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Retention rate of tumor necrosis factor inhibitors, anti-interleukin 17, and anti-interleukin 12/23 drugs in a single-center cohort of psoriatic arthritis patients

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SUMMARY

The objective of this study was to evaluate biological disease-modifying anti-rheumatic drugs (bDMARDs) survival in several therapy courses of patients affected by psoriatic arthritis (PsA) and to compare tumor necrosis factor inhibitors (TNFi) and non-TNFi retention rates.

A total of 241 bDMARD therapy courses (155 TNFi drugs, 65 anti-interleukin (IL)-17 drugs, and 21 anti-IL12/23) were analyzed. Bivariate analyses were performed to assess the presence of demographic and clinical features, as well as comorbidities, associated with bDMARD discontinuation in TNFi and non-TNFi groups.

In the bivariate analyses of TNFi and non-TNFi groups, we found a lower age at the start of TNFi therapy in the former group [46 years, interquartile range (IQR) 45-54 *vs* 50.5 years, IQR 42-61; p=0.004] as well as a lower proportion of patients with skin psoriasis (65.8% *vs* 88.4%; p<0.001). Survival analysis showed no significant differences between TNFi and non-TNFi groups. Cox regression found fibromyalgia as a predictor of drug failure [hazard ratio (HR) 3.40, confidence interval (CI) 1.92-6.03; p<0.001] and first-line bDMARDs as a protective factor (HR 0.46, CI 0.25-0.88; p=0.019). Lastly, among TNFi courses, fibromyalgia was associated with drug suspension (HR 6.52, CI 3.16-13.46; p<0.001), while only a trend of significance for skin psoriasis as a risk factor for drug failure was shown (HR 2.38, CI 1.00-5.66, p=0.05).

This study provides information about clinical and demographic factors associated with retention rates of bDMARDs from a real-life, single-center cohort of PsA patients.

***Key words**: Psoriatic arthritis, retention rate, TNF inhibitors, anti-IL17, anti-IL12/23.*

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INTRODUCTION

Psoriatic arthritis (PsA) is a chronic, potentially disabling disease affecting 0.1-0.2% of the general population (1). PsA can manifest with variable articular distribution as first described by Moll and Wright (2), with polyarticular or oligoarticular patterns more frequent than axial, distal, or mutilans forms (3). Joint involvement represents a domain of a wider psoriatic disease spectrum, with skin psoriasis (PsO) as the predominant feature (4). The relationship between skin and articular diseases is biunivocal and asymmetric, as up to 30% of PsO patients eventually develop PsA (5), while only 1-2% of PsA patients do not present skin involvement (6). PsO usually precedes the onset of PsA, as articular manifestations appear concomitantly to or precedes skin disease in 10% and 5% of cases, respectively (7).

During the last decades, it has been proposed to widen the horizons of psoriatic patients under a broader clinical concept of psoriatic disease (8), encompassing both articular and extra-articular features, such as inflammatory bowel disease and uveitis as well as cardiovascular, metabolic, and psychological comorbidities, which are highly prevalent in both PsO and PsA (9).

The most recent international recommenda-

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tions on PsA management highlight the need to personalize therapeutic strategies based on articular and extra-articular manifestations, such as axial or peripheral involvement and severity of skin psoriasis (10). Lacking specific recommendations for PsA comorbidities treatment, management decisions are often driven by drug safety profiles (11, 12) and experience gathered from other rheumatologic diseases, such as rheumatoid arthritis (13).

In the last years, new drugs have been approved for PsA management, expanding the possibility of personalizing treatment choices for PsA patients. Hence, real-life data are needed to identify the drivers of choice among different mechanisms of action (MoA) and their weight on drug survival. The aim of our study is to evaluate the retention rate of biological disease-modifying anti-rheumatic drugs (bDMARDs) with different MoA [tumor necrosis factor inhibitors (TNFi) *vs* non-TNFi] and factors associated with drug suspension in a single-center cohort of PsA patients. Furthermore, we aim to investigate whether demographic and clinical factors (among which comorbidities) could drive the choice of bDMARDs between TNFi and non-TNFi.

