EULAR 2016.[13] Contemporary approaches to the management of RD also include the possibility of intra-articular administration of GC. Such interventions are appropriate for gout[14] osteoarthritis,[15] psoriatic arthritis,[16] reactive arthritis,[17] axial spondyloarthritis.[18]

It should be noted that the management of connective tissue diseases (CTD) has undergone significant changes. EULAR 2023 guidelines for the treatment of systemic lupus erythematosus (SLE) for the first time stated that GCs, if necessary, are dosed depending on the type and severity of organ damage, and should be reduced to a maintenance dose of ≤5 mg/day (equivalent to prednisone) and, if possible, discontinued; in patients with moderate and severe disease, pulse intravenous methylprednisolone (125–1000 mg per day, for 1–3 days) can be considered.[19,20]

Systemic GC prescription in primary care for systemic scleroderma (SSc) should also be done very carefully, monitoring blood pressure, renal function and careful analysis of the required dose, as there is some evidence that GCs are associated with a higher risk of renal crisis. In contrast to other CTDs, in polymyositis, dermatomyositis, and antisynthetase syndrome, prednisone is usually prescribed orally at a dose of 0.5–1.0 mg/kg per day, and in particularly acute and severe cases, therapy is started with intravenous administration of a high dose of GC (250–1000 mg).[21]

RA therapy is traditionally associated with the appointment of GC. Currently, the implemented standards are considered to be: «bridge therapy» when verifying the diagnosis, in case of flare and the need to change treatment.[22,23] The possibilities of rational GC therapy have been confirmed in a number of RCTs. Thus, in CAPRA-2, reduce of disease activity (low doses of prednisone with the addition of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs)) was diagnosed during 12 weeks compared to placebo.[24,25]

In another study, CareRA, patients with early RA were randomized into 2 groups: in one group, patients received GC with methotrexate (MTX) with a gradual reduction of GC to 5 mg/day, while in the other group, MTX was initiated without GC. According to the data after 1 and 2 years, the rates of those who achieved remission were higher in the group of MTX with GC than MTX alone.[26]

Well, of course, it is impossible to recall the ten-year observation data of BeSt. The researchers randomized 508 patients with early RA into 4 groups: MTX monotherapy, MTX and sulfasalazine monotherapy, MTX and GC initially 60 mg/day, with progressive

Citation: Rekalov D, Golovach I, Briner I, et al. Glucocorticoids in rheumatology: myths vs. reality. *MOJ Orthop Rheumatol.* 2024;16(1):17–23. DOI: 10.15406/mojor.2024.16.00657

tapering to 7.5 mg/day over 6 weeks, and the MTX and infliximab group. When summing up the data, greater efficiency is shown in the group of GC.[27]

However, the latest updates of the European guidelines for the treatment of RA emphasize an even greater need to focus on the benefits and risks of GC treatment, compared to previous versions. For example, the updated recommendations of EULAR 2022[22] underline that short-term therapy with low doses of GC should be considered as part of the initiation or replacement of traditional DMARDs, in different doses and routes of administration, but correction in side or withdrawals should be made as quickly as clinically possible.

Nevertheless, we strongly believe that GCs have been, are, and will be a part of contemporary RA management, because the optimized use of GCs in RA has led to significant savings, especially at the expense of delaying or needing to exclude expensive biological drugs. The most up-to-date basic work that allows us to make this assessment, examining the harms, benefits, and side effects of low-dose GC, the GLORIA study, was presented in 2022. The goal of GLORIA is to demonstrate that the duration of low-dose GC to current antirheumatic therapy is highly cost-effective and safe for elderly RA care. And this goal was achieved, as the results show that adding a low-dose prednisolone has beneficial long-term effects in senior patients with established RA, with a trade-off of 24% increase in patients with mostly non-severe AE; this suggests a favourable balance of benefit and harm. The resulting data, which were presented in two presentations on EULAR 2022 congress, also show that GC can be successfully reduced after 2 years, with only modest increases in disease activity, risk of flare, and no evidence of adrenal insufficiency.[28]

Glucocorticoid toxicity and side effects

GC toxicity is one of the most common causes of iatrogenic disease associated with chronic RD. The side effects of GC have been known for decades. But the exact risk-benefit ratio is incomplete and/or controversial because it is usually difficult to distinguish the effects of GC from the effects of underlying comorbidities, other comorbidities, or other medications. AE associated with GCs depend on both the average dose and the duration of therapy. In general, it can be said that long-term use is a high risk factor, while the total dose is of secondary importance. Even with therapy with low doses of GC can lead to serious AE. Severity ranges from more cosmetic aspects (eg, telangiectasia, hypertrichosis) to serious, disabling and even life-threatening situations (eg, gastric bleeding). One or more side effects may occur.[29,30] Side effects of GCs are the main limiting factor for the use of these agents. An overview of the most common and serious AE of GCs is given in Table 3.

