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Hacettepe Vasculitis Workshop, 2023: Glucocorticoids in Management of Vasculitis
15 December 2023, Sheraton Hotel Ankara 13:30-18:00

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INVITED REVIEW

Therapeutic mechanisms of glucocorticoids, their administration and chronotherapy

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ABSTRACT

Glucocorticoids represent a cornerstone in the treatment of inflammatory and autoimmune diseases due to their potent anti-inflammatory and immunosuppressive effects. These steroid hormones, including endogenous cortisol and synthetic analogs like prednisone and dexamethasone, exert their effects through genomic and non-genomic pathways, targeting key inflammatory mediators. While genomic mechanisms regulate long-term gene expression, non-genomic pathways enable rapid modulation of immune responses, particularly at high doses. Despite their therapeutic efficacy, glucocorticoid use is often limited by significant adverse effects, including osteoporosis and metabolic disorders. Chronotherapy, which aligns medication timing with circadian rhythms, enhances therapeutic outcomes while reducing side effects, particularly in diseases like rheumatoid arthritis where inflammation peaks in the early morning. Emerging innovations, such as selective glucocorticoid receptor agonists (SEGRAs) and liposomal drug delivery systems, offer targeted anti-inflammatory effects with reduced systemic toxicity. These advancements highlight the potential for optimizing glucocorticoid therapy to achieve maximum efficacy while mitigating adverse effects. This review underscores the importance of understanding glucocorticoid mechanisms, administration methods, and novel therapeutic strategies to improve outcomes in inflammatory and autoimmune diseases.

Keywords: glucocorticoid mechanisms, chronotherapy, glucocorticoid resistance.

Introduction and Terminology

Glucocorticoids are a pivotal class of steroid hormones extensively utilized in managing inflammation, immune responses, and various metabolic processes [1,2]. Cortisol is the primary endogenous glucocorticoid in humans, known therapeutically as hydrocortisone. It is essential for life, secreted in a circadian rhythm, with physiological secretion ranging from 10-20 mg per day [3]. Approximately 10% of circulating cortisol is free, while the remainder is bound to corticosteroid-binding globulin (transcortin) and after CBG saturation, about 80% binds to albumin. The level of free cortisol varies between 1-100 nanomole/L, depending on the diurnal rhythm [4]. Plasma cortisol concentrations typically measure around 16 mcg/dL in the morning and 4 mcg/dL in the evening, with a half-life of 60-90 minutes, metabolized in the liver and excreted by the kidneys [5]. Blood cortisol levels are influenced by many factors besides the diurnal rhythm; in the presence of estrogen, CBG concentrations increase, potentially altering cortisol levels. Also, in cases of very low serum albumin levels, it may be necessary to reduce the steroid dose, although there is no specific research in rheumatology regarding this adjustment

Synthetic glucocorticoids have been structurally modified to enhance their binding affinity to glucocorticoid receptors (GRs) (Figure 1) [1,6]. Their

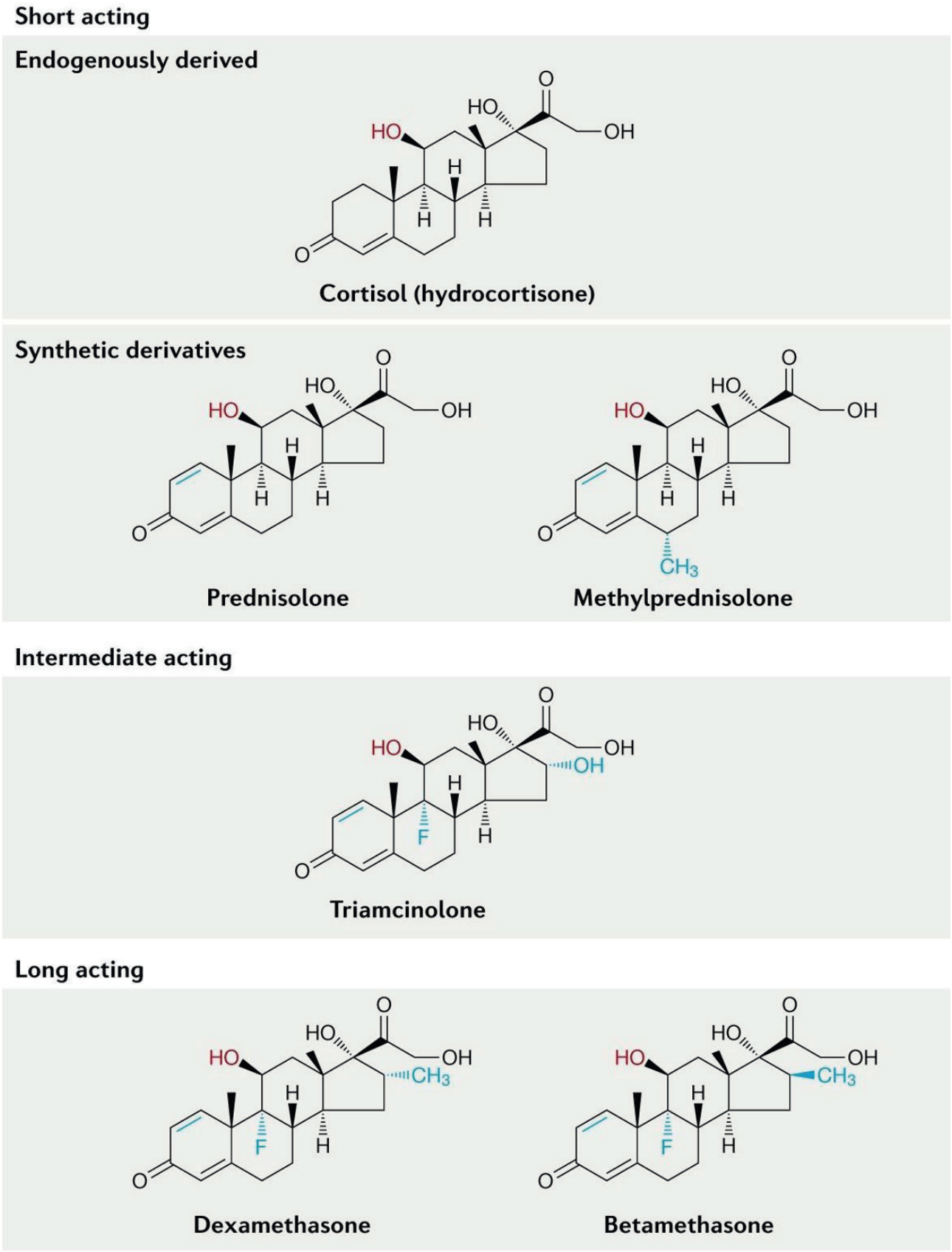

Figure 1. Chemical structures of glucocorticoids based on duration of action, [10] Blue indicates differences, red indicates similarities.

potent anti-inflammatory and immunosuppressive effects make them indispensable in treating a wide range of conditions, including autoimmune diseases like vasculitis [7]. Overall, they have been used in 1% of general population, and more in elderly as 3% [8].

Despite their effectiveness, the use of glucocorticoids in chronic rheumatic diseases, particularly rheumatoid arthritis (RA), appears to be decreasing. This decline is largely driven by the advent of biologic therapies, which offer more targeted immune modulation with fewer systemic side effects. However, for certain autoimmune conditions such as systemic vasculitis, systemic lupus erythematosus (SLE), and polymyalgia rheumatica, glucocorticoids remain indispensable, particularly for achieving rapid immunosuppression in acute settings. The clinical challenge lies in balancing the need for inflammation control with the long-term risks posed by glucocorticoid therapy. To maximize therapeutic efficacy and minimize adverse effects, a comprehensive understanding of their molecular mechanisms, administration methods, and the role of chronotherapy is essential [9].

Mechanisms of Action of Glucocorticoids

The effects of glucocorticoids are primarily mediated through their interaction with the glucocorticoid receptor (GR), a ligand-activated transcription factor that regulates gene expression [1,10]. Endogenous glucocorticoids, such as cortisol, can bind to both the glucocorticoid receptor (encoded by NR3C1) and the mineralocorticoid receptor (encoded by NR3C2). The glucocorticoid receptor, found in most body cells, is responsible for mediating both the anti-inflammatory effects and the adverse effects of therapeutic glucocorticoids. It contains structural domains for ligand binding, nuclear localization, and DNA interaction. When unbound, it resides in the cytoplasm but moves to the nucleus upon activation by glucocorticoids. The mineralocorticoid receptor, mainly expressed in tissues regulating salt and water balance, such as the kidneys and sweat glands, binds to glucocorticoids like cortisol but is protected from overactivation by 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2), which inactivates glucocorticoids in these tissues. These effects are exerted through both genomic and non-genomic pathways, each contributing to the overall therapeutic profile of these agents [11].

Genomic and Non-Genomic Pathways

1. Genomic Mechanisms: Glucocorticoids exert their effects largely through genomic mechanisms. Upon entering the cell, glucocorticoids bind to cytoplasmic GRs, which then translocate to the nucleus. This complex either activates or represses the transcription of target genes, suppressing inflammatory cytokines, chemokines, and enzymes integral to inflammatory processes. These genomic actions, taking several hours to manifest, underpin the long-term effects of glucocorticoids [1].

2. Non-Genomic Mechanisms: In addition to their genomic actions, glucocorticoids also exert rapid effects through non-genomic pathways. Non-genomic effects do not involve changes in gene transcription. These include interactions with membrane-bound receptors and cellular components, leading to the swift modulation of signaling pathways like MAPK and PI3K [12]. These actions can occur within minutes, providing immediate anti-inflammatory benefits. Non-genomic effects are particularly prominent at doses exceeding 100 mg/day of prednisone or its equivalent. Methylprednisolone and dexamethasone are especially responsive to non-genomic pathways, which include:

   - Direct Inhibition of Phospholipase A2: The GC-GR complex directly inhibits phospholipase A2, reducing arachidonic acid production independently of transcription.
   - Activation of Membrane-Bound GRs: Activation of membrane-bound GRs (mGRs) reduces lymphocyte activity through the p38 MAP kinase pathway.
   - Interaction with Cellular Membranes: GCs interact with immune cell membranes via chaperone proteins, leading to ATP production inhibition and decreased cell activity.

Immune Response Modulation

Glucocorticoids exert a broad and potent immunosuppressive effect by inhibiting the expression of genes that regulate cytokine production. This suppression affects both the

pre-inflammatory and inflammatory phases of immune response.Unbound receptors reside in the cytoplasm, but after binding to glucocorticoids, they are transported to the nucleus. In the nucleus, the receptor binds to the promoter region of cytokine genes, regulating their transcription and inhibiting the activation of nuclear factor kappa B (NF-κB) and AP1.These factors are crucial in initiating the expression of cytokines and other inflammatory mediators. By inhibiting the activity of NF-κB and AP1, glucocorticoids reduce inflammation at the molecular level, preventing the escalation of immune responses. This mechanism is pivotal in the treatment of autoimmune diseases like vasculitis and rheumatoid arthritis, where controlling inflammation is critical. Unlike some other immunosuppressive agents, glucocorticoids do not prevent T and B lymphocytes from recognizing antigens. Instead, they inhibit T lymphocyte differentiation and cytokine secretion (e.g., interleukins and tumor necrosis factor-alpha), thereby preventing the initiation of cellular immune responses [1,13].

The mineralocorticoid receptor (MR) is primarily found in cells involved in salt and water regulation, such as those in the distal tubule, salivary glands, sweat glands, and colonic epithelium.

Glucocorticoids have a broad immunosuppressive effect by inhibiting cytokine production, particularly affecting T and B lymphocyte function. This results in the prevention of T-cell differentiation and cytokine secretion (e.g., interleukins, TNF-α), thereby curbing cellular immune responses without compromising antigen recognition.

The action of glucocorticoids involves several critical pathways:

1. Inhibition of T-Cell Differentiation and Cytokine Secretion: Glucocorticoids prevent T cells from differentiating and secreting cytokines such as interleukin-1, -2, -3, -5, tumor necrosis factor-alpha, and interferon-gamma, thereby inhibiting the initiation of cellular immune responses. This effect is achieved through the binding of glucocorticoids to specific cytoplasmic receptors in cells, which then translocate to the nucleus to bind promoter regions of cytokine genes, inhibiting transcription and the activation of nuclear factor kappa B (NF-κB).
2. Inhibition of B-Cell Antibody Production and Induction of Apoptosis: Glucocorticoids suppress the ability of B cells to produce antibodies and increase their apoptosis.
3. Inhibition of Macrophage and Polymorphonuclear Leukocyte Function: The migration and phagocytic abilities of macrophages, their monocyte precursors, and polymorphonuclear leukocytes are inhibited, and the lysosomal stability of these cells is increased.
4. Reduction of Circulating Lymphocytes: Glucocorticoids enhance the migration of lymphocytes from the bloodstream to lymph nodes and bone marrow, reducing circulating lymphocyte levels, particularly in T cells, leading to lymphopenia and the atrophy of lymphatic tissue.
5. Inhibition of Complement System Activation: Glucocorticoids also inhibit the activation of the complement system, which contributes to immunologic inflammatory responses.

Receptor Modulation and Resistance

The therapeutic efficacy of glucocorticoids can be undermined by the development of glucocorticoid resistance, a phenomenon driven by factors such as GR down-regulation, the presence of less active GR isoforms, and the inhibitory interactions between GRs and other transcription factors. Addressing these mechanisms is crucial for optimizing glucocorticoid therapy in resistant cases [1,14].

Glucocorticoid resistance, particularly in chronic inflammatory diseases, may result also from the upregulation of the GRβ isoform, or disease-induced chromatin changes that restrict receptor binding to gene promoters. GRβ functions as a **dominant-negative inhibitor**, preventing the classic GRα isoform from effectively binding to DNA and exerting its anti-inflammatory effects. Unlike GRα, which mediates most of the therapeutic actions of glucocorticoids, GRβ does not bind glucocorticoids and can **heterodimerize** with GRα, disrupting its ability to regulate inflammatory gene transcription. Studies have shown that **upregulation of GRβ** in response to chronic inflammation may lead to reduced glucocorticoid sensitivity, further complicating treatment efforts in diseases like vasculitis.

Administration Methods of Glucocorticoids

In clinical practice, glucocorticoids are employed as first-line agents at high doses to achieve rapid immunosuppression, particularly in conditions requiring urgent control of underlying immunologic and inflammatory processes [9]. The administration route and dosage of glucocorticoids are tailored to the nature of the disease, the organ system involved, and the severity of the condition [15]. Glucocorticoids exert their effects through both genomic and non-genomic mechanisms, with the dose being the determinant of which mechanism predominates. Doses between 40 mg and 100 mg increase the likelihood of side effects without significantly enhancing anti-inflammatory effects. Doses of 100 mg and above primarily affect inflammatory cells through non-genomic pathways, which forms the basis for new glucocorticoid dosing regimens.

Oral Administration

Commonly used for chronic conditions, oral glucocorticoids like prednisone and dexamethasone offer systemic absorption and convenience. Their effects are subject to pharmacokinetic factors, including bioavailability and half-life, making them suitable for long-term therapy.Orally administered synthetic steroids are rapidly absorbed, with most having a plasma half-life (t½) of 1–3 hours. The maximum biological effect is observed 2–8 hours post-administration, necessitating 2–3 doses per day in certain indications. These steroids are primarily metabolized in the liver, with a small portion excreted unchanged in the urine. Special caution is advised in patients with concurrent liver or kidney diseases, as these conditions may affect the drug's metabolism and excretion. Oral administration is commonly used for chronic conditions requiring long-term therapy [2].

Intravenous and Intramuscular Injection

For rapid systemic effects, as required in acute exacerbations of autoimmune diseases, intravenous or intramuscular glucocorticoids are preferred. These methods ensure swift bioavailability, critical in emergency settings [3].

Topical and Inhaled Administration

Targeted local therapy for conditions like asthma or dermatological issues minimizes systemic exposure and associated side effects. Inhaled and topical glucocorticoids are integral to managing localized inflammatory processes [4].

Dosing

In the context of immunosuppression, glucocorticoids like prednisone, prednisolone, and methylprednisolone are used at equivalent doses. For instance, 5 mg of prednisolone is equivalent in glucocorticoid effect to 4 mg of methylprednisolone, 6 mg of deflazacort, and 0.75 mg of dexamethasone (Table 1).

Glucocorticoid dosing can be categorized into several ranges based on their effects [15]:

- Low Dose (< 7.5 mg/day): Achieves approximately 50% saturation of cGRs.
- Medium Dose (7.5-30 mg/day): Saturation of cGRs ranges from 50% to 100%.
- High Dose (30-100 mg/day): Results in full saturation of cGRs, with transactivation becoming the dominant effect, often leading to side effects without significant additional anti-inflammatory benefits.
- Very High Dose (>100 mg/day): Activates non-genomic pathways predominantly.
- Pulse Therapy (≥250 mg/day): Administered for one or several days in acute situations.

Chronotherapy and Glucocorticoids

Chronotherapy refers to the timing of medication administration to align with the body's natural biological rhythms, which can enhance therapeutic outcomes and reduce side effects [16].

1. Circadian Rhythms: In rheumatoid arthritis, inflammation peaks during the night and early morning. Administering glucocorticoids to coincide with this peak, such as with night-time-release formulations, can better control nocturnal inflammation and alleviate morning symptoms. This approach maximizes therapeutic outcomes while minimizing the risk of side effects [17].

Table 1. Comparison of glucocorticoids: Duration, mineralocorticoid activity, and equivalent dosing

	Endogenous (Synthetic)	Duration of Action	Mineralocorticoid Activity	Equivalent Anti-inflammatory Dose
Cortisol (Hydrocortisone)	Endogenous	Short	Yes	20 mg
Prednisolone	Synthetic	Short	Yes	5 mg
Methylprednisolone	Synthetic	Short	No	4 mg
Triamcinolone	Synthetic	Intermediate	No	4 mg
Dexamethasone	Synthetic	Long	No	0.75 mg
Betamethasone	Synthetic	Long	No	0.6 mg

2. Cost-Effectiveness and Clinical Benefits: While chronotherapy may incur higher costs due to modified-release formulations, it proves cost-effective by improving symptom control and patient quality of life in cases where standard treatments fall short [18].

Chronotherapy, which involves aligning medication administration with the body's biological rhythms, holds significant promise in the management of vasculitis. In this context, timed-release glucocorticoid formulations such as Rayos® (delayed-release prednisone) offer an innovative approach. These formulations are designed to release glucocorticoids during the early morning hours when inflammation peaks in many autoimmune diseases, including vasculitis. By synchronizing drug release with the circadian rise in inflammatory cytokines, timed-release glucocorticoids can more effectively suppress constitutional symptoms, which are common in patients with vasculitis. This strategy not only enhances therapeutic efficacy but also helps to minimize adverse effects by reducing the overall dose needed to control symptoms. Early studies in rheumatoid arthritis have demonstrated improved symptom control and patient quality of life, suggesting that similar benefits may be achievable in vasculitis management. Different Glucocorticoid formulations are detailed at Table 2.

Despite their efficacy, glucocorticoids can induce a range of side effects, primarily due to their mineralocorticoid activity, which can lead to complications such as hypertension. To mitigate these effects, synthetic derivatives of cortisone have been chemically modified to reduce mineralocorticoid activity while enhancing glucocorticoid effects [7]. For example, fludrocortisone is a derivative with predominant mineralocorticoid properties and is not used for anti-inflammatory purposes, whereas dexamethasone and betamethasone have minimal clinically significant mineralocorticoid activity [19,20].

The placental transfer of glucocorticoids depends on the dosage, the lipophilicity of the compound, and the gestational age of the fetus. Dexamethasone, a lipophilic steroid, crosses the placenta, whereas prednisone and methylprednisolone are metabolized by the placenta, resulting in negligible fetal plasma levels when used at doses of <20 mg/day. Therefore, dexamethasone is preferred when fetal effects are desired, while prednisone derivatives (up to 20 mg) are used for maternal effects [21].

Side Effects and Management

The long-term use of high-dose glucocorticoids is associated with significant adverse effects, including metabolic effects such as weight gain, hyperglycemia, and increased risk of diabetes. In patients with rheumatoid arthritis, the risk of developing diabetes mellitus doubles with prednisolone doses of 7.5 mg or higher. This effect is primarily due to altered glucose metabolism, including decreased insulin sensitivity and increased hepatic gluconeogenesis. They can also lead to fluid retention, hypertension, and dyslipidemia.

Bone health may be compromised, leading to osteoporosis and an elevated risk of fractures. Glucocorticoids not only impair bone formation by reducing osteoblast proliferation and increasing osteoclast activity but also induce muscle wasting via the suppression of anabolic signaling pathway, shifting the balance between receptor activator of NF-κB ligand (RANKL) and osteoprotegerin (OPG) in favor of osteoclast activation. Glucocorticoids not only impair bone formation by reducing osteoblast proliferation and increasing osteoclast activity but

Table 2. Overview of glucocorticoid medications: Dosage, availability, and indications according to Food Drug Administration as of February 2023

Drug	Manufacturer	Dosage	Availability
Prednisone delayed-release (Rayos®)	Horizon	**Adults and Children:** Initial dose: 5 mg administered once daily Maintenance dose: Use the lowest dosage that will maintain clinical response depending on specific condition treated Swallow tablet whole	Tablet: 1 mg, 2 mg, and 5 mg
Prednisone (Prednisone Intensol™)	Roxane	**Adults and Children:** 5 mg to 60 mg per day, depending on specific condition treated	Oral solution: 5 mg/mL (contains 30% alcohol)
Budesonide	Generic	**Treatment of mild to moderate active Crohn's disease:** **Adults:** 9 mg once daily in the morning for up to 8 weeks; repeated 8-week courses for recurring episodes **Children (8-17 years, >25 kg):** 9 mg once daily for up to 8 weeks, followed by 6 mg once daily for 2 weeks	Enteric-coated capsule: 3 mg
Budesonide (Ortikos™)	Ferring	**Maintenance of clinical remission of mild to moderate Crohn's disease:** **Adults:** 6 mg once daily for up to 3 months; taper after 3 months if effective	Extended-release capsule: 6 mg, 9 mg
Budesonide extended-release (Uceris®)	Generic, Salix	**Induction of remission in adults with active, mild to moderate ulcerative colitis:** 9 mg orally once daily for up to 8 weeks	Extended-release capsule: 9 mg
Budesonide delayed-release (Tarpeyo™)	Calliditas	**Reduction of proteinuria in adults with primary IgA nephropathy (IgAN) at risk of rapid progression:** **Adults:** 16 mg once daily for 9 months, reduce to 8 mg daily for ≥2 weeks when discontinuing	Delayed-release capsule: 4 mg
Cortisone	Chartwell	**Adults and Children:** 25-300 mg per day or on alternate days depending on specific condition treated	Tablet: 25 mg
Deflazacort (Emflaza®)	PTC	**Treatment of Duchenne muscular dystrophy (DMD):** **Patients 2 years of age and older:** 0.9 mg/kg/day; discontinue gradually if administered for more than a few days Tablets may be crushed and mixed with applesauce; consume immediately The oral suspension should be mixed with 3-4 ounces of juice (except grapefruit juice) or milk, administer immediately Unused drug should be discarded 1 month after opening the container	Tablet: 6 mg, 18 mg, 30 mg, 36 mg - Oral suspension: 22.75 mg/mL
Dexamethasone (Dex™)	Generic, Roxane, Levin, Plight, Xspire, Scite	**Adults:** 0.75 mg to 9 mg per day in 2-4 divided doses depending on condition treated **Children:** 0.03 to 0.3 mg/kg per day, in 2-4 divided doses	Tablets: 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, 6 mg Oral solution: 0.5 mg/5 mL Intensol oral solution: 1 mg/mL Various dose packs (Dex™, Taperdex™) available

Drug	Manufacturer	Dosage	Availability
Dexamethasone (Hemady®)	Acrotech	**Treatment of multiple myeloma:** **Adults:** 20 mg or 40 mg once daily, depending on treatment regimen as used in combination with other anti-myeloma agents	Tablet: 20 mg
Hydrocortisone (Cortef®)	Generic, Pfizer	**Adults:** 20-240 mg per day, in 2-4 divided doses depending on condition treated **Children:** 2-8 mg/kg per day in 3-4 divided doses	Tablet: 5 mg, 10 mg, 20 mg

also induce muscle wasting via the suppression of anabolic signaling pathways, such as PI3K-AKT-mTOR, while promoting autophagy and proteolysis. This shift leads to increased bone resorption, further exacerbating glucocorticoid-induced osteoporosis. Long-term GC therapy lasting more than 3 months increases the risk of vertebral fractures by 30%. Muscle weakness, thinning skin, and easy bruising are also common. Furthermore, glucocorticoids increase the risk of infections. Psychiatric effects like mood swings, insomnia, and even psychosis may occur in some patients. Other side effects include adrenal suppression, cataracts, and glaucoma with prolonged usage. Effective management strategies involve close monitoring, dose adjustments, and the implementation of preventive measures such as osteoporosis prophylaxis and the use of antacids and vaccines [10,22]. For bone health, bisphosphonates and denosumab can be used to mitigate the risk. However, there are no specific medications available to prevent other side effects such as skin thinning, obesity, or the increased risk of diabetes [10].

