



Glucocorticoids – All-Rounders Tackling the Versatile Players of the Immune System

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Glucocorticoids regulate fundamental processes of the human body and control cellular functions such as cell metabolism, growth, differentiation, and apoptosis. Moreover, endogenous glucocorticoids link the endocrine and immune system and ensure the correct function of inflammatory events during tissue repair, regeneration, and pathogen elimination via genomic and rapid non-genomic pathways. Due to their strong immunosuppressive, anti-inflammatory and anti-allergic effects on immune cells, tissues and organs, glucocorticoids significantly improve the quality of life of many patients suffering from diseases caused by a dysregulated immune system. Despite the multitude and seriousness of glucocorticoid-related adverse events including diabetes mellitus, osteoporosis and infections, these agents remain indispensable, representing the most powerful, and cost-effective drugs in the treatment of a wide range of rheumatic diseases. These include rheumatoid arthritis, vasculitis, and connective tissue diseases, as well as many other pathological conditions of the immune system. Depending on the therapeutically affected cell type, glucocorticoid actions strongly vary among different diseases. While immune responses always represent complex reactions involving different cells and cellular processes, specific immune cell populations with key responsibilities driving the pathological mechanisms can be identified for certain autoimmune diseases. In this review, we will focus on the mechanisms of action of glucocorticoids on various leukocyte populations, exemplarily portraying different autoimmune diseases as heterogeneous targets of glucocorticoid actions: (i) Abnormalities in the innate immune response play a crucial role in the initiation and perpetuation of giant cell arteritis (GCA). (ii) Specific types of CD4+ T helper (Th) lymphocytes, namely Th1 and Th17 cells, represent important players in the establishment and course of rheumatoid arthritis (RA), whereas (iii) B cells have emerged as central players in systemic lupus erythematosus (SLE). (iv) Allergic reactions are mainly triggered by several different cytokines released by activated Th2 lymphocytes. Using these examples, we aim to illustrate the versatile modulating effects of glucocorticoids on the immune system. In contrast, in the treatment of lymphoproliferative disorders the pro-apoptotic action of glucocorticoids prevails, but their mechanisms differ depending on the type of cancer. Therefore, we will also give a brief insight into the current knowledge of the mode of glucocorticoid action in oncological treatment focusing on leukemia.

Keywords: glucocorticoids, immune system, inflammation, giant cell arteritis, rheumatoid arthritis, systemic lupus erythematosus, allergic diseases, leukemia

INTRODUCTION

Hormones enable intercellular communication as well as the exchange of information between different organ systems throughout the human body. They are involved in a variety of processes such as growth, development, and metabolism. The synthesis and secretion of hormones is subject to stringent regulations, comprising positive, and negative feedback loops as crucial mechanisms. Steroids are lipophilic hormones that are subdivided into mineralocorticoids produced in the zona glomerulosa of the adrenal cortex, glucocorticoids produced in the zona fasciculata as well as sex hormones produced in the zona reticularis and to a great extent in the gonads. Since it has been demonstrated that natural glucocorticoids also have some mineralocorticoid effects, the classification into these groups is not completely accurate. The term “glucocorticoids” is more suitable when talking about synthetic glucocorticoids (e.g., prednisolone or dexamethasone), because these drugs are more restricted to glucocorticoid effects only (1).

The initial step of steroid hormone biosynthesis is the conversion of cholesterol to the precursor pregnenolone in the mitochondria. Steroid hormone biosynthesis is mainly realized by enzymes of the cytochrome P450 family (2). Sex hormones affect growth, development and reproductive cycles whereas mineralocorticoids regulate sodium and water balance and glucocorticoids influence energy and metabolic processes as well as immune and stress responses.

Between 5 and 30 mg of the active endogenous (physiological) glucocorticoid cortisol is produced per day, regulated by the hypothalamic–pituitary–adrenal (HPA) axis. Glucocorticoids bind to glucocorticoid receptors that are present in cells throughout the body, including cells in the hypothalamus and pituitary gland, which are part of the negative feedback loop controlling the glucocorticoid production. Furthermore, the hormone concentration varies in a circadian manner peaking at 9 a.m. in the morning and reaching the lowest plasma concentration at midnight.

The dehydrogenation of cortisol to its inactive form cortisone is promoted by the enzyme 11 β -hydroxysteroid dehydrogenase (11 β -HSD) type 1 in the liver. The same enzyme also exhibits reductase activity promoting the reverse reaction. The type 2 11 β -HSD is only able to convert the active into the inactive form due to its sole dehydrogenase activity. Depending on the balance and activity of both enzymes, the intracellular glucocorticoid concentration and thus the tissue sensitivity for glucocorticoids varies (3). In addition to that, glucocorticoids have been demonstrated to possess immunomodulating effects which depend on concentration and time of administration: While an immunostimulatory effect is observed at lower concentrations (below serum level), higher concentrations (therapeutic range) lead to an immunosuppression (4). Due to their strong immunosuppressive, anti-inflammatory and anti-allergic effects, synthetic glucocorticoids have been established as important drugs in the treatment of diseases driven by immune and inflammatory dysregulation.

Glucocorticoid Signaling

Glucocorticoids are lipophilic substances with a low molecular weight that can easily pass cellular membranes and bind to the glucocorticoid receptor in the cytosol. The cytosolic glucocorticoid receptor is ubiquitously expressed by nucleated cells and resides in the cytoplasm as a multi-protein complex. Proteins and co-factors stabilize the receptor and support a specific conformation leading to a high binding affinity for its ligands (5–9). Two main receptor isoforms are described, the α glucocorticoid receptor, which is activated by glucocorticoids, and the β isoform with a deformed ligand-binding domain that cannot bind ligands (10–13). Further receptor isoforms which differ in their transcriptional activity as a result of alternative splicing and/or post-translational modifications, have been extensively described elsewhere (12–14).

The hormone-receptor complex is translocated into the nucleus as a homodimer and binds to palindromic DNA-binding sites in the promoter region of different target genes, so called glucocorticoid response elements. This genomic mechanism of glucocorticoid action is known as transactivation, which describes the binding to positive glucocorticoid response elements leading to the activation of the transcription of anti-inflammatory but also regulatory proteins. These include for example IL-10, Annexin 1, and I κ B as well as enzymes of gluconeogenesis such as tyrosine aminotransferase, serine dehydrogenase, or phosphoenol pyruvate carboxykinase. In contrast, the term transrepression refers to an impairment of the expression of immunoregulatory and proinflammatory proteins caused by (i) competition for nuclear co-activators between the hormone-receptor-complex and transcription factors; (ii) direct or indirect interaction with transcription factors like NF- κ B and AP-1. Similarly, glucocorticoids diminish gene expression by a mechanism referred to as cis-repression, which involves binding to negative glucocorticoid response elements. Genomic mechanisms of glucocorticoid action result in “delayed effects,” meaning that the protein level does not change directly after glucocorticoid administration. The duration of the delay depends on different factors, including transport within the bloodstream, onset of activation/translocation of the hormone-receptor complex and the transcriptional and translational processes themselves. Nevertheless, the description of rapid improvements which are observed within a few minutes—especially after intravenous or intraarticular injection of high glucocorticoid doses—demonstrates the existence of non-genomic effects. These are triggered by (i) proteins released from the multi-protein complex after the binding of glucocorticoids to the cytosolic receptor, (ii) interactions with membrane-bound receptors, and (iii) nonspecific effects resulting from the interaction of glucocorticoids with cellular membranes (15, 16).