Table 3 Common adverse effects of glucocorticoid therapy (McDonough AK et al)[32]

Onset early in therapy, essentially unavoidable	
• Emotional lability	• Insomnia
• Enhanced appetite, weight gain, or both	
Enhanced in patients with underlying risk factors or concomitant use of other drugs	
• Acne vulgaris	• Hypertension
• Diabetes mellitus	• Peptic ulcer disease
When supaphysiologic treatment is sustained	
• Cushingoid appearance	• Myopathy
• Hypothalmic–pituitary–adrenal suppression	• Osteonecrosis
• Impaired wound healing	• Increased susceptibility to infections
Delayed and insidious, probably dependent on cumulative dose	
• Atherosclerosis	• Growth retardation
• Cataracts	• Osteoporosis
• Fatty liver	• Skin atrophy
Rare and unpredictable	
• Glaucoma	• Pseudotumor cerebri
• Pancreatitis	• Psychosis

Glucocorticoid-induced osteoporosis

Osteoporosis (OP) induced by GC is the most common type of iatrogenic OP and a frequent cause of secondary OP.[31] Approximately 50% of patients who take gc for more than 6 months develop secondary OP.[29] A key point in the pathogenesis of GC-induced OP is the direct inhibitory effect of GC on osteoblasts, which leads to a decrease in bone formation. At the same time, GCs reduce the absorption of calcium in the intestine and the reabsorption of calcium in the renal tubules. This leads to a negative balance of calcium in the body and transient hypocalcemia, which, in turn, stimulates the secretion of parathyroid hormone and enhances the resorption of bone tissue.[32]

The simultaneous use of oral GCs and a proton pump inhibitor (PPI) is associated with an increased risk of OP fractures. At the same time, there are statistically different risks of OP fractures associated with oral GC or only with the use of PPIs. Therefore, it is emphasized that the risk of OP fracture increases with the simultaneous use of oral GCs and PPIs.[7]

It is quite "difficult to find" a dose of GC that is safe for bones in RD. Thus, in the study by Adami et al.[33] in patients who were prescribed long-term GC therapy without anti-OP drugs, a decrease in bone mineral density (BMD) was observed. A 4% loss in BMD was associated with a 30–40% increase in fracture risk. There are suggestions that patients on a dose of 5 mg/day and less mg, based on prednisone, will have no changes in BMD. Nevertheless, the recommendations of the American College of Rheumatology (ACR) indicate the need to take oral bisphosphonates in patients who have been taking GC for a long time.[34]

Glucocorticoids and infectious complications

As is known, high doses of GC can increase the risk of infectious complications. In a prospective cohort study of 2108 patients with inflammatory polyarthritis from the Mayo Clinic registry, the rate of hospitalization due to the infection was more than 2.5 times higher than in the general population. The use of GC was determined as an independent risk factor for hospitalization.[35]

Citation: Rekalov D, Golovach I, Briner I, et al. Glucocorticoids in rheumatology: myths vs. reality. *MOJ Orthop Rheumatol.* 2024;16(1):17–23. DOI: 10.15406/mojor.2024.16.00657

Herrinton LJ, et al.[36] reported the risk of serious infection for patients with SLE starting GC. Obtained data on a 4-fold increase in the risk of serious infections for GC patients who do not take hydroxychloroquine.

A lot of data emphasizes the relationship between GC use and increased infection rates and became especially relevant during the COVID-19 pandemic, which was reflected in the specially developed recommendations of the EULAR.[37] For real-world clinical practice, the recommendation on the importance of suspending or GC cessation associated with disease flares should be the management cornerstone, as this may have a huge impact on possible AEs of COVID-19.

Glucocorticoids and cardiovascular risk

Previous studies have shown that high-dose GC therapy is associated with a more than 2.5-fold increased risk of cardiovascular disease (CVD).[38] And what's more, only 30 days of taking GC in RA can increase risk of CVD by 15% within 6 months. Such data were obtained by Wallace B et al.[39] In particular, it was shown that the relationship between GC intake and the occurrence of acute myocardial infarction, stroke, transient ischemic attack, cardiac arrest or coronary revascularization does not depend on the initial level of risk, as well as indicators of disease activity and the use of bDMARDs, MTX.