MATERIALS AND METHODS

Patient population

A retrospective cohort study representing a single-center real-world clinical setting was performed. We collected 241 therapeutic courses of PsA adult patients routinely followed up in our outpatient clinic at Gaetano Pini Hospital, Milan, Italy. Patients who started treatment with TNFi drugs, interleukin (IL)-17 blockers, or IL-12/IL-23 blockers from the 1st of May 2016 were retrospectively selected; data were collected until the 28th of June 2021. Demographic and clinical data were extracted from a longitudinal observational registry (Ethics Committee Approval: 138_1999).

Patients' demographic data included gender and age at the start of bDMARD therapy. Clinical data on PsA patients at the beginning of each bDMARD course, such as predominantly axial or peripheral PsA involvement (PsA subset), and disease duration, were collected. Axial PsA was defined by inflammatory back pain associated with nuclear magnetic resonance finding of sacroiliitis and/or spondylitis according to Outcome Measures in Rheumatoid Arthritis Clinical Trials definition. The presence of comorbidities (namely cardiac disease, arterial hypertension, diabetes, dyslipidemia, osteoporosis, lung involvement, fibromyalgia, and skin psoriasis) was extracted by medical reports at the baseline of each therapy course. Lastly, information about bDMARD therapy duration, time of drug discontinuation, presence of previous bDMARD therapies, and concomitant conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and/or corticosteroid therapies was gathered.

Statistical analysis

Descriptive results are presented as median values or as numbers and percentages, as appropriate. Data normality was tested with both Shapiro-Wilk and Kolmogorov-Smirnov tests. Differences in the variable distribution were analyzed with the Mann-Whitney U test and chi-squared test or Fisher test for continuous and categorical variables, respectively. Multivariate analysis of discontinuation predictors was performed using the Cox proportional-hazards model. Results are presented as hazard ratios (HR) with 95% confidence intervals (CI). Lastly, we conducted an exploratory survival analysis (Kaplan-Meier curve) for the groups. A $p \leq 0.05$ was considered statistically significant. Statistical analysis was performed using Stata Statistical Software: Release 17.0 (StataCorp LLC, College Station, TX, USA).

RESULTS

Patients' characteristics at baseline

A total of 241 bDMARD therapeutic courses in PsA patients were analyzed in this study, among which 155 courses of TNFi, 65 courses of anti-IL-17, and 21 courses of anti-IL12/23 therapies (86 courses of non-TNFi). Patients' features for each group are reported in Table I.

Table I - Patients' characteristics for single mechanisms of action.

	TNF inhibitors (n=155)	Anti-IL-17 (n=65)	Anti-IL-12/23 (n=21)
Male	65 (41.9%)	30 (46.2%)	6 (28.6%)
Age (years)	46 (35-54)	50 (42-60)	51 (44-65)
Disease duration (months)	76 (34-122)	73 (37-109)	83 (63-108)
Peripheral predominant subset	124 (80%)	48 (73.8%)	19 (90.5%)
DAPSA	16.21 (8.73-24.08)	14.85 (8.1-20.49)	13.44 (9.48-21.9)
Psoriasis	102 (65.8%)	58 (89.2%)	18 (85.7%)
Uveitis	5 (3.2%)	2 (3.1%)	1 (4.8%)
IBD	3 (1.9%)	1 (1.5%)	0
First line bDMARD	77 (49.7%)	24 (36.9%)	8 (38.1%)
bDMARD duration (months)	24 (11-44)	24 (11-43)	22 (11-32)
csDMARDs use	64 (41.3%)	20 (30.8%)	5 (23.8%)
Steroid use	45 (29%)	20 (30.8%)	5 (23.8%)
Cardiopathy	7 (4.5%)	4 (6.2%)	1 (4.8%)
Diabetes	9 (5.8%)	6 (9.23%)	1 (4.8%)
Dyslipidemia	27 (17.5%)	18 (27.7%)	9 (42.9%)
Arterial hypertension	32 (20.6%)	14 (21.5%)	8 (38.1%)
Osteoporosis	11 (7.1%)	3 (4.6%)	4 (19%)
Lung disease	9 (5.8%)	3 (1.5%)	2 (9.5%)
Fibromyalgia	31 (20%)	14 (21.5%)	4 (19%)

DAPSA, disease activity index for psoriatic arthritis; IBD, inflammatory bowel diseases; bDMARD, biologic disease-modifying anti-rheumatic drug; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; TNF, tumor necrosis factor; IL, interleukin.

