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Case Report

The Risk of Creating Difficult-To-Treat Psoriasis by Switching Multiple Biologic Therapies: A Case Report and Relative Considerations

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Abstract

Despite the revolution represented by biologic drugs, it is safe to say that every dermatologist has known the frustrating experience of treating a "difficult" patient with psoriasis. Such patients may have been treated with numerous drugs, never achieving long-term disease control. We hereby present the case of a patient who, despite having been treated, over the course of 15 years, with 7 biologics and 3 traditional systemic agents, has never experienced lasting remission. We also discuss hypothetical reasons for these repeated treatment failures: while obesity and ANA positivity could have contributed significantly, a third, more complex, factor may be to blame. It is possible that frequently switching to the newest drug available, due to lack of other therapeutic options, interfered with the pathogenetic phenotype of the patient, and, consequently, with the response to other biologics. This disheartening and fascinating hypothesis clearly needs to be investigated, in the hope of finding solutions for all seemingly impossible-to-treat patients.

Keywords

Disease-Modifying Antirheumatic Drugs; Cyclosporine; Psoriasis; Biologic Drugs

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Introduction

Psoriasis is a chronic, immune-mediated cutaneous disease, with a worldwide estimated prevalence of 2% [1]. The introduction of biologics has revolutionized the treatment of psoriasis. These drugs, classified in 4 classes (TNF inhibitors, IL-12/23 inhibitors, IL-17 inhibitors and IL-23 inhibitors), are generally very effective and have limited contraindications and adverse effect [2]. In a few difficult cases, a combination therapy of biologics and conventional systemic agents is required to achieve disease control [3]. However, all dermatologists have experience of a difficult-to-treat patient who does not respond to any therapy. Often, these patients have suffered from psoriasis for years and have been periodically treated with Disease-Modifying Antirheumatic Drugs (DMARDs), before the first biologic was available on the market. Throughout the years, in the absence of the vast choice of biologics now available, these patients have been prescribed the newest drug on the market, rather than a treatment tailored to the patient characteristics. We hereby present a case of a difficult-to-treat patient and our considerations.

Case Report

The patient, a 71-year-old Caucasian female, has been suffering from plaque-type psoriasis since the age of 20. She has suffered from obesity (BMI 30-31) her entire adult life.

After years of exclusively topical treatment, in 2004 the patient started a cycle of cyclosporine, with improvement that lasted as long as the patient was on treatment.

In 2008, following the approval of adalimumab for the treatment of moderate-to-severe plaque psoriasis, the patient started treatment with standard dose adalimumab (40 mg every 2 weeks), which not only did not prove effective, but was accompanied by a worsening of the disease. This discouraged the patient, who refused other systemic therapies.

However, in 2012, a severe relapse (PASI 30) led the patient to seek treatment. She started a new cycle of cyclosporine.

In 2013 the dosage of cyclosporine was increased to 250 mg daily, later tapered to 100 mg/die and subsequently stopped with the aim of starting etanercept (50 mg twice a week for 3 months, later once a week). Due to its different molecular structure (etanercept is a fusion protein that acts as a TNF soluble receptor) this drug was thought to be potentially effective despite the failure with adalimumab.

However, there was no improvement, and in November 2013 she was switched to infliximab, another TNF inhibitor, which, because of its intravenous administration, was not considered as a first line therapy, even though it allows more appropriate dosing in obese patient (5 mg/kg

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instead of a predetermined standard dose). Once again, the treatment was not successful, and the patient was put back on cyclosporine.

Due to the numerous therapeutic failures, a biopsy was performed, but the diagnosis of psoriasis was confirmed.

In 2015 and 2016 she continued the treatment with cyclosporine, albeit periodically, because of fluctuations of creatinine levels. During this time, psoriasis was only partially controlled.

In 2016 the patient was diagnosed with psoriatic arthritis.

In 2017 the Italian Agency for Drugs admitted the refundability for apremilast, an orally administered drug with a favorable safety profile and effective for arthritis [4]. Because of these characteristics, apremilast seemed an ideal choice for the patient, who, at the time, was reluctant to have injections, so it was decided to put her on a standard dose (30 mg twice daily). However, despite a modest improvement of arthritis, the cutaneous response to the drug was totally unsatisfactory (Fig. 1). Consequently, in November the patient stopped the treatment with apremilast and was once again prescribed 200 mg of cyclosporin daily, which, as expected, was only effective on the cutaneous disease (Fig. 1).

