

# Clinical Practice Survey Regarding Management of Apremilast-Related Diarrhoeas' in Patients with Psoriasis

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Received: May 31, 2021; Accepted: June 11, 2021; Published: June 18, 2021

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## Abstract

Psoriasis affects about 2% of the population. Apremilast is the first oral phosphodiesterase 4 (PDEA4) inhibitor marketed in Europe. Diarrhoea is the most frequent side effect. No guideline on apremilast-induced diarrhoea management is currently available. We reviewed the literature and surveyed the current practices of dermatologists in France.

We sent via a French network (ResoPso) a questionnaire to hospital and private practice dermatologists. 90% of the dermatologists offer a symptomatic treatment, 10.2% non-pharmacologic interventions, 64.6% a combination of the two. 6.1% of the dermatologists definitively stop apremilast, 74% prescribe racecadotril as a first-line symptomatic treatment.

Diarrhoea due to apremilast affects 15% of patients, its pathophysiology is secretory. It is important to grade its severity and treat its complications. The first treatment step is dietary advice, followed by the prescription of racecadotril. We can also reduce the dose. After discontinuation and reversal of diarrhea, the treatment can be restarted with increasing doses.

**Keywords:** Psoriasis; Therapeutic; Apremilast; Diarrhoea.

## INTRODUCTION

Psoriasis is a frequent inflammatory skin disease, which affects about 2% of the world population. It is a chronic illness, which may have an important impact on quality of life, as shown in the (ESTEEM 2) trial [1]. Thus, its treatment often requires long-term use of ideally safe and effective therapeutic agents.

Among available therapeutic agents, apremilast was accepted by the European Medicines Agency (EMA) in 2015. It is the first oral phosphodiesterase 4 (PDEA4) inhibitor marketed in France (2016). It is a second-line treatment for moderate to severe plaque psoriasis in case of failure or contraindication of at least two systemic treatments (cyclosporine, methotrexate, phototherapy) [2]. It is widely prescribed in France in 2019, according to the French health insurance data, 85908 apremilast medicine boxes were reimbursed (not including in-hospital prescriptions).

The safety and efficacy profiles of apremilast were evaluated in the (ESTEEM 1) [3] and (ESTEEM 2) [1] trials. In the (ESTEEM 2) trial, the patients treated with apremilast experienced a significant benefit with a statistically significant increase in PASI 75 responses compared to placebo (reduction of 75% of Psoriasis Area and Severity Index): 28.8% vs 5.8% for placebo.

However, apremilast can have several side effects, the most important of which is diarrhoea. Apremilast causes phosphodiesterase 4 inhibition and interrupts the inflammatory cascade by blocking the degradation of cyclic adenosine monophosphate (cAMP). Therefore, it leads to an increase in intracellular levels of cAMP in several cell types, including duodenal crypt cells. This increase activates chloride channels promoting fluid secretion into the gut lumen, leading to secretory diarrhoea. In the (ESTEEM 2) trial, apremilast administration was correlated with a higher incidence of diarrhoea compared to placebo (15.8% vs 5.9% for placebo).

The aim of this study is to collect the current practical interventions for the management of apremilast-induced diarrhoeas, based on the literature and of a survey of the clinical practices of a few French dermatologists.

## MATERIALS AND METHODS

### Diagnosis and Grading of Diarrhoea

The World Health Organisation (WHO) defines diarrhoeas as the emission of at least 3 soft or fluid stools per day. Diarrhoeas are defined as chronic when they last at least 4 weeks [4]. The assessment of the severity is fundamental to support the choice of whether continuing, adjusting or discontinuing the treatment. Appropriate measures can be taken in order to avoid potential complications (like dehydration, acute kidney injury...): the grading is based on symptoms and the need for hospital admission.

The use of Common Terminology Criteria for Adverse Events (CTCAE) is recommended [5] (Table 1).

### Survey

An original questionnaire containing 7 multiple-choice questions and one open question was designed and internally validated. The questionnaire was sent by e-mail through the ResoPso: it is a French network that gathers about 50% of the 543 dermatologists active in the 5 French settings of Le Mans, Rennes, Angers, La Roche Sur Yon, Paris.

The questionnaire is available in the supplemental (Supplementary File 1) material.

## RESULTS

### Survey

We received 165 answers.

- Of the respondents, 32.1% are private-practice dermatologists, 36.4% are hospital dermatologists and 31.5% have a combined activity.

