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Pharmacology and Therapeutics - Report

Multi-failure psoriasis patients: characterization of the patients and response to biological therapy in a multicenter Italian cohort

Riccardo Viola, MD[1,†] Luca Mastorino, MD[2,†] Matteo Megna, MD[3] Giovanni Damiani, MD[4] Paolo Gisondi, MD[5] Giuseppe Argenziano, MD[6] Ketty Peris, MD[7] Francesca Prignano, MD[8] Martina Burlando, MD[9] Andrea Conti, MD[10] Francesco Loconsole, MD[1] Piergiorgio Malagoli, MD[11] Iris Zalaudek, MD[12] Sara Cacciapuoti, MD[3] Francesco Bellinato, MD[5] Anna Balato, MD[6] Clara De Simone, MD[7] Karin Chersi, MD[12] Michela Ortoncelli, MD[2] Pietro Quaglino, MD[2] Paolo Dapavo, MD[2,‡] and Simone Ribero, MD[2,‡]

[1]Section of Dermatology and Venereology, Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), University of Bari "Aldo Moro", Bari, Italy, [2]Department of Medical Sciences, Dermatology Clinic, University of Turin, Turin, Italy, [3]Section of Dermatology, Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy, [4]Clinical Dermatology, I.R.C.C.S. Istituto Ortopedico Galeazzi, Milan, Italy, [5]Department of Medicine, Section of Dermatology and Venereology, University of Verona, Verona, Italy, [6]Dermatology Unit, University of Campania L. Vanvitelli, Naples, Italy, [7]Institute of Dermatology, Università Cattolica-Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, [8]Section of Dermatology, Department of Health Sciences, University of Florence, Florence, Italy, [9]Section of Dermatology, Department of Health Sciences (DISSAL), IRCCS San Martino University Hospital, Genoa, Italy, [10]Dermatologic Unit, Department of Surgery, Infermi Hospital, AUSL Romagna, Rimini, Italy, [11]Department of Dermatology, Dermatology Unit Azienda Ospedaliera San Donato Milanese, Milan, Italy; and [12]Department of Dermatology and Venereology, Dermatology Clinic, Maggiore Hospital, University of Trieste, Trieste, Italy

Correspondence
Riccardo Viola, MD
Dermatology Clinic
University of Bari
Piazza Giulio Cesare 11
Bari (BA) 70124
Italy
E-mail: dott.riccardoviola@gmail.com

Abstract

Introduction Patients with psoriasis who have failed multiple biologic drugs have been defined as "multi-failure," although there are no clear data on the characteristics, comorbidities, and best treatment strategies for this population. Nowadays, given the next generation and the number of biologics available, patients are considered multi-failure when ≥4 biologics fail to achieve a good response.

Methods Demographic characteristics and efficacy of anti-interleukin drugs in multi-failure patients were compared to a cohort of general psoriatic patients treated with IL-23 or IL-17 inhibitors.

Results In total 97 multi-failure patients (≥4 lines of biologics) were compared with 1,057 patients in the general cohort. The current drugs in the multi-failure group were risankizumab (34), ixekizumab (23), guselkumab (21), brodalumab (7), tildrakizumab (5), ustekinumab (4), secukinumab (2), and certolizumab pegol (1). A significant difference was found in the multi-failure cohort for age of psoriasis onset (mean 29.7 vs. 35.1, $P < 0.001$), concurrent psoriatic arthritis (45.4 vs. 26.9%, $P < 0.001$), diabetes mellitus (30.9 vs. 10.9%, $P < 0.001$), and cardiovascular comorbidity (54.6 vs. 39.8%, $P = 0.005$). In multi-failure patients, current biological therapy showed a good initial response (PASI 90 and 100 of 41.24 and 27.84%, respectively, at 16 weeks); the response tended to decline after 40 weeks. Anti-IL-17 agents showed clinical superiority over IL-23 agents in terms of achieving PASI90 at 28 weeks ($P < 0.001$) and 40 weeks ($P = 0.007$), after which they reached a plateau. In contrast, IL-23 agents showed a slower but progressive improvement that was maintained for up to 52 weeks. A similar trend was also seen for PASI100 (28 weeks $P = 0.032$; 40 weeks $P = 0.121$).

