

# Apremilast induced chronic diarrhea and malnutrition

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## Summary

Apremilast is used as a systemic therapy for the treatment of psoriasis and psoriatic arthritis. This drug is considered relatively safe with a very low incidence of serious side effects. Common side effects are diarrhea, nausea, headache, nasopharyngitis, upper respiratory tract infections which are mild to moderate in severity. Diarrhea tends to occur within 2 weeks of starting treatment and resolve spontaneously within 4 weeks without dose adjustment or discontinuation of therapy. Chronic diarrhea and malnutrition due to apremilast have not been reported yet. We report a case of apremilast induced chronic diarrhea leading to malnutrition, necessitating discontinuation of therapy.

**Keywords:** Apremilast, chronic diarrhea, malnutrition

## 1. Introduction

Apremilast is an oral phosphodiesterase 4 (PDE-4) inhibitor and it is used as a systemic therapy for psoriasis and psoriatic arthritis (1). This drug is relatively safe at approved dose of 30 mg twice daily, causes a few self resolving mild to moderate side effects which generally do not require discontinuation of therapy (2). Common side effects are diarrhea, nausea, headache, nasopharyngitis, upper respiratory tract infections and the reported incidence of diarrhea is close to 10 per 100 person-years (3). Diarrhea due to apremilast is secretory in nature which resolves spontaneously and do not require medical intervention, dose adjustment or discontinuation (3). We report a case of apremilast induced chronic diarrhea leading to malnutrition.

## 2. Case Report

A 56-year-old man with psoriasis and psoriatic arthritis of 10 years duration now presented with chronic diarrhea, nausea and weight loss of 10 kg for the past 6 months. He had hemoglobin level was 9.2 g/dL; total leukocyte count was  $15,000 \times 10^3/\text{dL}$ ; and platelet count was  $3.25 \times 10^3/\text{dL}$ . He had hypoproteinemia

and hypoalbuminemia with protein and albumin level of 4.6 g/dL and 1.9 g/dL respectively. The results of other liver function test and kidney function test were normal, and her total bilirubin level was 0.4 mg/dL; aspartate transaminase level was 31 IU/L; alanine transaminase level was 21 IU/L; alkaline phosphatase level was 123 IU/L; urea level was 10 mg/dL and creatinine level was 0.7 mg/dL. To determine the cause of diarrhea, we performed the routine stool examination and culture, which were non-contributory. Further, the result of serological examination for celiac disease (IgA anti-tissue transglutaminase antibody) was negative and thyroid function test were normal. His upper gastrointestinal endoscopy, colonoscopy and computed tomography (CT) enterography was normal. Histopathological examination of duodenal mucosa and right sided colonic mucosa were also normal. Human immunodeficiency virus serology was negative. On drug review he had been treated with steroid, cyclosporine and methotrexate of variable duration. The patient had been prescribed only apremilast 30 mg twice daily for psoriasis for the past 6 months without other immunomodulators. After discontinuation of apremilast his diarrhea subsided and at 2 month follow-up he has gained significant weight with serum albumin level of 3.4 g/dL and for psoriasis he has been started on steroid.

## 3. Discussion

Apremilast causes phosphodiesterase 4 (PDE-4) inhibition and it interrupts the inflammatory cascade

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by blocking the degradation of cyclic adenosine monophosphate (cAMP) leading to increase in intracellular levels of cAMP which downgrade the production of several pro-inflammatory cytokines, like tumour necrosis factor (TNF)- $\alpha$  and interleukin (IL)-17 and IL-23 (4). This oral medication is well tolerated with minimal risk of serious side effects. Commonly reported side effects are diarrhea, nausea, headache, nasopharyngitis, upper respiratory tract infection which are generally self resolving and do not require dose adjustment or discontinuation of therapy (3).

Diarrhea due to apremilast is secretory in nature as it causes increases in intracellular cAMP levels within small intestinal crypt cells which activate chloride channels (5). Activated chloride channels promote fluid secretion into the gut lumen leading to development of diarrhea. Diarrhea usually resolves within 4 weeks and it might be due to effect of compensatory up-regulation of other phosphodiesterases in the small intestinal crypt cells (6). Recommended management of apremilast induced diarrhea is to begin with non-pharmacologic interventions such as ensuring adequate hydration, having small frequent meals and limiting consumption of other potential triggers for diarrhea (3). Patients not responding to non-pharmacologic interventions can be treated with over the counter medications like fibre supplement, bismuth subsalicylate or loperamide (3).

Most of the trials have reported that apremilast induced diarrhea were mild to moderate in severity, develop within 2 weeks of starting treatment and resolve spontaneously within 4 weeks (2,6). This drug has been approved 4 years ago and chronic diarrhea leading malnutrition due to apremilast has not

been reported yet. With increased use of apremilast, incidence of chronic diarrhea and malnutrition like our case is expected to be reported more frequently.

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