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Review

How to manage patients with corticosteroids in oncology in the era of immunotherapy?

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Abstract Corticosteroids are among the most prescribed drugs in oncology. The indications range from cancer-related indications for refractory symptoms, anti-cancer effects mainly in hematology, supportive measures for cancer-specific treatments and more recently immune-related adverse events induced by modern immunotherapies. In oncological emergencies, corticosteroids are common first-line treatments because of their rapid effect and wide variety of actions. In the last 5 years, with the advance of immune checkpoint inhibitors, corticosteroids are becoming routinely used to manage immune-related adverse effects. Preclinical studies suggested that corticosteroid-induced immunosuppression might dampen the activity of immunotherapies. Prospective clinical studies show that corticosteroid use is a prognostic marker for the cancer outcome in metastatic setting but does not significantly alter the patient's response to immunotherapies per se. Here, we review the state of the art on corticosteroid use in oncology, with a focus on the drugs' potential impact on immunotherapy activity. The

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comprehensive pharmacological characteristics of corticosteroid drugs, clinical indications, modality of administration and associated precautions for use are discussed in this article.

1. Introduction

Following the discovery of 'the hormones of the adrenal cortex' in the mid-20th century, the development of synthetic corticosteroids led to many applications in medicine in general and in oncology [1–3]. The corticosteroids' four main roles in oncology are related to the compounds' anti-inflammatory activity to control palliative symptoms, anti-cancer activity in some hematological malignancies, supportive prophylaxis for cancer-specific treatments and immunosuppressive activity to manage immune-related adverse events (irAEs) induced by immunotherapy [1,4,5]. This article will propose (i) to summarise the state of the art on corticosteroid use in oncology, (ii) to recap the pre-clinical data of drugs' impact on antitumor immunity and (iii) to discuss their clinical impact in patients treated with immune checkpoint inhibitors (ICIs).

1. What are the main differences in efficacy, safety and bioavailability between the various corticosteroids prescribed by oncologists?

The main mechanisms underlying the corticosteroids' activity are summarised in Figure 1 [1,6,7]. Corticosteroids can be administered systemically (orally or intravenously) or locally (e.g. by direct or topical application to the skin, delivered in the digestive tract, in joints, the eye or in the respiratory tract). Systemic administration is associated with a more rapid anti-inflammatory action, as the corticosteroids diffuse rapidly through the organs [3]. Conversely, local administration is preferable for the localised treatment of mild-to-moderate inflammatory lesions or reactions.

1.1. Systemic routes of administration for corticosteroids

The systemic administration of corticosteroids constitutes the first-line treatment for severe autoimmune reactions, such as those triggered by ICIs [4]. Systemic corticosteroid therapy provides strong and rapid anti-inflammatory activity (within 24 h of the first dose) [1,3]. As indicated in Table 1, the various corticosteroid drugs differ in their potency when administered systemically and so can be classified by their mean prednisone equivalent dose.

The two most frequently prescribed oral corticosteroids are prednisone and prednisolone. After absorption, prednisone is transformed into the active metabolite prednisolone by 11β-hydroxylation in the liver. Prednisolone is reputed to have less bioavailability than prednisone [3]. Accordingly, prednisone should be preferred for the long-term treatment of chronic inflammatory diseases.

1.2. Locally administered corticoids

Many corticosteroids can be given locally, via application to the skin (e.g. clobetasol propionate and betamethasone dipropionate), in the digestive tract (e.g. budesonide), the respiratory tract (e.g. fluticasone) or the joints (e.g. cortivazol). Locally administered corticosteroids have a powerful local action and a weak potential to diffuse and enter in the direct circulation; it could be estimated that 1% of the dose locally given enters the systemic circulation [3,8,9].

2 Which are the main measures associated with corticosteroid use in oncology?

In a medical emergency, there are generally no formal contraindications to corticosteroid therapy [1]. In other settings, it is important to carefully check for precautionary measures before initiating corticosteroid therapy because of the risk of adverse drug reactions [1,3]. Furthermore, these precautionary measures can be divided into those taken before corticosteroid initiation and those maintained throughout treatment. When corticosteroids are used locally, a local infection must be ruled out before utilization (e.g. staphylococcal or viral [shingles] skin infections) [3]. For the systemic route of administration, the key features of preventing adverse reactions of corticosteroid therapy are shown in Figure 2.

Overall, the six main precautionary measures for preventing adverse reaction with corticosteroids could be summarised as follows:

- *Prevention of infectious diseases*

As corticosteroids have an immunosuppressive effect, it is required to eliminate or control infections prior to the initiation of corticosteroids [3,10]. Corticosteroids are generally contraindicated in patients with an active bacterial infection (with pneumococci, staphylococci, enterococci etc.), active viral infection (with varicella zoster virus, shingles, herpes group viruses, viral hepatitis etc.) or other active fungal or parasitic infection [1]. Of note, the impact of corticoids in immunity towards the new Covid19 is not clearly defined [11], but a recent

preliminary report of the RECOVERY trial showed that 6 mg of dexamethasone reduced 28-day mortality among patients receiving invasive mechanical ventilation or oxygen [12]. In oncological patients, corticosteroid therapy may unmask an underlying infection. The treatment precautions for use to prevent reactivation of underlying infections is depending on the risk of viral infection (infection with the HBV), bacterial infection (mycobacteria) or parasitic infection (prevention of malignant strongyloidiasis), as shown in Figure 2. During prolonged treatment with corticosteroids, trimethoprim sulfamethoxazole is required to prevent the reactivation of pneumocystosis [13]. In patients at risk of reactivation of herpes group viruses, prevention with aciclovir or valaciclovir should be considered [14]. To avoid reactivation of tuberculosis in patients at risk, one can consider 2 months of combination therapy with rifampicin and isoniazid or isoniazid alone (300 mg/day for 6 months) [15]. Patients having traveled to the tropics, endemic areas for strongyloidiasis, should be dewormed, usually with a single dose of oral ivermectin or oral albendazole, before the initiation of corticosteroid treatment [16].