Conclusions The multi-failure patient is characterized by many comorbidities and longstanding inflammatory disease that frequently precedes the introduction of systemic biologic therapy. Further studies are needed to identify more specific criteria that could be applied as a guideline by clinicians.

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[‡]Shared senior authorship.

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Introduction

According to the latest global burden of disease (GBD) estimates, psoriasis is a very common chronic inflammatory disease in terms of incidence, prevalence, and years lived with disability (YLDs).[1] Over the past two decades, the advent of new biological therapies for moderate–severe psoriasis has led to astonishing results. At present, 12 biological agents over four generations are available that act by inhibiting different targets (IL-17, IL-23, IL-12, and TNF-α).

Over the years, there has been an increase in the number of patients receiving multiple biological drugs due to initial therapeutic failures or acquired resistance. This group of patients has been defined as "multi-failure,"[2,3] although no consensus has been reached on this definition since the latter has been attributed to patients who have failed an unspecified number of biologics. Based on these considerations and in the absence of a clear guideline definition, we believe that patients who have failed at least four biologics should fall into the "multi-failure" (or multi-resistant) category.[4]

There is little or conflicting data in the literature on the characteristics of this population or the predictive factors for failure with biological therapies. Furthermore, there are no guidelines indicating the most appropriate therapeutic strategies, in particular the parameters for switching among biological drugs of the same or different classes (known as therapeutic swap and switch, respectively).[2,3,5]

An initial experience of the Dermatology Clinic at the University of Turin did not identify any significant demographic or disease characteristics due to the small sample number of multi-failure patients ($n = 10$), but efficacy in maintaining response with modern IL-23 inhibitors was seen.[4]

To overcome the small sample, multicenter data collection involving 12 Italian dermatology secondary and tertiary centers was carried out.

Materials and methods

Population

Patients who failed four or more biologics for the treatment of psoriasis retrospectively collected in a shared database from 12 Italian dermatology secondary and tertiary centers, from April to July 2022, were included. All patients signed informed consent.

A control group, retrospectively collected from June 1, 2020, to June 1, 2022, of all the patients treated with IL-23 or IL-17 inhibitors at the Dermatology Clinic of the University of Turin Hospital with retrievable data from medical records of the hospital was used. The study was conducted in respect of the Declaration of Helsinki and approved by the Ethics Committee of Turin University Hospital (IT10771180014 SS-Dermo20).

Objectives

Demographic characteristics of patients with psoriasis who failed four or more biologics were compared to a cohort of general psoriatic patients treated with IL-23 or IL-17 inhibitors. We evaluated differences in sex, body mass index (BMI), smoking habits, mean age, mean age of onset of psoriasis, joint involvement, difficult-site involvement (i.e., scalp, palms and soles, genitals, fold, nails, cardiovascular comorbidities, and diabetes mellitus).

Follow-up was evaluated in months, and the cause of discontinuation of at least four failed biological drugs was noted. Clinical response and Psoriasis Area Severity Index (PASI) 90 and 100 were evaluated in the multi-failure cohort with the current biologic treatment. An indirect comparison of efficacy between IL-23 and IL-17 inhibitors in achieving PASI90 and 100 was made in the multi-failure cohort.

Statistical analysis

Statistical analysis of the observed cases was conducted without imputation of therapeutic discontinuation.

Data are presented as mean and standard deviation for continuous variables and as percentage and number for categorical variables. Statistical analysis was carried out using Student's *t*-test for parametric continuous variables, Mann–Whitney *U* test for nonparametric continuous variables, and chi-square test for comparison of categorical variables with significance at $P < 0.05$. Fisher's exact test for comparison of categorical variables was used as appropriate. Statistical analyses were performed using Stata/SE12.0 Statistical Software (STATA, College Station, TX, USA).

