GLUCOCORTICOIDS: THE MODE OF ACTION IN BULLOUS PEMPHIGOID

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WORD COUNT: 3877

NUMBER OF DISPLAY ITEMS: 1 table and 1 figure

ABSTRACT

Bullous pemphigoid (BP) is the most common of pemphigoid diseases caused by autoantibodies against the structures of dermoepidermal junction followed by complement activation, innate immune cell infiltration, neutrophil proteinase secretion and subepidermal blister formation. The first line treatment of BP is topical and systemic glucocorticoids (GC).

Regulation of the immune system and inflammatory cells is the main target of GC actions. GCs act through genomic and non-genomic mechanisms. The human glucocorticoid receptor (GR) mediates most of the biologic effects of glucocorticoids: cytosolic GR binds GCs and is capable to bind to glucocorticoid response elements in DNA and either transactivate or transrepress genes depending on the tissue and cell-type. In addition, GR exerts rapid, non-genomic effects possibly mediated by membrane-localized receptors or by translocation to mitochondria. GCs can also interact directly with several enzymes and cytokines.

As a target treatment for BP, the production of autoantibodies should be discontinued. GCs, in spite of their wide immunosuppressive actions, are weak to stop immunoglobulin G (IgG) autoantibody formation. However, both systemic and topical GCs are able to reduce the clinical symptoms of BP. GCs are used to inhibit the secondary inflammation and symptoms, such as blistering and pruritus, and it is shown that GC treatment will gradually decrease also the autoantibody formation. Our review article analyzes the mode of action of GC treatment in BP, as far it is possible due to paucity of modern immunological studies.

INTRODUCTION

Glucocorticoids (GCs) are the cornerstone of management in autoimmune skin diseases, including the pemphigoid diseases (1-3). Before the era of GCs, bullous pemphigoid (BP), the prototype of pemphigoid diseases, was fatal in 30% of the cases (4). The mortality has been reduced by GC treatment, but different dosing protocols, as well as steroid-sparing agents, have been searched to decrease the suggested contribution of GCs to the rate of deaths in BP (5). Long-term and high-dose treatment with GCs carries the well-known risk of side-effects (6). Understanding how GCs exert their actions in BP should help to develop novel dosing regimens to decrease the undesired side-effects of them (3,7).

Albeit GCs have been used to treat thousands of patients since their introduction in 1950s' (8,9), surprisingly little is known about their exact mechanism of action (10). Compared to modern biological therapies, GCs still give a challenge to scientists, as their role in controlling the activities of immune system are still not fully understood (10). In this article, we analyze the effects of GCs in BP.

THE BASIC ACTIONS OF GLUCOCORTICOIDS

Human glucocorticoid receptor

The diverse actions of GCs on immune system are mainly mediated by intracellular glucocorticoid receptor (GR) (11). GR belongs to the nuclear steroid receptor superfamily (12). The GR cDNA was cloned for the first time in 1985 (13). Due to alternative splicing, different GR isoforms are formed (14).

GR alpha (GRα), the classic GR isoform, is expressed in virtually all human cells (10). It mediates most of the known actions of GCs. GR beta (GRβ) transcript differs from GRα only in its shorter carboxy terminus (13). The region of the variation is located in the hormone-binding domain, so that GRα binds to cortisol or GC, but GRβ does not (15,16). Furthermore, by

alternative splicing, GR gamma (GRγ) (17), GR-A and GR-P (18) are generated. GRγ binds GCs, but GR-A and GR-P do not (14). The clinical relevance of these isoforms has been studied to some extent, but more studies are needed to evaluate their role in GC responses (14).

GRα and GRβ can undergo alternative translation initiations (19) in exon 2, which generates several translational GR isoforms (19). Eight translational isoforms of GRα with truncated N-terminus are generated: GRα-A, GRα-B, GRα-C1, GRα-C2, GRα-C3, GRα-D1, GRα-D2, and GRα-D3 (14,19). Similar translational isoforms can be also generated from GRβ, GRγ, GR-A and GR-P, since they all share the same initiation sites in exon 2 (14).

