CASE SERIES

Dupilumab in patients with moderate to severe atopic dermatitis and multiple sclerosis

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Key words: atopic dermatitis; dupilumab; multiple sclerosis.

INTRODUCTION

Atopic dermatitis (AD) is a common inflammatory cutaneous disease characterized by itchy eczematous lesions and xerosis with a chronic or relapsing/remitting course that presents as phenotypically diverse patterns.1 AD can be associated with other atopic disorders such as asthma and rhinoconjunctivitis, as well as non-atopic comorbidities.2 Dupilumab, a monoclonal antibody that inhibits interleukin (IL)-4 and IL-13 signaling by specifically binding to the IL-4R-alpha shared subunit, has demonstrated to be effective in adult and pediatric moderate-to-severe AD patients with a good tolerability profile and to improve patients’ health-related quality of life, both in clinical trials and in real-life experiences.3–7

Despite recent therapeutic advances, treating AD in patients with other major systemic disorders can be challenging, as in multiple sclerosis (MS). MS is a chronic autoimmune disease in which the antigenic target is the myelin of the central nervous system. Treatment of AD in patients with MS is difficult, particularly in the case of ongoing immunosuppressive treatment that contraindicates agents for the treatment of AD.8 Treatment of MS aims to treat symptoms and reduce the risk of relapse with disease-modifying therapies that include interferon, anti-integrins, anti-CD52, anti-CD20, anti-SIP agents, dimethyl fumarate, and teriflunomide.8 To date, there are no reports describing treatment with dupilumab in MS patients with AD. Given the common concern about the use of monoclonal antibodies in patients with MS, particularly when treated with systemic disease-modifying drugs, we report the effectiveness and safety of dupilumab in 3 patients with MS who had moderate-to-severe AD while continuing treatment with a disease-modifying agent for MS.

CASE 1

A 60-year-old woman presented to our clinic complaining of severe rash and pruritus for more than 10 years, with a diagnosis of AD. Physical examination revealed severe and generalized xerosis, excoriated erythematous papules, and nodules on the trunk and extremities associated with diffuse hyperpigmentation (Fig 1, A). She had a history of AD during childhood and adolescence followed by a long remission. The clinical phenotype was suggestive of moderate to severe prurigo-like AD. The Investigator’s Global Assessment (IGA) score was 4, Eczema area and severity index (EASI) score of 47, body surface area (BSA) 80%, pruritus visual analog scale (VAS) score of 10, and Dermatology Life Quality Index (DLQI 28). Laboratory investigations showed elevated immunoglobulin (Ig) E levels (585 IU/mL, normal values 1.5, 144 IU/mL) and eosinophilia.

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Abbreviations used:

AD: atopic dermatitis
BSA: body surface area
EASI: eczema area and severity index
Ig: immunoglobulin
IGA: investigator’s global assessment
IL: interleukin
MS: multiple sclerosis
VAS: visual analog scale
Because she also presented with fever and inguinal lymph node enlargement, a right inguinal lymph node biopsy was performed, which showed a dermopathic lymph node reaction. A skin biopsy specimen from the trunk revealed subacute spongiotic dermatitis with multifocal parakeratosis, consistent with an eczematous process. The patient failed ultraviolet B phototherapy and topical corticosteroids, while methotrexate 10 mg weekly for 3 months led to little improvement and was discontinued when she was diagnosed with MS and began treatment with fingolimod. After 2 months of fingolimod treatment, she had a transient ischemic attack with discontinuation of MS treatment. After a period of treatment discontinuation of several months, teriflunomide was started to control MS symptoms and reduce the risk of MS relapse. Following worsening of skin signs and symptoms and multidisciplinary consultation, treatment with dupilumab 300 mg was started. Significant improvement in AD signs and symptoms was observed after 1 month with IGA 2, EASI 5, BSA 15%, pruritus VAS 5, DLQI 8, and stable conditions after 3 and 6 months. At 9 months, IGA was 1, EASI 2, BSA 5%, pruritus VAS 2, and DLQI 5, with no adverse events.

