ORIGINAL ARTICLES

The impact of antinuclear antibodies seroconversion induced by anti-tumor necrosis factor α agents on the clinical outcomes in rheumatic patients

Martins A[1*], Oliveira D[1*], Martins FR[1], Rato MS[1], Pinheiro FO[1], Fonseca D[1], Garcia S[1], Fernandes BM[1], Pimenta S[1], Vaz C, Costa[1], Bernardes M[1]

ABSTRACT

Introduction: Anti-tumor necrosis factor α (anti-TNFα) agents can potentially induce the anti-nuclear antibodies (ANA) development over time. Evidence of the real impact of these autoantibodies on clinical response to treatment in rheumatic patients is still scarce.

Objectives: To explore the impact of ANA seroconversion induced by anti-TNFα therapy on clinical outcomes in biologic-naïve patients with Rheumatoid arthritis (RA), axial spondylarthritis (axSpA) and psoriatic arthritis (PsA).

Methods: An observational retrospective cohort study enrolling biologic-naïve patients with RA, axSpA and PsA who started their first anti-TNFα agent was conducted for 24 months(M). Sociodemographic data, laboratory findings, disease activity and physical function scores were collected at baseline, 12M and 24M. To examine the differences between the groups with and without ANA seroconversion, independent samples t-tests, Mann-Whitney U-tests and chi-square tests were performed. Linear and logistic regression models were used to assess the effects of ANA seroconversion on the clinical response to treatment.

Results: A total of 432 patients with RA (N=185), axSpA (N=171) and PsA (N=66) were included. ANA seroconversion rate at 24M was 34.6%, 64.3% and 63.6% for RA, axSpA and PsA, respectively. Regarding sociodemographic and clinical data in RA and PsA patients, no statistically significant differences between groups with and without ANA seroconversion were found. In axSpA patients, ANA seroconversion was more frequent in patients with higher body mass index (p=0.017) and significantly less frequent in patients treated with etanercept (p=0.01). Regarding disease activity, DAS28 for RA patients and ASDAS-CRP for axSpA patients were significantly higher in ANA seroconversion group at 12M (p=0.017 and p=0.009, respectively). For PsA patients, CDAI was significantly higher in ANA seroconversion group at 24M (p=0.043). Overall switching rate of biologic disease-modifying antirheumatic drugs (bDMARD) was significantly higher in the ANA seroconversion group over time (p=0.025). For RA patients, ANA seroconversion predicted DAS28 (β=-0.21, 95%CI [-1.86;-0.18], p=0.017) at 12M.

Conclusions: ANA seroconversion induced by anti-TNFα agents could interfere in clinical response of patients with rheumatic diseases. The presence of these autoantibodies can be considered as a potential predictor of poor treatment response and higher need for bDMARD switching over time.

Keywords: Biological therapies; Autoantigens and Autoantibodies; Outcome measures.

INTRODUCTION

Rheumatoid arthritis (RA), axial spondylarthritis (axSpA) and psoriatic arthritis (PsA) are the most frequent inflammatory rheumatic diseases with a prevalence in Europe of 0.5-1%, 0.05-0.42% and 0.03-1.8%, respectively[1, 2]. In the Portuguese population, the estimated prevalence is 0.7% for RA, 0.8% for axSpA and 0.3% for PsA[3]. These rheumatic diseases have a significant impact in physical and psychological health, quality of life and labour productivity of these patients[4]. To manage these burden conditions, anti-tumor necrosis factor α (anti-TNF α) agents have been increasingly recommended. These agents are extremely effective in controlling disease activity, even in patients with inadequate response to conventional synthetic disease-modifying antirheumatic drugs (csDMARD)[5]. However, anti-TNF α agents are inherently immunogenic[6]. Since

repeated administrations are required to keep the disease under control, there is a potential to anti-drug antibodies (ADA) development over time[7]. The presence of these antibodies not only leads to drug-induced allergic reactions, but can also cause drop of serum drug levels to sub-therapeutic levels, resulting in loss of clinical response[8-10]. Associated with ADA development, autoantibodies, such as anti-nuclear antibodies (ANA) and anti-double-stranded DNA antibodies (anti-dsDNA atbs), can be newly induced (seroconversion) or increase their titers during anti-TNF α therapy with a variable incidence[11, 12].

Nevertheless, evidence of the real impact of these autoantibodies on the clinical response to treatment in rheumatic patients over time is still scarce. Therefore, it is imperative to estimate the prevalence of ANA and anti-dsDNA atbs seroconversion and understand its impact in the disease activity and clinical response over time. Thus, this study aimed to explore the impact of ANA seroconversion induced by anti-TNF α therapy on the clinical response in biologic-naïve patients with RA, axSpA and PsA over 24 months (M).

MATERIAL AND METHODS

Study Design
An observational retrospective cohort study was conducted.

