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Is there today a place for corticosteroids in the treatment of scleroderma?

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ABSTRACT

In systemic sclerosis (SSc), the use of corticosteroids (CS) is controversial due to their association with scleroderma renal crisis (SRC). However, patients with very early and early disease, characterised by main inflammatory component, may benefit from CS therapy.

The aim of this review is to discuss pros and cons of CS treatment in SSc, providing current evidence about the use of CS in SSc. Moreover, we discuss also the underlying pathogenetic mechanisms that may be the background for the potential harms and efficacy of CS in SSc.

1. Introduction

Systemic sclerosis (SSc) is an autoimmune disease characterised by heterogenous clinical features and a complex pathophysiology [1]. Corticosteroids (CS) are the cornerstone of the treatment of systemic inflammatory and/or systemic autoimmune diseases despite the increasing use of corticosteroid-sparing agents, including immunosuppressive and immunomodulatory agents. In systemic sclerosis (SSc), the role of CS therapy is still a matter of debate [2] due to the association with scleroderma renal crisis (SRC) and no clear evidence for their efficacy [3,4]. Nevertheless, in clinical practice CS are commonly prescribed for some SSc manifestations, as musculoskeletal involvement, diffuse cutaneous disease and interstitial lung disease (ILD) [5,6].

The main question today is if in the era of biologic and synthetic targeted therapies, there still room for the use of CS in SSc.

2. Corticosteroids may be harmful in SSc

2.1. Corticosteroids are responsible for a number of adverse events not only in SSc patients

CS are responsible for multiple short- and long-term adverse events, particularly endocrine complications and osteoporosis (Table 1). The frequency of these adverse events, although positively correlated with the daily dose, the cumulative dose and the patient's age, is often ill-defined as are risk factors for their development. A population-based study conducted in 2006 revealed that > 90% of patients treated with CS developed at least one adverse event associated with CS use. Weight gain was the most common (70% of the individuals), cataracts (15%) and fractures (12%) were among the most serious. After multivariable adjustment, all events demonstrated a strong dose-dependent association with cumulative CS use [7]. In consequence, there is a general tendency to reduce the dose of glucocorticoids in other systemic autoimmune diseases such as in ANCA associated vasculitis [8].

2.2. Corticosteroids are responsible of specific adverse events in SSc patients

In SSc patients, CS may induce, in addition to usual complications, SRC which is today an infrequent complication. It presents as recent onset, accelerated-phase hypertension and/or rapidly deteriorating renal function, frequently accompanied by microangiopathic hemolysis [9]. Recently, a core set of items that characterize SRC was identified using consensus methodology [10]. These items covered five domains: blood pressure, acute kidney injury, microangiopathic hemolytic anemia, target organ dysfunction, and renal histopathology. Thus, classification criteria for SRC have been adjusted with a definition of hypertension over 140 mmHg for systolic blood pressure (BP) and over 90 mmHg for diastolic BP. Importantly, a rise in systolic BP ≥ 30 mmHg or in diastolic BP ≥ 20 mmHg above all are respectively considered to be sufficient to consider hypertension [10]. In addition, an increase in serum creatinine ≥26.5 μmoles within 48 h or ≥ 1,5-time baseline

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Table 1
Adverse events of glucocorticoid treatment.

Hypercortisolism
Facio-truncular obesity, lipomatosis
Endocrine perturbations: diabetes, hirsutism, alopecia, amenorrhea, decreased libido
Dyslipidemia
Protein catabolism
Hypertension
Osteoporosis
Aseptic osteonecrosis
Growth retardation (children)
Myopathy
Tendon ruptures
Skin involvement: acne, bacterial folliculitis, striae, erythrosis, purpura, ecchymosis, telangiectasia, skin atrophy, hypopigmentation
Infections
Bacterial: extra-cellular bacteria, listeriosis, legionellosis, nocardiosis, actinomycosis
Tuberculosis and atypical mycobacteria
Malignant anguillulosis
Viral: herpes viridae (HSV, VZV, HHV-8)
Opportunistic: pneumocystosis, aspergillosis, cryoptococcosis, mucormycosis
Weaning of glucocorticoids
Adrenal insufficiency
Weaning syndrome: anxiety, asthenia, depression, pain, fever
Disease flare
Gastroenterological complications:
Bowel perforation
Acute or chronic pancreatitis
Ocular complications
Cataract
Eye hypertonia and glaucoma
Infections
Delayed corneal scaring
Neuropsychological complications
Minor: hyperexcitability, euphoria, insomnia, logorrhea
Major: acute psychotic state
Hypersensitivity
Thrombosis
Hematological complications
Hyperleukocytosis with neutrophils
Polycythemia, eosinopenia
LYMPHOCYTOPENIA, hypogammaglobulinemia

