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Concise report

European bio-naïve spondyloarthritis patients initiating TNF inhibitor: time trends in baseline characteristics, treatment retention and response

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CLINICAL SCIENCE

Abstract

Objectives. To investigate time trends in baseline characteristics and retention, remission and response rates in bio-naïve axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA) patients initiating TNF inhibitor (TNFi) treatment.
Methods. Prospectively collected data on bio-naïve axSpA and PsA patients from routine care in 15 European countries were pooled. Three cohorts were defined according to year of TNFi initiation: A (1999–2008), B (2009–2014) and C (2015–2018). Retention, remission and response rates were assessed at 6, 12 and 24 months.
Results. In total, 27 149 axSpA and 17 446 PsA patients were included. Cohort A patients had longer disease duration compared with B and C. In axSpA, cohort A had the largest proportion of male and HLA-B27 positive patients. In PsA, baseline disease activity was highest in cohort A. Retention rates in axSpA/PsA were highest in cohort A and differed only slightly between B and C. For all cohorts, disease activity decreased markedly from 0 to 6 months. In axSpA, disease activity at 24 months was highest in cohort A, where also remission and response rates were lowest. In PsA, remission rates at 6 and 12 months tended to be lowest in cohort A. Response rates were at all time points comparable across cohorts, and less between-cohort disease activity differences were seen at 24 months.
Conclusion. Our findings indicate that over the past decades, clinicians have implemented more aggressive treatment strategies in spondyloarthritis. This was illustrated by shorter disease duration at treatment initiation, decreased retention rates and higher remission rates during recent years.

Key words: axial spondyloarthritis, psoriatic arthritis, time trends, TNFi retention, remission, response

Rheumatology key messages

- This study investigates time trends in bio-naïve European spondyloarthritis patients initiating TNFi from 1999–2018.
- We observed shortened disease duration at TNF initiation, decreased retention and increased remission rates over time.
- Our data support that more aggressive spondyloarthritis treatment strategies have been implemented over recent decades.

Introduction

In patients with axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA), it is widely accepted that treatment with biologic DMARDs (bDMARDs) should be started if treatments such as non-steroidal anti-inflammatory drugs in axSpA or conventional synthetic DMARDs in PsA are insufficient [1, 2]. TNF inhibitors (TNFi) improve signs and symptoms of both axSpA and PsA [1, 2].

Although the efficacy of new treatments is usually established through randomized controlled trials (RCTs), observational studies reflect everyday clinical practice and can therefore complement evidence from RCTs. The European Spondyloarthritis Research Collaboration Network (EuroSpA, https://eurospa.eu/) is a research network of multiple European registries created to strengthen research on patients with spondyloarthritis in real-world settings.

Over the past decades, international guidelines have increasingly focused on early diagnosis and the treat-to-target concept in patients with inflammatory arthritis [1–4]. In addition, more bDMARDs have become available, potentially allowing earlier switches in patients with inadequate treatment responses. Studies on Nordic spondyloarthritis patients investigating trends over time have shown decreased baseline disease activity and decreased disease duration at bDMARD initiation [5, 6], but it remains unknown whether this applies across European countries and whether this has resulted in improved patient outcomes.

The aim of this study was to investigate time trends in baseline characteristics and retention, remission and response rates in European axSpA and PsA patients initiating a first TNFi in routine care during the period 1999–2018.

Methods

Patients

Prospectively collected data on bio-naïve spondyloarthritis patients initiating TNFi in routine care from 1999 to 2018 were pooled from 15 European registries participating in the EuroSpA collaboration: SRQ/ARTIS (Sweden), DANBIO (Denmark), SCQM (Switzerland), ATTRA (Czech Republic), TURKBIO (Turkey), NOR-DMARD (Norway), ROB-FIN (Finland), Reuma.pt (Portugal), RRBR (Romania), BIOBADASER (Spain), bio-rx.si (Slovenia), ICEBIO (Iceland), BSRBR-AS (UK), ARC (Netherlands) and GISEA (Italy) (for additional information

about the registries, see Supplementary Table S1, available at *Rheumatology* online). Individual patient data from all registries were collected and subsequently pooled.