More pronounced glucocorticoid effects are observed with increasing glucocorticoid dosages, as receptor saturation is achieved (17). Unfortunately, rising dosages and duration of administration simultaneously increase the risk of adverse events. While the long-term use of dosages \leq 5 mg prednisone equivalent per day is generally associated with a low risk of adverse effects, the application of dosages >10 mg/day increases

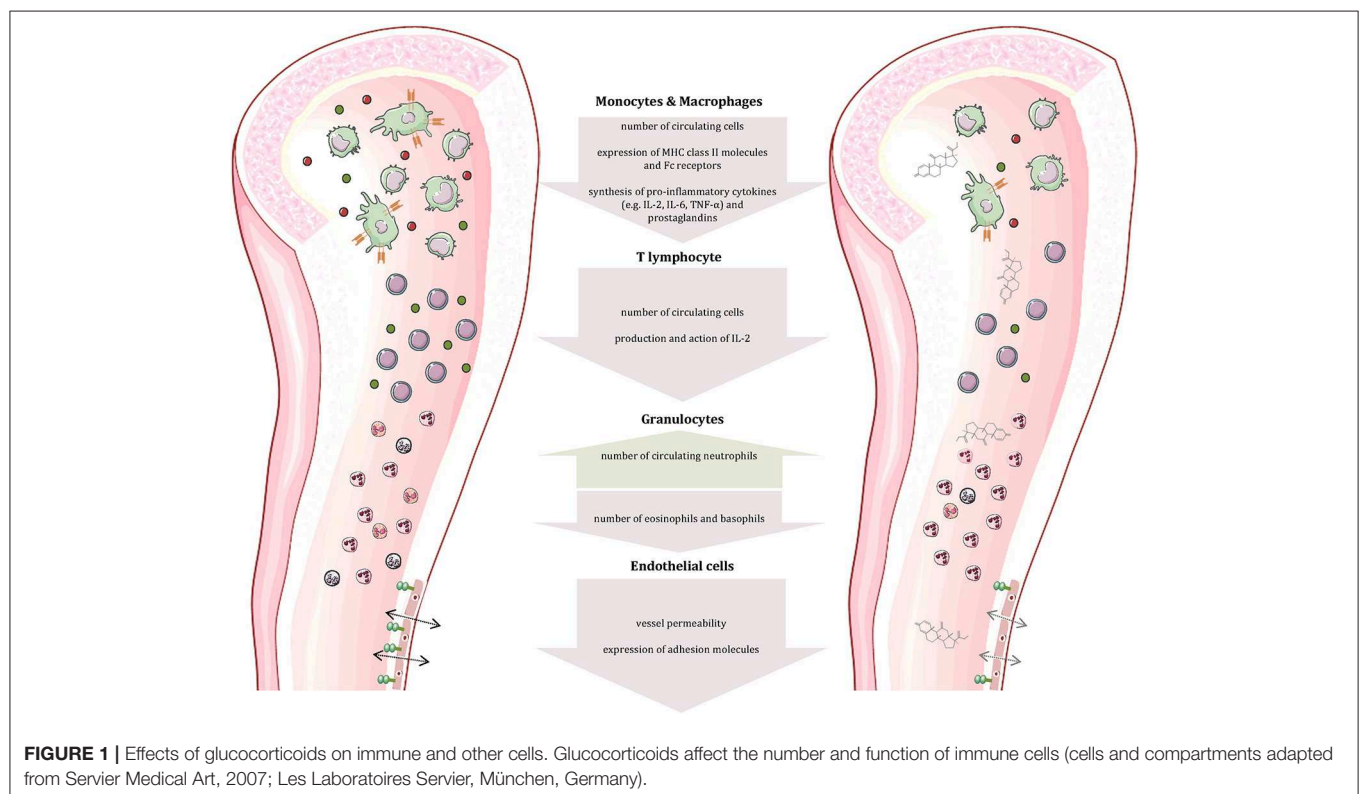
the frequency of the latter (18). These adverse effects are thought to depend on the mechanism of glucocorticoid action: Repression of cytokines such as IL-1, IL-2, IL-6, TNF- α , IFN- γ , and prostaglandins mediates the positive anti-inflammatory effects, while transactivation is thought to be responsible for the majority of adverse effects (19–21). However, this classification is not absolute. In contrast, it has been demonstrated that transactivation also contributes to the anti-inflammatory effects, e.g., by the upregulation of genes like GILZ and DUSP1. In addition, in a mouse model the prevention of receptor dimerization and thereby inhibition of DNA-binding impaired the anti-inflammatory capacity of glucocorticoid action (22–26).

Glucocorticoids and Inflammation

These findings clearly show that our knowledge concerning the mechanisms of glucocorticoid action—including the desirable anti-inflammatory and the undesirable adverse effects—is yet insufficient. Nevertheless, these drugs still represent an indispensable component of the treatment of most inflammatory diseases because of their efficient and cost-effective characteristics. However, the considerable toll taken by adverse events must not be neglected and the development of an equally effective alternative with a more favorable side-effect profile would be most desirable. The extent and importance of glucocorticoid toxicity has been reviewed elsewhere (27, 28) and will not be discussed in detail in this article.

The immune system consists of two major components: The innate immune response represents our first line of defense and includes physical and chemical barriers such as the skin

and tears. In addition, non-specialized cells recognize foreign invaders by components like bacterial lipopolysaccharide and destroy them by phagocytosis or release of toxic substances. The adaptive immune response—our second line of defense—includes B and T lymphocytes. While the former are responsible for antibody production, the latter can differentiate into distinct subpopulations that participate in B cell maturation or possess cytotoxic potential (29–31). The two lines of defense are linked by cytokines and cell-cell interaction, which is crucial for the initiation of the adaptive response. The most notable attribute of the adaptive immune response is memory, enabling an immediate and very specific pathogen defense following previous exposure. The protective actions of the immune system are accompanied by pain, swelling, itching, redness and heat, typical signs of an inflammation. At the same time, these symptoms represent a significant burden in autoimmune diseases. Normally, the immune response is strictly regulated to discriminate self from non-self—a mechanism known as tolerance (29, 30). It is realized by positive and negative selection of lymphocytes in the bone marrow or thymus. In more detail (for T cells), T cells that cannot bind MHC class 1 or class 2 complexes undergo apoptosis due to the lack of survival signals. The subsequent negative selection determines if T cells bind self-peptides presented by epithelial cells of the thymus. Naive T cells that have passed both, the positive and the negative selection are qualified to migrate into secondary lymphoid organs (29). Autoimmune diseases originate from a dysregulation of the immune response, while the particular cause of the disease is often unknown. Some factors, including genetic predisposition,



sex, and environment have been identified to promote the establishment of autoimmune diseases. Due to their strong anti-inflammatory and immunosuppressive effects on almost all immune cells (summarized in **Figure 1**), glucocorticoids are indispensable in the treatment of autoimmune diseases. In general, glucocorticoids inhibit leukocyte traffic and thereby the access of leukocytes to the site of inflammation. Furthermore, glucocorticoids interfere with immune cell function and suppress the production and actions of humoral factors involved in the inflammatory process.

Since the establishment and the course of autoimmune diseases are driven by different cell populations, glucocorticoid application targets diverse leukocyte populations and thus the mechanism of glucocorticoid action varies. Recently, Franco et al. have investigated the transcriptional effects of glucocorticoids on nine primary human cell types. They found 9,457 genes to be differentially expressed in response to glucocorticoids, whereas only 25 of them (0.3%) involved all cell types examined, demonstrating that the transcriptional response of each cell type is quite distinct (32).

The next chapters will illustrate the versatile modulating effects of glucocorticoids on the immune system on the basis of exemplary diseases involving the respective leukocyte population. Glucocorticoid regimens used in daily practice according to current guidelines are presented in **Table 1** for the selected diseases.

ABNORMALITIES IN INNATE IMMUNE RESPONSE PLAY A CRUCIAL ROLE IN THE INITIATION AND THE PERPETUATION OF GIANT CELL ARTERITIS

