

# Apremilast for chronic plaque psoriasis and ulcerative colitis

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## CASE

A man, aged 26 years, with an eight-year history of chronic plaque psoriasis (CPP) and a three-year history of ulcerative colitis (UC) presented to a dermatology outpatient clinic in a tertiary centre. He had a family history of psoriasis but not inflammatory bowel disease (IBD). His CPP affected his scalp, trunk and limbs with a Psoriasis Area and Severity Index (PASI) of 11. The patient was initially managed with topical calcipotriol 0.005%, betamethasone dipropionate 0.05% ointment daily and oral acitretin 25 mg daily (0.4 mg/kg), with prior approval from his gastroenterology team, with a resultant PASI of 6 after six months of therapy. Unfortunately, a flare of UC, refractory to ciclosporin, azathioprine and infliximab, necessitated total colectomy with end ileostomy and stoma formation.

## QUESTION 1

What is the prevalence of IBD in psoriasis? Is there an association between the two conditions?

## QUESTION 2

What is the Psoriasis Area and Severity Index (PASI)?

## ANSWER 1

Psoriasis is a chronic and multisystem disease with an estimated prevalence of 0.5–11.4% worldwide.<sup>1</sup> There is no sex predilection for psoriasis, with two peak ages of onset of 30–39 and 50–69 years.<sup>1</sup> Both psoriasis and IBD are immune-mediated inflammatory conditions. In a recent systematic review, it was reported that the prevalence of psoriasis in Crohn's disease and UC was 3.6% and 2.8%, respectively, and that the prevalence of Crohn's disease and UC in psoriasis was 0.7% and 0.5%, respectively.<sup>2</sup> This indicates that there are significant bidirectional associations between the two conditions.<sup>2</sup> Similar immunological mechanisms have been identified in both psoriasis and IBD, particularly the expression of interleukin (IL)-17, IL-23 and tumour necrosis factor- $\alpha$  cytokines.<sup>2,3</sup> Therefore, in patients with psoriasis and IBD, several immunomodulatory medications can be used to treat both disease entities.<sup>4</sup>

## ANSWER 2

PASI is a tool used to measure the severity and extent of psoriasis.<sup>5</sup> It assesses the severity of psoriasis based on the intensity of erythema, thickness and scaling of the lesions, as well as the percentage of body surface area of the head and neck, upper limbs, trunk and lower limbs affected.<sup>5</sup>

The PASI score provides a standardised way to assess the severity of psoriasis and

monitor changes in disease severity over time or in response to treatment. Scores range from 0 (no psoriasis) to 72 (severe psoriasis), with higher scores indicating more extensive and severe disease.<sup>5</sup> Furthermore, the PASI score determines treatment choice and whether a patient would be eligible to access advanced biologic therapy under the Pharmaceutical Benefits Scheme (PBS).

## CASE CONTINUED

The patient was seen postoperatively in the context of a moderate psoriasis flare (PASI 10), necessitating initiation of systemic therapy. His treating gastroenterology team was keen to avoid methotrexate. The patient was not eligible for biologic therapy as per Australian Medicare criteria. Apremilast was commenced and uptitrated to 30 mg twice daily for his psoriasis. The patient's psoriasis improved markedly, with PASI 0.5 at four months. Two and a half years after initiating treatment, the patient remains on Apremilast 30 mg twice a day with excellent control of his CPP (PASI 0), remission of UC and without gastrointestinal adverse effects.

## QUESTION 3

What are the PBS criteria for Apremilast?

## QUESTION 4

What is the mechanism of action of Apremilast?

**QUESTION 5**

What are common side effects of Apremilast?

**QUESTION 6**

What is the role of the general practitioner (GP) in this case?