Participants
Patients aged 18 years or older from a single rheumatology centre in the northern region of Portugal and diagnosed with RA, according to the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria[13], axSpA, according to Assessment of Spondylarthritis International Society (ASAS) classification criteria[14] and psoriatic arthritis (PsA), according to CASPAR (ClASsification criteria for Psoriatic ARthritis) criteria[15], registered in the Rheumatic Diseases Portuguese Register (Reuma.pt) and who started their first anti-TNF α agent as their first biologic between 2003 and 2018 were included. Patients with psychiatric or cognitive disorders that could interfere with data collection, physically or psychologically unable to communicate, or unable to speak Portuguese were excluded. Also, patients with systemic lupus erythematosus or with positive ANA (titer ≥1/100) and/or positive anti-dsDNA antibodies (≥100 UI/mL) on their first visit immediately prior to the start of the first biologic were excluded.

The Guideline for Good Clinical Practice of the International Conference on Harmonization and the ethical principles of the Declaration of Helsinki were followed[16]. All patients signed informed consent and data were anonymized in accordance with the Portuguese Data Protection Law and the General Data Protection Regulation.

Data collection and measures
Sociodemographic, clinical evaluation and laboratory data were collected from medical records and Reuma.pt at baseline, 12 and 24 M. Sociodemographic data included age, gender, education level and employment status. Clinical evaluation included disease duration, age at diagnosis, comorbidities, body mass index (BMI), smoking and drinking habits, concomitant treatment and Visual Analogue Scale (VAS) by patient and physician. Laboratory findings included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ANA and anti-dsDNA atbs.

For RA and PsA patients, Disease Activity Score for 28 joints (DAS28)[17], DAS28 with C-reactive Protein (DAS28-CRP)[18], Clinical Disease Activity Index (CDAI)[19] and Simplified Disease Activity Index (SDAI)[20] were calculated to measure disease activity. Ankylosing Spondylitis (AS) Disease Activity Score with CRP (ASDAS-CRP)[21] and Portuguese version of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[21, 22] were assessed to measure disease activity in axSpA patients. Disease activity in PsA (DAPSA)[23] was calculated to measure disease activity in PsA patients. Physical function was assessed through the Portuguese version of Health Assessment Questionnaire (HAQ) in RA and PsA patients[24, 25]. For axSpA and PsA patients, Bath AS Functional Index (BASFI) and Bath AS Metrological Index (BASMI) were also collected[21, 22]. To assess enthesitis in axSpA and PsA, the Maastricht AS enthesitis score (MASES) was used[21, 23]. Clinical response was evaluated by ASDAS response in axSpA and by ACR and EULAR criteria in RA and PsA. For EULAR criteria three response categories were defined: good, mild and no response. For all diseases, the switch rate to another bDMARD was assessed over 24M.

STATISTICAL ANALYSIS

Descriptive statistics for normally distributed continuous variables were presented with mean and standard deviation. For non-normally distributed continuous variables median, quartile 1 and quartile 3 were presented. Categorical variables were presented with absolute and relative (percentage) frequencies. Sociodemographic and clinical variables were described for each rheumatic disease and per group of ANA seroconversion. To examine the differences between groups with and without ANA seroconversion, independent samples t-tests for normally distributed continuous data, Mann-Whitney U-tests for non-normally distributed

continuous data and chi-square tests for categorical variables were performed. Linear and logistic regression models were used to assess the effects of ANA seroconversion on the disease activity scores and clinical response to treatment at 12 and 24 M. Data analysis was performed using IBM SPSS for Windows (version 26, IBM Corporation Software Group, New York, NY, USA). Statistical significance was set at a p-value<0.05.

RESULTS

A total of 432 patients with RA (N=185), axSpA (N=171) and PsA (N=66) were included.

Sample sociodemographic and clinical characteristics

Table I presents sociodemographic and clinical characteristics of each rheumatic disease. A total of 156 (84.3%) patients with RA were positive for rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (anti-CCP) antibodies and 62 (33.5%) patients had extra-articular manifestations. Radiographic erosions were present in 52.4% (N=97) of patients with RA and 42.4% (N=28) of patients with PsA. Regarding PsA patients, the majority (57.6%, N=38) had a predominant polyarticular pattern, 30.3% (N=20) an axial involvement pattern, 9.1% (N=6) an oligoarticular pattern and 3.0% (N=2) a predominant distal interphalangeal in-

Table I. Sociodemographic, clinical, treatment and immunological characteristics taking into account each rheumatic disease at baseline, 12M and 24M.