Future Directions in Glucocorticoid Therapy

Emerging strategies in glucocorticoid therapy focus on improving drug delivery to minimize off-target effects. Liposomal and nanoparticle-based delivery systems are being developed to enhance tissue specificity, allowing for higher concentrations of glucocorticoids at inflamed sites while reducing systemic exposure. For instance, liposomal encapsulation of glucocorticoids has shown promise in mouse models of arthritis, where the targeted delivery to inflamed joints significantly reduced symptoms with minimal impact on surrounding tissues. This innovation offers hope for mitigating the well-known side effects of systemic glucocorticoid therapy, such as bone loss and muscle wasting, by refining their pharmacokinetics and delivery. Selective glucocorticoid receptor agonists (SEGRAs) are a novel class of glucocorticoid-like drugs that aim to dissociate the therapeutic anti-inflammatory effects from the adverse metabolic effects of glucocorticoid treatment. By specifically targeting the transrepression function of the glucocorticoid receptor, SEGRAs hold the potential to suppress pro-inflammatory pathways, such as NF-κB and AP-1 signaling, without triggering the transactivation mechanisms responsible for side effects like osteoporosis and hyperglycemia. Early clinical trials of SEGRAs, such as fosdagrocorat, have shown encouraging results in reducing inflammation with fewer side effects, offering a promising future direction for glucocorticoid therapy.

Conclusion

A deep understanding of glucocorticoid mechanisms, appropriate administration, and the application of chronotherapy is vital for optimizing treatment outcomes in inflammatory and autoimmune diseases. Tailoring glucocorticoid therapy to individual patient needs, aligning with biological rhythms, and choosing the most appropriate administration routes allows for maximal therapeutic benefit while minimizing adverse effects.

Author contribution

Study conception and design: HB, ÖK; draft manuscript preparation: HB, ÖK. All authors reviewed the results and approved the final version of the manuscript.

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The authors declare that there is no conflict of interest.

REFERENCES

[1] Schaaf MJM, Cidlowski JA. Molecular mechanisms of glucocorticoid action and resistance. J Steroid Biochem Mol Biol 2002;83(1-5):37-48. https://doi.org/10.1016/s0960-0760(02)00263-7

[2] Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids--new mechanisms for old drugs. N Engl J Med 2005;353(16):1711-23. https://doi.org/10.1056/NEJMra050541

[3] Raff H, Findling JW. A physiologic approach to diagnosis of the Cushing syndrome. Ann Intern Med 2003;138(12):980-91. https://doi.org/10.7326/0003-4819-138-12-200306170-00010

[4] Westphal U. Steroid-protein interactions II: Glucocorticoid binding globulin (Transcortin) and corticosteroid binding globulin. Heidelberg, Berlin: Springer-Verlag; 1986. https://doi.org/10.1007/978-3-642-82486-9

[5] Czock D, Keller F, Rasche FM, Häussler U. Pharmacokinetics and pharmacodynamics of systemically administered glucocorticoids. Clin Pharmacokinet 2005;44(1):61-98. https://doi.org/10.2165/00003088-200544010-00003

[6] Beato M, Klug J. Steroid hormone receptors: An update. Hum Reprod Update 2000;6(3):225-36. https://doi.org/10.1093/humupd/6.3.225

[7] Schäcke H, Döcke WD, Asadullah K. Mechanisms involved in the side effects of glucocorticoids. Pharmacol Ther 2002;96(1):23-43. https://doi.org/10.1016/s0163-7258(02)00297-8

[8] Overman RA, Yeh JY, Deal CL. Prevalence of oral glucocorticoid usage in the United States: A general population perspective. Arthritis Care Res (Hoboken) 2013;65(2):294-8. https://doi.org/10.1002/acr.21796

[9] Barnes PJ. Corticosteroids: The drugs to beat. Eur J Pharmacol 2006;533(1-3):2-14. https://doi.org/10.1016/j.ejphar.2005.12.052

[10] Hardy RS, Raza K, Cooper MS. Therapeutic glucocorticoids: Mechanisms of actions in rheumatic diseases. Nat Rev Rheumatol 2020;16(3):133-44. https://doi.org/10.1038/s41584-020-0371-y

[11] Stahn C, Buttgereit F. Genomic and nongenomic effects of glucocorticoids. Nat Clin Pract Rheumatol 2008;4(10):525-33. https://doi.org/10.1038/ncprheum0898

[12] Hapgood JP, Avenant C, Moliki JM. Glucocorticoid-independent modulation of GR activity: Implications for immunotherapy. Pharmacol Ther 2016;165:93-113. https://doi.org/10.1016/j.pharmthera.2016.06.002

[13] Almawi WY, Beyhum HN, Rahme AA, Rieder MJ. Regulation of cytokine and cytokine receptor expression by glucocorticoids. J Leukoc Biol 1996;60(5):563-72. https://doi.org/10.1002/jlb.60.5.563

[14] Barnes PJ. How corticosteroids control inflammation: Quintiles Prize Lecture 2005. Br J Pharmacol 2006;148(3):245-54. https://doi.org/10.1038/sj.bjp.0706736

[15] Buttgereit F, Burmester GR, Straub RH, Seibel MJ, Zhou H. Exogenous and endogenous glucocorticoids in rheumatic diseases. Arthritis Rheum 2011;63(1):1-9. https://doi.org/10.1002/art.30070

[16] Smolensky MH, Peppas NA. Chronobiology, drug delivery, and chronotherapeutics. Adv Drug Deliv Rev 2007;59(9-10):828-51. https://doi.org/10.1016/j.addr.2007.07.001

[17] Cutolo M. Chronobiology and the treatment of rheumatoid arthritis. Curr Opin Rheumatol 2012;24(3):312-8. https://doi.org/10.1097/BOR.0b013e3283521c78

[18] Paolino S, Cutolo M, Pizzorni C. Glucocorticoid management in rheumatoid arthritis: Morning or night low dose?. Reumatologia 2017;55(4):189-97. https://doi.org/10.5114/reum.2017.69779

[19] Grzanka A, Misiołek M, Golusiński W, Jarząb J. Molecular mechanisms of glucocorticoids action: Implications for treatment of rhinosinusitis and nasal polyposis. Eur Arch Otorhinolaryngol 2011;268(2):247-53. https://doi.org/10.1007/s00405-010-1330-z

[20] Meikle AW, Tyler FH. Potency and duration of action of glucocorticoids. Effects of hydrocortisone, prednisone and dexamethasone on human pituitary-adrenal function. Am J Med 1977;63(2):200-7. https://doi.org/10.1016/0002-9343(77)90233-9

[21] Bandoli G, Palmsten K, Forbess Smith CJ, Chambers CD. A Review of Systemic Corticosteroid Use in Pregnancy and the Risk of Select Pregnancy and Birth Outcomes. Rheum Dis Clin North Am 2017;43(3):489-502. https://doi.org/10.1016/j.rdc.2017.04.013

[22] Fauci AS, Dale DC, Balow JE. Glucocorticosteroid therapy: Mechanisms of action and clinical considerations. Ann Intern Med 1976;84(3):304-15. https://doi.org/10.7326/0003-4819-84-3-304

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INVITED REVIEW

Management of hypertension and coronary artery disease in vasculitis patients using glucocorticoids

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ABSTRACT

Systemic vasculitis is an autoimmune disorder characterized by inflammation and damage to blood vessels, often involving multiple organ systems. Glucocorticoids (GCs) are a cornerstone in managing vasculitis and other rheumatologic conditions due to their potent anti-inflammatory properties, but their use is associated with significant systemic side effects. This review evaluates the cardiovascular (CV) risks associated with glucocorticoid use, focusing on hypertension and atherosclerosis, and highlights strategies for minimizing these risks while managing systemic inflammation in vasculitis patients. Glucocorticoids, despite their efficacy in disease management, contribute to CV complications in a dose- and duration-dependent manner. Hypertension arises through mechanisms such as nitric oxide suppression, renin-angiotensin-aldosterone system activation, and vascular effects. Atherosclerosis is accelerated by endothelial dysfunction, oxidative stress, and inflammation, increasing risks for coronary artery disease and acute CV events. Daily doses exceeding 5 mg of prednisolone are linked to a marked rise in CV risks, even with short-term use. Moreover, systemic inflammation from vasculitis compounds these risks, making it challenging to disentangle GC side effects from the underlying disease pathology. Glucocorticoid therapy requires careful management, prioritizing the lowest effective dose and shortest duration possible. Routine CV risk assessments, blood pressure monitoring, and targeted interventions such as lifestyle modifications and pharmacologic therapies are crucial for mitigating adverse outcomes. Future studies should aim to define "safe" GC thresholds and refine treatment protocols to balance efficacy and safety in vasculitis management.

Keywords: atherosclerosis, cardiovascular risk, glucocorticoids, hypertension, systemic vasculitis, rheumatology.

Introduction

Systemic vasculitis is an autoimmune disorder that damages blood vessels of various sizes, affecting one or multiple organ systems [1]. These conditions can be categorized by vessel size and may arise as primary pathologies or secondary to connective tissue disorders or drug effects. Chronic inflammation from these disorders is also associated with myocardial ischemia and fibrosis and higher incidences of pericarditis and cardiomyopathies, which impair cardiac function and contribute to heart failure [2].

Glucocorticoids regulate physiological processes as critical modulators in energy metabolism, blood pressure (BP) regulation, mood, memory, and stress responses [3]. They are produced in the zona fasciculate of the adrenal cortex and released into the bloodstream. After their release, they trigger circadian and pulsatile effects throughout the body. Their secretion is regulated by adrenocorticotropic hormone (ACTH) through the hypothalamic-pituitary-adrenal (HPA) axis [4].

The physiological effects of endogenous glucocorticoids are well-documented. In 1929, Philip Hench and colleagues discovered their anti-inflammatory properties [5]. Since then, exogenous steroids have been utilized in both endocrine and non-endocrine conditions [6]. Although they are used diagnostically for conditions like Cushing's disease and adrenal insufficiency, their anti-inflammatory properties are also applied in treating non-endocrine disorders such as asthma, chronic obstructive pulmonary disease (COPD), and chronic inflammatory bowel disease [7]. Due to their potent anti-inflammatory and immunosuppressive properties, glucocorticoids have become a mainstay in treating many rheumatologic conditions, such as vasculitis and rheumatoid arthritis [8].

The use of exogenous glucocorticoids entered therapeutic protocols in the late 1940s. Their potent effects and inadequate alternatives in treating rheumatologic diseases have resulted in widespread use. Their impact on disease control during acute flare-ups of vasculitis cannot be underestimated [9]. New-generation agents, while promising, have yet to demonstrate the same efficacy as glucocorticoids during acute exacerbations. Because of their systemic side effects, American and European Rheumatology societies advise using glucocorticoids as first-line therapy or as a bridging treatment until the effects of disease-modifying antirheumatic drugs (DMARDs) or biological agents become evident [10]. If used, they should be given at the lowest effective dose until other therapies become effective. Subsequently, a tapering regimen is recommended to discontinue GC therapy [11]. Despite these recommendations, a study conducted between 2006 and 2019 discovered that glucocorticoids were part of the initial treatment for 37.7% of patients diagnosed with from 0.5% to 1.8%, with the frequency of use increasing notably with age [12]. Glucocorticoids remain among the top 10 most prescribed medications in the United Kingdom [13,14].

Although glucocorticoids offer significant therapeutic benefits, they carry many side effects affecting multiple organ systems. Chronic use can lead to conditions such as osteoporosis, dysglycemia, cerebrovascular events, and infections [15,16]. Glucocorticoids are also known to increase CVD risk, particularly by precipitating hypertension, hyperlipidemia, and diabetes mellitus [17].

In earlier periods, it was believed that non-systemic applications might limit side effects. However, research has demonstrated that glucocorticoids produce similar systemic side effects regardless of the route of administration [16,18]. Aside from intravenous use, side effects are most commonly observed with oral and intra-articular administration [19]. Given the current therapeutic landscape, it is unlikely that glucocorticoids will be completely phased out from treating vasculitis and other rheumatologic disorders. Therefore, clinicians must be aware of the potential side effects, especially CV morbidity and mortality, to ensure early detection and primary prevention.

The CV risks and benefits associated with glucocorticoid use remain controversial, and the question of whether there is a safe and effective dose or duration of glucocorticoid therapy is still debated. It is generally believed that the risk of CVD may be minimized with low doses and short durations of use. However, some research indicates that even a single dose or short-term treatment (66-72 hours) can have systemic side effects. For instance, the use of 20 mg for four days may induce hypertension [17].

Glucocorticoids have been associated with an increased risk of all-cause-of mortality. Most studies have indicated that a dose of 5 mg of prednisolone or its equivalents is considered a safe dose [20]. In a study involving glucocorticoid naïve RA patients, the risk of CV events associated with chronic glucocorticoid use was evaluated based on daily dose, cumulative dose, and treatment duration of six months to one year. After adjusting for traditional CVD risk factors and disease duration, it was shown that prednisolone use at a daily dose of less than 5 mg, a cumulative dose of less than 750 mg over six months, and less than 1100 mg over one year did not increase CVD risk [20]. However, doses exceeding 5 mg per day and short-term cumulative doses exceeding these thresholds were associated with an increased risk of CVD. The group that developed CV events tended to have higher mean ages, more traditional risk factors, higher disease activity, longer disease durations, and were less likely to use DMARDs. A meta-analysis found that RA patients have a 50% increased risk of CV events [21].

Glucocorticoids may increase the risk of CV events by promoting two critical CV risk factors: HT and atherosclerosis.

Hypertension

Glucocorticoid-induced hypertension gained attention due to its high prevalence (25-93%) as a comorbidity in Cushing's syndrome patients [22]. Following the recognition of hypertension in patients with endogenous steroid excess, the effects of exogenous steroid use on BP have been studied [23]. Both endogenous and exogenous excess glucocorticoids have been shown to cause hypertension. Studies have identified daily glucocorticoid dose and family history of essential hypertension as significant risk factors for glucocorticoid-induced hypertension.

Initially, it was thought that the hypertensive effects of glucocorticoids were primarily due to their mineralocorticoid activity [24]. While mineralocorticoid receptor activation plays a role in hypertension development, it is not the sole or even primary factor, as synthetic glucocorticoids exhibit minimal mineralocorticoid effects. Furthermore, research in human and animal models has shown that spironolactone cannot prevent glucocorticoid-induced hypertension [25]. Sodium reabsorption at the renal level is not an essential mechanism in glucocorticoid-induced hypertension either [26]. No significant increase in sympathetic activity has been observed. Over time, it has become clear that glucocorticoid-induced hypertension is a complex condition involving multiple systems.

Glucocorticoids contribute to hypertension by affecting nitric oxide (NO) release in the central nervous system, activating the renin-angiotensin-aldosterone system (RAAS), and promoting cardiac hypercontractility while increasing sodium reabsorption in the kidneys [23]. They also promote hypertension through mechanisms that potentiate their systemic effects on the liver and adipose tissue. Glucocorticoid receptors are known to be present in both vascular smooth muscle and endothelial cells [27]. Although glucocorticoids do not alter plasma arginine vasopressin levels, their impact on vascular smooth muscle increases angiotensin II V1a receptor expression and enhances sodium and calcium influx into cells [28]. In vitro studies have also shown that glucocorticoids reduce vascular reactivity and inhibit the synthesis of prostacyclin and nitric oxide, leading to vasoconstriction and, ultimately, hypertension.

In Addison's disease, the hypertensive response to glucocorticoid therapy occurs too rapidly to be explained by renal mechanisms alone, highlighting the role of the vascular bed in the acute regulation of BP [29]. This suggests that glucocorticoid-induced hypertension may develop via direct effects on vascular smooth muscle even during short-term use [30]. In general, acute glucocorticoid-induced hypertension is mediated through vascular mechanisms, while chronic hypertension develops through renal mechanisms. In addition, secondary hypertension resulting from glucocorticoid use tends to elevate systolic BP more than diastolic BP. After oral glucocorticoid administration, BP increases within 24 hours and peaks within the first few days [31]. Glucocorticoids disrupt circadian rhythms, resulting in inadequate nocturnal BP reduction [32]. This condition leads to non-dipping hypertension.

In the general population, an increase of 20 mmHg in systolic BP and 10 mmHg in diastolic BP doubles the risk of cardiovascular disease and ischemic heart disease mortality [33]. Vasculitis patients often receive glucocorticoid therapy for at least three months following disease flare-ups, with the cumulative dose increasing with prolonged use. In one study, hypertension developed in 9% of patients after three months of glucocorticoid therapy [34]. Among patients receiving high doses, the incidence of hypertension reached 30%, and among those over 65 years old, the rate was 37% [35] . Although daily doses under 7.5 mg are considered relatively safe, the risk of hypertension increases with both daily and cumulative doses [36]. A retrospective cohort study involving 71,642 patients confirmed that the incidence of hypertension rises with increasing cumulative glucocorticoid exposure. Patients were stratified into low, medium, and high cumulative dose groups, with hypertension incidence rates of 14%, 20%, and 30%, respectively [31].

In RA patients without a prior diagnosis of hypertension, glucocorticoid use was associated with a 17% increase in the risk of developing hypertension [36]. Additionally, 40% of patients who developed secondary hypertension from glucocorticoid use did not receive antihypertensive therapy, leaving them untreated for one of the most modifiable CVD risk factors. Furthermore,

30% of patients did not take BP measurements during follow-up visits within two years of initiating glucocorticoid therapy [36].

Regular BP monitoring should be performed during follow-up visits, and patients should be encouraged to monitor their BP. Most patients under GC treatment develop Grade-1 or Grade-2 hypertension. Before establishing a treatment protocol, scoring patients based on their CVD risk using their BP measurements and identifying their position on the risk scale is crucial [37]. The most critical step in treatment is to discontinue glucocorticoids or administer the lowest effective dose. Lifestyle changes, including dietary modifications, increased physical activity, smoking cessation, and weight loss, should be recommended to patients. Medical intervention, in addition to lifestyle modifications, is vital for preventing hypertensive organ damage and for the ongoing management of vasculitis. Medical treatment aims to reduce BP to below 130/80 mmHg [38]. From a pharmacological standpoint, due to the increased activation of the RAAS, angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), and nitric oxide (NO) donors such as L-arginine may be considered as first-line treatment options. Mineralocorticoid receptor antagonists (MRAs) and diuretics can be the next option. Contrary to their anticipated outcomes, calcium channel blockers (CCBs) and beta blockers are generally found to be ineffective in managing glucocorticoid-induced hypertension. Additionally, clinicians should consider using beta-blockers and thiazide diuretics, with careful attention to their potential adverse effects on glucose metabolism. It is also essential to monitor for hypokalemia, which can occur as a side effect of thiazide diuretics.

Atherosclerosis and Coronary Heart Disease

Atherosclerosis is a chronic, progressive inflammatory condition characterized by arterial narrowing, primarily due to vascular remodeling and the buildup of atherosclerotic plaques [39]. In patients with Cushing's syndrome, conditions indicating the presence of atherosclerosis, such as elevated levels of low-density lipoprotein (LDL), increased carotid intima-media thickness (IMT) and reduced carotid artery lumen diameter, are observed compared to individuals without the syndrome, independent of traditional cardiovascular risk factors such as smoking, body mass index (BMI), and hypertension [40]. Experimental studies using animal models further support these findings, demonstrating the pivotal role of glucocorticoids in the progression of atherosclerosis. In patients with prolonged glucocorticoid use (≥ five years), carotid plaques and peripheral artery disease are more prevalent compared to those with short-term use [41].

Glucocorticoids affect vascular function by modulating both vasoconstriction and vasodilation pathways. Elevated levels of endothelin-1 (ET-1), a potent vasoconstrictor, have been linked to atherosclerosis and contribute to increased vascular constriction [42]. Additionally, the overactivation of the RAAS, mainly through AngII, exacerbates vasoconstriction and endothelial injury. Regarding vasodilation, glucocorticoids inhibit the production of critical vasodilators such as nitric oxide (NO) and prostacyclin [43,44]. Chronic glucocorticoid use has been associated with increased production of reactive oxygen species (ROS), which decreases NO bioavailability and further damages the vascular endothelium. The other cause of endothelial dysfunction is impaired endothelial progenitor cell (EPC) regulation. In individuals using glucocorticoids, there is a reduction in circulating EPCs. Consequently, endothelial-related vasodilation decreases, and the mechanisms for endothelial repair become compromised. In damaged endothelium, the balance between thrombotic and antithrombotic factors is disrupted [44]. The balance between NO, thromboxane A2, and prostacyclin is altered, von Willebrand factor levels increase, fibrinolysis mechanisms decrease, and platelet aggregation is accelerated [45]. As a result, atherosclerosis is accelerated, and the risk of acute coronary events increases.

The ESC Prevention 2022 guidelines emphasize that patients with elevated systemic inflammation may face an increased risk of CV events [37]. Higher inflammatory burdens have been strongly associated with increased CV event risk, and C-reactive protein (CRP) is recognized as an essential indicator of this risk. However, most glucocorticoid studies have not adjusted their outcomes for disease activity or CRP levels. In rheumatologic diseases, key inflammatory molecules such as TNF-alpha and IL-6 play a significant role in

chronic inflammation and vascular damage [46]. Glucocorticoids suppress both these molecules, inhibiting the pro-inflammatory cascade. Nonetheless, glucocorticoids' metabolic effects may also contribute to CVD risk by promoting atherosclerosis.

In a cohort study involving 70,000 individuals, glucocorticoid doses exceeding 7.5 mg/day were associated with a 2- to 4-fold increase in adverse cardiovascular outcomes [47]. Notably, the risks of coronary heart disease (CHD) and heart failure (HF) were found to be greater than those of stroke (SVO). Due to their widespread use in treatment, ongoing research is into a "safe" daily dose of glucocorticoids. While some studies suggest that doses under 5 mg/day do not increase CVD mortality, others indicate that even with a daily dose of 5 mg, the CVD risk doubles. Furthermore, at 25 mg/day, the risk increases sixfold. This suggests that patients using glucocorticoids to manage inflammatory burden in rheumatic diseases remain in a high-risk category for CVD [17].

The cardiovascular risks associated with glucocorticoid use are comparable to those seen in patients with diabetes or diagnosed cardiovascular disease. Although glucocorticoid use in patients with inflammatory conditions is not explicitly included in CVD risk scoring, recent prevention guidelines for cardiovascular disease stress the importance of accounting for these factors.

Assessment of patients' risk profiles for coronary heart disease (CHD) is recommended. Although a constant multiplier has not been established for vasculitis patients, it is suggested that the risk determined by the SCORE-2 CVD risk calculator be multiplied by a factor of 1.5 for patients with RA [37]. This situation underlines the increased risk of CVD in systemic inflammatory processes. For secondary prevention, guidelines recommend administering low-dose colchicine (0.5 mg daily) to patients with uncontrolled risk factors despite other interventions. Additionally, research into IL-6 inhibitors and suppressing systemic inflammation in CHD patients is ongoing.

The necessity for coronary artery stenting should be thoroughly evaluated, as the metallic shafts of stents can provoke a foreign body reaction in already dysfunctional endothelium, potentially causing local plaque destabilization and accelerating atherosclerosis [48]. Many patients display ectatic coronary arteries due to chronic inflammation, which are more prone to frailty and have a higher risk of complications [49]. Antithrombotic therapy should be optimized, and the dosage of statin treatment should be adjusted to achieve the targets recommended by guidelines.

Take Home Messages

- Glucocorticoid use is associated with hypertension and atherosclerosis, with these effects being dose- and duration-dependent.
- When disease activity is high, systemic inflammation increases, leading to higher doses of glucocorticoids. Consequently, it is difficult to determine whether systemic complications arise from the glucocorticoid dose or the intense inflammation. Moreover, a "safe" glucocorticoid dose may not apply uniformly to all side effects. It is crucial to use glucocorticoids for the shortest duration and at the lowest effective dose possible, especially when the disease is in remission.
- Due to the elevated CVD risk in vasculitis patients, lifestyle modifications alone are insufficient. Instead, they should be regarded as high-risk, and appropriate medical treatment should be administered when necessary.