CASE 2

A 53-year-old woman suffering from severe pruritus for 5 years with a previous diagnosis of prurigo-like AD was referred to our attention. Physical examination revealed diffuse and severe xerosis, excoriated erythematous papules and nodules located on the upper extremities and trunk, and localized hyperpigmentation. She reported a family history of atopic disorders including allergic rhinitis and food allergies. Clinical examination revealed IGA 3, EASI 15, BSA 18%, pruritus VAS 10 and DLQI 15. She presented with normal IgE levels, normal eosinophil count and increased lactate dehydrogenase levels (335 U/L, normal value, 140-280 U/L). She was diagnosed with MS 12 years earlier and was treated with interferon beta-1a, peginterferon beta-1a, fingolimod, and most recently, teriflunomide. She reported worsening of prurigo during treatment with fingolimod with no improvement after treatment discontinuation. After a multidisciplinary consultation, dupilumab 300 mg was started achieving rapid and progressive improvement of signs and symptoms after 1 month with IGA 2, EASI 5, BSA 15%, pruritus VAS 5, DLQI 8, and stable conditions after 3 and 6 months. At 9 months, IGA was 1, EASI 2, BSA 5%, pruritus VAS 2, and DLQI 5, with no adverse events.

CASE 3

A 47-year-old woman with severe AD for more than 7 years presented with classic flexural localization of excoriated macules, plaques and papules, xerosis, nodules of the upper extremities and trunk, and severe eczematous involvement of the face and neck. She suffered from rhinitis and conjunctivitis during childhood and developed vitiligo during adolescence. She reported a recent worsening of AD; IGA was 4, EASI 26, BSA 19%, pruritus VAS 10, and DLQI 28. She presented with normal IgE levels,
eosinophil count, and lactate dehydrogenase levels. She was diagnosed with MS 20 years earlier and has been treated with interferon beta-1a, peginterferon beta-1a, and most recently, teriflunomide. Dupilumab was started with rapid improvement in signs and symptoms after 1 month (IGA 2, EASI 5.1, BSA 8%, pruritus VAS 0, and DLQI 10), further improvement after 3 months (IGA 1, EASI 2, BSA 5%, pruritus VAS 0, and DLQI 9), and stability through 6 months associated with a marked reduction of DLQI, with a value of 2 and no adverse events.

**Neurological evaluation**

Routine neurological evaluation showed clinical stability of MS during the course of treatment for all 3 patients. Patient 1 complained since MS onset of balance problems and dizziness, fatigue, and muscle weakness which improved gradually after the beginning of teriflunomide and remained stable during the course of dupilumab. Patient 2 had a MS disease onset characterized by muscle spasm and motor symptoms, and more recently increasing pain and fatigue which improved during teriflunomide treatment; she presented with walking impairment and muscle weakness which remained stable during the course of dupilumab. Patient 3 had a MS disease onset characterized by diffuse tingling and numbness and presented a completely asymptomatic MS when dupilumab was started and during the whole treatment course.

During dupilumab treatment magnetic resonance imaging (MRI) evaluation showed unchanged status for patients 1 and 2 and improvement of spinal cord lesions in patient 3. The dose of teriflunomide was not modified during treatment with dupilumab.

A summary of patient demographics, clinical characteristics, and disease course during dupilumab treatment is presented in Table I.

**DISCUSSION**

The association between MS and atopy is controversial, and although the prevalence of atopy in MS patients has not been assessed, MS patients show a lower incidence of atopic disorders.9 The exact mechanism is not fully understood, but reduced release of T helper cell type 2 (Th2) cytokines has been observed in MS.9 A history of atopic allergies, particularly asthma, appears to confer protection from MS.9 Some evidence has shown no association between MS and atopy,10,11 whereas recent studies have shown an inverse relationship between them.12-14 In a review of the medical records of 320 matched patients and controls, an inverse relationship between MS and asthma was demonstrated, but no significant association was observed between MS and other Th2-associated diseases (eczema and dermatitis) or any Th1-associated disease.13

Treatment of AD in patients with other major medical conditions can be challenging.1 MS is characterized by a multifactorial pathogenesis, involving a complex interaction between the immune and central nervous systems, which provides multiple targets for therapeutic intervention.8 Treatment of coexisting inflammatory conditions in patients with MS can be difficult because of ongoing...
treatments with potential interaction, cumulative immunosuppressive activity, and organ toxicity.

