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ORIGINAL RESEARCH

"Full-naïve" patients: the impact of previous methotrexate, cyclosporine, and acitretin on first-line biologics response in the treatment of moderate-to-severe psoriasis – a monocentric retrospective study

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ABSTRACT

Background: The impact of traditional systemic drugs to treat psoriasis (ciclosporin, methotrexate, and acitretin) in a subsequent response to biologics has not been adequately addressed in the literature. In clinical practice, it is increasingly necessary to initiate, due to concomitant comorbidities, biologics in patients with psoriasis or psoriatic arthritis (PsA) who have not undergone prior treatment with systemics, i.e. full-naive.

Objectives and methods: This study analyzed the possible impact of non-biological systemic therapies on the effectiveness and drug survival of first-line biologic drug up to 12 months in bio-naive psoriatic and PsA patients consecutively enrolled from January 2017 to March 2021.

Results: Ninety-five patients with severe psoriasis (13.5%) were full-naive. Being full-naive and having or not having undergone methotrexate or cyclosporine therapy did not impact response to subsequent years of biologic therapy. Only acitretin promotes faster response to subsequent biologic drugs with 59.6% and 74.2% of patients achieving Psoriasis Area Severity Index (PASI) 90 at 16 and 28 week, respectively, vs. 50.5% and 65% ($p = 0.034$ and 0.026). In multivariate analysis, the advantage given by acitretin was lost.

Conclusion: Previous systemic therapy in bio-naive patients does not appear to result in a differential response to biologics during the first year of treatment.

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KEYWORDS
Psoriasis; methotrexate; cyclosporine; acitretin; PASI; drug survival

1. Introduction

Psoriasis is a chronic, inflammatory skin disease characterized by erythematous patches and scaling plaques [1]. Traditional systemic treatments such as methotrexate, cyclosporine, and acitretin are widely used for the moderate-to-severe forms of psoriasis as first-line treatment [2]. These treatments are affected by inherent limitations due to their frequent side effects, and relative or absolute contraindications in patients with comorbidities [2].

Biological therapies have demonstrated high efficacy and safety in the treatment of moderate-severe psoriasis over the past years. Interleukin (IL)-17 and IL-23 inhibitors allow patients not only allow to achieve clinical endpoints such as Psoriasis Area Severity Index (PASI) 90 and PASI100 but also have important benefits on the quality of life [3].

Modern biologic drugs including anti-TNF-alpha are superior in controlling the disease and reducing the risk of progression to psoriatic arthritis (PsA) compared with traditional systemic drugs and phototherapy; they are also associated with fewer adverse effects [4–7]. In many European countries, the prescription of a biologic drug is contingent on the failure of a previous traditional systemic therapy, treatment-related adverse events, or contraindication due to comorbidities [4].

While numerous real-life studies have shown a faster response in so-called bio-naive patients, i.e. those taking biologic treatment for the first time, the impact of traditional systemic therapies on the response to the next biologic has not been adequately evaluated [8–10]. Efficacy data on patients who initiated a biologic without a prior traditional systemic line of therapy are similarly scarce; these patients may be termed full-naïve or non-biological systemic (NBS)-naïve [10–13].

The present study analyzes the therapeutic responses between full-naive and bio-naïve patients who underwent previous systemic therapy (NBS-experienced) and between those who did or did not take a traditional systemic drug considering cyclosporine, acitretin, and methotrexate.

2. Patients and methods

2.1. Study population

This is a monocentric, retrospective clinical study including all consecutive psoriatic or PsA bio-naïve patients receiving at least 1 dose of IL-17 or IL-23 inhibitors, or anti-TNF-alpha biologics with retrievable medical records between January 2017 and March 2021 at the Dermatology Clinic of

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the Turin University Hospital, Italy. The last date of follow-up is 30 June 2023. Biologics were administered in the standard dosing regimen for patients with plaque psoriasis. Demographic and general characteristics at baseline were retrieved. The present study was conducted under the protocol named SS-DERMO-20 approved by the IRB of the institution (CE Interaziendale Territoriale di Torino). Written informed consent was obtained from patients. The authors are the owners of the dataset.

2.2. Objectives

The primary objectives of the study were: (i) to investigate possible differences between full-naïve patients and bio-naïve patients who had underwent previous systemic therapy (non-biological-systemic-experienced, NBS-experienced), in response to biologic therapies at baseline, and at 16, 28, and 52 weeks, using mean PASI, being super-responders (PASI 100 at 16 weeks maintained at 28 weeks), achievement of PASI 90, and PASI ≤ 3; (b) to investigate drug survival (DS) between the two populations; (c) investigate possible differences between methotrexate, acitretin, and cyclosporin naïve patients and experienced patients, in response to biologic therapies at baseline, and at 16, 28, and 52 weeks using PASI, being super-responders, achievement of PASI 90, and PASI ≤ 3.

Secondary objectives included: (i) evaluation of possible differences in response to biological therapy, as defined by mean PASI, being super-responders, achievement of PASI90, and PASI ≤ 3, according to the follow-up time on traditional systemic therapy as a group and for each systemic treatment (cyclosporin, acitretin, and methotrexate).