Author contribution

Study conception and design: SA, EBK; draft manuscript preparation: SA, EBK. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] Clifford AH, Cohen Tervaert JW. Cardiovascular events and the role of accelerated atherosclerosis in systemic vasculitis. Atherosclerosis 2021;325:8-15. https://doi.org/10.1016/j.atherosclerosis.2021.03.032

[2] Silveira LH. Cardiovascular Manifestations of Systemic Vasculitides. Curr Rheumatol Rep 2020;22(10):72. https://doi.org/10.1007/s11926-020-00952-1

[3] Ramamoorthy S, Cidlowski JA. Corticosteroids: Mechanisms of Action in Health and Disease. Rheum Dis Clin North Am 2016;42(1):15-31. https://doi.org/10.1016/j.rdc.2015.08.002

[4] Burford NG, Webster NA, Cruz-Topete D. Hypothalamic-Pituitary-Adrenal Axis Modulation of Glucocorticoids in the Cardiovascular System. Int J Mol Sci 2017;18(10):2150. https://doi.org/10.3390/ijms18102150

[5] 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(8):181-97.

[6] Yanase T, Tajima T, Katabami T, et al. Diagnosis and treatment of adrenal insufficiency including adrenal crisis: A Japan Endocrine Society clinical practice guideline [Opinion]. Endocr J 2016;63(9):765-84. https://doi.org/10.1507/endocrj.EJ16-0242

[7] Kaplan AG. Inhaled Corticosteroid Treatment in Chronic Obstructive Pulmonary Disease (COPD): Boon or Bane?. J Am Board Fam Med 2020;33(2):289-302. https://doi.org/10.3122/jabfm.2020.02.190227

[8] Buttgereit F. Views on glucocorticoid therapy in rheumatology: The age of convergence. Nat Rev Rheumatol 2020;16(4):239-46. https://doi.org/10.1038/s41584-020-0370-z

[9] Kermani TA, Warrington KJ, Dua AB. Treatment Guidelines in Vasculitis. Rheum Dis Clin North Am 2022;48(3):705-24. https://doi.org/10.1016/j.rdc.2022.03.006

[10] Smolen JS, Landewé R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017;76(6):960-77. https://doi.org/10.1136/annrheumdis-2016-210715

[11] Nagy G, Roodenrijs NM, Welsing PM, et al. EULAR definition of difficult-to-treat rheumatoid arthritis. Ann Rheum Dis 2021;80(1):31-5. https://doi.org/10.1136/annrheumdis-2020-217344

[12] van Staa TP, Leufkens HG, Abenhaim L, Begaud B, Zhang B, Cooper C. Use of oral corticosteroids in the United Kingdom. QJM 2000;93(2):105-11. https://doi.org/10.1093/qjmed/93.2.105

[13] Bénard-Laribière A, Pariente A, Pambrun E, Bégaud B, Fardet L, Noize P. Prevalence and prescription patterns of oral glucocorticoids in adults: A retrospective cross-sectional and cohort analysis in France. BMJ Open 2017;7(7):e015905. https://doi.org/10.1136/bmjopen-2017-015905

[14] NHS Business Service Authority. (2021). Prescription cost analysis-England 2020/21.

[15] Box CD, Cronin O, Hauser B. The Impact of High Dose Glucocorticoids on Bone Health and Fracture Risk in Systemic Vasculitides. Front Endocrinol (Lausanne) 2022;13:806361. https://doi.org/10.3389/fendo.2022.806361

[16] Phan K, Smith SD. Topical corticosteroids and risk of diabetes mellitus: Systematic review and meta-analysis. J Dermatolog Treat 2021;32(3):345-9. https://doi.org/10.1080/09546634.2019.1657224

[17] Pofi R, Caratti G, Ray DW, Tomlinson JW. Treating the Side Effects of Exogenous Glucocorticoids; Can We Separate the Good From the Bad?. Endocr Rev 2023;44(6):975-1011. https://doi.org/10.1210/endrev/bnad016

[18] Heffler E, Madeira LNG, Ferrando M, et al. Inhaled Corticosteroids Safety and Adverse Effects in Patients with Asthma. J Allergy Clin Immunol Pract 2018;6(3):776-81. https://doi.org/10.1016/j.jaip.2018.01.025

[19] Habib GS. Systemic effects of intra-articular corticosteroids. Clin Rheumatol 2009;28(7):749-56. https://doi.org/10.1007/s10067-009-1135-x

[20] Ocon AJ, Reed G, Pappas DA, Curtis JR, Kremer JM. Short-term dose and duration-dependent glucocorticoid risk for cardiovascular events in glucocorticoid-naive patients with rheumatoid arthritis. Ann Rheum Dis 2021;80(12):1522-9. https://doi.org/10.1136/annrheumdis-2021-220577

[21] Hannawi SM, Hannawi H, Al Salmi I. Cardiovascular Risk in Rheumatoid Arthritis: Literature Review. Oman Med J 2021;36(3):e262. https://doi.org/10.5001/omj.2021.25

[22] Pivonello R, Isidori AM, De Martino MC, Newell-Price J, Biller BMK, Colao A. Complications of Cushing's syndrome: State of the art. Lancet Diabetes Endocrinol 2016;4(7):611-29. https://doi.org/10.1016/S2213-8587(16)00086-3

[23] Goodwin JE, Geller DS. Glucocorticoid-induced hypertension. Pediatr Nephrol 2012;27(7):1059-66. https://doi.org/10.1007/s00467-011-1928-4

[24] Whitworth JA, Mangos GJ, Kelly JJ. Cushing, cortisol, and cardiovascular disease. Hypertension 2000;36(5):912-6. https://doi.org/10.1161/01.hyp.36.5.912

[25] Mangos GJ, Whitworth JA, Williamson PM, Kelly JJ. Glucocorticoids and the kidney. Nephrology (Carlton) 2003;8(6):267-73. https://doi.org/10.1111/j.1440-1797.2003.00215.x

[26] Li M, Wen C, Fraser T, Whitworth JA. Adrenocorticotrophin-induced hypertension: Effects of mineralocorticoid and glucocorticoid receptor antagonism. J Hypertens 1999;17(3):419-26. https://doi.org/10.1097/00004872-199917030-00016

[27] Provencher PH, Saltis J, Funder JW. Glucocorticoids but not mineralocorticoids modulate endothelin-1 and angiotensin II binding in SHR vascular smooth muscle cells. J Steroid Biochem Mol Biol 1995;52(3):219-25. https://doi.org/10.1016/0960-0760(94)00168-I

[28] Kornel L, Nelson WA, Manisundaram B, Chigurupati R, Hayashi T. Mechanism of the effects of glucocorticoids and mineralocorticoids on vascular smooth muscle contractility. Steroids 1993;58(12):580-7. https://doi.org/10.1016/0039-128x(93)90099-9

[29] Johannsson G, Falorni A, Skrtic S, et al. Adrenal insufficiency: Review of clinical outcomes with current glucocorticoid replacement therapy. Clin Endocrinol (Oxf) 2015;82(1):2-11. https://doi.org/10.1111/cen.12603

[30] Brotman DJ, Girod JP, Garcia MJ, et al. Effects of short-term glucocorticoids on cardiovascular biomarkers. J Clin Endocrinol Metab 2005;90(6):3202-8. https://doi.org/10.1210/jc.2004-2379

[31] Mebrahtu TF, Morgan AW, West RM, Stewart PM, Pujades-Rodriguez M. Oral glucocorticoids and incidence of hypertension in people with chronic inflammatory diseases: A population-based cohort study. CMAJ 2020;192(12):E295-301. https://doi.org/10.1503/cmaj.191012

[32] Ivy JR, Oosthuyzen W, Peltz TS, et al. Glucocorticoids Induce Nondipping Blood Pressure by Activating the Thiazide-Sensitive Cotransporter. Hypertension 2016;67(5):1029-37. https://doi.org/10.1161/HYPERTENSIONAHA.115.06977

[33] Baid S, Nieman LK. Glucocorticoid excess and hypertension. Curr Hypertens Rep 2004;6(6):493-9. https://doi.org/10.1007/s11906-004-0046-0

[34] Fardet L, Flahault A, Kettaneh A, et al. Corticosteroid-induced clinical adverse events: Frequency, risk factors and patient's opinion. Br J Dermatol 2007;157(1):142-8. https://doi.org/10.1111/j.1365-2133.2007.07950.x

[35] Sato A, Funder JW, Okubo M, Kubota E, Saruta T. Glucocorticoid-induced hypertension in the elderly. Relation to serum calcium and family history of essential hypertension. Am J Hypertens 1995;8(8):823-8. https://doi.org/10.1016/0895-7061(95)00149-J

[36] Costello RE, Yimer BB, Roads P, Jani M, Dixon WG. Glucocorticoid use is associated with an increased risk of hypertension. Rheumatology (Oxford) 2021;60(1):132-9. https://doi.org/10.1093/rheumatology/keaa209

[37] Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2021;42(34):3227-337. https://doi.org/10.1093/eurheartj/ehab484

[38] Mancia G, Kreutz R, Brunström M, et al. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). J Hypertens 2023;41(12):1874-2071. https://doi.org/10.1097/HJH.0000000000003480

[39] Libby P. The changing landscape of atherosclerosis. Nature 2021;592(7855):524-33. https://doi.org/10.1038/s41586-021-03392-8

[40] Barahona MJ, Resmini E, Viladés D, et al. Coronary artery disease detected by multislice computed tomography in patients after long-term cure of Cushing's syndrome. J Clin Endocrinol Metab 2013;98(3):1093-9. https://doi.org/10.1210/jc.2012-3547

[41] Faggiano A, Pivonello R, Spiezia S, et al. Cardiovascular risk factors and common carotid artery caliber and stiffness in patients with Cushing's disease during active disease and 1 year after disease remission. J Clin Endocrinol Metab 2003;88(6):2527-33. https://doi.org/10.1210/jc.2002-021558

[42] Winkles JA, Alberts GF, Brogi E, Libby P. Endothelin-1 and endothelin receptor mRNA expression in normal and atherosclerotic human arteries. Biochem Biophys Res Commun 1993;191(3):1081-8. https://doi.org/10.1006/bbrc.1993.1327

[43] Iuchi T, Akaike M, Mitsui T, et al. Glucocorticoid excess induces superoxide production in vascular endothelial cells and elicits vascular endothelial dysfunction. Circ Res 2003;92(1):81-7. https://doi.org/10.1161/01.res.0000050588.35034.3c

[44] MacLeod C, Hadoke PWF, Nixon M. Glucocorticoids: Fuelling the Fire of Atherosclerosis or Therapeutic Extinguishers?. Int J Mol Sci 2021;22(14):7622. https://doi.org/10.3390/ijms22147622

[45] Rogers KM, Bonar CA, Estrella JL, Yang S. Inhibitory effect of glucocorticoid on coronary artery endothelial function. Am J Physiol Heart Circ Physiol 2002;283(5):H1922-8. https://doi.org/10.1152/ajpheart.00364.2002

[46] Yoshifuji H. Pathophysiology of large vessel vasculitis and utility of interleukin-6 inhibition therapy. Mod Rheumatol 2019;29(2):287-93. https://doi.org/10.1080/14397595.2018.1546358

[47] Wei L, MacDonald TM, Walker BR. Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. Ann Intern Med 2004;141(10):764-70. https://doi.org/10.7326/0003-4819-141-10-200411160-00007

[48] Khanna S, Garikapati K, Goh DSL, et al. Coronary artery vasculitis: A review of current literature. BMC Cardiovasc Disord 2021;21(1):7. https://doi.org/10.1186/s12872-020-01813-6

[49] Mavrogeni S, Manoussakis MN, Karagiorga TC, et al. Detection of coronary artery lesions and myocardial necrosis by magnetic resonance in systemic necrotizing vasculitides. Arthritis Rheum 2009;61(8):1121-9. https://doi.org/10.1002/art.24695

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INVITED REVIEW

Management of glucocorticoid-induced diabetes

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ABSTRACT

Glucocorticoid-induced diabetes (GID) is a frequent metabolic complication of glucocorticoid therapy. It results from both insulin resistance and impaired insulin secretion, exacerbated by glucocorticoid use. Despite its prevalence, consensus guidelines on screening and management remain limited. GID affects approximately one in five patients receiving long-term glucocorticoid therapy. Risk factors include older age, high BMI, prediabetes, ethnicity, and high-dose systemic glucocorticoids. All patients initiated on moderate to high doses of glucocorticoids should be assessed for GID risk factors and closely monitored for the development of hyperglycemia and diabetes. In addition, glucocorticoid therapy can significantly exacerbate hyperglycemia in individuals with pre-existing diabetes, and stringent glucose monitoring is crucial. Treatment should be tailored to individual patient. Oral anti-diabetics such as metformin and sulfonylureas might be used in selected patients with mild GID. However, insulin is the primary treatment for severe hyperglycemia. Early detection and individualized management strategies are critical to mitigate GID's impact. Further research is needed to develop consensus guidelines and optimize treatment approaches.

Keywords: glucocorticoid, diabetes, hyperglycemia, risk factors, treatment.

Introduction

Glucocorticoid-induced diabetes (GID) is a well-recognized complication of glucocorticoid therapy, particularly in patients receiving long-term or high-dose glucocorticoid treatment. This review discusses the epidemiology, risk factors, diagnostic criteria, management strategies, and includes key algorithms and tables to aid in clinical decision-making.

Epidemiology

The use of glucocorticoids is common, with data from the United Kingdom and the United States of America indicating that approximately 1% of the population uses glucocorticoids [1,2]. Orally administered glucocorticoids may account for up to 2% of new-onset diabetes cases in the primary care setting [3]. There is also data showing that approximately 19% of patients on glucocorticoid therapy for more than one month could develop diabetes [4]. Hospitalized patients are particularly vulnerable, with 56% experiencing at least one hyperglycemic event when on glucocorticoids [5].

Risk Factors

Several factors contribute to the development of GID. The route of glucocorticoid administration, the dosage, and the duration of therapy are critical determinants [6]. For instance, systemic administration presents a higher risk than intra-articular or intra-lesional injections. However,

even intra-articular glucocorticoid injections may induce hyperglycemia for several days in patients with diabetes mellitus [7]. Additionally, higher doses of glucocorticoids significantly escalate the risk of hyperglycemia, particularly at doses equivalent to more than 120 mg of hydrocortisone being associated with a 10-fold increase in risk [6]. Moreover, the type of glucocorticoid administration is critical, as daily long-term use causes higher hyperglycemia risk than cyclic use. Research shows that 6 weeks of continuous glucocorticoid administration increases the risk of hyperglycemia by 50% compared to 5 days on, 15 days off usage [8]. Other risk factors for GID are older age, renal dysfunction, prediabetes, family history of diabetes, overweight or obesity, and co-administration of other medications associated with hyperglycemia risk (Table 1). Furthermore, genetic variations found in the population have been shown to be useful in predicting the metabolic responses to glucocorticoid therapy that are unique to each individual, such as hyperglycemia and diabetes mellitus [9].

Screening and Diagnosis

The diagnostic criteria for GID mirror those of common diabetes mellitus, with fasting plasma glucose (FPG) levels of ≥126 mg/dL or a 2-hour plasma glucose (2h PG) level of ≥200 mg/dL during a 75 g oral glucose tolerance test (OGTT) (Table 2).

There is no consensus regarding who should be screened for GID and when, and the American Diabetes Association (ADA) suggests 'considering' screening for diabetes in patients on long-term glucocorticoid therapy [10]. Fasting plasma glucose alone may not be the best method for screening GID, as short- and intermediate-acting glucocorticoids administered in the morning would increase plasma glucose in the afternoon or evening [6]. OGTT may therefore be a better approach for GID screening in long-term low-dose glucocorticoid users. In a study involving 150 patients who used low-dose glucocorticoids (≤10 mg/day of prednisolone) for more than 3 months, OGTT revealed that 19% had impaired glucose tolerance compared to 5% with impaired fasting glucose [11]. It is controversial whether prednisolone dosages as low as 5 mg per day could also increase the risk of GID [12,13].

Management

Management of GID should be individualized, taking into account the patient's risk factors, the type, dosage and duration of glucocorticoid treatment, and the severity of hyperglycemia. In patients without a history of diabetes, the focus should be on monitoring and early intervention. Patients with GID risk factors need a more frequent glucose monitoring, and persistent hyperglycemia (PG ≥180 mg/dL in two or more readings) require treatment [6,10] (Figure 1).

Non-Pharmacological Interventions

Lifestyle modifications, including dietary adjustments and physical activity, are essential components of GID management. However, due to the rapid onset of hyperglycemia with glucocorticoid use, these often need to be supplemented with pharmacological therapy.

Table 1. Risk factors for glucocorticoid-induced diabetes

Age	>60 years
BMI	>25 kg/m^2 (also abdominal obesity)
Hypertriglyceridemia	
Prediabetes	HbA1c >6.5%
Renal dysfunction	GFR < 40 mL/min/1.73 m^2
Family history of diabetes	
Ethnicity	e.g., black ethnic group
Concurrent medications	e.g., MMF, calcineurin inhibitors, furosemide

BMI: body mass index, GFR: glomerular filtration rate, MMF: mycophenolate mofetil.

Table 2. Diagnostic criteria for diabetes [10]

FPG	≥126 mg/dL
2-h PG during 75 g OGTT	≥200 mg/dL
Random PG in a person with classical symptoms of hyperglycemia	≥200 mg/dL
HbA1c*	≥6.5%

*The test should be performed in a laboratory using a National Glycohemoglobin Standardization Program-certified method.

FPG: fasting plasma glucose, OGTT: oral glucose tolerance test.

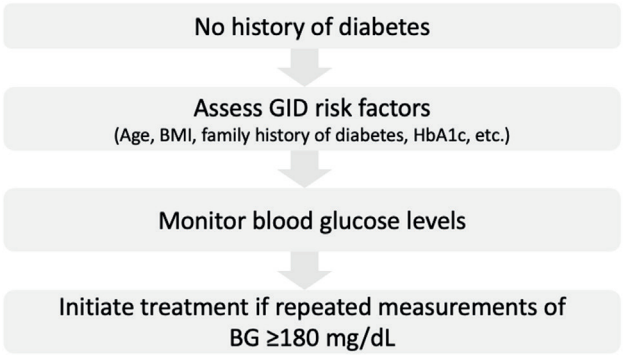

Figure 1. Diagnostic approach to glucocorticoid-induced diabetes

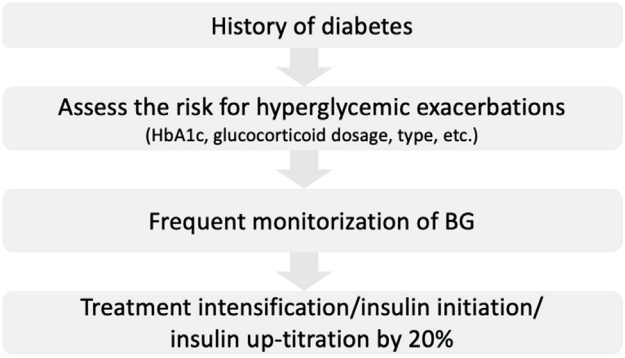

Figure 2. An approach for managing hyperglycemic exacerbations in diabetic patients induced by glucocorticoids

Pharmacological Interventions

The treatment of GID is similar to that of common diabetes in the population. However, managing GID with oral antidiabetic drugs (OADs) is challenging because being flexible with these medications in treatment is often difficult. A significant percentage of patients with GID would therefore need insulin. Still, OADs might be used in selected patients with mild hyperglycemia (BG levels <180 mg/dL) who receives low-dose glucocorticoids. On the other hand, acute severe glucocorticoid-induced hyperglycemia with PG levels exceeding 200 mg/dL requires insulin treatment [14]. In patients with diabetes, it may be advisable to intensify anti-diabetic treatment, initiate insulin therapy if it is not already being used, or increase the insulin dose if it is already being administered, even before starting glucocorticoids [6,15] (Figure 2). It should be noted that patients may need higher doses of prandial insulin rather that basal insulin, since peak concentrations of intermediate-acting glucocorticoids are reached 4 to 6 hours after administration, and last for 12 to 16 hours [6]. It is therefore common to have near-normal fasting BG measurements in the morning which tend to increase during the afternoon.

Insulin treatment should be tailored to individual patient. Insulin choices can be made based on whether the patient's glucocorticoid is short (hydrocortisone), intermediate (prednisone, methylprednisolone), or long-acting (dexamethasone). Intermediate-acting glucocorticoids like prednisolone and methylprednisolone typically begin their peak effect between 4-8 hours and last for 12-16 hours. Since the timing of the peak effect of NPH insulin coincides with this range, some experts recommend adding morning NPH insulin for patients taking a morning dose of prednisolone or methylprednisolone [16]. However, a meta-analysis revealed no advantage of NPH insulin use over insulin glargine or detemir in GID management [15]. The severity of hyperglycemia determines whether basal insulin alone will be sufficient or if bolus injections will be needed [6]. Nevertheless, "sliding scale" insulin injections should be avoided in favor of basal-bolus insulin regimens [15].

Oral anti-diabetics might be used in selected patients with mild GID. Sulfonylureas may be considered in patients using intermediate- to long-acting glucocorticoids due to their rapid onset and prolonged effect, though they carry a risk of nocturnal hypoglycemia. Glinides, which are fast-and short-acting agents administered before meals, previously offered flexibility in managing blood glucose levels in GID, although they are no longer available in some regions. Incretin-based therapies, targeting postprandial glucose, can be used, although study results are mixed; they are generally reserved for selected cases with mild glucose increase on long-term, low-dose glucocorticoids. Metformin is also an option for these patients due to its well-established efficacy in managing mild hyperglycemia. Thiazolidinediones, despite their potential as insulin sensitizers, present a double-edged sword; while they counteract some of the metabolic effects of glucocorticoids, their adverse effects—such as fluid retention, weight gain, and osteoporosis—often mirror the side effects associated with glucocorticoid therapy [6,14].

In long-term management, as the dose of glucocorticoids is tapered, the need for anti-diabetic treatment may decrease. Additionally, it is important to remember that suppression of endogenous cortisol can increase susceptibility to nocturnal hypoglycemia [17].

Conclusion

Glucocorticoid-induced diabetes is a common complication, and while a consensus on screening protocols has yet to be established, it may be prudent to consider OGTT screening in patients receiving long-term low-dose glucocorticoid therapy. All patients initiated on moderate to high doses of glucocorticoids, on the other hand, should be assessed for GID risk factors and closely monitored for the development of hyperglycemia and diabetes, with regular blood glucose monitoring being essential. In individuals with pre-existing diabetes, glucocorticoid therapy can significantly exacerbate hyperglycemia. Therefore, stringent glucose monitoring is crucial. Treatment may be tailored based on the type and dose of glucocorticoid, as well as individual patient factors. In cases of acute severe hyperglycemia, insulin remains the sole effective treatment option.

Author contribution

Study conception and design: SHO; draft manuscript preparation: SHO. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] Overman RA, Yeh JY, Deal CL. Prevalence of oral glucocorticoid usage in the United States: A general population perspective. Arthritis Care Res (Hoboken) 2013;65(2):294-8. https://doi.org/10.1002/acr.21796

[2] van Staa TP, Leufkens HG, Abenhaim L, Begaud B, Zhang B, Cooper C. Use of oral corticosteroids in the United Kingdom. QJM 2000;93(2):105-11. https://doi.org/10.1093/qjmed/93.2.105

[3] Gulliford MC, Charlton J, Latinovic R. Risk of diabetes associated with prescribed glucocorticoids in a large population. Diabetes Care 2006;29(12):2728-9. https://doi.org/10.2337/dc06-1499

[4] Liu XX, Zhu XM, Miao Q, Ye HY, Zhang ZY, Li YM. Hyperglycemia induced by glucocorticoids in nondiabetic patients: A meta-analysis. Ann Nutr Metab 2014;65(4):324-32. https://doi.org/10.1159/000365892

[5] Donihi AC, Raval D, Saul M, Korytkowski MT, DeVita MA. Prevalence and predictors of corticosteroid-related hyperglycemia in hospitalized patients. Endocr Pract 2006;12(4):358-62. https://doi.org/10.4158/EP.12.4.358

[6] Li JX, Cummins CL. Fresh insights into glucocorticoid-induced diabetes mellitus and new therapeutic directions. Nat Rev Endocrinol 2022;18(9):540-57. https://doi.org/10.1038/s41574-022-00683-6

[7] Habib G, Safia A. The effect of intra-articular injection of betamethasone acetate/betamethasone sodium phosphate on blood glucose levels in controlled diabetic patients with symptomatic osteoarthritis of the knee. Clin Rheumatol 2009;28(1):85-7. https://doi.org/10.1007/s10067-008-1023-9

[8] Gonzalez-Gonzalez JG, Mireles-Zavala LG, Rodriguez-Gutierrez R, et al. Hyperglycemia related to high-dose glucocorticoid use in noncritically ill patients. Diabetol Metab Syndr 2013;5:18. https://doi.org/10.1186/1758-5996-5-18

[9] Hu W, Jiang C, Kim M, et al. Individual-specific functional epigenomics reveals genetic determinants of adverse metabolic effects of glucocorticoids. Cell Metab 2021;33(8):1592-609. https://doi.org/10.1016/j.cmet.2021.06.004

[10] American Diabetes Association Professional Practice C. 2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes-2024. Diabetes Care 2024;47(Suppl 1):S20-42.