The repertoire of GR subtypes is further expanded by posttranslational modifications (14). Phosphorylation (20,21), ubiquitination (22), sumoylation (SUMO; small ubiquitin-related modifier) (23) and acetylation (24) all provide receptor heterogeneity. All the isoforms, translational isoforms and posttranslational modifications, give rise to a massive possibility for cells to respond to GC therapy.

The ligand-free GRα resides predominantly in the cytoplasm of cells, where it is bound to a large multiprotein complex containing heat-shock protein 90 (hsp90), hsp70, p23 as well as immunophilins FKBP51 and FKBP52 (25). Once the ligand (cortisol or GC) binds to GRα, the multiprotein complex dissociates and GRα is translocated to the nucleus through nuclear pores (14). GRα binds as a homodimer to specific glucocorticoid response elements (GRE) in DNA, modulating the expression of glucocorticoid-responsive genes (26,27). This binding mediates GC signalling (14). In addition, ligand-activated GRα can act as a monomer, modulating gene expression with other transcription factors, making the response to GCs more complex (27).

GR has also been reported to localize at the cell plasma membrane in caveolae in interaction with caveolin 1 (28) as well as in mitochondria in several cell lines (29). The rapid GC effects that occur within minutes after administration can, at least partly, be explained by these mechanisms that override the primary transcriptional mechanism.

Transactivation and transrepression of genes by glucocorticoids

Genes related to resolution of inflammation that are known to be upregulated by GCs include lipocortin I (annexin A1; ANXA1) and p11/calpactin binding protein (30,31). Both lipocortin I and p11/calpactin binding protein are involved in the suppression of the release of arachidonic acid (30,32). Interleukin (IL)-1 type II receptors are also upregulated by GCs (33). In addition, the expression of IL-10, β2-adrenoreceptors and secretory leucocyte protease inhibitor (SLPI) is upregulated by GCs (34,35). The role of these proteins might be in the longer term anti-inflammation, since their induction kinetics are generally slow: over a 24–48 hour period (30).

The major biological function transrepressed by GCs is the hypothalamus-pituitary - axis through decreasing corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) expression (30). However, the negative GRE sites are not generally found in the promoter region of inflammatory genes and transrepression without GC binding to DNA has been proposed (30). GRs can bind to transcription factors such as activator protein (AP)-1 and nuclear factor (NF)-κB and via this protein-protein interaction suppress the expression of inflammatory genes (30), for example expression of tumor necrosis factor (TNF)-α, IL-1β, IL-6 and transforming growth factor (TGF)-β (35).

GCs are also known to regulate several biologic actions of their target cells independently of transcriptional regulation inside the nucleus. These actions are rapid and take place within seconds to minutes (35). In immune cells, for example, GCs can alter the circulation of Na^+ and K^+ across the plasma membrane leading to suppression of the inflammatory reaction (36). Furthermore, mitochondrial GR might induce cell apoptosis by directly changing the transcription of the mitochondrial genes (37).

PATHOGENESIS OF BULLOUS PEMPHIGOID

The group of pemphigoid diseases includes a series of chronic autoimmune blistering skin diseases (1). Pemphigoid diseases are characterized by subepidermal blisters and presence of tissue bound and circulating autoantibodies against the structural components of hemidesmosomes in the dermoepidermal junction (1). Pemphigoid diseases can be divided according to their clinical, histologic, immunopathologic or molecular biological features (1). In this review, the pathogenesis of BP as the most common of pemphigoid diseases is discussed.

BP is a blistering skin disease mainly affecting senior patients over 70 years of age (1). The risk of BP increases up to 300-fold above the age of 90 compared with patients below the age of 60 (3). It is the most common autoimmune blistering skin disease worldwide (2); incidence varies from 12.1 to 21.7 new cases per 1 million people per year depending on the study population (5,38,39). A recent study from Germany showed prevalence of 259.3 patients per million people (40).