In one of the largest analyzes of dose- and duration-dependent short-term risk of cardiovascular events (CVE) in GC-naïve RA patients enrolled in the CorEvitas RA registry, strong evidence was presented for no association of CVE risk with daily using prednisolone ≤4 mg or shorter cumulative doses and duration, as opposed to dosing ≥ 5 mg per day.[40]

Similar data were also obtained by So H. et al..[41], when analyzing the data of 12,233 patients with RA without major adverse cardiovascular events (MACE) from 2006 to 2018 and with an average follow-up of 8.7 years, 7% developed MACE, and in patients who received daily prednisolone ≥ 5 mg, the risk of MACE increased by 7% per month. Therefore, the use of GCs is associated with a duration- and dose-dependent increased risk of MACE, for example, very low doses of prednisolone (<5 mg/day) do not confer an excess risk.

Tapering and discontinuation of glucocorticoids

GC therapy, despite its important role in the successful treatment of RD, can cause significant morbidity among long-term users and at high doses. Physicians should constantly try to reduce the excessive dose of GCs by implementing GC-sparing therapy and gradually tapering the dosasge to the minimum effective.[42] Thus, as part of a treatment-to-target (T2T) strategy, GC tapering should be considered once the treatment goal of remission or at least low disease activity is achieved. However, when GC therapy is restarted due to a flare, it is unclear whether a second attempt to taper and discontinue is likely to be successful. Maassen JM et al. examined first- or second- attempt GC successful discontinuation and assessed patient characteristics associated with successful discontinuation in two T2T studies.[43] In the BeSt trial, 40% of patients experienced a flare after initial withdrawal of prednisone, and of the other 60%, 38% had to be re-treated later.[1] Of those who restarted (secondary cessation), 47% relapsed. In the IMPROVED study, 39% of flares occurred after initial discontinuation, and of the other 61%, 40% had to resume treatment later. After secondary termination - 49% of RA exacerbations. Therefore, the standard basic characteristics are not sufficient for personalization.

Considering that patients with SLE are usually treated with GC even during periods of remission, it is a practical necessity to assess the frequency of flares and progression of organ damage in patients who have gradually reduced the dosage of GC. Among 204 patients with SLE who participated in the trial by Tselios K et al.[44] flare rates were lower in the withdrawal group at both 12 and 24 months. Moderate and severe flares did not differ at 12 months, but were less frequent at 24 months. It was concluded that gradual withdrawal of GC is safe in clinically inactive SLE and is associated with fewer exacerbations and less organ damage at 24 months.[44]

In an interesting paper, patients with RA who started GC therapy and concomitant csDMARD therapy were again treated. The results of the changes in GC dosage and disease activity, the frequency of discontinuation of GC, as well as the frequency of flares within 6 months after cessation of GC were obtained.[45–7]

Among the conclusions, it should be noted that patients with RA who start taking GCs, in addition to csDMARDs, cessation can be reached, provided that the disease activity is controlled in real life, preferably without a short-term flare. But the time and duration to withdrawal of GC is far from recommended, indicating a gap between the routine clinical practice and the current scientific recommendations.[48–50]

Conclusion

1. GCs are highly effective anti-inflammatory and immunosuppressive drugs, but their use is limited by fears of AEs.
2. Many AEs can be avoided or successfully treated, provided an adequate and prudent approach.
3. The optimal choice for the use of GCs in the treatment of RD is a specific and individual approach in dosage and routine monitoring.
4. Advantages and disadvantages must be evaluated individually for each patient.
5. Prednisone 5 mg equivalent is effective and safe over a longer period of time, except in patients with high cardiovascular risk factors.

Acknowledgments

None.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. 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(8):718–722.
2. Fuller PJ, Lim Tio SS, Brennan FE. Specificity in mineralocorticoid versus glucocorticoid action. *Kidney Int.* 2000;57(4):1256–1264.
3. Schmid D, Burmester GR, Tripmacher R, et al. Bioenergetics of human peripheral blood mononuclear cell metabolism inquiescent, activated, and glucocorticoid-treated states. *Bioscience Rep*. 2000;20:289–302.
4. Buttgereit F, Scheffold A. Rapid glucocorticoid effects on immune cells. *Steroids*. 2002;67(6):529–534.
5. Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. *N Engl J Med*. 2003;348(8):727–734.