Variables	Rheumatic disease		
Sociodemographic and clinical characteristics	**RA (N=185)**	**axSpA (N=171)**	**PsA (N=66)**
Age, mean (SD), years	49.3 (10.9)	49.8 (11.9)	3.8 (10.8)
Female, n (%)	157 (85.3)	79 (46.2)	31 (47.0)
BMI, median (Q1-Q3), Kg/m^2	25.7 (23.3-29.4)	25.9 (22.6-29.8)	27.5 (24.3-29.4)
Disease duration, median (Q1-Q3), years	10.1 (4.4-16.7)	20.8 (15.2-31.2)	15.0 (11.1-21.1)
Age at diagnosis, mean (SD), years	38.6 (12.2)	34.0 (11.3)	36.1 (10.6)
Smoking status, n (%)			
Current	25 (13.5)	45 (26.3)	11 (16.7)
Former	21 (11.4)	40 (23.4)	11 (16.7)
Never	139 (75.1)	86 (50.3)	44 (66.7)
Alcohol consumption, n (%)			
Current	28 (15.1)	29 (17.0)	15 (22.7)
Former	2 (1.1)	1 (0.6)	1 (1.5)
Never	155 (83.8)	141 (82.5)	50 (75.8)
Employment status, n (%)			
Full-time employee	61 (33.0)	95 (55.6)	40 (60.6)
Part-time employee	2 (1.1)	7 (4.1)	2 (3.0)
Retired	94 (50.8)	45 (26.3)	14 (21.2)
On sick leave	9 (4.9)	3 (1.8)	4 (6.1)
Unemployed	19 (10.3)	21 (12.3)	6 (9.1)
Comorbidities, n (%)			
Hypertension	47 (25.4)	22 (12.9)	15 (22.7)
Diabetes	9 (4.9)	5 (2.9)	7 (10.6)
Cardiovascular disease	16 (8.6)	6 (3.5)	3 (4.5)
Thyroid disease	6 (3.2)	5 (2.9)	1 (1.5)
Sjogren syndrome	17(9.2)	0	0
Treatment regimen at baseline moment, n (%)			
Glucocorticoids	148 (80.0)	19 (11.1)	25 (37.9)
NSAIDs	123 (66.5)	101 (59.1)	44 (66.7)
			continues on the next page

Table I. continuation

Variables	Rheumatic disease		
Sociodemographic and clinical characteristics	**RA (N=185)**	**axSpA (N=171)**	**PsA (N=66)**
csDMARDs	158 (85.4)	48 (28.1)	39 (59.1)
MTX	115 (62.2)	17 (9.9)	33 (43.4)
LFN	49 (26.5)	0	5 (7.6)
SLZ	22 (11.0)	33 (19.3)	3 (4.5)
HCQ	18 (9.7)	0	0
Ciclosporin	6 (3.2)	0	0
Anti-TNF α agent			
Etanercept	86 (46.5)	35 (20.5)	25 (37.9)
Adalimumab	43 (23.2)	51 (29.8)	19 (28.8)
Infliximab	25 (13.5)	41 (24.0)	8 (12.1)
Golimumab	25 (13.5)	39 (22.8)	14 (21.2)
Certolizumab pegol	6 (3.2)	5 (2.9)	0
Immunology profile, n (%)			
ANA seroconversion			
Overall	64 (34.6)	110 (64.3)	42 (63.6)
At 12M	40 (21.6)	81 (47.4)	33 (50.0)
Titer	**N=40**	**N=81**	**N=33**
1/100	22 (55.0)	50 (61.7)	17 (51.5)
1/320	12 (30.0)	19 (23.5)	7 (21.2)
1/1000	6 (15.0)	12 (14.8)	9 (27.3)
Pattern	**N=40**	**N=81**	**N=33**
Homogeneous	24 (60.0)	35 (43.2)	14 (42.4)
Speckled	6(15.0)	30 (37.0)	12 (36.4)
Midbody	5 (12.5)	8 (9.9)	3 (9,1)
Homogeneous and another pattern	3 (7.5)	0	0
Nucleolar	1 (2.5)	8 (9.9)	4 (12.1)
Nuclear dots	1 (2.5)	0	0
At 24M	24 (13.0)	71 (41.5)	31 (47.0)
Titer	**N=24**	**N=71**	**N=31**
1/100	15 (62.5)	35 (49.3)	14 (45.2)
1/320	7(29.2)	27 (38.0)	9 (29.0)
1/640	1(4.2)	0	0
1/1000	1(4.2)	12 (16.9)	8 (25.8)
Pattern	**N=24**	**N=71**	**N=31**
Homogeneous	13 (54.2)	32 (45.1)	15 (48.4)
Speckled	6 (25)	28 (39.4)	10 (32.3)
Mitotic or chromatic spindle	2 (8.3)	0	0
Midbody	1(4.2)	3 (4.2)	3 (9.7)
Nucleolar	1(4.2)	8 (11.3)	2 (6.5)
Centriole	1(4.2)	3 (4.2)	1 (3.2)
Anti-dsDNA seroconversion			
Overall	19 (10.3)	11 (6.4)	5 (7.6)
At 12M	14 (7.6)	9 (5.3)	4 (6.1)
At 24M	9 (4.9)	7 (4.1)	2 (3.0)

RA: rheumatoid arthritis; axSpA: axial spondylarthritis; PsA: Psoriatic arthritis; SD: standard deviation; BMI: body mass index; Q: quartile; NSAIDs: Non-steroidal anti-inflammatory drugs; csDMARD: conventional synthetic disease modifying antirheumatic drugs; MTX: Methotrexate; LFN: Leflunomide; SLZ: Sulfasalazine; HCQ: hydroxychloroquine; TNF: tumour necrosis factor; ANA: antinuclear antibodies; M: Month; Anti-dsDNA: Anti-double stranded DNA antibody. *Statistically significant.