Results

Altogether, 97 multi-failure patients (40 women, 57 men) who had failed at least four biologics were evaluated. The

Table 1 Characteristics of the multi-failure cohort (n = 97) and control group (n = 1,057)

	Multifailure population		Control group		*P*-value
Sex (M) *N*/%	57	58.8	689	65.2	0.205
Mean age	55.2 (12.2 SD)		54.7 (15.6 SD)		0.705
Mean BMI	28.1 (5.6 SD)		27.1 (5.8 SD)		0.088
Mean age of onset of psoriasis	29.7 (12.5 SD)		35.1 (17.6 SD)		<0.001
Concurrent PsA *N*/%	44	45.4	284	26.9	<0.001
Difficult sites *N*/%	71	73.2	813	76.9	0.408
Smoking habits *N*/%	57	58.8	717	67.8	0.088
CV comorbidities *N*/%	53	54.6	421	39.8	0.005
Diabetes mellitus *N*/%	30	30.9	115	10.9	<0.001

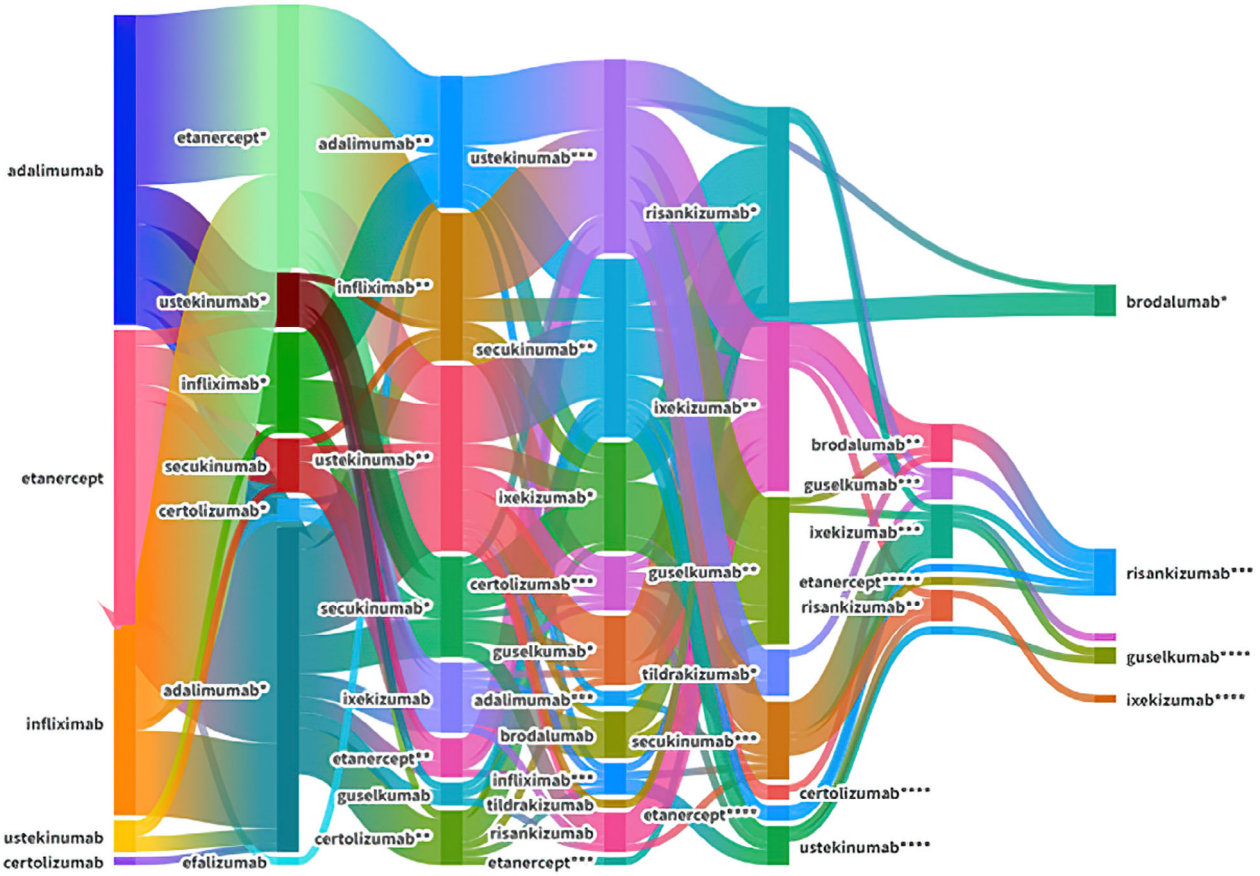

Figure 1 Sankey diagram as a visual representation of switch from line 1 to line 2 for each treatment in the multi-failure cohort. The graph is to be read from right to left, and the thickness of the line corresponds to the number of patients. Sequential "*" means sequential lines after the first for each treatment

mean age was 55.2 (SD: 12.2) years, BMI was 28.1 (SD: 5.6) kg/m^2, and the age of psoriasis onset was 29.7 (SD: 12.5) years. The control group was composed of 1,057 patients treated with IL-17 and IL-23 inhibitors. The mean age was 54.7 (SD: 15.6) years, BMI was 27.1 (SD: 5.8) kg/m^2, and the age of psoriasis onset was 35.1 (SD: 17.6) years. Other characteristics of the two groups are compared in Table 1.

