Review

What about glucocorticoids in primary Sjögren's syndrome?

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ABSTRACT

Glucocorticoids (GCs) are involved in several physiological processes such as metabolism, water and electrolyte balance, growth, cardiovascular and cognitive functions, reproduction. Furthermore, they exert different effects on innate and adaptive immune cells. Due to their anti-inflammatory and immunosuppressive functions, these drugs are largely used for the treatment of inflammatory and autoimmune diseases.

In comparison to other autoimmune rheumatic diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), to date no reliable evidence is available for the use of systemic GCs in Sjögren's syndrome (SS), which is still based on case reports, case studies, retrospective or prospective studies and a small number of randomised controlled trials (RCTs). Despite this gap in our knowledge, GCs are commonly used in SS for glandular, joint, cutaneous, lung, haematological, renal, neurological involvement. More recently, some sets of recommendations for the management of SS have provided a few pieces of advice regarding the use of GCs in this condition.

Future studies should not neglect the role of GCs, as this traditional therapeutic weapon can still have a role in the management of SS. Accordingly, this review will address and discuss the use of systemic GCs in isolated or primary SS.

Introduction

The use of glucocorticoids (GCs) has spread in several diseases since 1948 when P. Hench successfully used the compound E (cortisol), previously isolated by E. Kendall, in a patient with rheumatoid arthritis (RA) (1). Over the last seventy years, GCs has contributed to save lives and improve the conditions of hundreds of thousands of patients with autoimmune disorders and their use is generally encouraged for the shortest time and with the lowest possible dose because of their well-known side effects (2, 3).

GCs are also employed in Sjögren's syndrome (SS) where their use seems to be more eminence- than evidence-based, as it is principally grounded on the results obtained in other autoimmune diseases, such as systemic lupus erythematosus (SLE) and RA (4, 5). Unfortunately, the therapeutic panorama for SS is rather poor and nowadays the classic approach is still based on symptomatic treatment for glandular manifestations and immunosuppressive and/or anti-inflammatory therapy for systemic manifestations, which can occasionally be life-threatening. One of the reasons for the low number of dedicated randomised controlled trials (RCTs) so far available might be the long-lasting perception of SS as a minor slowly progressive disease.

However, even in the absence of systemic complications, SS patients have a reduced quality of life (6-11) and the treatment of the disease still represents a true challenge for the clinician.

In this article, the use of systemic GCs in isolated or primary SS will be reviewed and discussed.

Glucocorticoids: biology and mechanism of actions

GCs are steroid hormones produced by the adrenal glands' cortex, precisely in the zona fasciculata, and their secretion is mainly regulated by the hypothalamic-pituitary-adrenal axis with a circadian rhythm. They derive, together with aldosterone and dehydro-epi-androsterone (DHEA), from the same precursor, cholesterol, thanks to the action of different enzymes. GCs are involved in several physiological processes such as metabolism, water and electrolyte balance, immune system, growth, cardiovascular functions, cognitive functions, and reproduction (12).

Corticosteroid-binding globulin (CBG) is the major serum GC-binding protein which keeps GCs inactive, therefore only a small amount of cortisol is free and active in the bloodstream. Two enzymes, 11β-hydroxysteroid dehydrogenase (11β-HSD) type 1 and type 2, which can be influenced by multiple stimuli such as cytokines like tumour necrosis factor (TNF) and interleukin-1β (IL-1β), contribute to maintaining the equilibrium between active cortisol and inactive cortisone (13).