- *Prevention of ion imbalances and hypokalemia*

Corticosteroids increase renal potassium excretion [3]. Before initiating corticosteroids, it is important to check carefully for the absence of ionic imbalances in general and hypokalemia. The potassium level should be monitored daily when high methylprednisolone doses are used, and a potassium supplementation can be proposed to prevent hypokalemia during treatment [1].

- *Prevention of carbohydrate imbalance*

Corticosteroids raise the metabolic rate and can lead to hyperglycemia or decompensation of diabetes mellitus [3,17]. Before initiating corticosteroid therapy, a check for carbohydrate imbalance should be performed. If the patient is known to have diabetes, the blood sugar levels should be monitored more closely throughout the course of corticosteroid treatment, and the doses of antidiabetic treatments should be increased if necessary.

- Mood disorders

Corticosteroids have a psychostimulatory effect and thus can induce mood disorders, such as irritability, depression or even psychotic states [3,18]. Before initiating a course of corticosteroids, a clinical interrogation

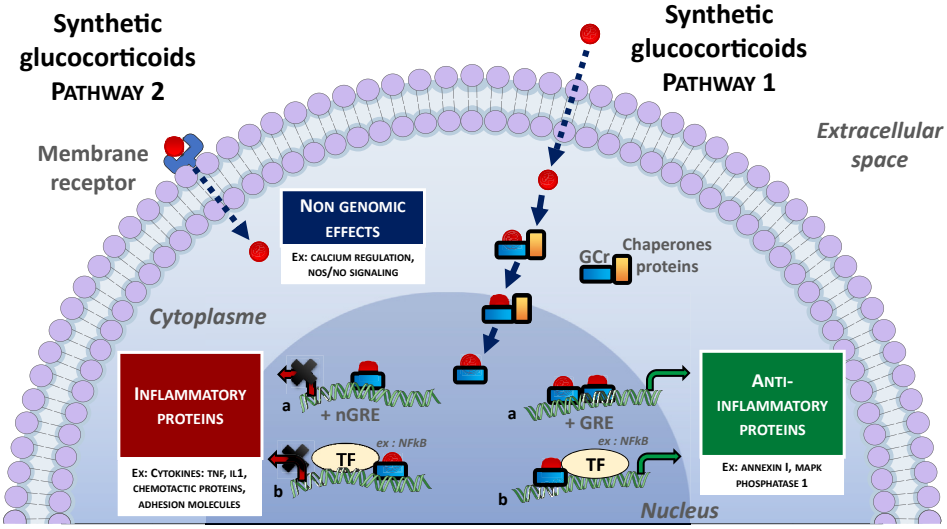

Fig. 1. Mechanisms of action of synthetic glucocorticoids (GCs) in human. Two distinct pathways are described through synthetic GCs deliver their actions. **Pathway 1:** Synthetic GCs are lipid-soluble molecules and diffuse through cell membranes. Cytoplasmic GC binds the GC receptor (GCr) and chaperones proteins involved in the nuclear import of the GCr. Within the nucleus, the GC-GCr complex alters gene expression through two mechanisms: (a) Direct genomic effect: GC-GCr homodimers bind glucocorticoid response elements (GREs) to enhance gene expression. By contrast, GC-GCr monomers can bind negative GREs and recruit the co-repressors to inhibit gene transcription. (b) Indirect genomic effect: It develops protein–protein interactions with other transcription factors (ex: NFkB and activator protein 1), that affect their transcriptional activity. These mechanisms block the transcription of inflammatory proteins (ex: cytokines: TNF, IL-1; chemotactic proteins, adhesion molecules) and induce the expression of anti-inflammatory proteins such as IkB, annexin I, MAPK phosphatase I, resulting in decreased production of inflammatory compounds (ex: prostaglandins, leukotrienes). **Pathway 2:** Other mechanisms are described, including the non-genomic effects, particularly on intracellular calcium homeostasis, smooth muscle reactivity, Reactive oxygen species generation and the involvement of nitric oxide, and inflammatory and apoptotic pathways. *GCr – glucocorticoid receptor; GRE – glucocorticoid response elements; nGRE – negative glucocorticoid response elements; IL-1 – interleukin-1; MAPK – mitogen-activated protein kinase; NF-kB – nuclear factor-kappa B; NO – nitric oxide; NOS – nitric oxide synthase; TF – transcription factor; TNF – tumor necrosis factor.*