2.3. Statistical analysis

Continuous variables were described by mean ± standard deviation (SD) or median and range, based on the distribution of each variable. For categorical variables, absolute and relative frequencies were provided. Percentages were based on the number of non-missing values. Univariate linear regression followed by a mixed-effects logistic regression model was employed to investigate possible differences in the achievement of PASI90 and PASI ≤ 3 responses and univariate linear regression to describe possible differences in mean PASI at each time point. To analyze drug discontinuation, survival analysis techniques were employed. The event was defined as drug discontinuation for any reason while the time of observation was calculated as the date of the last follow-up – the date of baseline.

Statistical analysis was conducted with STATA 15.1 SE (StataCorp., 2017), all tests were two-sided, and the statistical significance was set to $\alpha = 0.05$. The absence of differences between groups was considered a null hypothesis for all inferential analyses. The analysis was conducted on observed populations.

3. Results

In total, 702 patients with psoriasis, of whom 479 males (68.2%), received at least one dose of a biologic drug for the first time, and as such were considered bio-naïve. Additionally, 95 (13.5%) patients had not previously experienced a traditional systemic drug for the treatment of psoriasis, as the decision to proceed directly with biologic medication was dictated by the severity of disease or the presence of comorbidities that relatively or absolutely contraindicated the initiation of disease modifying antirheumatic drugs (DMARDs). Cyclosporine had been used in 333 patients (47.4%), methotrexate in 443 (63.1%), and acitretin in 205 (29.2%). Moreover, 211 (30%) patients were treated with both methotrexate and cyclosporine, 144 (20.5%) both acitretin and methotrexate, 114 (16.2%) acitretin and cyclosporine, and 84 patients (11.9%) treated with three treatments. Mean follow-up for patients on systemic treatment was 24.4 (SD 28) months (median 15, 9–28 Q1-Q3). Data for each systemic agent is summarized in Table 1. In all, 387 patients took a biologic from the IL-17 inhibitor class (55%), 238 an IL-23 inhibitor (34%), and 77 an anti-TNF-alpha (11%). The first biologic drug prescribed in most cases was secukinumab (154 patients, 21.9%), followed by brodalumab (120/17.1%), risankizumab, ixekizumab, adalimumab, tildrakizumab, and guselkumab, in that order (Table 1). Lastly, 247 patients (35.2%) achieved complete response at week 16 and maintained it at 28 as such were considered super-responders. The remaining baseline characteristics are summarized in Table 1.

No significant differences were observed between full-naive and NBS-experienced populations in the achievement of response outcomes. Mean PASI decreased from 14.6 (SD 8.1) and 14.8 (SD) to 1.3 (2.9) and 0.9 (SD 2), respectively, in the two populations at 52 weeks, with almost 70% of patients achieving PASI90 at the last time points, and more than 85% PASI ≤ 3. In addition, 34.7% of the full-naive were super-responders vs. 35.3% in NBS-experienced patients ($p = 0.922$) (Table 2, Figure 1). No difference was found in DS in the two populations ($p = 0.297$) (Figure 2). Patients with prior cyclosporine use had lower mean PASI than those who did not at 16 and 28 weeks (16 weeks, 1.9 vs. 2.7, $p = 0.0012$; 28 weeks, 1.1 vs. 1.7, $p = 0.01$), but no significant difference was found in achieving relative PASI and being a super-responder (Table 2, Figure 1). Previous use of methotrexate did not seem to have any benefit in subsequent responses to biologic drugs (Table 2, Figure 1). Previous acitretin use appeared to be favorable in rapid response with 41% super-responders at first-line of biologic vs. 32.8% in the population who had not taken it prior to initiation of biologic therapy. Not surprisingly, attainment of PASI90 at 16 and 28 weeks was also greater in patients who took acitretin (16 weeks, 59.6% vs. 50.5%, $p = 0.034$; 728 weeks, 4.2% vs. 65%, $p = 0.026$) (Table 2, Figure 1). There was no impact of previous systemic therapies on DS (Figure 2).

At multivariate analysis, also considering the drug class used, mean body mass index (BMI), mean age of onset, mean baseline PASI, being full-naive or being exposed to methotrexate, cyclosporine, and acitretin before starting the first biologic drug did not appear to significantly impact

Table 1. Baseline demographics and treatment histories of the patients included in the study.