Giant cell arteritis (GCA) is defined as a granulomatous large-vessel vasculitis, which primarily involves medium- and large-caliber branches of the aorta (34, 58, 59). Both the innate and the adaptive immune responses are involved in the pathogenesis of this disease which can be divided into different phases (59). The initiation of inflammation is followed by its amplification and the constitution of feed forward loops leading to arterial remodeling and ultimately vascular damage. Recently, the current knowledge on the pathophysiology of GCA has been discussed in detail in two reviews (59, 60). Al-Mousawi et al. describe this disease as being mainly mediated by T cells (60). The first step, however, is the abnormal maturation of vascular dendritic cells (DC) in the adventitia of the affected vessels. An unknown trigger, perhaps microorganisms or viral agents, drives this initial step (59). Predisposing factors include a certain genetic background, female sex, and alterations of the immune and arterial systems related to aging (59). The activated DC recruit and activate CD4+ naïve T cells in the arterial wall where they polarize into T helper (Th) 1 cells, Th17 and regulatory T (Treg) cells (59, 60). The secreted products of these cells, namely and most importantly interferon- γ , interleukin (IL)-2, and IL-17, facilitate both the recruitment and activation of neutrophils, macrophages and vascular smooth muscle cells, and the formation and activation of multinucleated giant cells (**Figure 2**). These giant cells are

also capable of secreting cytokines and growth factors. Of note, Th17 cells also secrete other cytokines such as IL-21, IL-22, IL-8, and IL-26. Macrophages produce IL-6 and IL-1 β within the adventitia. The latter cytokines are thought to mainly drive the systemic manifestations of GCA such as fatigue, fever, and weight loss. The fact that the levels of these cytokines largely determine glucocorticoid requirements underlines the importance of the innate immune response in the pathogenesis of GCA (61). Macrophages also produce matrix metalloproteinases (MMP) such as MMP-9, a type IV collagenase. Watanabe et al. have very recently identified this enzyme in vasculitic lesions of GCA and have shown MMP-9 to control the access of monocytes and T cells to the vascular wall. MMP-9-producing monocytes facilitate migration of T cells through the collagen IV-containing basement membrane. The enzymatic activity of MMP-9 is required for invasion of vasculitogenic T cells and monocytes, formation of neoangiogenic networks, and neointimal growth (62). As a consequence, the elastic lamina and growth factors are destroyed, which propagates intimal hyperplasia. Of note, macrophages also produce reactive oxygen species which contribute to the damage of smooth muscle cells in the media (60). Ultimately, the injured arterial cells respond to the damaging immunological events mentioned above by initiating dysfunctional repair processes. This vascular remodeling leads to inflammatory wall thickening, decreased luminal diameter, and ischemic manifestations of GCA with potential organ damage (34).

Glucocorticoids represent a most effective therapy and, therefore, remain—despite the recently shown favorable effects of the IL-6 receptor inhibitor Tocilizumab (63)—the primary treatment in GCA (34). These drugs have been the mainstay of treatment since the 1950s. Their genomic and non-genomic effects contribute to the successful treatment of this disease. We have recently summarized details regarding glucocorticoids in the management of polymyalgia rheumatica and GCA (64). In brief, glucocorticoids induce important anti-inflammatory and immunosuppressive effects on both primary and secondary immune cells involved in the pathophysiology as described above. Glucocorticoids inhibit some of their crucial functions with key mechanisms being the suppression of the production of pro-inflammatory cytokines, and the prevention and inhibition of activation of T cells and monocytes/macrophages.

Innate immune cells that are predominantly responsible for the features of systemic inflammation present in GCA are most susceptible to glucocorticoid treatment (65, 66). By inhibiting the NF κ B pathway by direct or indirect interaction with this transcription factor as described in the introduction, glucocorticoids efficiently suppress the production of central cytokines (**Figure 2**) (67). In this context, Linden and Brattsand demonstrated that GM-CSF showed the highest susceptibility to glucocorticoid treatment compared to IL-1 β and IL-6 (68). These findings conform to the beneficial effects of IL-6 blockade in GCA therapy (63). Of note, higher glucocorticoid sensitivity has been attributed to monocytes compared to more differentiated macrophages (68). Consequently, it can be inferred that glucocorticoids are most potent in inhibiting freshly attracted monocytes in states of acute inflammation. In addition, glucocorticoids affect the recruitment of cells of the

TABLE 1 | Glucocorticoid regimens in selected diseases.

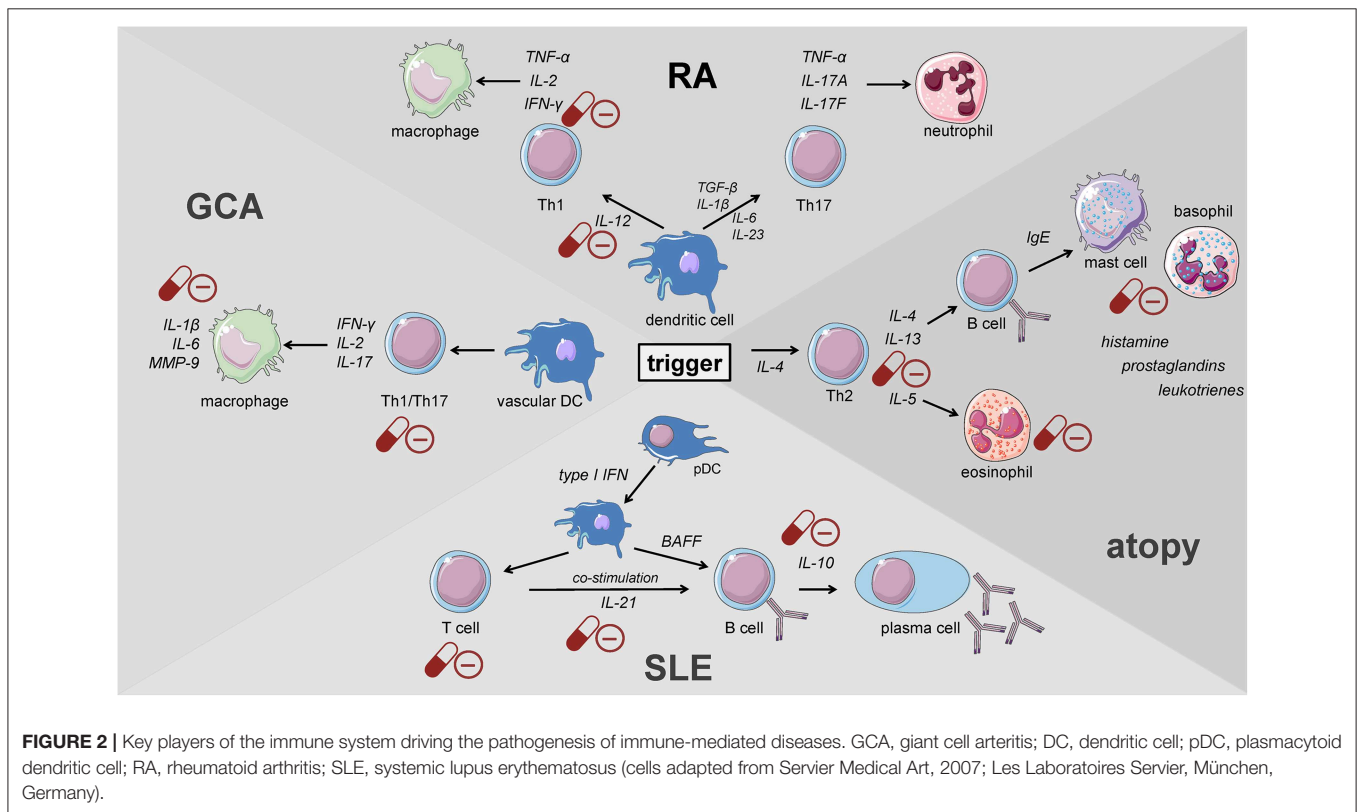
Disease	Induction	Tapering	Maintenance	Relapse
INFLAMMATORY RHEUMATIC DISEASES				
Giant cell arteritis	- Immediate treatment with 40–60 mg/day* for induction of remission in active GCA** (33)	- Tapering is recommended when the disease is under control to achieve a target dose of 15–20 mg/day* within 2 to 3 months - After 1 year target dose should be ≤ 5 mg/day* (33)	- If long-term therapy is required a dose of 5 mg/day* or less should be used - GC therapy should ideally be tapered to zero as early as clinically feasibly (18)	- Increase to pre-relapse dose or by up to 5–10 mg/day* - Taper within 4–8 weeks to pre-relapse dose - Repeat induction therapy for ischemic complications (34)
Rheumatoid arthritis	- When initiating/changing csDMARDs short-term GC therapy should be considered (35)	- GC tapering should start as soon as clinically feasible (35)	- If long-term therapy is required a dose of 5 mg/day* or less should be used - GC therapy should ideally be tapered to zero as early as clinically feasibly (18)	- Usually doses between 10 and 20 mg/day* are sufficient to treat flares in this disease
Systemic lupus erythematosus	- Therapy depends on disease manifestations and severity (36) - In acute, organ-threatening disease high-dose intravenous pulse therapy (usually 250–1,000 mg/day* for 3 days) is often used (36)	- GC should be tapered or at least minimized as rapidly as clinically feasible	- Long-term aim is to minimize daily dose to ≤ 7.5 mg/day* or to discontinue GC therapy (36)	- The characteristic of flare therapy depends on disease, as has been similarly stated for the induction therapy
ATOPY				
Atopic dermatitis	- Stepwise approach: adjust treatment based on disease severity assessed by SCORAD (37) → Mild disease: class II topical glucocorticoids (e.g., flumethasone 0.02%) (38) → Moderate disease: class II/III topical glucocorticoids (e.g., mometasone 0.1%) (39) → Severe disease: short-term oral glucocorticoids may be considered in adults (38)			
Allergic rhinitis	- Moderate to severe rhinitis: nasal glucocorticoids, e.g., fluticasone, mometasone, beclametasone (40, 41) - Oral glucocorticoids should only be used in severe persisting disease (40, 41) - stepped-care approach according to disease severity (42)			
Asthma	- Most patients initially receive low dose ICS (e.g., 200–400 μ g/d budesonide) (43) - Frequent troublesome symptoms justify medium (400–800 μ g/d) to high dose ICS (>800 μ g/d) (44) - Low dose oral corticosteroids (≤ 7.5 mg/day*) should only be considered in adults with severe asthma or poor symptom control (45)	- ICS should not be stopped completely, cessation is associated with a higher risk of exacerbations (46) - In stable disease ICS doses can be reduced by 25–50% every 3 months (47)	- ICS are recommended as controller treatment in all asthma patients either as-needed or daily depending on disease severity (43) - Dose adjustment according to a stepwise approach*** ranging from 200–400 to >800 μ g/d budesonide or comparable doses of other formulations in adults, reduced doses are used in the treatment of children <12 years (48)	- <i>Worsening symptoms</i> : adjustment of the treatment (increase reliever/controller use, step up to higher dose) according to a written asthma action plan*** - Severe exacerbation: → adults: 40–50 mg/d prednisolone → Children: 1–2 mg/kg/d, max. 40 mg/d prednisolone to be continued for 5–7 days (49, 50)
Anaphylactic shock	- Glucocorticoids are used to prevent protracted anaphylactic symptoms, while their efficacy in the acute phase is limited due to slow onset of action (51, 52) - 250–1,000 mg i.v. prednisolone (weight-adjusted dosing in children) (53)			
LEUKEMIA				
Chronic lymphoblastic leukemia****	- Patients with diagnosed limited-stage Hodgkin's lymphoma (HL) and a positive interim positron-emission tomography after two cycles of ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) should be treated with two cycles of bleomycin/etoposide/doxorubicin/cyclophosphamide/vincristine/procarbazine/prednisone in escalated dose before ISRT - Patients with refractory or relapsed HL dexamethasone can be given in combination with high-dose cytarabine/cisplatin (DHAP) before high-dose chemotherapy followed by autologous stem cell therapy - Patients diagnosed for nodular lymphocyte predominant Hodgkin lymphoma benefit from the combination of rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone (R-CHOP) - CLL patients with transformation into a diffuse large B-cell lymphoma benefit from therapies used in DLBCL such as rituximab plus CHOP (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) (54–56)			