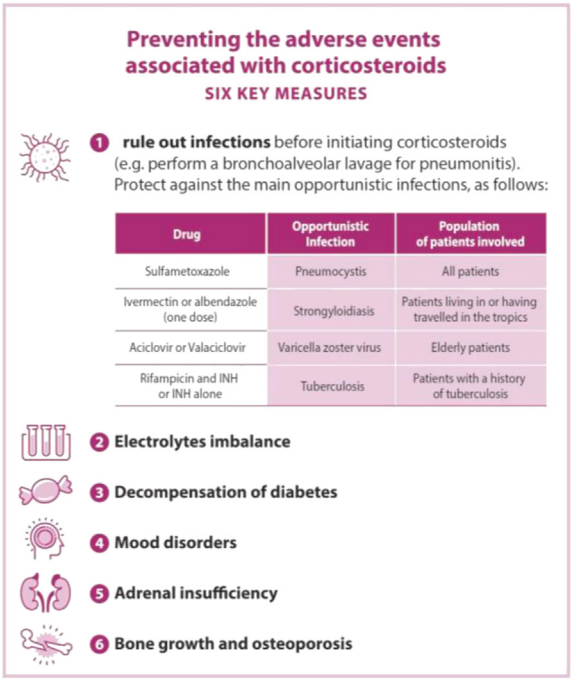

Fig. 2. Key points to help to optimise corticosteroid treatment in routine clinical practice.

for mood disorder should be performed. In patients with past-medical history of psychiatric disorders, their mood disorder should therefore be well under control before corticosteroid therapy is initiated, and patients should be monitored closely for their psychiatric symptoms during treatment.

- *Adrenal insufficiency*

Prolonged systemic use of corticosteroids can progressively inhibit the endogenous hormonal secretion of the adrenal glands and subsequently lead to adrenal insufficiency [3,19]. The latter may even occur when the daily corticosteroid dose is below 7.5 mg prednisone equivalent. The signs and symptoms of adrenal insufficiency are fatigue, low blood pressure, nausea/vomiting, abdominal pain and ion disorders (hyponatremia with inappropriate natriuresis, hyperkalemia and hypoglycemia). Patients should therefore be informed about these symptoms of adrenal insufficiency in the weeks and months after corticosteroids discontinuation [1]. If suggestive signs and symptoms occur, the patients should be advised to consult rapidly so that the presence or absence of adrenal insufficiency could be established with a cosyntropin adrenocorticotropic hormone stimulation test. Cosyntropin stimulates the release of corticosteroids (such as cortisol) from the adrenal glands and is used to assess adrenal gland function. If adrenal insufficiency is confirmed, hormone replacement therapy (with hydrocortisone) will be required [1].

- *Effects on the skeleton, muscle and other miscellaneous adverse events.*

The long-term use of corticosteroids use could affect the skeletal function and could sometimes lead to osteopenia [3,9,20]. To mitigate the long-term risk of bone fragility, patients (and especially those at risk of osteoporosis) must be screened. Given that the risk depends on the duration of corticosteroid therapy, these measures apply only to patients who are going to receive long-term treatment. In patients with brittle bones and known osteopenia or a history of osteoporosis, supplementation with vitamin D and calcium is recommended and can be followed by bisphosphonate prevention therapy to reduce bone fractures risks [1]. Other adverse events of corticosteroids include an increase in muscle catabolism that may lead to muscle weakness, cortisone myopathy, cardiovascular effects including hypertension and ocular adverse events such as glaucoma in some patients [1,3,9].

In summary, this section underlines that a careful general clinical examination is required before the initiation of corticosteroid therapy, that may be associated with miscellaneous adverse events, and patients must be regularly clinically and biologically monitored during and after their treatment.

3 What are the current indications for corticosteroids in oncology?

Corticosteroids are widely used in cancer care, as they reduce the symptoms caused by inflammation and edema and have antiemetic, antiallergic and even

Table 1
Main characteristics of the corticosteroid drugs used in clinical practice, with their dose equivalence.

Drug	Biological half-life (hours)	Anti-inflammatory potency[1]	Equivalent potency[1]	Mineral corticosteroid activity[2]
Hydrocortisone	8–12	1	20 mg	1
Prednisone	12–36	4	5 mg	0.8
Prednisolone	12–36	4	5 mg	0.8
Methylprednisolone	12–36	5	4 mg	0.5
Betamethasone	36–54	25–30	0.75 mg	0
Dexamethasone	36–54	25–30	0.75 mg	0

[1] Potency is defined for equivalence with hydrocortisone.
[2] Intended as a guide only. Adapted from Swartz and Dluhy [3].