Patients' characteristics at baseline were compared between TNFi and non-TNFi groups (Table II). Although gender distribution appeared homogeneous between the groups (40% of males patients in the TNFi group, 41.9% in the non-TNFi group; p=0.950), the median age at bDMARDs start was significantly lower in the TNFi group compared to the non-TNFi group [46 years, interquartile range (IQR) 35-54 *vs* 50.5 years, IQR 42-61, respectively; p=0.004).

Comparison of clinical characteristics between groups revealed no significant differences in disease duration (76 months, IQR 34-122 *vs* 82.5 months, IQR 14-145 for TNFi and non-TNFi, respectively; p=0.727), and PsA variant (80% of predominant peripheral involvement *vs* 77.9% in TNFi and non-TNFi respectively; p=0.701), while a significantly higher proportion of patients affected by skin psoriasis among non-TNFi courses was observed (65.8% *vs* 88.4% in TNFi and non-TNFi, respectively; p<0.001).

The proportion of comorbidities between groups was similar, except for a higher proportion of dyslipidemia in the non-TNFi group (17.4% *vs* 31.4% in TNFi *vs* non-TNFi groups, respectively; p=0.013).

No differences between groups were observed for the duration of therapies, first bDMARD therapies, csDMARD, and steroid therapies.

Drug survival

Survival analyses were conducted comparing TNFi and non-TNFi groups. A total of 60 patients discontinued the drug, respectively 21 patients in the former group and 39 in the latter. Among the TNFi group, in 10 patients (25.6%) drug discontinuation was due to primary failure, in 24 patients (64.1%) to secondary failure, in one patient (2.6%) to poor compliance, in 3 patients (7.7%) to adverse reaction. Similar results were found in the non-TNFi group, in which the cause of drug failure was a primary failure in 6 patients

Table II - Bivariate analysis between patients treated with tumor necrosis factor inhibitors (TNFi) and with non-TNFi (interleukin-17 or interleukin-12/23 inhibitors).

	TNF inhibitors (N=155)	Non-TNF inhibitors (N=86)	p value
Male sex	62/155 (40%)	36/86 (41,9%)	0.950
Age at bDMARD start (years, IQR)	46 (35-54)	50.5 (42-61)	0.004
Disease duration (months, IQR)	76 (34-122)	82.5 (14 – 145)	0.727
PsA variant Peripheral predominant Axial predominant	 124/155 (80%) 31/155 (20%)	 67/86 (77.9%) 19/86 (22.1%)	0.701
DAPSA	16.21 (8.73-24.08)	14.85 (9-20.58)	0.388
Psoriasis	102/155 (65.8%)	76/86 (88.4%)	<0.001
Uveitis	5/155 (3.2%)	3/86 (3.5%)	0.591
First bDMARD	77/155 (49.7%)	32/86 (37.2%)	0.062
Therapy duration (months, IQR)	24 (11-44)	24 (11-41)	0.539
csDMARD use	64/155 (41.3%)	25/86 (29.1%)	0.060
Steroid use	45/155 (29.0%)	26/86 (30.2%)	0.845
Cardiopathy	7/155 (4.5%)	9/86 (10.5%)	0.076
Diabetes	9/155 (5.8%)	7/86 (8.1%)	0.486
Dyslipidaemia	27/155 (17.4%)	27/86 (31.4%)	0.013
Arterial hypertension	32/155 (20.6%)	22/86 (25.6%)	0.379
Osteoporosis	11/155 (7.1%)	7/86 (8.1%)	0.786
Lung disease	9/155 (5.8%)	3/86 (3.5%)	0.428
Fibromyalgia	31/155 (20%)	18/86 (20.9%)	0.864

TNF, tumor necrosis factor; bDMARDs, biologic disease-modifying anti-rheumatic drugs; csDMARD, conventional synthetic disease-modifying anti-rheumatic drugs; IQR, interquartile range; DAPSA, disease activity index for psoriatic arthritis; PsA, psoriatic arthritis.

(28.6%), secondary failure in 12 patients (57.1%), adverse reaction in 2 patients (9.5%), and poor compliance in one patient (4.8%). No significant differences were seen between the two groups in terms of therapy duration [24 months (11-44) *vs* 24 months (11-41) for TNFi and non-TNFi, respectively; p=0.9986] (Figure 1).