Table II. Disease activity scores at 12M and 24M per groups of ANA seroconversion for RA.

Variable	Positive ANA at 12M (N=40)	Negative ANA at 12M (N=145)	p_{value}
HAQ, mean (SD)	1.4 (0.7)	1.2 (0.7)	0.137
HAQ delta, mean (SD)	-0.16 (0.45)	-0.37 (0.56)	0.073
Disease activity scores			
DAS28, mean (SD)	5.0 (3.4)	4.0 (1.4)	0.017*
DAS28 delta, mean (SD)	1.11 (1.48)	1.63 (1.59)	0.120
DAS28 (CRP), mean (SD)	3.9 (1.5)	3.5 (1.3)	0.251
CDAI, median (Q1-Q3)	9.4 (5.7-13.8)	10.0 (4.7-21.0)	0.557
SDAI, median (Q1-Q3)	11.0 (6.1-14.2)	10.8 (5.2-21.6)	0.470

Variable	Positive ANA at 24M (N=24)	Negative ANA at 24M (N=161)	p_{value}
HAQ, mean (SD)	1.2 (0.7)	1.2 (0.7)	0.968
HAQ delta, mean (SD)	-0.39 (0.42)	-0.33 (0.53)	0.638
Disease activity scores			
DAS28, mean (SD)	4.2 (1.3)	3.8 (1.4)	0.225
DAS28 delta, mean (SD)	1.2 (1.4)	2.2 (5.0)	0.428
DAS28 (CRP), mean (SD)	3.5 (1.2)	3.3 (1.2)	0.587
CDAI, median (Q1-Q3)	8.5 (6.4-23.8)	6.7 (4.1-11.6)	0.239
SDAI, median (Q1-Q3)	9.0 (6.7-21.0)	7 (5.0-11.9)	0.250
Overall switch rate over time, median (Q1-Q3)	1 (0-1)	0 (0-1)	0.025*

RA: rheumatoid arthritis; ANA: antinuclear antibodies; M: month; HAQ: Health Assessment Questionnaire SD: standard deviation; DAS28: Disease Activity Score for 28 joints; CRP: C-reactive protein; Q: quartile; CDAI: Clinical Disease Activity Index; SDAI: Simplified Disease Activity Index. *Statistically significant.

volvement pattern We found an ANA seroconversion rate of 34.6% (N=64) for RA, 64.3% (N=110) for axSpA and 63.6% (N=42) for PsA at 24M of therapy. For all patients, the most common titre and pattern was 1/100 and homogeneous, respectively.

In RA and PsA patients, there were no significant differences between the groups with and without ANA seroconversion regarding age, gender, disease duration, age at diagnosis, BMI, disease characteristics (erosive or not) and treatment regimen at baseline (including anti-TNF α agent). In axSpA, ANA seroconversion was more frequent in patients with higher BMI (p=0.017). On the other hand, ANA seroconversion was significantly less frequent in patients treated with etanercept (p=0.01). The Supplementary Data shows all these results with more detail (Tables I-III).

Disease activity and clinical response by seroconversion groups
Tables II, III and IV show the physical function assessment, disease activity scores and switch rate taking into account ANA seroconversion groups for RA, axSpA and PsA, respectively.

For RA (Table II), DAS28 was significantly higher in patients with positive ANA at 12M (5.0±3.4 vs 4.0±1.4, p=0.017). Also, overall switch rate to another bDMARD over time was significantly different between the two groups, being higher in patients with positive ANA [1 (0-1) versus 0 (0-1), p=0.025]. No differences were found in HAQ, CDAI, SDAI, ACR and EULAR responses (good, mild and no response) at 12M and 24M.

For axSpA (Table III), ASDAS-CRP was significantly higher in patients with positive ANA at 12M (3.9±0.9 vs 2.1±1.0, p=0.009). In these patients, no statistically significant differences were found in BASFI, BASMI, MASES, BASDAI, ACR and EULAR responses and switch rate over time.

For PsA (Table IV), all disease activity scores were higher in patients with positive ANA, however only CDAI was significantly different between the two groups [8.8 (4.1-14.9) vs 5.4 (2.0-8.8), p=0.043] at 24M. No differences were found between the two groups regarding disease activity scores at 12M and ACR and EULAR responses at 12M. Except for CDAI, no differences were found regarding the other variables at 24M.