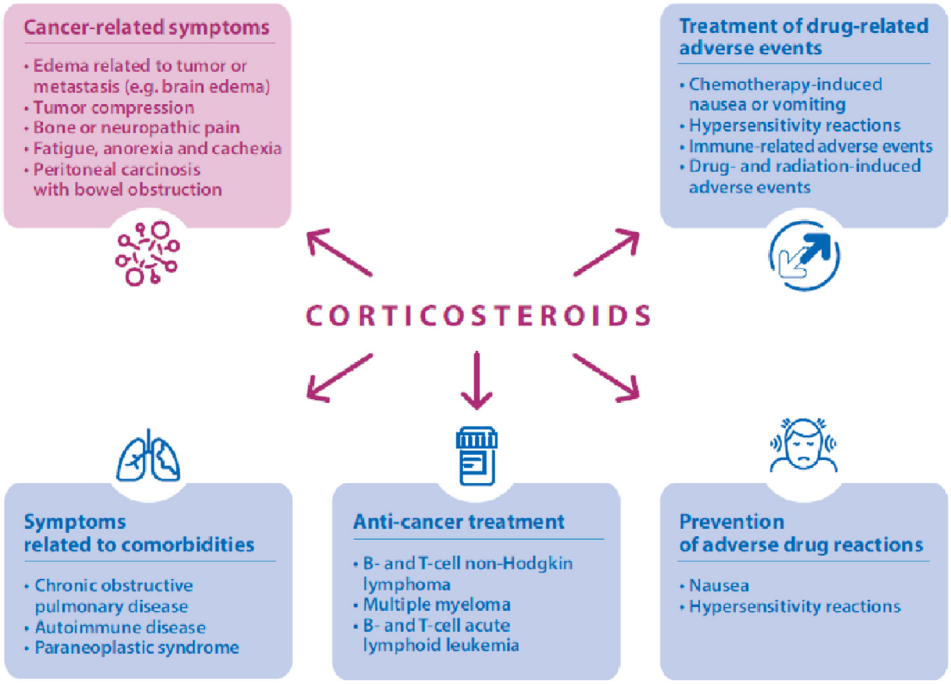

Fig. 3. Main indications for corticosteroid treatment in cancer care.

anticancer effects. Their indications range from cancer-related indications for refractory cancer symptoms, anticancer effects mainly in lymphoid hematological malignancies, supportive measures for cancer-specific treatments, including irAEs, and the treatment of non-cancer-related comorbidities [21] (Figure 3). In oncological emergencies, corticosteroids are common first-line treatments because of their rapid onset of action and wide availability.

Cancer-related symptoms. The most frequent cancer-related signs and symptoms treated with corticosteroids are symptomatic brain metastases, cancer-related dyspnea, bowel obstruction, spinal cord compression and pain from bone metastases [21–24]. When neurological symptoms are present, corticosteroid treatment should be initiated as soon as possible and dexamethasone is the best choice in patients with brain metastases [25]. Corticosteroid administration is associated with rapid symptom relief for headache, nausea, visual disturbances and neurological impairments [26,27]. In leptomeningeal carcinomatosis, however, the symptoms are more difficult to treat, and corticosteroids might have only a moderate effect. An intrathecal administration is possible, usually with chemotherapy [28,29]. In cases of malignant intestinal obstruction due to peritoneal carcinomatosis, corticosteroids are generally used with antiemetic drugs when the goal is to maintain gut function [30]. In randomised clinical trials with late-stage cancer patients, corticosteroids provided short-term relief of fatigue, better quality of life and greater appetite, relative to placebo [31,32]. The guidelines on cancer-related dyspnea or pain are less clear, and evidence from randomised controlled trials is needed [33,34]. In palliative care setting, common adverse drug reactions that limit the use of corticosteroids include buccal candidiasis, proximal myopathy and insomnia [24,35]. In older adults, corticosteroid could deregulate mood function and induce cognitive impairment. In view of these adverse drug reactions, corticosteroids should be administered at the lowest effective dose and for the shortest possible duration. In patients with clinical benefit on corticosteroids, the dose should be tapered carefully as soon as the signs or symptoms recede. In other cases of non-clinical benefit to corticosteroids, the treatment should be withdrawn to avoid unnecessary adverse effects.

Preventing adverse drug reactions. Corticosteroids are widely used in supportive care and are highly effective in the prevention and treatment of acute and delayed chemotherapy- and radiotherapy-induced nausea and vomiting. They are used in association with serotonin 5-HT3 receptor and neurokinin-1 receptor antagonists, if moderate or high emetogenic chemotherapy [36,37]. Corticosteroids have also antiallergic properties and so are recommended in the prevention and treatment of drug–infusion reactions, such as anaphylaxis and cytokine release/hypersensitivity reactions [38]. Prednisolone equivalent doses of 1–2 mg/kg I.V. every 6 h are indicated in the treatment of infusion reactions [38]. In a prophylactic setting for hypersensitivity reactions, corticosteroids are typically combined with docetaxel, paclitaxel, etoposide and asparaginase [38].

Corticosteroids are used effectively for radiotherapy-induced brain edema and pain flairs from spinal radiotherapy [26,39]. In the treatment of prostate cancer, corticosteroids are used with abiraterone to compensate for the cortisol reduction and to prevent mineralocorticoid-related adverse events caused by abiraterone-induced CYP17A1 inhibition [40]. Other potential indications include treatment-related pulmonary adverse events, such as drug-induced interstitial lung disease (DILD) and radiation pneumonitis when they occur. In the absence of formal guidelines, corticosteroids are generally used in oncology empirically, together with the modification of the anticancer drug dose or if necessary the discontinuation of the causative anti-cancer drug [41]. In a retrospective study of patients with moderate-to-severe treatment-related lung toxicity, high doses of prednisolone or pulse therapy with methylprednisolone were more frequently administered in DILD than in radiation pneumonitis because of the unfavorable natural course of DILD [42]. In the era of precision medicine, DILD mainly occurs with the mammalian target of rapamycin (mTOR), epidermal growth factor receptor and mitogen-activated protein kinase (MEK) inhibitors [43].

Symptoms related to comorbidities. Apart from cancer- or treatment-related indications, corticosteroids can also be used to treat non-cancer-related comorbidities (such as autoimmune diseases and exacerbations of chronic obstructive pulmonary disease [COPD]) or cancer-associated comorbidities such as paraneoplastic symptoms [21,23].