[11] Nowak KM, Rdzanek-Pikus M, Romanowska-Próchnicka K, Nowakowska-Płaza A, Papierska L. High prevalence of steroid-induced glucose intolerance with normal fasting glycaemia during low-dose glucocorticoid therapy: An oral glucose tolerance test screening study. Rheumatology (Oxford) 2021;60(6):2842-51. https://doi.org/10.1093/rheumatology/keaa724

[12] Movahedi M, Beauchamp ME, Abrahamowicz M, et al. Risk of Incident Diabetes Mellitus Associated With the Dosage and Duration of Oral Glucocorticoid Therapy in Patients With Rheumatoid Arthritis. Arthritis Rheumatol 2016;68(5):1089-98. https://doi.org/10.1002/art.39537

[13] Wu J, Mackie SL, Pujades-Rodriguez M. Glucocorticoid dose-dependent risk of type 2 diabetes in six immune-mediated inflammatory diseases: A population-based cohort analysis. BMJ Open Diabetes Res Care 2020;8(1):e001220. https://doi.org/10.1136/bmjdrc-2020-001220

[14] Roberts A, James J, Dhatariya K, Joint British Diabetes Societies (JBDS) for Inpatient Care. Management of hyperglycaemia and steroid (glucocorticoid) therapy: A guideline from the Joint British Diabetes Societies (JBDS) for Inpatient Care group. Diabet Med 2018;35(8):1011-7. https://doi.org/10.1111/dme.13675

[15] Tatalovic M, Lehmann R, Cheetham M, Nowak A, Battegay E, Rampini SK. Management of hyperglycaemia in persons with non-insulin-dependent type 2 diabetes mellitus who are started on systemic glucocorticoid therapy: A systematic review. BMJ Open 2019;9(5):e028914. https://doi.org/10.1136/bmjopen-2019-028914

[16] Clore JN, Thurby-Hay L. Glucocorticoid-induced hyperglycemia. Endocr Pract 2009;15(5):469-74. https://doi.org/10.4158/EP08331.RAR

[17] Descours M, Rigalleau V. Glucocorticoid-induced hyperglycemia and diabetes: Practical points. Ann Endocrinol (Paris) 2023;84(3):353-6. https://doi.org/10.1016/j.ando.2023.03.011

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INVITED REVIEW

Glucocorticoid toxicity index

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ABSTRACT

The Glucocorticoid Toxicity Index (GTI) is a glucocorticoid-related toxicity measurement tool which was recently developed by an international expert panel. GTI can be calculated with two different methods: Cumulative Worsening Score (CWS) and Aggregate Improvement Score (AIS). The total glucocorticoid-related toxicity during follow-up can be calculated with CWS. All parameters that develop over time continue to be included, and a decrease in the CWS is not possible. On the contrary, both increase and decrease in toxicity can be assessed in scoring with the AIS method. A drug that reduces glucocorticoid toxicity should be able to reduce the AIS score. Cumulative glucocorticoid dose was found to be associated with higher GTI scores in studies. Although not all glucocorticoid-related toxicities can be covered, parameters that are common, dynamic, and more likely to be glucocorticoid-related are included in GTI. GTI has some limitations such as the possibility of not detecting chronic damage, the difficulty in interpreting the score in the patients who have already sterted the glucocorticoid treatment, some parameters requiring direct interaction with the patient, and difficulty in calculation.

Keywords: glucocorticoid toxicity index, cumulative dose, glucocorticoid toxicity, inflammatory diseases.

Introduction

Glucocorticoids (GCs) has been the mainstay of the treatment in inflammatory diseases. However, the toxicity risk and comorbidities related to GC use remains a concern, especially in long-term and high dose GC treatment. Therefore, additional immunosuppressive (IS) agents aim to reduce the GC dose and thus GC-related adverse events. An effective IS should have a GC sparing effect and reduce GC-related toxicity [1].

To date, GC toxicity has been defined in many different ways. In a study comparing budesonide and prednisolone in Crohn Disease, GC-related main side effects were listed as moon face, acne, swollen ankles, easy bruising, hirsutism, buffalo hump and skin striae [2]. In another study evaluating the effectiveness of low-dose steroids in rheumatoid arthritis (RA), toxicity assessment was based on blood pressure, body mass index (BMI) and DEXA [3]. Weight, blood pressure, glucose levels, depression, osteoporotic fractures, glaucoma, cataract were recorded in every visit for adverse event evaluation in the study which involved early RA patients with very low dose prednisolone treatment [4].

Glucocorticoid Toxicity Index (GTI), which was developed by an international group of experts is an instrument which aims to assess GC related toxicity and the change in toxicity over time [5]. The index was developed and initially validated in 2017 and revised in 2022 (GTI 2.0) defining two analytic approaches: Cumulative Worsening Score (CWS) and Aggregate Improvement Score (AIS). The principles adopted in selecting items were choosing the most frequent items which have the likelihood of occurrence >%5 over 6 months to 3 years duration,

importance of the items for both clinician and the patient, choosing independent items and dynamic items that can reflect the change over time. After the selection of the parameters, the items were voted by experts for weighting [6]. To evaluate changes in glucocorticoid toxicity, measurements should be taken at least at two different time points. The first measurement establishes a baseline GTI score to assess the patient's current condition. The second measurement evaluates any improvement or worsening compared to baseline. These measurements can be performed for both newly initiated GC patients and those with a history of GC use. It is recommended that GTI be applied at 3-month intervals during GC therapy.

Glucocorticoid Toxicity Index Scoring

Cumulative worsening score

CWS was developed to assess the total toxicity over time. Every damage item that develops after the initial visit continues to be counted, even if it is temporary and resolves during follow-up. Therefore, the CWS can increase or remain the same during time, but cannot decrease. An effective GC sparing agent will provide lower CWS compared to the standard therapy. This score ranges between 0 and 439 [6].

Aggregate improvement score

In clinical trials, patients may have been exposed to GCs before the trial and some GC-related toxicity parameters may have developed at initial visit. AIS allows to evaluate the decrease in toxicity which is already present at the baseline visit. If a damage item improves during follow-up, that item provides a corresponding point reduction in the AIS. Therefore, reduction in GC toxicity can be measured with AIS. On the contrary, in case of worsening in the relevant toxicity, the score increases. Corresponding improvement and worsening in the same item cause an equal increase or decrease in the AIS (Table 1). If a drug is effective in reducing GC toxicity, AIS should decrease over time in the treatment arm. This score ranges between -346 and 439 [6].

Glucocorticoid toxicity index studies

The GTI has been used in several real-life studies and clinical trials. In a retrospective study which assessed GTI in patients with ANCA associated vasculitis, GTI score was associated with cumulative GC dose. In this study, the most common toxicity parameter was infections which were mostly mild, such as oral candidiasis and varicella zoster [7].

In a post hoc analysis of the Tocilizumab in Giant Cell Arteritis (GIACTA) trial, baseline GTI scores of the giant cell arteritis (GCA) patients was evaluated. The mean GTI score was 111.3 ± 53.2 in the overall group. The domains that caused the greatest increase in GTI score were blood pressure (24.0%), glucose tolerance (22.6%) and neuropsychiatric effects (15.9% of the overall score). Patients with a relapsing disease had higher GTI scores compared to newly-diagnosed GCA patients (GTI relapsing vs newly-diagnosed: 122.5 vs. 98.9; $P < 0.001$) [8].

In the ADVOCATE trial, the RCT investigating the efficacy and safety of avacopan in ANCA associated vasculitis, GTI was designated as a secondary outcome. CWS and AIS were lower in the avacopan group than prednisone group (CWS avacopan vs prednisone: 39.7 vs 56.6 points), (AIS avacopan vs prednisone: 11.2 vs 23.4 points) at 26th week of the study [9].

GC-related toxicity was assessed in lupus nephritis patients using GTI, in a retrospective study. Higher cumulative GC dose was associated with higher CWS and AIS in lupus nephritis patients at 5 years of follow-up [10].

In a Turkish Takayasu arteritis cohort, mean baseline GTI score was 51.5 ± 52.4 and GTI score was correlated with age ($r=0.32$, $p=0.014$), cumulative GC dose ($r=0.34$, $p=0.017$) and the duration of the GC exposure ($r=0.27$, $p=0.041$) [11].

In a study conducted in a rheumatology outpatient clinic, the median (min-max) GTI-AIS score at 6 months was 29 (-42 to 190) in the GC-naive patients and 0 (-82 to 40) in the GC-experienced patients (GC treatment for ≤2 years). Higher cumulative GC dose was associated with higher GTI scores in both groups ($p< 0.001$). In addition, in the GC-naive group, patients with vasculitis had higher GTI scores than inflammatory arthritis ($p< 0.001$) [12].

Table 1. Glucocorticoid toxicity index 2.0 domains and weights of the items [6]

1.Change in Body Weight (BMI)	
Decrease by >/= 5 BMI units	-36
Decrease by >2 but <5 BMI units	-21
No significant change (+/- 2 BMI units)	0
Increase of >2 to <5 BMI units	21
Increase of 5 or more BMI units	36
2. Glucose Metabolism	
Improvement in HbA1c AND decrease in medication	-44
Improvement in HbA1c OR decrease in medication	-32
No significant change	0
Increase in HbA1c OR increase in medication	32
Increase in HbA1c AND increase in medication	44
3. Blood Pressure	
Improvement in BP AND decrease in medication	-44
Improvement in BP OR decrease in medication	-19
No significant change	0
Increase in BP OR increase in medication	19
Increase in BP AND increase in medication	44
4. Hyperlipidemia	
Decrease in LDL AND decrease in medication	-30
Decrease in LDL OR decrease in medication	-10
No significant change	0
Increase in LDL OR increase in medication	10
Increase in LDL AND increase in medication	30
5. Bone Health (BMD)	
Increase in BMD (gain of more than 3%)	-29
No significant change in BMD (+/- 3%)	0
Decrease in BMD (loss of more than 3%)	29
6. Steroid Myopathy	
Moderate weakness to none	-63
Moderate to Mild weakness	-54
Mild weakness to none	-9
No significant change	0
None to Mild weakness (without functional limitation)	9
Mild to Moderate weakness	54
None to Moderate weakness (with functional limitation)	63
7. Skin steroid-related Toxicity	
Decrease in Skin Toxicity - Moderate to None	-26
Decrease in Skin Toxicity - Moderate to Mild	-18
Decrease in Skin Toxicity - Mild to None	-8
No significant change	0
Increase in Skin Toxicity - None to Mild	8
Increase in Skin Toxicity - Mild to Moderate	18
Increase in Skin Toxicity - None to Moderate	26
8. Neuropsychiatric - steroid related symptoms	
Decrease in NP Toxicity - Moderate to None	-74
Decrease in NP Toxicity - Moderate to Mild	-63
Decrease in NP Toxicity - Mild to None	-11
No significant change	
Increase in NP Toxicity - None to Mild	11
Increase in NP Toxicity - Mild to Moderate	63
Increase in NP Toxicity - None to Moderate	71
9. Infection	
No infection	0
Oral or vaginal candidiasis or non-complicated zoster (<Grade3)	19
Grade 3, 4, or 5 infection	93

Limitations and Strengths of Glucocorticoid Toxicity Index

GTI has several weaknesses and limitations as well as strengths. Glucocorticoids have approximately 70 toxicities. Not all of these toxicities are included in the GTI. Toxicities that were common, easy to measure, are of a dynamic nature that may show improvement or worsening of toxicity over time and are more likely to be due to the effect of GC treatment were included in the GTI. Toxicities that were difficult to separate from co-morbidities or the effects of the underlying disease were also excluded. For example, toxicities such as atherosclerosis, myocardial infarction, and stroke were not included in the GTI because all these toxicities are often confounded with either co-morbidities (e.g. smoking) or the effects of the disease under treatment (e.g. systemic lupus erythematosus). Additionally, some GC toxicities occur acutely (within hours to days), others subacutely (weeks to months), and others chronically (months to years). Chronic toxicity may not be captured during GTI assessment [6].

Another limitation is that the toxicities may not be attributed to glucocorticoids alone. Drugs frequently used with GCs may have a synergistic effect with certain GC toxicities. For example, immunomodulatory agents may increase the risk of infection, and this effect may be difficult to distinguish from GCs. Patients may have comorbidities (e.g. obesity, hypertension, etc.) that precede GC treatment and vary across patient populations and disease states [6,13].

Baseline GTI scoring is different from the scoring performed at later follow-up. In the baseline GTI

score, the minimum score is 0 and assesses the patient's current condition. However, subsequent scoring may be negative or positive according to the improvement or worsening of GC toxicity compared to baseline. Therefore, in order to assess the GTI, it is first necessary to calculate the patient's baseline GTI score [5,13]. In patients who have already started glucocorticoid therapy, baseline GTI is calculated at the time point at which GTI is first assessed, not at the time glucocorticoid is first started. It is therefore difficult to interpret the GTI in patients who have already started glucocorticoid therapy and to relate it to cumulative glucocorticoid exposure. On the contrary, it would be more rational to assess the GTI from the time glucocorticoid therapy is initiated.

Several domains in the GTI (such as skin toxicity or neuropsychiatric effects) require direct patient interaction. These domains require careful objective consideration of GC toxicity. Assessing by the same person ensures standardization in these domains and provides more accurate results [6,13].

Finally, GTI scores are difficult to calculate. A digital platform has been developed to facilitate the use and scoring of the GTI but there is a need for a charge for use. The application records the data from the patient visit required for GTI and analyses, tabulates, and scores it in 2-3 minutes. Thus, it provides accurate results in a short time by eliminating the user error. The manual calculation on the other hand can be complicated and lead to errors during calculation and is time-consuming [6,13].

Author contribution

Study conception and design: SKT, MBK; draft manuscript preparation: SKT, MBK. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] McDonough AK, Curtis JR, Saag KG. The epidemiology of glucocorticoid-associated adverse events. Curr Opin Rheumatol 2008;20(2):131-7. https://doi.org/10.1097/BOR.0b013e3282f51031

[2] Rutgeerts P, Löfberg R, Malchow H, et al. A comparison of budesonide with prednisolone for active Crohn's disease. N Engl J Med 1994;331(13):842-5. https://doi.org/10.1056/NEJM199409293311304

[3] Capell HA, Madhok R, Hunter JA, et al. Lack of radiological and clinical benefit over two years of low dose prednisolone for rheumatoid arthritis: Results of a randomised controlled trial. Ann Rheum Dis 2004;63(7):797-803. https://doi.org/10.1136/ard.2003.014050

[4] Wassenberg S, Rau R, Steinfeld P, Zeidler H. Very low-dose prednisolone in early rheumatoid arthritis retards radiographic progression over two years: A multicenter, double-blind, placebo-controlled trial. Arthritis Rheum 2005;52(11):3371-80. https://doi.org/10.1002/art.21421

[5] Miloslavsky EM, Naden RP, Bijlsma JWJ, et al. Development of a Glucocorticoid Toxicity Index (GTI) using multicriteria decision analysis. Ann Rheum Dis 2017;76(3):543-6. https://doi.org/10.1136/annrheumdis-2016-210002

[6] Stone JH, McDowell PJ, Jayne DRW, et al. The glucocorticoid toxicity index: Measuring change in glucocorticoid toxicity over time. Semin Arthritis Rheum 2022;55:152010. https://doi.org/10.1016/j.semarthrit.2022.152010

[7] Floyd L, Morris A, Joshi M, Dhaygude A. Glucocorticoid Therapy in ANCA Vasculitis: Using the Glucocorticoid Toxicity Index as an Outcome Measure. Kidney360 2021;2(6):1002-10. https://doi.org/10.34067/KID.0000502021

[8] Patel NJ, Fu X, Zhang Y, Stone JH. Baseline Glucocorticoid-Related Toxicity Scores in Giant Cell Arteritis: A Post Hoc Analysis of the GiACTA Trial. ACR Open Rheumatol 2023;5(1):51-8. https://doi.org/10.1002/acr2.11520

[9] Jayne DRW, Merkel PA, Schall TJ, Bekker P, ADVOCATE Study Group. Avacopan for the Treatment of ANCA-Associated Vasculitis. N Engl J Med 2021;384(7):599-609. https://doi.org/10.1056/NEJMoa2023386

[10] Usiskin IM, Kyttaris VC. Estimating glucocorticoid-related morbidity in lupus nephritis using the glucocorticoid toxicity index. Lupus 2023;32(4):565-70. https://doi.org/10.1177/09612033231160969

[11] Kaymaz Tahra S, Alibaz Oner F, Direskeneli H. Glucocorticoid related damage assessed with glucocorticoid toxicity index (GTI) in patients with Takayasu's arteritis. 20th International Vasculitis & ANCA Workshop, 2022.

[12] Bahap-Kara M, Sariyildiz E, Zengin HY, Karadag O, Bayraktar-Ekincioglu A. Prospective Assessment of Glucocorticoid Toxicity in Rheumatology Practice: A Focus on the Glucocorticoid Toxicity Index. Rheumatology (Oxford) 2024;keae288. https://doi.org/10.1093/rheumatology/keae288

[13] McDowell PJ, Stone JH, Zhang Y, et al. Quantification of Glucocorticoid-Associated Morbidity in Severe Asthma Using the Glucocorticoid Toxicity Index. J Allergy Clin Immunol Pract 2021;9(1):365-72. https://doi.org/10.1016/j.jaip.2020.08.032

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INVITED REVIEW

Glucocorticoid doses according to tissue/organ involvement in ANCA-associated vasculitis

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ABSTRACT

Antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitides (AAV) are a group of disorders that include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), renal-limited vasculitis, and eosinophilic granulomatosis with polyangiitis (EGPA). Infections and cardiovascular diseases are the main causes of death in patients with AAV. New treatment regimens with low-dose glucocorticoidsare proposed to reduce the frequency of side effects. Studies related to the use of glucocorticoids in AAV patients were searched in the literature and results were summarized. Low-dose steroid protocols are not inferior to standard dose treatment and have fewer side effects. Although their effectiveness appears to be similar and their side effects appear to be less, the long-term results of low-dose regimens should also be evaluated.New studies are needed for alternative treatment regimens.

Keywords: ANCA-associated vasculitis, treatment, glucocorticoid, low-dose regimen.

Introduction

Antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitides (AAV) are a group of disorders that include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), renal-limited vasculitis, and eosinophilic granulomatosis with polyangiitis (EGPA) [1,2].

AAV is a life-threatening disease, especially in untreated patients [3]. The main causes of death in patients with AAV are infections and cardiovascular diseases rather than the disease itself [3]. New treatment regimens with lowertoxicity is proposed for reduced frequency of side effects.

Treatment of AAV consists of remission induction and maintenance therapies. The affected organ and severity determine induction therapy. Kidney involvement in AAV has a great impact on survival and long-term prognosis. High doses of glucocorticoids are the cornerstone of the treatment but low-dose regimens are being considered due to long-term side effects.

Organ-life-threatening manifestations of AAV are glomerulonephritis, pulmonary hemorrhage, cerebral vasculitis, progressive peripheral or cranial neuropathy, orbital pseudotumor, scleritis, gastrointestinal hemorrhage, and cardiac involvement [4]. Episcleritis,non-cavitating pulmonary nodules, skin involvement without ulceration, myositis, and nasal and paranasal disease without bony involvement or cartilage collapse or olfactory dysfunction or deafness are identified as non-organ-life-threatening manifestations of AAV [4].

In patients with non-organ-life-threatening manifestations, methotrexate combined with 0.5 mg/kg/day prednisolone equivalent is the treatment of choice. Maintenance treatment is planned according to a low-dose regimen [5].

In organ-life-threatening disease 1 mg/kg/day prednisolone equivalent is the preferred

regimen. In the presence of rapidly progressive glomerulonephritis, alveolar hemorrhage, mononeuritis multiplex, or optic neuritis pulse steroid (1 g/day) is recommended. A low-dose regimen is used in combination with immunosuppressives. In refractory disease or relapse, it is recommended to use glucocorticoids for 4-6 months, tapering off more slowly [6].

Current literature contains studies comparing low-dose and standard-dose glucocorticoid regimens. Of these, the PEXIVAS trial is an important study conducted in patients with severe ANCA-associated vasculitis to compare the efficacy of plasma exchange with no plasma exchange with respect to death or end-stage kidney disease (ESKD).The PEXIVAS trial also compared the reduced-dose regimen of glucocorticoids with a standard-dose regimenover the first 6 months of the treatment period to determine whether the reduced dose was non-inferiorto the standard dose concerningdeath or ESKD [6]. Table 1 shows the glucocorticoid doses of patients in both groups.

It has been observed that the low-dose glucocorticoid regimen is not inferior to the standard dose regimen on mortality and end-stage CRF and has fewer side effects.

In the LoVAS study [3], patients were randomized to receive reduced-dose prednisolone(0.5mg/kg/d) plus rituximab (RTX) (375mg/m2/wk, 4 doses) (n = 70) or high-dose prednisolone (1mg/kg/d) plus RTX (n = 70). In newly diagnosed GPA patients (without severe GN or alveolar hemorrhage), combined therapy of low-dose glucocorticoid and RTX is non-inferior to the combination of high-dose glucocorticoid and RTX.Infections and other GC-related side effects were less common in patients receiving a low-dose treatment regimen.

EULAR recommendations for the management of AAV were published in 2022. As part of regimens for induction of remission in GPA orMPA, treatment with oral GCs at a starting doseof 50–75 mg prednisolone equivalent/day, depending on body weight is recommended. stepwise reduction in GCs according toPEXIVAS protocoland achieving a dose of 5 mg prednisolone equivalent perday for 4–5 months [7].

In patients with new-onset or relapsed EGPA, a combination of high-dose glucocorticoids and cyclophosphamide is recommended if there is a life/organ-threatening situation. Unlike MPA and GPA, EGPA does not have a different glucocorticoid protocol. A similar protocol can be used, but asthma and ear-nose-throat (ENT) exacerbations may increase steroid requirements, and tapering may take longer. Glucocorticoid treatment is recommended for remission induction in patients with new-onset or relapsed EGPA, even if there is no life/organ-threatening condition. In the absence of poor prognostic factors, remission is achieved in >90% of patients treated with GC alone.

Table 1. Glucocorticoid doses in standard and reduced-dose groups in the PEXIVAS trial

Week	Standard			Reduced-dose		
	<50 kg	50-75 kg	>75 kg	<50 kg	50-75 kg	>75 kg
	Pulse	Pulse	Pulse	Pulse	Pulse	Pulse
1	50	60	75	50	60	75
2	50	60	75	25	30	40
3-4	40	50	60	20	25	30
5-6	30	40	50	15	20	25
7-8	25	30	40	12.5	15	20
9-10	20	25	30	10	12.5	15
11-12	15	20	25	7.5	10	12.5
13-14	12.5	15	20	6	7.5	10
15-16	10	10	15	5	5	7.5
17-18	10	10	15	5	5	7.5
19-20	7.5	7.5	10	5	5	5
21-22	7.5	7.5	7.5	5	5	5
23-52	5	5	5	5	5	5
>52	Investigator's local practice			Investigator's local practice		

Relapse is common when the dose is reduced, but studies with immunosuppressives have shown that they do not affect recurrence. In this case, there is no recommended reduction scheme, it is recommended to make an individual decision by evaluating the risks of recurrence and infection [7].

Avacopan is a complement 5a receptor inhibitor and according to EULAR and ACR recommendations, avacopan reduces exposure to glucocorticoids. But long-term results are not known yet.

It seems that low-dose steroid protocols are not inferior to standard dose treatment and have fewer side effects. New studies are needed for alternative treatment regimens.

Author contribution

Study conception and design: NŞYB; draft manuscript preparation: NŞYB. All authors reviewed the results and approved the final version of the manuscript.

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REFERENCES

[1] Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 2013;65(1):1-11. https://doi.org/10.1002/art.37715

[2] Jennette JC, Falk RJ, Andrassy K, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum 1994;37(2):187-92. https://doi.org/10.1002/art.1780370206

[3] Furuta S, Nakagomi D, Kobayashi Y, et al. LoVAS Collaborators. Effect of Reduced-Dose vs High-Dose Glucocorticoids Added to Rituximab on Remission Induction in ANCA-Associated Vasculitis: A Randomized Clinical Trial. JAMA 2021;325(21):2178-87.

[4] Casal Moura M, Gauckler P, Anders HJ, et al. Management of antineutrophil cytoplasmic antibody-associated vasculitis with glomerulonephritis as proposed by the ACR 2021, EULAR 2022 and KDIGO 2021 guidelines/recommendations. Nephrol Dial Transplant 2023;38(11):2637-51. https://doi.org/10.1093/ndt/gfad090

[5] Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. N Engl J Med 2005;352(4):351-61. https://doi.org/10.1056/NEJMoa041884

[6] Walsh M, Merkel PA, Peh CA, et al. PEXIVAS Investigators. Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis. N Engl J Med 2020;382(7):622-31.