6. Banting Frederick G. Nobel Prize Laureates: Encyclopedia: A-L: Trans. from English M. Progress, 1992. p. 55–58.
7. Bijlsma JWJ. Annals of the Rheumatic Diseases collection on glucocorticoids (2020–2023): novel insights and advances in therapy. *Annals of the Rheumatic Diseases.* 2024;83:4–8.
8. Bijlsma JWJ, Hachulla É, Pereira da Silva JA, et al. Textbook on Rheumatic diseases. *BMJ Publishing Group BMJ.* 2015;1437.
9. Lipworth BJ. Therapeutic implications of non-genomic glucocorticoid activity. *Lancet*. 2000;356(9224):87–89.
10. Fenton C, Martin C, Jones R, et al. Local steroid activation is a critical mediator of the anti-inflammatory actions of therapeutic glucocorticoids. *Ann Rheum Dis*. 2021;80(2):250–260.
11. Duru N, Van der Goes MC, Jacobs JWG, 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(12):1905–1913.
12. Reynold P, Schaafsma D, Amrani Y, et al. Non-genomic Effects of Glucocorticoids: An Updated View. Trends in Pharmacological Sciences. 2018;40(1):38–49.
13. Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. *Ann Rheum Dis*. 2017;76(1):29–42.
14. Wechalekar MD, Vinik O, Schlesinger N, et al. Intra-articular glucocorticoids for acute gout. *Cochrane Database Syst Rev*. 2013;(4):CD009920.
15. Bruyère O, Honvo G, Veronese N, et al. An updated algorithm recommendation for the management of knee osteoarthritis from the european society for clinical and economic aspects of osteoporosis, osteoarthritis and musculoskeletal diseases (ESCEO). *Semin Arthritis Rheum.* 2019;49(3):337–350.
16. Coates L, Gossec L. The updated GRAPPA and EULAR recommendations for the management of psoriatic arthritis: Similarities and differences. *Joint Bone Spine*. 2023;90(1):105469.
17. Jubber A, Moorthy A. Reactive arthritis: a clinical review. *J R Coll Physicians Edinb*. 2021;51(3):288–297.
18. Ramiro S, Nikiphorou E, Sepriano A, et al. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. *Ann Rheum Dis.* 2023;82(1):19–34.
19. Fanouriakis A, Kostopoulou M, Andersen J, et al EULAR recommendations for the management of systemic lupus erythematosus: 2023 update. *Anna Rheum Dis.* 2024;83(1):15–29.
20. 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(12):1560–1507.
21. Schmidt J. Current Classification and management of inflammatory myopathies. *J Neuromuscul Dis.* 2018;5(2):109–129.
22. 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(1):3–18.
23. Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis.* 2020;79(6):685–699.
24. Bakker MF, Jacobs JW, Welsing PM, et al. Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial. *Ann Intern Med.* 2012;156(5):329–339.
25. Buttgereit F, Mehta D, Kirwan J, et al. Low-Dose prednisone chronotherapy for rheumatoid arthritis: a randomised clinical trial (CAPRA-2). *Ann Rheum Dis.* 2013;72(2):204–210
26. Stouten V, Joly J, De Cock D, et al. Sustained effectiveness after remission induction with methotrexate and step-down glucocorticoids in patients with early rheumatoid arthritis following a treat-to-target strategy after 2 years [abstract]. *Arthritis Rheumatol*. 2017;69(Suppl 10).
27. Goekoop Ruiterman YPM , de Vries Bouwstra JK , Allaart CF, et al . Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the best study): a randomized, controlled trial. *Arthritis Rheum*. 2005;52(11):3381–3390.
28. Boers M, Hartman L, Opris-Belinski D, et al. GLORIA Trial consortium. Low dose, add-on prednisolone in patients with rheumatoid arthritis aged 65+: the pragmatic randomised, double-blind placebo-controlled GLORIA trial. *Ann Rheum Dis.* 2022;81(7):925–936.
29. Gudbjornsson B, Juliusson UI, Gudjonsson FV. Prevalence of long term steroid treatment and the frequency of decision making to prevent steroid induced osteoporosis in daily clinical practice. *Ann Rheum Dis*. 2002;61(1):32–36.
30. Huscher D, Thiele K, Gromnica IE, et al. Dose-related patterns of glucocorticoid-induced side effects. *Ann Rheum Dis*. 2009;68(7):1119–1124.
31. van Staa TP, Leufkens HG, Cooper C. The epidemiology of corticosteroidinduced osteoporosis: a meta-analysis. *Osteoporos Int*. 2002;13(10):777–787.
32. Kanis JA, Cooper C, Rizzoli R, Reginster JY, et al. Scientific advisory board of the European society for clinical and economic aspects of osteoporosis (ESCEO) and the committees of scientific advisors and national societies of the international osteoporosis foundation (IOF). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int*. 2019;30(1):3–44.
33. Adami G. Abstract L01. Presented at: ACR Convergence 2022; Nov. 11–14, 2022; Philadelphia (hybrid meeting
34. Humphrey M. American college of rheumatology guideline for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Rheumatol.* 2017;69(8):1521–1537.
35. Franklin J, Lunt M, Bunn D, et al. Risk and predictors of infection leading to hospitalisation in a large primary-care-derived cohort of patients with inflammatory polyarthritis. *Ann Rheum Dis*. 2007;66(3):308–312.
36. Herrinton LJ, Liu L, Goldfien R, et al. Risk of serious infection for patients with systemic lupus erythematosus starting glucocorticoids with or without antimalarials. *J Rheumatol*. 2016;43(8):1503–1509.
37. Landewé RBM, Kroon FPB, Alunno A, et al. EULAR recommendations for the management and vaccination of people with rheumatic and musculoskeletal diseases in the context of SARS-Cov-2. *Ann Rheum Dis*. 2022;81(12):1628–1639.
38. Wei L, MacDonald TM, Walker BR. Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. *Ann Intern Med*. 2004;141(10):764–770.
39. Wallace B. Abstract 1428. Presented at: ACR Convergence 2021; November 5-9, 2021 (virtual meeting).
40. Ocon AJ, Reed G, Pappas DA, et al. Short-term dose and duration-dependent glucocorticoid risk for cardiovascular events in glucocorticoid-naive patients with rheumatoid arthritis. *Ann Rheum Dis*. 2021;80(12):1522–1529.
41. So H, Lam TO, Meng H, et al. Time and dose-dependent effect of systemic glucocorticoids on major adverse cardiovascular event in patients with rheumatoid arthritis: a population-based study. *Ann Rheum Dis.* 2023;82(11):1387–1393.