The initial cause of BP is unknown. Drugs (diuretics, antihypertensives, gliptins) (3,41), UV light (42), PUVA therapy (43) and ionizing radiation (44) are proposed as inductors of BP in genetically susceptible patients (3). Inducing factors are identified approximately from 15% of BP patients (45). The strong association between BP and several neurological diseases, such as multiple sclerosis, Alzheimer's disease and Parkinson's disease (46) has led to an assumption that neurodegeneration or neuroinflammation could be one of the factors leading to the initiation of BP (47).

The immunological pathogenesis of BP was first introduced in 1967: immunoglobulin G (IgG) and complement C3 were shown to bind to basement membrane in the dermoepidermal junction of the skin (48). Tissue bound and circulating autoantibodies against the two major autoantigens, structural components of hemidesmosome, BP180 and BP230, are the immunological characteristics to BP (49,50). BP180 is more important of the two autoantigens in BP; the

pathogenic role of BP230 is not clear (1,3). BP180 (also known as collagen XVII or BPAg2) is a transmembrane glycoprotein with a type II orientation; the N-terminus is intracellular and the C-terminus extracellular (1,51). The extracellular domain contains around 1000 amino acids, making 16 non-collagenous (NC) and 15 collagenous domains (52). The 16^{th} NC domain (NC16A) is located just outside the cell membrane of epidermal basal keratinocytes spanning the lamina lucida of basement membrane, and is the immunodominant component of autoantigen BP180 (49). BP230 (dystonin or BPAg1e) is a part of the intracellular hemidesmosomal plaque (1). Patients with certain HLA –subtypes (HLA-DQB1.03:01 allele) have been shown to have an increased T cell activity to several epitopes of BP180, particularly NC16A domain (53). Also polymorphism in the mitochondrially encoded ATP synthase 8 (MT-ATP8) (54) and in the CYP2D6, one of cytochrome P450 isoenzymes, gene (55) may be associated with the risk of drug-induced BP in some cases. It is also generally agreed, that individuals with suitable genetic background may develop autoimmune disease when confronted with certain environmental triggers (such as UV radiation) (56).

The autoreactive T and B cells recognise the immunodominant NC16A domain of BP180 (57). NC16A-specific peripheral T cell response is a mixture of T helper 1 (Th1)/Th2 type reaction with Th2 predominance, followed by presence of Th1 regulated IgG1 and Th2 regulated IgG4 autoantibodies (58). Regulatory T cells (Treg) are suggested to balance the inflammatory T cell responses in BP (59), however their exact role is still unknown. In untreated BP, the amount of Tregs is lower than in healthy controls (60).

Previous studies have demonstrated that the pathogenesis of BP includes IgG1 and IgG3 autoantibody formation leading to complement activation and fixation (3). Complement activation-derived fractions C3a and C5a induce neutrophil and eosinophil chemotaxis and mast cell degranulation (3). Leukotriene B4 (LTB_4), formed from arachidonic acid, has recently been suggested as a critical driver of neutrophil recruitment in BP (61). LTB_4 is a potent granulocyte chemoattractant and has been shown to be abundant in the blister fluid of BP patients (61).

Neutrophils secrete and release proteolytic enzymes such as matrix metalloproteinase (MMP)-9 and neutrophil elastase (NE) (3). Eosinophil migration also follows early mast cell degranulation leading to release of a variety of inflammation mediators, such as leukotrienes and TNF-α (3). All these events together, lead to subepidermal blister formation (1,3,62). Complement activation is a key event in the pathogenesis of BP (3), and downregulation of CD46, a key inhibitor of complement activation, may be involved in the pathogenesis of BP (63).

New studies have revealed a complex interplay between innate and adaptive immunity behind the formation of blisters, however not yet well understood. Overexpression of nod-like receptor P3 (NLRP3) inflammasome components and IL-18 seems to correlate with the titre of serum autoantibodies, as well as disease severity (64). It is also suggested, that there is an interaction between periostin and CD163+ skin-resident macrophages in BP (65). IL-8 produced by keratinocytes attracts neutrophils to the dermoepidermal junction (66). In addition to IL-8, basal keratinocytes produce IL-6 upon stimulation by autoantibodies (3). Th2 cell related IL-5 attracts eosinophils (67). Eventually, due to all these inflammatory processes, lamina lucida is split and the blister formed (49).