The free and biologically active GCs are lipophilic and can penetrate into the cell through diffusion where they exert genomic or non-genomic effects. In the first case, GCs bind to their specific cytoplasmic glucocorticoid receptors (GRs), ubiquitously expressed in the body, which have some reactivity with the mineral corticoid receptors (MRs). In fact, MRs are activated not only by their own ligands, mineralocorticoids, but also by GCs, while on the contrary GRs are activated only by GCs (14). The GR regulates the expression of GCs responsive genes in a positive (transactivation) or negative (transrepression) manner through different mechanisms (12): the first one is the direct binding to the so-called glucocorticoid response elements (GRE), which are palindromic DNA binding sites in the promoter region of the target genes. Alternatively, GR can tether to other DNA-binding proteins, such as transcription factors STAT3, STAT5, and nuclear factor (NF)-KB, to potentiate activation or repression of genes. Additionally, a mixed mechanism involving composite binding to DNA and protein substrates can play a role in this complex, highly regulated system (15, 16). The attractive but oversimplified concept that anti-inflammatory effects are linked to transrepression mechanisms, whereas side effects are associated with transactivation, has led to intensive research in the pharmaceutical field to find glucocorticoid receptor-binding compounds that selectively promote the transrepressive activity of the GR with low transactivation (17, 18). The genomic effects of GCs are delayed as the protein level does not change immediately after GCs administration, while the non-genomic effects are rapid because they do not require transcription or protein synthesis. Up to now, limited knowledge is available on the non-genomic GC/GR effects (16).

In clinical practice, we use synthetic GCs (*e.g*, prednisolone, methylprednisolone, fluticasone, budesonide, and dexamethasone), structurally similar, but not identical, to endogenous cortisol. They have different features (pharmacokinetics, bioavailability, cross-reactivity with the MR), and display different potency, specificity, and availability. Since their discovery, and in spite of their well-known adverse effects linked to the prolonged use (glucose elevation, obesity, hypertension, osteoporosis, cataract, striae, and skin thinning, mood change, necrosis of the femoral head, impaired wound healing, peptic ulcers) (19), the use of synthetic GCs has been enormously spreading in a growing spectrum of inflammatory and autoimmune disorders such as RA, SLE, rheumatic polymyalgia, systemic vasculitis, chronic obstructive pulmonary disease, bronchial asthma, inflammatory bowel diseases, immune-mediated glomerulonephritis, multiple sclerosis, and several others (20), among which SS as well.

Glucocorticoids in SS

Clinical evidence regarding the use of glucocorticoids in SS

The therapeutic armamentarium for SS is rather limited and has not changed significantly during the last decades; in fact, SS treatment is still based on symptomatic drugs for sicca syndrome and immunomodulators/immunosuppressants for systemic disease, with scarce information on the differential efficacy and safety of the available options.

Taking into account the number of the clinical trials on SS in comparison to other autoimmune diseases, a huge difference sticks out and SS might be considered a true Cinderella among RA, SLE, or multiple sclerosis. SS has been long neglected and posed a challenge for several reasons: firstly, it has been perceived as a mild, slowly progressing disease with a small interest for pharmaceutical companies. Secondly, several sets of classification criteria have been used in the past and only more recently the international scientific community has converged on a common result (21). Moreover, as SS clinical spectrum is large and continuously expanding, we face different forms of the disease with distinct therapeutic needs and, even if some tools have been recently developed, disease activity and damage are challenging to evaluate (22-24). Lastly, the underlying pathogenetic mechanisms are still partially unknown.

The literature does not show reliable evidence for the use of systemic GCs in SS, which is still based on case reports, numerically limited case studies, and retrospective or prospective not randomised studies. Some non-controlled studies have shown efficacy of GCs for the glandular involvement in SS, especially in the paediatric form (25). An improvement in Schirmer's test and Rose Bengal score as well as in the degree of minor salivary glands (MSG) infiltration was described with PDN (40mg/every other day) for six months (26). An increase in saliva production at 3 and 6 months with a concomitant a decrease of IgG and IgA levels, anti-SS-A, anti-SS-B, and IgM rheumatoid factor were detected in an open prospective study with a low dose regimen of prednisolone starting with 30-10 mg/day and then tapering to 7.5–5.0 mg/day. Furthermore, a significant improvement of oral symptoms such as dry feeling, increased frequency of drink water, sticky sensation, and lips dryness was reported (27). An isolated case report described the history of a 35-year-old man with SS, Klinefelter's syndrome, and neurovasculitis where the treatment with high dose prednisone (60 mg daily) led to modifications in the focus score from 1 at diagnosis to 0.4 after 2 months. Also, sicca syndrome disappeared while on treatment, however, when the dose was tapered to 30 mg daily, the symptoms reappeared (28). In a small, presumably underpowered study, Pijpe *et al*. found no significant differences in glandular flow rates between primary and secondary SS patients treated with low dose (5–7.5 mg daily) prednisolone and those who did not receive such treatment in a four-year-long prospective study (29).