In March 2019 cyclosporine was suspended because of cyclosporine-induced renal dysfunction.

Cyclosporine was no longer a feasible option, but, fortunately, many new biologics had become available since 2013, so it was decided to start treatment with a biologic drug. Along with TNF antagonists, which had repetitively failed in this patient, IL-17 inhibitors are considered a first-line therapy to adults with psoriasis and who also have psoriatic arthritis (with the exception of brodalumab), so we chose ixekizumab (80 mg every 4 weeks) [5].

In April 2019 the disease was in complete remission (Fig. 1).

However, in February 2020 the drug seemingly started losing effectiveness, with the appearance of psoriatic plaques that increased in number over the course of the year (Fig. 1).

In September, after 18 months of treatment with ixekizumab and having reached a PASI of 15, the patient was switched to brodalumab (210 mg every 2 weeks). Being an anti-IL17-receptor antibody, brodalumab was thought to be potentially effective despite the previous secondary failure with an IL-17A inhibitor, a fact that, as of 2021, has been well documented in literature [6].

Despite an apparent improvement during the first months of treatment (Fig.1), psoriasis soon relapsed (Fig. 1), and in March 2021 the patient was switched to a new class of biologics: IL-23 inhibitors.

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In particular, the chosen drug was risankizumab (150 mg every 12 weeks), the newest biologic on the market and the one with the highest efficacy according to network meta-analyses [7].

Once again, after a brief period of improvement, the disease progressed (Fig. 1). In June 2021, risankizumab was stopped and recently-approved dimethyl fumarate was started (slowly increasing from 30 mg daily to 120 mg daily). Unfortunately, the patient experienced gastrointestinal adverse effects, but a slight improvement of the disease was noticed (Fig. 1).

At this point, questioning again our own diagnosis, we performed a new biopsy, which confirmed the diagnosis of psoriasis, and we investigated the serology of the patient, detecting high titer (1:640) Antinuclear Antibodies (ANA) and anti-Ro antibodies, typical, although not pathognomonic, of systemic lupus erythematosus. A direct immunofluorescence study was not performed, since it was believed that the diagnosis of psoriasis was perfectly coherent with the clinical and histologic findings, so the hypothesis of lupus was considered highly unlikely and was not further investigated. Moreover, since the patient had no symptoms that suggested other autoimmune diseases, she did not undergo additional diagnostic tests.

In the light of the above information, it was decided to put the patient on standard dose ustekinumab (90 mg every 12 weeks), associated to 90 mg/daily of dimethyl fumarate, despite the previous failure with another IL-23 inhibitors. The choice of this biologic was mainly led by the fact that ustekinumab inhibits both IL-12 and IL-23, moreover, a phase 2 study supported the use of ustekinumab as a treatment in systemic lupus erythematosus (Fig. 2) [8].

Dimethyl fumarate was associated because it had previously led to a positive, although slight, improvement.

Three months after stating treatment with ustekinumab and dimethyl fumarate, the patient's psoriasis appeared less inflamed, although far from complete remission. The patient reported good tolerability of dimethyl fumarate, so we plan to increase the dosage to 120 mg.

Discussion

Despite the general effectiveness of biologic drugs, it is known that not all patients respond well to their first biologic treatment. Failure can be classified in primary failure (lack of initial efficacy), secondary failure (loss of efficacy over time) or adverse effects that require a suspension of the treatment [9]. Switching between biologics is not a rare occurrence in clinical practice: a recent multicentric study conducted on 427 patients over a period of 12 years showed a 34% switching rate. In most cases, a switch was required because of inefficacy of the first biologic agent. Moreover, patients who switched to a different biologic showed a similar improvement compared to naïve patients [10]. The latter observation confirms a principle stated in the 2009 British Association of Dermatologists: even in the context of apparent

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treatment failure, loss of a drug's efficacy in psoriasis may not equate to loss of all pharmacological activity [11].

However, our reported case seems to represent an exception to this norm: the patient was administered 7 different biologic drugs (adalimumab, etanercept, infliximab, ixekizumab, brodalumab, risankizumab, ustekinumab) and 3 oral agents (cyclosporine, apremilast, dimethyl fumarate) over the course of 17 years, never achieving a satisfactory disease control. Not even the association of biologics and traditional systemic agents was long-term effective.

