Can we treat systemic lupus erythematosus and other autoimmune diseases without oral steroids?

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Glucocorticoids (GCs) have traditionally been the center of systemic lupus erythematosus (SLE) treatment and they continue to be recommended by the EULAR and ACR as the first line therapy for several autoimmune diseases (1,2). In the last decade, the trend has been to replace them with other immunosuppressive drugs in an effort to minimize GC side effects and at the same time to achieve better control of disease activity.

However, regardless of the fact that GC efficacy in SLE is unquestionable , some issues still need to be addressed.

First of all, GC dosage. While the concept "the lower the better" is generally accepted when referring to the chronic use of GC, treatment with high dose steroids may nonetheless be required to manage severe manifestations of autoimmune conditions. However, there is still ongoing debate about the difference in terms of efficacy and safety of medium vs. high doses of GCs for the management of acute flares since there is limited evidence on this topic.

Buttgereit et al. proposed a specific classification for prednisone doses according to the level of activation of the genomic and non-genomic pathways [Buttgereit F, Straub RH,Wehling M, Burmester GR. GC in the treatment of rheumatic diseases: an update on the mechanisms of action. Arthritis Rheum 2004;50:3408–17.]: low doses (up to 7.5 mg/day), medium doses (up to 30 mg/day), high doses (≥30 mg/day), very high doses (≥ 100 mg/day) and pulses (≥ 250 mg/day). Clinical studies have shown both a great increase in

toxicity, including irreversible damage, with the use of high doses [Autoimmun Rev 2014;13:206–14. Rheumatology 2014;53:1470–6], and a good safety profile of low doses [J Rheumatol 2009;36:560–4; Rheumatology 2014;53:1470–6.] and short-term pulse therapy [Autoimmun Rev. 2015 Oct;14(10):875-9.]

Recently, we pooled data from 8 randomized control trials (RCTs) investigating the rate of adverse effects (AEs) of medium vs. high doses of GCs in SLE, and after adjusting for treatment duration we observed a rate of 9/100 patients/year for hyperglycemia/diabetes, 25/100 patients/year for infections and 12/100 patients/year for avascular necrosis of the hip(4).

Interestingly, after adjusting for GC dose, we observed no differences in term of AEs when comparing patients receiving medium versus high doses.

The AEs of steroids in various inflammatory rheumatologic conditions are well known. Musculoskeletal damage includes osteoporosis, myopathy and osteonecrosis, the latter being more often/closely - choose related to high doses than to the accumulated dose (5,6) Bone mass is affected very early in treatment, but the risk of fracture and osteoporosis is related to the duration and cumulative dose of steroids. Treatment with high doses of steroids is associated with an increase in severe infections. Infections are not as frequent in patients receiving less than 5mg/day. GCs increase the risk of developing hyperglycemia even at a dose of 2.5 mg/d, and Cushing

syndrome may appear at the beginning of treatment even with low doses of GCs. Ophthalmologic side effects include cataracts and glaucoma. Cataracts are dose- and time- dependent. Skin atrophy, striae, purpura, acne, and other skin manifestations may appear and it seems that they could be associated with prolonged treatment with medium-high doses of GCs . (5,6). During pregnancy, GC treatment increases the risk of gestational diabetes and infections, as well as of premature rupture of the membranes (5).

Taken together, the above considerations encourage us to reduce the daily dosage of GCs; however, in the daily clinical practice, there is still no consensus when to consider a GCs dosage "low enough". Most studies consider doses of up to 7.5 mg of prednisone as low, although a growing body of evidence suggests this figure should be lowered to 5mg/day since it has been shown that an increase of 1 mg per day of methylprednisolone-equivalent is associated with a 2.8% increase in the risk of organ damage progression(6)

Another question consequently arises regarding how to achieve the goal of GC dose reduction without impacting on disease control.

There are several potentially helpful strategies which could be used to reduce - long-term, daily GC dose, including the administration of i.v. pulses (5) and the intramuscular administration of depot (triamcinolone100 mg i.m.) (9). Adding other drugs such as hydroxychloroquine (10) in the early stages of the disease and

maintaining treatment over time, together with immunosuppressants if necessary, can lead to a steroid-sparing effect.

Among others, Ruiz-Irastorza and his team intensively investigated the GC-sparing protocols for the management of patients with lupus, including those with lupus nephritis (LN).

They showed that a combination of medium-dose prednisone, methylprednisolone pulses, cyclophosphamide and hydroxychloroquine is at least as effective in achieving remission of lupus nephritis as regimens containing high-dose prednisone, and moreover this combination results in less toxicity (Autoimmun Rev. 2014 Feb;13(2):206-14. d). These observations were confirmed in a further study showing that the so-called *Lupus-Cruces nephritis protocol* improves the outcome of LN. Repeated methylprednisolone pulses help to reduce the dose of oral GCs and enhance clinical response (Autoimmun Rev. 2015 Oct;14(10):875-9.).

Finally, the use of biologic agents, even as first line treatment, is an option to be considered as a steroid-sparing approach.

Pego-Reigosa published two systematic reviews, respectively to analyze the efficacy and safety of immunosuppressive drugs (11) and rituximab (12) in the treatment of non-renal manifestations of SLE. With regard to - B-cell depletion therapy, Rituximab showed an showed an acceptable degree of control over disease activity with a robust steroid-sparing effect (12).

Our group suggested the possible GC-sparing role of rituximab as part of an intensified protocol of induction therapy (the so-called 4+2 protocol) in patients for whom avoiding immunosuppressive maintenance therapy and sparing steroids are particularly appealing (Autoimmun Rev. 2015 Dec;14(12):1123-30). In one of the longest follow-ups available to date, our data confirmed the need to reconsider the regimen of B-cell depletion in the treatment of the most severe or refractory forms of SLE, despite the disappointing results of RCTs.

Similarly, Condon et al. showed that oral steroids can be safely avoided in the treatment of LN in a cohort of 50 patients receiving the RITUXILUP protocol that includes 2 i.v. doses of methylprednisolone bolus (500 mg each) and 2 doses of Rituximab 1 gr on days 1 and 15, followed by maintenance treatment with mycophenolate mofetil (MMF) (13). After 5 years of follow-up the majority of these patients are still in remission with preserved renal function (14).

In conclusion, are we heading towards treating SLE without oral steroids?.

Understanding the overall risk of organ damage and risk to individual organ systems associated with exposure to medium/high-dose prednisone over time (i.e., ≥7.5 mg/day) as well as further understanding the risk of an average of a 1 mg/day or 5 mg/day increase in prednisone dose would help clinicians better understand the long-term benefits to be gained from the use of corticosteroid-

sparing therapies that are currently being developed in SLE clinical trials.

Nevertheless, some question are still unanswered. Will a steroid-free approach be able to concomitantly control disease activity and reduce damage accrual? Will a patient's quality of life improve?

Will the cost of biological therapies be compensated by savings related to decreased GC-induced damage? It is extremely tempting to answer these questions affirmatively, but only future, specifically designed clinical trials will tell.

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