What about more stringent studies? Only one out of 32 RCTs evaluating the effects of 19 different therapeutic agents considered in a recent meta-analysis involved prednisone (30). In this dated, double-blind, randomised, placebo-controlled study the effects of prednisone (30 mg/every other day) were compared to piroxicam (20 mg/daily) and to placebo on 24 patients (8 for each group) (31). No differences were recorded in lacrimal and salivary function evaluated by objective tests among groups while a significant decrease of serum IgG, serum IgA, and erythrocyte sedimentation, as well as an improvement in the perception of sicca symptoms, were demonstrated in prednisone treated patients, even if such modifications were not sustained after drug's withdrawal. No changes were detected in the extent of inflammatory infiltration, expressed as the focus score, in the MSG. The authors conclude that the use of GCs remains questionable in SS at least for the glandular components, while it might be suggested for systemic manifestations. After 27 years, a RCT demonstrating this last advice is still lacking.

In spite of this gap in our knowledge, GCs, often in association with other immunosuppressants, are commonly used in SS for joint (32), lung (33-35), haematological (36, 37), renal (38, 39) and neurological (40-43) involvement. In particular, in the French ASSESS cohort, GCs were administered to 77% out of 74 SS patients with neurological manifestations in comparison to a lower percentage (50% out of 318) of those without. Among the first group, 79% and 66% with peripheral and central nervous systems respectively were treated with GCs (44). No information is available regarding the efficacy of this approach.

A Spanish analysis on 1120 patients examined how they were treated over the years; they found that GCs were used in 65% of patients, in 7% in high-dose (>20 mg/day) even in the presence of a low EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI <4) or to treat clinical manifestations out of ESDDAI (45) which may lead to suspect, at least in some cases, an inadequate treatment. An Italian multicentre study reported the use of low dose GCs in 45% out of 1343 patients with primary SS (46). Intravenous high dose GCs are rarely used, as confirmed by Uei-Han *et al*. (0.81% out of 12,640) (47) and by Torres-Ruiz *et al*. in 2018 (4%), while current or former use of oral prednisone was observed in 36.7% out of 155 SS patients (48). In the same report, arthritis and a cumulative high ESSDAI were the variables associated with the use of GCs. Within the larger GEAS-SS cohort of 1580 patients, 85% (excluding the ones with lymphoma who received GCs plus rituximab) used GCs, especially those with systemic manifestations and a high ESSDAI (49) (Table I). Hence, it appears that CGs are commonly used without solid scientific evidence in SS, without knowing which dose is advisable, for how long or how to escalate it, and in spite of the well-known adverse effects among which cardiovascular (CV) events are noteworthy. According to one of the first case-control studies evaluating this topic, patients who receive GCs present a higher frequency of hypertension, diabetes mellitus, and hypertriglyceridaemia. SS patients with at least three CV risk factors have received corticosteroids more frequently than those without or those with one or two. In summary, GCs can be considered as an independent significant variable for CV risk (50). Bartoloni *et al*. demonstrated that patients who develop at least one CV event are more frequently treated with GCs (8% *vs*. 4%; p=0.006) and GCs use is associated to an increased risk of cardiovascular events with an OR of 1.97 (95% CI 1.083–3.582; p=0.026) (46). A further notable adverse effect of GCs is osteoporosis (51): the use of prednisone (even low doses and for periods of treatment less than 18 months) seems to be significantly associated with osteoporosis and low bone mass density in patients with SS (52).