It is difficult to identify potential causes for such repeated failures. One possible factor may be the patient weight, since obesity is known to negatively affect the clinical response of biological drugs in psoriatic patients, with anti-interleukin drugs being more affected by BMI than anti-tumor necrosis factor drugs [12].

Moreover, the reported ANA positivity may also be involved, since it has been shown that higher pretreatment ANA titres correlate with the development of infliximab-Antibodies, which are associated with loss of response to infliximab [13].

However, such factors do not seem to fully justify the multiple treatment failures we observed.

At this point, it is impossible to ignore the hypothesis that exposure to multiple biologics may have compromised the effectiveness of other drugs of the same category. First of all, the positivity to ANA could possibly be a consequence of previous therapy with TNF inhibitors, since the induction of antinuclear antibodies has been reported in patients treated with such therapies [14]. However, it must be noted that high-titre ANA persisted for years after the discontinuation of anti-TNF drugs.

TNF inhibitors, as well as many other drugs prescribed to the patient, were simply picked because they were the only options available at the time. On the contrary, today we have the luxury of choosing between the numerous options on the market, and the knowledge to prescribe the right biologic to the right patient. The notion that we may have unknowingly "polluted" the pathogenetic phenotype of the patient is hard to accept. However, there is evidence that exposure to previous treatment with biologics may affect the quality of response to other ones. This has been proved for various drugs, including ixekizumab, brodalumab, risankizumab and ustekinumab [15]. The question of whether the (theoretical) damage can be undone remains unanswered. We are hopeful that, with the development of new drugs against completely different targets, even difficult patients will finally benefit from the biologics revolution in dermatology.

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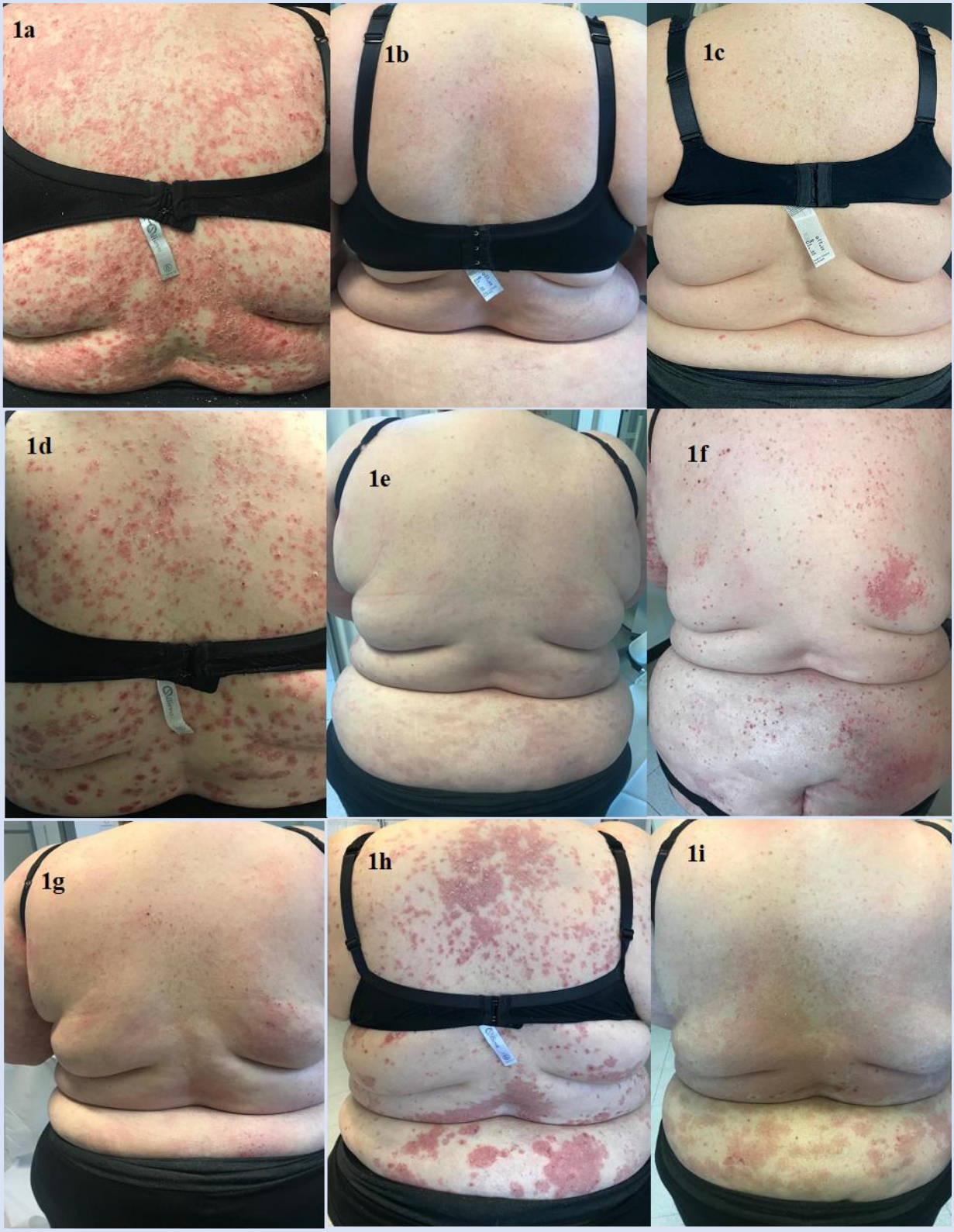

