

safely discontinued, without exposing remitted patients to a significant risk of flare, has not yet been clearly determined. Accordingly, available recommendations for the management of SLE underline the importance of progressive tapering of glucocorticoids (GCs) until withdrawal, but do not remark on the possibility of discontinuing IS in remitted patients. Moreover, the timing of IS discontinuation has not yet been established and in clinical practice it is quite common that remitted patients continue to receive the same treatment which led to remission, with the aim of preventing flares, for an indefinite period of time.

It has been recently reported that ISs were safely withdrawn after remission achievement in more than 75% of patients with SLE in a cohort of 319 patients treated with IS for different manifestations, including lupus nephritis (LN) (47%), arthritis (15.7%), haematological abnormalities (5.3%), skin rash (6.3%), neuropsychiatric SLE (1.9%), vasculitis (1.3%), serositis (0.6%), and multi-organ involvement (21.9%).³ The independent predictors of a safe discontinuation were hydroxychloroquine (HCQ) maintenance therapy after IS discontinuation and a longer duration of remission at IS discontinuation. Notably, being on HCQ and in remission for at least two consecutive years reduced the risk of flare by 81% and being on HCQ and in remission for at least three consecutive years by 86%. These findings are in keeping with recent recommendations, as antimalarials have been regarded as standard of care in all SLE patients unless contraindicated, including patients with LN, where antimalarials are proposed as an additional therapy. Interestingly, in this study maintenance therapy with 5 mg/day prednisolone equivalent alone did not protect against flares, as patients with low-dose maintenance therapy experienced a similar flare-rate compared to patients who discontinued all treatment at the time of IS withdrawal.

In LN, different studies found a variable flare rate after IS discontinuation due to achievement of stable remission, ranging from 15% to 38.7%. Antimalarial therapy and a longer duration of remission at IS discontinuation resulted predictive of flare-free remission in some but not all these studies. Notably, the protective role of HCQ therapeutic levels against LN flares has recently been reported.⁴ Indeed, among remitted patients, those with a subsequent renal flare during the follow-up had significantly lower HCQ levels compared with those in persistent remission. To date, different authors suggested a wide range of duration of IS maintenance therapy after remission achievement in LN, varying from 3 to 6.5 years.

Based on available data, we can conclude that IS may be withdrawn in selected SLE patients, based on the characteristics of the individual patient, including their maintenance therapy and the duration of remission, which requires a personalised approach. In this regard, long-term therapy with antimalarials should be recommended in all SLE patients.⁵ Continuous surveillance should be planned during treatment tapering and after withdrawal, to ensure any early signs or symptoms of disease relapse are detected.

Learning Objectives

- Explain why, although GCs should be de-escalated and withdrawn as early as possible in remitted patients, the timing of IS tapering until discontinuation in these patients is still an unresolved issue
- Describe the recent data suggesting that maintenance therapy with HCQ and a longer duration of remission at the time of IS withdrawal are protective against lupus flares

- Explain the importance of tight surveillance of lupus patients, during IS therapy tapering and after IS withdrawal in order to detect early signs or symptoms predictive of a disease relapse

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Workshop

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MANAGEMENT OF REFRACTORY SKIN LUPUS

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Management of refractory skin lesions in patients with lupus erythematosus involves combinations of local measures and systemic agents requiring adjustment to activity and development of the disease. The treatment options are fairly similar for the different cutaneous manifestations; however, no drugs have been licensed specifically for the treatment of skin lesions in this disease. Therefore, the aim of the European guideline was to achieve a broad consensus on treatment strategies for patients with cutaneous lupus erythematosus (CLE) by a European subcommittee, guided by the European Dermatology Forum (EDF) and supported by the European Academy of Dermatology and Venereology (EADV).

Standard treatment of CLE includes preventive measures such as smoking cessation and photoprotection. Ultraviolet (UV) A and B light is one of the most important risk factors for CLE, clearly documented by photoprovocation studies in large patient cohorts. In the past years, several trials have been performed to investigate the preventive effect of sunscreens in patients with UV-induced CLE. A randomised controlled trial demonstrated that the application of a broad-spectrum sunscreen with a high protection factor prevents UV-induced skin lesions under standardised conditions. First-line treatment options in CLE include topical corticosteroids or calcineurin inhibitors. Currently available topical calcineurin inhibitors (0.03% and 0.1% tacrolimus ointment, 1% pimecrolimus cream) have been licensed for the use in patients with atopic dermatitis. The major advantage of these agents is their better safety profile when compared to topical corticosteroids. A multicentre, randomised, double-blind, vehicle-controlled trial showed significant improvement for oedema and erythema of CLE lesions using 0.1% tacrolimus ointment compared to the vehicle.

