Withdrawal of therapy in non-renal systemic lupus erythematosus: is this an achievable goal?

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ABSTRACT

Survival of patients with systemic lupus erythematosus (SLE) has greatly improved over the decades. Many reasons for treatment withdrawal may be faced by the physician during the disease course, such as inactivity of disease, damage accrual, risks of long-term side effects, or potential interactions with other drugs required to treat concomitant conditions, as well as patients' preferences.

Therefore, analysis of long-term therapy and treatment withdrawal is important. We have examined the available literature concerning withdrawal of therapy, with attention to glucocorticoids, antimalarial drugs and traditional immunosuppressive drugs in SLE patients who did not have renal disease. We expanded our search to address two questions: i) advantages of long-term therapy in SLE (i.e. reduction of flares, reduction of damage accrual, improved survival); and (ii) burden/side effects of therapy in SLE.

Studies are needed to: i) define remission in SLE; ii) define the advantages of long-term therapy in non-renal lupus in terms of prevention of flares; iii) clarify the risks related with long-term immunosuppressive therapy; iv) identify the appropriate patient at the appropriate time for withdrawal of corticosteroids or immunosuppressive therapy; and v) define withdrawal/tapering strategies.

Introduction

Over recent decades, both short-term and long-term survival of patients with systemic lupus erythematosus (SLE) have greatly improved (1-5). Therefore, over time, variable features of disease activity, disease-induced damage, comorbidities, and drug toxicities accumulate and interact in influencing the clinical picture in individual patients who have SLE (6-16).

Several groups have shown that many patients with long disease duration experience reduced disease activity, while damage and comorbidities have an increasing impact on quality of life and prognosis, often requiring introduction of additional therapies (2, 4, 7-9, 11-13, 17-19).

Glucocorticoids (GC) are a cornerstone of SLE treatment (6). These drugs have changed the history of the disease and are largely used to obtain rapid control of disease activity (6, 20). Usually, doses are defined on the basis of the severity of organ involvement. However, long-term GC are clearly associated with important side effects and comorbidities. Therefore, steroid sparing is essential (2, 4, 6, 7, 10, 21-24, 25-26). Moreover, GC by themselves are not likely to mantain sufficient control of disease activity over time.

Likewise, antimalarials are a cornerstone therapy for SLE (27-29). Their capacity to control disease activity, prevent flares and damage accrual, and improve survival has been documented in a number of reports (27-29). In contrast to GC, however, even their long-term effects seem to be protective rather than troublesome. In particular, antimalarials may have a protective effect on thrombosis and beneficially influence the lipid profile, thus reducing atherosclerosis accrual. Nevertheless, perceived risks and subjective discomfort are an issue with antimalarials.

Finally, traditional immunosuppressive drugs are used in the treatment of SLE for a number of indications, either to reduce disease activity, maintain disease remission, or as steroid-sparing agents. In a recently published systematic literature review on the use of immunosuppressive drugs in non-renal lupus, the authors have concluded that, although data support the efficacy of these drugs in non-renal SLE, no recommendations on the efficacy of a specific drug on a specific organ manifestation can be derived from the literature. Moreover, there are indications of long-term risks for these drugs (30-32, 35).

During disease course, circumstances may emerge that would favour drug withdrawal, including inactivity of disease, patient preferences and compliance, risks of long-term side effects, or potential interactions with other drugs required to treat concomitant conditions or consequences of damage accrual (36).

One particular reason for stopping immunosuppressive drugs is a potential increase in the long-term risk to develop a cancer (33-35). Such increase also has been seen in patients after organ transplantation. A number of studies have hypothesised that the increased cancer risk observed among SLE patients may in part be due to immunosuppressive drugs, particularly referring to cervical cancer, bladder cancer, and leukaemia. Accordingly, patients and their physicians are insecure, and often desire to stop therapy after long-term treatment.

Therefore, it is important to understand whether long-term therapy with any of these classes of drugs is associated with better outcomes or not, and to define modalities of safe treatment withdrawal.

In the present report, we reviewed the existing literature concerning the withdrawal of treatment in non-renal SLE, focusing on GC, antimalarial drugs, and traditional immunosuppressive drugs (azathioprine, mycophenolate mofetil, methotrexate, cyclosporine A), and tried to identify preliminary indications for therapy withdrawal, based on the available data. Cyclophosphamide was not included in the analysis as the majority of data on its use refer to lupus nephritis which is examined in another review of this Supplement.