Moreover, Cox regression was performed including disease duration at baseline, male sex, axial subset, psoriasis, first-line bDMARDs and fibromyalgia as independent variables. Analyses were conducted for all the bDMARDs courses, TNFi, and non-TNFi courses. Fibromyalgia significantly affected overall drug survival, with an HR of 3.40 (CI 1.92-6.03; p<0.001) for drug suspension. Moreover, first-line bDMARDs appeared to be associated with an overall longer drug survival (HR 0.46; CI 0.25-0.88; p=0.019), although the data was not replicated when analyzing for TNFi and non-TNFi inhibitors (Tables III-V). When analyzing TNFi courses, drug suspension was significantly associated with fibromyalgia (HR 6.52, CI 3.16-13.46;

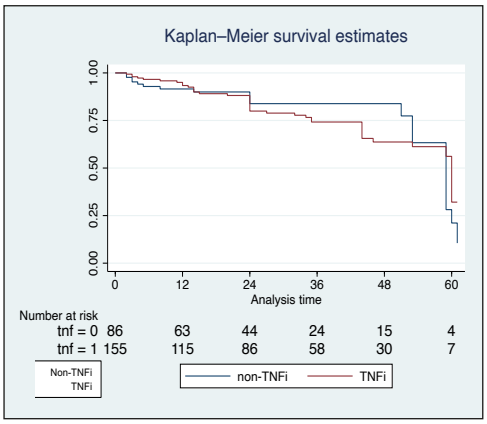

Figure 1 - Kaplan-Meier survival estimates of tumor necrosis factor inhibitors (TNFi) and non-TNFi.
TNFi, tumor necrosis factor inhibitors.

Table III - Cox-regression analysis of predictors of drug discontinuation for the overall psoriatic arthritis population.

	HR	Std. Err.	p value	95% CI
Age	0.992	0.011	0.456	0.970 - 1.014
Male sex	0.649	0.202	0.165	0.353-1.195
Psoriasis	1.299	0.483	0.483	0.626-2.696
Fybromialgia	2.931	0.877	<0.001	1.630-5.27
Disease duration	1.003	0.003	0.302	0.997-1.010
Axial subset	0.618	0.179	0.096	0.350-1.090
First line	0.465	0.151	0.019	0.246-0.881

HR, hazard ratio; Std. Err., standard error; CI, confidence interval.

Table IV - Cox-regression analysis of predictors of tumor necrosis factor inhibitor discontinuation.

	HR	Std. Err.	p value	95% CI
Age	0.977	0.016	0.159	0.946-1.009
Male sex	0.577	0.236	0.179	0.258-1.287
Psoriasis	2.380	1.053	0.05	1.000-5.662
Fibromyalgia	5.578	2.130	<0.001	2.639-11.789
Disease duration	1.003	0.002	0.219	0.998-1.007
Axial subset	0.531	0.195	0.085	0.259-1.091
First line	0.485	0.192	0.067	0.223-1.053

HR, hazard ratio; Std. Err., standard error; CI, confidence interval.

Table V - Cox-regression analysis of predictors of non-tumor necrosis inhibitor discontinuation.

	HR	Std. Err.	p value	95% CI
Age	0.975	0.022	0.228	0.932-1.019
Male sex	0.523	0.294	0.249	0.174-1.573
Psoriasis	0.468	0 .63	0.328	0.102-2.141
Fibromyalgia	1.408	0.788	0.541	0.470-4.216
Disease duration	1.020	0.013	0.123	0.995-1.046
Axial subset	0.428	0.248	0.142	0.137-1.331
First line	0.398	0.230	0.112	0.128-1.238

HR, hazard ratio; Std. Err., standard error; CI, confidence interval.

p<0.001), while skin psoriasis came close to statistical significance (HR 2.38, CI 1.00-5.66; p=0.05). No associations were observed between non-TNFi survival and independent variables taken into consideration (Tables IV and V).

First-line drug choice

A secondary subanalysis focused on first-line therapy was performed - for a total of 108 courses - to define which patients' features and comorbidities drove the drug choice (TNFi *vs* non-TNFi) in bDMARDs naive patients.

Clinical features, such as sex, PsA subset and disease duration seemed to not significantly affect drug choice, as well as cardiopathy, diabetes, hyperlipidemia, arterial hypertension, fibromyalgia, uveitis, and IBD. However, non-TNFi were preferred over TNFi drugs in patients with psoriasis (78.1% *vs* 56.7%; p=0.034) and with higher

age at baseline (52 years, IQR 41.5-62.5 *vs* 45 years, IQR 32.5-55; p=0.021). Additionally, csDMARDs or steroid use at baseline did not significantly differ between the two groups (data not shown).