- The range of patients treated with apremilast for each of the dermatologists ranged from none to 96 with a median value of 10.
- 90% of the dermatologists had observed at least one case of apremilast-correlated diarrhoea.
- As for treatment choices, when patients have diarrhoeas attributable to apremilast, 10.2% offer dietary and lifestyle interventions, 19 % of dermatologist's asymptomatic medical treatment, 64.6 % a combination of the two. 6.1% of dermatologists discontinue apremilast.
- Racecadotril is the most common medication for symptomatic treatment being used by 74% of dermatologists. However, 67.3% of dermatologists do not know the physiopathology of diarrhoeas caused by apremilast.
- When diarrhoeas persist despite appropriate measures, 34.3% of them reduce the apremilast dose by half, 32.1% temporarily discontinue it and restart it at half-dose after symptom regression, while 33.6% discontinue the drug.
- 62.3% of dermatologists consider starting again apremilast after a period of discontinuation once diarrhoeas are over.

### Advice from the Literature

Apremilast appears to be well tolerated when its posology is gradually increased (Table 2).

The pathophysiology of apremilast induced diarrhea is secretory. Phosphodiesterase-4 inhibition increases in cAMP levels within bowel crypt cells. This activates enterocyte chloride channels and promotes fluid secretion into the gut lumen, which enhances bowel movement [6].

Table 1: CTCAE grade (v5.0) modified from U.S. department of health and human services.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhoea	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline, limiting instrumental ADL	Increase of ≥ 7 stools per day over baseline; hospitalisation indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life threatening consequences; urgent intervention indicated	Death

ADL: activities of daily living.

CTCAE: Common Terminology Criteria for Adverse Event.

Table 2: Progressive rise apremilast's posology at the initiation of the treatment (from VIDAL).

DAY 1	DAY 2		DAY 3		DAY 4		DAY 5		DAY 6	
Morning	Morning	Evening								
10 mg	10 mg	10 mg	10 mg	20 mg	20 mg	20 mg	20 mg	30 mg	30 mg	30 mg

A recent observational paper of a Japanese cohort [7] of 43 patients corroborated the results of the randomized trials in a 'real-life' setting) and reported that the most frequent adverse event was diarrhoea. About 30% of patients reported diarrhoea, but less than 5% discontinued treatment because of this adverse event.

Quite reassuringly, these adverse events generally occurred early during therapy, were rarely severe (around 0.3 %), and often resolved within 4 weeks [8].

In a Spanish article published in 2020 [9], a multidisciplinary team of 14 experts recommend taking apremilast during meals and observing some dietetic hygiene advice (preventive measure: avoid lactose, caffeine, artificial sweeteners, eating small and frequent meals...). Among anti-diarrhoic agents, racecadotril seems to be the first choice, but indications are drawn from this paper also mention loperamide and codeine. The authors generically suggest reducing the dose of apremilast (30 mg per day instead of 30 mg twice a day). They also state that diarrhoeas decrease over time and tend to disappear from the third year onwards.

Therapeutic alternatives are loperamide, which is widely used and effective in several types of diarrhoea<sup>9</sup>. Another possible therapy is bismuth, which is occasionally used in another subtype of secretory diarrhoea, i.e. microscopic colitis [10]. To the best of our knowledge, there are no studies evaluating its efficacy in patients under apremilast.

Recently, probiotics have strongly emerged as useful agents in the management of diarrhoea. This

complementary therapy, which appears to have no side effects, is often effective and therefore prescribed in order to restore a healthy and balanced intestinal microbiota. Nevertheless, these products are not reimbursed in France, which may limit care access [11].

### Advice from the Survey

A proposed algorithm for the management of diarrhoeas under apremilast is summarized in (Figure 1), Management of diarrhoeas depending on CTCAE scale.

The first fundamental step is the assessment of hydration status. Adequate hydration is important in order to compensate for fluid loss. This can be achieved by increasing oral hydration or by using oral rehydration solutions (ORS) [12] which stimulate intestinal Na<sup>+</sup> absorption, by SLC5A1 and Na<sup>+</sup>-coupled amino acid transporters.

The second step regards the prevention of further episodes of diarrhoea. For this, we recommend beginning with non-pharmacologic interventions such as following some simple dietetic / hygiene advice: consuming small and frequent meals and paying attention to the quality of food. Some foods are to be avoided since they represent potential diarrheal triggers: milk (lactose is harder to digest because lactase is less produced in the acute phase), artificial sweeteners, fibre rich foods (wholemeal bread, lentils, chickpeas...), raw fruits and vegetables, alcohol, nuts...

Eating less is not a good option though: the absence of residues in the colon leads to microbial's pullulation, the