HSV: herpes simplex virus; VZV: varicella zona virus; HHV-8: Human Herpesvirus 8.

within 7 days and/or a urine volume < 0,5 ml/kg/h for 6 h were also considered to be sufficient to consider renal insufficiency [10].

The use of CS is a potent risk factor in the development of SRC as other factors such as rapidly progressive diffuse skin (dSSc) involvement [11] and the presence of anti-RNA polymerase III antibodies (anti-RNAP) [12]. In fact, some studies support this hypothesis. First, Steen et al. reported in 1998 in a case–control study found that in the 6 months before SRC onset or the first visit for medical care, SRC patients more frequently showed use of a medium- to high-dose CS (≥15 mg/day prednisone or its equivalent) than controls (36% vs. 12%; odds ratio [OR] 4.37, 95% confidence interval [95% CI] 2.03–9.43) [13]. In 2012, in a retrospective multicentric study conducted on 91 patients with SRC and 427 controls [14] it was found that significantly more SRC patients had been treated with CS in the weeks or months preceding the crisis (70.3% vs 36.5% of controls). SRC patients had also received a significantly higher mean maximum CS dose than controls (29.3 vs 3.6 mg; $P < .001$). In a cohort of 50 SSc patients with SRC, we observed that 30 (60%) had been exposed to a CS before SRC onset and the OR for developing SRC with CS exposure during the preceding 3 months and 1 month was 24.1 (95% CI 3.0–193.8) and 17.4 (2.1–144.0), respectively [15]. In addition, Helfrich et al. found an association of high-dose CS (> 30 mg/day) and normotensive SRC [16]. However, patients with normotensive SRC have often been exposed to a CS, and confounding variables cannot definitively be ruled out. Nevertheless, from the current literature, which documents an association of CS dose and risk of SRC, we strongly suggest avoiding medium to high dose CS therapy for SSc.

Moreover, two systematic reviews support the association between CS and SRC. Trang et al. [17] conclude their paper with this sentence, speaking about the risk of SRC: "*great caution must continue to be exerted when initiating such therapy [CS], especially in high doses and in the early diffuse subset of SSc patients*". However, it should be noted that the authors state also that « CS are associated with SRC, although this may be due to confounding by disease severity and/or co-intervention ». In fact, in this study 7 out of 10 SRC occurred in patients who underwent autologous hematopoietic stem cell transplantation [17].

The second review by Iudici et al. [3] based on 44 studies and 93 case reports found 23 cases of SRC among 891 patients treated by CS. Those 23 patients had mostly dSSc and received high dose of CS [3].

However, before a final connection between SRC and kidney failure is made it must be kept in mind that another autoimmune disease or the ANCA dependent kidney involvement should be always excluded in SSc patients that display acute kidney disease in the absence of hypertension [18,19].

There is some pathophysiologic evidence that CS might induce SRC. The mechanisms leading to SRC are very close to those leading to malignant hypertension: this explains the very similar clinical presentation such as headache, visual disturbance and encephalopathy [20]. It is known that cortisol-induced hypertension is characterised by sodium retention and volume expansion [21]. Moreover, cortisol increases pressure responsiveness to endogenous and exogenous catecholamines leading to vasoconstriction, without evidence of any increase in sympathetic nervous activity. Then CS impaired production of prostaglandin by endothelium leading to vasospasm [9]. Thus, one of the triggers of SRC is an altered perfusion of the juxtaglomerular apparatus [22] suggesting that CS, which act mainly as a cox2 inhibitor with a reduced synthesis of the vasodilator prostanoid prostaglandin E2(PGE2), could trigger SRC by favoring the vasoconstriction the renal arteries/oles [23].