DISCUSSION AND CONCLUSIONS

This is a real-life study including PsA patients followed in the outpatient clinic of a tertiary care center. Results from our study provide a panoramic view of TNFi and non-TNFi drug survival and how clinical and demographic factors could act as a driver of choice and could affect the retention rate.

When assessing the characteristics of patients treated with bDMARDs with different MoA, we found substantial homogeneity among groups with slight differences in disease features. These differences may represent clinical drivers in the choice of drugs in real-life clinical practice and were replicated in subgroup analyses on patients treated with a first bDMARD. Even if previous European League Against Rheumatism (EULAR) recommendations pointed to TNFi as bDMARDs of first choice in patients with both peripheral or axial PsA and recent evidences identified the axial involvement as driver of retention rate (14, 15), our cohort showed a similar rate of bDMARD-naive patients among patients treated with TNFi and non-TNFi.

While sex distribution was similar among groups, we observed a lower age at the start of TNFi compared to non-TNFi. The decades of experience with TNFi provided more precise safety profiles compared to the other, newer MoA (16, 17), and since younger patients generally bear fewer safety concerns (18), this could explain the difference we observed in age at the therapy start. Since PsA management should take into account comorbidities and non-articular manifestations as highlighted in the latest EULAR recommendations among the *overarching principles* (10), we investigated whether different comorbidities profiles were associated with different MoA. Comorbidities of our population were globally similar compared to literature evidence (9, 19). Furthermore, in our cohort, we did not find significant differences in terms of comorbidities between the two groups except for a higher rate of dyslipidemia in the non-TNFi group.

In our study, we considered only consecutive patients starting bDMARDs in 2016, *i.e.* the year when TNFi, IL-17 inhibitors, and IL12/23 inhibitors were all approved for PsA treatment in Italy. Even though TNFi were available long before the other MoA, median disease duration at baseline of patients appeared similar between those treated with TNFi and non-TNFi and comparable to disease durations described in precedent studies (20, 21).

In both TNFi and non-TNFi groups, more than 75% of patients displayed a peripheral phenotype of PsA. We observed no differences in the use of TNFi and other MoA between peripheral and axial SpA. This data is supported by the evidence of a comparable efficacy of TNFi and non-TNFi on the management of PsA articular manifestations (22). Conversely, the highest prevalence of skin psoriasis in patients treated with either anti-IL17 or anti-IL12/23 compared to TNFi could be explained by a higher efficacy of these MoA than TNFi in the treatment of skin psoriasis (22) and could represent a potential driver of choice in clinical practice, as also suggested by the last EULAR recommendations (10).

Even though a high percentage of patients treated with TNFi received concomitant csDMARDs, they did not significantly differ from non-TNFi. Although data from the EuroSpA collaboration showed that combination therapy with TNFi and methotrexate was associated with higher remission rates in PsA (23), a recent meta-analysis of randomized controlled trials found that combination therapy of bDMARDs plus methotrexate did not improve the clinical efficiency of PsA management (24). Although EULAR recommends using systemic glucocorticoids at the lowest effective dose for the management of PsA (10), we found concomitant systemic steroid therapy in nearly one-third of our patients. Similar frequencies of systemic glucocorticoid thera-

py in PsA patients were reported in a systematic literature review (25), thus highlighting how steroid therapy is frequently prescribed for PsA.

While most studies focused on TNFi, real-world data on anti-IL-17 and anti-IL-12/23 retention rates show a similar retention rate between TNFi and other mechanisms of action as anti-IL17 (20, 26-28). Though the BIOBADASER register found an older age at baseline associated with higher rates of adverse events-related bDMARDs withdrawals (28); the same association was not reported in other studies (20, 21, 29, 30). Similarly, age at the start of bDMARDs was not associated with drug retention in our cohort.

