RESEARCH LETTER

Multiple Biologics Treatment Failures in Patients with Psoriasis: A Case Series of 4 Patients

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To the Editor,

Psoriasis affects approximately 0.14% to 1.99% of the global population (1), posing a considerable burden on patients' physical, emotional, and social well-being. Although biologics have improved management of moderate to severe psoriasis, some patients exhibit refractory disease, estimated at around 6% (2). Although different definitions exist, treatment-refractory psoriasis is often defined as patients with treatment failure of at least 3 different biologics that act on at least 2 distinct pathways (2, 3). Treatment failures can be categorized as primary, where there is no initial response, or secondary, where there is a loss of effectiveness after an initial response. Contributing factors to lack or loss of response include genetic predisposition (4), smoking, high body mass index (BMI), metabolic or cardiovascular comorbidities (5).

Here, we present 4 cases that highlight the multifactorial challenges of psoriasis unresponsive to multiple biologics.

Case 1: A 68-year-old male with 38 years of severe psoriasis and hypertension experienced only transient improvements despite multiple systemic agents (methotrexate, cyclosporine) and successive biologics (infliximab, ustekinumab, adalimumab, apremilast, secukinumab, ixekizumab, brodalumab, and guselkumab). Most recently, bimekizumab was introduced at a shortened interval every 4 weeks (Q4W), yielding significant skin improvement (**Tables I** and **II**) (Fig. S1A).

Case 2: A 69-year-old male had a 24-year history of severe plaque psoriasis, multiple comorbidities (hypertension, coronary artery disease, chronic obstructive pulmonary disease, psoriatic arthritis [PsA]). He was treated with numerous treatments (topical agents, phototherapy, traditional systemics, and biologics (infliximab, adalimumab, ustekinumab, etanercept, secukinumab, ixekizumab, and brodalumab), the latest being guselkumab Q4W without sustained control. Adverse reactions and limited effectiveness led to multiple therapy switches (Tables I and II) (Fig. S1B).

Case 3: A 40-year-old male with psoriasis and PsA showed partial or temporary responses to methotrexate, sulfasalazine, and subsequent biologics (adalimumab, infliximab, ustekinumab, etanercept, secukinumab, ixekizumab, brodalumab, certolizumab pegol). Additionally, tofacitinib was added and most recently combined with bimekizumab, which has led to disease control of both skin and joint symptoms (Tables I and II) (Fig. S1C).

Case 4: A 64-year-old female with severe psoriasis and multiple comorbidities (obesity, type 1 diabetes, fibromyalgia, cirrhosis) responded initially but relapsed after several biologics (adalimumab, ustekinumab, secukinumab, ixekizumab, brodalumab, infliximab, risankizumab, apremilast, risankizumab). Her most recent treatment with bimekizumab, administered at an increased interval Q4W, provided only transient efficacy (Tables I and II) (Fig. S1D).

Despite the availability of multiple biologics, some patients either fail to respond initially or lose their treatment response over time, presenting significant management challenges. Our case series documents 4 such cases, exploring the context of treatment failure. The reasons for these failures are complex, but several contributing factors have been proposed.

Studies have linked metabolic conditions, such as obesity and diabetes, to exacerbated inflammatory pathways in psoriasis, potentially reducing the effectiveness of biologics. Cases 2, 3, and 4 were obese, with case 4 also having diabetes, factors that likely impacted their treatment outcomes. Consistently, a high BMI has been linked to reduced responsiveness (6), possibly due to underdosing. This is illustrated by cases 1, 2, and 4, which achieved better responses after increasing the dosing intervals for bimekizumab and guselkumab. However, each patient had previously received infliximab, a fully weight-adjusted therapy, suggesting that underdosing alone cannot fully account for the lack or loss of treatment response.

Temporary improvements followed by quick relapses in cases 1 and 4 may indicate immunogenic responses, where the development of neutralizing antibodies negates the effects of biologics. This underscores the need for improved tools to monitor and manage such immunogenicity.