[7] Hellmich B, Sanchez-Alamo B, Schirmer JH, et al. EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. Ann Rheum Dis 2024;83(1):30-47. https://doi.org/10.1136/ard-2022-223764

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INVITED REVIEW

Glucocorticoids in IgA vasculitis

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ABSTRACT

IgA vasculitis (IgAV) is an immune complex vasculitis affecting small vessels characterized by IgA1 immune deposits. IgA vasculitis typically resolves spontaneously in most cases, especially in pediatric cases but may have more severe outcomes in adults and the optimal treatment for IgAV remains controversial. Although glucocorticoids are the mainstay of treatment, studies are investigating the role of alternative immunosuppressive agents and biologics, particularly in adult onset, severe or resistant cases. The efficacy of glucocorticoids appears to vary according to the specific manifestations and severity of IgAV. They may be effective in treating complications when combined with immunosuppressive agents but glucocorticoids should not be used prophylactically as they do not prevent complications.

Keywords: disease management, glucocorticoids, IgA vasculitis.

Introduction

IgA vasculitis (IgAV), formerly known as Henoch-Schönlein purpura, is an immune complex vasculitis affecting small vessels characterized by IgA1 immune deposits. IgAV can affect both children and adults, and its clinical course, prognosis and treatment approaches differ. IgAV affects multiple organs, including the skin, joints, gastrointestinal tract, and kidneys [1]. IgAV is the most common pediatric vasculitis, with nephritis (IgAVN) being its most significant chronic manifestation [2]. IgA vasculitis typically resolves spontaneously in most cases, especially in pediatric cases but may have more severe outcomes in adults [3-5]. Adult-onset IgAV is associated with more severe skin and renal involvement, including ulcerative lesions and nephrotic-range proteinuria [6].

Several factors are associated with organ dysfunction or damage in this condition. Renal involvement is a major concern, with risk factors including older age at onset, lower glomerular filtration rate, nephrotic or nephritic-nephrotic syndrome, and crescentic nephritis on biopsy [7]. Gastrointestinal involvement and elevated diastolic blood pressure are also predictive of renal involvement [8]. Long-term end-stage renal disease is associated with baseline renal dysfunction, proteinuria, and specific histological findings [5].A subset of IgAV patients experience renal complications that may persist and relapse [1]. Infections, particularly bacterial and viral, are common triggers of IgA vasculitis [9]. Relapses in IgA vasculitis (IgAV) are common and are associated with several factors. In IgAV, younger age and lack of initial glucocorticoid treatment are associated with higher relapse rates [10]. Other factors include older age at onset, persistent rash, abdominal pain, haematuria, underlying disease, severe leukocytoclasis and absence of IgM deposition on vessel walls [11]. Understanding these risk factors may help to guide monitoring and treatment strategies for IgAV patients.

Glucocorticoids in management

Glucocorticoids are commonly used to treat IgA vasculitis but their effectiveness remains controversial. Some immunosuppressive agents, such as azathioprine, cyclophosphamide, cyclosporine, mycophenolate, rituximab, and dapsone have been used in combination with glucocorticoids, but their effectiveness has not been definitively established [12,13].

Treatment approaches for pediatric IgAV vary widely, with glucocorticoids being the primary intervention. A large cohort study found that conservative management, including observation and RAAS blockade, was the most common approach for IgAVN, with immunosuppression reserved for more severe cases. Overall, renal outcomes were generally favorable, with low rates of chronic kidney disease and renal failure [14]. For mild cases, oral glucocorticoids are recommended, while moderate to severe cases may require parenteral or pulsed doses [2]. However, there is considerable variability in glucocorticoid dosing, and higher doses do not necessarily lead to improved outcomes [15]. Cyclophosphamide is sometimes used for severe cases, but its efficacy in preventing progression of nephritis is questionable [16].

Treatment approaches for adult IgAV vary depending on disease severity. For moderate to severe cases, systemic steroids are recommended [3]. High-dose methylprednisolone followed by oral steroids has shown success in managing severe abdominal symptoms. In cases of organ-threatening IgAV, combination therapies including systemic corticosteroids, oral immunosuppressants, rituximab, and cyclophosphamide have been used [4]. For glomerulonephritis and other complications, high-dose steroids, cyclosporine, and mycophenolate have demonstrated efficacy in randomized trials [1]. Long-term prognosis depends on the extent of renal involvement, necessitating follow-up to assess for relapse or remission. Rituximab has shown promise in treating adult IgA vasculitis with nephritis, achieving complete remission in some cases. Rituximab, an anti-CD20 monoclonal antibody, has shown promise in treating steroid-dependent IgAV cases, particularly those with gastrointestinal involvement [17]. However, the optimal treatment for adult IgAV remains controversial, and more research is needed to establish standard protocols for various treatment options in managing IgAV and preventing relapses. In cases of severe abdominal pain resistant to corticosteroids, intravenous γ globulin has shown promise as a safe alternative [18].

The long-term use of glucocorticoids in IgAV remains controversial. Studies have shown that steroids do not prevent complications and should not be used prophylactically. However, high-dose steroids may be beneficial in treating glomerulonephritis and other severe complications [1]. For chronic cutaneous IgAV, corticosteroids are often ineffective [19]. Relapse of IgAV occurs in about 15% of patients, more frequently in younger patients and those without baseline glucocorticoid treatment [10].Intravenous steroid pulses have shown a lower relapse risk compared to oral steroids in IgA nephropathy treatment. In patients receiving steroid therapy, relapse, non-remission, time-averaged eGFR, and time-averaged serum albumin are independent predictors of long-term prognosis [20].

In summary, the optimal treatment for IgAV remains controversial. Although glucocorticoids are the mainstay of treatment, studies are investigating the role of alternative immunosuppressive agents and biologics, particularly in adult onset, severe or resistant cases. The efficacy of glucocorticoids appears to vary according to the specific manifestations and severity of IgAV. They may be effective in treating complications when combined with immunosuppressive agents, but systematic reviews suggest that steroids should not be used prophylactically as they do not prevent complications. Further research is therefore needed to determine optimal treatment strategies for IgA vasculitis.

Author contribution

Study conception and design: BA; draft manuscript preparation: BA. All authors reviewed the results and approved the final version of the manuscript.

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REFERENCES

[1] Reamy BV, Servey JT, Williams PM. Henoch-Schönlein Purpura (IgA Vasculitis): Rapid Evidence Review. Am Fam Physician 2020;102(4):229-33.

[2] Sestan M, Jelusic M. Diagnostic and Management Strategies of IgA Vasculitis Nephritis/Henoch-Schönlein Purpura Nephritis in Pediatric Patients: Current Perspectives. Pediatric Health Med Ther 2023;14:89-98. https://doi.org/10.2147/PHMT.S379862

[3] Amarapur M, Biradar S. Adult-onsetimmunoglobulin A vasculitis. APIK J Int Med 2021;9:120-2. https://doi.org/10.4103/AJIM.AJIM_6_20

[4] Cai F, Phipps L, Wu P, Lin MW. A Case Series of Adult Patients Diagnosed with IgA Vasculitis Requiring Systemic Immunosuppression. Am J Case Rep 2021;22:e933407. https://doi.org/10.12659/AJCR.933407

[5] Audemard-Verger A, Pillebout E, Guillevin L, Thervet E, Terrier B. IgA vasculitis (Henoch-Shönlein purpura) in adults: Diagnostic and therapeutic aspects. Autoimmun Rev 2015;14(7):579-85. https://doi.org/10.1016/j.autrev.2015.02.003

[6] Villatoro-Villar M, Crowson CS, Warrington KJ, Makol A, Ytterberg SR, Koster MJ. Clinical Characteristics of Biopsy-Proven IgA Vasculitis in Children and Adults: A Retrospective Cohort Study. Mayo Clin Proc 2019;94(9):1769-80. https://doi.org/10.1016/j.mayocp.2019.04.034

[7] Shi D, Chan H, Yang X, et al. Risk factors associated with IgA vasculitis with nephritis (Henoch-Schönlein purpura nephritis) progressing to unfavorable outcomes: A meta-analysis. PLoS One 2019;14(10):e0223218. https://doi.org/10.1371/journal.pone.0223218

[8] Demirtaş S, Dursun İ, Pınarbaşı AS, et al. The Factors Affecting the Occurrence of Renal Involvement in Children with IgA Vasculitis: Renal Involvement of IgA Vasculitis. The Journal of Pediatric Academy 2020;1(2):50-5. https://doi.org/10.38092/JPA-2020-9

[9] Sugino H, Sawada Y, Nakamura M. IgA Vasculitis: Etiology, Treatment, Biomarkers and Epigenetic Changes. Int J Mol Sci 2021;22(14):7538. https://doi.org/10.3390/ijms22147538

[10] Hočevar A, Ostrovršnik J, Jurčić V, Tomšič M, Rotar Ž. Short-term outcome of patients with adult IgA vasculitis: A single-center experience. Front Med (Lausanne) 2023;10:1210307. https://doi.org/10.3389/fmed.2023.1210307

[11] Byun JW, Song HJ, Kim L, Shin JH, Choi GS. Predictive factors of relapse in adult with Henoch-Schönlein purpura. Am J Dermatopathol 2012;34(2):139-44. https://doi.org/10.1097/DAD.0b013e3182157f90

[12] Maritati F, Fenoglio R, Pillebout E, et al. Brief Report: Rituximab for the Treatment of Adult-Onset IgA Vasculitis (Henoch-Schönlein). Arthritis Rheumatol 2018;70(1):109-14. https://doi.org/10.1002/art.40339

[13] Schinzel V, Fernandez JD, Clemente G, et al. The profile and clinical outcomes of patients with renal involvement due to IgA vasculitis: Is azathioprine a good option for treatment?. Adv Rheumatol 2019;59(1):21. https://doi.org/10.1186/s42358-019-0064-x

[14] Stone HK, Mitsnefes M, Dickinson K, et al. Clinical course and management of children with IgA vasculitis with nephritis. Pediatr Nephrol 2023;38(11):3721-33. https://doi.org/10.1007/s00467-023-06023-8

[15] Chen XQ, Tu L, Zou JS, Zhu SQ, Zhao YJ, Qin YH. The Involvement of Neutrophil Extracellular Traps in Disease Activity Associated With IgA Vasculitis. Front Immunol 2021;12:668974. https://doi.org/10.3389/fimmu.2021.668974

[16] KobrovÃ K, MinxovÃ L, Zieg J, et al. Severe IgA Vasculitis: Cyclophoshamide in Question Annals of the Rheumatic Diseases 2019;78:1965. https://doi.org/10.1136/annrheumdis-2019-eular.6731

[17] Zhang X, Ji L, Zhang H, Zhang Z. Successful treatment of rituximab in a steroid-dependent immunoglobulin A vasculitis patient with gastrointestinal involvement: A case report. Scand J Rheumatol 2023;52(3):324-5. https://doi.org/10.1080/03009742.2022.2154525

[18] Naifa G, Totikidis G, Alexiadou S, Kolona C, Mantadakis E. Intravenous γ Globulin for Intractable Abdominal Pain due to IgA Vasculitis. Case Rep Pediatr 2020;2020:8867621. https://doi.org/10.1155/2020/8867621

[19] Bech AP, Reichert LJ, Cohen Tervaert JW. Dapsone for the treatment of chronic IgA vasculitis (Henoch-Schonlein). Neth J Med 2013;71(4):220-1.

[20] Laranjinha I, Matias P, Cassis J, et al. IGA nephropathy - Are intravenous steroid pulses more effective than oral steroids in relapse prevention?. Nefrologia (Engl Ed) 2018;38(4):355-60. https://doi.org/10.1016/j.nefro.2017.08.004

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INVITED REVIEW

The use of glucocorticoids in Behçet's disease

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ABSTRACT

Behçet's disease (BD) is a chronic, multifactorial inflammatory disorder characterized by episodic involvement of multiple systems, including mucocutaneous, ocular, vascular, gastrointestinal, joint, and neurological domains. Glucocorticoids (GC) play a pivotal role in managing BD, especially during acute flares and severe organ involvement. This review highlights the tailored use of GC across various manifestations of BD. For mucocutaneous lesions, topical GC are effective, where as short-term low-dose systemic GC are reserved for colchicine-resistantcases. In ocular BD, systemic GC are in dispensable for sight-threatening conditions, often combined with disease-modifying anti-rheumatic drugs (DMARDs) or biologics to minimize GC dependency. In vascular involvement, particularly pulmonary artery aneurysms, high-dose or pulse GC are essential to control vessel wall inflammation, often alongside immunosuppressive agents like cyclophosphamide. Neurological BD necessitate surgent high-dose GC therapy, complemented by DMARDs for sustained control. Joint involvement can be managed with intraarticular GC, reducing systemic exposure. In gastrointestinal BD, GC use is limited due to potential mucosal irritation, with biologics and DMARDs serving as adjunctive options. Across all manifestations, GC tapering is prioritized to mitigate adverse effects, while combination therapy with DMARDs or biologics ensures comprehensive disease control. This comprehensive review underscores the critical role of GC in BD management, advocating for individualized treatment strategies to balance efficacy and safety.

Keywords: Behçet's disease, glucocorticoids, anti-inflammatory agents, mucocutaneous lesions, vascular, ocular, systemic inflammation, immunomodulatory treatment.

Introduction

Behçet's disease (BD) is a multifactorial, chronic inflammatory disease with an unknown etiopathogenesis, characterized by recurrent manifestations of oral and genital aphthousulcers, uveitis, erythema-nodosum-like lesions, arthritis, and involvement of major vessels, gastrointestinal, and central nervoussystems [1,2]. Given its natural course as a relapsing and remitting disease, the primary goal of treatment is to suppress flare-ups and prevent long-term damage. Treatment options include immunomodulatory agents, primarilyglucocorticoids (GC), disease-modifying anti-rheumaticdrugs (DMARDs), and biologics. The treatment regimen should be tailored to the patient's characteristics (such as gender, age, fertility expectations, comorbidities, and major organ involvement), as well as prognostic factors and the disease's activity and severity [3]. Major organ involvement serves as a warning sign of BD, with ocular, vascular, neurologic, and gastrointestinal involvement associated with a poor prognosis, requiring the administration of immunosuppressive therapy [4,5].

Glucococorticoids are available in several forms, including topical, oral, and systemic routes. The choice of type and dosage of GC should be individualized, and the lowest effective dose should be used for the shortest possible duration to minimize adverse effects. In Figure 1, we summarize the EULAR treatment guidelines based on organ involvement and the forms of GC used [6,7].

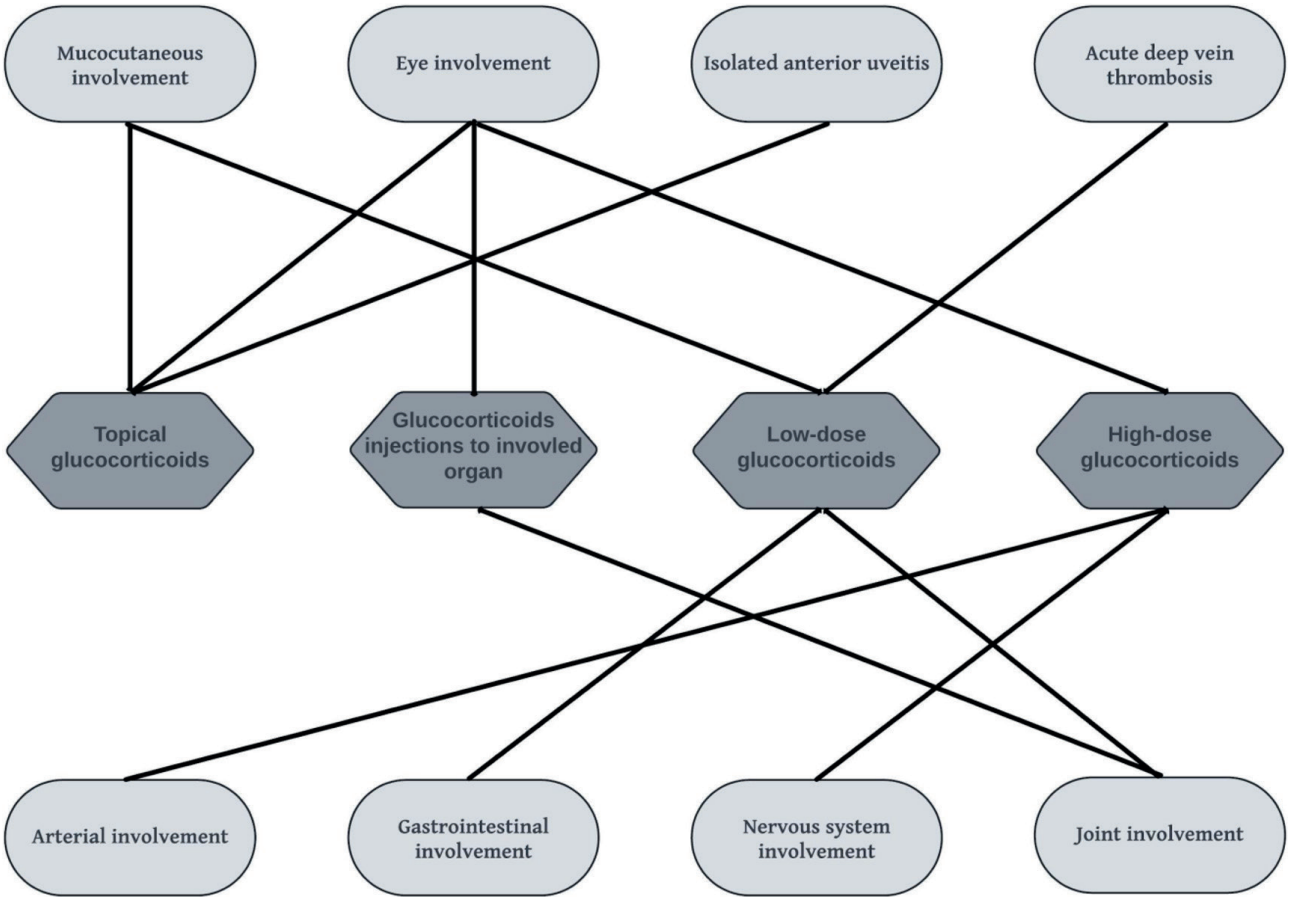

Figure 1. The main disease manifestation groups and used of glucocorticoids according to administration route and dose [7].

Glucocorticoids treatment in mucocutaneous involvement

Mucocutanous involvement includes oral aphtae, genital ulcers, papulopustular and acne-like lesions, erythema nodosum. Although colchicine is the main treatment agent for mucocutaneous involvement, glucocorticoids may also be used in various forms. For oral aphthae, genital ulcers, and papulopustular lesions, topical GC can be used without the risk of systemic adverse effects. In colchicine-resistant or intolerant patients, short-term, low-dose GC can be effective in all manifestations of mucocutaneous involvement, particularly erythema nodosum [8].

Glucocorticoids treatment in eye involvement

The prototype lesion of eye involvement in BD is uveitis, particularly affecting the posterior segment. Uveitis is more common in younger patients and males, and timely, effective treatment is crucial to suppress inflammation, prevent recurrence, and avoid permanent decrease in visual acuity or vision loss. The use and dosage of GC should be determined based on the severity of eye involvement and the presence of sight-threatening conditions. It is highly recommended to combine GC with systemic DMARDs or biologics to reduce GC dependency, and they never be used as a monotherapy [9].

Isolated anterior uveitis, on the other hand, can be managed with topical agents alone [10]. Intravitreal injections of GC may be used as an adjunctive treatment option to systemic treatment, especially in case of single-eye involvement [7]. High-dose systemic GC are employed for rapid control of acute-attacks but should be tapered as soon as the effects of concomitantly used immunosuppressive agents become apparent.

Glucocorticoids treatment in acute deep vein thrombosis

In BD patients, thrombosis is considered a result of inflammation rather than hypercoagulability. Therefore, anti-inflammatory treatment is the cornerstone of management rather than anticoagulation. The primary goals are the early and effective control of thrombosis, the preservation of vascular flow, or the achievement of re-canalization,

all of which are crucial to preventing chronic leg ulcerations and post-thrombotic syndrome. In most cases, low-dose GC and DMARDs combination is recommended and successful, but in refractory cases biologics and addition of anti-coagulant can be needed [11].

Glucocorticoids treatment in arterial involvement

The most frequent arterial involvement in BD is pulmonary artery aneurysms and thrombosis, both of which carry a high risk of increased morbidity and mortality. Aortic and peripheral aneurysms as well as rare instances of thrombosis, are also observed. In selected cases, surgical or endovascular repair, in addition to systemic treatment, may be considered. In all cases, high-dose GC should be initiated to control vessel wall inflammation and prevent complications. For pulmonary artery involvement, initial pulse GC are administered. For invasive procedures, preoperative administration of GC is crucial to enhance perioperative success and prevent postoperative complications and recurrences. Given the severity of the disease manifestations and the need for long-term immunosuppression, the addition of potent systemic agents like cyclophosphamide or TNF-alpha blockers, along with adjunctive DMARDs, should be initiated as soon as possible [12].

Glucocorticoids treatment in gastrointestinal involvement

Gastrointestinal involvement is a less common but significant manifestation of BD, requiring careful diagnostic evaluation to exclude other inflammatory and infectious causes. For the rapid healing of ulcers and control of acute exacerbations, GC can be used. However, due to their mucosal irritation effects, high-dose GC use is not recommended, particularly in cases where there is a risk of perforation. In managing these cases, a combination of locally effective agents, DMARDs, and biologics should be included in the treatment plan [13].

Glucocorticoids treatment in joint involvement

In cases of acute monoarthritis, intra articular GC can be administered after the aspiration of excess synovial fluid, there by reducing the need for systemic immunosuppressive therapy and GC. However, in cases of recurrent monoarthritis or oligo/polyarthritis that are refractory to colchicine, low-dose GC can be used in conjunction with DMARDs, for the shortest duration possible [14,15].

Glucocorticoids treatment in nervous system involvement

In both types of acute central nervous system involvement—parenchymal involvement and cerebral venous thrombosis—urgent treatment with high-dose GC is required. To better control inflammation and facilitate GC tapering, at least one DMARD should be initiated alongside GC [16].

Conclusion

In summary, for mucocutaneous involvement, topical GC are typically sufficient, with short-term low-dose GC reserved for rare, resistant cases. In joint involvement, intra articular or low-dose GC can be used as well. However, in acute flares involving the ocular, vascular, gastrointestinal, and nervous systems, GC remain the primary and life-saving initial therapy. Long-term and high-dose GC should be avoided due to their adverse effects, and the use of combinations with DMARDs and biologics, along with careful tapering, can help minimize these effects and reduce the cumulative GC dose.

Author contribution

Study conception and design: RD, CB; draft manuscript preparation: RD, CB. All authors reviewed the results and approved the final version of the manuscript.