4 When and how should corticosteroids be used to counter irAEs in patients treated with ICIs?

The last decade has seen tremendous progress in the field of immuno-oncology. Monoclonal antibodies against cytotoxic T lymphocyte–associated antigen (CTLA)-4 and programmed death (PD)-1/programmed death ligand (PD-L)1 have become the standard of care for various types of cancer. These ICIs enhance anti-tumor immunity by reinvigorating exhausted T cells. However, irAEs can occur as a result of the increased immune system activity induced by ICIs, with a loss of self-tolerance [44]. Various mechanisms for irAEs have been suggested, such as the exacerbation of a pre-existing autoimmune condition or the induction of a new inflammatory syndrome [44]. Although irAEs can affect any organ system, they most frequently affect the skin, the gastrointestinal tract, the endocrine glands, the lungs and the liver. More rarely, the nervous system, kidney, blood, muscles, joints, heart or eyes can be affected [45]. The irAE frequency depends on the ICI used. In monotherapy, irAEs are more common with anti-CTLA-4s (any treatment-related AE was documented in 87% of treated cancer patients, with 29% being grade 3 and 4) than with anti-PD-1s (72–75%, and 14–20% respectively) or anti-PD-L1s (66% and 15%, respectively) [46]. The incidence of irAEs is higher in patients on combination therapy with anti-CTLA4. Most irAEs generally occur within 10 weeks after ICI initiation, although late events after treatment discontinuation are occasionally reported [47]. The time scale for the main irAEs is often dictated by the affected organ system [48].

The management of irAEs is based on discontinuation – generally temporary-of the ICI and (for grade $\geq$ 2 irAEs) treatment with an immunomodulatory drug (i.e. primarily corticosteroids) is generally recommended. Corticosteroids have immunosuppressive properties related to their effect on inflammation (Figure 4) [49]. Corticosteroids inhibit the production of inflammatory mediators, repress the recruitment of leukocytes to the tissues and promote the resolution phase of inflammation [7]. The management of irAEs is covered by several sets of guidelines, including those issued by the National Comprehensive Cancer Network [50], the European Society of Medical Oncology [51] and the Society for Immunotherapy of Cancer [52] Toxicity Management Working Group. The therapeutic strategy depends on the irAE's severity grade, defined according to the Common Terminology Criteria for Adverse Events. A moderate-to-severe irAE usually requires discontinuation of the ICI and initiation of corticosteroid therapy [53]. Guidelines relate initial dose of steroids to CTCAE grade, with higher dose and intravenous route in high grade of toxicity [50,52]. In the treatment of irAEs, the corticosteroid dose depends on the affected organ [54]. For example, arthralgia induced by immunotherapies requires generally lower doses (0.2–0.4 mg/kg/day) compared with pneumonitis or colitis, which require higher doses (0.7–1.0 mg/kg/day) [54]. To maintain an anti-inflammatory effect and avoid irAE relapse, the dose of corticosteroids should be given daily (preferably in the morning) until irAE resolution and must be then decreased gradually [54]. Generally, for the treatment of irAEs, full-dose corticosteroid treatment is typically given for 2–3 weeks, then tapered over 4–6 weeks and then withdrawn. The key aspects of corticosteroid management for treatment of irAEs are shown in Figure 5. In the vast majority of irAEs, corticosteroids are rapidly effective. If this is not the case and infection has been ruled out, additional immunosuppressive therapy should be considered [4,54].

A and B. Effects of corticosteroids on the innate immune system. A. Glucocorticoids inhibit the production of inflammatory mediators by immune cells (macrophages, mast cells and stromal cells), including cytokines (IL-1, IL-6 and TNF) and prostaglandins (PGE-2). Glucocorticoids also repress leukocyte recruitment to tissues by inhibiting adhesion molecules (integrins and E-selectins) and the production of several chemokines. B. Glucocorticoids promote the resolution of inflammation, with the production of anti-

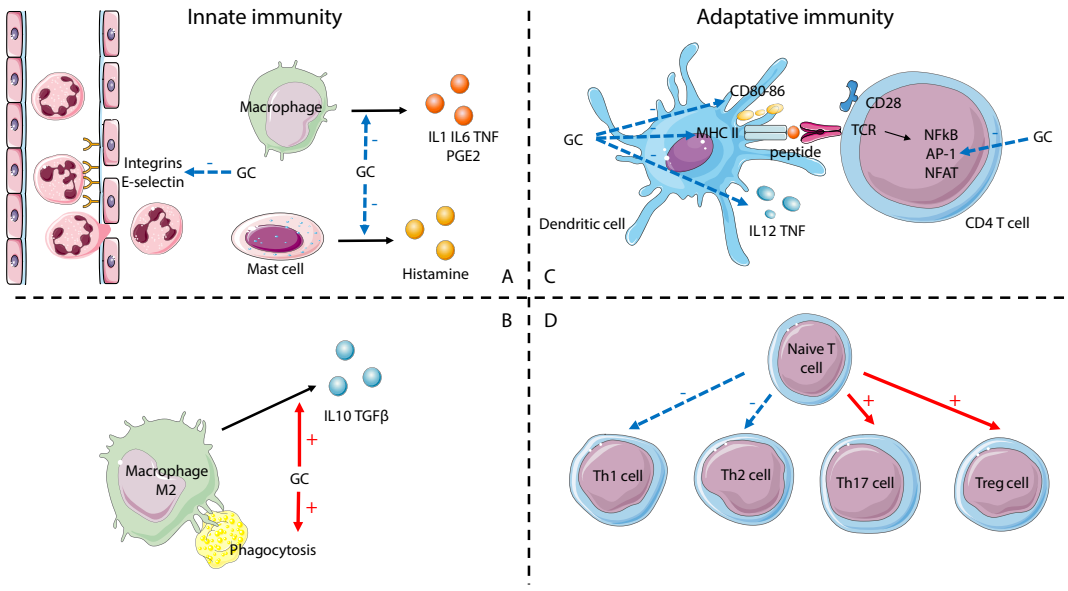

Fig. 4. Main effects of corticosteroids on the human immune system.