A recent study showed that BP blister fluids display high levels of IL-6, IL-17, IL-22 and IL-23 cytokines, mainly excreted by neutrophils and mast cells, and that TGF-β is increased in BP sera (68). Although these cytokines belong to Th17 lineage, Le Jan and co-workers found no Th17 cells in BP skin biopsies (68). Instead, innate immune cells, especially neutrophils, but also mast cells, seemed to produce IL-17 to the blister fluid (68). In the same study, IL-17 was also shown to upregulate MMP-9 and NE (68). The result by Le Jan and co-workers explain why a previous study failed to detect Th17 cells among the T cells participating in the autoreactivity against NC16A epitopes in BP (59): IL-17 producers in BP are innate immune cells, not Th17 cells.

GLUCOCORTICOID TREATMENT IN BULLOUS PEMPHIGOID

GCs are the first-line of treatment in BP according to both international (2) and national (69-71) guidelines. The goal of treatment is to inhibit the pathological intracellular signaling cascades induced by the autoantibodies (3). Systemic prednisolone therapy is usually suggested to be initiated in doses lower than 0.5-0.6 mg/kg/day (72), despite the lack of evidence in extensive diseases (5,73,74). Doses greater than 0.75 mg/kg/day are generally not beneficial or supported, as the risk of side-effects and mortality increases (73,75). For maintenance therapy, GC dose should be tapered gradually with the aim of achieving minimal dose that still controls the symptoms (2). The total treatment duration is usually from 9 to 12 months and prior to the cessation of treatment, possible adrenal insufficiency should be excluded (2). Topical potent or very potent GCs are recommended either as the first-line treatment or to mild, limited disease (2). The long-term use of topical therapy may be less favorable to patients due to cutaneous side-effects, tolerability, cost and the time required to application (2). Other immunosuppressive agents; azathioprine, mycophenolate mofetil, methotrexate, dapsone and cyclosporine; are the most commonly used steroid-sparing agents in pemphigoid diseases (1), although having almost no evidence from clinical studies. Recently, doxycycline monotherapy has also been shown to have safer long-term effect in BP than GCs (76). Intravenous immunoglobulin, plasmapheresis and rituximab are also used in very severe individual cases (1). Altogether, the treatment of pemphigoid diseases is based more on clinical expertise than controlled studies, systemic GCs being the best-validated and therefore the standard therapeutic option (77). GC equivalents are shown in Table 1 and Figure 1 gives an overview of GC effects in BP.

Glucocorticoid receptors in bullous pemphigoid

Insensitivity, even resistance to GCs has been observed in patients with glucocorticoid-resistant asthma (78-80), rheumatoid arthritis (81), nasal polyposis (82) and atopic dermatitis (83). The

common feature of the studies listed above is, that GRβ was found to be highly expressed in the patients insensitive to GCs. In the study by Kubin and co-workers, both GRα and GRβ were shown to be expressed in BP patients, and their expression was altered during treatment with a systemic GC (prednisolone) (84). However, no connection with the level of GRα or GRβ expression and clinical response was observed, indicating that the alteration of GR activity is not relevant in the treatment of BP with GCs. The sensitivity of cells to GCs might be, however, influenced by the abundance of different receptor isoforms, or tissue-specific responsiveness to GCs (85,86).

The effect of glucocorticoid treatment on IgG and IgE autoantibodies in bullous pemphigoid

IgG is the main type of immunoglobulins found in the blood and extracellular fluid of BP patients. IgG1 and IgG3 activate complement (3). IgG4, related to Th2 dominant inflammation, does not activate complement, but may have inhibitory role in BP by blocking the binding of IgG1 and IgG3 to NCA16A region (87). Also healthy persons or patients with neurological disease, but without any BP-like skin symptoms, can have circulating BP180 autoantibodies (47,88), however the functional significance of these autoantibodies is currently poorly understood.

