No correlation between anti-drug antibodies and therapeutic response in Tunisian patients with chronic inflammatory diseases treated by TNF blockers

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Abstract

INTRODUCTION: Tumor necrosis factor alpha (TNF alpha) blockers such as infliximab (IFX) and adalimumab (ADA) had significantly changed the course of inflammatory diseases such as rheumatoid arthritis (RA), spondyloarthritis (SpA) and Crohn's disease (CD). However, about 30% of patients do not respond to these treatments. This lack of response may be due to the formation of antibodies against these drugs (anti-drug antibodies: ADAbs). The aim of this study was to determine the prevalence ADAbs against IFX and ADA, and the trough serum concentration of IFX and ADA in RA, SpA or CD patients and to assess their impact on the therapeutic response. METHODS: A cross sectional, multi-centric study was conducted including patients with RA, SpA or CD treated with IFX or ADA as a first biotherapy for at least 6 months. ADAbs and trough levels were measured by an Enzyme Linked Immunosorbent assay (ELISA). RESULTS: 137 patients were included (37 RA, 53 SpA and 47 CD). ADAbs were positive in 40% of cases for IFX and 25% for ADA. They were positive in 39% of SpA, 35% of RA, and 21% of CD. The presence of ADAbs was inversely correlated to the trough levels of IFX and ADA during RA ($p=0.01$ and $p<0.0001$), SpA ($p<0.01$ and $p<0.0001$) and CD ($p=0.001$ and $p=0.04$). For all pathologies, the presence of ADAbs was not correlated with disease activity. CONCLUSION: In our study, the presence of ADAb and low trough levels seem to not affect the therapeutic response in patients on TNF alpha antagonists.

INTRODUCTION

Tumor necrosis factor alpha (TNF alpha) blockers such as infliximab (IFX) and adalimumab (ADA) had significantly changed the course of inflammatory diseases such as rheumatoid arthritis (RA), spondyloarthritis (SpA) and Crohn's disease (CD). However, about 30% of patients do not respond to these treatments [1]. This lack of response may be due to an immediate non-response known as primary failure, or to a loss of response after an initial good response called secondary failure. In the case of secondary failure, immunogenicity has been incriminated [2]. It is defined by the development of antidrug antibodies (ADAbs) [2].

The presence of ADAbs can decrease serum drug levels by neutralizing the functional part of the biologic or by forming immune complexes between the biologic and the ADAbs, increasing thereby the clearance of the drug [3-5]. Many studies have been performed in order to evaluate the impact of immunogenicity on the

clinical response [5]. The aim of this study was to determine the prevalence anti ADAbs against IFX and ADA, and the trough serum concentration of IFX and ADA in RA, SpA or CD patients and to assess their impact on the therapeutic response.

PATIENTS AND METHODS

Study population

One hundred thirty-seven patients (37 with RA, 53 with SpA and 47 with CD) treated by TNF alpha blockers (IFX=68, ADA=69) were included in the study. All patients fulfilled the ACR/EULAR 2010 criteria for RA [6], the Assessment of Spondyloarthritis international Society (ASAS) 2010 criteria for SpA [7] or the 2006 Montreal classification for CD [8]. All included patients had to be TNF alpha blockers naïve, and had to receive the current biologic for at least 6 months.

Study design

This was a cross sectional, multi-centric study conducted from January 2015 to June 2017. Patients were recruited from La Rabta hospital, Charles Nicolle hospital, Mongi Slim hospital, FSI hospital in tunis, Military hospital in tunis and Farhat Hached hospital. It was approved by the local Ethics Committee. Informed consent was obtained from each patient before any data collection.

Data collection

Data collection was carried out before the initiation of the biologic, at the same time of blood samples collection and 6 months later. It concerned:

-Demographics: age, sex, body mass index (BMI)

-Disease activity information's: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), the diseased activity score in 28 joints (DAS28) for RA patients [19], the bath ankylosing spondylitis disease activity index (BASDAI) [10] and the ankylosing spondylitis disease activity score (ASDAS) [11] for SpA patients and the Harvey Bradshaw index (HBI) [12] for CD patients.

We divided patients into responders and non-responders. For RA patients, DAS28 < 2.6 means remission, DAS28 between 2.6 and 3.2 means low disease activity, DAS28 between 3.2 and 5.1 means moderate activity and DAS 28 > 5.1 means high activity [9]. Patients in remission or low disease activity were considered as responders, and others as non-responders.

For SpA patients, ASDAS (calculated with CRP) < 1.3 means inactive disease, ASDAS between 1.3 and 2.1 means moderate disease activity, ASDAS between 2.1 and 3.5 means high disease activity and ASDAS > 3.5 means very high disease activity [11]. Patients with inactive disease or moderate disease activity were considered as responders, and others as non-responders.

For CD patients, responders were those whom HBI decreased to 4 points or less or by 3 points or less from baseline [12].

-Data related to the treatment: the type of TNF alpha blocker, duration of intake, levels and frequency of intake and concomitant use of conventional synthetic disease modifying anti rheumatic drugs (csDMARDs).

