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ARTICLE

Lymphopenia in atopic dermatitis patients treated with oral immunosuppressive drugs

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ABSTRACT

Introduction: Oral immunosuppressive drugs are commonly used in the treatment of atopic dermatitis (AD). In patients with autoimmune- and rheumatic diseases, these drugs have been associated with lymphopenia. Lymphopenia is related to an increased risk of opportunistic infections. The incidence of lymphopenia in patients with AD treated with oral immunosuppressive drugs is yet unknown.

Objective: To evaluate the occurrence of recurrent lymphopenia in patients with AD treated with oral immunosuppressive drugs and to make recommendations for screening in daily practice.

Methods: Patients with recurrent lymphopenia (i.e. >5 times lymphocyte counts below 0.8×10^9/L) during treatment with oral immunosuppressive drugs were included from our immunosuppressive drugs database and further analyzed.

Results: A total of 360 AD patients, treated with oral immunosuppressive drugs, were screened. A recurrent lymphopenia during treatment was found in 11 patients. In 8/11 patients, recurrent lymphopenia was observed during concomitant treatment with prednisone. No serious infections were observed.

Conclusion: Lymphopenia is occasionally seen in AD patients treat with oral immunosuppressive drugs. Concomitant treatment with prednisone seems to be a risk factor. We suggest to include monitoring of lymphocyte counts in the standard follow-up for all AD patients treated with oral immunosuppressive drugs.

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KEYWORDS
Atopic dermatitis; lymphopenia; oral immunosuppressive drugs

Introduction

Atopic dermatitis (AD) is a common chronic inflammatory skin disease, with a prevalence of 2–10% in adults (1–3). The majority of AD patients can be adequately treated with topical treatment and/or phototherapy. However, in patients with moderate to severe AD without sufficient response or the need of continuous treatment with mid to high potent topical corticosteroids, long-term oral immunosuppressive treatment is often required. Drugs that are commonly used in the treatment of AD include cyclosporine A (CsA), methotrexate (MTX), azathioprine (AZA), enteric-coated mycophenolate sodium (EC-MPS), mycophenolate mofetil (MMF), tacrolimus and systemic corticosteroids (4).

These immunosuppressive drugs have the potential to achieve controlled disease, but can also cause a broad spectrum of side effects, which often require discontinuation of therapy. One of these side effects is the development of lymphopenia, as an effect of myelosuppression (5). Drug-induced lymphopenia is a known phenomenon in patients with autoimmune and rheumatic diseases, inflammatory bowel disease (IBD), and in organ transplantation recipients (6–9). Although it is a common finding, the clinical implications are currently not fully understood. Mild lymphopenia might be a reflection of a sufficient immunosuppressive effect of the drugs, but it is known that persistent lymphopenia, regardless of its cause, is associated with an increased risk of opportunistic infections, as seen in HIV-positive patients, primary immunodeficiency and idiopathic CD4 + lymphopenia (5,10,11). Recently, treatment-induced lymphopenia in patients with psoriasis and multiple sclerosis, treated with the immunosuppressive drug dimethyl fumarate, has been associated with the development of progressive multifocal leukoencephalopathy (PML), caused by activation of the John Cunningham (JC) virus (12–17). Due to the assumption that PML develops when cellular immunity is severely disturbed, it could thereby also be associated with other immunosuppressive drugs. It is suggested that long-term treatment and higher doses of immunosuppressive drugs are associated with a higher risk of PML development.

Remarkably, although oral immunosuppressive drugs are commonly used in severe, difficult to treat AD for long-time periods, data on the incidence and the clinical implication of lymphopenia in these patients is lacking. Therefore, the aim of this study is to evaluate the occurrence of lymphopenia in patients with AD treated with oral immunosuppressive drugs and to make recommendations for screening in daily practice.

Methods

Study population

This study was exempted from review by our institutional review board. A retrospective explorative study was conducted at the Dermatology and Allergology Department of the University

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Medical Center Utrecht, the Netherlands. Patients were selected from our immunosuppressive drugs database, which includes all AD patients treated with oral immunosuppressive drugs in our center, including CsA, MTX, AZA, EC-MPS, MMF, tacrolimus and prednisone (>3 months). Electronic medical records were manually screened for the appearance of a recurrent lymphopenia, defined as five or more lymphocyte counts below 0.8×10^9/L during the study period.