Experimental evidence regarding the use of glucocorticoids in SS

It is estimated that 1% of the general population uses GCs, mainly for their anti-inflammatory properties, with an increase of 34% along the last two decades (20). GCs have a large spectrum of effects on the immune system (Fig. 1) (53-57). Nucleated cells almost ubiquitously express GRs but their response to GCs is variable, thus also the cells of both the innate and adaptive immune system involved in the pathogenetic processes of SS might be differentially sensitive to GCs (55, 58, 59).

In particular, B cells are sensitive to GC-induced apoptosis (60). Moreover, GCs reduce activation-induced levels of cytidine deaminase (AICDA) (which is the principal regulator of Ig gene somatic hypermutation and class-switch recombination in B cells) mRNA (61). LTh1 are susceptible to GC-induced apoptosis, too, whereas Th2 and possibly Th17 cells are resistant (62). Actually, a decrease in both peripheral Th1 and Th17 cells after glucocorticoid treatment has been reported in patients with giant cell arteritis (63). GCs induce a shift from Th1 to Th2 immunity at physiologic doses by inhibiting the production of IL-12, interferon-α (IFN-α), IFN-γ, and TNF-α by antigen-presenting cells and T-helper (Th)1 cells, at the same time inducing the production of IL-4, IL-10, and IL-13 by Th2 cells (64-66). Lastly, GCs seem to be able to increase the number of Tregs and their ability to produce the immunosuppressive cytokine IL-10 (67, 68).

Antigen uptake by dendritic cells (DCs) is stimulated by GCs which makes DCs tolerogenic, down-regulating expression of MHC-II molecules, cytokines such as IL-1, IL-6, and IL-12, and co-stimulatory molecules (55, 69).

Biological evidence supporting a therapeutic role of GCs in modulating inflammation and damage at both glandular and systemic levels in SS is currently lacking. Only a few studies have addressed the possible effects of GCs on the cells of the immune system in patients with SS. Alunno *et al*. demonstrated the expansion of a population of double-negative CD4-, CD8- (DN) T cells able to produce IL-17 in the peripheral blood and minor salivary glands of SS patients which, in contrast to DN T cells of healthy controls, are insensitive to dexamethasone (DEX) (70). This observation acquires great importance in the light of the role of

Table I. Use of GCs in the most recently published cohorts of at least 150 SS patients.

	Year	Country	n. of patients	Mean age ± SD at enrolment	Disease duration (years)	Frequency of oral GC	Frequency of iv GC
Alegria *et al*. (44)	2016	France	392	58 ± 12	n.a.	55%	n.a.
Gheitasi *et al*. (45)	2015	Spain	1120	54.4 ± 15.2	n.a.	65.2%*	n.a.
Bartoloni *et al*. (46)	2015	Italy	1343	57± 14	5 ± 6**	45%	n.a.
Uei-Han *et al*. (47)	2019	Taiwan	12640	53.4	n.a.	n.a.	0,81%
Torres-Ruiz *et al*.(48)#	2018	Mexico	155	57.4 ± 14.7	n.a.	36.70%	4%
Flores-Chàvez *et al*. (49)	2018	Spain	1580	n.a.	n.a.	85%***	n.a.
Jaurez *et al*. (96)	2014	UK	538	59 ± 12.4	11.5 ± 8.5****	10%	n.a.
Fauchais *et al*. (95)	2010	France	445	n.a.	n.a.	38%	n.a.
Sandhya *et al*. (94)	2015	India	229	n.a.	5.2 ± 5.05**	55.9%	n.a.

*>20 mg/daily in 22.8% out of 1120, the remaining with <20 mg/daily. **from diagnosis. ***excluding lymphoma patients. ****from symptoms onset. #Only this study reported the rate of extra-glandular manifestations (81.2%).