N° bio-naive patients	702
Mean Age (SD), median age (Q1-Q3)	53.9 (16.5). 55 (43–65)
Mean age of onset (SD), median age of onset (Q1-Q3)	34.5 (15.8), 35 (24–42)
Mean BMI (SD), median BMI (Q1-Q3)	26.6 (SD 5.3), 26 (17–60)
Sex, M N°/%	479/68.2%
Smoking habits N°/% (missing 7):	
• Smokers	274/43%
• Ex-Smokers	154/24.2%
• Non-smokers	209/32.8%
Difficult-site involvement N°/%	481/78%
PsA N°/%	173/24.6%
Full-naïve N°/%	95/13.5%
Previous cyclosporin N°/%	333/47.4%
Previous methotrexate N°/%	443/63.1%
Previous acitretin N°/%	205/29.2%
Mean FU on systemic therapies (SD), median (Q1-Q3), in months	24.4 (28), 15 (9–28)
Mean FU on cyclosporin, median (Q1-Q3), in months	10.5 (8.8), 9 (9–9)
Mean FU on methotrexate, median (Q1-Q3), in months	15.5 (22.4), 9 (9–9.5)
Mean FU on acitretin, median (Q1-Q3), in months	14.5 (21.3), 8 (7–8)
Current biologic class N°/%:	
• IL-17	387/55%
• IL-23	238/34%
• Anti-TNFalfa	77/11%
Current biologics N°/%:	
• Secukinumab	154/21.9%
• Brodalumab	120/17.1%
• Risankizumab	115/16.4%
• Ixekizumab	113/16.1%
• Adalimumab	77/11%
• Tildrakizumab	75/10.7%
• Guselkumab	48/6.8%
Super-responders N°/%	247/35.2%

PASI (Psoriasis Area Severity Index), SD (Standard Deviation), BMI (Body Mass Index), Q (quartile), FU (follow-up), PsA (psoriatic arthritis).

achieving PASI90 or PASI ≤ 3 at 16, 28, and 52 weeks, as well as being or not a super-responder. In contrast, as observed in Table 3, the use of an anti-IL-17 agent was advantageous in achieving PASI 90 and in being a super-responder (PASI90, OR 4.07, confidence interval (CI) 1.62–10.18, $p = 0.003$; super-responder, odds ratio (OR) 6.15, CI 2.04–18.49, $p = 0.001$). High mean BMI as well as late onset of disease negatively impacted response. High mean PASI at baseline and joint involvement were advantageous in achieving PASI 90 at 28 and 52 weeks; in contrast, high PASI was disadvantageous in achieving PASI ≤ 3 at 16 weeks (OR 0.96, CI 0.93–0.99, $p = 0.007$; Table 3).

Considering mean follow-up on previous traditional systemic drugs, there were no differences between those who achieved PASI 90, PASI ≤ 3, and those who did not, nor was being a super-responder (Table 4). Dichotomizing according to median follow-up while describing a tendency for best response in those who had a follow-up longer than 9 months for cyclosporine, and 8 months for acitretin, and the least response was seen in those who used methotrexate for more than 9 months, although the differences were no significant (Table 5).

At multivariate analysis considering mean follow-up under each traditional systemic drug, mean age of onset, mean BMI, joint involvement, and mean baseline PASI, only high weight was an unfavorable predictive factor in achieving PASI 90 and PASI ≤ uniformly at the various time points; high initial mean PASI was a predictive factor for achieving PASI 90 at 28 weeks (OR 1.16, CI 1.02–1.33, $p = 0.022$) and disadvantageous in achieving PASI ≤ 3 (OR 0.89, CI 0.79–0.99, $p = 0.037$; Table 3).

4. Discussion

In the population analyzed, previous use of traditional systemic drugs does not seem to provide any advantage or disadvantage in the subsequent response to biologic treatment. Regarding the response to first-line biologics, the inhibitor class used, BMI, age of onset, and mean initial PASI seem to have an impact that is greater than prior DMARDS treatment, even considering follow-up under the same systemic. The treatment retention rate also does not seem to be affected by prior use or nonuse of cyclosporine, methotrexate, and acitretin. On linear analysis, our data might suggest a slight disadvantage of prolonged therapy with methotrexate compared with cyclosporine and acitretin, but the difference was not statistically significant and could be related to the profile of the patient accessing therapy. Despite this, it must be remembered that a delay in achieving disease control can result in a progression in joint damage in the case of psoriatic arthritis or a pathology that is more resistant to subsequent treatments in the case of plaque psoriasis. This latter aspect was not analyzed in our cohort, since it was not an endpoint of our study.

Data in the literature on possible differences between full-naive and NBS-experienced patients are scarce and in general are reported on specific biologic drugs, with substantial differences in outcomes [10–13].

Table 2. Comparisons of mean PASI reduction (from baseline to 52 weeks), PASI 90, and PASI ≤ 3 achievement (from 16 weeks to 52 weeks), and super responder status between full-naive and NBS-experienced patients, and patients who have previously used methotrexate, acitretin, cyclosporine, or not.