Regression Models
For RA, ANA seroconversion only predicted DAS28

Table III. Disease activity scores at 12M and 24M per groups of ANA seroconversion for axSpA.

Variable	Positive ANA at 12M (N=81)	Negative ANA at 12M (N=90)	p$_{value}$
BASFI, mean (SD)	3.8 (2.7)	3.8 (2.6)	0.961
BASMI, mean (SD)	3.8 (1.6)	4.3 (1.7)	0.143
MASES, median (Q1-Q3)	0 (0-2)	0 (0-0.8)	0.066
Disease activity scores			
BASDAI, mean (SD)	3.4 (2.1)	2.9 (2.0)	0.195
ASDAS-CRP, mean (SD)	3.9 (0.9)	2.1 (1.0)	0.009*
Variable	Positive ANA at 24M (N=71)	Negative ANA at 24M (N=100)	p$_{value}$
BASFI, mean (SD)	4.3 (1.3)	4.9 (2.2)	0.585
BASMI, mean (SD)	3.6 (1.6)	4.6 (1.8)	0.680
MASES, median (Q1-Q3)	2 (0-3)	0.5 (0-3.8)	0.225
Disease activity scores			
BASDAI, mean (SD)	4.2 (1.4)	3.5 (2.2)	0.083
ASDAS-CRP, mean (SD)	2.8 (0.5)	2.5 (0.8)	0.985
Overall switch rate over time, mean (SD)	1 (0-1)	1 (0-1)	0.984

axSpA: axial spondylarthritis; ANA: antinuclear antibodies; M: month; SD: standard deviation; Q: quartile; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrological Index; MASES: Maastricht Ankylosing Spondylitis enthesitis score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-reactive protein. *Statistically significant.

score (β=-0.21, 95%CI [-1.86; -0.18], p=0.017) at 12M. In axSpA and PsA, ANA seroconversion did not predict disease activity over time. For all rheumatic diseases, ANA seroconversion did not predict switch rate and clinical response over time (Table IV, Supplementary data).

DISCUSSION

This study showed a high seroconversion rate of ANA in our sample of bio-naïve rheumatic patients after treatment with an anti-TNFα agent. No differences were found in the ANA seroconversion rate regarding the type of anti-TNFα except for etanercept in PsA patients. RA and axSpA patients with positive ANA had a higher disease activity after 12M of anti-TNFα therapy. PsA patients with positive ANA had higher disease activity scores, however, only the CDAI at 24M was significantly different between the 2 groups.

In the present study, the prevalence of ANA seroconversion ranged from 34.6% for RA, 64.3% for axSpA and 63.6% for PsA, with the most common titre and pattern being 1/100 and homogeneous, respectively. Furthermore, in this study, anti-dsDNA atbs seroconversion was observed in 10.3% of RA patients, 6.4% of axSpA patients and 7.6% of PsA patients. There is scarce literature about the temporal relationship between anti-TNF

α therapy and seroconversion of autoantibodies, namely ANA and anti-dsDNA atbs. The few previous studies reported a high ANA seroconversion rate in patients with rheumatic diseases under anti-TNF α, ranging from 23% to 57%, which is similar in magnitude to what we found[26, 27]. In addition, anti-dsDNA atbs seroconversion can also occur with anti-TNF αagents however, with a lower incidence than ANA seroconversion, according to other studies and our findings[26].

The mechanism by which some patients with rheumatic conditions develop these autoantibodies isn't completely understood. Some authors claim that seroconversion of autoantibodies could be a consequence of anti-TNF αblockade, as this blockade could promote humoral autoimmunity by inhibiting the induction of cytotoxic T lymphocyte response, which normally suppresses autoreactive B-cells[28]. Other authors argue that seroconversion of autoantibodies is linked to an increase in lymphocyte and monocyte apoptosis and release of nuclear autoantigens induced by anti-TNF α[29-31].

In this study, both ANA and anti-dsDNA atbs seroconversion were higher at 12M compared to 24M of anti-TNFαtreatment. According to previous research, these findings can be explained by the fact that the induced autoantibodies are mainly of the IgM and IgA isotypes, which are associated with a short-term humoral immunity and, consequently, disappear from the circulation after a short period of exposure to the treatment[32, 33].

Table IV. Disease activity scores at 12M and 24M per groups of ANA seroconversion for PsA.

