



## BRIEF REPORT

# Combination therapy of recalcitrant severe psoriasis with psoriatic arthritis, diabetes nephropathy, and liver cirrhosis

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## Abstract

**Objective:** Treatment of recalcitrant moderate-to-severe psoriasis can be challenging. Combination therapy of biologics and immunosuppressive agents can be a new strategy for treating therapy-resistant cases with comorbidities, where many systemic medications are contraindicated.

**Case presentation:** We report a case of a 62-year-old diabetic man with a 30-year history of severe plaque psoriasis and psoriatic arthritis with cirrhosis and diabetic nephropathy that was treated successfully in combination with apremilast and etanercept after multiple previous unsuccessful treatment attempts.

**Conclusion:** There are no data supporting the combination of apremilast and etanercept in the management of recalcitrant cases of moderate-to-severe psoriasis and multiple comorbidities including psoriatic arthritis, diabetic nephropathy, and cirrhosis. In patients who do not respond to multiple approaches for the treatment of psoriasis, combination therapy with biologic agents and new systemic medications may lead to dramatic disease control.

## KEYWORDS

apremilast, cirrhosis, etanercept, guselkumab, moderate-to-severe psoriasis

## 1 | INTRODUCTION

Psoriasis is an autoimmune systemic disease affecting not only the skin but also the joints in approximately 2 percent of the world population. There is currently no cure for psoriasis, and available treatment options result in variable patient responses, in part because disease pathogenesis is not yet completely understood. Recently, psoriasis has been found to be associated with systemic diseases such as diabetes, hypertension, and cardiovascular disease.<sup>1</sup> There are conditions like pregnancy and liver failure (cirrhosis) where some of the commonly used systemic agents are contraindicated. Therapy with agents like apremilast and some biologics can be considered in recalcitrant cases of chronic plaque

psoriasis and psoriatic arthritis (PsA). Apremilast is an oral phosphodiesterase 4 (PDE4) inhibitor and currently has been licensed for the treatment of psoriasis vulgaris and PsA. There are limited data regarding the treatment of psoriasis with biologic agents in patients with liver cirrhosis. Etanercept, a tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) inhibitor, is approved for use in patients with inflammatory diseases. Approximately 33–49% of patients with psoriasis achieve a 75% decrease in psoriasis area and severity index (PASI 75) score with etanercept, which varies based on the dose and frequency of administration.<sup>2</sup> The newest treatment option, besides interleukin-17 (IL-17) inhibitors, is anti-IL-23, for example, guselkumab, risankizumab, and tildrakizumab. The latter group of biologic agents utilizes an IgG1 monoclonal antibody that binds

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to the p19 subunit and inhibits IL-23. It represents a very promising therapy, providing an alternative mechanism of action with high efficacy and safety, sustained total skin clearance, and rapid onset of action even in psoriasis patients who previously showed no or inadequate response to anti-TNF- $\alpha$  or anti-IL-12/23 therapy.<sup>3</sup> Herewith, we describe the efficacy of an initial combination of apremilast and etanercept followed by guselkumab therapy in a diabetic patient with recalcitrant plaque psoriasis, cirrhosis, and diabetic nephropathy.

## 2 | CASE PRESENTATION

A 62-year-old insulin-dependent diabetic man with a history of hypertension, obesity (BMI 34 kg/m<sup>2</sup>), liver cirrhosis, diabetic nephropathy, plaque psoriasis, and psoriatic arthritis presented with moderate extent of plaque. He was treated earlier with fumaric acid, ciclosporin, methotrexate, infliximab, efalizumab, adalimumab, ustekinumab, and ixekizumab in chronological order with either only temporary efficacy or primary lack of response. His PASI score was under all treatment options between 5 and 10, often with a high Dermatology Life Quality Index (DLQI) >10. On physical examination, he had erythematous fine-scaly plaques on all four extremities and guttate-like appearing plaques, some with scale, on his trunk, which developed to vulgaris plaques. His scalp was clear, he had pitting of his nails, and there were joint involvement and features of psoriatic arthritis, which was radiologically confirmed. Due to the comorbidities, especially cirrhosis and renal failure, and the unresponsiveness to all other known and licensed therapies and also due to the fact that the lesions had worsened, the case was discussed in the rheumatology board. We started a combination therapy with an oral PDE4-inhibitor (apremilast 30 mg per os twice daily) along with TNF- $\alpha$  antagonist (etanercept 25–50 mg twice a week) subcutaneously. The treatment continued for two weeks. Due to joint pain, especially in the hands, the dose of etanercept was increased to 75 mg weekly plus a topical therapy combination of calcipotriol and betamethasone for 6 weeks, with substantial improvement of the PASI to a score of 0.3 but no significant improvement of joint pain. The dose was further increased to 100 mg weekly along with apremilast 30 mg twice daily. After 3 months, the disease severity was assessed using PASI with a score of 1.8. At the same time, the level of creatinine had decreased significantly. The dose of apremilast was decreased to 30 mg daily because of gastrointestinal disturbances, and after 3 months, the PASI score increased to 3.2. The treatment with etanercept and apremilast continued for 28 months with some dose adjustments due to treatment efficacy. No side effects appeared. On the contrary, renal function improved further and liver enzymes decreased significantly. Furthermore, demand for insulin decreased. The PASI and DLQI scores were almost on the same level during this period between 2 and 4. After 28 months, the PASI score increased unexpectedly to 11.8 and DLQI to 10, however,

