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Review

The skin in autoimmune diseases—Unmet needs

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ABSTRACT

Treatment of skin manifestations in systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and dermatomyositis (DM) is based on the results of only few randomized controlled trials. The first-line treatment for disfiguring and widespread cutaneous involvement in SLE is antimalarials, but some patients are therapy resistant. Recently, the monoclonal antibody belimumab was approved 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. However, a validated skin score has not been used to confirm the efficacy of belimumab on mucocutaneous manifestations. In SSc, another multi-systemic progressive disease, involvement of the lung, kidney, and the heart is frequently treated with corticosteroids and immunosuppressives, but therapeutic modalities for cutaneous lesions, such as skin sclerosis and digital ulcers, are limited. In the past years, treatment with the endothelin-receptor antagonist bosentan has been proven to reduce the occurrence of new digital ulcers in SSc patients but has no or limited effect on healing of digital ulcers. DM is an idiopathic autoimmune disease characterized by inflammation of the muscles and skin, which is treated with immunosuppressives. Corticosteroids are the first-line treatment for muscle involvement in DM, but skin lesions often flare by reduction or discontinuation. In summary, there is a high unmet need for new therapeutic strategies focusing on skin involvement in systemic autoimmune diseases. Therefore, innovative designs of randomized controlled trials with validated skin scores are warranted to develop new therapeutic strategies for patients with cutaneous manifestations.

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1. Introduction

Systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and dermatomyositis (DM) are three disorders within the broad spectrum of autoimmune diseases, which show heterogeneous clinical manifestations reaching from primarily cutaneous lesions to severe systemic organ involvement [1–3]. Although the skin manifestations of these conditions have a highly negative impact on the quality of life [4–6], most clinical trials focus on therapeutic options for the systemic involvement of the diseases. An overview of ongoing trials in SLE, SSc, and DM can be found in Table 1.

2. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an inflammatory autoimmune disease with systemic organ involvement, which often initially affects the skin [7]. Cutaneous lesions appear in 73–85% of SLE patients [8] and may present at any stage of the disease as LE-specific or LE-nonspecific manifestations [9]. The LE-specific cutaneous manifestations encompass the various subtypes of cutaneous lupus erythematosus (CLE). In the "Duesseldorf classification," CLE is subdivided into four different categories: (i) acute cutaneous LE (ACLE); (ii) subacute cutaneous LE (SCLE); (iii) chronic cutaneous LE (CCLE), which consists of discoid LE (DLE), LE panniculitis (LEP), and chilblain LE (CHLE); and (iv) intermittent cutaneous LE (ICLE), synonymously LE tumidus (LET) [10,11]. The LE-nonspecific cutaneous manifestations include, e.g., vascular skin changes, such as livedo racemosa, urticarial vasculitis, and Raynaud's phenomenon, and may be associated with active systemic organ involvement or other autoimmune diseases.

2.1. Diagnosis

In 1982, the American College of Rheumatology (ACR) developed 11 criteria for the classification of SLE [12]. These criteria were recently revised and validated by the group of the Systemic Lupus International Collaborating Clinics (SLICC) [13]. The SLICC criteria comprise 17 clinical and immunological criteria in order to improve clinical relevance and incorporate new knowledge regarding the immunology of SLE. The diagnosis of skin manifestations in SLE is based on the evaluation of the clinical picture, histological examinations of skin biopsy specimens, and laboratory tests and is completed by patient's history (i.e., photosensitivity, drug intake, smoking) [14–16]. The histological picture of most CLE subtypes is characterized by an interface dermatitis, the infiltration of lymphocytes in the dermo-epidermal junction and perivascular and periadnexal inflammation [17].

2.2. Prevention and treatment

Preventive measures for skin manifestations in SLE include the avoidance of trigger factors and disease-exacerbating influences [18]. Most importantly, photoprotection with broad spectrum sunscreens and avoidance of potentially photosensitizing drugs are required [19–22]. Furthermore, it has been observed that smoking has a negative influence on cutaneous lesions of the disease [23–25], and several studies confirmed that smoking interferes with the efficacy of antimalarials [26–30]. Therefore, SLE patients and skin manifestations should be motivated to cease smoking.