Variable	Positive ANA at 12M (N=33)	Negative ANA at 12M (N=33)	p_{value}
HAQ, mean (SD)	0.9 (0.6)	0.8 (0.7)	0.459
HAQ delta, mean (SD)	0.12 (0.60)	-0.10 (0.47)	0.323
BASFI, mean (SD)	3.6 (2.5)	4.1 (3.0)	0.543
BASMI, median (Q1-Q3)	3.4 (2.6-3.9)	3.6 (2.6-4.9)	0.909
MASES, median (Q1-Q3)	0 (0-1)	0 (0-1)	0.800
Disease activity scores			
DAS28, mean (SD)	3.0 (1.3)	2.6 (1.3)	0.275
DAS28 (CRP), mean (SD)	2.7 (1.2)	2.4 (1.0)	0.316
DAS28 delta, mean (SD)	0.44 (1.26)	0.43 (0.85)	0.967
CDAI, median (Q1-Q3)	5.3 (3.5-10.8)	6.7 (3.5-7.7)	0.973
SDAI, median (Q1-Q3)	6.2 (3.4-11.0)	7.2 (3.9-8.0)	0.927
BASDAI, mean (SD)	3.6 (2.3)	3.6 (2.0)	0.956
ASDAS-CRP, mean (SD)	2.2 (1.0)	2.2 (0.7)	0.965
DAPSA, mean (SD)	10.8 (9.5)	13.7 (7.9)	0.299
Variable	Positive ANA at 24M (N=31)	Negative ANA at 24M (N=35)	p_{value}
HAQ, mean (SD)	0.9 (0.6)	0.8 (0.7)	0.459
HAQ delta, mean (SD)	0.12 (0.60)	-0.10 (0.47)	0.323
BASFI, mean (SD)	4.6 (3.0)	3.1 (2.7)	0.097
BASMI, median (Q1-Q3)	3.5 (2.0-4.6)	2.6 (1.9-2.9)	0.071
MASES, median (Q1-Q3)	0 (0-4)	0 (0-1)	0.384
Disease activity scores			
DAS28, mean (SD)	3.1 (1.6)	2.6 (1.1)	0.226
DAS28 (CRP), mean (SD)	2.8 (1.2)	2.3 (0.9)	0.211
DAS28 delta, mean (SD)	0.5 (1.9)	0.6 (1.5)	0.901
CDAI, median (Q1-Q3)	8.8 (4.1-14.9)	5.4 (2.0-8.8)	0.043*
SDAI, median (Q1-Q3)	8.9 (4.3-15.3)	5.4 (2.1-9.3)	0.054
BASDAI, mean (SD)	4.6 (2.7)	3.3 (2.0)	0.059
ASDAS-CRP, mean (SD)	2.4 (1.1)	2.2 (1.0)	0.375
DAPSA, mean (SD)	15.3 (9.9)	10.5 (9.8)	0.174
Overall switch rate over time, median (Q1-Q3)	1 (0-1)	1 (0-2)	0.946

PsA: Psoriatic arthritis; ANA: antinuclear antibodies; M: month; SD: standard deviation; Q: quartile; Health Assessment Questionnaire; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrological Index; MASES: Maastricht Ankylosing Spondylitis enthesitis score; DAS28: Disease Activity Score for 28 joints; CRP: C-reactive protein; CDAI: Clinical Disease Activity Index; SDAI: Simplified Disease Activity Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; DAPSA: Disease activity in psoriatic arthritis. *Statistically significant.

Although previous studies have reported a higher ANA seroconversion with infliximab, the present study found no significant difference in the ANA seroconversion rate regarding the type of anti-TNF α agent, except for etanercept, but only in PsA patients[34, 35]. Previous research didn't detect any relevant ADA in patients treated with etanercept ant this agent seems to be the least immunogenic anti-TNFα agent, which support our finding, although we only found it in PsA patients[34, 35].

Furthermore, in agreement with some previous studies, our study found no significant difference in the ANA seroconversion rate in patients with and without concomitant csDMARD[30, 36, 37]. However, a previous metanalysis showed that methotrexate reduced the seroconversion of autoantibodies, namely ADA[38]. Thus, in the future there is a need to explore the effect not only of methotrexate, but also of others csDMARD on seroconversion of autoantibodies.

In this study, RA was the rheumatic disease with the lowest ANA seroconversion. This finding can be explained by the fact that the majority of these patients were treated with methotrexate and, according to previous research this csDMARD was associated with less seroconversion of autoantibodies over the time[38].

Regarding disease activity and clinical response, our study found that patients with RA and positive ANA had a higher DAS28 than patients with negative ANA after 12M of therapy with a first anti-TNF α agent. In addition, the switch rate was higher among RA patients who seroconverted to positive ANA. Similarly, for axSpA patients, we found a higher ASDAS-CRP in the group with positive ANA after 12M of therapy with a first anti-TNF α agent. Regarding patients with PsA, all disease activity scores were higher in the ANA positive group, however only the CDAI was significantly different between the 2 groups at 24M of therapy. These findings seem to suggest that seroconversion of ANA could interfere in the clinical outcomes of patients with rheumatic diseases on anti-TNF α therapy over time. In fact, previous studies reported a poor clinical response in RA patients with ANA and anti-dsDNA atbs seroconversion or with an increase in their titers under anti-TNF α therapy[39]. More recently, Ishikawa et al. reported that ANA development during treatment with infliximab, as well as with other anti-TNF α agents, could be a marker of poor clinical response to the therapy in RA patients[40]. Furthermore, Fonseca et al. also found a poorer clinical response in the first 6 months of anti-TNF α therapy, a higher switch rate and a lower anti-TNF α therapy survival in RA patients with baseline positive ANA[41]. Similarly, other studies support that the development of ANAs and anti-dsDNA atbs with anti-TNF α agents may also act as a marker of forthcoming treatment failure in patients with psoriasis[42, 43].