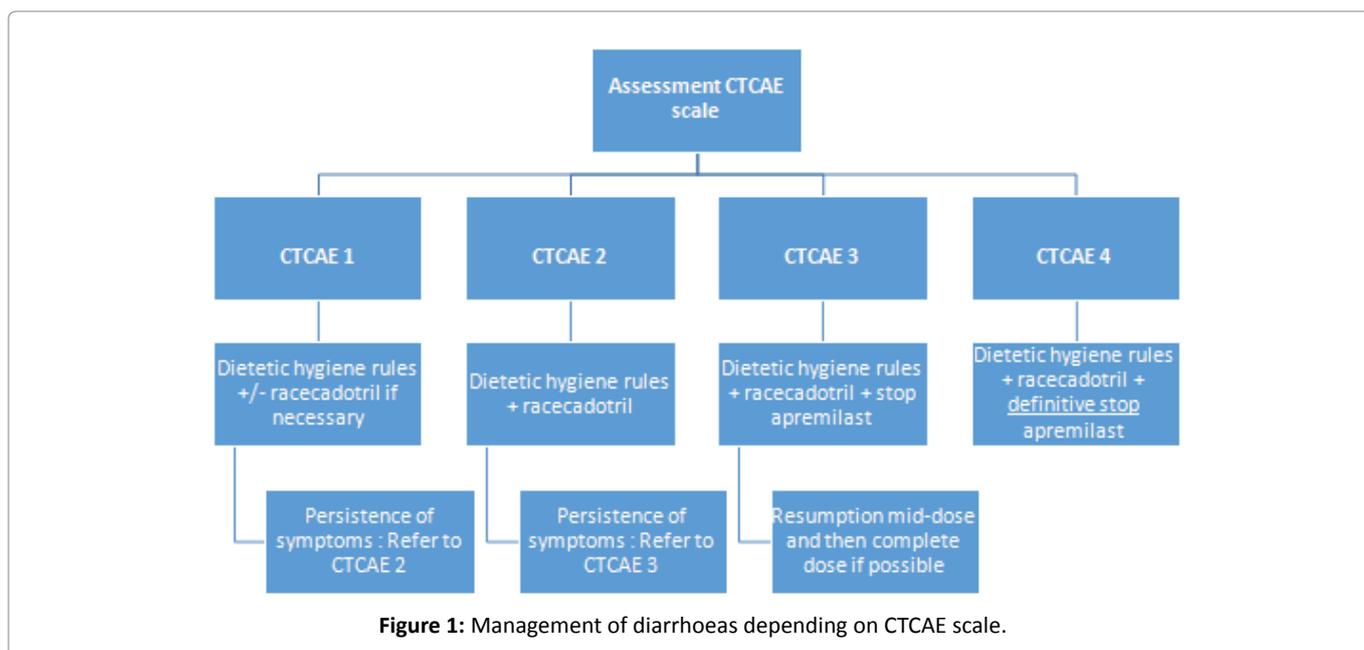


Figure 1: Management of diarrhoeas depending on CTCAE scale.

rise of fermentation, disruption of gut flora and finally, diarrhoeas.

If non-pharmacologic interventions are not sufficient, pharmacologic treatment may be tested. Before treatment, the presence of "diarrhoea's" «red flags» should be evaluated: fever, blood or mucus in the stool, recent foreign travel, antibiotic use, severe dehydration, recent hospitalization... While loperamide and diosmectite were initially recommended, racecadotril is now the first choice in secretory diarrhoeas. This drug is contraindicated in patients treated by Angiotensin-converting enzyme inhibitors (ACE-inhibitors) since it increases the risk of angioedema due to bradykinin increase.

Racecadotril is a specific inhibitor of enkephalinase, therefore prolonging the antisecretory effect of the endogenous enkephalins. Hamza et al. reported a rapid onset of action [13] and reported that racecadotril produced a significant decrease in stool weight within the first 24h of treatment compared to placebo.

Racecadotril is well tolerated: it does not induce constipation [14] and the patients reported less abdominal distension and abdominal pain than with loperamide [15].

The recommended dose is 100 mg three times per day and is continued until obtaining normal stool for two days.

Finally, some cases require dose adjustment or discontinuation of apremilast. In case of failure of the previous approaches, we propose to reduce by half the dose of apremilast (30 mg per day) in case of grade 2 diarrhoeas on the CTCAE scale. When diarrhoea resolves, apremilast can be increased again. In the case of diarrhoeas grade 3 or 4 on the CTACE scale, stopping treatment is probably wiser. Apremilast may be tried again in the case of diarrhoea grade 3; nevertheless, this choice seems more delicate in grade 4.

## DISCUSSION AND CONCLUSION

Apremilast is an efficient and safe therapy for psoriasis, as shown in the (ESTEEM 1 and ESTEEM 2) trials. Diarrhoea is a frequent adverse effect, but is mostly self-limiting within 4 weeks, and does not require medical treatment in most cases. The self-limiting characteristic in apremilast induced diarrhoeas might be due to the compensatory up-regulation of other phosphodiesterase's [16]. This time-limited characteristic supports a symptomatic treatment strategy.

Considering the absence of guidelines regarding this topic, we recommend step-by-step management of apremilast induced diarrhoea starting with non-pharmacologic interventions. Patients not responding to these measures can be treated with racecadotril. In non-responders, dose adjustment or discontinuation, also considering the severity of the adverse effect, should be taken into consideration.

## CONFLICT OF INTEREST

None.

## FUNDING SOURCES

None.

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