	Full-naive	Previous systemic	*p*-value	No-cyclosporin	Previous cyclosporin	p-value	No-Methotrexate	Previous methotrexate	*p*-value	No-acitretin	Previous Acitretin	p-value
Baseline PASI, mean (SD)	14.6 (8.1)	14.8 (6.4)	0.754	14.7 (6.9)	14.9 (6.3)	0.657	15.4 (7.2)	14.5 (6.3)	0.071	14.8 (6.8)	14.8 (6.2)	0.988
PASI 16W, mean (SD)	2.7 (5.3)	2.3 (3.8)	0.422	2.7 (4.6)	1.9 (3.3)	**0.012**	2.1 (3.9)	2.4 (4.1)	0.348	2.5 (4.3)	1.8 (3.1)	**0.037**
PASI 90 16W N°/%	46/51.1	304/53.5	0.67	170/49.6	180/57.1	0.052	139/57	211/51	0.136	235/50.5	115/59.6	**0.034**
PASI ≤3 16W N°/%	60/66.7	389/68.5	0.731	224/65.3	225/71.4	0.092	172/70.5	277/66.9	0.34	308/66.2	141/73.1	0.087
PASI 28W, mean (SD)	1.9 (5)	1.4 (2.6)	0.288	1.7 (3.7)	1.1 (2.1)	**0.01**	1.5 (3.6)	1.4 (2.7)	0.547	1.6 (3.2)	1.2 (2.7)	0.154
PASI 90 28W N°/%	54/63.5	361/68.4	0.376	206/64.8	209/70.8	0.108	156/67.8	259/67.6	0.959	280/65	135/74.2	**0.026**
PASI ≤3 28W N°/%	71/83.5	434/82.2	0.765	259/81.4	246/83.4	0.528	190/82.6	315/82.2	0.909	352/81.7	153/84	0.477
PASI 52W, mean (SD)	1.3 (2.9)	0.9 (2)	0.271	1.1 (2.5)	0.9 (1.8)	0.319	1.1 (2.5)	0.9 (2)	0.356	1.1 (2.5)	0.6 (1.1)	**0.001**
PASI 90 52W N°/%	55/69.6	340/74.2	0.39	200/71.9	195/75.3	0.38	149/74.9	246/72.8	0.595	269/71.4	126/78.8	0.075
PASI ≤3 52W N°/%	68/86.1	407/89.1	0.441	246/88.8	229/88.4	0.887	172/86.4	303/89.9	0.22	332/88.1	143/89.9	0.533
Super-responders N°/%	33/34.7	214/35.3	0.922	118/32	129/38.7	0.061	96/37	151/34.1	0.425	163/32.8	84/41	**0.039**

PASI (Psoriasis Area Severity Index), NBS (non-biological systemic), W (weeks).

