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Research Article

# The Therapeutic Challenge of Treating Refractory Psoriasis: An Educational Article and Expert Opinion

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## Abstract

**Background:** Therapies that are commonly used in the treatment of refractory psoriasis include mycophenolate mofetil, methotrexate, acitretin, apremilast, and tofacitinib. The medications can be used in refractory psoriasis either as monotherapy or in combination with other medications. The use of biological medications such as infliximab and etanercept in the treatment of refractory psoriasis has been increasingly reported.

**Patients and methods:** After one month, treatment with mycophenolate and topical calcipotriol was associated with improvement in the activity of skin disease and the arthritic symptoms, but there was no significant reduction the affected area of skin. Therefore, tazarotene 0.1% cream was added. At two months of treatment, both skin and joint symptoms were slightly worsening and the patient needed a non-steroidal anti-inflammatory medication to control joint symptoms. Acitretin was added in an initial dose of 10 mg daily with intention of increasing it to 25 mg daily gradually. However, on the fourth day after adding of oral acitretin the patient reported a significant reduction in the severity of the disease and the affected area that have not achieved long time ago. The patient also reported experiencing unpleasant taste that was attributed to acitretin.

**Conclusion:** The current expert opinion suggests that the choice of the treatment of methotrexate and mycophenolate refractory psoriasis should be based on the available evidence, and it generally depends mostly on the availability and cost of the medications, and the experience of the treating physician with the available medications. In cases of resistance to methotrexate, and mycophenolate, acitretin can be added mycophenolate, and the use of newer safe biological agents such as etanercept and Infliximab can be considered.

**Keywords:** refractory; psoriasis; expert opinion; mycophenolate mofetil; acitretin

## Introduction

Psoriasis is a chronic skin disease that can be associated with systemic features particularly arthritic manifestations. Mildly affected patients can generally be treated with topical medications including corticosteroids, coal tar, anthralin (Dithranol), salicylic acid, vitamin D analogues such as calcipotriol, retinoid such as tazarotene (AGN 190168), and calcineurin inhibitors such as pimecrolimus.

Commonly used safe oral non-biological medications, include methotrexate which has been used for more than half century, mycophenolate mofetil which has been used for decades. Patients who do not respond to these agents can represent a therapeutic challenge, and may need treatments with other safe systemic medications such as acitretin, an oral retinoid which has also been used for the treatment of psoriasis for decades. The use of safe biological medications such as infliximab in the treatment of refractory psoriasis has been increasingly reported [1].

## Patients and Methods

We have previously reported the treatment of 51-year-old diabetic and hypertensive patient who had moderately severe psoriasis with arthritic manifestations.

Before referral, the patient was treated with topical therapies for years; however, treatments caused worsening of hyperglycemia which was attributed to the steroid content of topical therapies. The earlier treating doctor discontinued topical therapy and prescribed methotrexate given orally in a dose of 5 mg two times a week. Several weeks of oral methotrexate treatment resulted in slight improvement, and the earlier treating doctor tried to increase the dose of methotrexate to 7.5 mg two times a week, however, the patient's awareness of the risk of methotrexate

hepatotoxic effect made the patient stopped methotrexate. Discontinuation of methotrexate was associated with some worsening of the condition.

On referral the patient had large area of his body affected and systemic treatment was considered necessary. Leukocyte count and liver function testes showed normal findings.
The patient was treated with oral mycophenolate 2000 in two divided doses and methotrexate discontinued gradually.

As the available evidence suggests that the use of mycophenolate alone in such case of psoriasis results in a good therapeutic response in approximately 70% or less, topical calcipotriol 0.005% was added and given once daily at night [1].

## Results

After one month, treatment was associated with improvement in the activity of skin disease and the arthritic symptoms, but there was no significant reduction the affected area of skin. Therefore, tazarotene 0.1% cream was added and given once daily in the morning. The patient was receiving oral valsartan 160 mg plus amlodipine 5 mg daily hypertension for the treatment of hypertension. Antihypertensive medications were replaced with oral pentoxifylline 400 mg twice daily. The change of the antihypertensive was based on the evidence provided by Gilhar et al (1996) suggesting that pentoxifylline on can provide an antiproliferative effect on psoriatic epidermis [2].

At two months of treatment, both skin and joint symptoms were slightly worsening and the patient needed oral aceclofenac (100 mg daily), a non-steroidal anti-inflammatory medication plus paracetamol to control joint symptoms. The patient was not experiencing any treatment side effects.

Aceclofenac was considered the preferred non-steroidal anti-inflammatory based on the evidence provided by Ardigò et al (2013) which suggested that aceclofenac may have a beneficial effect in psoriasis.

The patient diabetes was controlled with oral glimepiride (5 mg daily) plus metformin (1000 mg daily). Glimepiride was replaced with sitagliptin (50 mg daily) based on the evidence provided by Lynch et al (2016) and Singh and Bhansali (2017) suggesting that metformin and sitagliptin have a beneficial effect in psoriasis [4,5].

Acitretin was added in an initial dose of 10 mg daily with intention of increasing it to 25 mg daily gradually based on the evidence presented by John B Kelly 3rd and colleagues (2015) and Michael S Heath and his research group (2018) [6,7]. The decision was also made to replace topical calcipotriol and tazarotene with topical pimecrolimus based on the evidence provided by Ayer J and Young (2013) [8].

The use of newer topical biological therapies that are not immediately available including, subcutaneously administered etanercept, and infliximab was considered based on the evidence provided by de Vries et al (2017) [9].

However, on the fourth day after adding of oral acitretin the patient reported a significant reduction in the severity of the disease and the affected area (Figure-1) that have not achieved long time ago. The patient also reported experiencing unpleasant taste that was attributed to acitretin.

## Discussion

As there are many therapeutic options, the choice of the medications in cases of refractory psoriasis depends on the availability and cost of the medication, and the experience of the treating physician with the chosen medication.

In 2015, John B Kelly 3rd and colleagues from the United States emphasized that mycophenolate mofetil, methotrexate, acitretin, apremilast, and tofacitinib can be used be safely with careful monitoring in refractory psoriasis either as monotherapy or in combination with other medications [5,6].

**Figure-1:** The addition of low dose acitretin to mycophenolate resulted in a rapid a significant reduction in the severity of the disease and the affected area

In 2018, Michael S Heath from the United States and his research group suggested that oral acitretin and tazarotene are retinoids for treatment of psoriasis. Both topical tazarotene and oral acitretin act on gene expression of cytokines which mediates inflammation and can inhibit proliferation of keratinocytes in psoriasis patients. The emphasized that tazarotene and acitretin can be combined with other topical and systemic medical to improve treatment effectiveness [7].

## Conclusion

The current expert opinion suggests that the choice of the treatment of methotrexate and mycophenolate refractory psoriasis should be based on the available evidence, and it generally depends mostly on the availability and cost of the medications, and the experience of the treating physician with the available medications. In cases of resistance to methotrexate, and mycophenolate, acitretin can be added mycophenolate, and the use of newer safe biological agents such as etanercept and Infliximab can be considered.

**Conflict of interest:** None.

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