All patients receiving oral immunosuppressive drugs for the treatment of AD between January 1 2005 and September 10 2016 and a recurrent lymphopenia during treatment were included. AD was diagnosed by a dermatologist, according to the Hanifin and Rajka criteria (18). Patients' lymphocyte counts were monitored according to local treatment protocols. In case of a persistent lymphopenia, an immunologist was consulted. Immunosuppressive treatment was continued, unless otherwise advised.

Exclusion criteria were age below 18 years, a history of organ transplantation, treatment with chemotherapy or insufficient documentation of either lymphocyte counts or medication. AD should have been the primary indication for the treatment with oral immunosuppressive drugs. Lymphopenia should have been measured during treatment with oral immunosuppressive drugs or within three months after cessation of medication. Lymphopenia that did not occur within this time frame was assumed not to be related to the use of oral immunosuppressive drug.

The following data were systematically collected from the medical records of the included patients: sex, age at initiation of systemic treatment, type and dose of oral immunosuppressive drugs used, start and stop date of immunosuppressive drugs, date and value of all lymphocyte counts and total white blood cell counts at the time of decreased lymphocyte counts. When available, lymphocyte immunophenotyping including CD4 + and CD8 + T cells were analyzed. The lower limit of normal for CD4 + and CD8 + T cell counts were identified as 560 and 216 cells per μl (C/μl), respectively. The electronic patient files were screened for the documentation of severe (opportunistic) infections.

Statistical analysis

Data were analyzed using SPSS 21.0 (Version 21.0.0.0, SPSS Inc., Chicago, IL, USA). Absolute numbers and percentages were presented. Median with interquartile range (IQR) was calculated in case of not normally distributed variables.

Results

Patient characteristics

Patients were selected from our immunosuppressive drugs database, which contained 360 patients at the moment of data collection. In 84 patients, no lymphocyte measurements were performed. Eleven AD patients (six male, 54.5%) met the inclusion criteria and were included for further analysis (Table 1). Median age at the start of the immunosuppressive therapy was 39.0 years (IQR 32.5–43.8). Patients were treated with oral AZA, CsA, MTX, EC-MPS, and tacrolimus, as monotherapy or in combination with prednisone, and prednisone monotherapy (Figure 1(A–K)). The median number of different types of immunosuppressive drugs used per patient was 3 (IQR 3–5). Median nadir (lowest lymphocyte count) during treatment was 0.59×10^9/L (IQR 0.46–0.68).

Table 1. Patient characteristics and lymphocyte measurements.

Demographics	Total $n = 11$
Male *n* (%)	6 (54.5)
Age at start therapy (years) median [IQR]	39.0 [32.5–43.8]
Immunosuppressive drugs per patient median [IQR]	3 [3–5]
Nadir during treatment median [IQR]	0.59 [0.46–0.68]

IQR: inter quartile range; Nadir: lowest lymphocyte count.

Analysis of lymphopenia

Most of the patients had fluctuating lymphocyte counts during therapy. In one patient (Figure 1(K)) lymphopenia was found before start of the treatment with oral immunosuppressive drugs and persisted during the whole treatment period and after cessation.

Fluctuations of lymphocyte counts during a period with continuous oral immunosuppressive treatment in different doses were carefully analyzed. No associations with dosage adjustment were found. Dosage was reduced due to lymphopenia in two patients (patient 3 and 10). In patient 10, EC-MPS treatment was discontinued due to a persistent lymphopenia. However, concomitant prednisone was continued and the lymphopenia did not recover after discontinuation of EC-MPS.

Eight patients (patient 2–5 and 7–10) used an oral immunosuppressive drug taken in combination with prednisone at the time of lymphopenia. In patient 2, 4, 5, and 9 lymphocyte counts increased or normalized after cessation of prednisone, despite continuation of the combined oral immunosuppressive drug.

Remarkably, almost all total white blood cell counts were within the normal range at the time a decreased lymphocyte count was measured (Figure 2).

No lymphopenia-related opportunistic infections or other serious infectious pathology were documented during the observation period. However, in patient 10, antibiotic prophylaxis for Pneumocystiis jirovecii pneumonia (PJP) was started by the immunologist due to a persistent lymphopenia.