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REFERENCES

[1] Gül A. Behçet's disease as an autoinflammatory disorder. Curr Drug Targets Inflamm Allergy 2005;4(1):81-3. https://doi.org/10.2174/1568010053622894

[2] Gül A. Pathogenesis of Behçet's disease: Autoinflammatory features and beyond. Semin Immunopathol 2015;37(4):413-8. https://doi.org/10.1007/s00281-015-0502-8

[3] Hatemi G, Uçar D, Uygunoğlu U, Yazici H, Yazici Y. Behçet Syndrome. Rheum Dis Clin North Am 2023;49(3):585-602. https://doi.org/10.1016/j.rdc.2023.03.010

[4] Çakan ZK, Yağız B, Pehlivan Y. Clinical features of Behçet's disease and prediction of the use of biologics in 488 cases: A single tertiary center study. Rheumatol Int 2023;43(11):2089-97. https://doi.org/10.1007/s00296-023-05416-0

[5] Yazici Y, Hatemi G, Bodaghi B, et al. Behçet syndrome. Nat Rev Dis Primers 2021;7(1):67. https://doi.org/10.1038/s41572-021-00301-1

[6] Ozguler Y, Leccese P, Christensen R, et al. Management of major organ involvement of Behçet's syndrome: A systematic review for update of the EULAR recommendations. Rheumatology (Oxford) 2018;57(12):2200-12. https://doi.org/10.1093/rheumatology/key242

[7] Hatemi G, Christensen R, Bang D, et al. 2018 update of the EULAR recommendations for the management of Behçet's syndrome. Ann Rheum Dis 2018;77(6):808-18. https://doi.org/10.1136/annrheumdis-2018-213225

[8] Leccese P, Ozguler Y, Christensen R, et al. Management of skin, mucosa and joint involvement of Behçet's syndrome: A systematic review for update of the EULAR recommendations for the management of Behçet's syndrome. Semin Arthritis Rheum 2019;48(4):752-62. https://doi.org/10.1016/j.semarthrit.2018.05.008

[9] Li B, Li H, Huang Q, Zheng Y. Optimizing glucocorticoid therapy for Behçet's uveitis: Efficacy, adverse effects, and advances in combination approaches. Int Ophthalmol 2023;43(11):4373-81. https://doi.org/10.1007/s10792-023-02808-w

[10] Parvizi S, Petrushkin H, Foot B, Stanford MR. Incidence of ophthalmic involvement in Behçet's disease in the United Kingdom: A British Ophthalmic Surveillance Unit (BOSU) study. Eye (Lond) 2022;36(5):1074-9. https://doi.org/10.1038/s41433-021-01585-z

[11] Emmi G, Bettiol A, Silvestri E, et al. Vascular Behçet's syndrome: An update. Intern Emerg Med 2019;14(5):645-52. https://doi.org/10.1007/s11739-018-1991-y

[12] Bettiol A, Alibaz-Oner F, Direskeneli H, et al. Vascular Behçet syndrome: From pathogenesis to treatment. Nat Rev Rheumatol 2023;19(2):111-26. https://doi.org/10.1038/s41584-022-00880-7

[13] Hatemi I, Hatemi G, Çelik AF. Gastrointestinal Involvement in Behçet Disease. Rheum Dis Clin North Am 2018;44(1):45-64. https://doi.org/10.1016/j.rdc.2017.09.007

[14] Tono T, Kikuchi H, Sawada T, et al. Clinical features of Behçet's disease patients with joint symptoms in Japan: A national multicenter study. Mod Rheumatol 2022;32(6):1146-52. https://doi.org/10.1093/mr/roab092

[15] Hatemi G, Seyahi E, Fresko I, Talarico R, Hamuryudan V. One year in review 2018: Behcet's syndrome. Clin Exp Rheumatol 2018;36(6Suppl115):13-27.

[16] Uygunoğlu U, Siva A. Nervous system involvement in Behçet's syndrome. Curr Opin Rheumatol 2019;31(1):32-9. https://doi.org/10.1097/BOR.0000000000000562

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INVITED REVIEW

Why are glucocorticoids recommended at a high dose in the Takayasu arteritis guidelines?

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ABSTRACT

Takayasu arteritis is one the large vessel vasculitis affecting the aorta and major branches. Glucocorticoid treatment plays an important role in the treatment of this disease, as in all vasculitis.According to the most recent evidence, theguidelines suggested initiating GCs at high dosages, particularly in patients who had just received a diagnosis. This review aims to analyze this research and identify the rationale behind the current guidelines' recommendations.

Keywords: glucocorticoids, large vessel vasculitis, Takayasu arteritis.

Introduction

Takayasu arteritis (TA) is a large vessel vasculitis that often affects women and involves the aorta and its major branches. Although it is predominantly an insidious disease, it can escalate to fatal complications in some patients (myocardial infarction, stroke, etc.) [1]. The treatment of TA is challenging, because of the rarity and heterogeneity of the disease. The disease can present with a range of clinical symptoms, including fever, weight loss, malaise, and vascular problems [2]. Additionally, observational studies involving a small number of patients provide the majority of the data for management of the disease [3].

Glucocorticoid Therapy in Takayasu arteritis

In the management of TA, glucocorticocorticoids (GCs) consistently served the main role. Nevertheless, there is insufficient data to determine the optimal GC dose and duration in TA treatment [4].

GC monotherapy is a treatment option that has been previously examined in TA [5, 6]. In a systematic review and meta-analysis which included 28 observational studies and totally 1098 patients with TA assessed the clinical response, normalization of acute phase reactants (APRs), relapses and adverse events after GC monotherapy [5]. The study concluded, nearly 60% of the patients experienced clinical response, 84% of the patients had normalization of the APRs, and 66% of the patients had relapses under GC monotherapy. High relapse rates during GC tapering seem to be a major concern with GC monotherapy. In a study, TA patients who received high dose GCs for remission induction and continued with GC tapering after remission had a relapse incidence of 96%. The median GC dose at the time of relapse was reported as 10 mg/day [7].

In the systemic literature review of The European Alliance of Associations for Rheumatology (EULAR) guideline, no research has centered on

the role of GCs in TA; so they mentioned the GC recommendations as low level of evidence (LoE) 1b [3]. When tocilizumab versus GC monotherapy (0.2 mg/kg/day) given to TA patients presenting with relapse was evaluated, relapse was observed in 80% of patients receiving GC monotherapy during dose reduction between 8-16 weeks [8]. In this study, starting in week 4, the GC dose was reduced by 10% every week until it was at least 0.1 mg/kg/day. Similarly, in the randomized double-blind study of abatacept, in patients with TA, a 60% relapse rate was seen in the GC monotherapy group, in which treatment was initiated with 40-60 mg/day GC and gradually reduced [9]. This 60% relapse rate was reported in the 12th week, when the GC dose was decreased to 20 mg/day and in the study protocol the GC dose was reduced to 0 mg in the week 28.

Currently, immunosuppressive therapies, conventional synthetic (cs), and biological (b) disease modifying anti-rheumatic drugs (DMARDs) are recommended in addition to GCs in *American College of Rheumatology* (ACR) Vasculitis Foundation Guideline for the Management of LVV which is the most recent guideline for LVV management [10]. According to recent studies, the majority of the patients in high experienced vasculitis clinics are treated with immunosuppressive therapies in addition to GCs.In a study from National Institutes of Health (NIH) and the Vasculitis Clinical Research Consortium 86% of the TA patients received csDMARDs and 52% of the TA patientsreceived bDMARDs [2]. However, evidence supporting prioritization of a specific DMARD for the management of TA is an unmet need [11].

In the EULAR recommendations for the management of LVV, starting the therapy with 40-60 mg/day high dose GCs with a csDMARD was recommended in TA with LoE of 4 [12]. According to the ACR Vasculitis Foundation Guideline for the Management of LVV [10], for the patients with active, severe TA initiating therapy with high-dose GCs was recommended over low-dose (very low level of evidence). This recommendation is based on the aforementioned study [4], which highlights the substantial risk of relapse with low dose GC treatment. In this study, it was also shown that lower GC dose during active disease is a predictor for future relapses. So they concluded that a starting dose of GC monotherapy below 30 mg/day should be avoided even if disease activity seems mild at the time of diagnosis, according to the results of the study [4]. Studies that report the reverse also exist. In a Chinese cohort including 566 patients with TA, the treatment was started with a moderate dose of GC monotherapy in 85% of the patients and [6] authors, recommended moderate doses of GC therapy for the initial management of TA. In another study, starting with 1mg/kg/day or 0.5 mg/kg/day GC in addition to immunosuppressives was compared in patients with TA, and the cumulative risk of relapse was found to be similar [13]. Another study [14] reported that, adding bDMARD allows the GC dose to be reduced in relapsing TA patients.

Conclusion

Regarding the dosage of GC in the treatment of TA, further research is needed. Current guidelines including both the ACR and the EULAR, are based on a limited number of studies. According to the latest data, these guidelines recommended starting GCs with high doses, especially in newly-diagnosed patients ; in order to control the disease activity, reduce relapses, get possible positive effects on certain outcomes such as mortality.

Author contribution

Study conception and design: GKA; draft manuscript preparation: GKA. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] Misra DP, Rathore U, Mishra P, et al. Comparison of Presentation and Prognosis of Takayasu Arteritis with or without Stroke or Transient Ischemic Attack-A Retrospective Cohort Study. Life (Basel) 2022;12(11):1904. https://doi.org/10.3390/life12111904

[2] Quinn KA, Gribbons KB, Carette S, et al. Patterns of clinical presentation in Takayasu's arteritis. Semin Arthritis Rheum 2020;50(4):576-81. https://doi.org/10.1016/j.semarthrit.2020.04.012

[3] Águeda AF, Monti S, Luqmani RA, et al. Management of Takayasu arteritis: A systematic literature review informing the 2018 update of the EULAR recommendation for the management of large vessel vasculitis. RMD Open 2019;5(2):e001020. https://doi.org/10.1136/rmdopen-2019-001020

[4] Mutoh T, Shirai T, Fujii H, Ishii T, Harigae H. Insufficient Use of Corticosteroids without Immunosuppressants Results in Higher Relapse Rates in Takayasu Arteritis. J Rheumatol 2020;47(2):255-63. https://doi.org/10.3899/jrheum.181219

[5] Misra DP, Rathore U, Patro P, Agarwal V, Sharma A. Corticosteroid monotherapy for the management of Takayasu arteritis-a systematic review and meta-analysis. Rheumatol Int 2021;41(10):1729-42. https://doi.org/10.1007/s00296-021-04958-5

[6] Yang L, Zhang H, Jiang X, et al. Clinical manifestations and longterm outcome for patients with Takayasu arteritis in China. J Rheumatol 2014;41(12):2439-46. https://doi.org/10.3899/jrheum.140664

[7] Maksimowicz-McKinnon K, Clark TM, Hoffman GS. Limitations of therapy and a guarded prognosis in an American cohort of Takayasu arteritis patients. Arthritis Rheum 2007;56(3):1000-9. https://doi.org/10.1002/art.22404

[8] Nakaoka Y, Isobe M, Takei S, et al. Efficacy and safety of tocilizumab in patients with refractory Takayasu arteritis: Results from a randomised, double-blind, placebo-controlled, phase 3 trial in Japan (the TAKT study). Ann Rheum Dis 2018;77(3):348-54. https://doi.org/10.1136/annrheumdis-2017-211878

[9] Langford CA, Cuthbertson D, Ytterberg SR, et al. A Randomized, Double-Blind Trial of Abatacept (CTLA-4Ig) for the Treatment of Takayasu Arteritis. Arthritis Rheumatol 2017;69(4):846-53. https://doi.org/10.1002/art.40037

[10] Maz M, Chung SA, Abril A, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Giant Cell Arteritis and Takayasu Arteritis. Arthritis Rheumatol 2021;73(8):1349-65. https://doi.org/10.1002/art.41774

[11] Hanberg JS, Miloslavsky EM. Steroid sparing in vasculitis: Myth or reality?. Best Pract Res Clin Rheumatol 2023;37(1):101843. https://doi.org/10.1016/j.berh.2023.101843

[12] Hellmich B, Agueda A, Monti S, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis 2020;79(1):19-30. https://doi.org/10.1136/annrheumdis-2019-215672

[13] Goel R, Danda D, Joseph G, et al. Long-term outcome of 251 patients with Takayasu arteritis on combination immunosuppressant therapy: Single centre experience from a large tertiary care teaching hospital in Southern India. Semin Arthritis Rheum 2018;47(5):718-26. https://doi.org/10.1016/j.semarthrit.2017.09.014

[14] Shirai T, Sato H, Fujii H, Ishii T, Harigae H. The feasible maintenance dose of corticosteroid in Takayasu arteritis in the era of biologic therapy. Scand J Rheumatol 2021;50(6):462-8. https://doi.org/10.1080/03009742.2021.1881155

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INVITED REVIEW

Differences in glucocorticoid use in childhood vasculitis

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ABSTRACT

This review aimed to explore the differences in glucocorticoid use across various subtypes of childhood vasculitis, focusing on their effectiveness, potential side effects, and tapering strategies to minimize toxicity. A comprehensive review was conducted to evaluate the clinical applications of glucocorticoids in pediatric vasculitis subtypes. Recommendations from recent studies and guidelines were assessed, focusing on glucocorticoid protocols for conditions such as IgA vasculitis, Kawasaki disease, polyarteritisnodosa, ANCA-associated vasculitis, and Takayasu arteritis. Glucocorticoid tapering strategies and toxicity indices, such as the Pediatric Glucocorticoid Toxicity Index (pGTI), were also analyzed. Glucocorticoid use varied across vasculitis subtypes. For IgA vasculitis, mild cases were managed with oral prednisolone, while severe nephritis required intravenous methylprednisolone and immunosuppressants. In Kawasaki disease, corticosteroids were used for refractory cases alongside IVIG and aspirin. Severe polyarteritis nodosa cases showed better outcomes with cyclophosphamide and high-dose glucocorticoids, whereas non-severe cases benefitted from low-dose glucocorticoids and NSAIDs. ANCA-associated vasculitis studies reported no significant correlation between glucocorticoid dose and outcomes, although side effects were dose-dependent. In Takayasu arteritis, children generally received lower doses than adults, based on adult treatment guidelines. The pGTI was highlighted as a valuable tool to monitor and assess glucocorticoid toxicity in pediatric patients. Glucocorticoids remain a cornerstone of treatment in pediatric vasculitis, but their use must be carefully tailored to balance efficacy and toxicity. Early tapering and transitioning to alternative therapies, when feasible, are critical to minimizing adverse effects.

Keywords: Glucocorticoids, pediatric vasculitis, glucocorticoid tapering, pGTI (Pediatric Glucocorticoid Toxicity Index).

Introduction

Steroid treatment is widely used in pediatric vasculitis cases, although it varies according to the vasculitis subtype. Most treatment protocols include intensive induction followed by maintenance therapy. Glucocorticoids are the most potent anti-inflammatory agents used in the treatment of rheumatic diseases. These agents are synthetic analogues of endogenous molecules produced by the body. Glucocorticoids show anti-inflammatory and immunosuppressive effects in both early and late phases of inflammation. Their main effects on the immune system are mediated through T lymphocytes [1]. Since the side effects associated with long-term systemic use of these agents are an important issue, the risk/benefit ratio should be carefully evaluated in theuse of glucocorticoids in children, including pediatric vasculitis cases (Table 1) [2].

The aim of glucocorticoid treatment should be to prevent or minimise toxicity as much as possible. For this purpose, glucorticoids with short half-life should be preferred. Prednisone is the most commonly used oral agent among other synthetic steroid analogues due to it slow risk/benefit ratio in children. A single daily administration in the morning is recommended. Dose reduction should be planned in a personalised manner according to the patient. Vitamin D should be supplemented with calcium to prevent osteoporosis [3].

Table 1. Side effects and mechanisms related to glucocorticoid drugs in children

Growth suppression	The most undesirable long-term effect, especially in young children
	Inhibition of IGF-1 production
	Decrease in chondrocyte proliferation
Central nervous system	Psychosis (high dose, first 4 days)
	Acute onset euphoria, mania
	Depression in the late period
	Pseudotumour cerebri
Osteoporosis	Directly reduces bone formation
	Reduces calcium absorption
	Increases urinary calcium excretion
	Increases bone destruction
	Treatment everyother day is not preventive
Muscle disorders	After high dose
	Myopathy, atrophy of proximal muscles
	Pain, tenderness
	Muscle enzymes and EMG may be normal
Cataract	>9 mg/m^2 prednisone equivalent dose and
	significant risk in use for> 1 year
Infection and Immunity	Effects due to immunesuppression
Cardiovascular system	Hypertension
	Dyslipidaemia
Hematological changes	Lymphopenia
	Notrofilia

The perioperative management of children receiving glucocorticoids should be carefully planned. Patients receiving any dose of glucocorticoids for less than three weeks [4], patients receiving less than 5 mg/day prednisone (or equivalent) in the morning for any period [5] and patients receiving less than 10 mg prednisone (or equivalent) every other day [6] do not require additional glucocorticoids perioperatively. However, perioperative glucocorticoid use is required in patients with functional suppression of the hypothalamo-pituitary-adrenal (HPA) axis who use more than 20 mg/day prednisone (or equivalent) for more than three weeks or who develop Cushing's syndrome clinically. However, in patients receiving 5-20 mg/day prednisone (or equivalent) for more than three weeks, perioperative evaluation is also required in these patients in terms of possible HPA axis suppression [5].

The classification criteria for the most prevalent vasculitides in childhood, including immunoglobulin A vasculitis/Henoch-Schonlein purpura (IgAV/HSP), Kawasaki Disease (KD) , polyarteritis nodosa (PAN), granulomatous polyangiitis/Wegener granulomatosis (GPA/WG), and Takayasu arteritis (TA), were established and validated at the 2008 Ankara Consensus Conference with the support of the European League Against Rheumatism (EULAR), Pediatric Rheumatology European Society (PReS), and the Pediatric Rheumatology International Trials (PRINTO) (Table 2) [7].

IgAV/HSP

IgAV/HSP is the most common vasculitis in childhood and is frequently observed in the age range of 3-15 years [8]. Nontrombocytopenic purpura, arthritis/arthralgia, gastrointestinal system involvement and renal involvement constitute the clinical picture. According to Ankara 2008 classification criteria for IgAV/HSP in children, typical purpura (mandatory criterion) with lower limb predominance and at leastone of the following; abdominal pain, histopathology (typical leucocytoclastic vasculitis or proliferative glomerulonephritis with predominant IgA deposits), arthritis/arthralgia, and renal involvement (proteinuria or hemorrhagia) are needed [7].

Table 2. Classification of childhood vasculitis [6]

Predominantly large sized vessel vasculitis	**Takayasu arteritis**
Predominantly medium-sized vessel vasculitis	Childhood polyarteritis nodosa Cutaneous polyarteritis Kawasaki disease
Predominantly small-sized vessel vasculitis	Granulomatous √ Wegener granulomatosis * √ Churg-Strauss syndrome* Nongranulomatous √ Microscopicpolyangitis √ Henoch-Schönlein purpura √ Isolated cutaneous leukocytoclastic vasculitis √ Hypocomplementemic urticarial vasculitis
Other vasculitides	Behçet disease Vasculitis secondary to infection, malignancy and drugs Vasculitis associated with connective tissue diseases Isolated central nervous system vasculitis Cogan sydrome Unclassified

*This classification was established prior to the eradication of eponyms and histopathological subclassification by the 2012 Chapel Hill Consensus on Nomenclature of Systemic Vasculitis.

A pediatric initiative (Single Huband Access point for pediatric Rheumatology in Europe; SHARE) has developed recommendations by European experts based on systematic literature reviews [9-11]. According to the SHARE recommendations for IgAV the conditions indicating steroid treatment are orchitis, cerebralvasculitis, pulmonary hemorrhage, and other severe organ/life-threatening vasculitic involvement. In these cases, oral corticosteroid (CS) (prednisolone/prednisone) doses of 1-2 mg/kg/day and methylprednisolone (10-30 mg/kg, maximum 1 g/day for three consecutive days) in severe cases are recommended [11].

SHARE recommendations for the treatment of pediatric IgAV nephritis (IgAVN) are evaluated separately according to mild, moderate, and severe involvement of the disease. According to these oral prednisolone is recommended as first-line treatment for patients with mild IgAV nephritis. For patients with moderate IgAV nephritis, oral prednisol or pulsed intravenous (i.v.) methylprednisolone (IVMP) has been recommended as first-line treatment. In severe IgAV nephritis, treatment with high-dose CS and i.v. cyclophosphamide to induce remission and lower-dose CS in combination with azathioprine (AZA) or mycophenolate mofetil (MMF) as maintenance therapy is usually recommended [11].

In a study of a total of 359 children with IgAVN, 108 patients (30%) received oral steroids alone, 207 patients (51%) received three methylprednisolone pulses followed by oral steroids, and 44 patients (12.5%) were followed up without steroids in a study published in 2023, involving 14 centres in France, aimed at evaluating the role of steroids on IgAVN outcomes. When 32 children treated with oral steroids alone were compared with 32 matched control patients who did not receive steroids, one year after disease onset, the IgAVN remission rate was similar between these two groups (62% vs. 68%, respectively). When 93 children treated with oral steroids alone were compared with 93 matched control patients treated with oral CSs followed by three methylprednisolone pulses, the IgAVN remission rate was not different between these two groups (77% vs. 73%, respectively). The benefit of oral steroids and methylprednisolone pulses alone cannot be determined on the basis of this observational study and randomised controlled trials are needed [12].

Kawasaki disease

Kawasaki disease (KD) is a vasculitis that predominantly affects medium and small sized

arteries. There is nospecific test to diagnose KD, but according to the American Heart Association, patients are classified as having KD if they have a fever lasting at least 5 days (a mandatory criterion) and four of the following criteria: oropharyngeal changes, peripheral limb changes or changes in the perineal region, bilateral conjunctival injection, polymorphous rash, cervical lymphadenopathy [13].

According to SHARE recommendations for the treatment of KD, intravenous immunoglobuline (IVIG), 2 g/kg single dose, and aspirin (30-50 mg/kg/day, 4 divided doses) should be started in the first 10 days of the disease as initial treatment of KD. A second IVIG infusion, most commonly 2 g/kg i.v., is recommended as a treatment option in patients with refractory KD. Corticosteroids are recommended in high-risk patients, those who are resistant to IVIG (with or without a second IVIG dose), those with Kobayashi score≥5 , hemophagocytic lymphohistiocytosis, shock clinic, patients younger than 1 year of age, patients with coronary aneurysm. If CS sare indicated, the following regimens would be reasonable:

Regimen 1: Methylprednisolone 0.8 mg/kg i.v. for 5-7 days or until C-reactive protein (CRP)normalises; then oral prednisone/prednisolone 2 mg/kg/day and discontinued over the next 2-3 weeks.

Regimen 2: Methylprednisolone 10-30 mg/kg (maximum 1 g/day) once daily for 3 days, followed by oral prednisone/prednisolone 2 mg/kg per day until day 7 or until CRP normalizes. Then it can be planned to be discontinued within the next 2-3 weeks (10).

According to European consensus-basedrecommendations for the diagnosis and treatment of rare pediatric vasculitides; IVMP 10-30 mg/kg (max 1g/day) is used for 3 days in induction treatment and then oral prednisone is started. Oral prednisolone is given as 1-2 mg/kg/day (max 60 mg/day). After the first month of treatment, the dose is reduced to 0.8 mg/kg/day and it is recommended to reduce the dose to 0.2 mg/kg (or 10 mg, whichever is lower) in the 6th month by decreasing the dose every month at a dose of 0.1-0.2 mg/kg/day. There commended dose of prednisolone in the maintenance phase is 0.1-0.2 mg/kg/day. Incase of minor relapse during the maintenance phase, prednisolone treatment is increased to 0.5 mg/kg/day, followed by a return to the basal steroid dose in 4 weeks. In case of refractory disease or failure in primary induction, IVMP (10-30 mg/kg maximum 1 gr/day) is given for 3 days, the prednisolone dose is increased to 1 mg/kg/day and decreased to 0.25 mg/kg/day in 4 weeks, and subsequent dose reductions are recommended according to the clinical picture [9].

Childhood Polyarteritis Nodosa

According to EULAR/PRINTO/PRES, Ankara 2008 criteria, the diagnosis of PAN in childhood is defined as the presence of necrotising vasculitis or angiographic abnormality in medium or small sized arteries (mandatory criterion) togethe rwith skin involvement (livedo reticularis, skin nodules, superficial or infarcts), myalgia or muscle tenderness, hypertension, peripheral neuropathy and renal involvement [7]. PAN treatment recommendations in children are based on retrospective pediatric data and recommendations for adult PAN patients. In patients presenting with skin involvement, in the absence of severe systemic inflammation and other major organ involvement, nonsteroidalanti-inflammatory drugs (NSAIDs) and/or CS therapy alone may be appropriate with careful monitoring of clinical and laboratory parameters [9].

According to the American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Polyarteritis Nodosa 2021, the treatment approach of active PAN differs according to whether the disease is severe or non-severe. For newly diagnosed patients with active, severe PAN, it is recommended to start treatment with cyclophosphamide and high-dose glucocorticoids instead of high-dose glucocorticoid salone. For newly diagnosed patients with active, non-severe PAN, treatment with non-glucocorticoid immunosuppressive agents and glucocorticoids is conditionally recommended instead of glucocorticoids alone. The optimal duration of glucocorticoid therapy for PAN (e.g. taper every 6 months or longer than 6 months) is not wellestablished and therefore the duration of therapy should be guided by the patient's clinical condition, values and preferences [14].

ANCA Associated Vasculitis

Chen et al., [15] analysed patients younger than 18 years with pAAV, biopsy-confirmed pauci-immune glomerulonephritis according to their initial steroid therapy doses of none, low-moderate (≤90mg/kg) and high (>90mg/kg) cumulative IVMP and low (<0, 5mg/kg/day prednisone equivalent), moderate (0.5-1.5mg/kg/day) and high (>1.5mg/kg/day) oral steroid doses of patients, comparing baseline characteristics and 12-month outcomes (eGFR, glucocorticoid-related side effects). Renal failure at diagnosis and plasmapheresis use were associated with high-dose IVMP. Rates of glucocorticoid-related adverse effects ranged from 15-31% across dose levels, and glucocorticoid dosing did not associate with 12-month outcomes. In this study, higher glucocorticoid doses were not associated with better outcomes [15].