Other mechanisms have been considered by which CS may trigger SR. Endothelin 1 (ET-1) might be involved because increased circulating levels of ET-1 were found in SSc patients with SRC and in those with pulmonary arterial hypertension [24] In agreement are immunohistological findings of Kobayashi et al. revealing the expression of ET-1 and ET-1 type B receptor in kidney biopsies of 2 patients who died of SRC [25]. Further evidence was obtained from Penn et al. who reported that ET-1 and both ET A and B receptor expression was increased in SRC biopsies [26]. However, the mechanism by which CS could increase the circulating levels of ET-1 and/or increase the expression of ET-1 and ET-1 type B receptor in kidney remains to be determined and other mechanisms by which CS could be associated with SRC including effects on prostacyclin, blood pressure, fluid shifts, confounding, etc. Both literature and pathophysiology are consistent with a strong association between CS use and SRC. As a result, many physicians prescribe a limited dose of CS in patients with SSc in order to avoid complications, especially SRC.

3. Corticosteroids may be helpful in SSc

3.1. Rationale for corticosteroid use in SSc

Pathogenesis of SSc is a complex interplay of endothelial dysfunction, immune system dysregulation, inflammation, and fibrosis [1]. Innate and adaptive immune system activation and subsequent inflammatory response play a pivotal role in promoting vascular damage and fibrosis in SSc [27–29]. The early phase of SSc is characterised by perivascular and tissue inflammatory infiltrates consisting of monocytes, macrophages and CD4+ T lymphocytes [30–33]. With clinical progression of the disease, inflammation is replaced by progressive collagen accumulation and fibrosis and irreversible skin and internal organ damage [30,31,34,35]. The kidney involvement is not only

characterised by SRC but usually by a progressive decline in function following the pattern of a chronic kidney disease [36].

It is well known that CS are anti-inflammatory and immunosuppressive through an efficient modulation of all immune cells, in particular monocytes, macrophages and T lymphocytes [37–39]. Thus, they are used as a part of treatment strategies to induce remission in numerous inflammatory and autoimmune conditions [40].

These CS effects might be exploited in the very early and early SSc, characterised by predominant tissue inflammation, before irreversible tissue injury and fibrosis occur and in inflammatory disease manifestations such as synovitis or myositis.

3.2. Corticosteroids for very early and early disease

The inflammatory mechanism that distinguish the early phases of SSc and the inadequate response of more advanced disease to glucocorticoids suggest a possible window of opportunity for the steroid treatment in early and very early disease [41].

In this clinical scenario, the patient with puffy fingers is an ideal prototype characterised by main inflammatory skin disease before turning into sclerodactyly. In fact, puffy fingers reflect an early oedematous phase of SSc [42,43] where Raynaud's phenomenon and vascular dysfunction are followed by endothelial injury leading to the opening of the tight junctions, adhesion and homing of the inflammatory cells, hyperpermeability and continuous vascular leak [28,44–46]. This results in interstitial oedema clinically evident as digital swelling [28,43] which may be easily modulated by CS that interfere with the inflammatory response and immune system activation secondary to the vascular injury blocking vascular damage and remodelling and collagen deposition [28,45].

On this basis, a randomised clinical trial has been recently designed to investigate the effect of high-dose methylprednisolone on very early SSc. Vessel abnormalities on nailfold capillaroscopy, levels of inflammatory biomarkers and signs/symptoms of SSc progression will be evaluated [41]. According to the study protocol, patients with puffy fingers fulfilling VEDOSS diagnostic criteria [46] having disease duration < 3 years and no clinically significant internal organ involvement will be randomised to receive three consecutive pulses of methylprednisolone (1000 mg) for three consecutive months [41].