**ANSWER 3**

Apremilast is indicated for moderate to severe CPP. For patients to be eligible for PBS-subsidised treatment with Apremilast; they must have severe psoriasis; conventional therapy with methotrexate must have been unsuccessful (or it is contraindicated or caused a toxicity); the patient's quality of life must be significantly impacted; and the patient must not be receiving the following concurrent PBS-subsidised treatments for psoriasis: biologics, ciclosporin or deucravacitinib. In addition, the treatment must be initiated by a dermatologist, rheumatologist or general physician.<sup>6</sup>

**ANSWER 4**

Apremilast is considered an immunomodulatory agent. Apremilast is a phosphodiesterase 4 inhibitor, which results in increased intracellular cyclic adenosine monophosphate (cAMP) concentrations. Increased concentrations of cAMP lead to downregulation of inflammatory responses by reducing the expression of tumour necrosis factor, IL-23, IL-17 and interferon- $\gamma$ , while increasing regulatory cytokines, such as IL-10.<sup>7,8</sup> This might explain Apremilast's efficacy in patients with CPP and concurrent UC. Apremilast's efficacy in UC has been investigated in a Phase 2 clinical trial, in which 31.6% of UC patients taking 30 mg Apremilast twice a day achieved clinical remission at Week 12.<sup>9</sup> In that study, patients taking Apremilast demonstrated improvements in Mayo score (a score that evaluates the severity of UC with four main components: stool frequency, rectal bleeding, endoscopic findings and physician global assessment) and biomarkers of UC disease severity, including C-reactive protein and faecal calprotectin.<sup>9</sup>

**ANSWER 5**

Gastrointestinal side effects, such as diarrhoea and nausea, are the most commonly reported side effects with Apremilast (17% according to

clinical trials).<sup>10</sup> Gastrointestinal side effects tend to occur during the initial 14 days of therapy and typically resolves within 28 days. Accordingly, Apremilast is initiated with a gradual dose titration by an increase of 10 mg daily for six days, up to the maintenance dose of 30 mg twice daily.<sup>8</sup> These gastrointestinal symptoms can be managed by standard anti-diarrhoeal and anti-nausea treatments; however, dose reduction or cessation should be prompted in case of severe gastrointestinal tract symptoms.<sup>10,11</sup> Of note, in patients with renal impairment (creatinine clearance <30 mL/min), dose adjustment of Apremilast is required to 30 mg once daily.<sup>8</sup> Other side effects include headache (6%), upper respiratory tract infection (9%), fatigue (3%), depression (1%) and weight loss (12%), as per clinical trial data.<sup>10</sup> Patients with a psychiatric history should be closely monitored and discussions regarding suitability should be had with relevant care providers, such as treating physician/psychologists.<sup>10,11</sup> In addition, patients' weight should be monitored because weight loss can occur and might require dose reduction or treatment cessation.<sup>11</sup>

In terms of drug interactions, the concomitant use of potent cytochrome P450 inducers, such as rifampin, phenytoin, carbamazepine and phenobarbital, with Apremilast is not recommended due to the potential reduction in Apremilast's efficacy.<sup>10</sup>

**ANSWER 6**

Treatment with Apremilast is typically long term, because psoriasis is a chronic inflammatory skin disorder. Regular blood monitoring is not routinely needed; however, this is patient dependent.<sup>10</sup> Maintenance dosing of Apremilast for psoriasis can now be facilitated by GPs. Accordingly, knowledge of Apremilast's indications, mechanism of action and side effect profiling is important. Given the mounting evidence for Apremilast's use in the setting of IBD, it presents itself as an attractive therapeutic option to address both psoriasis and UC. It is crucial in the primary care setting to facilitate collaborative, multidisciplinary care with both dermatology and gastroenterology for patients with psoriasis and IBD in order to determine optimal therapy for concurrent disease entities.

**Key points**

- There are significant bidirectional associations between psoriasis and IBD.
- Apremilast, a phosphodiesterase 4 inhibitor, presents an appealing treatment option for patients with both psoriasis and UC.
- Common side effects of Apremilast include diarrhoea, nausea, headache, upper respiratory tract infection and weight loss.
- Apremilast initiation must be conducted by a dermatologist, whereas GPs can now manage maintenance dosages.
- Regular blood monitoring is not routinely needed as per the product information; however, this depends on the patient. For those at risk of renal impairment, it might be a prudent adjunct, noting the need for dose reduction in this setting.

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