A history of multiple biologic therapies, particularly among those switching between drug classes due to inadequate responses, tends to correlate with lower success rates in subsequent treatments. However, emerging insights suggest that switching within the same drug class can still be effective, highlighting the nuanced role of individual patient factors in treatment outcomes (7).

Furthermore, the presence of PsA complicates treatment, as it often requires strategies that simultaneously target both joint and skin symptoms, necessitating tailored therapeutic approaches (8). Our study includes case 3, in which the patient was successfully treated with a

Table I. Demographic, treatment, and comorbidity profiles of psoriasis cases

Clinical characteristics	Case 1	Case 2	Case 3	Case 4
Age	68	69	40	64
Sex	Male	Male	Male	Female
Weight (kg)	82.0	102.0	102.2	124.0
BMI	25.25	34.31	30.23	41.91
Current PASI	0.0	7.5	0.0	0.0
Max PASI	16.0	36.0	30.9	28.9
Current DLQI	3.0	0.0	1.0	0.0
Max DLQI	21.0	27	16	19
Current treatment	Bimekizumab	Guselkumab	Bimekizumab	Bimekizumab
Current concomitant treatment	None	None	Tofacitinib	None
Number of previous biologics	9	9	9	9
Previous systemics (non-biologics)	2	0	2	1
Psoriasis debut	1986	2000	1999	2011
Psoriatic arthritis	No	Yes	Yes	No
HLA-C*06:02	Pos.	Neg.	Pos.	Neg.
Other comorbidities	Hypertension	Coronary artery disease, hypertension, chronic obstructive pulmonary disease, alcohol abuse	None	Obesity, type-2 diabetes, fibromyalgia, cirrhosis, and grade 2 steatosis

BMI: body mass index; DLQI: Dermatology Life Quality Index; Neg: negative; PASI: Psoriasis Area and Severity Index; Pos: positive.

combination of an interleukin-17 inhibitor (bimekizumab) and a Janus kinase 1 and 3 inhibitor (tofacitinib) without additional adverse events.

These cases highlight the complexity of treating psoriasis in patients with multiple biologics failures. A multifactorial approach that considers genetic predispositions, comorbidities, and potential immunogenicity is crucial. Future research should aim to identify predictive factors that can guide personalized treatment approaches.

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Table II. Treatment response overview

Case	1	2	3	4	5	6	7	8	9	10	11
1	IFX (48M) SN	UST (3M) PN	ADA (48M) SN	APR (12M) PN	SEC (24M) SN	IXE (30M) SN	GUS (3M) PN	BRO (36M) SN	BIM (12M) SN	BIM Q4W ACI(3M) PN	BIM Q4W SR
2	IFX (7M) AE	ADA (3M) PN	UST (6M) PN	ETA (6M) SN	UST (12M) PN	SEC (4M) PN	IXE (13M) SN	BRO (3M) SN	GUS (24M) SN	GUS Q6W (12M) SN	GUS Q4W (36M) SR
3	ADA (12M) SN	IFX (10M) SN	UST (6M) PN	ETA (18M) SN	SEC (60M) SN	IXE (12M) SN	BRO (8M) SN	TOF (3M) PN	GUS (24M) SN	GUS + TOF (24M) SN	BIM (21M)+ TOF (20M) SR
4	ADA (18M) SN	UST (6M) SN	SEC (15M) SN	IXE (19M) SN	BRO (3M) SN	IFX (22M) SN	RIS (13M) SN	ADA Q1W (3M) PN	APR (3M) PN	BIM (24M) SR	

ADA: adalimumab; AE: adverse events; APR: apremilast; BIM: bimekizumab; BRO: brodalumab; CEP: certolizumab pegol; ETA: etanercept; GUS: guselkumab; IFX: infliximab; IXE: ixekizumab; PN: primary non-response; RIS: risankizumab; SEC: secukinumab; SN: secondary non-response; SR: still response; TIL: tildrakizumab; TOF: tofacitinib; UST: ustekinumab.

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