CD4 + and CD8 + T cell counts

In seven of the eleven patients (patient 1, 5–9, and 10) CD8 + and CD4 + T cell counts were measured as suggested by the consulted clinical immunologist (Figure 3). These patients were treated with AZA (patient 1 and 6), AZA combined with prednisone (patient 5, 8, and 9), tacrolimus combined with prednisone (patient 7) and prednisone monotherapy (patient 10). In patient 10, the immunophenotyping was performed twice.

All CD4 + T cell counts in these seven patients were decreased (Figure 3). The median CD4 + T cell count was 342 C/μl (IQR 126–470). CD4 + T cell counts were <200 C/μl in two cases, assuming an increased risk of (opportunistic) infections. The number of CD8 + T cells was decreased in six of the seven patients. The median CD8 + T cell count was 98 C/μl (IQR 57–136).

Discussion

In this retrospective study, we investigated the occurrence of lymphopenia in AD patients treated with oral immunosuppressive drugs. A recurrent lymphopenia was seen in 11 patients. Patients were treated with different immunosuppressive drugs, but concomitant treatment with prednisone seems to be a risk factor for the development of lymphopenia. CD4 + T cell counts were decreased in all patients in which immunophenotyping was performed. In two patients, CD4 + T cell counts reached critically low

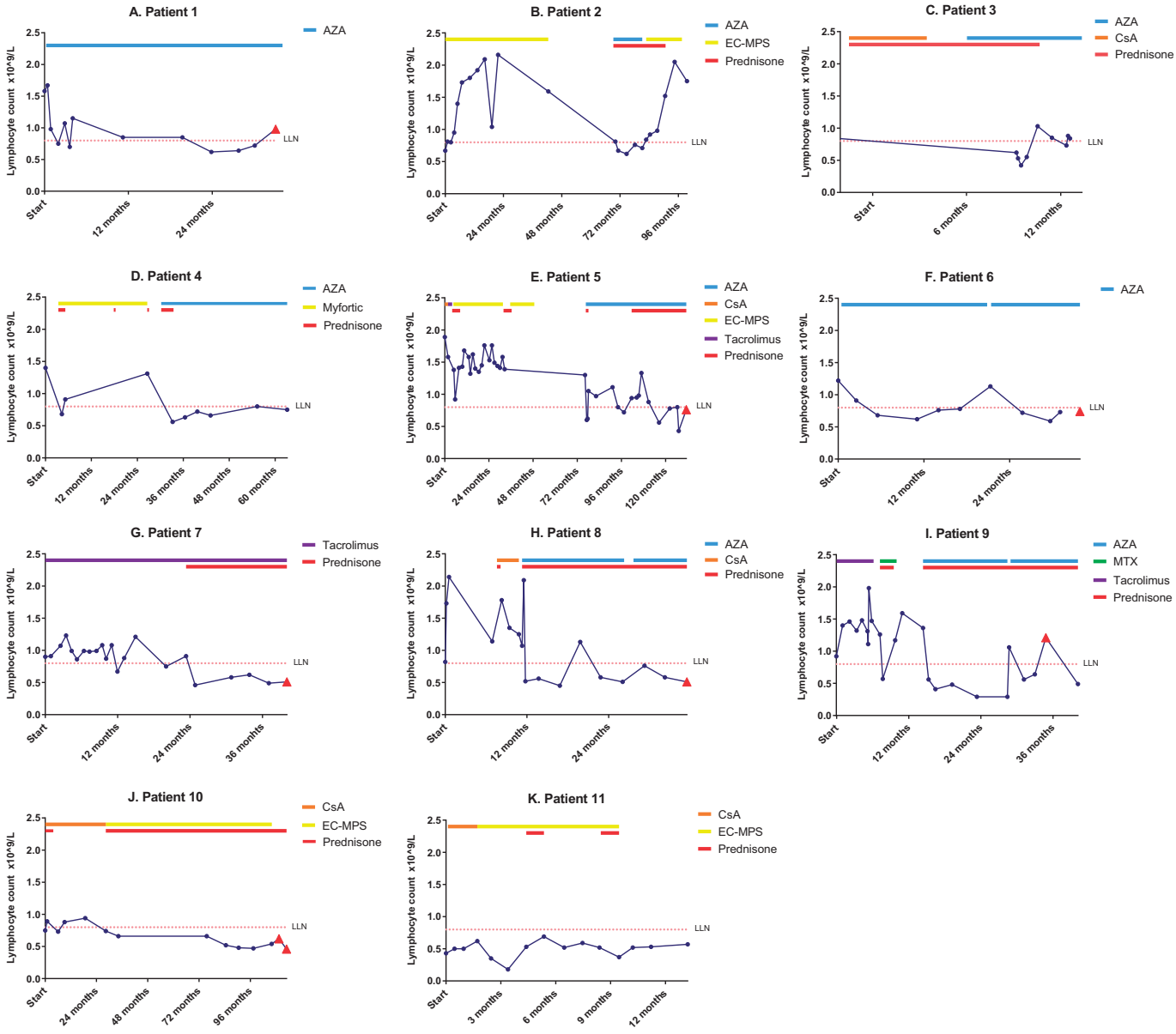

Figure 1. Lymphocyte counts and treatment characteristics. A) Patient 1 (female, 62 years old); B) Patient 2 (male, 48 years old); C) Patient 3 (female, age 25); D) Patient 4 (female, age 52); E) Patient 5 (male, age 55); F) Patient 6 (female, age 48); G) Patient 7 (male, age 49); H) Patient 8 (male, age 43); I) Patient 9 (female, age 55); J) Patient 10 (male, age 64); K) Patient 11 (male, age 43). AZA: azathioprine; CsA: cyclosporine A; EC-MPS: enteric-coated mycophenolate sodium; MTX: methotrexate; LLN: Lower limit of normal (0.8×10^9/L); ▲ moment of immunophenotyping.

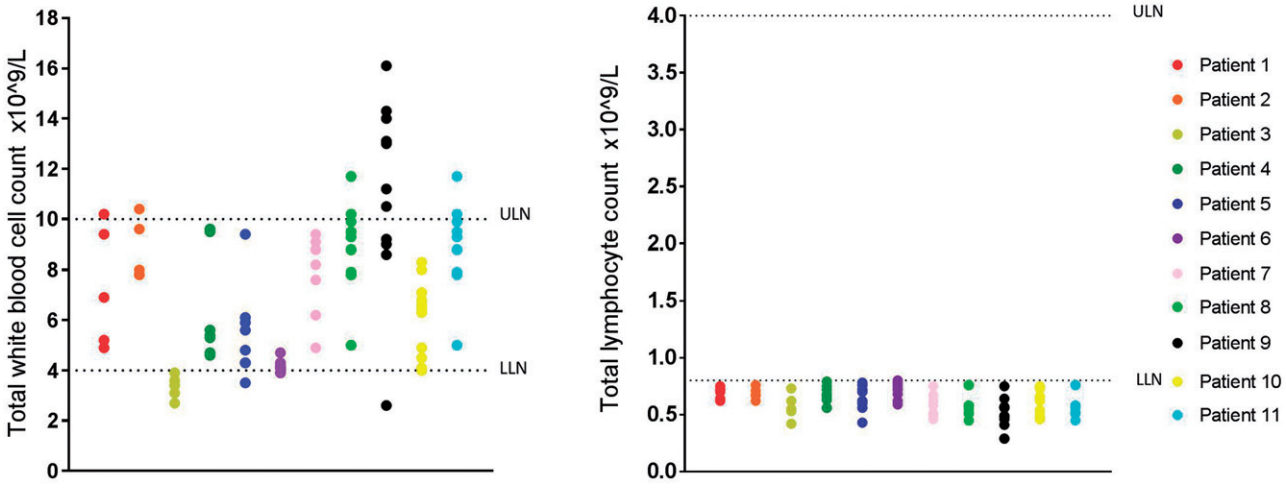

Figure 2. Total white blood cell counts and corresponding total lymphocyte counts. LLN: lower limit of normal; ULN: upper limit of normal.