The pooled data were analysed separately for axSpA and PsA patients. *A priori*, based on bDMARD availability, three patient cohorts were defined according to the year of TNFi initiation: cohort A (1999–2008), cohort B (2009–2014) and cohort C (2015–2018). The cut-off year 2009 was chosen, as the first three bDMARDs (adalimumab, etanercept and infliximab) from that year were all well-established treatment options across the European countries. The cut-off year 2015 was chosen, as secukinumab was approved as the first non-TNFi bDMARD treatment option that year.

All patient data were anonymized and collected in accordance with national legal and regulatory requirements in the different countries. Individual patient consent was not required. The study was approved by the respective national data protection agencies and ethical committees if required, and it was conducted in accordance with the Declaration of Helsinki.

Clinical variables

Baseline variables included age, gender, time since diagnosis, smoking status (current/non-current smoker), BMI, CRP (mg/l), swollen/tender 28-joint counts (PsA only) and HLA-B27 status (axSpA only). Data on classification criteria and radiographic status were not consistently available in registries and therefore not included.

Crude and LUNDEX adjusted [7] remission rates for axSpA and PsA patients were assessed at 6, 12 and 24 months [axSpA: Ankylosing Spondylitis Disease Activity Score (ASDAS) <1.3 [8] and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) <2 [9]; PsA: 28-joint Disease Activity Score (DAS28) <2.6 [10], 28-joint Disease Activity index for PsA (DAPSA28) ≤ 4 [11] and Clinical Disease Activity Index (CDAI) ≤ 2.8 [10]]. Crude and LUNDEX adjusted [7] response rates for axSpA and PsA were also assessed at 6, 12 and 24 months [axSpA: ASDAS Major and Clinically Important Improvement (MI/CII) [12] and BASDAI 50 [13], PsA: ACR 50% response (ACR50) [14]]. Visit time windows were defined as previously described [15, 16].

Statistical analyses

Analyses were conducted separately for the three patient cohorts (A, B and C) of axSpA and PsA patients, respectively. All analyses were performed on both pooled axSpA and PsA datasets and also stratified per registry. Descriptive statistics (median, interquartile range and/or percentage) were applied for baseline characteristics and disease activity measures. TNFi retention rates were investigated by Kaplan–Meier estimation with assumptions as previously described [15, 16]. Remission and response rates were calculated as both crude rates and LUNDEX adjusted rates, where the LUNDEX adjustment integrates clinical response and adherence to therapy in a composite value [(fraction of patients adhering to therapy) $\times$ (fraction of patients fulfilling remission/response criteria)] [7]. No statistical comparisons were made. No data imputation was performed. Statistical analyses were performed using R v3.4.3 software (R Foundation for Statistical Computing, Vienna, Austria).

Results

In total, 27 149 axSpA and 17 446 PsA patients were included. In axSpA, 5941 patients were in cohort A, 11 240 in cohort B and 9968 in cohort C. In PsA, 4069 patients were in cohort A, 7547 in cohort B and 5830 in cohort C (Table 1).

Baseline characteristics

In both axSpA and PsA, the mean age at time of TNFi initiation was comparable over time (Table 1). However, axSpA and PsA patients in cohort A had longer disease duration compared with cohort B and C patients (median of 5 years for cohort A axSpA/PsA, 2 years for cohort B/C axSpA, 3 years for cohort B/C PsA). In axSpA, cohort A patients were more frequently men and HLA-B27 positive compared with cohorts B and C.

For axSpA patients, baseline BASDAI and ASDAS were similar across cohorts whereas CRP was highest in cohort A. For PsA patients, baseline disease activity was higher in cohort A than in cohort B, which again was higher than in cohort C (Table 1).