No significant differences between multi-failure patients and the general nonmulti-failure population were observed for sex (58.8 vs. 65.2% male, P = 0.205), BMI (28.1 vs. 27.1 kg/m^2, P = 0.088), difficult site involvement (73.2 vs. 76.9%,

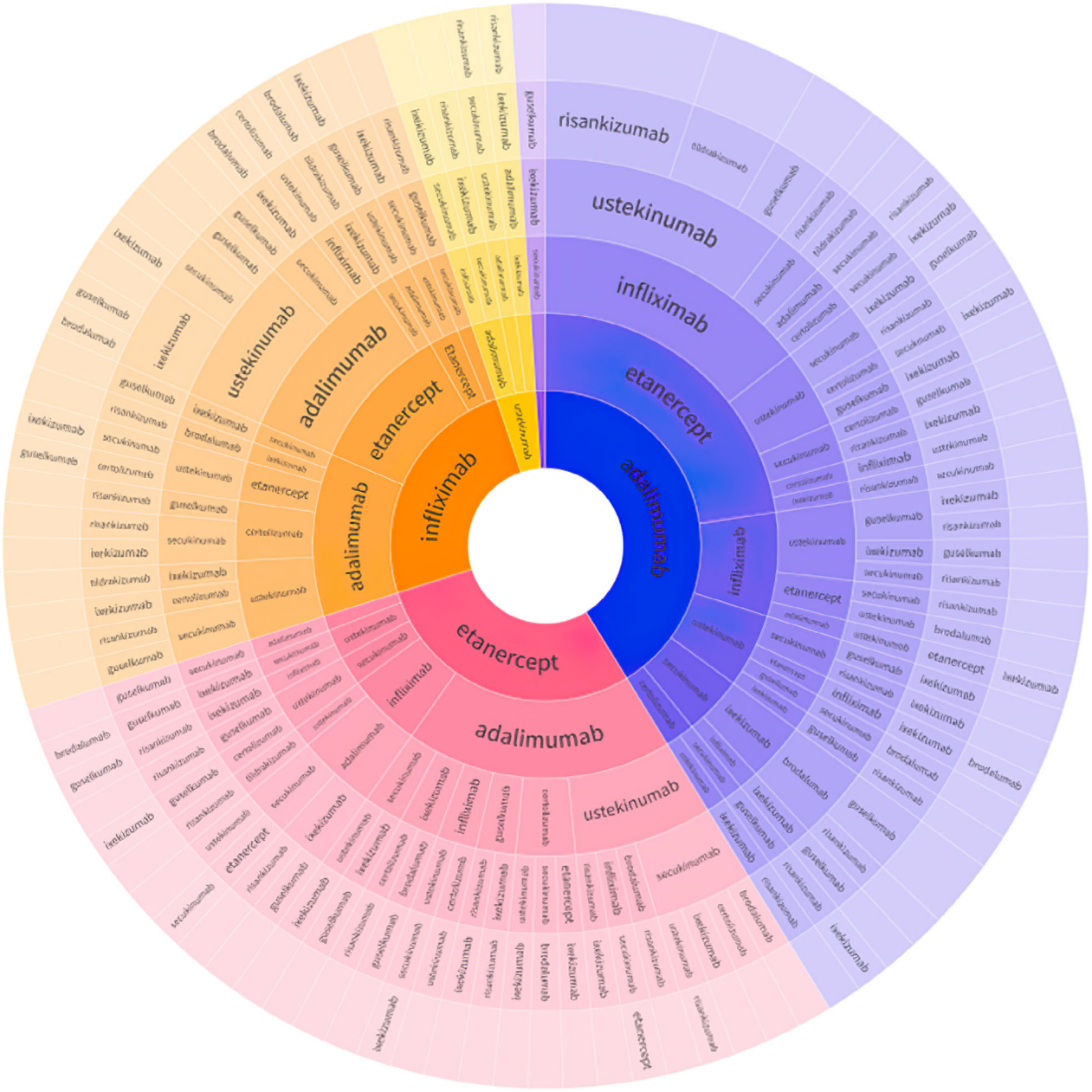

Figure 2 Sunburst diagram as a visual representation of switch from line one to line two for each treatment in the multi-failure cohort. The graph is to be read from the center to the margins meaning the first drug given to the last. From the outside to the inside, one can instead trace the therapeutic line of each patient. The more frequent sequential observed was adalimumab > etanercept > infliximab > ustekinumab > risankizumab with five patients (%) sharing the same flow

$P = 0.408$), or smoking habit (58.8 vs. 67.8%, $P = 0.088$), respectively.

However, a significant difference was found for the age of psoriasis onset (mean 29.7 vs. 35.1 years, $P < 0.001$), concurrent psoriatic arthritis (45.4 vs. 26.9%, $P < 0.001$), diabetes mellitus (30.9 vs. 10.9%, $P < 0.001$), and cardiovascular comorbidity (54.6 vs. 39.8%, $P = 0.005$).

The mean follow-up on biologics was 78.3 months (30.7 SD). For first-line treatment, the mean follow-up was 14.9 months (SD: 14.8), 15.5 months (SD: 14.6) for the second line, 16.6 months (SD: 15.2) for the third line, and 16.2 months (12.5 SD) for the fourth line. The numbers and flows of therapeutic switches are summarized in the Sankey diagram and sunburst in Figures 1 and 2.

Table 2 Mean follow-up in months for each line of treatment

	Infliximab	Adalimumab	Etanercept	Ustekinumab	Certolizumab	Secukinumab	Risankizumab	Brodalumab	Guselkumab	Ixekizumab	Efalizumab	Tildrakizumab
First biologic (text)	15	12	19	19.5	14							
Second biologic (text)	13	15.7	28	33	6.7	13.1					28	
Third biologic (text)	19	21	9	24.6	11	14			6.7	9.6		
Fourth biologic (text)	4.8	19.5	38	19.6	7	16	13	16.6	19.6	20		3
Fifth biologic (text)			14.5	41.3	7	12	10		12	16.2		3