Takayasu Arteritis

Takayasu Arteritis is defined as granulomatous arteritis that predominantly affects the aorta and/or its major branches [16]. Given the lack of evidence in children and the higher level of evidence in adult studies of Takayasu arteritis, the EULAR recommendations on adult-onset large vessel vasculitis (related to Takayasu arteritis, not GCA) are used in pediatric Takayasu arteritis patients [9]. In a study published by Bolek et al., [17] with 154 adult and 25 pediatric patients in which the different course of Takayasu disease in adult and pediatric patients was investigated, it was reported that acute phase reactants were higher, abdominal involvement was more frequent, left ventricular hypertrophy, aortic valve insufficiency and hypertension were more frequent in children. It was also reported that the total steroid dose administered in pediatric patients was lower compared to adult patients [17]. Another study by Jales-Netoand his colleagues found that steroids and other immunosuppressive therapies were used similarly in adults and children [18]. In a cohort of 29 children and 48 adult patients from Canada, steroid-only treatment was to be more frequently used in adult Takayasu patients [17].

Steroid reduction regimens for pediatric patients

According to current recommendations for steroid with drawal regimen in children, it is applied in the following stages [19].

1-) Glucocorticoid dose should be reduced according to the underlying condition until 30 mg/m^2/day hydrocortisone equivalent is reached.

2-) Then, it should be reduced by 10-20% every 3-7 days until the patient reaches the physiological glucocorticoid dose (8-10 mg/m^2/day hydrocortisone equivalent).

3-) After reaching 8-10 mg/m^2/day hydrocortisone, a decision should be made whether to stop or continue hydrocortisone according to the morning cortisol level evaluation (by evaluating the recovery of the HPA axis).

In our center, if the steroids are used for more than 14 days, the basal ACTH and cortisol levels are checked and if there is no adrenal suppression, the treatment has been stopped. In case of adrenal suppression, the dose is reduced to 30 mg/m^2/day hydrocortisone, then reduced by 25% at 3-day intervals to 10 mg/kg/day hydrocortisone. After 2-4 weeks of use at this dose, the basal ACTH cortisol control is checked and if the HPA axis is suppressed, an ACTH stimulation test is performed; if HPA suppression is not detected, the steroid treatment has been discontinued.

Glucocorticoid toxicity index

A pediatric glucocorticoid toxicity index (pGTI) was developed to measure glucocorticoid-related morbidity and toxicity across the age range of 2–18 years. Using group consensus methods and multicriteria decision analysis, the pGTI organized glucocorticoid-related toxicities into health domains rated as minor, moderate, or major and weighted according to severity. The overall toxicity profile derived from the pGTI data is composed of two quantitative scores: (1) Cumulative Worsening Score; and (2) Total Improvement Score. The pGTI also includes a qualitative, unweighted GC adverse event record known as the Harm Checklist,

which documents less common toxicities that are potentially severe but unlikely to change with changing glucocorticoid doses. One hundred and seven (107) toxicity items are included in the pGTI and thirty-two (32) items are included in the Harm Checklist. This Checklist is designed to identify irreversible persistent toxicities despite reduced exposure to steroids. In conclusion, the development and initial evaluation of the pGTI, a glucocorticoid toxicity assessment tool intended for use in pediatrics and pediatric practice as well as in prospective, randomized clinical trials, is described. This tool can be used across clinical disciplines to assess the clinical and economic value of glucocorticoid-sparing therapies, as well as to quantify the impact of steroid toxicity. Given the wide spread use of glucocorticoid and the pace of immunological drug discovery, this tool may represent a significant advance in our ability to assess the utility of new pharmacologic agents [20].

Conclusion

Glucocorticoids are agents widely used in our pediatric rheumatology practice however side efects should always be considered, especially in childhood. Early discontinuation of therapy, switching to alternative treatments should be pursued for patients.

Author contribution

Study conception and design: YB, DÜ; draft manuscript preparation: YB, DÜ. All authors reviewed the results and approved the final version of the manuscript.

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REFERENCES

[1] Weston WL, Claman HN, Krueger GG. Site of action of cortisol in cellular immunity. J Immunol 1973;110(3):880-3.

[2] Schäcke H, Döcke WD, Asadullah K. Mechanisms involved in the side effects of glucocorticoids. Pharmacol Ther 2002;96(1):23-43. https://doi.org/10.1016/s0163-7258(02)00297-8

[3] Adachi JD, Bensen WG, Hodsman AB. Corticosteroid-induced osteoporosis. Semin Arthritis Rheum 1993;22(6):375-84. https://doi.org/10.1016/s0049-0172(05)80029-0

[4] Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. N Engl J Med 2003;348(8):727-34. https://doi.org/10.1056/NEJMra020529

[5] Axelrod L. Perioperative management of patients treated with glucocorticoids. Endocrinol Metab Clin North Am 2003;32(2):367-83. https://doi.org/10.1016/s0889-8529(03)00008-2

[6] Harter JG, Reddy WJ, Thorn GW. Studies on an intermittent corticosteroid dosage regimen. N Engl J Med 1963;269:591-6. https://doi.org/10.1056/NEJM196309192691201

[7] Ozen S, Pistorio A, Iusan SM, et al. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. Ann Rheum Dis 2010;69(5):798-806. https://doi.org/10.1136/ard.2009.116657

[8] Piram M, Maldini C, Biscardi S, et al. Incidence of IgA vasculitis in children estimated by four-source capture-recapture analysis: A population-based study. Rheumatology (Oxford) 2017;56(8):1358-66. https://doi.org/10.1093/rheumatology/kex158

[9] de Graeff N, Groot N, Brogan P, et al. European consensus-based recommendations for the diagnosis and treatment of rare paediatric vasculitides - the SHARE initiative. Rheumatology (Oxford) 2019;58(4):656-71. https://doi.org/10.1093/rheumatology/key322

[10] de Graeff N, Groot N, Ozen S, et al. European consensus-based recommendations for the diagnosis and treatment of Kawasaki disease - the SHARE initiative. Rheumatology (Oxford) 2019;58(4):672-82. https://doi.org/10.1093/rheumatology/key344

[11] Ozen S, Marks SD, Brogan P, et al. European consensus-based recommendations for diagnosis and treatment of immunoglobulin A vasculitis-the SHARE initiative. Rheumatology (Oxford) 2019;58(9):1607-16. https://doi.org/10.1093/rheumatology/kez041

[12] Mary AL, Clave S, Rousset-Rouviere C, et al. Outcome of children with IgA vasculitis with nephritis treated with steroids: A matched controlled study. Pediatr Nephrol 2023;38(10):3317-26. https://doi.org/10.1007/s00467-023-05981-3

[13] Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: A statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation 2004;110(17):2747-71. https://doi.org/10.1161/01.CIR.0000145143.19711.78

[14] Chung SA, Gorelik M, Langford CA, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Polyarteritis Nodosa. Arthritis Care Res (Hoboken) 2021;73(8):1061-70. https://doi.org/10.1002/acr.24633

[15] Chen A, Mammen C, Guzman J, Wide variation in glucocorticoid dosing in paediatric ANCA-associated vasculitis with renal disease: Apaediatric vasculitis initiative study. Clin Exp Rheumatol 2022;40(4):841-8.

[16] Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 2013;65(1):1-11. https://doi.org/10.1002/art.37715

[17] Bolek EC, Kaya Akca U, Sari A, et al. Is Takayasu's arteritis more severe in children?. Clin Exp Rheumatol 2021;39(Suppl129):32-8. https://doi.org/10.55563/clinexprheumatol/kr357t

[18] Jales-Neto LH, Levy-Neto M, Bonfa E, de Carvalho JF, Pereira RMR. Juvenile-onset Takayasu arteritis: Peculiar vascular involvement and more refractory disease. Scand J Rheumatol 2010;39(6):506-10. https://doi.org/10.3109/03009741003742730

[19] Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy Asthma Clin Immunol 2013;9(1):30. https://doi.org/10.1186/1710-1492-9-30

[20] Brogan P, Naden R, Ardoin SP, et al. The pediatric glucocorticoid toxicity index. Semin Arthritis Rheum 2022;56:152068. https://doi.org/10.1016/j.semarthrit.2022.152068

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INVITED REVIEW

Glucocorticoid treatment for primary and secondary central nervous system vasculitis

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ABSTRACT

Although the first-line treatment of central nervous system vasculitis (CNSV) is glucocorticoids (GC), the duration and dose of GC is still unknown. Although CNSVs seem to be a disease limited to a single area, they are a heterogeneous group of diseases clinically, in terms of involvement pattern and course. Due to the highly heterogeneous nature of the disease, patient-specific determination of the initial dose of GC is essential. Considering the disease courses, it may be more appropriate to consider 1mg/kg oral GC treatment if small/distal vessels are involved and intravenous bolus GC treatment if large/proximal vessels are involved in primary-CNSVs. In secondary-CNSVs (Anca-associated vasculitis, Behçet's syndrome, Systemic Lupus Erythematosus) intravenous high dose GC treatment is recommended.

Keywords: central nervous system vasculitis, glucocorticoids, disease management.

Introduction

Central nervous system vasculitis (CNSV) can manifest as either primary or secondary forms. Primary central nervous system vasculitis (P-CNSV) specifically targets the central nervous system, while secondary central nervous system vasculitis (S-CNSV) is a result of systemic disorders affecting the central nervous system.

To avoid mistakes in diagnosing and treating vasculitis in the central nervous system, it is important to look at other conditions that can affect the system, like systemic vasculitis, infection, or connective tissue disease.

What is the primary central nervous system vasculitis?

Primary central nervous system vasculitis is a rare condition that only affects the brain and spinal cord. The median age of diagnosis is 47 years, with 50% of the patients being diagnosed between the ages of 37 and 59 [1]. It is observed with equal frequency in males and females [2].

Previous case reports have characterized P-CNSV as a lethal disease that does not respond to immunosuppressive therapy. However, recent studies have shown that the disease consists of distinct subtypes and that treatment responses differ depending on the extent of clinical involvement [1,3,4].

The symptoms of P-CNSV can manifest across a broad range, encompassing chronic headache, cognitive dysfunction, and ischemic findings [5,6]. A specific algorithm for diagnosis is not available; however, a thorough examination of the patient's medical history and physical condition, along with imaging and laboratory tests, as well as a biopsy of the central nervous system, are crucial for accurate diagnosis [5,7].

Calabrese and Mallek established diagnostic criteria for primary central nervous system vasculitis in 1988. This criterion briefly included the items listed below [8,9];

- The presence of neurological deficits that are not explicable by another disease
- Vasculitis affecting the central nervous system as revealed by histopathology or angiography
- There is no systemic illness that would resemble the results

Birnbaum and Hellmann updated the diagnostic criteria in 2009. They incorporated the definitions of definite and probable into the criteria. Definite P-CNSV necessitates a histopathological diagnosis, whereas Probable P-CNSV requires angiographic evidence of a highly likely disease along with abnormal magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) findings [9, 10].

P-CNSV is a complex disease characterized by multiple subgroups rather than just one condition entity. These subgroups have different clinical profiles and treatment responses. Therefore, it is important to distinguish them. Some of the subgroups are [11]:

Angiography negative biopsy positive subgroup: Only arterioles and arteries of extremely small diameter are affected. Responds favorably to treatment. The prognosis is favorable [11,12].

Subtype exhibiting substantial leptomeningeal enhancement on MRI: Their clinical presentation is acute. The biopsy reveals the presence of granulomatous vascular inflammation. Typically, patients exhibit a positive response to glucocorticoid therapy [11,13].

Rapidly progressive primary CNS; Rapidly progressive P-CNSV is the most severe form of P-CNSV. This cohort of patients exhibits poor response to glucocorticoids and conventional immunosuppressive treatment. The disease is fatal, despite the administration of high-dose glucocorticoids [11,14].

Solitary tumour-like mass lesion; Immunosuppressive therapies or surgical procedures may be favorable to the patient [11,15].

What is the appropriate dosage of glucocorticoids for treating P-CNSV?

P-CNSV is a rare condition. There is a lack of randomized controlled trials that provide guidance on the appropriate dosage of glucocorticoids for administration. The most important data originates from the patient cohorts studied by Salvarani et al., Over a 35-year period, Salvarani et al., analyzed the treatments and outcomes of 191 P-CNSV patients. For 47% of the patients, induction therapy was combined with intravenous pulse glucocorticoid therapy.Three-fourths of the patients had been administered five or less doses of 1 g of methylprednisolone. Nevertheless, there was no evidence to support the notion that administering this treatment initially provided any benefit. The study is performed retrospectively, and patients with unfavorable prognostic findings may have undergone more intensive treatment. Therefore, when selecting treatment, it is essential to consider both the patient's involvement characteristics and their general characteristics [16].

Patient glucocorticoids strategies vary depending on whether the small/distal vessels or large/proximal vessels are affected. The group with small vessel involvement recommended to be given 1 mg/kg of oral prednisolone daily. The group with large vessel involvement should be administered a methylprednisolone bolus at a dosage of 1g per day for 3-5 days, followed by a daily dose of 1mg/kg [17].

Secondary central nervous system vasculitis

Secondary central nervous system vasculitis refers to the development of central nervous system vasculitis as a result of a systemic inflammatory or infectious condition.

ANCA-associated vasculitis, Behçet syndrome, systemic lupus erythematosus, infectious causes (Streptococcus pneumoniae, Neisseria meningitidis, Mycobacterium tuberculosis, Treponema pallidum, and Borrelia burgdorferi), and malignancies are a few examples of conditions that may affect the central nervous system.

ANCA-Associated Vasculitis

Currently, there is a lack of conclusive data regarding the optimal glucocorticoid dosage for treating

neurological complications associated with ANCA-associated vasculitis. After reviewing the conducted studies, it is worth noting the recommendation to begin treatment with high-dose glucocorticoids.

In cases of nervous system involvement in ANCA-associated vasculitis, immediate intervention is required. There are two types of treatment: induction and maintenance. In addition to the immunosuppressive therapies, administer a remission induction regimen of 1 mg/kg prednisone for approximately 30 days, followed by the initiation of a dose reduction plan. Low-dose glucocorticoid therapy and an appropriate immunosuppressive therapy are recommended in maintenance treatment [18-20].

According to some publications, the first treatment should be a pulse intravenous methylprednisolone dose of 1 gram per day for three days, followed by a reduction to 1 mg/kg of oral glucocorticoid therapy. Additionally, they recommend reducing the glucocorticoid dose to 7.5 to 10 mg/day over a period of three to five months [10,21-23].

The 2021 ACR/vasculitis Foundation ANCA-associated vasculitis guideline suggests the use of intravenous pulse or high-dose oral glucocorticoids [24].

Behcet's Syndrome

Behçet syndrome (BS) is a disease of the blood vessels. Biopsies of people with Neuro Behçet's disease showed perivasculitis instead of vasculitis [25-27].

While there is no definite data on the specific glucocorticoid treatment for BS, there are numerous publications available to provide guidance. For cerebral venous sinus thrombosis(CVST), treatment is typically effective, with the recommendation to use high-dose glucocorticoids [28-30].

Parenchymal involvement is more resistant to treatment than CVST. IV methylprednisolone treatment is recommended for a period of 5-10 days in cases of parenchymal involvement. In addition, it is advised to gradually decrease the glucocorticoid dosage over a period of 3-6 months, depending on the patient's condition [28,30]

Systemic Lupus Erythematosus

Systemic lupus erythematosus can lead to severe central nervous system complications, such as myelitis and cerebritis. For central nervous system involvement in SLE, intravenous pulse methylprednisolone therapy is recommended [31].

Author contribution

Study conception and design: EU; draft manuscript preparation: EU. All authors reviewed the results and approved the final version of the manuscript.

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REFERENCES

[1] Salvarani C, Brown RD, Calamia KT, et al. Primary central nervous system vasculitis: Analysis of 101 patients. Ann Neurol 2007;62(5):442-51. https://doi.org/10.1002/ana.21226

[2] Calabrese LH, Duna GF, Lie JT. Vasculitis in the central nervous system. Arthritis Rheum 1997;40(7):1189-201. https://doi.org/10.1002/1529-0131(199707)40:7<1189::AID-ART2>3.0.CO;2-4

[3] Salvarani C, Brown RD Jr, Morris JM, Huston J 3rd, Hunder GG. Catastrophic primary central nervous system vasculitis. Clin Exp Rheumatol 2014;32:S3-4.

[4] Salvarani C, Pipitone N, Hunder GG. Management of primary and secondary central nervous system vasculitis. Curr Opin Rheumatol 2016;28(1):21-8. https://doi.org/10.1097/BOR.0000000000000229

[5] Hecker C, Welponer T, Herold M, Trinka E, Broussalis E, Killer-Oberpfalzer M. Update on treatment strategies for vasculitis affecting the central nervous system. Drug Discov Today 2022;27(4):1142-55. https://doi.org/10.1016/j.drudis.2021.11.020

[6] Sarti C, Picchioni A, Telese R, et al. "When should primary angiitis of the central nervous system (PACNS) be suspected?": Literature review and proposal of a preliminary screening algorithm. Neurol Sci 2020;41(11):3135-48. https://doi.org/10.1007/s10072-020-04583-3

[7] Rice CM, Scolding NJ. The diagnosis of primary central nervous system vasculitis. Pract Neurol 2020;20(2):109-14. https://doi.org/10.1136/practneurol-2018-002002

[8] Calabrese LH, Mallek JA. Primary angiitis of the central nervous system. Report of 8 new cases, review of the literature, and proposal for diagnostic criteria. Medicine (Baltimore) 1988;67(1):20-39. https://doi.org/10.1097/00005792-198801000-00002

[9] Pascarella R, Antonenko K, Boulouis G, et al. European Stroke Organisation (ESO) guidelines on Primary Angiitis of the Central Nervous System (PACNS). Eur Stroke J 2023;8(4):842-79. https://doi.org/10.1177/23969873231190431

[10] Birnbaum J, Hellmann DB. Primary angiitis of the central nervous system. Arch Neurol 2009;66(6):704-9. https://doi.org/10.1001/archneurol.2009.76

[11] Salvarani C, Brown RD, Hunder GG. Adult primary central nervous system vasculitis. Lancet 2012;380(9843):767-77. https://doi.org/10.1016/S0140-6736(12)60069-5

[12] Kadkhodayan Y, Alreshaid A, Moran CJ, Cross DT, Powers WJ, Derdeyn CP. Primary angiitis of the central nervous system at conventional angiography. Radiology 2004;233(3):878-82. https://doi.org/10.1148/radiol.2333031621

[13] Salvarani C, Brown RD, Calamia KT, et al. Primary central nervous system vasculitis with prominent leptomeningeal enhancement: A subset with a benign outcome. Arthritis Rheum 2008;58(2):595-603. https://doi.org/10.1002/art.23300

[14] Salvarani C, Brown RD, Calamia KT, et al. Rapidly progressive primary central nervous system vasculitis. Rheumatology (Oxford) 2011;50(2):349-58. https://doi.org/10.1093/rheumatology/keq303

[15] Molloy ES, Singhal AB, Calabrese LH. Tumour-like mass lesion: An under-recognised presentation of primary angiitis of the central nervous system. Ann Rheum Dis 2008;67(12):1732-5. https://doi.org/10.1136/ard.2008.096800

[16] Salvarani C, Brown RD, Christianson TJH, Huston J, Giannini C, Hunder GG. Long-term remission, relapses and maintenance therapy in adult primary central nervous system vasculitis: A single-center 35-year experience. Autoimmun Rev 2020;19(4):102497. https://doi.org/10.1016/j.autrev.2020.102497

[17] Salvarani C, Brown RD, Christianson T, et al. An update of the Mayo Clinic cohort of patients with adult primary central nervous system vasculitis: Description of 163 patients. Medicine (Baltimore) 2015;94(21):e738. https://doi.org/10.1097/MD.0000000000000738

[18] Luqmani RA. State of the art in the treatment of systemic vasculitides. Front Immunol 2014;5:471. https://doi.org/10.3389/fimmu.2014.00471

[19] Sokołowska B, Szczeklik W, Mastalerz L, et al. Effect of delayed diagnosis on disease course and management of Churg-Strauss syndrome: A retrospective study. Clin Rheumatol 2013;32(3):349-54. https://doi.org/10.1007/s10067-012-2127-9

[20] Wludarczyk A, Szczeklik W. Neurological manifestations in ANCA-associated vasculitis - assessment and treatment. Expert Rev Neurother 2016;16(8):861-3. https://doi.org/10.1586/14737175.2016.1165095

[21] Kallenberg CGM. Key advances in the clinical approach to ANCA-associated vasculitis. Nat Rev Rheumatol 2014;10(8):484-93. https://doi.org/10.1038/nrrheum.2014.104

[22] Sznajd J, Mukhtyar C. How to treat ANCA-associated vasculitis: Practical messages from 2016 EULAR/ERA-EDTA recommendations. Pol Arch Med Wewn 2016;126(10):781-8. https://doi.org/10.20452/pamw.3598

[23] Zheng Y, Zhang Y, Cai M, Lai N, Chen Z, Ding M. Central Nervous System Involvement in ANCA-Associated Vasculitis: What Neurologists Need to Know. Front Neurol 2019;9:1166. https://doi.org/10.3389/fneur.2018.01166

[24] Chung SA, Langford CA, Maz M, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. Arthritis Rheumatol 2021;73(8):1366-83. https://doi.org/10.1002/art.41773

[25] Al-Araji A, Kidd DP. Neuro-Behçet's disease: Epidemiology, clinical characteristics, and management. Lancet Neurol 2009;8(2):192-204. https://doi.org/10.1016/S1474-4422(09)70015-8

[26] Arai Y, Kohno S, Takahashi Y, Miyajima Y, Tsutusi Y. Autopsy case of neuro-Behçet's disease with multifocal neutrophilic perivascular inflammation. Neuropathology 2006;26(6):579-85. https://doi.org/10.1111/j.1440-1789.2006.00734.x

[27] Hirohata S. Histopathology of central nervous system lesions in Behçet's disease. J Neurol Sci 2008;267(1-2):41-7. https://doi.org/10.1016/j.jns.2007.09.041

[28] Hatemi G, Christensen R, Bang D, et al. 2018 update of the EULAR recommendations for the management of Behçet's syndrome. Ann Rheum Dis 2018;77(6):808-18. https://doi.org/10.1136/annrheumdis-2018-213225

[29] Karadag O, Bolek EC. Management of Behcet's syndrome. Rheumatology (Oxford) 2020;59(Suppl3):iii108-17. https://doi.org/10.1093/rheumatology/keaa086

[30] Uygunoğlu U, Siva A. Nervous system involvement in Behçet's syndrome. Curr Opin Rheumatol 2019;31(1):32-9. https://doi.org/10.1097/BOR.0000000000000562

[31] Bertsias GK, Ioannidis JPA, Aringer M, et al. EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: Report of a task force of the EULAR standing committee for clinical affairs. Ann Rheum Dis 2010;69(12):2074-82. https://doi.org/10.1136/ard.2010.130476

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INVITED REVIEW

Rational use of glucocorticoids during pregnancy in patients with systemic vasculitis

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ABSTRACT

Glucocorticoids (GC) are important in fetoplacental development and GC production increases in pregnant women.GCs can be used for various reasons during pregnancy, but there are some things to keep in mind.In patients with systemic vasculitis, GC exposure may be associated with complications such as low birth weight and preterm birth. When planning pregnancy in patients with systemic vasculitis, the aim should be to control disease activity with the lowest possible dose of GC. Pregnant women who are required to use GC should also be monitored more closely for gestational diabetes and hypertension.

Keywords: glucocorticoids, pregnancy, systemic vasculitis.

Physiology related to pregnancy and glucocorticoids

Immune adaptation mechanisms are needed for a healthy pregnancy. Glucocorticoids (GC) play an important role in normal fetoplacental growth, and GC production increases in pregnant women [1]. GC production progresses in balance with the increase in progesterone, reducing the risk of fetomaternal complications (Figure 1). On the other hand, GC is used in the prevention or treatment of some fetomaternal complications that develop for various reasons [2]. Indications for pregnancy-related GC treatment are shown in Figure 2. The main determinant of which GC will be used in treatment is the GC dose to which the fetus will be exposed. Placental passage rates according to GC types are shown in Table 1 [3].