Retention rates

In both axSpA and PsA, retention rates at 6, 12 and 24 months were highest in cohort A (axSpA 88%/80%/68%, PsA 88%/77%/64%), but differed little between B (axSpA 84%/73%/60%, PsA 83%/69%/55%) and C (axSpA 85%/74%/60%, PsA 84%/70%/56%).

Treatment response and remission/response rates

In both axSpA and PsA, all disease activity measures in all cohorts had decreased markedly from baseline to 6 months (Table 1).

In axSpA, the median ASDAS values at 12 and 24 months and median BASDAI at 24 months were higher in cohort A (ASDAS 1.9 and 1.9, BASDAI 2.2) compared with cohort B (ASDAS 1.7 and 1.7, BASDAI 2.1) and cohort C (ASDAS 1.6 and 1.5, BASDAI 1.6) (Table 1). Similarly, crude remission and response rates for ASDAS at 12/24 months and BASDAI at 24 months were lowest in cohort A (Table 1, Fig. 1). After LUNDEX adjustments, remission and response rates showed less pronounced between-cohort differences regarding ASDAS measures and no relevant differences regarding BASDAI measures (Table 1).

In PsA, crude and LUNDEX adjusted remission rates at 6 and 12 months tended to be lower in cohort A as compared with cohorts B and C (Table 1, Fig. 1).

Table 1 Time trends in baseline characteristics, and retention, remission and response rates in European spondyloarthritis patients

Axial spondyloarthritis patients (n = 27 149)			
Baseline characteristics	**Cohort A (1999–2008)** (n = 5941)	**Cohort B (2009–2014)** (n = 11 240)	**Cohort C (2015–2018)** (n = 9968)
Age, median (IQR), years (n available)	42 (34–51) (5931)	41 (33–51) (11 238)	41 (32–51) (9965)
Male, % (n available)	66 (5929)	60 (11240)	57 (9968)
HLA-B27 positive, % (n available)	87 (2044)	77 (5036)	72 (4247)
Years since diagnosis, median (IQR) (n available)	5 (1–12) (4107)	2 (0–8) (8999)	2 (0–7) (8599)
Smokers, % (n available)	23 (3807)	24 (8969)	25 (8725)
BMI, median (IQR), kg/m^2 (n available)	25.5 (22.8–28.4) (2327)	25.5 (22.9–28.7) (5136)	26.2 (23.4–29.7) (4327)
CRP, median (IQR), mg/l (n available)	14 (5–31) (4101)	9 (3–21) (7525)	8 (3–19) (6062)
ASDAS, median (IQR) (n available)	3.5 (2.8–4.1) (774)	3.4 (2.8–4.1) (4120)	3.5 (2.9–4.2) (4809)
BASDAI, median (IQR) (n available)	5.8 (4.3–7.1) (1526)	5.9 (4.4–7.2) (6191)	5.8 (4.1–7.1) (6105)
TNFi drug (ADA/ETN/IFX/CZP/GOL), %	22/35/43/0/0	37/21/20/4/18	27/28/24/8/13
Numbers of registries providing data	11/15	14/15	14/15