Sixth biologic (text)			16		36	36	14	5	14	16		
Seventh biologic (text)							3	4	48			

First-line causes of discontinuation were 22.68% for primary inefficacy, 60.82% for secondary inefficacy, 11.34% for adverse events, and 5.16% for unknown causes. For the second line, these were 18.37, 70.41, 8.16, and 3.06%, respectively. For the third line, these were 16.33, 72.45, 8.16, and 3.06%, respectively. For the fourth line, these were 15.46, 75.27, 6.18, and 3.09%, respectively. In the fifth line (25 patients), four (16%) discontinued for primary inefficacy, 18 (72%) for secondary inefficacy, and three (12%) for adverse events. In the sixth line (10 patients), two (20%) discontinued for primary inefficacy and eight (80%) for secondary inefficacy. In the seventh line (three patients), two (66.7%) and one (33.3%) patients, discontinued for primary and secondary inefficacy, respectively.

Follow-up for each biologic showed the superiority of etanercept and ustekinumab. The mean follow-up on each biological line was, however, longer than 12 months (specifically between 14 and 18 months) confirming a trend toward secondary failure of therapies in the multi-failure population (Table 2).

Anti-TNF-α is the most widely used drugs in the first lines of treatment, after which the use of ustekinumab, secukinumab, and ixekizumab increased from the third line onwards. The other drugs are less represented.

Current biologic therapies in multi-failure patients and follow-up in months are summarized in Table 3. Risankizumab, ixekizumab, and guselkumab appear as the most used treatment from the fifth therapeutic line.

In multi-failure patients, current biologic therapy, whether anti-TNFα, IL-23, IL-17, or IL-12/IL-23 agents, showed an initial good response in PASI90 and 100 of 41.24 and 27.84%, respectively, at 16 weeks, with further improvement at 28 weeks. The response tended to decrease at 40 and 52 weeks (Figure 3).