inflammatory factors (IL10 and TGFβ) by M2 macrophages and the increased phagocytosis of apoptotic cells. C and D. Effects of corticosteroids on the adaptive immune system. C. Glucocorticoids suppress CD4 T cell activation by modulating dendritic cell function. These drugs inhibit dendritic cell maturation and antigen presentation, and downregulate the dendritic cells' expression of co-stimulatory molecules and production of pro-inflammatory cytokines. These drugs also regulate TCR signaling by inhibiting transcription factors (NFkB, NFAT and AP-1), reducing proliferative T cell responses and diminishing cytokine production. D. Glucocorticoids influence the polarization of TH cells, with the preferential differentiation of TH2 and Treg cells and the inhibition of TH1 and TH17 cells.

Red lines: Enhanced by glucocorticoids. Blue lines: inhibited by glucocorticoids.

AP-1: activator protein 1; CD: cluster of differentiation; GC: glucocorticoids; IL: interleukin; MHC: major histocompatibility complex; NFAT: nuclear factor of activated T-cells; NFkB: nuclear factor-kappa B; TCR: T cell receptor; TGFβ: transforming growth factor beta; TH: T helper cells; TNF: tumor necrosis factor; Treg: regulatory T cells; PGE2: prostaglandin E2.

5 Do corticosteroids affect antitumor immunity?

1.2.1. Antitumor immunity mechanism

Immunosurveillance is a concept whereby cells of the immune system are able to recognize and destroy tumor cells [55,56]. An association between the immune system and tumorigenesis was first postulated at the beginning of the 20th century. Robert Schreiber subsequently defined the three 'Es' of cancer immunoediting: elimination of tumor cells by the host immune system, equilibrium between tumor cells and the immune system and tumor escape [55]. Immunoediting during the equilibrium phase involves the positive selection of mutated tumor cells under the influence of the immune system [56]. The new variants then escape the immune system's antitumor defenses via a variety of mechanisms. Several factors are involved, including innate immune system cells (NK cells, macrophages and dendritic cells). Dendritic cells have an important role because they constitute the main gateway to specific responses by the adaptive immune system, mediated by CD4 and CD8 T cells. After the T cells have been primed and activated by antigen-presenting cells, they develop specific responses against cancer antigens, infiltrate the tumor and kill the cancer cells [57]. At each step, inhibitory factors (such as ICIs) oppose continued T cell amplification and can repress the antitumor immune response, leading to T cell dysfunction [58]. One of the characteristics of these cells is the intense, sustained co-expression of various inhibitory ICIs, including CTLA-4, PD-1, T-cell immunoglobulin mucin-3 (Tim-3), lymphocyte-activation gene 3 (LAG-3), T cell immunoglobulin and ITIM domain (TIGIT) and others. Reversal of T cell dysfunction is one of the key objectives of cancer immunotherapy. The ICIs were designed to restore T cell function and thus exert an effective, specific, antitumor T cell response.

1.2.2. Corticosteroids and anti-tumor immunity

Corticosteroids theoretically could affect various components of the adaptive immune system (Figure 4). Firstly, they suppress CD4 T cell activation by modulating dendritic cell function and by regulating T cell receptor signaling. Secondly, they influence the

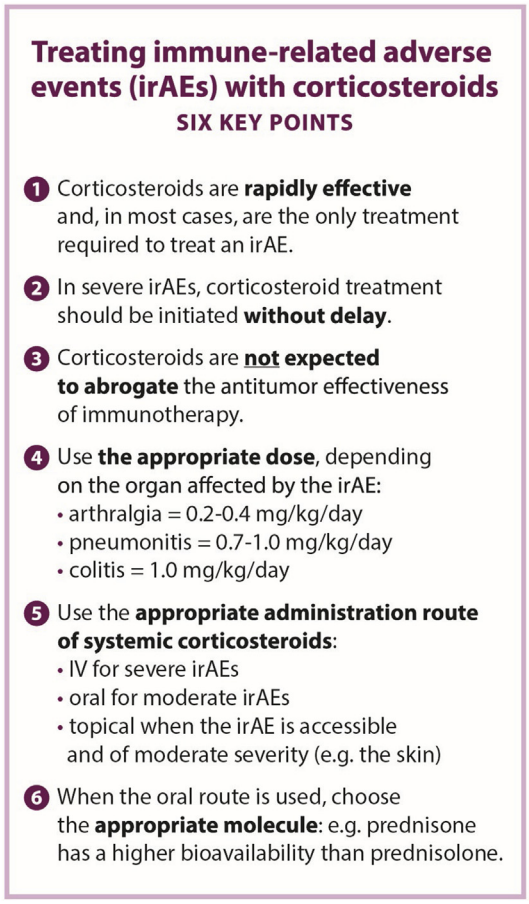

Fig. 5. Key points of treating immune-related adverse events with corticosteroids.

polarization of T helper (TH) cells by (i) preferentially promoting the differentiation of TH2 cells and regulatory T (Treg) cells and (ii) inhibiting the differentiation of TH1 and TH17 cells [7].