Figure 1: Evolution of the patient's psoriasis.

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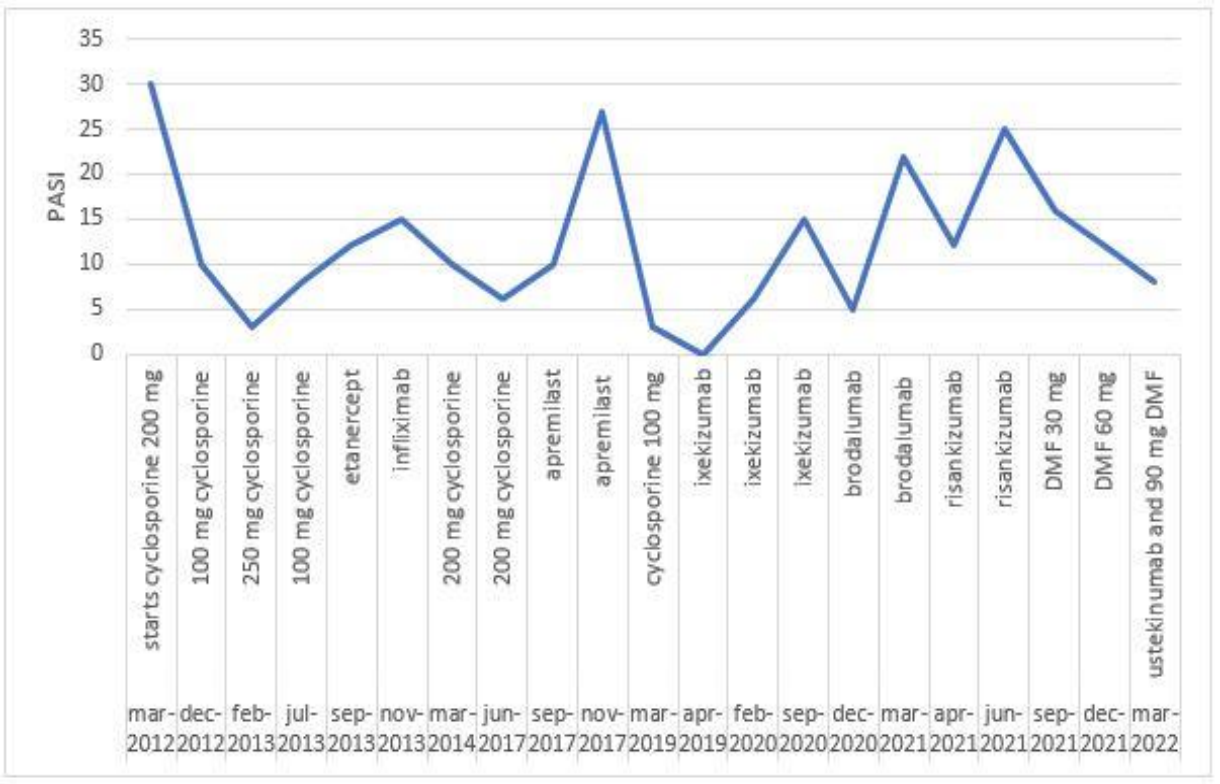

Figure 2: Evolution of the patient's psoriasis from 2012 to 2022.