Pregnancy in systemic vasculitis

In systemic vasculitis, the process should be considered for three different periods listed below in the evaluation of pregnancy.

i. Family planning

ii. Pregnancy course

iii. Postpartum period

First of all, pregnancy should be considered from the first visit in a systemic vasculitis patient of childbearing age, and information should be provided about the timing of conception and contraceptive methods. The expectation of a negative effect on the course of the disease in a planned pregnancy is quite low. However, even in

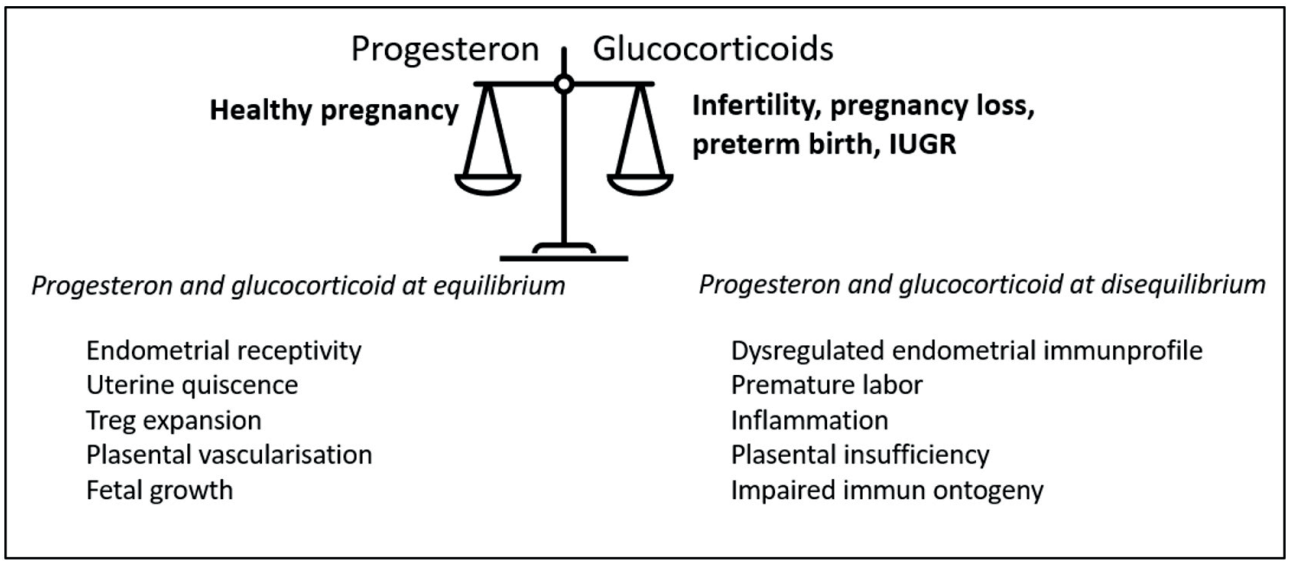

Figure 1. The importance of equilibrium between glucocorticoids and progesterone in pregnancy.

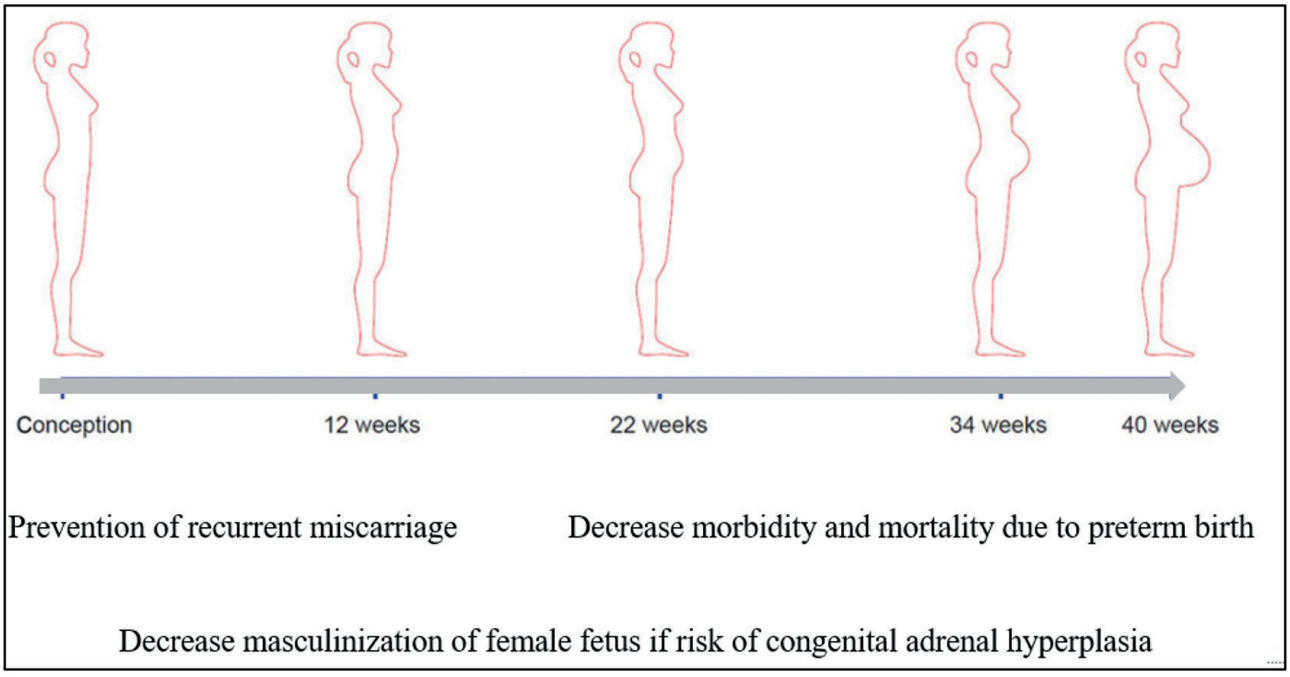

Figure 2. Indications for glucocorticoid treatments according to pregnancy time.

Table 1. Placental passage rates of glucocorticoids

Hydrocortisone	15 %
Prednisolone	10 %
Methylprednisolone	45 %
Betamethasone	30 %
Dexamethasone	65%

planned pregnancies, the risk of some fetomaternal complications, including abortion, preeclampsia, premature birth, intrauterine growth retardation and postpartum thrombosis, is still increased [4]. It is known that factors such as disease flare, uncontrolled hypertension and renal artery involvement increase the risk of fetomaternal complications [5].

The assessment of disease flare becomes more complicated in pregnancy. Clinical findings of tachycardia, tachypnea, murmur, arthralgia and morning stiffness and laboratory findings of acute phase elevation and moderate proteinuria are the most important confounders in the determination of disease activity due to the physiological changes of pregnancy. Acute phase indicators may increase significantly, especially in the last trimester [6].

Adverse effects of glucocorticoid drugs in pregnancy

It is thought that there is a relationship between GC exposure and low birth weight and preterm birth in patients with systemic vasculitis, as in patients with rheumatoid arthritis and systemic lupus erythematosus, due to maternal effects [7]. Although there are conflicting results regarding preeclampsia, GC use probably increases the risk of preeclampsia. The risk of cleft palate/lip is probably increased in children of pregnant women exposed to GC, especially in the first trimester. There is also an increase in the risk of gestational diabetes. GC side effect risks are related to dose and duration.

In a case-specific setting, ensuring disease control with low-dose GC can protect against additional immunosuppressive load. For example, it has been reported that disease control can be achieved with only low-dose GC throughout pregnancy in patients with Takayasu arteritis [8]. When general population data are examined, longer hospitalisation in neonatal intensive care unit, increased risk of hypoglycemia, reduced head diameter, and neuropsychological developmental problems have been reported more frequently in children of pregnant women exposed to GC before the 34th week [9].

In conclusion, when planning pregnancy, it is advisable to aim for controlling systemic vasculitis disease activity with the lowest effective dose of GC. The risk of fetomaternal complications may increase in pregnant women using GC, depending on the dose and duration. These pregnancies should be monitored more closely for gestational diabetes and hypertension. More clinical studies are needed on topics such as the effects of GC use on the newborn in patients with systemic vasculitis, the effects of high-dose GC on the fetomaternal and neonatal outcomes, the effect of continuing low-dose GC on pregnancy loss, the effect of antenatal GC use on preterm birth, and the comparison of low-dose GC with immunosuppressive treatments in disease control.

Author contribution

Study conception and design: NAK; draft manuscript preparation: NAK. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

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REFERENCES

[1] Solano ME, Arck PC. Steroids, Pregnancy and Fetal Development. Front Immunol 2020;10:3017. https://doi.org/10.3389/fimmu.2019.03017

[2] Kemp MW, Newnham JP, Challis JG, Jobe AH, Stock SJ. The clinical use of corticosteroids in pregnancy. Hum Reprod Update 2016;22(2):240-59. https://doi.org/10.1093/humupd/dmv047

[3] Chi CC, Wang SH, Wojnarowska F, Kirtschig G, Davies E, Bennett C. Safety of topical corticosteroids in pregnancy. Cochrane Database SystRev 2015;(10):CD007346. https://doi.org/10.1002/14651858.CD007346.pub3

[4] Ross C, D'Souza R, Pagnoux C. Pregnancy Outcomes in Systemic Vasculitides. Curr Rheumatol Rep 2020;22(10):63. https://doi.org/10.1007/s11926-020-00940-5

[5] Gönenli MG, Kaymaz Tahra S, Kara M, et al. Pregnancy in Takayasu's arteritis has a high risk of hypertension-related fetomaternal complications: A retrospective study of a Turkish cohort. Int J Rheum Dis 2022;25(2):140-6. https://doi.org/10.1111/1756-185X.14247

[6] Wirestam L, Pihl S, Saleh M, Wetterö J, Sjöwall C. Plasma C-Reactive Protein and Pentraxin-3 Reference Intervals During Normal Pregnancy. Front Immunol 2021;12:722118. https://doi.org/10.3389/fimmu.2021.722118

[7] Bandoli G, Palmsten K, Forbess Smith CJ, Chambers CD. A Review of Systemic Corticosteroid Use in Pregnancy and the Risk of Select Pregnancy and Birth Outcomes. Rheum Dis Clin North Am 2017;43(3):489-502. https://doi.org/10.1016/j.rdc.2017.04.013

[8] Alpay-Kanitez N, Omma A, Erer B, et al. Favourable pregnancy outcome in Takayasu arteritis: A single-centre experience. Clin Exp Rheumatol 2015;33(2Suppl89):S-7-10.

[9] Ninan K, Gojic A, Wang Y, et al. The proportions of term or late preterm births after exposure to early antenatal corticosteroids, and outcomes: Systematic review and meta-analysis of 1.6 million infants. BMJ 2023;382:e076035. https://doi.org/10.1136/bmj-2023-076035

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INVITED REVIEW

Perioperative management of patients receiving glucocorticoids in rheumatology

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ABSTRACT

Glucocorticoids are a cornerstone in the management of rheumatic diseases due to their potent anti-inflammatory and immunomodulatory effects. However, their perioperative use presents distinct challenges, including an elevated risk of infection, impaired wound healing, and the potential for glucocorticoid-induced adrenal insufficiency (GI-AI). This review examines the perioperative implications of glucocorticoid therapy, with a focus on infection risk, adrenal insufficiency, and recommendations from clinical practice guidelines. Evidence indicates a correlation between glucocorticoid use and increased perioperative complications, although the efficacy of dose reduction strategies in mitigating these risks remains uncertain. GI-AI, a common complication of prolonged glucocorticoid use, necessitates careful perioperative management to prevent adrenal crises. Guidelines from British, American, and German societies propose slightly differing approaches, albeit with low levels of evidence, emphasizing the importance of individualized patient care.

Keywords: glucocorticoids, perioperative management, infection risk, adrenal insufficiency.

Introduction

Glucocorticoids play a crucial role in managing various rheumatic diseases due to their potent anti-inflammatory and immunomodulatory effects [1]. However, their use in the surgical setting is associated with an increased risk of significant complications, particularly infection and adrenal insufficiency [2]. Prolonged glucocorticoid therapy may further exacerbate these risks, leading to impaired wound healing, increased skin fragility, hematoma formation, skin ulceration, and a heightened susceptibility to skin tears [1]. These complications can significantly impact patient outcomes, necessitating careful management strategies. Clinicians are thus faced with the complex challenge of balancing the therapeutic benefits of glucocorticoids against their potential perioperative risks.

Infection

Among different factors increasing the risk of infection in a patient with a rheumatic disease undergoing surgery, both historical and current corticosteroid use is an important risk factor [2]. Other factors are also related with corticosteroid use and overall risk of infection, such as disease activity and longer disease duration [3]. They both increase the risk of infection by themselves and by being associated with higher corticosteroid use.

Data regarding the increased risk of infection in the perioperative period are derived from large cohort studies. In a retrospective cohort of fourteen thousand patients undergoing total knee or hip arthroplasty, steroid use was associated with adverse outcomes such as wound dehiscence, surgical site infection, pneumonia, urinary tract infection and readmission, but not

with mortality, venous thromboembolism, post-operative cerebrovascular events, myocardial infarction or sepsis [4]. In a study involving Danish rheumatoid arthritis patients registries, steroid use was associated with about 2.5 to 3 times higher risk of joint infection and death in one year [5]. In two retrospective cohort studies from United States that use post-market surveillance data, among rheumatoid arthritis patients receiving biological therapy, steroid use was found to have dose-dependent risk increase for both non-urinary and urinary hospitalized infection, prosthetic joint infection, 30-day readmission and 90-day mortality [6,7]. Patients using a dose greater than 10 mg/day prednisone equivalent had 1.5 to 2 times higher risk for adverse outcomes than those who did not use steroids.

Various rheumatological societies have published guidelines regarding steroid use in the perioperative period. 2017 British guidelines recommend steroid exposure to be minimized prior to surgical procedures, without going into further detail [8]. American College of Rheumatology and the American Association of Hip and Knee Surgeons guideline published in 2022 make no recommendations regarding pre-operative reduction of steroid dose [9].In the 2017 edition of this guideline, there was a recommendation of tapering to lower than 20 mg/day prednisone equivalent prior to surgery when possible [10], but this was removed in 2022 edition. German guidelines published in 2022 suggest reducing the steroid dose to the lowest possible dose, 10 mg/day prednisone equivalent if possible, in the two to three months preceding surgery [11].However, while higher steroid does are in fact related with adverse outcomes,reducing the dosepreceding the surgery has not been proven to decrease the rate of perioperative complications [6].

Adrenal insufficiency

Glucocorticoid-induced adrenal insufficiency (GI-AI) is a typical side effect associated with exogenous use of corticosteroids [12]. Spectrum of GI-AI ranges from otherwise asymptomatic "biochemical" GI-AI to potentially lethal adrenal crisis [13].However, despite wide-spread use of steroids both for rheumatological and non-rheumatological conditions, data regarding the definition, epidemiology, diagnosis and treatment of this condition come from heterogeneous studies, resulting in a low level of evidence [13].

GI-AI results from suppression of adrenocorticotrophic hormone (ACTH) and corticotropin-releasing hormone (CRH) from pituitary gland and hypothalamus respectively. Chronic suppression of ACTH leads to atrophy of the adrenal cortex, which results in reduced cortisol production during periods of increased requirement [14].

Risk factors

Dose and duration of the steroid therapy are the most important risk factors for the development of GI-AI [15]. When steroids are no longer required to control the underlying condition, various tapering regimens are used to prevent both disease flares and development of GI-AI. A suggested tapering regimen by the 2024 American Endocrine Society (ES) and European Society of Endocrinology (ESE) guideline is given in Table 1 [15].

Pharmacokinetically, dexamethasone has the highest potency and the longest duration of action compared to other steroid formulations [16]. However, when equivalent doses are used, type of steroid used does not have an effect in adrenal suppression [14]. Pulse steroid therapy, alternative single day dosing and shorter duration (less than 14 days) are unlikely to cause GI-AI [14]. Concomitant use of other CYP3A4 inhibitors, such as clarithromycin and azole type of antifungals increase the level of active metabolites of steroid and thus the risk of GI-AI [14]. Other risk factors for developing GI-AI include age and obesity [15].

Clinical findings

Clinical findings of GI-AI are non-specific can overlap with a myriad of other conditions [17].

Table 1. Suggested tapering regimen by 2024 ESE/ES guideline

Current daily dose	Suggested dose decrement
>40 mg	5-10 mg every week
20–40 mg	5 mg every week
10–20 mg	2.5 mg every 1–4 weeks
5–10 mg	1 mg every 1–4 weeks
5 mg	1 mg every 4 weeks

* Doses are given as prednisone equivalent. ES: Endocrine Society, ESE: European Society of Endocrinology

Onset of the symptoms can be insidious, and the level of symptoms depend on the level of stress. Many findings such as fatigue, arthralgia and myalgia can also be associated with underlying rheumatological condition. If the body is unable to secrete an appropriate amount of endogenous cortisol for the stress faced, the condition may progress to an adrenal crisis, which is characterized by severe fatigue, nausea and vomiting, hypotension, hypoglycemia, shock and death [15].

Diagnosis

Measurement of basal morning cortisol can be used as a screening test [14]. Diagnosis if adrenal insufficiency is based on the measurement of the hypothalamus-pituitary-adrenal axis by a stress test. ACTH stimulation test (also known as Synacthen test) is the most common one used in clinical practice [14]. However, guidelines used in rheumatology currently do not recommend routine screening for GI-AI using screeningtests [8,9,11].

Treatment

Cornerstone of the treatment for GI-AI is steroid replacement to mimic normal physiology as closely as possible [17]. Hydrocortisone is the preferred steroid formulation given its pharmacokinetic properties, however other preparations such as prednisone can also be used. Based on the physiological requirements of the body, approximately 15–25 mg hydrocortisone per day is used, usually one or two divided doses [14]. In a patient with suspected adrenal crisis, prompt steroid administration is essential. An initial 100 mg bolus of parenteral hydrocortisone, followed by 200 mg hydrocortisone over 24 hours. Additional measures such as fluid resuscitation, electrolyte and glucose requirement, and treatment of possible triggers of adrenal crisis are other components of the treatment [15].

Peri-operative care for prevention

Patients at risk of developing GI-AI should receive priority when scheduling for procedures, to minimize potential triggers such as fasting and dehydration [18]. 2017 British, 2022 American and 2023 German guidelines by rheumatology societies do not recommend routine increase in steroid doses in the perioperative period [8,9,11]. Summary of recommendations by American Endocrine Society and European Society of Endocrinology are given in Table 2 [15].

Conclusion

List of recommendation by various societies are given in Table 3.

Author contribution

Study conception and design: RCK, HK; draft manuscript preparation: RCK, HK. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

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Table 2. Summary of perioperative recommendations from 2024 ESE/ES guideline [15]

Type of procedure	Level of stress	Recommendation
• Minor surgery and procedures requiring local anesthesia	Minor stress	• Patients taking ≥10 mg/day prednisone equivalent: No extra dose needed • Patients taking <10 mg/day predisone equivalent: Increase to 10 mg total daily dose, to be given one hour prior to the procedure. Continue increased dose in patient who remain unwell after the procedure until clinically stable.
• Surgery and procedures requiring general or regional anesthesia • Labor, including vaginal delivery and cesarean section	Moderate to major stress	• Intra-operative: IV hydrocortisone 100 mg at induction, followed by 200 mg of hydrocortisone over 24 hours • Post-operative: Resume oral steroid at increased dose for 48 hours (prednisone 10 mg/day). After 48 hours, resume pre-surgical dose. In case of post-operative complications, maintain an increased oral dose or give stress-dose steroid IV as clinically appropriate

Table 3. Recommendations regarding peri-operative steroid use

	2017 BSR/BHPR	2022 ACR/AAHKS	2023 GSR
Infection	Steroid exposure should be minimized prior to surgical procedures	No recommendation	Must be reduced to the lowest possible dose, 10 mg/day if possible in the last 2–3 months before surgery.
Adrenal insufficiency	Increase in dose to prevent adrenal insufficiency is not recommended.	Continuation of the current daily dose, rather than supraphysiological doses, is recommended	Peri-operative steroid dose is recommended to remain constant.

AAHKS: American Association of Hip and Knee Surgeons, ACR: American College of Rheumatology, BHPR: British Health Professionals in Rheumatology, BSR: British Society of Rheumatology, GSR: German Society for Rheumatology.

REFERENCES

[1] Saag KG, Buttgereit F. Chapter 62: Systemic glucocorticoids in rheumatology. In: Hochberg MC, editor. Rheumatology. Philadelphia, PA: Elsevier;2023:490-500.

[2] Zisa D, Goodman SM. Perioperative Management of Rheumatic Disease and Thera-pies. Rheum Dis Clin North Am 2022;48(2):455-66. https://doi.org/10.1016/j.rdc.2022.02.005

[3] Baker JF, George MD. Prevention of Infection in the Perioperative Setting in Patients with Rheumatic Disease Treated with Immunosuppression. Curr Rheumatol Rep 2019;21(5):17. https://doi.org/10.1007/s11926-019-0812-2

[4] Kittle H, Ormseth A, Patetta MJ, Sood A, Gonzalez MH. Chronic Corticosteroid Use as a Risk Factor for Perioperative Complications in Patients Undergoing Total Joint Ar-throplasty. J Am Acad Orthop Surg Glob Res Rev 2020;4(7):e2000001. https://doi.org/10.5435/JAAOSGlobal-D-20-00001

[5] Cordtz RL, Zobbe K, Højgaard P, et al. Predictors of revision, prosthetic joint infection and mortality following total hip or total knee arthroplasty in patients with rheumatoid arthritis: A nationwide cohort study using Danish healthcare registers. Ann Rheum Dis 2018;77(2):281-8. https://doi.org/10.1136/annrheumdis-2017-212339

[6] George MD, Baker JF, Winthrop K, et al. Risk of Biologics and Glucocorticoids in Pa-tients With Rheumatoid Arthritis Undergoing Arthroplasty: A Cohort Study. Ann In-tern Med 2019;170(12):825-36. https://doi.org/10.7326/M18-2217

[7] George MD, Baker JF, Winthrop KL, et al. Immunosuppression and the risk of read-mission and mortality in patients with rheumatoid arthritis undergoing hip fracture, abdominopelvic and cardiac surgery. Ann Rheum Dis 2020;79(5):573-80. https://doi.org/10.1136/annrheumdis-2019-216802

[8] Ledingham J, Gullick N, Irving K, et al. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. Rheumatol-ogy (Oxford) 2017;56(6):865-8. https://doi.org/10.1093/rheumatology/kew479

[9] Goodman SM, Springer BD, Chen AF, et al. 2022 American College of Rheumatolo-gy/American Association of Hip and Knee Surgeons Guideline for the Perioperative Management of Antirheumatic Medication in Patients With Rheumatic Diseases Un-dergoing Elective Total Hip or Total Knee Arthroplasty. Arthritis Care Res (Hoboken) 2022;74(9):1399-408. https://doi.org/10.1002/acr.24893

[10] Goodman SM, Springer B, Guyatt G, et al. 2017 American College of Rheumatolo-gy/American Association of Hip and Knee Surgeons Guideline for the Perioperative Management of Antirheumatic Medication in Patients With Rheumatic Diseases Un-dergoing Elective Total Hip or Total Knee Arthroplasty. Arthritis Care Res (Hoboken) 2017;69(8):1111-24. https://doi.org/10.1002/acr.23274

[11] Albrecht K, Poddubnyy D, Leipe J, et al. Perioperative management of patients with inflammatory rheumatic diseases: Updated recommendations of the German Society for Rheumatology. Z Rheumatol 2023;82(Suppl1):1-11. https://doi.org/10.1007/s00393-021-01150-9

[12] Husebye ES, Pearce SH, Krone NP, Kämpe O. Adrenal insufficiency. Lancet 2021;397(10274):613-29. https://doi.org/10.1016/S0140-6736(21)00136-7

[13] Prete A, Bancos I. Glucocorticoid induced adrenal insufficiency. BMJ 2021;374:n1380. https://doi.org/10.1136/bmj.n1380

[14] Borresen SW, Klose M, Glintborg D, Watt T, Andersen MS, Feldt-Rasmussen U. Ap-proach to the Patient With Glucocorticoid-induced Adrenal Insufficiency. J Clin Endo-crinol Metab 2022;107(7):2065-76. https://doi.org/10.1210/clinem/dgac151

[15] Beuschlein F, Else T, Bancos I, et al. European Society of Endocrinology and Endocrine Society Joint Clinical Guideline: Diagnosis and Therapy of Glucocorticoid-induced Adrenal Insufficiency. J Clin Endocrinol Metab 2024;109(7):1657-83. https://doi.org/10.1210/clinem/dgae250

[16] Nachawi N, Li D, Lansang MC. Glucocorticoid-induced adrenal insufficiency and glu-cocorticoid withdrawal syndrome: Two sides of the same coin. Cleve Clin J Med 2024;91(4):245-55. https://doi.org/10.3949/ccjm.91a.23039

[17] Martin-Grace J, Tomkins M, O'Reilly MW, Sherlock M. Iatrogenic adrenal insufficiency in adults. Nat Rev Endocrinol 2024;20(4):209-27. https://doi.org/10.1038/s41574-023-00929-x

[18] Simpson H, Tomlinson J, Wass J, Dean J, Arlt W. Guidance for the prevention and emergency management of adult patients with adrenal insufficiency. Clin Med (Lond) 2020;20(4):371-8. https://doi.org/10.7861/clinmed.2019-0324