Generally, circulating IgG BP180 antibody titre measured by enzyme-linked immunosorbent assay (ELISA) has been shown to correlate with the clinical severity of BP (1,89,90). Patients with high BP180 titre (>200 IU/mL) might need higher doses of prednisolone (72). If BP180 titre is > 27 IU/mL, the cessation of treatment is not recommended due to a risk of relapse (2). Total anti-BP180 IgG titre decreases with GC therapy (90), but the exact doses and time needed to decrease serum anti BP180 IgG below < 27 IU/mL is not known. It has been shown that BP180 antibody titres were gradually decreased with systemic GC treatment (90), but on the other hand, treatment with topical or systemic GCs only for some weeks seems to clear all clinical symptoms, although serum autoantibody levels remain high (91,92).

The presence of IgE autoantibodies against BP180 has been reported to vary between 22% and 100% of BP serum samples (93,94). Bing and co-workers showed that the level of BP180 NC16A IgE antibodies did not correlate with severity of disease in the early stages of BP and that the levels continued to rise despite the effective control of the disease in the initial six weeks of diagnosis (95). However, in a recent study positive anti-BP180 IgE titre was detected from 40.2% of 117 patients, and the level also correlated with disease activity (93). The pathogenic relevance of BP180 IgE autoantibodies has been suggested in some experimental models and by the use of omalizumab (IgE antibody) in individual patients with BP (93,94,96). Although detection of anti-BP180 IgE from BP patients' sera is not of diagnostic importance, it may be relevant for therapeutic decisions in the future, e.g. initiation of anti-IgE treatment.

The effect of glucocorticoid treatment on lymphocytes in bullous pemphigoid

Immature B cells are more sensitive to GC-induced apoptosis than mature B cells. B cells express GR throughout development (97). The survival and proliferation of B cells is regulated by the B cell activating factor (BAFF), which is a member of the tumor necrosis factor family (98). BAFF is expressed in many immune cells, but its three receptors are primarily present in B cells (98,99). BAFF regulates the survival and maturation of B cells, antibody production and immunoglobulin switching, as well as stimulates T cells (100). Importantly, an excessive expression of BAFF favours the development of autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis (91). Treatment with GCs may determine apoptosis of autoreactive B cells by reducing the expression of BAFF (101). There is no known significant association between the serum BAFF levels and titre of anti-BP180 antibodies in the patients with BP. However, serum BAFF levels tend to be more elevated in patients with shorter disease duration (99). There is a tendency that BAFF levels increase before the anti-BP180 antibody levels increase at the onset of

BP and quickly decrease in response to GC treatment (99). Currently it is largely unknown, what is the significance of BAFF in the initiation of the autoantibody formation in BP.

In low-to-moderate dose range, GCs have pleomorphic effects on T cells. The sensitivity and response to GCs is different in various types of T cells. In general, GCs influence the polarization of Th cells by inhibiting the differentiation of Th1 and Th17 cells while enhancing the activity of Th2 and Treg cells (97). The polarization is dependent on dendritic cells (DC) and GCs inhibit antigen presentation, co-stimulation, cytokine production and directly regulate T cell receptor (TCR)(97). Naïve CD4+ T cells are primarily affected more than mature CD4+ effector and memory T cells (101).

Apoptosis is essential for the development and maintenance of the immune system and GCs can induce T cell apoptosis (102). The GC-induced apoptosis of lymphocytes differs by activation state, lymphocytic type and the stage of differentiation (97). In T cells, initiation of GC-induced apoptosis requires the presence of functional GR and some events may involve non-genomic actions (102).