Citation: Rekalov D, Golovach I, Briner I, et al. Glucocorticoids in rheumatology: myths vs. reality. *MOJ Orthop Rheumatol.* 2024;16(1):17–23.
DOI: 10.15406/mojor.2024.16.00657

42. McDonough AK, Curtis JR, Saag KG. The epidemiology of glucocorticoid-associated adverse events. *Curr Opin Rheumatol.* 2008;20(2):131–137.

43. Maassen JM, Dos Santos Sobrín R, Bergstra SA, et al. Glucocorticoid discontinuation in patients with early rheumatoid and undifferentiated arthritis: a post-hoc analysis of the BeSt and IMPROVED studies. *Ann Rheum Dis.* 2021;80:1124–1129.

44. Tselios K, Gladman DD, Su J, et al. Gradual glucocorticosteroid withdrawal is safe in clinically quiescent systemic lupus erythematosus. *ACR Open Rheumatol.* 2021;3(8):550–557.

45. Xie W, Huang H, Li G, et al Dynamical trajectory of glucocorticoids tapering and discontinuation in patients with rheumatoid arthritis commencing glucocorticoids with csDMARDs: a real-world data from 2009 to 2020. *Annals of the Rheumatic Diseases*. 2021;80:997–1003.

46. Steinbuch M, Youket TE, Cohen S. Oral glucocorticoid use is associated with an increased risk of fracture. *Osteoporos Int.* 2004;15(4):323–328.

47. Stojan G, Petri M. The risk benefit ratio of glucocorticoids in SLE: have things changed over the past 40 years? *Curr Treatm Opt Rheumatol.* 2017;3(3):164–172.

48. Hardman JG, Limbird LE, eds. *Goodman and Gilman's the pharmacological basis of therapeutics*. 9th ed. New York: Mc Graw-Hill; 1998.

49. Heimans L,Wevers BKVC,Visser K,et al . A two-step treatment strategy trial in patients with early arthritis aimed at achieving remission: the improved study. *Ann Rheum Dis*. 2014;73(7):1356–1361.

50. Goodwin JS. Antiinflammatory drugs. In: Stites DP, Terr AI, Parslow TG, editors. *Basic and Clinical Immunology*. 8th edn. East Norwalk: Appleton and Lange; 1994. pp. 786-795.

Citation: Rekalov D, Golovach I, Briner I, et al. Glucocorticoids in rheumatology: myths vs. reality. *MOJ Orthop Rheumatol.* 2024;16(1):17–23.
DOI: 10.15406/mojor.2024.16.00657