Topical corticosteroids (CS) are the first-line treatment for all LE-specific skin manifestations in SLE [31], but due to their well-known side effects, such as atrophy, telangiectasia, and steroid-induced rosacea-like dermatitis, treatment with topical CS should be intermittent and time limited [18]. In recent years, topical calcineurin inhibitors (CI), such as tacrolimus and pimecrolimus, were observed to be efficient in various CLE subtypes [32,33]. A further topical treatment option is R-salbutamol, which demonstrated a good efficacy in a multicenter, double-blind, randomized, placebo-controlled phase II trial [34]. However, this agent is not commercially available and further trials are still necessary.

Antimalarials, preferentially hydroxychloroquine (HCQ), are the first-line therapy for disfiguring and widespread skin manifestations in SLE patients, irrespective of the subtype of the disease [35]. If HCQ is not efficient, the treatment can be changed to chloroquine or quinacrine can be applied in combination with either antimalarial agent added [36]. In all SLE patients, treatment with antimalarials is highly recommended unless there are contraindications [37]. HCQ and CQ are approved for SLE, but not specifically for isolated CLE without systemic organ manifestations. Treatment with HCQ is associated with a higher rate of remission, fewer relapses, and reduced damage in the course of the disease [38]. In most of the longterm recommendations, the dosage of HCQ and CQ is adjusted to the ideal bodyweight of the patients [35]. In thin patients, the real bodyweight may be less than the ideal bodyweight, in these cases the real body weight should be used for calculation of the maximum daily dosage. However, the calculation of the maximum daily dosage is currently discussed in the literature [35]. In the past years, only two randomized, double-blind, placebo-controlled trials focused on the efficacy of antimalarials in patients with SLE and skin lesions or patients with isolated CLE (in combination with acitretin [39] or clofazimine [40], respectively). Recently, a randomized, placebo-controlled, double-blind trial investigating the efficacy and safety of HCQ in patients with isolated CLE was completed in Japan (ClinicalTrials.gov Identifier: NCT01551069), but the results are not yet published. Although several open-label studies, case series, retrospective analyses and in particular expert opinions confirm the high efficacy of antimalarials for skin lesions in SLE or isolated CLE, the data also demonstrate that not all patients respond to treatment with these agents [18]. In some cases, it needs to be considered that the lack of efficacy might be due to non-compliance of these patients [41,42].

In case of highly acute and severe skin lesions of SLE the application of systemic CS may be indicated, but treatment should be intermittent and time limited due to their well-known side effects, such as osteoporosis, Cushing's syndrome, and type 2 diabetes. Second-line systemic treatment for LE-specific skin manifestations include methotrexate or mycophenolate mofetil (or mycophenolate sodium) [43]. In rare cases, retinoids or dapsone may be applied [43], but these agents were only reported to be effective in single case reports and smaller case series. Current approaches in the understanding of the molecular pathogenesis of SLE and isolated CLE enabled the development of further new agents, which target molecules such as interleukin-6 (IL-6) and interferon (IFN). Recently, Manzi et al. [44] pooled data collected in two phase III trials applying belimumab in 1684 autoantibody-positive SLE patients and reported a reduced disease activity on musculoskeletal and mucocutaneous parameters [45,46]. The mucocutaneous manifestations in SLE patients, however, were not further specified and a validated skin activity and damage score, e.g., the "Revised Cutaneous Lupus Erythematosus Disease Area and Severity Index" (RCLASI) [47], was not applied in these phase III trials. Therefore, it is difficult to evaluate and reproduce the efficacy of belimumab on mucocutaneous lesions in SLE patients and future prospective clinical trials using a validated skin score are required.

3. Systemic sclerosis

Systemic sclerosis (SSc) is an autoimmune-mediated, connective tissue disorder characterized by microvascular damage and excessive fibrosis [2]. The disease is classified into limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc), based on the extent of skin involvement. In lcSSc, hands and feet distal from elbows and knees and the face are involved, whereas in dcSSc skin sclerosis affects the proximal limbs and trunk [48]. In 95%