GCs have immunosuppressive effects on pro-inflammatory T cells, while they stimulate Treg activity (101). GCs inhibit the synthesis and function of some cytokines, particularly Th1 cytokines and to a lesser extent the secretion of chemokines and co-stimulatory molecules from immune and endothelial cells (101). In general, GCs impair the release of inflammatory cells from lymphoid tissues and enhance circulatory emigration, inhibit the signal transmission pathway mediated by TCR, up-regulate CD25 expression (Tregs), reduce IL-2 synthesis and secretion as well as inhibit the expression of Th17 and Th1 effector cytokines IL-17 and IFN-γ (101).

As mentioned, GCs inhibit cytokines belonging to the Th17 family (103). In the study by Le Jan and co-workers, super potent topical GCs reduced both IL-17 expression and clinical symptoms of BP without decreasing serum autoantibody concentration rapidly in few days (68).

Rapid reduction of IL-17 expression has also been shown in psoriatic patients treated with potent topical GCs (104).

The effect of glucocorticoid treatment on neutrophils and eosinophils in bullous pemphigoid

Strong topical GCs are able to decrease dermal polynuclear cell infiltration as well as proteinases such as MMP-9 and neutrophil elastase (NE), which are essential for blister formation in BP (105). GCs have profound effects on the cellular functions of leukocytes and endothelial cells, resulting in reduced ability of leukocytes to adhere to vascular endothelium and exit from circulation (106). Thus the entry to the sites of infection and tissue injury is impaired, resulting in the suppression of inflammatory responses (107).

Tissue damage in experimental model of BP has been shown to be dependent on the release of reactive oxygen species (ROS) by neutrophils (108). GCs can inhibit the release of ROS (108) and IL-8 (Hellberg: unpublished data) by neutrophils, as well as degranulation. There are some support that topically applied methylprednisolone can inhibit ROS mediated tissue damage initiated by neutrophils (108).

Eosinophils found abundantly in the upper dermal inflammatory infiltrate are characteristic to BP (1). The role of eosinophils and their toxic mediators in blister formation is represented in the study by de Graauw and co-workers (67). Their results provide evidence that IL-5 activated eosinophils directly contribute to BP blister formation in the presence of BP autoantibodies (67). Eosinophils are exquisitely sensitive to GCs; GCs induce eosinophil apoptosis (109). Neutrophil apoptosis, in contrast, seems to be inhibited by GC treatment (109).

GCs also inhibit release of histamine by basophils, increase the transcription of leukocyte proteinase inhibitors, reduce basophile count and induce eosinophil apoptosis in Fas-mediated pathway (109).

The effect of glucocorticoid treatment on dendritic cells in bullous pemphigoid

GCs induce a marked reduction in circulating plasmacytoid dendritic cells and prevent generation of dermal CD34+ derived dendritic cells (DCs) in healthy adults (110), without any inhibition in Langerhans cell development *in vitro* (111). GC treatment may impair immunity to newly-encountered antigens. GC treatment also may induce DC apoptosis (97). The role of dendritic cells in the initiation and modulation of autoimmune diseases is the object for novel studies trying to find tolerogenic DCs with capacity of blocking undesired autoimmune responses (112).

The effect of glucocorticoid treatment on monocytes and macrophages in bullous pemphigoid

The interaction of antibodies and inflammatory cells is regulated by binding of the Fc-region of IgG antibodies to their corresponding receptors. FcγRIIIa, a particular Fc-receptor subtype, is expressed on macrophages playing a role in BP pathogenesis (113,114). *In vitro* low concentrations of GCs exert an immunomodulatory effect on macrophage functions, adhesion, chemotaxis, phagocytosis and cytokine function, while higher concentrations exert an immunosuppressive effect, especially on activated cells (115). GCs also stimulate the phagocytosis of apoptotic material by macrophages, as shown by Giles and co-workers: GC treatment for 24 hours increases the up-take of apoptotic bodies (116). GCs also increase IL-10 excretion and re-programme monocyte differentiation to anti-inflammatory phenotypes (101).