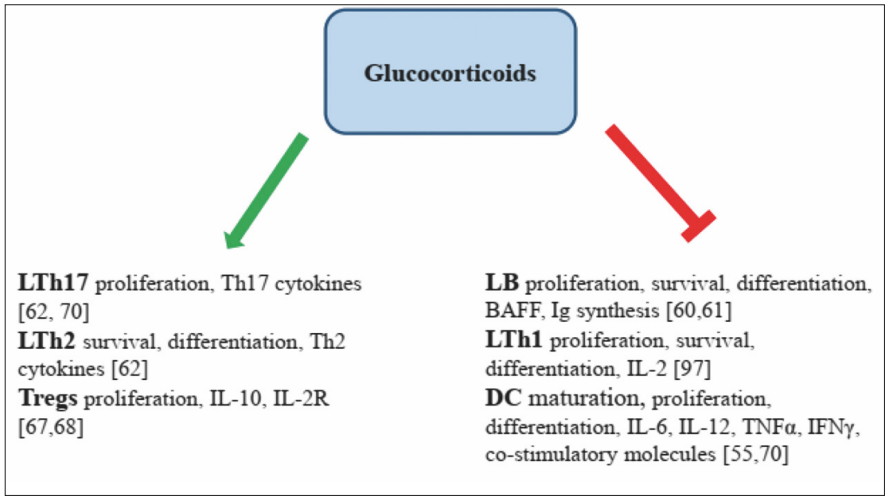

Fig. 1. Effects of GCs on the cells of the immune system (53-55, 57, 97).

the pro-inflammatory cytokine IL-17 in SS (71) as well as of the pathogenetic importance of DN T cells in other autoimmune disorders (72).

The impact of DEX in SS was analysed in another couple of studies. In a SS mouse model, DEX was able to partially prevent lymphocytic infiltration in salivary glands, and induce down-regulation of pro-apoptotic genes such as Foxp3, TNF-α, and NF-κB (73).

In a subsequent study of the same research group, DEX alone was able to maintain cell cluster formation, increased lumen size, reduced apoptosis, and preserved cell survival signalling responses, all considered TNF-α-mediated alterations in the salivary epithelium. These effects were increased when DEX was administrated together with aspirin-triggered Resolvin D1, which belongs to the family of resolvins, well-known anti-inflammatory agents (74). These positive effects of DEX on salivary glands should be balanced with its reported negative impact on salivary function: DEX can worsen oral dryness in older people (75) and reduce salivary secretion in mice (76-77). More recently, Kasuda *et al*. demonstrated that long-term DEX treatment significantly decreased salivation from mice, whereas short-term dexamethasone treatment did not. This effect was not associated with any morphologic change of salivary glands nor with any modification in membrane protein expression such as acquaporin 5 but to an impaired store-operated Ca2+ entry in the cells (78).

Switching from bench to bed, Chen *et al*. examined the effect of GCs on the expression of FcγRIIb on B cells of SS patients. FcγRIIb is a key negative regulator of B cells whose expression is reduced in SS and inversely correlated with the levels of anti-SSA antibodies and disease activity. In particular, SS patients with severe thrombocytopenia have reduced FcγRIIb expressions on B cells. An up-regulation of FcγRIIb on memory B cells and an increased platelet count was demonstrated with iv high dose methylprednisolone pulse (HD-MP) therapy for 3 days in SS patients (79).

Current recommendations

The backbone of good clinical guidelines and recommendations should be the use of the most adequate techniques and involvement of multidisciplinary experts relying on solid scientific evidence. This last point is difficult to satisfy for SS because of the paucity of RCT (30). However, several efforts have been made to offer help to physicians in choosing the best therapeutic approach for their SS patients. The state of the art of clinical practice guidelines (CPGs) has been recently addressed in the framework of the European Reference Network (ERN) dedicated to Rare and Complex Connective Tissue and Musculoskeletal Diseases (ReCONNET) (80). Four CPGs written in English have been recently published on the treatment/management of glandular and extraglandular manifestations (81-84) and some others on the management of dryness (85, 86).