Methods

A systematic literature search was conducted on PubMed in August 2013, using MeSH headings and keywords for "(steroids OR immunosuppressive agents) AND (discontinuation OR stopping OR withdrawal) AND systemic lupus erythematosus". A total of 206 records were retrieved. Articles were excluded if they were paediatric, not in English language, if they were narrative reviews or did not report data of interest. Studies involving only lupus nephritis patients were also excluded. At the end of this process, only three articles were found to be relevant, from 1973 (37), 1991 (29) and 1998 (38). These three reports were included in the review.

In view of the small number of studies retrieved, we did not perform a systematic literature review; rather, we summarised the existing literature data for the study drugs.

Considering the paucity of the published data on this topic, we decided to expand our search by rephrasing our clinical issue as two additional search questions: i) advantages of long-term therapy in SLE (*i.e.*, reduction of flares, reduction of damage accrual, improved survival); and ii) burden/side effects of therapy in SLE.

Results

Glucocorticoids

Although there is general agreement on the toxicity of GC and the need to avoid long-term administration of these drugs, up to 80% of patients are chronically treated with these drugs in the majority of the published cohorts. There are little data on GC withdrawal for patients with non-renal SLE. Therefore, tapering schedules, the choice of the right patient, and the choice of the right moment are largely based on physician judgment, and highly variable. An exercise aimed at defining GC-sparing criteria in SLE confirmed the great variability in opinion among expert physicians (24). Also, there are arguments that withdrawal of low-dose steroids may be fraught with increased risks of flares even after years of SLE inactivity (11).

Recently, Zahr *et al*. have reported that younger patients, and those with higher levels of education, lower disease activity, no proteinuria and without ongoing cutaneous or articular manifestations were more likely to have GC tapering in the Hopkins lupus cohort (21). Bootsma *et al*. and Tseng *et al*. found that an increase of the GC dose in patients with clinically quiescent but serologically active disease (increase in anti-dsDNA antibodies and decrease in serum level complement) was associated with a lower incidence of severe disease flares (39,40).

Based on the few available data, it could be proposed that withdrawal of GC therapy in patients with non-renal lupus can be attempted in younger patients with low disease activity, no ongoing cutaneous and articular manifestations, and no recent serological changes (increase in anti-dsDNA antibodies or reduction in complement levels).

Studies are needed to define a number of questions concerning GC therapy and withdrawal. How long should the disease be stable before GC withdrawal is attempted? Should GC already be stopped as soon as possible when disease activity has been lowered and disease can be controlled with antimalarials and/or immunosuppressive drugs? If so, are both clinical and serological inactivity required, or is clinical inactivity sufficient, independent of the serology? Finally, as far as the tapering schedule is concerned, how fast should we withdraw treatment?

Antimalarial drugs

In 1991, a six-month, randomised, placebo-controlled study on hydroxychloroquine (HCQ) withdrawal was conducted in 47 SLE patients. Inclusion criteria were a stable HCQ dose ranging between 100 and 400 mg/day for at least six months and stable disease, defined as clinical remission or minimal disease activity for at least three months. The relative risk of flares among patients taking placebo was 2.5 higher than in patients who were treated with HCQ (29).

Similar results associating treatment with HCQ and lower disease activity have been obtained in the PLUS study (28). Thus, all available evidence suggests that withdrawal of antimalarials is associated with an increased risk of SLE flares.

Based on these data and on the safety profile of these drugs, antimalarials can be viewed as a long-term background therapy for SLE and should be continued long-term, whenever tolerated.

Immunosuppressive drugs

The analysis of cohorts of SLE patients with long disease duration sug-

Table I. Withdrawal of therapy with glucocorticoids, antimalarials, immunosuppressive drugs.

	Glucocorticoids	Antimalarials	Immunosuppressives
% of SLE patients	80%	50%	40%
Long-term adverse events	Severe >7.5 mg q.d. Controllable <7.5 mg q.d.	Unlikely	Possible (tumours, infections, bone marrow toxicity)
Flares upon discontinuation	Possible	Established (28, 29)	Probable in active disease (37)
Other long-term benefits	None established	Established (27)	None established
Recommendation	Reduce to <7.5 mg q.d.	Maintain	Discontinue if SLE in prolonged remission

gests that immunosuppressive drugs are stopped in a variable number of patients. However, no data are available on when, how, and in which patients, these drugs are stopped (5, 11, 13).