	6 months			12 months			24 months		
Follow-up	**Cohort A**	**Cohort B**	**Cohort C**	**Cohort A**	**Cohort B**	**Cohort C**	**Cohort A**	**Cohort B**	**Cohort C**
Retention rates (95% CI), % (n available)	88 (88, 89) (5284)	84 (83, 85) (9527)	85 (84, 86) (8471)	80 (79, 81) (4820)	73 (72, 73) (8376)	74 (73, 74) (7156)	68 (67, 70) (4050)	60 (59, 61) (6678)	60 (59, 61) (4152)
ASDAS, median (IQR) (n available)	1.8 (1.3–2.8) (565)	1.9 (1.2–2.8) (3939)	1.8 (1.2–2.6) (4945)	1.9 (1.3–2.6) (566)	1.7 (1.2–2.5) (3398)	1.6 (1.1–2.4) (3598)	1.9 (1.4–2.6) (474)	1.7 (1.1–2.4) (2507)	1.5 (1.1–2.2) (2077)
ASDAS inactive disease, c/L, %	27/24	28/24	30/25	23/19	32/24	34/26	23/16	34/20	38/23
ASDAS CII, c/L, %	59/52	59/50	63/54	62/51	64/47	67/51	60/41	69/41	74/45
ASDAS MI, c/L, % (n available)	32/28 (398)	32/27 (2633)	37/32 (3178)	33/27 (373)	37/27 (2067)	42/32 (2274)	31/21 (299)	43/25 (1462)	47/28 (1336)
BASDAI, median (IQR) (n available)	2.3 (1.0–4.0) (1217)	2.7 (1.2–4.8) (5563)	2.5 (1.0–4.5) (5802)	2.1 (1.0–3.8) (1225)	2.3 (1.0–4.2) (4889)	2.0 (0.8–3.9) (4398)	2.2 (0.9–4.0) (1050)	2.1 (0.8–3.9) (3538)	1.6 (0.6–3.5) (2556)
BASDAI remission, c/L, %	46/41	41/35	43/37	48/39	46/34	51/39	47/32	49/29	57/35
BASDAI 50 response, c/L, % (n available)	54/48 (928)	50/42 (4255)	53/45 (4065)	57/46 (899)	56/42 (3514)	58/44 (3069)	58/40 (713)	60/36 (2560)	63/38 (1789)

(continued)