Among the key recommendations for the inflammatory musculoskeletal pain, the Sjögren's Syndrome Foundation CPGs from the USA include two re-

garding the use of GCs: with a strong strength they suggest the use of short-term corticosteroids (less the 15 mg daily for less than one month) only if hydroxychloroquine plus methotrexate is not effective, while the recommendation to use higher doses for a longer period of time has moderate strength and the adjunct of a steroid-sparing agent is encouraged (81).

The British Society for Rheumatology guidelines do not recommend GCs for routine use in SS, but they recognise the role of short oral or intramuscular courses to control systemic flares, associated or not to other immunosuppressive agents (level of evidence III/C). Moreover, it is stated that low-dose prednisolone could be useful to treat constitutional symptoms in patients who do not respond to other first-line therapy (level of evidence IIb/B) (82).

The Japanese CPGs are organised in 38 clinical questions related to the diagnosis and treatment of SS in paediatric, adult, and pregnant patients. It is suggested for adults that systemic administration of GCs can improve articular, muscle, and skin involvements as well as glandular swelling but with a very weak strength of recommendation while a higher level of evidence, but still weak, is reported for systemic administration of GCs in dry mouth without improving salivary and lacrimal secretion (83). For paediatric cases, there is a quite obvious warning regarding GCs use because of the well-known side effects, such as growth suppression and osteoporosis.

The result of a huge, collaborative effort involving an international task force composed by specialists in rheumatology, internal medicine, oral health, ophthalmology, gynaecology, dermatology and epidemiology, statisticians, GPs, nurses and patient representatives from 29 countries of the 5 continents following the 2014 EULAR standardised operating procedures (87), has been very recently published as recommendations for the management of SS with topical and systemic therapies endorsed by EULAR itself (84). The recommendation to use systemic therapies, such as GCs and other synthetic/biologic disease-modifying anti-rheumatic drugs (DMARDs), as a possible approach active systemic disease (clinESSDAI ≥1) stands out among the overarching ones: "Systemic therapies may be considered for the treatment of active systemic disease" where may is knowingly chosen instead of should as not all patients with active systemic disease necessarily require systemic therapy. Furthermore, GCs should be used at the minimum dose and length of time necessary to control active systemic disease and, if a longer period is needed, GCs should be administered with a steroid-sparing immunosuppressive agent (level of evidence-LoE 4, grade of recommendations-GoR C, level of agreement-LoA 9.6) (84). This advice is in line with what stated in previously published CPGs for other autoimmune diseases such as SLE and RA (2-3). Going more in detail, the administration of pulses of methylprednisolone followed by doses of 0.5 mg/kg/d or lower as induction therapy in severe presentations, and doses<0.5 mg/kg/d in moderate/less-severe presentations, with a final target of stopping GCs in inactive patients as soon as possible or at least trying to maintain a dose of 5 mg/daily or less with the adjunct of GC-sparing agents, is suggested.

A further important recommendation is to follow the sequential (or combined) use of GCs, immunosuppressive agents and biologics (LoE 5, GoR D, LoA 8.6), again mainly based on what is generally suggested for other rheumatologic disorders more than what comes out from the available literature on SS. A series of useful consensus-based algorithms

Table II. First line use of glucocorticoids according to EULAR recommendations for the management of Sjögren's syndrome, all with LoE 4 (84).