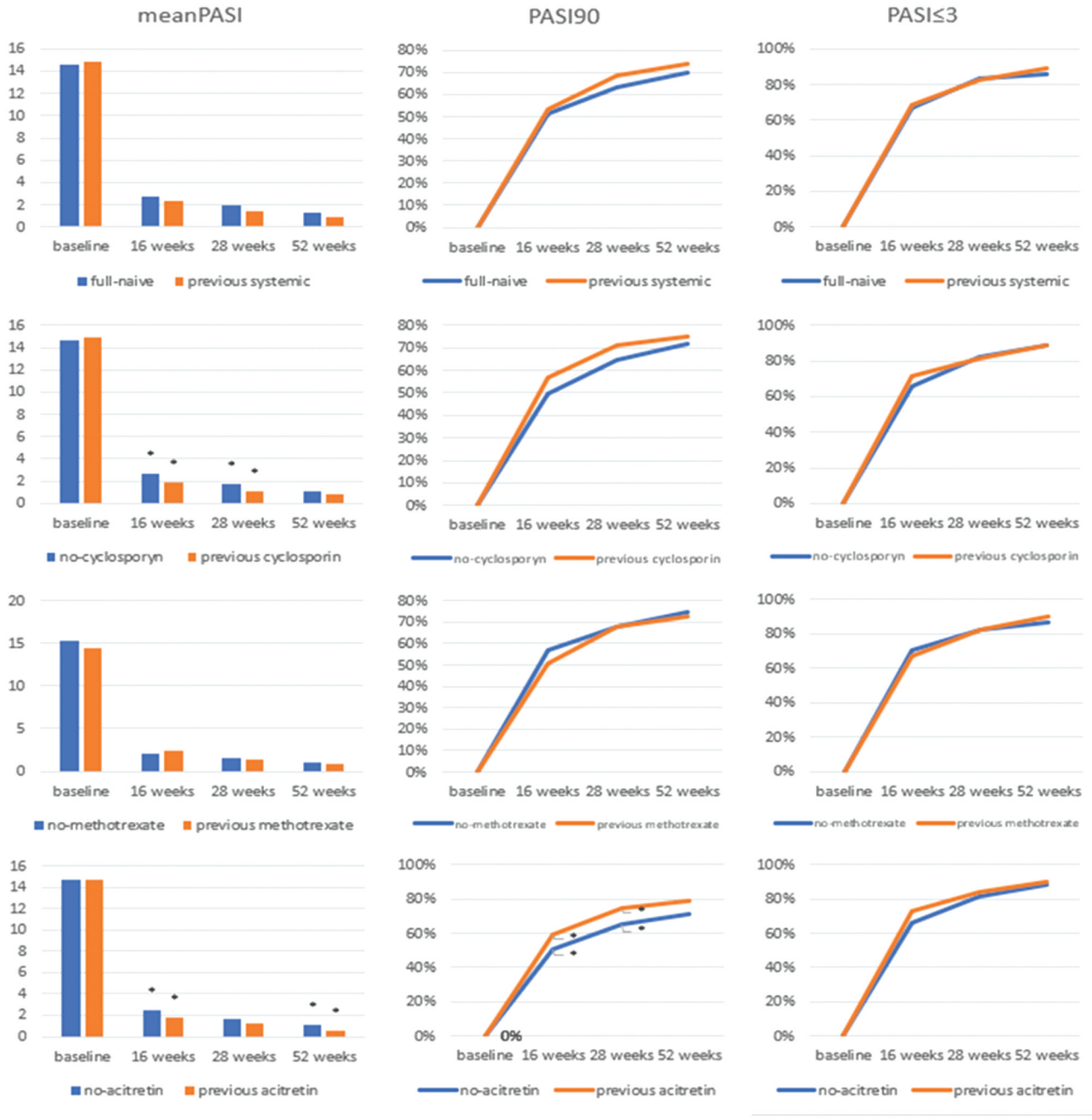

Figure 1. The figure shows comparisons in mean PASI reduction (from baseline to 52 weeks) and PASI 90, and PASI ≤ 3 achievement (from 16 weeks to 52 weeks), between full-naive and NBS-experienced patients, patients who have previously done methotrexate, acitretin, cyclosporine or not.

*significant different value (p-value <0.05).

PASI (Psoriasis Area Severity Index), NBS (non-biological systemic).

In the post hoc analysis by Hampton et al., secukinumab appeared to be effective at 20 weeks regardless of prior systemic nonbiologic treatment, confirming a benefit for bio-naïve patients [10]. In general, prior treatment with NBS had little effect on the efficacy of secukinumab; overall, the response rates for IGA, PASI, and DLQI responses on secukinumab vs. placebo were similar in full-naïve patients and NBS-experienced patients. The authors suggested that the NBS-experienced patient for a single drug might have an advantage over those on multiple traditional lines of therapy [10].

Also, for secukinumab, the PROSE study reported a nonsignificant advantage in improving patient-reported-outcomes and family-reported-outcomes in NBS-naive/full-naive patients compared to NBS-experienced and even more so compared to bio-experienced [11].

Formerly, in another post hoc analysis, Papp et al. observed that failure of a previous systemic drug (methotrexate and

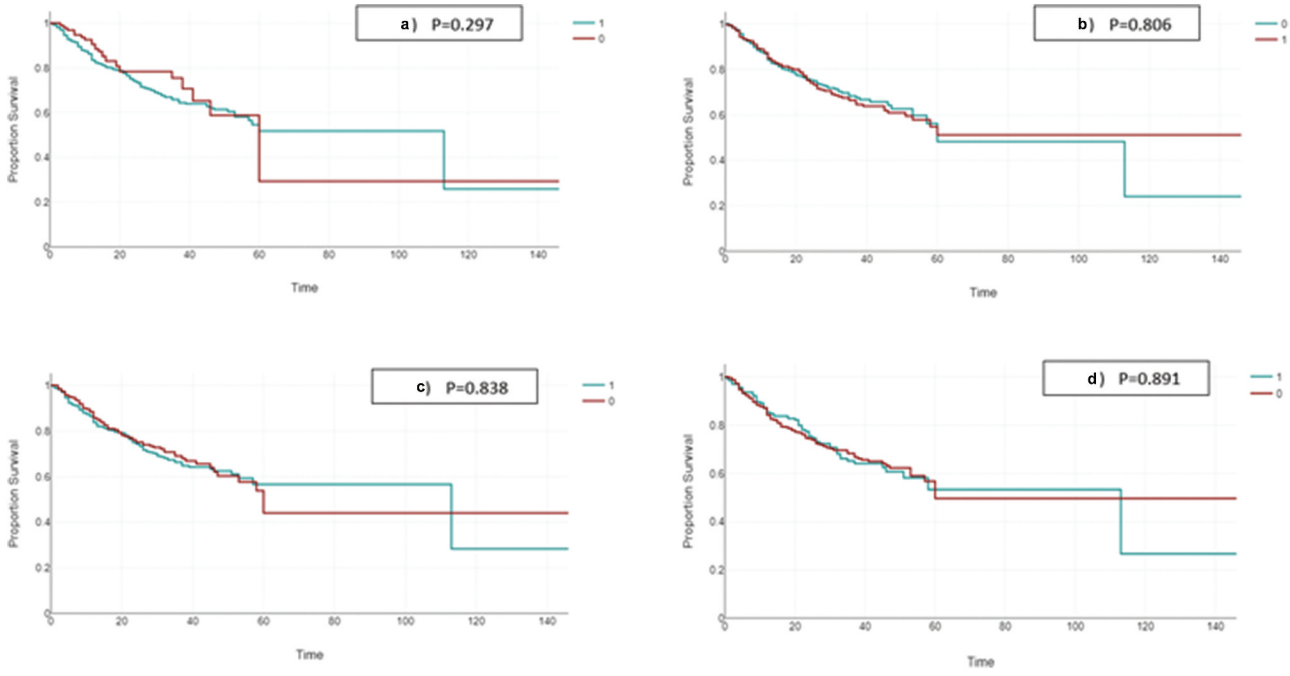

Figure 2. The figure shows comparisons in drug survival between full-naive and NBS-experienced patients (a) Patients who have previously done methotrexate (c) Acitretin (d), (b) or not. On the x-axis, time is expressed in months.