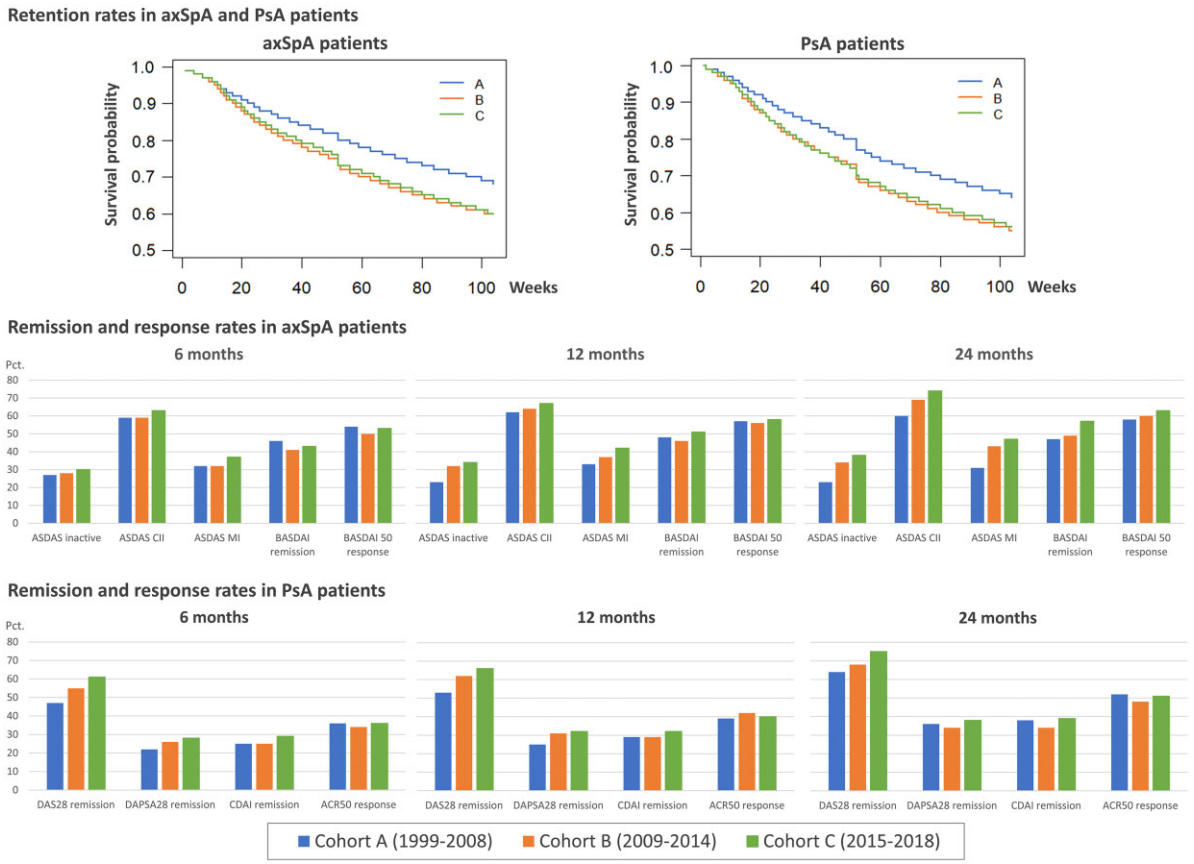
Table 1 Continued

Baseline characteristics	PsA patients (n = 17 446)		
	Cohort A (1999–2008) (n = 4069)	Cohort B (2009–2014) (n = 7547)	Cohort C (2015–2018) (n = 5830)
Age, median (IQR), years (n available)	48 (39–57) (4067)	49 (40–58) (7544)	50 (40–58) (5829)
Male, % (n available)	51 (4067)	48 (7546)	47 (5829)
Years since diagnosis, median (IQR) (n available)	5 (2–10) (2464)	3 (1–9) (5639)	3 (1–8) (4700)
Smokers, % (n available)	16 (2648)	17 (5967)	17 (4993)
BMI, median (IQR) (n available)	26.5 (24.1–29.8) (1373)	26.8 (23.9–30.1) (3063)	27.3 (24.2–31.1) (1753)
CRP, mg/l, median (IQR) (n available)	10 (5–24) (2649)	6 (3–15) (4734)	5 (2–13) (3542)
Swollen 28-joint count (IQR) (n available)	3 (1–7) (2982)	2 (0–5) (5428)	2 (0–4) (4011)
Tender 28-joint count (IQR) (n available)	5 (2–11) (2976)	4 (2–9) (5428)	4 (1–8) (4023)
DAS28, median (IQR) (n available)	4.6 (3.7–5.3) (2333)	4.3 (3.4–5.1) (4114)	4.0 (3.2–4.8) (3033)
DAPSA28, median (IQR) (n available)	29.9 (19.3–41.8) (2191)	25.7 (17.2–38.1) (3888)	24.0 (16.1–35.5) (2993)
CDAI, median (IQR) (n available)	21.0 (13.8–30.5) (1380)	18.7 (12.0–28.0) (2940)	17.0 (11.1–25.0) (2468)
TNFi drug (ADA/ETN/IFX/CZP/GOL), %	27/43/30/0/0	36/31/14/5/14	21/40/21/8/10
Numbers of registries providing data	10/15	12/15	13/15