JOINTS	0.5 + HCQ in the presence of moderate/high ESSDAI if: severe synovitis >5 joints or severe, widespread tenosynovitis after ruling out RA or if synovitis <5 joints or less diffuse tenosynovitis without response to HCQ/NSAIDs.
SKIN	0.3 with HCQ in diffuse annular erythema or limited annular erythema not responsive to topical GCs. 0.3 in the presence of moderate ESSDAI in cutaneous vasculitis in the form of limited purpura. 0.5-1 in the presence of high ESSDAI cutaneous vasculitis in the form of diffuse purpura, ischaemic ulcers or not responsive limited purpura.
LUNG	0.5 in the presence of moderate ESDDAI in bronchial involvement resistant to inhaled treatment. 0.5 in the presence of moderate ESDDAI in interstitial lung disease* (LoE4). 0.5-1 in the presence of high ESDDAI in interstitial lung disease* or no response in the previous situation.
KIDNEY	0.5 in the presence of moderate ESSDAI or mild ESSDAI without response to correction of the metabolic acidosis/potassium levels. 0.5-1 in the presence of high ESSDAI or no response in the previous situation.
BLOOD	0.5-1 if autoimmune thrombocytopenia (platelets <20.000/mm^3) or haemolytic anaemia (Haemoglobin 8-10 g/dl). Add IvIG to GCs if haemoglobin < 8 g/dl or if no response to the previous situation. 0.5-1 if neutropenia (<500/mm^3) with no response to G-CSF.
PNS	0.5-1 if multineuritis after ruling out non-cryoglobulinaemic vasculitis or in vasculitis-related axonal polyneuropathy.
CNS	0.5-1 in CNS vasculitis or neuromyelitis optica spectrum disorders or lymphocytic meningitis with no response to symptomatic or with encephalitic involvement.
CHB	second-degree block (1 month) and complete third-degree block in the presence of foetal poor cardiac function, hydrops, or endocardial fibroelastosis and in association with IvIg**.

For GCs the number indicates the recommended dose in mg/kg/day. Systemic activity is classified as low if ESSDAI is 1-4 (if not only due to biological domain), moderate between 5-13 and high ≥14.
G-CSF: granulocyte stimulating factor; PNS: peripheral nervous system; CNS: central nervous system; CHB: congenital heart bock; IvIg: intravenous immunoglobulin.
*especially indicated for lymphocytic interstitial pneumonia and organising pneumonia, less in non-specific interstitial pneumonia and even less in usual interstitial pneumonia.
**fluorinated GCs can be considered for first degree block but it is advised to repeat echo next day (LoE 5).

for the therapeutic approach to patients with primary SS with organ-specific systemic involvements are provided by the EULAR recommendations, including specific different suggestions for first-, second-line, and rescue therapy. Table II shows a list of the indications for GCs as first-line treatment in SS as recommended by the EULAR task force (84).

Even if congenital heart block (CHB) linked to anti-SSA/Ro is a threatening complication for SS women wishing a pregnancy (88), its management falls beyond the scope of the review. However, it is noteworthy to remind that, according to the EULAR recommendations, the use of fluorinated GCs should be considered as first-line therapy also for pregnant SS women carrying anti-SSA/Ro antibodies in the presence of a newly diagnosed 1st- and 2nd-degree block or in the presence of a confirmed 3rd-degree block associated to foetal poor cardiac function, hydrops, or endocardial fibroelastosis and in association with IvIg (84). Actually, there are conflicting reports regarding fluorinated GCs efficacy for either treatment or prophylaxis of CHB, in particular, they do not seem to reduce mortality (89, 90).

Conclusions

Almost 40 years have passed since Fauci wrote that "since most of the complications of therapy with corticosteroids are related to the dose size, dose interval and length of therapy, these drugs should be prescribed in the smallest dose, at the longest interval, and for the shortest period of time required to control disease activity" (91), and we have not gone very far, as in the most recent sets of therapeutic recommendations for SS this concept is still true. Despite the introduction of new biologic agents in the therapeutic armamentarium of SS (92) and new insight into therapy is discussed (93), the research agenda for the management of SS is still rich in points to be addressed, among which the role of GCs shouldn't be neglected.

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