(Continued)

TABLE 1 | Continued

Disease	Induction	Tapering	Maintenance	Relapse
Chronic myeloid leukemia	N/A			
Acute myeloid leukemia	N/A			
Acute lymphoblastic leukemia	<ul style="list-style-type: none"> - Glucocorticoids are given as a so-called pre-phase therapy (usually prednisone 20–60 mg/day or dexamethasone 6–16 mg/day, both <i>i.v.</i> or <i>p.o.</i>) alone, or in combination with another drug (e.g., vincristine, cyclophosphamide), but often given together with allopurinol and hydration for ~5–7 days. The response to pre-phase therapy defines the chemosensitivity of the disease, and is included in some studies for risk assessment, since good responders to prednisone may have a better outcome. - Regimens of induction therapy are centered on vincristine, glucocorticoids, and anthracycline (daunorubicin, doxorubicin, rubidazole, idarubicin), with or without cyclophosphamide or cytarabine. Dexamethasone is often preferred to prednisone, since it penetrates the blood–brain barrier and also acts on resting leukemic blast cells (LBCs). - In adult ALL glucocorticoids are often used in the hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) protocol, preferentially used in the United States, but also in other parts of the world - Maintenance therapy usually consists of daily 6-mercaptopurine and weekly methotrexate. In some treatment regimens, repeated cycles of vincristine, dexamethasone or other drugs in monthly or longer intervals are given (57) 			

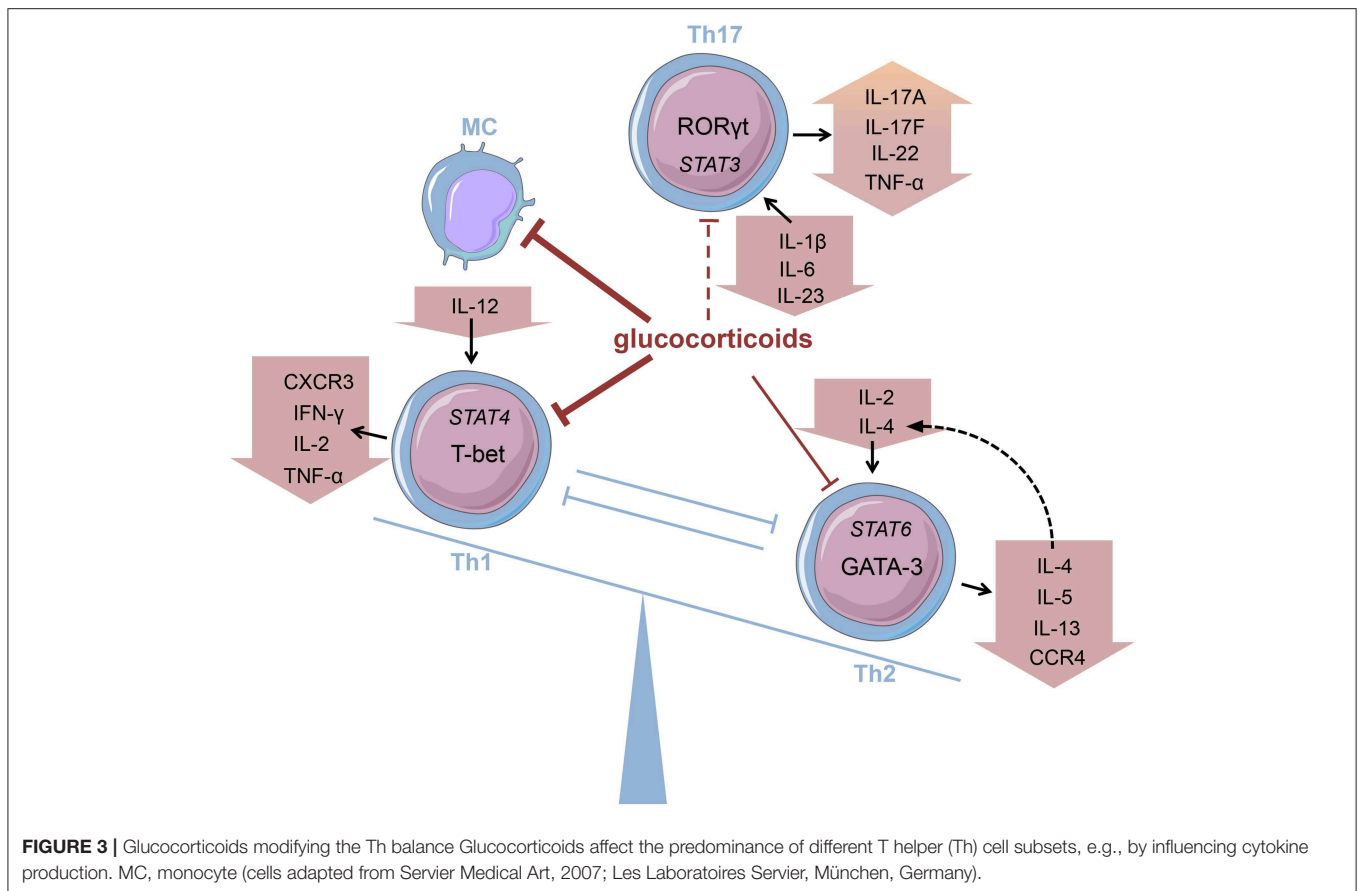
*Doses are given as prednisone-equivalent. **In patients with GCA suffering from acute visual loss or amaurosis fugax, the use of very high GC dosages, namely 0.25–1 g *i.v.* methylprednisolone daily for up to 3 days should be considered. ***Details are provided by the Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019. Available from: www.ginasthma.org N/A: glucocorticoids are not used as standard therapy in these diseases. ****The transformation into a diffuse large B-cell lymphoma (DLBCL) or Hodgkin's lymphoma occurs in 2%–15% of CLL patients during the course of their disease.



mononuclear phagocytic system by suppressing the expression of adhesion molecules on the surface of the endothelium (69). With respect to monocyte function, Blotta et al. demonstrated that the incubation of monocytes with dexamethasone led to a decreased IL-12 production *in vitro* (Figure 3) (70). In line with this, they presented a limited capacity to induce Th1 differentiation.