Follow-up	6 months			12 months			24 months		
	Cohort A	Cohort B	Cohort C	Cohort A	Cohort B	Cohort C	Cohort A	Cohort B	Cohort C
Retention rates (95% CI), % (n available)	88 (87, 89) (3621)	83 (82, 84) (6329)	84 (83, 85) (4883)	77 (76, 79) (3236)	69 (68, 70) (5473)	70 (69, 71) (3969)	64 (63, 66) (2622)	55 (54, 56) (4161)	56 (55, 57) (2212)
DAS28, median (IQR) (n available)	2.7 (1.9–3.6) (1928)	2.4 (1.7–3.4) (3638)	2.3 (1.7–3.2) (3066)	2.5 (1.8–3.4) (1676)	2.2 (1.6–3.1) (2885)	2.1 (1.6–2.9) (1941)	2.1 (1.6–3.1) (645)	2.0 (1.6–2.9) (1543)	1.9 (1.5–2.6) (874)
DAS28 remission, c/L, %	47/42	55/46	61/51	53/43	62/45	66/48	64/42	68/37	75/41
DAPSA28, median (IQR) (n available)	10.6 (4.8–20.0) (1808)	9.5 (3.9–18.3) (3431)	8.7(3.6–15.9) (3014)	9.1 (4.1–17.8) (1560)	7.7 (3.1–15.4) (2714)	7.6 (2.9–14.4) (1914)	6.7 (2.7–13.7) (556)	6.6 (2.7–13.5) (1447)	5.9 (2.4–11.8) (857)
DAPSA28 remission, c/L, %	22/19	26/22	28/23	25/20	31/22	32/23	36/23	34/19	38/21
CDAI, median (IQR) (n available)	7.0 (2.8–14.0) (899)	7.0 (2.9–13.0) (2415)	5.9 (2.4–10.3) (2407)	5.8 (2.2–11.8) (868)	5.5 (2.3–10.7) (2119)	5.0 (2.0–9.0) (1673)	4.3 (1.6–9.6) (699)	5.0 (2.0–9.8) (1735)	4.0 (1.9–7.7) (892)
CDAI remission, c/L, %	25/23	25/21	29/24	29/23	29/21	32/23	38/25	34/19	39/21
ACR50 response, c/L, % (n available)	36/32 (1567)	34/28 (2591)	36/30 (1980)	39/31 (1326)	42/30 (1939)	40/29 (1245)	52/34 (530)	48/26 (1042)	51/28 (515)

The table lists time trends in baseline characteristics, and treatment retention, remission and response rates in European axSpA and PsA patients initiating a first TNFi, stratified by year of treatment start (cohort A, B, C). ACR50: ACR 50% response; ADA: Adalimumab; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CDAI: Clinical Disease Activity Index; CII: Clinically Important Improvement; c/L: crude/LUNDEX adjusted rates; CZP: certolizumab pegol; DAPSA28: 28-joint Disease Activity index for PsA; DAS28: Disease Activity Score in 28 joints; ETN: etanercept; GOL: golimumab; IFX: infliximab; IQR: interquartile range; MI: major improvement; TNFi: TNF inhibitor.

Fig. 1 Time trends in crude remission and response rates in European spondyloarthritis patients



The figure shows time trends in crude remission and response rates in European axSpA and PsA patients initiating a first TNF inhibitor, stratified by year of treatment start (cohort A, B, C). ACR50: ACR 50% response; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CDAI: Clinical Disease Activity Index; CII: Clinically Important Improvement; DAPSA28: 28-joint Disease Activity index for PsA; DAS28: Disease Activity Score in 28 joints; MI: Major Improvement; Pct.: Percentage.

Response rates were at all time points comparable across cohorts. Less between-cohort differences in disease activity levels were seen at 24 months (Table 1, Fig. 1).

Stratification by registries

The baseline characteristics and retention, remission and response rates in PsA and axSpA patients initiating a first TNFi during the period 1999–2018 stratified by registry are shown in Supplementary Table S2 and Supplementary Fig. S1 (available at *Rheumatology* online). Although differences were observed between registries, the general trends described in the above sections were also observed across registries.

Discussion

In this longitudinal observational study, including data from 15 European registries, we investigated time trends in spondyloarthritis patients from 1999 to 2018. We demonstrated decreased disease duration over time at the start of the first TNFi in both axSpA and PsA patients. The proportion of male and HLA-B27 positive axSpA patients decreased over time, while baseline ASDAS and BASDAI were unchanged. In contrast, in PsA patients, disease activity level at the start of the first TNFi decreased over time.

Our findings are in line with previous smaller studies. A Norwegian study by Lie *et al.* investigated time trends in disease activity and disease duration at bDMARD initiation in 391 PsA and 649 axSpA patients between 2002 and 2011 [5]. A decrease in disease duration for both patient cohorts was observed as were drops in baseline disease activity (DAS28+CRP for PsA and ASDAS+CRP for axSpA patients) [5]. This decreasing trend over time was also observed in our study although not for the baseline ASDAS, which we found to be unchanged over time. Lund Hansen *et al.* investigated time trends in 18 089 Nordic PsA patients initiating bDMARDs

from 2006 to 2017 and did not reveal changes in disease duration over these years [6]. However, this investigated period mostly resembles our later cohorts (B and C) and when comparing only these, we could not find a decrease in disease duration either. In line with our results, Lund Hansen *et al.* found that in later years bDMARDs are initiated in PsA patients with less active inflammatory phenotypes than previously, since both decreased baseline CRP and swollen/tender joint counts were detected [6].