Biological analysis:

Blood samples were collected from all patients in the hospital: IFX patients were collected just before their infusion, and ADA patients were called to the hospital 24h before their injection.

An aliquote of serum and plasma was stored at -80°C. ADAbs and trough serum concentration of the biologics were measured by an Enzyme Linked Immunosorbent assay (ELISA) (Lisa-tracker, Theradiag®).

The threshold of detection of IFX and ADA was 0.1µg/ml. ADAbs were considered positive > 10 IU/ml.

Statistical analysis

Statistical package for social sciences (SPSS) version 22.0 was used to perform statistical analysis. Means, standard deviation and proportions were calculated. Comparisons were performed using Student's t-test and analysis of variance (ANOVA) for normally distributed variables. The Chi2 test was used to analyse categorical data. Significance level was set at P-value < 0.05.

RESULTS

Population:

One hundred thirty-seven patients (37 with RA, 53 with SpA and 47 with CD) treated by TNF alpha blockers (IFX=68, ADA=69) were included in the study. Table 1 illustrates the baseline clinical characteristics and disease activity scores of our patients.

Treatment characteristics of our patients including the type of TNF alpha blockers, the treatment duration and the combined treatment are summarized in table 2.

Prevalence of ADAbs and relation with drug levels

ADAbs were detected in 44 patients: 27 treated with IFX (40%) and 17 receiving ADA (25%) (p=0.195). ADAbs were positive among 13 RA patients (35%), 21 SpA patients (39%) and 10 CD patients (21%) (p=0.354) (table 3). The presence of ADAbs was inversely correlated to the trough levels of IFX and ADA during RA (p=0.01 and p<0.0001) (figure 1), SpA (p<0.01 and p<0.0001) (figure 2) and CD (p=0.001 and p=0.04) (figure 3).

Comparison of patients' characteristics between ADAbs+ and ADAbs– patients:

Table 4 illustrates the comparison between ADAbs+ and ADAbs- patients. Demographic data including age, sex, disease duration, age at disease beginning were not statically different between the 2 groups, except for BMI. Indeed, RA ADAbs+ patients had higher BMI than ADAbs- ones (p=0.04). Concerning the concomitant drug used, there was not any significant association between AZA and immunogenicity. However, the use of MTX was significantly associated with immunogenicity in CD (p=0.04), with a dose effect in RA and CD (p=0.04 and p=0.005 respectively).

Comparison of disease activity between ADAbs + and ADAbs – patients

Laboratory and clinical data related to disease activity was not significantly different between ADAbs+ and ADAbs- patients (Table 5).

Safety

3 patients had infusion reactions to IFX. These 3 patients were ADAbs+ (p=0.01) and had lower trough levels of IFX (p<0.001).

DISCUSSION

To our knowledge, this is the first study that has investigated immunogenicity in both rheumatic (RA and SpA) and digestive (CD) pathologies.

In our study, the presence of ADAbs was not correlated with disease activity. However, the presence of ADAb was inversely correlated to the trough levels of IFX and ADA.

Our study had some limitations. Firstly, the number of patients for each pathology was not large. Besides, we did use the solid phase ELISA. It is the simplest and most widely used method [13]. However, it can give false positives due to its possible interaction with RF (frequently associated with inflammatory conditions), but also false negatives as it does not detect complexed ADAbs. It is a method that only allows the determination of free ADAbs, thus we cannot differentiate between neutralising and non-neutralising ADAbs [14,15].

Our results showed that IFX was the most immunogenic biologic (40%) compared to ADA (25%), without a statistically significant difference. Several authors agree that IFX is more immunogenic than ADA [16,17].

This could be explained by the fact that ADA, being a human antibody, is less likely to form ADAbs than IFX which is a chimeric antibody [4].

Besides, we found that IFX which is administered through intravenous courses, was more immunogenic than ADA which is administered subcutaneously. Schellekens et al. compared the intravenous and subcutaneous routes for Abatacept and found an increase in immunogenicity in patients who received the intravenous route [18]. However, the subcutaneous route is known to be more immunogenic than the intravenous route, as it exposes more antigen presenting cells such as dendritic cells [19].

In our study, the combination of MTX with biologic in CD reduced immunogenicity (p=0.04). The dose of MTX was higher in ADAbs- patients in RA (p=0.04) and CD (p=0.005). This protective role of MTX on ADAbs formation was not found in SpA. Maini et al. were the first to investigate the role of MTX in reducing the immunogenicity of IFX in RA. They included 101 patients receiving 1mg/kg or 3mg/kg or 10mg/kg of IFX, and found that the combination of 7.5mg/week MTX reduced ADAbs formation by 53%, 21% and 7% respectively [20]. In SpA, the question of the role of synthetic DMARDs in immunogenicity has also been raised. Plasencia et al. included 94 SpA patients and reported that ADAbs was more frequently found in patients receiving IFX alone than in those receiving it in combination with MTX (34% versus 11%). They also reported that MTX delayed the formation of ADAbs during patient follow-up, which may partly explain why other short-term studies have not demonstrated a beneficial role for MTX in the immunogenicity of SpA [21].