Deng et al., however, have shown that glucocorticoids suppress the production of Th17-promoting cytokines (IL-1 β , IL-6, and

IL-23) (Figure 3), but IFN- γ -producing Th1 responses persist in treated patients (71). Also, patients presenting prominent expression of IL-17A in temporal artery biopsies demonstrated favorable responses to glucocorticoid treatment (72). Therefore, it was assumed that the IL-6-IL-17 cluster is highly responsive to glucocorticoid therapy, whereas the IL-12-IFN- γ cluster is resistant to glucocorticoid-mediated immunosuppression (73). Nevertheless, there are reports of a reduction in Th1 response



after glucocorticoid treatment in patients with Takayasu's arteritis—a condition closely linked to GCA (74). Moreover, further studies revealed a decrease in both Th1 and Th17 cells, and a reduction of IFN- γ in GCA patients after glucocorticoid treatment (75, 76). Reviewing the pathogenesis of GCA, Samson et al. thus concluded that the conflicting results regarding glucocorticoid response result from prevalent plasticity between Th1 and Th17 cells influenced by the surrounding cytokine milieu (77).

At higher glucocorticoid dosages, for instance in form of pulse therapy in complicated GCA and in case of established visual loss, rapid non-genomic effects as already described in the introduction contribute to their therapeutic efficacy [reviewed in (64)].

AUTOIMMUNE DISEASES DRIVEN BY IRREGULARITIES IN THE ADAPTIVE IMMUNE SYSTEM

Th1 and Th17 Cells Represent Important Players in the Establishment and Course of Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a systemic autoimmune disease that affects up to 1% of the population worldwide with a higher prevalence in women than in men. RA patients suffer from

pain, immobility, and fatigue leading to decreased quality of life (78). The pathogenesis of RA is characterized by chronic inflammation mainly localized in the synovial joints leading to the destruction of articular cartilage and the establishment of bone erosions. Joint inflammation is accompanied by the infiltration of the synovium with immune cells such as T cells, B cells, macrophages, and dendritic cells and the proliferation of fibroblast-like synoviocytes of the synovial sub-lining layer which finally contribute to the joint destruction (79).

Glucocorticoids play a very important role in the treatment of RA, rapidly suppressing inflammatory activity especially at disease onset and during flares (15, 16, 80–82). Although glucocorticoids satisfactorily suppress inflammation and reduce symptoms such as pain and morning stiffness, data regarding their ability to manage cartilage degradation and bone erosions remain controversial (83, 84). Only limited success with regard to remission rates using glucocorticoids has been reported, e.g., in early treatment of undifferentiated arthritis (85) but also the SAVE trial (remission-rate: 17%) (86) and the STIVEA trial (remission-rate: 20%) (87). However, glucocorticoids still efficiently limit inflammation. Although the exact mechanism of RA pathogenesis remains unclear, it has become evident that Th cell subsets play an important role in the course of the disease. CD4⁺ T cells, especially Th1 and Th17 cells, play a major role in RA (88). RA patients present an enrichment of effector memory CD4⁺CD45RO⁺ T cells in the affected joints (89) and a massive

expansion CD4⁺ T cell clones in synovial tissue of early disease, which suggests a local antigen-induced proliferation (90). In this context, it should be noted that blocking co-stimulation targeting CD80/CD86-CD28 interaction significantly improved the signs and symptoms of RA illustrating the importance of T cells in the pathogenesis (91). Moreover, genetic association of certain HLA-DRB1 alleles with increased susceptibility to RA further supports the central role of Th cells in RA (92).

When the Th1/Th2 paradigm dominated the understanding of the pathogenesis of autoimmune diseases, RA was defined as a Th1-driven disease because CD4⁺ T cells identified to be enriched in synovial fluids from RA patients were prone to secrete IFN- γ but not IL-4 (93, 94). These findings were further supported by the enrichment of the IFN- γ -induced chemokines CXCL9 and CXCL10 and the chemokine receptor CXCR3 binding both of the latter in RA synovium (95–98). Th1 cells classically activate macrophages and increase their capacity to produce pro-inflammatory cytokines present in RA synovium such as TNF (Figure 2) (99). Moreover, IL-12, IL-18, and IFN- γ , the drivers of Th1 differentiation have been also identified in synovial tissues of RA patients (100, 101), although the levels of Th1-mediated IFN- γ were relatively low compared with those of TNF- α , IL-1, or IL-6 derived from synovial fibroblasts (102, 103).

The discovery of Th17 cells (100, 101) and the delineation of the IL-17 family members (104) as well as the shift from Th17 cells to Th1 cells (i.e., “non-classic Th1 cells”) being more pathogenic than Th17 cells *per se* shed new light on the contribution of inflammatory Th subsets to the initiation of RA (Figure 2) (105–108). Th17 cells are highly unstable and easily shift to Th1 cells but can also transdifferentiate back as demonstrated for Th1 cells in the gut (109–112). At the onset and in the early phase of the pathogenesis of RA, Th17 cells shift to Th1 cells, whereas methotrexate (MTX) reduced the ratio of Th17 cells but not Th1 cells (113). Finally, these findings demonstrate that Th17 and ex-Th17 or “non-classic Th1 cells” cells play important roles in the early phase of RA and for the treatment using a combination of MTX and glucocorticoids according to the EULAR recommendations for the management of rheumatoid arthritis (35). While MTX reduces the ratio of Th17 cells, which are—depending on the immunopathological setting—resistant to glucocorticoid mediated suppression in terms of survival and the production of IL-17A and IL-17F but not IL-22 (114), glucocorticoids induce Th1 cell apoptosis via induction of BIM (114, 115). Moreover, glucocorticoids decrease IFN- γ production by T cells from patients with rheumatoid arthritis *ex vivo* and *in vitro* mechanistically via their suppressive action on the IL-12-induced STAT4 phosphorylation and by direct protein-protein interaction with the transcription factor T-BET—described as transrepression in the introduction (Figure 3) (116–119). Inhibition of Th1 activity by glucocorticoids may reduce overall inflammation in RA patients while the glucocorticoid resistant joint destruction can be assumed to be Th17 mediated. Mechanistically, glucocorticoid resistant joint destruction may be maintained by the glucocorticoid-mediated promotion of intrinsic Th17 differentiation (120), and the induction of bone resorption via synovial IL-17 (121). IL-17 also contributes to

neutrophil recruitment (122) and an increase in neutrophil survival, a hallmark of RA synovial fluid promoting joint damage (Figure 2) (122–124).

B Cells Have Emerged as Central Players in Systemic Lupus Erythematosus

Components of the innate and the adaptive immune system play an important role in the pathogenesis of systemic lupus erythematosus (SLE). Clinical manifestations of this autoimmune disease are diverse, affecting a wide spectrum of organs and tissues. The pathogenesis of the disease is not yet fully understood, but beside environmental factors a genetic susceptibility to SLE has been described including a variety of nucleotide polymorphisms [reviewed elsewhere (125)]. Plasmacytoid dendritic cells (pDC) produce type I interferon in response to viral infections. A large number of SLE patients possess an ongoing production of type I interferons and subsequently an increased expression of type I interferon regulated genes, termed IFN-signature, which correlates with autoantibodies and disease activity (126–128). This type I interferon synthesis is induced by immune complexes containing nucleic acid via Toll-like receptor (TLR) ligation. In addition to their antiviral features, type I interferons contribute to the activation of the adaptive immune system, e.g., by activation of autoreactive T and B cells (Figure 2) (129, 130). T cell signaling alterations and hyperactive B cells, producing and presenting autoantibodies against nuclear complexes to T cells, constitute the main drivers of SLE. The important role of B cells has been demonstrated in a murine model lacking this lymphocyte population (131). In addition to that, the same group showed that B cells also play an antibody-independent role in murine lupus in their function as antigen presenting and cytokine secreting cells (132).