In both axSpA and PsA, we found decreased TNFi retention rates over time, whereas remission rates increased, the latter possibly due to fewer patients with longstanding disease in the later cohorts. To our knowledge, no other observational studies have investigated these time trends in spondyloarthritis patients. However, Aga *et al.* investigated time trends in 2573 Norwegian RA patients starting DMARDs from 2000 to 2010 [17]. A more than 2-fold increase in 6-month remission rates was observed over time [17]. Although the changes over time in our study are not quite as prominent as for the RA cohort, our data support that European clinicians over the past decades have increased the focus on targeting disease remission in both axSpA and PsA patients in agreement with the treat-to-target recommendations [1, 2, 4].

Decreasing retention rates over time could potentially be caused by the increased number of bDMARDs available and lower cost of these due to biosimilars. This might encourage clinicians to earlier switching in patients with inadequate treatment responses. This hypothesis is supported by findings from a study investigating 9222 PsA patients initiating conventional synthetic DMARD or bDMARD treatment from 2004 to 2015 [18]. Here, the authors found a trend for more frequent treatment modification after use of the initial DMARD but also a trend for less complete DMARD discontinuations during the study period [18]. Lund Hansen *et al.* similarly reported changes in prescription patterns of both first and subsequent bDMARDs in all Nordic countries from 2006 to 2017 with an increasing palette of medications prescribed [6]. For the axSpA cohort, a potential change in diagnostic subgroups with inclusion of more non-radiographic axSpA patients in later cohorts (related to the ASAS classification criteria published in 2009 [19]) may also have contributed to decreasing retention rates [20]. Unfortunately, data on classification criteria and radiographic status were not of sufficient quantity to be analysed for time trends.

The LUNDEX adjusted remission and response rates indicated less improvements over time when compared with crude rates. However, since external factors—such as increased drug availability over time—may have affected retention rates, the LUNDEX adjusted rates potentially underestimate true improvements over time.

The major strength of our study is the longitudinal observational design including over 27 000 axSpA and over 17 000 PsA patients from 15 European countries. We consider our results to be widely generalizable for European patients since the observed trends were largely similar across the individual registries. In contrast to RCTs, this study was not limited by strict inclusion or exclusion criteria. Hence, our findings can be stated to reflect routine clinical practice across countries.

The limitations of this study are common to all observational registry studies. Here, incompleteness of data is an inherent problem. Furthermore, the risk of selection bias based on data availability cannot be ruled out since compliant subjects may be more likely to visit their physician regularly, resulting in more complete registry data potentially leading to overestimation of, for example, remission rates. Finally, the inclusion of only a 28-joint count in PsA disease activity measures results in a less complete patient evaluation compared with a 66/68 joint count, but this assessment was not systematically performed in most registries.

In conclusion, European axSpA and PsA patients initiating their first TNFi in recent years had shorter disease duration than previously, which may indicate an increased focus on early diagnosis of and early bDMARD initiation in spondyloarthritis. AxSpA patients were more frequently female and HLA-B27 negative than previously, while baseline disease activity was unchanged over time. This might reflect more patients with non-radiographic axSpA being treated in later years while at the same time maintaining a stable disease activity threshold for TNFi initiation. In contrast, PsA patients showed decreasing baseline disease activity over time, indicating a lowered threshold for TNFi initiation in PsA patients over the past decades. While drug retention rates have decreased in both axSpA and PsA, remission rates have increased, suggesting an increased focus on targeting disease remission and more available treatment options when managing patients in routine care.

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Data availability statement

The data underlying this article will be shared upon reasonable request to the corresponding author.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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