As for the comparison between IL-17 and IL-23 inhibitors in the multi-failure patient group, the former showed a clear superiority over IL-23 inhibitors in achieving PASI90 at 28 ($P < 0.001$) and 40 weeks ($P = 0.007$), after which it reached a plateau. In contrast, IL-23 inhibitors showed slower but progressive improvement that was maintained for up to 52 weeks (Figure 3).

Table 3 Number of patients and follow-up in months (mean at the time of data collection) of the current biological drug

Biological drugs currently in use	No. of patients	Follow-up in months
Risankizumab	34	8.3
Ixekizumab	23	9.6
Guselkumab	21	8
Brodalumab	7	9.7
Tildrakizumab	5	9.6
Ustekinumab	4	8
Secukinumab	2	12
Certolizumab	1	9

A similar trend was also seen for PASI100 (28 weeks, $P = 0.032$; 40 weeks, $P = 0.121$) (Figure 3).

Discussion

The multi-failure population is progressively achieving attention in real life and in the literature. For this reason, there is still no consensus in terms of its definition (number of failures) and characteristics (comorbidities).[2–4] These patients often present an early age of onset, high number of joints involved, cardiovascular comorbidities, and type 2 diabetes mellitus. The early age at onset in part explains why these patients have tried multiple biological drugs over time, as already observed.[4] The longer follow-up for ustekinumab and etanercept is linked to the longer use in a time in which there were no other therapeutic choices. Furthermore, the availability of additional therapies in the last 5 years explains the shorter follow-up with IL-17 and IL-23 inhibitors since switches and therapeutic swaps are easier.

Anti-TNFα agents are the most used drugs in the first-line treatment in this multi-failure cohort, not only for historical reasons (they were the first biologic drug on the market) but also due to Italian legislation requiring anti-TNFα biosimilars to be used first in many regions. The common trend thereafter is to switch from anti-TNF-alfa to a newer class of biologics such as anti-IL-17 agents or IL-12/23 inhibitors and more recently to anti-IL-23 agents. Notwithstanding the switch from the latest generations of biologics to the previous ones has been reported in the literature with good results.[6–8] The switching trend shown in our study is in line with the work of Curmin et al.[9] which shows a pattern of progressive shift from anti-TNFα agents to ustekinumab, if the first line was started before 2016, and to IL-17 inhibitors if started after 2016, in accordance with the timing of approval and marketing of new therapeutic alternatives.

As shown in the trends for PASI90 and 100 of the last treatment line of our multi-failure cohort, an acceptable initial response with progressive loss of effectiveness as time progresses was observed. This is confirmed by the higher frequency of discontinuation due to secondary failure in all treatment lines in this population. The faster efficacy of IL-17 inhibitors compared to IL-23 inhibitors is in line with the results reported in registration and real-life studies in the literature. The progressive improvement in the response to anti-IL-23 is also in line with previous observations.[10,11] Although from a treat-to-target perspective, the therapeutic switch should be avoided, preferring effective clinical response with the first biological line used, the switch from anti-TNFα to IL-17 and IL-23 inhibitors did not limit the therapeutic response in trials and real-life studies.[12,13]