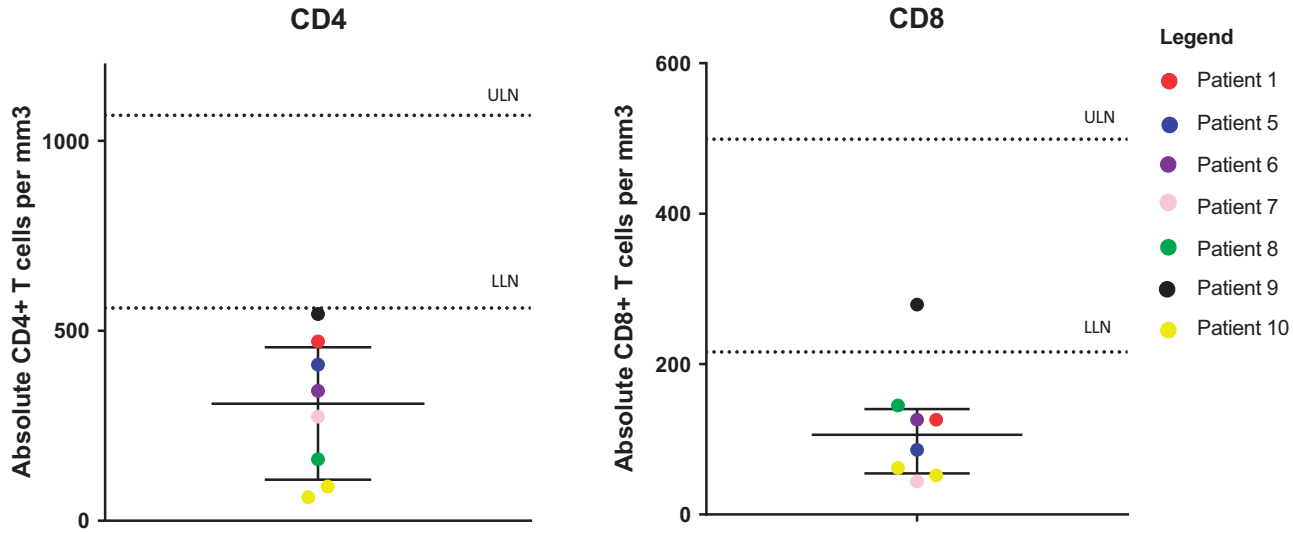

Figure 3. Immunophenotyping in 7 patients. LLN: lower limit of normal; ULN: upper limit of normal.

levels of <200 C/µl (one patient using AZA + prednisone and one patient using prednisone monotherapy). No lymphopenia-related opportunistic infections or other serious infectious pathology were documented during the study period.

Studies on the occurrence of lymphopenia in patients with AD are lacking and limited data is available on other chronic inflammatory skin diseases. Lehman et al. (19) analyzed 198 patients treated with immunosuppressive drugs for different dermatologic indications (AD not included). Total lymphocyte counts were not analyzed in this cohort, since this study was designed to define the incidence of pneumocystis pneumonia. However, CD4 + T lymphocyte counts were tested in 12 patients, of whom 5 patients (41.7%) had low levels. Pneumocystis pneumonia developed in one patient in this study, but CD4 + T cell counts were not measured in this patient.

Most data on the risk of lymphopenia in patients treated with oral immunosuppressive drugs are derived from studies in non-dermatological diseases (5–9). Lymphopenia is common in patients with chronic inflammatory diseases treated with AZA, MTX, cyclophosphamide, and prednisone and transplant recipients treated with several combinations of immunosuppressive agents, including AZA, MMF, CsA, and prednisone (5,7,8). Treatment with combined immunosuppression appears to have a greater risk for the development of lymphopenia (5,7). Al Rifai et al. (7) found that in 66% of their IBD cohort treated with AZA, lymphopenia resolved spontaneously with no change of AZA dosing. In most of these cases, lymphopenia occurred within the first 3 months of treatment.

In our study, most decreased lymphocyte counts were found during concomitant treatment with prednisone. This is in line with previous studies in patients receiving chronic immunosuppressive therapy for other conditions, that showed that the co-prescription of systemic corticosteroids can be an additional risk factor for the development of lymphopenia and opportunistic infections (5,7,20).

Total white blood cell counts measured at the time of a decreased lymphocyte count, were almost all within the normal range or even increased. This can be explained by the fact that eosinophil numbers, one of the other subsets of the total white blood cell count, are elevated in the peripheral blood in most AD patients (21). In addition, prednisone can induce leukocytosis, predominantly due to the increase of neutrophils (22). Increased eosinophil and neutrophil counts may compensate a decreased lymphocyte count in making the total white blood cell count normal. As a result, lymphopenia can be overlooked. It is therefore important to monitor white blood cell count differential, instead of total white blood cell counts in AD patients treated with oral immunosuppressive drugs.