The use of corticosteroids appears to be associated with a rapid decrease in the blood lymphocyte count. In a study of 20 healthy volunteers, Olnes *et al.* found that systemic administration of dexamethasone led to a decrease in the lymphocyte count, with a trough after 4 h [59]. The decline in the lymphocyte count was rapidly reversed, with an increase above baseline 24 h after the dexamethasone infusion [59]. This effect has been seen for both CD4 and CD8 T cells, with a particular impairment in the proliferation and differentiation of naïve T cells (relative to memory T cells) [60].

Corticosteroids also influence the expression of ICI molecules on T cells and are expected to increase the exhaustion of T lymphocytes. Dexamethasone induced the upregulation of CTLA-4 on CD4 and CD8 T cells and attenuated CD28 co-stimulation [60]. Similarly, in a mouse model, a dexamethasone infusion strongly upregulated PD-1 expression on T cells, with a peak on day 2 and a return to baseline on day 6 [61]. The impact of corticosteroids on the tumor microenvironment has been studied using tumor-infiltrating lymphocytes (TILs) derived from metastatic melanoma lesions; dexamethasone affected the activation and killing ability of TILs. The corticosteroids' immunosuppressive effect was generally rapid and quickly reversed after withdrawal. In an *in vitro* model, steroid withdrawal restores the activity of TILs after 3 days [62]. Furthermore, a dose-dependent effect has been observed in preclinical (mouse) model and in humans [60,61].

Accordingly, corticosteroids are potent negative regulators of inflammation and T cell activity. In preclinical models, corticosteroids appear to affect antitumor immunity − particularly T cell activation and differentiation. However, based on our clinical experience and literature review, we now have more than 50 years of hindsight on the clinical use of corticosteroids [1–3,21]. Although the use of immunosuppressive drugs were associated with an increased risk of secondary malignancy especially in the context of solid organ transplant, to the best of our knowledge, the long-term use of corticosteroids was not associated with an increased risk of cancer in large studies [63,64]. In summary, the theoretical risk of weakened antitumor immunity was suggested by the preclinical studies of corticosteroids, however, has not translated into a greater incidence of cancer development in large clinical studies.

6 Do corticosteroids impact the efficacy of immunotherapy?

The pooled analysis of prospective phase 3 studies in the treatment of melanoma showed no impact of systemic corticosteroid therapy on the anti-tumor response [71]. Several other retrospective studies have then suggested a potentially negative effect of corticosteroid therapy on the antitumor response. But as summarized in Supplementary Table 1, in these retrospective studies, the effect of corticosteroid therapy was in fact probably mainly due to the indication for corticosteroid therapy itself, which was given for symptoms of advanced cancers and palliative indications.

In the adjuvant setting of treatment of stage III melanoma with pembrolizumab, a potential negative impact of corticosteroids has been suggested on the therapeutic effect of immunotherapy in a large prospective study [79]. In real-world studies of metastatic patients, doses of more than 10 mg of prednisone are commonly administered; for example, in 14% of patients with non-small-cell lung carcinoma (NSCLC) on ICI initiation and in nearly a third of patients on nivolumab [65,66]. In two independent cohorts of patients with NSCLC monitored at Memorial Sloan Kettering Cancer Center (n = 455) and Gustave Roussy Cancer Center (n = 185), baseline corticosteroid use was associated with a lower overall response rate, worse progression-free survival (PFS) and worse overall survival (OS) with PD-(L)1 blockade. After adjusting for smoking

history, performance status and a history of brain metastases, baseline corticosteroids remained significantly associated with worse PFS (hazard ratio [HR] = 1.3; p = 0.03) and OS (HR = 1.7; p < 0.001) in the multivariate analysis [65,66]. Similarly, studies evaluating patients who received corticosteroids during ICI therapy also reported worse outcomes. In a retrospective study of 210 patients with advanced NSCLC, those receiving corticosteroids during the first 30 days of nivolumab treatment (n = 25) had a significantly higher risk of death (HR = 2.3) and a significantly shorter median OS time than those not receiving corticosteroids (4.3 versus 11 months, respectively; p = 0.006) [65]. Fuca *et al.* obtained similar results, in that early use of steroids was associated with a low disease control rate, poor PFS and poor OS [67]. Early use of steroids was also associated with poor performance status, the number of metastatic sites and the presence of brain metastases [67]. Patients who used corticosteroids after the first month of ICI therapy showed longer PFS that those patients without steroids (median PFS time: 6.03 versus 3.01 months; HR = 0.62; p = 0.02) [67].

Ricchiuti *et al.* used a different clinical criterion to investigate the impact of corticosteroids on ICI therapy in 650 NSCLC patients treated with PD-L1 inhibitors [23]. Importantly, the researchers addressed the reason for corticosteroid administration since many patients were using steroids for cancer-related symptoms that were independently associated with a worse prognosis. In line with previous results, patients receiving ≥10 mg prednisone at baseline had shorter median PFS and OS times than patients receiving less than 10 mg of prednisone (median PFS time: 2.0 versus 3.4 months, respectively; p = 0.01; median OS time: 4.9 versus 11.2 months, respectively; p < 0.001) [23]. However, this significant detrimental impact was seen for palliative indications only and not for non-palliative indications. Moreover, the median duration of pre-ICI corticosteroid use was longer for non-palliative indications than for palliative indications (70 versus 35 days, respectively; p = 0.005), suggesting that the duration of steroid use before the initiation of ICI therapy does not impact anticancer efficacy [23]. In a retrospective study of 424 patients with advanced NSCLC treated with single ICI [68], 49 patients received steroids within the first 8 weeks of ICI therapy. In the 11 patients receiving steroids for non-palliative indications, the main reasons for use were irAEs and exacerbations of COPD. Patients receiving steroids for cancer-related symptoms had a lower median OS time (1.9 months), relative to those receiving corticosteroids for other indications (13.4 months). Early steroid use for cancer-related symptoms proved to be an independent prognostic factor for OS [HR = 4.53; 95%CI = 1.84–11.12; p < 0.0001] [68]. A meta-analysis including 16 studies with 4045 patients treated with ICI confirmed that the use of corticosteroids for adverse events did not seem to impact OS, in contrast to their use for disease-related symptoms, where both PFS and OS were negatively impacted [69].