Alterations in B cell maturation and differentiation affect several B cell subsets, targeting different checkpoints of B cell development. In SLE patients the frequency of antibody producing plasma cells in the peripheral blood is increased and correlates with autoantibody production and disease activity (133). It has been demonstrated that amongst others the overexpression of BAFF/BLyS (B-cell activating factor/B-lymphocyte stimulator), type I interferon and Blimp-1 (B lymphocyte-induced maturation protein-1) is responsible for these alterations in SLE patients (134–136).

Although B cells have emerged as central players in SLE, B cell depletion failed repeatedly as a therapeutic strategy in clinical trials. For example, the EXPLORER study demonstrated that rituximab, a CD20 antibody, did not show any statistically significant efficacy in achieving treatment response compared to placebo. Moreover, a recent reanalysis confirmed these findings, reevaluating the data with the help of newly available disease activity scores (137, 138).

There is only one therapeutic antibody approved by the FDA and the EMA for SLE therapy, namely belimumab, which neutralizes BAFF/BLyS and thereby decreases the number of newly formed B cells (139, 140).

The management of SLE strongly depends on the course of the disease. Glucocorticoids represent highly effective agents in order to immediately control the inflammatory process in SLE. Systemic glucocorticoids are required as initiation therapy in severe SLE, whereas maintenance immunosuppressive therapy is added in order to enable steroid tapering. Nevertheless, especially in acute, organ-threatening disease high-dose intravenous pulse therapy (usually 250–1,000 mg prednisone equivalent per day for 3 days) is often used to reduce disease activity (36). Interestingly, Guiducci et al. demonstrated that oral glucocorticoids (5–20 mg per day) modulate multiple gene expression pathways but the IFN pathway (including 36 type-I-IFN-inducible transcripts) is not affected in SLE patients. In contrast, the IFN signature was normalized after intravenous pulse therapy, which correlates with a reduction in pDC. The IFN- α production was reduced after a combined inhibition of TLR7 and 9 in purified pDC indicating that continuous triggering of TLR7 and 9 in these cells by immune complexes containing nucleic acid in SLE patients counteracts the activity of glucocorticoids on the IFN pathway. Thus, TLR7, and 9 inhibitors could be effective as glucocorticoid-sparing drugs (128).

However, the mechanism of glucocorticoid action in SLE patients is largely unknown. A study in MRL/MpSlac-lpr mice with systemic autoimmune symptoms similar to human SLE analyzed prednisone action on plasma cell differentiation with regard to the impact of regulatory factors, including IL-21, Blimp-1, and Bcl-6 (B cell lymphoma-6—essential for germinal center development). The percentages of plasma cells and plasma cell precursors as well as activated T cells were decreased after 13 weeks of prednisone treatment (**Figure 2**). In addition, serum IL-21 and the expression of splenic Blimp-1 and Bcl-6 were reduced, which may be correlated with the restriction of B lymphocyte differentiation into plasma cells in these mice (141).

Haneda et al. went further in order to analyze which step of B cell differentiation is affected by glucocorticoids. They differentiated human B cells by sequential addition of cytokines and other agents in a three-step culture system to obtain activated B cells [CD19(hi)CD38(lo)IgD(-)], plasmablasts [CD19(hi)CD38(hi)IgD(-)], and plasma cells [CD19(lo/-)CD38(hi)IgD(-)]. They added low and high concentrations of prednisolone at the beginning of each differentiation step and found a significant inhibition of B cell proliferation and differentiation in the last step, whereas IgG production was decreased in step 2 and 3 only at high glucocorticoid concentrations (100 ng/ml) (142). Interestingly, the number of circulating B cells was less affected by glucocorticoids compared to T cells which showed a rapid depletion in the circulation. In contrast, plasma cells and naive B cells are markedly decreased in the peripheral blood of SLE patients upon immunosuppressive therapy (143)—indicating that the inhibition of T cell help might contribute to the immediate glucocorticoid responses in SLE (144). Using transcriptome data to generate a pathway-level map of glucocorticoid effects across immune cell types, Franco et al. identified that glucocorticoid treatment (i) up-regulated the expression of *PRDM1*, which encodes BLIMP-1 involved in terminal differentiation and reduced proliferation of B cells and

IL10, (ii) functionally impaired BCR signaling by suppressing *CR2* and *CD19* which encode the two components of the B cell co-receptor complex that serve as an enhancer of BCR-mediated signaling and (iii) selectively impaired TLR signaling by downregulation of *TLR1*, *TLR6*, and *TLR7* (32).

However, responses to glucocorticoids differ from patient to patient suffering from SLE. This may, at least in part, be related to the glucocorticoid receptor α whose alteration has been demonstrated in several autoimmune diseases (145–150). In SLE patients, the receptor expression is reduced compared to healthy controls. In addition, treatment with glucocorticoids further reduces the receptor mRNA and protein expression and it has been demonstrated that the receptor expression is negatively associated with SLE disease activity. Thus, the determination of receptor expression may be of importance with regard to insensitivity to glucocorticoids or determination of therapeutically effective dosages (151).

The glucocorticoid-induced leucine zipper (GILZ), an anti-inflammatory protein whose expression is upregulated by endogenous and exogenous glucocorticoids, has been in the focus of an *in vitro* study in human B cells. In general, GILZ mRNA and protein expression in peripheral blood mononuclear cells obtained from patients with SLE were downregulated compared to controls and correlated negatively with different markers of disease activity. An analysis of human B cell subsets revealed that intracellular GILZ was significantly decreased in circulating HLA-DR^{lo} plasmablasts [precursors of HLA-DR^{hi} cells which indicate active disease (152)] in patients with SLE. Treatment with prednisolone restored the GILZ expression to the level of control donors, a process described as transactivation—the activation of the transcription of anti-inflammatory proteins—in the introduction. Furthermore, an impaired induction of GILZ in SLE patients under glucocorticoid treatment was associated with an increased disease activity (153).

In the past decade, several additional factors including p-glycoprotein and the macrophage migration inhibitory factor (MIF) have been identified in the context of glucocorticoid resistance in SLE [reviewed in (154)]. P-glycoprotein (P-gp), a product of the multidrug resistance gene *MDR-1*, mediates the excretion of numerous drugs including antibiotics and cytotoxins but also glucocorticoids (155). P-gp is widely expressed in a variety of tissues, including peripheral blood T and B lymphocytes (156). However, P-gp expression is increased in these cells in SLE patients and is correlated with disease activity (157). Thus, elevated levels of P-gp lead to poor disease control by systemic glucocorticoid therapy and are associated with glucocorticoid resistance (157, 158). Beside P-gp, the inflammatory cytokine macrophage MIF actively reduces glucocorticoid action, participates in multiple stages of the inflammatory response and is widely associated with autoimmune disorders such as RA and SLE (159). MIF is also known as a naturally occurring counter-regulator of glucocorticoid action, correlates with disease activity in SLE and mediates the development of glucocorticoid resistance in SLE (159–162).

Although glucocorticoids are highly effective in the treatment of SLE, these drugs bear the risk of severe adverse effects,

especially when given over a longer period of time and/or at higher dosages. A study analyzing the relationship between glucocorticoids and damage accrual in SLE demonstrated that medium to high mean daily prednisone doses and higher cumulative doses were associated with an increased occurrence of adverse effects. Eighteen patients developed new damage attributable to glucocorticoid treatment including cataracts, osteoporotic fractures, avascular necrosis, and diabetes mellitus (163). New drug developments or improved formulations for SLE therapy are promoted with the objective of reducing the glucocorticoid dosage and thereby attenuating adverse effects. The therapeutic effect of a liposome-based steroidal methylprednisolone nano-drug has been evaluated in a murine model of SLE compared to the free agent. The study revealed that the steroidal nano-drug formulation is significantly more effective in suppressing anti-dsDNA antibody levels, proliferation of lymphoid tissue and renal damage, and in prolonging survival compared to free methylprednisolone given at the same dosage (164). The advantage of nano-liposomes is that they passively reach the inflamed site due to the enhanced permeability of the inflamed tissue vasculature, ensuring a reduced level in non-inflamed tissues (165, 166). Due to these advantages, liposomal glucocorticoids are also of great interest in the treatment of other inflammatory diseases (167–170).