Previous research has shown that ADA-positive patients developed ANA at a titer greater than 160 and that anti-dsDNA atbs increased significantly in these patients compared to those without ADA[44]. Furthermore, Mori *et al.* also showed a higher rate of ADA development in patients with positive ANA before anti-TNF α therapy and/or with increasing titer over time[45]. Thus, the presence of ANA prior to anti-TNF α therapy is a risk factor for development of ADA, as well as for treatment ineffectiveness[45].

This study has some limitations that should be acknowledged. The major limitations are related to the single-center retrospective nature of this study and the missing data on Reuma.pt. Other limitations include the small sample in the PsA group, the technical unavailability of our routine laboratory to carry out ADA titer determinations and the absence of data regarding the anti-TNF α safety. Moreover, since RA can be as-

sociated with systemic lupus erythematosus or Sjögren disease, the assumption that ANA seroconversion is induced by anti-TNF α may not always be accurate. In the extreme, the later may represent a translating sign of a preclinical stage of another connective tissue disease superimposed on RA, which only a careful and long-term follow-up will reveal.

To the best of our knowledge, this is the first study in real clinical practice that explored the impact of ANA seroconversion induced by anti-TNF α therapy on clinical outcomes of Portuguese patients with Rheumatoid arthritis (RA), axial spondylarthritis (axSpA) and psoriatic arthritis (PsA).

CONCLUSIONS

Autoantibodies, such as ANA and anti-dsDNA atbs can be induced (seroconversion) or increase their titers during anti-TNF α therapy in Portuguese patients with rheumatic diseases.

Seroconversion of ANA over time have impact on clinical outcomes in patients with RA and axSpA patients. The presence of these auto-antibodies can eventually be used as a potential marker of poor response and higher need to switch over time, mainly if present persistently and in high titers over time. Therefore, ANA test should be considered in the assessment and follow up of rheumatic patients under anti-TNF α therapy.

The present findings suggest that more attention should be given by all rheumatologists to the impact of ANA seroconversion during anti-TNF α therapy. Further prospective multicentric studies with larger samples are needed to assess the generalizability of these findings and to identify potential predictive factors of ANA seroconversion and anti-TNF α therapy failure over time.

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SUPPLEMENTARY DATA

Table I. Baseline clinical characteristics per groups of ANA seroconversion for RA

Variable	Positive ANA (N=64)	Negative ANA (N=121)	p $_{value}$
Sociodemographic characteristics			
Age, mean (SD), years	49.6±10.6	49.2±11.1	0.789
Female, n (%)	56 (87.5)	101 (83.5)	0.324
Disease duration, median (Q1-Q3), years	11 (4.1-16.2)	9.05 (23.2-28.4)	0.715
Age at diagnosis, mean (SD), years	38.3±11.9	38.8±12.5	0.812
BMI	26.9 (23.3-31.2)	24.2 (23.2-28.4)	0.159
Disease characteristics			
Seropositivity (RF and/or anti-CCP), n (%)	53(82.8)	103(85.1)	0.949
Erosive disease, n (%)	35(54.7)	62(51.2)	0.996
Extra-articular manifestations, n (%)	25(39.1)	37(30.6)	0.245
Treatment options at baseline moment, n (%)			
Glucocorticoids	54(84.4)	94(77.7)	0.761
NSAIDs	47(73.4)	76(62.8)	0.279
MTX	43(67.2)	72(59.5)	0.305
Other csDMARDs	29(45.3)	52(42.9)	0.761
Anti-TNF drug			
Etanercept	31(48.4)	55(45.4)	
Adalimumab	16(25.0)	27(22.3)	
Infliximab	8(12.5)	17(14.0)	0.145
Golimumab	7(10.9)	18(14.9)	
Certolizumab pegol	2(3.1)	4(3.3)	

RA: rheumatoid arthritis; SD: standard deviation; ANA: antinuclear antibodies; M: Month; Q: quartile; RF: rheumatoid factor; anti-CCP: anti-cyclic citrullinated peptide; NSAIDs: Non-steroidal anti-inflammatory drugs; MTX: Methotrexate; csDMARD: conventional synthetic disease modifying antirheumatic drugs; TNF: tumour necrosis factor.