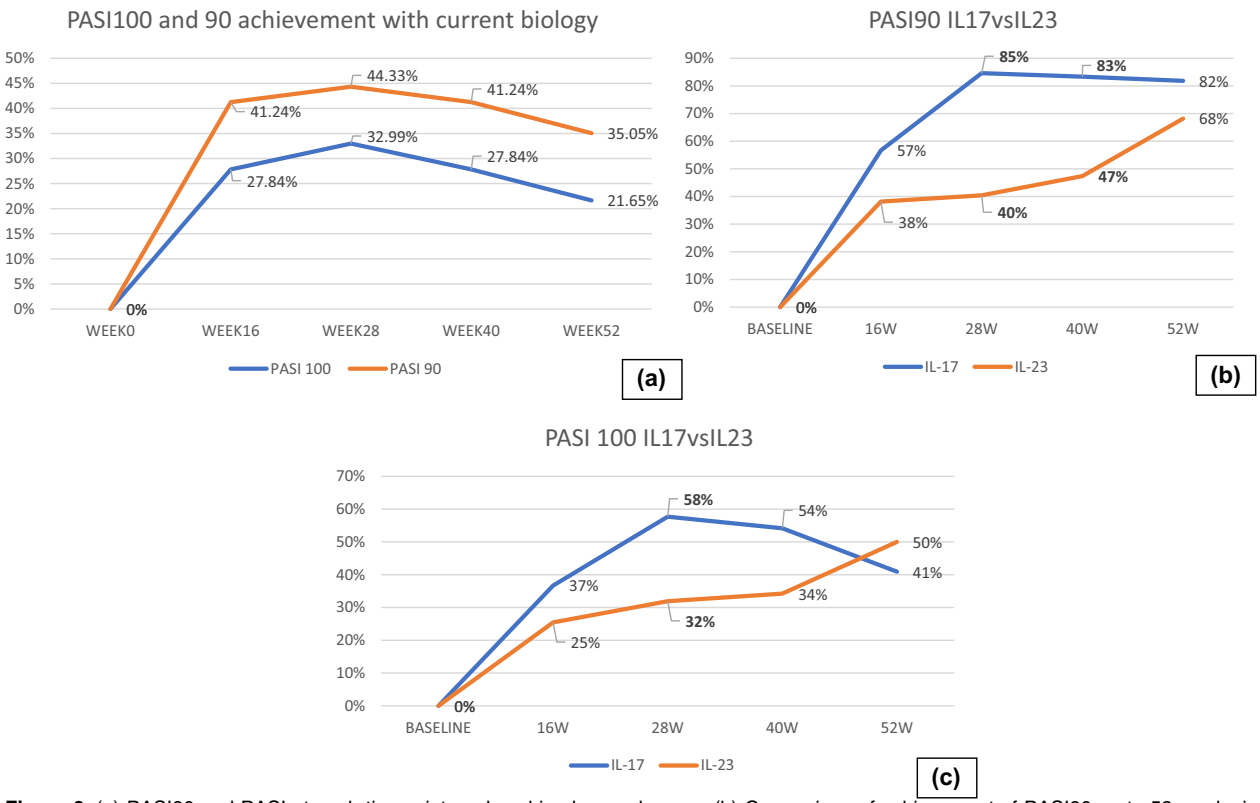

Figure 3 (a) PASI90 and PASI at each timepoint analyzed in observed cases. (b) Comparison of achievement of PASI90 up to 52 weeks in patients on IL-17 inhibitors vs IL-23 inhibitors. (c) Comparison of achievement of PASI100 up to 52 weeks in patients on IL-17 inhibitors vs. IL-23 inhibitors

If the interclass switch between IL-17 or IL-17RA inhibitors seems to show good efficacy, similar results do not seem to be achieved with the switch between TNFα inhibitors; this is due to the different causes of primary and secondary failure.[12] In the case of anti-TNFα, the production of autoantibodies against the biological inhibits possible response after the switch.[14] In the case of IL-17 inhibitors, the failure of a given molecule is likely not linked to neutralizing autoantibodies but to increased production of the same cytokine IL-17 and other cytokines involved (such as IL-23), thus leaving it open to treatment with different kinetics and dynamics of the same class or IL-23 inhibitors.[12,15–17]

In the context of a patient resistant to more than one biological line, a possible therapeutic option could be the return or addition to biological treatment of less selective treatments, such as the systemic drugs cyclosporine and methotrexate, whose known side effects, however, limit therapeutic manageability.[18] Treatment with TYK inhibitors appears promising, although no conclusive data are available on efficacy and safety profile.[19]

The main limitation of this study, apart from the small size of the cohort, consists of having only clinical and temporal data to characterize these patients. Pharmacogenomic studies will be increasingly needed to identify genetic or epigenetic markers that are capable of guiding the most appropriate therapeutic strategies.[20,21] It has been seen, for example, that the evaluation of HLA-C alleles, together with other genetic variants, could be useful in defining patients who are likely to benefit more from some biological drugs than others.[22,23]

Conclusions

The multi-failure patient in our cohort is a patient with more joint involvement, cardiovascular disease, diabetes, and long-standing psoriasis. IL-17 inhibitors show a faster response. However, multi-failure patients show a progressive loss of response after 28 weeks. The early introduction of appropriate biological therapy could ease the patient's inflammatory burden, prevent the development of psoriatic arthritis, and consequently decrease the risk of multiple failures, lowering the high cost of management of these patients.

Further studies are needed to identify the correct biomarkers to guide the most appropriate treatment choices. Future guidelines should also provide parameters for the best therapeutic switch and swap.

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