In 1973, a small controlled trial of azathioprine withdrawal included 9 patients with stable disease; disease flares were observed in 7 out of 9 patients, a mean of 89 days after withdrawal (37). In 2005, Urowitz *et al*. have shown that complete remission lasting 5 years is achieved in a very small percentage of SLE patients only with medication available at this time (11). Similar data have been published by other authors who have shown that more commonly patients with SLE have either a flare or chronically active disease (41, 42).

In conclusion, the available data show that immunosuppressive drug withdrawal is common. Such withdrawal may be prompted by longer-term disease control, although flares may be common despite therapy. Data from one small trial performed for demonstrating efficacy of immunosuppression may be seen as suggesting that withdrawal of immunosuppressive therapy commonly leads to disease flares (37). However, the patients included would not meet current concepts concerning long-term control, and further studies are needed.

Discussion

Very little data are available on drug withdrawal in non-renal SLE. The best available data concern antimalarials, as often seen in non-renal SLE. Hydroxychloroquine has been found to prevent SLE flares, and the risk of flares upon withdrawal is significant. Moreover, antimalarials are also protective against atherosclerosis, a major threat for SLE patients (27). Given that retinal drug toxicity is rare, we can therefore clearly recommend that antimalarials not be stopped, unless necessary. This is also in line with published recommendations.

For GC, the question is mostly unresolved. There is little doubt that long-term daily doses of more than 7.5 mg or 5 mg prednisolone equivalent are dangerous, and that prednisolone can often be reduced to as little as 2.5 mg *q.d.*, where severe adverse effects are much less common (26). Some authors feel that withdrawal of very low-dose GC may lead to severe flares even after very long intervals for complete quiescence, but this concept can neither be proved nor refuted based on the literature. Nevertheless, very low-dose GC may be a useful compromise, as doses <5 mg/day do not affect the hypothalamic-pituitary-adrenal (HPA) axis (45).

Withdrawal of immunosuppressive drugs may appear almost unavoidable in most SLE patients inactive over the longer term. Unfortunately, no data are available that could help us in deciding when this practice is safe (Table I).

In our opinion, treatment withdrawal must be based on a shared decision between patients and physicians, and this may impact on the type of drugs that are stopped. In fact, some patients are willing to continue low doses of glucocorticoids (methylprednisolone 4 mg/day or lower) as this improves their well being. Withdrawal of immunosuppressive drugs is usually started in patients with clinically silent disease and stable serology for at least two years. If acceptable to the patient, antimalarial drugs should be maintained long term and may be re-started in those patients who have stopped this treatment prior to starting corticosteroids or immunosuppressive drugs withdrawal.

One major limitation in defining in which patients and when therapy could be stopped is constituted by the fact that until now there is no accepted definition of remission, or even adequate disease control, in SLE (44). Therefore decisions in clinical practice are based on the judgment and experience of the treating physician, making them extremely variable.

It is obvious that inflammatory disease activity is not compatible with disease control. However, many other issues need to be resolved, from the relevance of serology to the optimal choice of validated disease indices or the variables contained therein, the exclusion of certain therapeutic modalities, and minimal duration. Again, registry data might be helpful to resolve these issues.

Withdrawal of immunosuppressive drugs in inactive SLE is common, but the conditions under which this is appropriate are not sufficiently investigated. Even the question of potential adverse effects associated with the long-term treatment with these drugs is not sufficiently answered. For GC, long-term adverse effects are well characterised, as are their benefits in active SLE. However, no data exist to guide the treating physician on whether to stop GC, which appears mainly based on personal experience.

Therefore, studies are needed to: i) define remission in SLE; ii) define the advantages of long-term therapy in non-renal lupus in terms of prevention of flares iii) clarify risks of long-term immunosuppressive therapy; (iv) identify the appropriate patient at the appropriate time for withdrawal of glucocorticoid or immunosuppressive therapy; and (v) define withdrawal/tapering strategies. Reassuringly, long-term therapy with antimalarial drugs is associated with increased survival and reduced damage accrual. Therefore, data strongly suggest that SLE patients should continue these drugs as background therapy as long as possible.

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