with significant relief of the psoriatic arthritis and nail psoriasis. Finally, because of the known effectiveness of guselkumab in patients who were initially treated with biologics, our patient was given injections of guselkumab every 8 weeks, showing a decrease in PASI score from 10 to 8 after 4 weeks and currently, after the third injection, to a PASI score of 5 and DLQI of 2. There is no sign of PsA, and the disease is currently under control, including nails and joints.

## 3 | DISCUSSION

This case shows the efficacy of combination therapy with apremilast and etanercept in controlling psoriasis and PsA in a cirrhotic individual with diabetic nephropathy and renal insufficiency. Although biologics are generally used as monotherapy, traditional systemic agents are used in up to 30% of the cases in Europe.<sup>4</sup> In our case, neither of the monotherapies with etanercept or apremilast showed inadequate disease control. Addition of a biologic to traditional systemic therapy can enhance efficacy and permit discontinuation or dose adjustment of the traditional systemic agent without compromising disease control. On the other hand, addition of a systemic agent, phototherapy, or topical therapy to a biologic can enhance efficacy, including speed of onset, degree of clearing, and in some cases duration of remission and also improve safety. The decision to add etanercept was based on the fact that it targets TNF- $\alpha$ , which is not addressed directly by apremilast and the mode of action which in contrast is extracellular. Currently, there are only limited data on the combined use of apremilast and a biologic agent. Few reports support its combination with secukinumab or adalimumab to be very efficacious and safe, but none has examined its combination with etanercept.<sup>5,6</sup> Etanercept has been successfully combined with topical calcipotriol, phototherapy, methotrexate, acitretin, and cyclosporine.<sup>7–11</sup> There have been reports that apremilast had to be stopped due to its side effects and the absence of any benefit when combined with ustekinumab.<sup>12</sup> Few of the studies have shown unsatisfactory outcome with apremilast or etanercept, and hence, they have been replaced with each other.<sup>13–15</sup> To the best of our knowledge, this is the first reported case of combined use of apremilast and etanercept for chronic plaque psoriasis and PsA in a patient with cirrhosis and diabetic nephropathy. Interestingly, our patient showed a remarkable improvement and stable disease in the arthritis component with few recalcitrant but negligible plaques on the skin. Moreover, we could detect a decrease in liver enzymes and creatine levels under the combination therapy. This is not what we had expected when we initiated a therapy with multiple agents in a patient with liver cirrhosis. We propose that cirrhosis and renal insufficiency function were not caused by previous treatments like methotrexate and ciclosporin but rather by the insufficient control of systemic inflammation. A further benefit was observed in the exocrine function of the pancreas. Previous study demonstrated that

guselkumab is an effective medication in patients who are initially treated with biologics<sup>16</sup>, so we decided to change the combination therapy after their response failure to guselkumab and the disease is under control.

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## CONFLICT OF INTEREST

None.

## AUTHOR CONTRIBUTION

Sebastian Zimmer, Joanna Wegner, and Petra Staubach-Renz manage the case, and reviewed and revised the manuscript. Mohamad Goldust wrote and revised the manuscript. Stephan Grabbe reviewed and revised the manuscript. Shashank Bhargava wrote and revised the manuscript.

## DISCLAIMER

"We confirm that the manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work."

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## ETHICAL APPROVAL

Authors declare human ethics approval was not needed for this study.

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