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Short Commentry

Glucocorticoids in Maintenance of Systemic Lupus Erythematosus: Is Complete Withdrawal a Possibility?

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ABSTRACT

Systemic lupus erythematosus [SLE] is a potentially life-threatening disease and the treatment consists of immunosuppression. Glucocorticoids have played a major role in remission induction and maintenance in SLE for a very long time. Prolonged use of glucocorticoids leads to vast array of steroid related adverse effects. Also, steroid use is associated with increased damage accrual in SLE as seen in various studies. This effect can be mitigated by using minimum doses of glucocorticoids, for shortest periods. However, lack of clear guidelines on steroid dose and duration, leads to variations in clinical practice. The paucity of randomized controlled trials and alternative drugs, make the withdrawal of steroids in SLE difficult. This review discusses the various studies addressing steroid tapering and withdrawal, and areas of future research. Longer duration of remission before attempting withdrawal, and use of additional immunosuppression might be the key to successful withdrawal.

Keywords: steroid-free remission; glucocorticoid withdrawal; SLE damage accurate; steroid-sparing therapy; biologics in lupus

INTRODUCTION

Systemic lupus erythematosus [SLE] is a multisystem autoimmune disease with potentially organ-threatening and life-threatening manifestations. Patients of SLE often requires treatment for prolonged periods. Disease activity of SLE, as well as the adverse effects of the therapy, may cause significant morbidity and mortality. Glucocorticoids [GCs] have always been the mainstay of therapy and are recommended for both induction and maintenance of remission in SLE.[1] However, prolonged use of GCs is associated with its own complications.

Glucocorticoid use is associated with a multitude of adverse effects including diabetes mellitus, osteoporosis, myopathy, cushingoid habitus, ocular defects, and increased risk of infections.[2] Several studies have shown use of GCs to increase damage and morbidity in SLE. In the Hopkins lupus cohort study, the investigators found that the cumulative dose of prednisolone was significantly associated with an increased risk of osteoporotic fracture, cardiovascular diseases, cataract, stroke, and avascular necrosis.[3] An observational study on SLICC inception cohort of 1722 patients showed GC use to be associated with the development and progression of organ damage, and as an independent predictor of damage accrual.[4] In a similar study by Apostolopoulos et al, damage accrual was significantly more in GCs exposed patients compared to non-exposed patients, and increased with increasing cumulative doses.[5] Also, increased damage was seen at a mean dose of > 4.4 mg/day.[5] In another observational study, GC use at a mean adjusted dose of >5mg/day, contributed to damage accrual, irrespective of disease activity.[6]

To minimise the damage caused by prolonged GC therapy, it needs to be used in lowest doses for shortest periods. EULAR recommends the use of prednisolone or prednisolone equivalent of 7.5 mg/day or less in the maintenance of SLE, and complete withdrawal of GCs when possible.[1] But the guideline doesn't offer any recommendation upon the criteria for glucocorticoid withdrawal. Currently there are no guidelines to provide clarity on the dose and duration of glucocorticoid therapy. There is a wide variability in the clinical practice when it comes to steroid use and withdrawal after induction therapy.[7]

The question remains whether it's really possible to completely withdraw GCs from maintenance therapy of lupus in clinical practice. None of the above-mentioned studies have addressed

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the effect of GC withdrawal on disease activity or relapse. Though GC withdrawal has been tried in clinical practice, there is a lack of randomised controlled trials [RCTs]. The evidence supporting GC withdrawal in lupus maintenance comes largely from observational studies or real-world experience. Rituxilup was the first RCT designed to study the steroid sparing effect of rituximab in SLE, but was terminated prematurely.[8] The follow up data of 50 patients on Rituxilup protocol [rituximab and mycophenolate mofetil] showed complete remission in 45 patients, and only two patients required steroid maintenance.[9] Steroid sparing effect of methotrexate was also studied in a RCT, where methotrexate significantly reduced the mean daily dose of steroids in treatment arm.[10] However, the effect of complete withdrawal of steroids was not studied in this trial. A small pilot study was conducted in 15 lupus nephritis patients to study the feasibility of steroid withdrawal trials where flares were more in the continuation group than withdrawal group.[11] In an inception cohort of lupus nephritis patients, complete steroid withdrawal was achieved in approximately half of the patients, and steroid - free remission was maintained for long periods in one third of the patients.[12]

The recently published CORTICOLUP trial by Mathian et al is the first RCT to compare steroid withdrawal versus steroid maintenance in SLE.[13] A significant increase in relapse rate [27% vs 7%] was seen in the steroid withdrawal group compared to steroid maintenance group at 52 weeks follow up. More than half of the patients in this study were not on additional immunosuppression in both groups and the mean duration of remission was 56 and 68 months, respectively. The results of this study raises a debate over the feasibility of steroid-free remission maintenance.[14] However, it is also noticeable, that almost 75% of patients in the withdrawal group maintained steroid free remission. Another RCT is underway to compare the relapse rates in steroid withdrawal and continuation in quiescent lupus over a period of 36 months.[15] The results from this study may be able to provide further information on the sustainability of steroid-free remission.

Important aspects to be considered while attempting steroid withdrawal, are the predictors of successful steroid tapering, and timing of withdrawal. A prospective observational study from India showed a steroid free remission for a median of 611 days with relapse free survival in approximately 80% of patients in the study group.[16] Additional immunosuppression and long disease duration were associated with less relapses in this study. Tani et al found complete remission and lower SLEDAI scores at the time of steroid withdrawal, as predictors of successful GC withdrawal.[17] Duration of previous treatment and duration of remission were also observed as predictors of successful tapering and withdrawal of therapy in lupus nephritis.[18,19]

In future, long term use of steroids in maintenance may be replaced by newer drugs, mainly biologics. Multiple drugs are under research for their steroid sparing effects in various autoimmune diseases including SLE. As mentioned above, rituximab was tried in Rituxilup trial.[8] Belimumab has also shown steroid sparing potential in an observational study in lupus nephritis.[20] A meta-analysis was performed on the steroid sparing effects of biologics in clinical trial in lupus.[21] Although most of these trials failed to meet their primary end points, rituximab, belimumab, tabalumab, and epratuzumab showed a steroid sparing effect.[21] Avacopan [C5a receptor antagonist] has shown efficacy in replacing steroids in the induction therapy in anti-neutrophilic cytoplasmic antibody associated vasculitis [AAV] in clinical trials.[22] This drug is yet to be studied in SLE.

CONCLUSION

To conclude, complete GC withdrawal in SLE in desirable in long term. It is achievable in a subset of lupus patients. Long duration of therapy and remission, along with additional immunosuppression, may be the key to achieve successful steroid withdrawal. Further research and more RCTs are needed to assess the feasibility of prolonged steroid free remission, and steroid sparing effects of newer drugs. The benefits of the newer biological agents also need to be balanced against their potential adverse effects.

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