Teriflunomide is an active metabolite of leflunomide and acts as an immunomodulatory agent by inhibiting pyrimidine synthesis.\textsuperscript{15} It selectively and reversibly inhibits dihydro-orotate dehydrogenase, a key mitochondrial enzyme in the de novo pyrimidine synthesis pathway, leading to reduced proliferation of activated T and B lymphocytes.\textsuperscript{15} It is indicated for the treatment of MS, particularly relapsing forms, with an important warning about the risk of hepatotoxicity and teratogenicity.\textsuperscript{15}

Although dupilumab is considered safe given its specific immunomodulatory action, compared with immunosuppressive agents, there may be concerns when used in patients who are immunosuppressed or have an increased risk of drug immunosuppression due to concomitant treatments. An additional critical issue is the potential Th2 suppression with secondary dysregulation of Th1/17 in patients with MS. Recently, a temporal association was observed between flare-up of relapsing-remitting MS and treatment with dupilumab in an AD patient, who had a long-term untreated MS.\textsuperscript{16} In this regard, the authors hypothesized that dupilumab’s inhibition of the effects of IL-4 downstream actions may have altered the patient’s cytokine milieu, shifting the balance of Th profiles in favor of Th1/17 pathways, which is, the T-cell phenotype thought to drive MS pathogenesis.\textsuperscript{16} However, it is frequent that in young women the MS disease course is characterized by incoming, relapsing, and unstable episodes of multiple disease localization, especially if not treated, thus the clear attribution of a causal link seems undue.

AD is a chronic pruritic inflammatory disease characterized by substantial morbidity, including sleep disturbance, mental health symptoms, and impaired quality of life.\textsuperscript{1,2} Indeed, our patients complained of very intense pruritus and sleep disturbance, in addition to the clinical burden of AD, leading to great personal distress and impaired quality of life. Dupilumab demonstrated rapid and high efficacy, especially on skin symptoms leading to an almost complete resolution of pruritus during the treatment course, a substantial reduction in EASI and BSA, as well as a DLQI improvement. Although uncommon, MS represents an important AD comorbidity that requires special attention and management. In our patients, during the observation period, while AD resolved, MS was stable and well controlled by teriflunomide, as before dupilumab treatment.

In our 3 patients, the combination regimen with teriflunomide and dupilumab was discussed in a multidisciplinary setting. Patients were considered contraindicated to traditional systemic agents for AD due to the cumulative immunosuppression and hepatotoxicity risk. Dupilumab was initiated with a close neurological monitoring of patients’ MS disease activity and symptoms. During treatment, no clinical changes in signs or symptoms of MS activity or changes in MRI were observed; notably, an improvement in the MRI appearance of a MS lesion of the spinal cord was observed in one patient. These cases highlight the importance of a multidisciplinary approach in patients with AD with comorbid conditions.

Conflicts of interest

Dr Esposito has served as a speaker/board member for Abbvie, Almirall, Biogen, Celgene, Eli Lilly, Janssen, Leo Pharma, Novartis. Dr Fargnoli has served on advisory boards, received honoraria for lectures and research grants from AMGEN, Almirall, Abbvie, BMS, Galderma, Kyowa Kyrin, Leo Pharma, Pierre Fabre, UCB, Lilly, Pfizer, Janssen, MSD, Novartis, Sanofi-Regeneron, Sunpharma. Drs De Berardinis and Totaro have no conflict of interest to declare.

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