The effect of glucocorticoids treatment on mast cells, cytokines and other mediators in bullous pemphigoid

GCs inhibit maturation of mast cells and production of cytokines, chemokines and FcεRI expression in mast cells (117). In addition, GCs also inhibit secretion of inflammatory cytokines found in BP lesions (IL-1b, IL-5, IL-6, IL-8, IL-10, IL-13, IL-17, IL-22, IL-23, TGF-β, TNF-α and

INF-γ) (3,118). In addition, the stability of mRNA encoding IL-1, IL-2, IL-6, TNF and granulocyte-macrophage colony-stimulating factor (GM-CFS) is diminished (119).

CONCLUDING REMARKS

GCs are the most efficient anti-inflammatory molecules successfully used in the treatment of BP. The response of human immune system to GC treatment is variable, and understanding the actions of GCs is important in clinical practice. Although potent topical or systemic GCs exert mostly rapid improvement of all clinical symptoms of BP, the underlying disease processes may continue, because of the slow decrease of IgG autoantibodies. Before we can develop any novel target therapies to suppress the inflammatory cascades in BP activated by autoantibodies, we need better understanding of the key events in the initiation of autoinflammatory processes.

ACKNOWLEDGEMENTS

All authors took part in designing the paper. M.K. and R.P. wrote the text, L.H. draw the figure. We thank professor Kaisa Tasanen, MD, PhD and Nina Kokkonen, PhD for revising the article.

CONFLICTS OF INTEREST: The authors state no conflict of interest.

ABBREVIATIONS

BAFF	B cell activating factor belonging to the tumor necrosis factor family
BP	bullous pemphigoid
BP180	bullous pemphigoid antigen 180
BP230	bullous pemphigoid antigen 230
ELISA	enzyme-linked immunosorbent assay
GC	glucocorticoid

GR	glucocorticoid receptor
GRE	glucocorticoid response elements
IFN	interferon
IL	interleukin
MMP	matrix metalloproteinase
NE	neutrophil elastase
TGF	transforming growth factor
TNF	tumour necrosis factor

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Table 1. Pharmacology of glucocorticoids.

	Equivalent GC dose (mg)	**Mineralocorticoid potency (relative)**	**Duration of action (hours)**
Short-acting			
Cortisone	25	1.0	8-12
Hydrocortisone	20	0.8	8-12
Intermediate-acting			
Prednisone	5	0.25	24-36
Prednisolone	5	0.25	24-36
Methylprednisolone	4	0	24-36
Triamcinolone	4	0	24-36
Long-acting			
Dexamethasone	0.75	0	36-54
Betamethasone	0.6	0	36-54

FIGURE LEGENDS

Figure 1: Overview of glucocorticoid (GC) effects in bullous pemphigoid. **1:** Neutrophils are recruited by interleukin (IL)-8 secreted by keratinocytes and neutrophils. Reactive oxygen species (ROS), neutrophil elastase (NE) and matrix metalloproteinase-9 (MMP-9) produced by neutrophils contribute to tissue damage. GCs block production of ROS, NE, MMP-9, IL-8 and IL-17. **2:** Eosinophils are recruited to the dermoepidermal junction by Th2-related IL-5 and contribute to tissue damage. GCs induct and initiate eosinophil apoptosis. **3:** Proliferation and survival of autoreactive B cells is stimulated by B cell activating factor (BAFF). GCs inhibit the release of BAFF. GCs reduce numbers of dermal CD34+ derived DCs and may impair immunity to newly-encountered antigens. **4:** GCs inhibit Th1-polarization of naïve T cells and favour development of regulatory T cells (Treg). GCs suppress IL-5 production by Th2 cells. **5:** GCs block production of numerous inflammatory cytokines by mast cells. **6:** GCs stimulate clearance of apoptotic cells by macrophages. Uncleaned apoptotic cells can stimulate inflammatory processes. **7:** Basophils contribute to production of histamins; production is blocked by GCs. **8:** Subepidermal blisters form as a result of destruction of hemidesmosomes (HD) after anti-BP180 and BP203 auto-antibody binding and C3 deposition as well as ROS, NE and MMP-9 release.