NBS (non-biological systemic).

cyclosporine) did not impact response to adalimumab compared to the general population [12].

The PSUMMIT1 and PSUMMIT2 studies reported no significant differences between NBS-naive and NBS-experienced patients, or between methotrexate naive and experienced, on treatment with ustekinumab, while noting a slight disadvantage in patients with previous systemic methotrexate treatment [13]. It was concluded that there may be a disadvantage of a first-line biologic with an anti-TNFalpha in response to a IL-12/23 inhibitor [14].

The scarce evidence available to date appears to be largely in line with our results, with no relevant role of an NBS drug in the response to subsequent biologics, suggesting a possible slight disadvantage, even if not statistically significant, of prolonged methotrexate therapy.

In general, the role of traditional systemic drugs appears to be increasingly limited in the treatment of psoriasis, gradually assuming an ancillary role to biologic therapy as a result of legislation in the prescription of modern biological therapies, or used in first-line and maintained in the mild and moderate forms of psoriasis and in psoriatic arthritis in which the poor effect of cyclosporine and methotrexate on the axial component further limits their use in favor of an anti-TNF-alpha [15–17]. It should also be highlighted that, compared to biologic drugs, traditional systemic agents are associated with a high rate of adverse events.

The role of traditional systemic agents, and especially methotrexate, in combination therapy with biological drugs to achieve better outcomes or increase DS is still debated [18]. The role of methotrexate together with adalimumab appears to confer a unique advantage in rheumatoid arthritis; as for PsA, the data are contradictory [19,20]. The same combination according to van Huizen et al. does not appear to confer any substantial benefit in psoriasis but does increase adverse effects [20]. In contrast, some authors have suggested that there is a beneficial effect of methotrexate in combination with etanercept [21]. Methotrexate does not appear to increase the efficacy of ixekizumab in either PsA or psoriasis [22].

Some studies have compared the efficacy of specific biological drugs or small molecules in NBS-naive patients. In a post hoc analysis, Kristensen et al. observed that ixekizumab was superior to adalimumab in PsA regardless of the severity of skin involvement [23]. The PRIME trial demonstrated the superiority of secukinumab over fumaric acid esters in the treatment of psoriasis in NBS-naïve patients, with differences of more than 40% in the achievement of efficacy outcomes and patient-reported outcomes with fewer side effects [24].

The limitations of our study are its retrospective design, analysis of observed cases only, and all conditions inherent to the real-world nature of the study. The population of full-naive /NBS-naive patients is numerically small (due to Italian regulations on drug prescription) compared to that of NBS-experienced patients, which may have negatively affected the statistical analysis. Another limitation of the study is the lack of detailed analysis of the individual biological drugs initiated, although their classes were included in multivariate analysis.

Table 3. (a) Multivariate analysis of achievement of PASI 90, PASI ≤ 3, and super responder status, with respect to class of biologic drug in use, mean age of onset, mean BMI, PsA status, mean baseline PASI, NBS status, and previous use of methotrexate, cyclosporine, or acitretin. (b) Multivariate analysis of achievement of PASI 90, PASI ≤ 3 (at 16, 28, and 52 weeks), and super responder status, with respect to mean age of onset, mean BMI, PsA status, mean baseline PASI, and follow-up on methotrexate, cyclosporine, or acitretin.