Table II. Baseline clinical characteristics per groups of ANA seroconversion for SpA

Variable	Positive ANA (N=110)	Negative ANA (N=61)	p value
Sociodemographic characteristics			
Age, mean (SD), years	49.5±11.7	49.4±13.2	0.651
Female, n (%)	54.0 (49.1)	25 (41.0)	0.308
Disease duration, median (Q1-Q3), years	20.5 (15.0-27.4)	23.8 (16.1-33.3)	0.772
Age at diagnosis, mean (SD), years	34.3±11.4	33.6±11.3	0.70
BMI, median (Q1-Q3), Kg/m²	26.4 (23.9-31.3)	23.9 (21.7-27.1)	0.01*
Treatment options at baseline moment, n (%)			
Glucocorticoids	13 (11.8)	6 (9.8)	0.693
NSAID	68 (61.8)	33 (54.1)	0.325
csDMARDs	29 (26.4)	19 (31.1)	0.505
Anti-TNF drug			
Etanercept	16 (14.5)	19 (31.1)	0.010*
Adalimumab	34 (30.9)	17 (27.9)	0.677
Infliximab	29 (26.4)	12 (19.7)	0.326
Golimumab	27 (24.5)	12 (19.7)	0.467
Certolizumab pegol	4 (3.6)	1 (1.6)	0.656

axSpa: axial spondyloarthritis; SD: standard deviation; ANA: antinuclear antibodies; M: Month; Q: quartile; NSAIDs: Non-steroidal anti-inflammatory drugs; MTX: Methotrexate; csDMARD: conventional synthetic disease modifying antirheumatic drugs; TNF: tumour necrosis factor. *Statistically significant.

Table III. Baseline clinical characteristics per groups of ANA seroconversion for PsA.

Variable	Positive ANA (N=42)	Negative ANA (N=24)	p value
Sociodemographic characteristics			
Age, mean (SD), years	38.5±9.9	41.4±13.1	0.522
Female, n (%)	22 (52.4)	9 (37.5)	0.244
Disease duration, median (Q1-Q3), years	14.9 (10.7-21.1)	15.0 (11.0-21.3)	0.654
Age at diagnosis, mean (SD), years	38.5±9.9	41.4±13.1	0.314
BMI, median (Q1-Q3), Kg/m²	27.5 (23.4-29.5)	27.6 (24.9-29.4)	0.778
Treatment options at baseline moment, n (%)			
Glucocorticoids	14 (33.3)	11 (45.8)	0.314
NSAIDs	29 (69.0)	15 (62.5)	0.587
csDMARDs	23 (54.8)	16 (66.7)	0.344
Anti-TNF drug			
Etanercept	17 (40.5)	8 (33.3)	0.565
Adalimumab	12 (28.6)	7 (29.2)	0.959
Infliximab	6 (14.3)	2 (8.3)	0.700
Golimumab pegol	7 (16.7)	7 (29.2)	0.232

PsA: psoriatic arthritis; SD: standard deviation; ANA: antinuclear antibodies; M: Month; Q: quartile; NSAIDs: Non-steroidal anti-inflammatory drugs; MTX: Methotrexate; csDMARD: conventional synthetic disease modifying antirheumatic drugs; TNF: tumour necrosis factor.

Table IV. Regression analysis to predict the effect of ANA seroconversion on the main clinical outcome variables for patients with RA, SpA and PsA.

ANA seroconversion	RA				PsA				axSpA			
	At 12M		At 24M		At 12M		At 24M		At 12M		At 24M	
	β	p	β	p	β	p	β	p	β	p	β	p
DAS28	-0.21	0.017*	-0.21	0.017*	0.64	0.42	1.35	0.77	NA			
HAQ	-0.13	0.14	-0.13	0.14	-0.63	0.59	0.20	0.89				
CDAI	-0.18	0.12	0.09	0.50	-0.46	0.58	0.04	0.64				
SDAI	-0.18	0.13	0.12	0.39	0.74	0.43	3.15	0.28				
ASDAS-CRP					-1.12	0.27	0.22	0.91	-0.24	0.59	0.18	0.63
DAPSA					-0.14	0.45	0.19	0.18	NA			
BASDAI	NA								0.38	0.13	-0.03	0.85
BASFI					NA				-0.12	0.44	-0.09	0.51
BASMI									-0.19	0.27	-0.02	0.90
Eular response	-0.16	0.72	-0.16	0.72	-0.58	0.40	-1.36	0.16	NA			
ASAS response	NA				NA				0.02	0.59	0.01	0.80
Switch rate	-0.01	0.97	-0.01	0.97	1.19	0.28	0.46	0.69	-0.04	0.88	0.35	0.16

ANA: antinuclear antibodies; ASAS: Assessment of Spondyloarthritis International Society; ASDAS: Ankylosing Spondylitis Disease Activity Score; axSpA: axial spondylarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrological Index; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAPSA: Disease Activity Index for Psoriatic Arthritis; DAS28: Disease Activity Score for 28 joints; HAQ: Health Assessment Questionnaire; M: Month; NA: not applicable; PsA: psoriatic arthritis; RA: rheumatoid arthritis; SDAI: Simplified Disease Activity Index. *Statistically significant.