The results of these studies strongly suggest that corticosteroid use is a prognostic clinical marker for the cancer symptoms and outcome but does not predict the patient's response to ICIs per se. Some detailed and instructive clinical examples of efficacy of immunotherapies despite the use of high doses of corticosteroids have been reported [70]. Large pooled studies in both melanoma and NSCLC settings have shown that the use of corticosteroids to treat irAEs did not alter the response to ICIs [71–73]. This was observed for both anti-PD1 therapy (nivolumab or pembrolizumab) and anti-CTLA4 therapy (ipilimumab) [71–75]. Moreover, it has been suggested that late-stage cancer patients with irAEs can have a higher overall response rate and a longer PFS or OS time than those without irAE [71,73,76–78]. A similar potential association was suggested in stage III melanoma patients treated with pembrolizumab, where patients experiencing irAE had longer recurrence-free survival [79]. These observations must be considered with caution because of immortal time bias; patients treated for longer have more time to develop an irAE.

The data on ICI treatment in cancer patients with concomitant autoimmune diseases requiring corticosteroids are contradictory [76,80–84]. In a multicenter study of 112 cancer patients with preexisting autoimmune diseases, immunosuppressive therapy (mainly with corticosteroids) was used in 24 (22%) of the patients at baseline and in 48 (43%) of the patients experiencing autoimmune disease flares and/or irAEs. Immunosuppressive therapy at the time of ICI initiation was associated with shorter PFS (a median of 3.8 months, versus 12 months in patients not receiving immunosuppressants; p = 0.006; HR = 2.10). Furthermore, PFS was shorter in patients who experienced an autoimmune disease flare or an irAE (n = 79), with a trend towards better survival in the subgroup not having received immunosuppressants or having discontinued ICI [83]. Given that immunosuppressive therapy can also involve steroid-sparing agents [80], it would be useful to evaluate the potential impact of these drugs, relative to corticosteroids. The results of a few clinical studies suggest that patients experiencing flares, irAEs or lasting responses have better survival despite the use of corticosteroids; however, these studies had small sample sizes [76,81,82]. The potential impact of the intensity and duration of high-dose corticosteroid administration (i.e. various degrees of immunosuppression) has not been firmly defined [85]. For instance, in a sub-group analysis of 98 patients with ipilimumab-induced hypophysitis, the use of low-dose

corticosteroids was independently associated with a lower treatment failure rate of ipilimumab and better OS [86]. This study suggest that corticosteroid dose might matter in case of concomitant ICI and suggests that the minimum effective corticosteroid dose should be preferred.

Another setting is the short, repeated use of steroids in chemotherapy regimens combined with an ICI. At present, there is no evidence to suggest that steroids have a detrimental effect on chemo-immunotherapy regimens. Chemo-immunotherapy regimens with paclitaxel (requiring corticosteroid administration) and nab-paclitaxel (not requiring corticosteroid administration) gave similar clinical benefits [87].

In summary, although corticosteroids have immunosuppressive effects by their mechanism of action, they do not appear to alter antitumor immunity and significantly reduce the efficacy of immunotherapy in patients in metastatic setting (suppl. Table 1). A possible impact of corticosteroids on effect of immunotherapy was seen in adjuvant setting [79]. It is not clear whether early corticosteroid use during ICI therapy influences the latter's efficacy, relative to later use for non-palliative indications. Early steroid use might be associated with more serious or more frequent irAEs, which in turn might be associated with more frequent permanent discontinuation of ICIs. Late-onset irAEs are usually non-serious and clinically manageable, with a low treatment discontinuation rate [88]. Another hypothesis is that early steroid use might prevent the activation of an immune response and limit the activity of ICIs, which potentially require a certain time of action before they can be safely discontinued. In case of non-palliative indications, the early use and the doses of corticosteroids should be evaluated in larger, prospective studies. Overall, the results of retrospective clinical studies (suggesting a potential impact of corticosteroids on the efficacy of immunotherapy) are subject to debate [65,66], and this putative negative impact has not been demonstrated in robust pooled-analyses of clinical trials or in studies that distinguished between palliative and non-palliative indications [23,68,69,71] (Supplementary Table 1).

2. Conclusion

Although corticosteroids have immunosuppressive effects by their mechanism of action, they do not appear to significantly alter antitumor immunity and reduce the efficacy of immunotherapy in metastatic patients. A possible impact of corticosteroids on effect of immunotherapy was seen in adjuvant setting. Corticosteroids are widely used in oncology in both palliative and supportive settings. Corticosteroids have been given a new role in the management of irAEs induced by immunotherapies. Corticosteroids have miscellaneous side-effects and should be used at the lowest but effective dose and for the shortest time possible, regardless of the anticancer therapy.

Conflict of interest statement

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Appendix A. Supplementary data

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