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Single Case

Worsening of Lymphopenia during Apremilast Treatment

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Abstract
Apremilast is an oral phosphodiesterase IV inhibitor recently registered for the treatment of psoriasis and psoriatic arthritis in Switzerland and other countries. Even though it offers only moderate efficacy compared to biologics, many patients prefer drugs given by the oral route. Apremilast is frequently used in private practice, as it showed no relevant safety signals in clinical trials and often, laboratory tests are omitted completely. Here we report a patient who developed acute lymphopenia and worsening of psoriasis during apremilast treatment, which resolved with discontinuation of apremilast. We suggest that at least in prospective registries, that regular monitoring of laboratory surrogate markers should be performed on a long-term basis to detect rare but potentially important safety signals.

Introduction

Apremilast is an oral phosphodiesterase IV (PDE4) inhibitor recently registered for the treatment of psoriasis and psoriatic arthritis. Apremilast is frequently used in private practice, as it showed no relevant safety signals in clinical trials and currently, no laboratory tests are recommended during treatment.

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Case Report

Here we report the case of a man in his 40ies with plaque-type psoriasis for 3 years. He presented with a Psoriasis Area and Severity Index (PASI) of 10.3 and a Dermatology Life Quality Index of 8. Previous treatments included topical combined calcipotriol/betamethasone (Daivobet®) and UVB narrowband therapy. His medical history included hypercholesterinemia and Gilbert-Meulengracht disease with slightly elevated bilirubin of 23 μmol/L (reference <21 μmol/L). A differential blood count showed a mild lymphopenia of 1.05 × 10^9/L (reference 1.5–4.0 × 10^9/L) of unknown etiology. Other laboratory investigations were inconspicuous.

Treatment with apremilast was initiated using the recommended titration scheme. One month later, the lymphopenia had worsened to 0.64 × 10^9/L without any clues suggestive of an underlying event such as a viral infection, for example. A HIV test was negative and the CD4/CD8 ratio was normal. Psoriasis plaques had worsened at 1 month of therapy, resulting in a higher PASI of 16.6. Apremilast treatment was interrupted, and 2 days later, lymphocyte counts increased to 0.78 × 10^9/L and 3 weeks later to 1.14 × 10^9/L (Fig. 1). Leukocyte and especially neutrophil counts had almost doubled during apremilast therapy, remaining, however, within normal range, and returned to baseline levels after cessation of apremilast. A topical treatment with clobetasol propionate 0.05% (Clarelux® foam) was initiated and PASI improved to a value of 12 within 4 weeks. The negative temporal correlation of the lymphocyte counts with apremilast led us to the clinical conclusion that the drug might have been causally related to the lymphopenia. Hence, apremilast was not reinitiated and another treatment was introduced.

Discussion

Lymphopenia during apremilast treatment in humans has not been reported before and we expect that our observation is a rare event. Clinical trials showed consistently good laboratory safety data, leading to some expert recommendations that blood sample monitoring can be omitted [1]. Newer guidelines, such as the Swiss S1, recommend several obligatory and optional laboratory safety checks before treatment initiation [2].

In monkey studies with apremilast, lymphopenia and neutrophilia were reported but evaluated as negligible in magnitude and/or in the range of pretest values [3]. In mice and rat studies, lymphopenia and neutrophilia and also CRP elevation and albumin decrease were associated with arteritis and perivascular inflammation in various tissues. CRP and albumin were normal during apremilast in our patient.

In general, with PDE4, inhibition by apremilast through accumulation of cAMP leads to inhibition of pro-inflammatory cytokines like TNF-α, IL-17, IFN-γ, and IL-23, whereas IL-10 is increased [4]. Apremilast acts nonselective on PDE4 isoforms A–D. T lymphocytes (CD4 and CD8) contain mostly the PDE4B and to a lesser extent the PDE4A subtype as well as PDE3 and PDE7 [5]. In COPD patients, treatment with cilomilast, a PDE4 inhibitor selective for PDE4D [6], or roflumilast, a PDE4 inhibitor almost nonselective on PDE4 isoforms besides being less selective for PDE4C [7], airway inflammation by lymphocytes and other cells like neutrophils was reduced. There is inconsistent evidence that PBMCs of atopic patients have a higher susceptibility to PDE inhibitors [8]. Interestingly it was shown that structural and molecular differences in the M-loop region of PDE4 can enhance the potency of its lig-

ands [9]. In summary, it could be speculated that a structural variance in PDE4 or an overexpression of a certain isotype of PDE4, like PDE4B, lead to reduced cell numbers.

From our single case, no conclusions on a causal effect of apremilast on lymphocyte counts can be drawn. As the clinical use of apremilast increases, it will be interesting to see whether our observation will also be made by others. Such safety signals would not necessarily be seen in clinical trials, because clinical trials include only highly selected patient populations that may not represent the general population. Hence, reporting of rare clinical observations in the post-marketing phase and ideally long-term registry data are crucial for developing a solid basis for recommendations on whether laboratory investigations for new drugs should be routinely performed or not.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors declare no conflicts of interest. All authors have been speakers and advisory board members for Celgene Corporation. A.G.A. Kolios[1, 2, 3], A.A. Navarini[1, 2, 3], L.E. French[1, 2, 3, 4] ([1]consultancies, [2]honoraria, [3]expert testimony, [4]grants). This study was funded by HSM-2 of Kanton of Zurich (Switzerland), Promedica, and Bruno Bloch Foundation, all to A.A.N.

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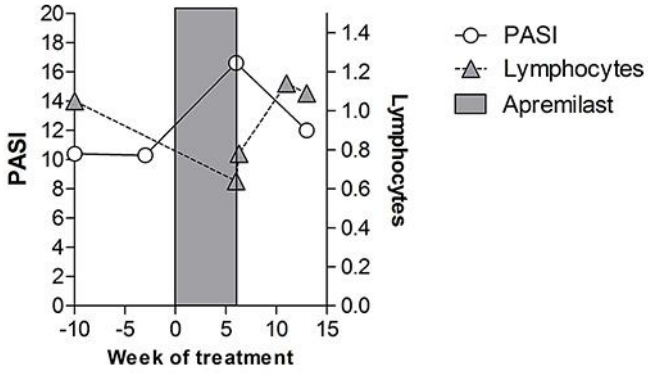

Fig. 1. Lymphocyte count versus PASI score. This case shows the course of lymphocytes compared to PASI during apremilast treatment. Lymphocytes in n × 10^9/L.