	Super responders			PASI 90 16 W			PASI 90 28 W			PASI 90 52 W			PASI ≤3 16 W			PASI ≤3 28 W			PASI ≤3 52 W		
	p	Odds ratio	95% conf. interval	*P*	Odds ratio	95% conf. interval	*p*	Odds ratio	95% conf. interval	*p*	Odds ratio	95% conf. interval	*p*	Odds ratio	95% conf. interval	*p*	Odds ratio	95% conf. interval	*p*	Odds ratio	95% conf. interval
IL-23 inhibitors	0.155	2.28	0.73–7.08	0.072	2.39	0.93–6.18	0.111	2.08	0.85–5.09	0.102	2.47	0.83–7.33	0.842	1.09	0.45–2.63	0.095	2.39	0.86–6.62	**0.037**	3.97	1.08–14.55
IL-17 inhibitors	**0.001**	6.15	2.04–18.49	**0.003**	4.07	1.62–10.18	0.07	2.2	0.94–5.14	0.051	2.77	0.99–7.71	0.093	2.06	0.89–4.81	0.131	2.006	0.81–5.27	0.205	2.07	0.67–6.35
Mean BMI	**<0.001**	0.93	0.9–0.97	**0.016**	0.96	0.93–0.99	**0.039**	0.96	0.93–1	**0.001**	0.93	0.89–0.97	0.408	0.98	0.95–1.02	0.739	0.99	0.95–1.04	0.402	0.98	0.92–1.03
Mean age of onset	0.078	0.99	0.98–1	**0.033**	0.99	0.98–1	**0.041**	0.99	0.98–1	0.51	1	0.99–1.02	<0.**001**	0.97	0.96–0.98	**0.004**	0.98	0.96–0.99	0.084	1.02	1–1.04
PSA	0.741	1.07	0.71–1.63	0.226	1.29	0.85–1.94	**0.016**	1.74	1.11–2.72	**0.003**	2.16	1.31–3.57	0.31	1.26	0.81–1.95	**0.004**	2.16	1.28–3.63	0.109	1.68	0.89–3.16
Previous systemic therapies	0.299	1.43	0.73–2.82	0.502	1.26	0.64–2.45	0.985	1.01	0.48–2.12	0.341	0.65	0.27–1.57	0.47	1.31	0.63–2.72	0.616	1.25	0.52–3.04	0.714	0.82	0.28–2.37
Previous cyclosporin	0.379	0.84	0.57–1.24	0.223	0.79	0.54–1.16	0.384	0.82	0.53–1.28	0.725	1.1	0.65–1.85	0.349	0.82	0.54–1.24	0.48	0.82	0.48–1.41	0.764	0.9	0.45–1.79
Previous methotrexate	0.673	0.91	0.59–1.4	0.992	1	0.65–1.54	0.196	0.72	0.44–1.19	0.985	1.01	0.55–1.82	0.907	1.03	0.64–1.66	0.072	0.58	0.32–1.05	0.174	0.61	0.3–1.25
Previous acitretin	0.052	0.68	0.46–1	0.079	0.7	0.48–1.04	0.116	0.69	0.44–1.09	0.703	0.9	0.53–1.53	0.073	0.67	0.44–1.04	0.189	0.69	0.39–1.2	0.992	1	0.51–1.98
Mean Baseline PASI	0.373	0.99	0.96–1.02	0.144	1.02	0.99–1.05	**0.004**	1.05	1.02–1.09	**<0.001**	1.09	1.05–1.14	0.**007**	0.96	0.93–0.99	0.198	0.98	0.94–1.01	0.537	1.02	0.97–1.07
BMI	0.065	0.9	0.8–1.01	0.15	0.93	0.84–1.03	0.**042**	0.87	0.77–1	**0.002**	0.78	0.67–0.91	0.345	0.95	0.85–1.06	0.53	0.96	0.83–1.1	**0.028**	0.82	0.69–0.98
Mean Age of onset	0.841	1	0.97–1.04	0.886	1	0.96–1.03	0.95	1	0.96–1.04	0.533	1.02	0.97–1.07	0.794	1.01	0.96–1.05	0.879	1	0.96–1.05	0.06	1.1	1–1.22
PSA	0.819	0.87	0.27–2.8	0.617	0.74	0.22–2.45	0.445	1.74	0.42–7.18	0.272	0.36	0.06–2.24	0.084	0.22	0.04–1.23	0.653	1.48	0.27–8.04	0.892	0.82	0.04–14.87
Months under cyclosporin	0.373	1.04	0.96–1.13	0.545	1.03	0.93–1.14	0.929	1	0.91–1.11	0.88	0.99	0.91–1.08	0.571	1.04	0.91–1.19	0.765	1.02	0.9–1.16	0.088	1.42	0.95–2.12
Months under acitretin	0.33	1.01	0.99–1.03	0.224	1.02	0.99–1.05	0.608	1.01	0.98–1.04	0.485	0.99	0.96–1.02	0.699	1.01	0.98–1.04	0.661	0.99	0.97–1.02	0.181	0.97	0.92–1.02
Months under methotrexate	0.666	1.01	0.97–1.05	0.676	0.99	0.95–1.03	0.715	0.99	0.93–1.05	0.058	0.94	0.89–1	0.782	1.01	0.96–1.05	0.71	0.99	0.93–1.05	0.063	0.92	0.85–1
Mean Baseline PASI	0.648	1.02	0.94–1.11	0.725	1.02	0.93–1.11	**0.022**	1.16	1.02–1.33	0.053	1.14	1–1.31	**0.037**	0.89	0.79–0.99	.674	1.03	0.9–1.17	0.706	1.04	0.85–1.28

PASI (Psoriasis Area Severity Index), BMI (Body Mass Index), PsA (psoriatic arthritis), NBS (non-biologic systemic), W (weeks).

Table 4. Mean follow-up on systemic treatment according to achievement of PASI 90, and PAS ≤ 3 at 16, 28, and 52 weeks. Mean follow-up on systemic treatment according to super responder status.