Th2 Lymphocytes Constitute Major Contributors to the Pathogenesis of Allergic Diseases

Contrary to Th1 cells CD4⁺ T helper cells type 2 (Th2) are mainly involved in eosinophil activity as well as IgE production caused by an immunoglobulin class-switch in B cells (171). Th2 cells are characterized by the expression of GATA-3 and the secretion of Th2 cytokines, namely interleukin (IL)-4, IL-5, and IL-13 (172). Their development is promoted by a milieu abundant in IL-2 and IL-4 that activate STAT6 signaling and thereby promote Th2 differentiation (Figure 3). Thus, the key role of IL-4 consists in both mediating Th2 cell function and maintaining Th2 predominance by autocrine secretion.

Physiologically, Th2 cells exert their main function in the control of helminth infections. This mechanism of defense, referred to as the “type 2 response,” involves players of both the innate and adaptive immune system. Besides the activation and proliferation of Th2 cells and the secretion of their characteristic cytokines, this cascade comprises eosinophil and basophil granulocytes, mast cells as well as IgE secreted by plasma cells (173). Considered to possess anti-inflammatory characteristics, the type 2 response is thought to have evolved as a mechanism of parasite control that simultaneously confines collateral damage and promotes tissue repair (174). In this regard, the antibody isotype IgE fulfills an important function in responding to metazoan infections. Cross-linking of IgE bound to high-affinity receptors (FcεRI) on mast cells and basophils triggers the release of mediators that facilitate healing without activating complement. However, rising hygienic standards have reduced the necessity of antihelminthic defense mechanisms, thereby depriving Th2 cells of their original target pathogens.

In this context, the role of a dysregulated type 2 response in the pathogenesis of immune-mediated diseases has attracted increasing attention.

With a lifetime prevalence of about 40%, allergic diseases represent the most common immune disorder in western countries, affecting both children and adults (175). The German Health Interview and Examination Survey for Children and Adolescents (KiGGS) revealed a prevalence of 22.6% among children and adolescents with three main diagnoses in descending order: atopic dermatitis (AD), allergic rhinoconjunctivitis (AR), and asthma (176). The pathogenesis of atopic disorders is defined by a predominant type 2 response involving all major players described above (177–180). The allergic cascade is set into motion by IL-4 and thymic stromal lymphopoietin (TSLP) secreted from basophils (181). This step promotes Th2 differentiation followed by the secretion of IL-4 and IL-13 from activated T lymphocytes (Figure 2). Subsequently, these cytokines cause B cells to undergo a class-switch to IgE producing plasma cells. Upon allergen exposure cross-linking of these antibodies bound to mast cells results in a release of histamine, prostaglandins, and leukotrienes that enhance paracellular permeability (Figure 2). As a result, dendritic cells (DCs) infiltrate the affected tissue and maintain T cell stimulation in their role as antigen-presenting cells (APCs). Activated Th2 cells produce type 2 cytokines that sustain the mechanisms underlying allergic reactions. While IL-4 mainly induces the class-switch toward IgE production, IL-13 additionally causes mucus production and airway hyperresponsiveness (182, 183). On the other hand, IL-5 supports eosinophil survival and function (Figure 2) (184, 185). The substantial role of the type 2 response in the pathogenesis of allergic diseases has also been highlighted by the examination of samples from patients suffering from AD (186), AR (187), and asthma (188–191) demonstrating the preponderance of Th2 cells and cytokines in the affected tissues.

Glucocorticoids, administered both topically and systemically, represent indispensable agents in the treatment of atopic disorders (192). Generally, these drugs are capable of reducing the number of immune cells present at the site of allergic reactions (Figure 2) (193, 194). On examining the effect of glucocorticoids on Th2 cells in greater detail, a contradiction becomes evident. Although these agents are successfully administered to atopic patients, glucocorticoids have been described to promote Th2 cell predominance (Figure 3)—a well-described driver of allergic diseases (195–201). In order to solve this apparent conflict, the mechanism of action of glucocorticoids in Th2-driven disorders needs to be reviewed more closely.

Firstly, one has to distinguish between short-term and long-term drug effects. Temporary application of suprphysiological glucocorticoid doses results in an inhibition of Th2 cytokine production (Figures 2, 3) (202–205). This effect is mainly mediated by glucocorticoid action on transcription factors as described in the introduction (206–208). For instance, binding of the GR to the IL-5 gene promoter region results in the repression of the cytokine by interfering with GATA-3 signaling (209). Moreover, this process seems to involve

histone deacetylation. Similarly, inhibition of GATA-3, the key transcription factor of Th2 differentiation, plays an important role (210). Maneechotesuwan et al. showed that ligand-activated GR and GATA-3 compete for importin- α interaction enabling nuclear localization (211). Application of inhaled fluticasone propionate (FP) prevented nuclear transport of GATA-3 by means of this mechanism in asthmatic patients. The authors also demonstrated that the induction of MAPK phosphatase-1 (MPK-1) by FP results in the inhibition of p38 MAPK function, thus preventing GATA-3 phosphorylation. Also, dexamethasone treatment decreased GATA-3 expression in an asthmatic mouse model by inhibiting Notch1 signaling (212). In contrast, chronic exposure to glucocorticoids may cause a shift toward Th2 predominance. On the one hand, this thesis is underlined by multiple studies analyzing the role of stress in atopic diseases. Periods of stress are marked by elevated levels of endogenous cortisol that promote Th2 predominance and thereby susceptibility to allergy (213). The impact of psychological stress on the course of disease in asthmatic patients has been reviewed by Miyasaka et al. (214). On the other hand, Ramirez revealed that prior glucocorticoid exposure provokes type 2 cytokine production in T cells (201).

Secondly, the effect of glucocorticoid administration on Th2 cells in atopic patients appears to differ from the Th2 enhancement generally caused by these drugs. Hydrocortisone significantly reduced the presence of IgE, histamine, and type 2 cytokines in serum and skin samples from AD patients (215). Correspondingly, AR patients presented a decrease in eosinophils, IgE, IL-4, and IL-5 in their nasal fluid after topical and oral glucocorticoid application (**Figure 2**) (187, 216–218). Lastly, the suppression of the type 2 response by glucocorticoid treatment was also observed in bronchial tissue and bronchoalveolar lavage fluid from asthmatics (219–221).

Finally, the beneficial glucocorticoid actions in allergic diseases are not only caused by their impact on Th2 lymphocytes. On the contrary, several players of the type 2 immune response are equally affected by glucocorticoid treatment. Namely, mast cell maturation and activation, Fc ϵ RI expression as well as mediator production and release are inhibited by glucocorticoid exposure (222–227). Furthermore, glucocorticoids impede histamine release from basophils and induce eosinophil apoptosis (228, 229). Recruitment and function of APCs as well as the class-switch to IgE in B cells are also restrained (230–232). Additionally, Klaffen et al. demonstrated the importance of non-hematopoietic cells in mediating glucocorticoid effects in a mouse model of allergic asthma (233). In the end, it has to be mentioned that recent findings emphasize the involvement of other CD4+ T helper cell subsets in the pathogenesis of allergic diseases. Increasing importance has been ascribed to Th17, Th9, Th22, and Th25 cells in this context (234). Similarly, the impact of regulatory T cells (Treg) must not be neglected. Several studies describe defective Treg activity as a major contributor to the development and maintenance of atopy (235–242). In this regard, glucocorticoids greatly contribute to the restoration of Treg function, thereby controlling the dysregulated type 2 immune response (243–246).