In patients with disfiguring and widespread disease, systemic agents need to be applied. The first-line systemic treatment is antimalarials, such as hydroxychloroquine, chloroquine

or quinacrine, which are particularly recommended in patients with a high risk of scarring and/or the development of systemic disease. In addition, systemic corticosteroids are recommended as first-line treatment in highly active and/or severe CLE. Second- and third-line systemic treatments include methotrexate, retinoids, dapsone and mycophenolate mofetil or mycophenolate acid, respectively. Thalidomide should only be used in selected therapy-refractory CLE patients, preferably in addition to antimalarials. Several new therapeutic options, such as B-cell- or interferon alpha-targeted agents, need to be further evaluated in clinical trials to assess their efficacy and safety in the treatment of patients with CLE.

In 2011, the monoclonal antibody belimumab, a B lymphocyte stimulator-specific inhibitor, was introduced for SLE as an adjunct therapy for patients with autoantibody-positive disease who despite standard therapy show high disease activity, intolerance of other treatments, or an unacceptably high need for corticosteroids. Currently, a validated skin score is used to confirm the efficacy of belimumab on mucocutaneous manifestations.

In summary, there is a high unmet need for new therapeutic strategies, such as B-cell- or interferon-targeted agents, focusing on cutaneous manifestations in lupus erythematosus. Therefore, innovative designs of randomised controlled trials are warranted to develop new therapeutic options for patients with refractory skin manifestations in this disease.

Case 1: 40-year-old man with SLE and painful erythematous-violaceous lesions

Marzia Caproni

A 40-year-old man was diagnosed with systemic lupus erythematosus (SLE) in 2013 based on photosensitivity, Raynaud's phenomenon, positive direct Coombs test, ANA, anti-dsDNA, Sm, Ro, La, RNP antibodies and low complement, followed by malar rash and discoid lesions on the ears. He started hydroxychloroquine (HCQ) 400 mg/day, nicotinamide 500 mg/day, topical corticosteroids and calcineurin inhibitors with benefit, followed by reactivation of malar rash, worsening of immunological parameters, proteinuria and lupus nephritis two years later. Prednisone 25 mg/day and mycophenolate mofetil (MMF) 640 mg/day were added with good clinical and laboratory control. In March 2018 he was hospitalised because of suspected macrophage activation syndrome triggered by cytomegalovirus and MMF was withdrawn. As lupus reactivated, in May 2018 he restarted MMF 320 mg/day with prednisone 25 mg/day and HCQ 200 mg/day. In August 2018, rituximab was administered because of the development of sensory neuropathy with no improvement, thus he underwent intravenous immune globulin treatment with control. In 2020, he developed painful erythematous-violaceous lesions associated with small bullae and ulcers on the distal phalanges of the fingers and toes and of the tip of the nose. Skin lesions were consistent with chilblain lupus. Topical corticosteroid was added. Systemic treatments were replaced by belimumab.

Discussion Points

- Specific and non-specific skin manifestations during SLE course
- Cutaneous lupus erythematosus (CLE) guidelines
- Chilblain lupus: differential diagnosis at the time of Covid-19

Case 2: 35-year-old female with SLE and erythematous-desquamative plaques

Marzia Caproni

A 35-year-old female was diagnosed with SLE in 2013 on the basis of discoid lesions of the face and head,

photosensitivity, ANA positivity, lymphadenopathy, hypocomplementemia, leukopenia, low-grade fever and diffuse arthralgias. Comorbidities included Hashimoto's thyroiditis and fibromyalgia under L-tyroxine, baclofen and escitalopram treatment. She started HCQ 400 mg/day and prednisone 25 mg/day, tapering to 5 mg/day with initial control. After 2 years of treatment arthralgias worsened as well as skin lesions and laboratory findings. On examination, atrophic painful plaque of the scalp and erythematous-desquamative plaques on the face were revealed. Topical and IV corticosteroids were added without improvement. Patient also underwent methotrexate, cyclosporine, mycophenolate, rituximab and azathioprine treatment without improvement. We introduced mepacrine 100 mg/day with skin lesion improvement. Due to the difficulty in finding the drug, the patient stopped the treatment with reactivation of the skin manifestations and systemic involvement. We started belimumab 660 mg IV with HCQ 400 mg/day, prednisone 5 mg/day, azathioprine 50 mg/day and duloxetine 60 mg/day with control.

Discussion Points

- Discoid lupus erythematosus: clinical and histopathological findings
- CLE guidelines: topical treatments of discoid lupus erythematosus
- CLE guidelines: mepacrine in recalcitrant cutaneous lupus erythematosus
- Belimumab and skin lesions in SLE

Learning Objectives

- Discuss specific and non-specific skin manifestations of SLE
- Describe optimal clinical management of skin lupus in line with CLE guidelines and the role of biologic therapy
- Explain the challenges of differential diagnosis in patients with CLE

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Case 1: 39-year-old female with a premature atherosclerotic event

Murray Urowitz

This case is of historical importance as it initiated the investigations leading to the description of the bimodal mortality program in systemic lupus erythematosus (SLE).

MB is a 39-year-old female with a history of SLE diagnosed at 19 years old. Lupus manifestations included