Both the DANBIO register and the BIOBADASER register found a greater risk of bDMARD discontinuation in female patients (20, 29, 31, 32). The protective role of the male sex with respect to bDMARD discontinuation was further confirmed by other studies and meta-analyses (30, 33, 34), although not universally (20). Interestingly, a previous analysis from the BIOBADASER registry on Golimumab retention rate across patients diagnosed with PsA, rheumatoid arthritis (RA), or axial spondiloarthritis did not find an association between gender and drug discontinuation when analyzing the cohort as a whole (35). Similarly, data from the FEARLESS cohort associated the female sex to etanercept discontinuation only in PsA patients, while the association was not replicated in patients with rheumatoid arthritis (RA) (21). However, our analysis found no association between drug survival and gender.

Noteworthy, our cohort showed a higher survival rate in patients treated with a first-line bDMARD. Even though the literature reports higher survival rates for TNFi used in the first line *vs* subsequent courses (36-39), the data in our cohort was not replicated when analyzing MoA.

The most recent recommendations provided by EULAR and the Group for research and assessment of psoriasis and psoriatic arthritis for PsA management indicate anti-IL17 and anti-IL12/23 as drugs of choice in patients with prominent cutaneous involvement, considering their superiority compared to TNFi in terms of skin outcomes (10, 17). Although our multivariate analysis did not narrowly reach statistical significance (p=0.05), skin psoriasis affected negatively TNFi survival. This finding was not confirmed among the non-TNFi group, confirming the higher effectiveness of anti-IL17 and anti-IL23 on the skin subset.

In our population, the prevalence of fibromyalgia in PsA patients reflects what is reported in the literature, even though prevalence rates may vary when using different criteria or tools for fibromyalgia detection (40, 41). As described elsewhere, fibromyalgia negatively impacts PsA outcome measures (40) and TNFi retention rate (27), similarly to the results from our cohort. Interestingly, this data was not replicated in the non-TNFi inhibitors cohort. Literature data regarding the role of fibromyalgia in IL-17 and IL-12/23 inhibitor survival are still scarce and contrasting. In fact, Alonso *et al.* reported a reduced secukinumab survival in patients with depression (among which fell patients with fibromyalgia) (30), while Dougados *et al*. reported depression or fibromyalgia as factors associated with higher secukinumab survival at one year in axial spondyloarthritis (SpA) (42).

Comorbidities are known to negatively impact TNFi survival in RA patients, in particular in the form of multimorbidity, as recently reported by different retention rate studies (43-45). To the best of our knowledge, there are very few studies reporting comorbidity impact on bDMARDs withdrawal in PsA. A Spanish study demonstrated comorbidities increase drug discontinuation in PsA and other SpA (32). Another study revealed a significant association between first bDMARD discontinuation and any metabolic comorbidity (46); contrasting results have been reported (47, 48). Notably, a higher Charlson comorbidity index (CCI) appeared to be associated with poorer bDMARD adherence, as reported elsewhere (32, 40).

Although our study results substantially overlap with the literature findings, several limitations should be mentioned. Firstly, a

validated score including several comorbidities - such as CCI - has not been collected as well as data on neoplastic and infective events. Moreover, our work analyzed only comorbidities at baseline, losing track of comorbidities arising during the treatment course.

Even though the clinical experience gathered with anti-IL-17 and anti-IL-12/23 is growing, the number of patients treated with secukinumab, ixekizumab, and/or ustekinumab was significantly lower than that of patients treated with TNFi: the mismatch in population numerosity affected our study analysis, requiring a selection among variables to be introduced in the multivariate analysis.

Finally, we could not evaluate the impact of other factors, such as economic limitations and biosimilar bDMARD use, potentially influencing treatment choice.

Our data showed a similar retention rate of TNFi *vs* non-TNFi in PsA patients. We also observed that extra-articular manifestations (*i.e*. skin psoriasis) and comorbidities (*i.e*. fibromyalgia) may influence bDMARD survival. We think that prospective, longitudinal studies on the issue could provide further insights to personalize the therapy according to the presence of comorbidities and their burden on PsA patients, as pointed out in the EULAR research agenda for PsA management recommendations (10).

Contributions

The authors contributed equally.

Conflict of interest

MM, declares personal fees from Lilly, MSD, Novartis, Angelini; EGF, declares personal fees from AbbVie, Galapagos, Janssen, Lilly, MSD, Novartis, Pfizer, UCB, BMS. The other author declare no potential conflict of interest.

Ethics approval and consent to participate

Ethics committee approval 138_1999.

Informed consent

Informed consent was obtained from the patients.

Availability of data and materials

Data and materials are available from the corresponding author upon request.

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