	Mean FU under previous systemic (Months)			Mean FU under previous cyclosporin (Months)			Mean FU under previous methotrexate (MONTHS)			Mean FU under previous Acitretin (Months)		
	yes	no	*p*-value	yes	no	*p*-value	yes	no	*p*-value	yes	no	*p*-value
PASI 90 16W (Mean, SD)	24.1 (27.6)	24.6 (28.7)	0.841	9.9 (6.2)	11.3 (11.4)	0.2	14.2 (19.9)	16.2 (24.6)	0.361	16.1 (24.4)	12.8 (17.5)	0.313
PASI ≤3 16W (Mean, SD)	23.9 (26.2)	25.4 (31.8)	0.559	10.2 (6.6)	11.5 (12.8)	0.24	14.3 (19.5)	17.1 (27.2)	0.227	15.6 (23.2)	12.5 (17.8)	0.394
PASI 90 28W (Mean, SD)	24.3 (27.1)	25.5 (30.7)	0.65	9.9 (6.4)	11.3 (12.7)	0.305	14 (18.3)	17.3 (27.4)	0.172	16 (24.4)	13.3 (15.6)	0.474
PASI ≤3 28W (Mean, SD)	23.9 (26.2)	25.4 (31.8)	0.2	10 (6.7)	11.8 (15.4)	0.408	14 (17.8)	20.1 (34)	0.153	15.8 (23.6)	12.8 (15.2)	0.391
PASI 90 52W (Mean, SD)	23.6 (27.3)	25.3 (27.1)	0.578	10.3 (9.1)	10.6 (9.1)	0.794	13.7 (18.4)	16 (23.6)	0.333	14.3 (22)	14.2 (21.1)	0.979
PASI ≤3 52W (Mean, SD)	23.8 (27)	27.2 (28.8)	0.408	10.5 (9.2)	9.5 (8.4)	0.572	14 (19.9)	17.8 (20.4)	0.285	14.2 (21.3)	15.8 (27.1)	0.783
Super-responders (Mean, SD)	23.7 (27.2)	24 (26.7)	0.923	10 (6.7)	11.4 (11)	0.197	14 (18.9)	14.7 (20.3)	0.723	17.6 (26.9)	12.3 (16.1)	0.109

PASI (Psoriasis Area Severity Index), SD (Standard Deviation), W (weeks).

Table 5. Dichotomic comparison according to median follow-up on systemic treatment according to achievement of PASI 90 and PAS ≤ 3 at 16, 28, and 52 weeks. Median follow-up on systemic treatment according to super responder status.

	FU under systemic therapies ≥15 months	FU under systemic therapies <15 months	*p*-value	FU under cyclosporin ≥9 months	FU under cyclosporin <9 months	*p*-value	FU under methotrexate ≥9 months	FU under methotrexate <9 months	*p*-value	FU under acitretin ≥8 months	FU under acitretin <8 months	*p*-value
PASI 90 16W N°/%	149/55	149/51.9	0.468	144/57.8	36/54.5	0.632	161/50.3	50/53.2	0.624	89/61.8	26/53.1	0.281
PASI ≤3 16W N°/%	192/70.8	189/65.9	0.205	180/72.3	45/68.2	0.511	213/66.6	64/68.1	0.783	110/76.4	31/63.3	0.074
PASI 90 28W N°/%	171/68.7	183/67.8	0.826	167/73.2	42/62.7	0.095	198/66.2	61/72.6	0.268	102/73.9	33/75	0.886
PASI ≤3 28W N°/%	210/84.3	217/80.4	0.237	194/85.1	52/77.6	0.148	246/82.3	69/82.1	0.978	117/84.8	36/81.8	0.64
PASI 90 52W N°/%	168/74.7	166/73.8	0.829	153/75.7	42/62.7	0.75	187/71.6	59/76.6	0.389	95/78.5	31/79.5	0.897
PASI ≤3 52W N°/%	198/88	203/90.6	0.368	180/89.1	49/86	0.512	234/89.7	69/90.8	0.773	109/90.1	34/89.5	0.913
Super-responders N°/%	119/51.7	133/44.9	0.121	114/79.2	119/77.3	0.692	113/74.8	227/77.7	0.493	74/78.7	58/66.7	0.068

PASI (Psoriasis Area Severity Index), W (weeks).

5. Conclusions

Biologic agents for the treatment of psoriasis and psoriatic arthritis appear to be effective regardless of prior use of conventional systemic drugs.

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Declaration of interest

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Ethics statement

The present study was conducted under the protocol named SS-DERMO-20 approved by the IRB of the institution (CE Interaziendale Territoriale di Torino). Written informed consent was obtained from patients. The authors are the owners of the dataset.

Author contributions

L. Mastorino and S. Ribero were involved in the conception, study design, execution, acquisition of data, analysis, interpretation, reviewing, and drafting the work. O Crespi, C Sarda, E Bongiovanni, and U Santaniello were involved execution, acquisition of data, analysis, interpretation, and reviewing. P Dapavo was involved in the

conception, execution, acquisition of data, analysis, interpretation, and reviewing of the study. P Quaglino and G Gallo were involved in the analysis, interpretation, and reviewing of the study. All authors read and approved the final manuscript.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author, L Mastorino. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

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