In SSc, the alterations of the microvasculature are also present in internal organs [47] and therefore vascular leakage, interstitial oedema and perivascular inflammation, can be hypothesized as very early events also in organ involvement [28]. For this reason, steroid treatment may be useful as a part of management strategy in the early “edematous/inflammatory” phases of interstitial lung disease (ILD) and myocardial involvement, detectable by high resolution computed tomography (HRCT) of the lung [48,49] and by cardiac magnetic resonance (MR) [50,51], respectively. Lung and heart involvement account for the overwhelming majority of SSc-related deaths [52], thus is of pivotal importance to treat these complications early in order to prevent organ damage and loss of function.

Glucocorticoids are still the most prescribed drugs for ILD, and a recent retrospective analysis of the largest multicentre observational cohort on SSc, EUSTAR, has shown that 60% of patients with ILD were on glucocorticoids with marginal effect on lung function tests [53]. The authors did not perform clear sub-analysis of different stages of ILD and did not distinguish between early and more advanced disease [53].

The ideal candidates for steroid treatment in the setting of ILD are patients with ground glass opacities on lung HRCT, reflecting oedema and inflammation [48] and no evidence of fibrosis. A recent retrospective analysis has failed to demonstrate a correlation between the extension of HRCT ground glass opacities and response to immunosuppressive therapy, but 95% of the patients enrolled presented signs of fibrosis at the beginning of the treatment [54]. Therefore, a better stratification of patients that may benefit from steroid and more in general, immunosuppressive treatment is warranted.

Corticosteroids (< 15 mg/day), either with cyclophosphamide or alone, have been recently recommended for SSc-related cardiomyopathy by the experts of the UK Systemic Sclerosis Study group [55]. Endomyocardial biopsies of patients with myocarditis show infiltration of activated T lymphocytes [56] and small case series reported beneficial effect of steroids on clinically manifest myocarditis [56–59].

Ideal candidates for steroid use are patients with myocardial oedema on MRI and no signs of myocardial fibrosis. It has been reported that oedema may completely recover with pulses of steroids [60]. However, the effect of the early treatment on the progression towards fibrosis and cardiac dysfunction has still to be determined.

3.3. Corticosteroids for inflammatory disease manifestations

SSc patients may develop significant inflammatory articular and muscular involvement configuring in some cases overlap syndromes with rheumatoid arthritis and polymyositis [61].

In SSc, low doses of glucocorticoids are commonly used for the arthritis to improve pain control and quality of life. However, beyond observations in everyday clinical practice, no clinical trial has specifically addressed their efficacy for SSc-related arthritis. In this context, steroids are often used together with synthetic and biological DMARDS or other immunosuppressive drugs.

The use of steroids to induce remission of SSc-related myositis has been translated from the treatment of idiopathic inflammatory myopathies such as polymyositis and dermatomyositis [62]. A French multicentric retrospective study reported that high doses of corticosteroids (1 mg/kg/die) were effective in 75% of 24 patients with muscular involvement and that the presence of inflammatory infiltrates in muscle biopsies were predictive of therapeutic effect of glucocorticoids [63]. However, there were two cases of SRC [63]. Patients with myositis are at risk of developing myocarditis, thus CS may be useful for both indications [57,64,65].

In addition, CS are commonly used for inflammatory conditions as pericarditis and other serositis [66]. It is important to bear in mind that pericardial effusion is one of the risk factors for the occurrence of SRC [21], therefore caution is warranted when prescribe steroids in these patients.

4. Conclusions and future perspectives

There is a strong evidence that CS use is associated with SRC in SSc. For this reason, when.

considering CS, it is important to stratify patients according to the probability of response to the treatment and of risk for SRC. Patients with very early and early disease and initial stages of organ involvement, characterised by prevalent inflammation and no established fibrosis, may be ideal candidates for CS use. Another issue in treating SSc patients is a safe dosage of CS, since medium-high dosages seem to display the strongest association with SRC [13].

The ongoing trial on high dosage pulse CS therapy for very early SSc will inform on safety and efficacy of steroids in preventing disease progression and damage in SSc [41].

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