Immunosuppressive drugs can reduce all lymphocyte subsets, but the circulating CD4 + T lymphocytes are generally the most affected (9). In seven of our patients, immunophenotyping was performed. CD4 + T lymphocyte counts were decreased in all these patients. A low CD4 + T cell count is associated with an increased risk of opportunistic infections, especially when CD4 + T cells reach critically low levels (<200 C/µl) (23). In our study, two patients had CD4 + T cell counts <200 C/µl; in these patients, no opportunistic infections or other serious infectious pathology were documented during the observation period. However, current guidelines for the treatment of HIV infection recommend antibiotic prophylaxis for Pneumocystis jirovecii pneumonia when CD4 + T cell counts are <200 C/µl (24).

Due to the retrospective design of this evaluation study, decisions about (dis)continuing immunosuppressive treatment and about starting antibiotic prophylaxis for PJP differed among individual patients and physicians. Recently, more attention was paid to the risk of infections in patients with persistent lymphopenia, especially for the development of PML, but at the time these patients received immunosuppressive treatment, no standardized protocol was available. Since lymphocyte monitoring was not recommended in guidelines for the treatment of AD with oral immunosuppressive drugs, there was no official recommendation for dosage adjustment in the case of lymphopenia.

In this study, in all patients, immunosuppressive treatment was continued, despite a recurrent or persistent lymphopenia, but an immunologist was consulted in most of the cases. Patients were frequently controlled and monitored for signs and symptoms of viral or opportunistic infections. Dose reductions were made just in a few patients. No serious infectious pathology was reported. PJP prophylaxis was advised by the immunologist in one patient, but not in the other cases. In the same patient, EC-MPS treatment was discontinued due to a persistent lymphopenia. However, concomitant prednisone was continued and the lymphopenia did not recover after discontinuation of EC-MPS.

In one of the included patients (patient 11) immunosuppressive therapy was started, despite an already existing lymphopenia. This patient was screened for HIV infection, leukemia, and lymphoma before treatment. The results were all negative and

immunosuppressive therapy was started after consultation of a clinical immunologist. Lymphopenia remained mainly stable during immunosuppressive treatment and after discontinuation of treatment in this patient.

Limitations

In literature, there is discussion on the definition of lymphopenia, with lower limits of normal ranging from 0.8 up to 1.2×10^9/L (9). In our study, we defined lymphopenia as an absolute lymphocyte count $<0.8 \times 10^9$/L, according to the Common Terminology Criteria of Adverse Events (25).

One of the limitations of our study is the small number of included patients. Due to the retrospective design of our study, lymphocyte counts were measured inconsistently. Total white blood cell count differential, which includes the total lymphocyte count, was not included in the standard monitoring guidelines for prednisone monotherapy and CsA treatment. This resulted in absent lymphocyte counts in 84 patients out of the 360 patients in the screened database. Besides, we defined a recurrent lymphopenia as five or more lymphocyte counts below 0.8×10^9/L. Patients with four or less lymphocyte count measurements were not included. If lymphocyte counts were more frequently measured, the number of patients with a recurrent lymphopenia might have been higher. Therefore, we expect an underestimation of patients with recurrent lymphopenia in this study.

It needs to be considered that many other factors can influence lymphocyte counts, such as comorbidities, physical or physiological stress, co-medication, and age. This information was often lacking, due to the retrospective design. Besides, viral infections can induce lymphopenia and older age is associated with lower lymphocyte counts (26,27). Due to the tertiary character of our hospital, information about the incidence of viral infections (usually treated by the general practitioner or in secondary centers) was insufficiently documented. No severe infections were reported in the medical files in our hospital, but patients might have visited their general practitioner for mild infections in the meantime.

Conclusion and recommendation

This study shows that recurrent lymphopenia is occasionally seen in AD patients treated with oral immunosuppressive drugs. The co-prescription of prednisone seems to be a risk factor. We did not observe any major infectious pathology in the analyzed patients; therefore the clinical implication of a recurrent lymphopenia still remains unclear.

We suggest to include monitoring of lymphocyte counts in the standard follow-up for all AD patients treated with oral immunosuppressive drugs. Monitoring total white blood cell count, which is recommended in current guidelines, is not sufficient, since lymphocyte counts can be decreased while total white blood cell count is normal. Patients should be monitored for symptoms of viral or opportunistic infections. In case of persistent lymphopenia, consulting a clinical immunologist should be considered to decide whether further analysis including immunophenotyping, dosage adjustment or antibiotic prophylaxis for opportunistic infections is required. Apart from that, the indication for immunosuppressive treatment needs to be reevaluated in these patients.

Disclosure statement

The authors report no conflicts of interest.

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