MECHANISMS OF GLUCOCORTICIDS IN THE TREATMENT OF MALIGNANCIES WITH A FOCUS ON LEUKEMIA

The last chapter will give a brief insight into the mechanisms of glucocorticoid action in cancer therapies. Interestingly, the effects of glucocorticoids on different cancer subtypes and thereby the underlying mechanisms vary, even regarding opposite effects. This may be related to the subtype of cancer itself including its location, the affected cell type, the microenvironment and emerging comorbidities. Also, the glucocorticoid dose ranging from low to high daily dosages, and the level of glucocorticoid receptor expression and activity play an important role. In addition to that, the co-existence of other receptors of the steroid receptor family, namely the androgen and the estrogen receptors, can affect glucocorticoid action, especially in breast or prostate cancer, since there are also differences in receptor positive and receptor negative cancer subtypes. Another beneficial effect on different subtypes of cancer should not be neglected: Glucocorticoids are used as co-therapy during chemotherapy or radiotherapy in order to reduce side effects. They have been shown to improve mood, increase appetite and thereby lessen weight loss, reduce fatigue, diminish ureteric obstruction, prevent vomiting, and alleviate pain (247–250).

In the following, we will concentrate on hematopoietic malignancies which form a particular subset of cancerous conditions that were first discovered as such in the Nineteenth century when Rudolf Virchow coined the term “leukemia,” meaning “white blood.” Glucocorticoids play a crucial role in the treatment of these malignancies, among others as part of the CHOP regimen to treat non-Hodgkin lymphoma as well as in myeloma therapy. Nevertheless, due to the considerable differences of glucocorticoid effects on diverse cancer types, we will focus on one subtype here, namely leukemia. The epidemiology of the disease is summarized in **Table 2** according to the German and Austrian cancer register (www.gekid.de; www.statistik.at).

Four different types of leukemia are described: chronic lymphoblastic leukemia (CLL), chronic myeloid leukemia (CML), acute myeloid leukemia (AML), and acute lymphoblastic leukemia (ALL). CLL is the most common leukemic disease in western industrialized countries, where the disease constitutes 95% of the overall cases in older individuals (50 years and older) (251). The main reason for the therapeutic use of glucocorticoids in leukemia is their pro-apoptotic action.

Chronic Lymphoblastic Leukemia (CLL)

The inhibition of B cell apoptosis and the dysregulation of proliferation and differentiation are the main causes of CLL. They lead to an accumulation of mature CD5-positive, CD10-negative, CD20 weakly positive, and CD23-positive B cells within blood, bone marrow and solid lymphoid organs (252–254). Therefore, the B cell itself, the B cell receptor and the subsequent signaling pathways are novel targets of therapies using e.g., monoclonal antibodies like rituximab or small molecules such as the kinase inhibitor ibrutinib [reviewed in (253)].

TABLE 2 | Epidemiology of leukemia.

Registry	Cancer type	Female		Male		Total
		Rate	Number of cases	Rate	Number of cases	Number of cases
Germany	Cancer (total)	336.7	223.019	436.5	259.013	482.032
	Leukemia	8.1	5.550	13.2	7.489	13.039
	Leukemia (mortality)	4.0	3.575	6.4	4.168	7.743
Austria	Cancer (total)	421.8	19.393	581.4	21.342	40.735
	Leukemia	9.0	420	16.5	586	1.006
	Leukemia (mortality)	7.3	354	11.9	386	740

Rate and absolute numbers of cases of total cancer (without other tumors of the skin) and leukemic (including mortality) in Germany and Austria in the year 2014. Rate is given per 100,000 individuals per year (new disease) according to the German and Austrian cancer registry (www.gekid.de; www.statistik.at).

In healthy subjects, the administration of glucocorticoids affects different subsets of the peripheral blood leukocytes, resulting in a transient lymphocytopenia (255). This has been demonstrated to be mostly caused by a glucocorticoid induced redistribution of lymphocytes from the blood into the tissue, affecting mainly T cells and B cells to a lesser extent (252, 256). In CLL patients however, the administration of glucocorticoids leads to an increase in blood lymphocytes accompanied by a rapid reduction in spleen and lymph node sizes. Following the therapy, the number of lymphocytes decreased even beneath pretreatment levels (257, 258). Unfortunately, the underlying mechanism is still unknown and glucocorticoids are consequently not commonly used to treat CLL. Nevertheless, these drugs are currently of interest to complement treatment with monoclonal antibodies or small molecules. In 2016, Manzonei et al. analyzed the *in vitro* effects of the combination of ibrutinib and dexamethasone on the proliferation and metabolic stress markers in lymphocytes obtained from patients suffering from CLL. They demonstrated an enhanced inhibition of cell cycle progression, an increase in apoptosis and a decrease in DNA damage in lymphoid B cells by a combination of dexamethasone and ibrutinib compared to the tyrosine kinase inhibitor alone (259).

Chronic Myeloid Leukemia (CML)

Tyrosine kinase inhibitors also show remarkable success in controlling CML, a disease of myeloid progenitor cells. This is due to the knowledge of the underlying molecular pathogenesis of this disease which arises mainly from a translocation $t(9;22)(q34;q11)$, resulting in transcripts and fusion proteins with unusual tyrosine kinase activity (260). Thus, tyrosine kinase inhibitors, e.g., imatinib and dasatinib, are used as standard therapy with a high rate of remission (261). Consequently, the use of glucocorticoids has become dispensable. Unfortunately, this kind of molecular-targeted therapy is exceptional since the molecular target is unknown in all other types of leukemia.

Acute Myeloid Leukemia (AML)

The heterogeneous character of AML impedes such targeted therapies. Therefore, the treatment largely relies on the use of aggressive chemotherapy (262). AML is characterized by an infiltration of the bone marrow, blood, and tissues by hematopoietic progenitor cells which lose their ability

to differentiate physiologically due to heterogeneous clonal disorders. The extent of the genetic variability of AML patients has been the focus of different studies aiming at customized therapeutic approaches (263). In contrast to more recent findings, it has been demonstrated in 2006 that short-term treatment with high-dose methylprednisolone resulted in an induction of differentiation and apoptosis of leukemic cells in children with AML. Furthermore, the addition of this high-dose glucocorticoid therapy to chemotherapy led to increased remission rates and improved patient outcome (264). However, high rates of glucocorticoid resistance in AML patients have been reported in the last years, so that glucocorticoids are not suitable as standard therapy (265).

Acute Lymphoblastic Leukemia (ALL)

In contrast, leukemic cells in ALL are much more sensitive to glucocorticoids. Therefore, the administration of high-dose glucocorticoids (i.e., dexamethasone and prednisolone) represents the standard induction therapy in ALL (266). The specific genotypes of ALL are diverse, including aberrant expression of proto-oncogenes, chromosomal translocations resulting in fusion genes and hyperdiploidy involving more than 50 chromosomes [reviewed in (267)]. These genetic alterations contribute to changes in cellular function, such as a dysregulation of differentiation, proliferation, and programmed cell death of hematopoietic stem cells (254, 267, 268).

The glucocorticoid-induced cell death in leukemia is mediated by the glucocorticoid receptor via transrepression and transactivation (please see Introduction). It has been demonstrated that the repression of anti-apoptotic BCL2 and the activation of the antagonizing pro-apoptotic BIM induce cell death in ALL (269, 270). Other genes and even microRNAs have been described to be regulated by glucocorticoids and thereby mediate apoptosis (271–273). In addition, cell death is also triggered by calcium release from the endoplasmic reticulum into the cytosol and by an enhanced expression of thioredoxin-interacting protein (TXNIP) which induces cell death by increasing reactive oxygen species and/or blocking glucose transport (270).

Finally, the underlying mechanisms which mediate glucocorticoid-induced cell death in leukemia are

diverse and not yet well-understood. The existence and the development of glucocorticoid resistance after long-term therapy aggravate treatment strategies or reverse the achieved remission. This applies to both the treatment of cancer and the treatment of inflammatory autoimmune diseases.

CONCLUDING REMARKS

After highlighting the effects of glucocorticoids in different immune cells in the context of a variety of immunopathologies, we have to conclude that the understanding of the mode of glucocorticoid action in the scope of immune responses and glucocorticoid resistance is still incomplete. Although glucocorticoids have ranked among the most potent immunosuppressive drugs in daily clinical care for more than 70 years, knowledge on their mechanisms of action on cellular and sub-cellular levels in an immune cell type-specific

manner and in the context of the respective immunopathology remains scarce. Further research into this topic will enhance our comprehension of the capacity spectrum of glucocorticoid action and the establishment of glucocorticoid resistance, also providing guidance for personalized therapy.

AUTHOR CONTRIBUTIONS

TG, LE, and CS designed the concept. CS and LE prepared the figures. All authors wrote the manuscript and read and approved the final version of the manuscript.

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