Conclusion

While biologic therapies changed the life of many patients for the better, there are those for whom disease control still remains elusive. Further studies are needed to establish phenotypical similarities of difficult-to-treat patients, especially those previously exposed to biologics, in order to predict the risk of treatment failure and to determine an efficient protocol to guide drug switching. The notion that multiple exposure to biologics could negatively affect the response to others should be further investigated, in the hope of finding solutions for the small, yet significant, minority of seemingly impossible-to-treat patients.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

1. Rendon A, Schäkel K. Psoriasis pathogenesis and treatment. Int J Mol Sci. 2019;20(6):1475.
2. Armstrong AW, Read C. Pathophysiology, Clinical presentation, and treatment of psoriasis: a review. JAMA. 2020;323(19):1945-60.
3. Armstrong AW, Bagel J, Van Voorhees AS, Robertson AD, Yamauchi PS. Combining biologic therapies with other systemic treatments in psoriasis: evidence-based, best-practice recommendations from the Medical Board of the National Psoriasis Foundation. JAMA Dermatol. 2015;151(4):432-8.
4. Kavanaugh A, Gladman DD, Edwards CJ, Schett G, Guerette B, Delev N, et al. Long-term experience with apremilast in patients with psoriatic arthritis: 5-year results from a PALACE 1-3 pooled analysis. Arthritis Res Ther. 2019;21(1):1-8.
5. Smith CH, Yiu ZZ, Bale T, Burden AD, Coates LC, Edwards W, et al. British Association of Dermatologists guidelines for biologic therapy for psoriasis 2020: a rapid update. Br J Dermatol. 2020;183(4):628-37.
6. Loft N, Bregnhøj A, Fage S, Nielsen CH, Enevold C, Zachariae C, et al. Effectiveness of brodalumab after previous treatment failure of interleukin-17A inhibitors in patients with psoriasis. Dermatol Ther. 2021;34(6):e15106.
7. Armstrong AW, Puig L, Joshi A, Skup M, Williams D, Li J, et al. Comparison of biologics and oral treatments for plaque psoriasis: a meta-analysis. JAMA Dermatol. 2020;156(3):258-69.
8. Van Vollenhoven RF, Hahn BH, Tsokos GC, Wagner CL, Lipsky P, Touma Z, et al. Efficacy and safety of ustekinumab, an IL-12 and IL-23 inhibitor, in patients with active systemic lupus erythematosus: results of a multicentre, double-blind, phase 2, randomised, controlled study. The Lancet. 2018;392(10155):1330-9.
9. Hu Y, Chen Z, Gong Y, Shi Y. A review of switching biologic agents in the treatment of moderate-to-severe plaque psoriasis. Clin Drug Invest. 2018;38(3):191-9.
10. De Kivit S, Kraneveld AD, Knippels LM, Van Kooyk Y, Garssen J, Willemsen LE. Intestinal epithelium-derived galectin-9 is involved in the immunomodulating effects of nondigestible oligosaccharides. J Innate Immu. 2013;5(6):625-38.
11. Smith CH, Anstey AV, Barker JN, Burden AD, Chalmers RJ, Chandler DA, et al. British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. Br J Dermatol. 2009;161(5):987-1019.
12. Pirro F, Caldarola G, Chiricozzi A, Burlando M, Mariani M, Parodi A, et al. Impact of body mass index on the efficacy of biological therapies in patients with psoriasis: a real-world study. Clinical Drug Invest. 2021;41(10):917-25.
13. Hoffmann JH, Hartmann M, Enk AH, Hadaschik EN. Autoantibodies in psoriasis as predictors for loss of response and anti-infliximab antibody induction. Br J Dermatol. 2011;165(6):1355-8.
14. Oter-López B, Llamas-Velasco M, Sánchez-Pérez J, Dauden E. Induction of autoantibodies and autoimmune diseases in patients with psoriasis receiving tumor necrosis factor inhibitors. Actas Dermo-Sifiliográficas (English Edition). 2017;108(5):445-56.
15. Torres T, Puig L, Vender R, Lynde C, Piaserico S, Carrascosa JM, et al. Drug survival of IL-12/23, IL-17 and IL-23 inhibitors for psoriasis treatment: a retrospective multi-country, multicentric cohort study. Am J Clin Dermatol. 2021;22(4):567-79.

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