The exact mechanism behind the reduction of immunogenicity by DMARDs remains unclear. Indeed, it is well known that immunomodulators such as MTX interfere with the immune response, possibly inducing a decrease in antibody production [22].

Immunogenicity effect on the residual level of the biologic

In the different group of our study, RA, SpA and CD, the presence of ADAbs was inversely correlated to the trough levels of IFX and ADA. Similar data have been reported in a large number of studies in the literature [1,3,17,23-33].

The mechanisms involved in the decrease of the residual level of the biologic are thought to be the formation of immune complexes between the drug and ADAbs inducing acceleration of its clearance. In consequence, we noticed a decrease in its bioavailability [14].

Immunogenicity and therapeutic response

The data in the literature are very mixed. A meta-analysis with systematic review of the literature by Garcês et al., which included 865 patients with RA, SpA, psoriasis or IBD, showed that the presence of ADAbs reduced the therapeutic response by 68%, but with significant heterogeneity between studies (p=0.037) that did not allow a definite link between immunogenicity and clinical response to be established [5].

Indeed, there are studies which, in agreement with our results, found no link between immunogenicity and therapeutic response at the time of sampling [34-36]. Actually, in our study no association was found between the presence of anti IFX or anti ADA and therapeutic response at the time of sampling for RA, SpA or CD. In the study of Cludts et al. including patients with RA (n=18), psoriatic arthritis (n=9), SpA (n=12) treated with ADA, no significant differences in DAS28 or BASDAI scores were found between ADAbs+ and ADAbs- patients [35]. The lack of correlation between immunogenicity and therapeutic response could be explained by the fact that, as mentioned above, the ELISA technique only allows the determination of free ADAbs. However, complexed ADAbs are those that would have a real therapeutic impact [36]. Another theory was proposed, that there are transient ADA with no real clinical impact, while the persistent ADA are responsible for treatment failure [37]. The fact that the assay was performed only once did not allow us to differentiate whether the ADAbs detected in our study were persistent or not.

ADA and allergic reaction

In our study, the occurrence of allergic reactions was significantly correlated with the presence of ADAbs and with a lower residual level. Our data agree with several studies which have found that the presence of ADAbs is a risk factor for allergic reactions [24,25]. A meta-analysis with systematic review of the literature including 1185 IBD cases found that patients with anti-IFX ADAbs were 2 times more likely to develop acute infusion reactions and 6 times more likely to develop severe reactions [38]. Vande Casteele et al. demonstrated that a low residual IFX level <2.2 µg/ml was associated with the presence of allergic reactions in CD [39].

CONCLUSIONS

In our study, the presence of ADAb and low trough levels seem to not affect the therapeutic response in patients on TNF alpha antagonists. Other tracks more than immunogenicity should be investigated to explain the loss of response to these biotherapies.

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Conflict of interest: None

Informed consent: Informed consent was obtained from all individuals included in the study

Ethical approval: This study complies with the Declaration of Helsinki. An ethical approval vas obtained from our local ethics committee

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Table 1: Patients and disease characteristics at baseline

Patients, n (%)	RA, n=37 (27%)	SpA, n=53 (39%)	CD, n=47 (34%)
Age, years (mean ± SD)	53 ± 14.29	42.88 ± 8.71	39.04 ± 9.84
Sex ratio (men/female)	0.6 (14/23)	2.3 (37/16)	1.1 (25/22)
BMI, kg/m^2 (mean ± SD)	26.83 ± 4.02	20.22 ± 4.41	20.94 ± 5.11
Age of disease onset, years (mean ± SD)	37.71 ± 13.35	32.45 ± 9.35	28.63 ± 8.54
Mean disease duration, years (mean ± SD)	10.17 ± 7.56	7.09 ± 6.90	6.86 ± 5.7
ESR, mm/h (mean ± SD)	51.7 ± 30.59	35.94 ± 19.59	41.27 ± 25.95
CRP, mg/l (mean ± SD)	19 ± 3	22.27 ± 18.39	21 ± 2
DAS28 (mean ± SD)	5.80 ± 1.18	NA	NA
BASDAI (mean ± SD)	NA	5 ± 1.48	NA
ASDAS (mean ± SD)	NA	3.53 ± 0.46	NA
HBI (median, IQR)	NA	NA	6 [3-9]

Note: Data presented mean ± standard deviation (SD) or median and interquartile range (IQR)

Abbreviations: RA: rheumatoid arthritis; SPA: Spondyloarthritis; CD: Crohn's disease; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAS28: diseased activity score in 28 joints; BASDAI, bath ankylosing spondylitis disease activity index; ASDAS: ankylosing spondylitis disease activity score; HBI: Harvey Bradshaw index

Table 2: Treatment characteristics of patients

Type of TNF alpha blockers, n (%) IFX (n=68) ADA (n=69)	
Concomitant MTX use, n (%) MTX mean dosage (mg/week), (mean ± SD) Concomitant AZA use, n (%) AZA mean dosag	
Duration of TNF alpha blockers (months)	

Note: Data presented mean ± standard deviation (SD)

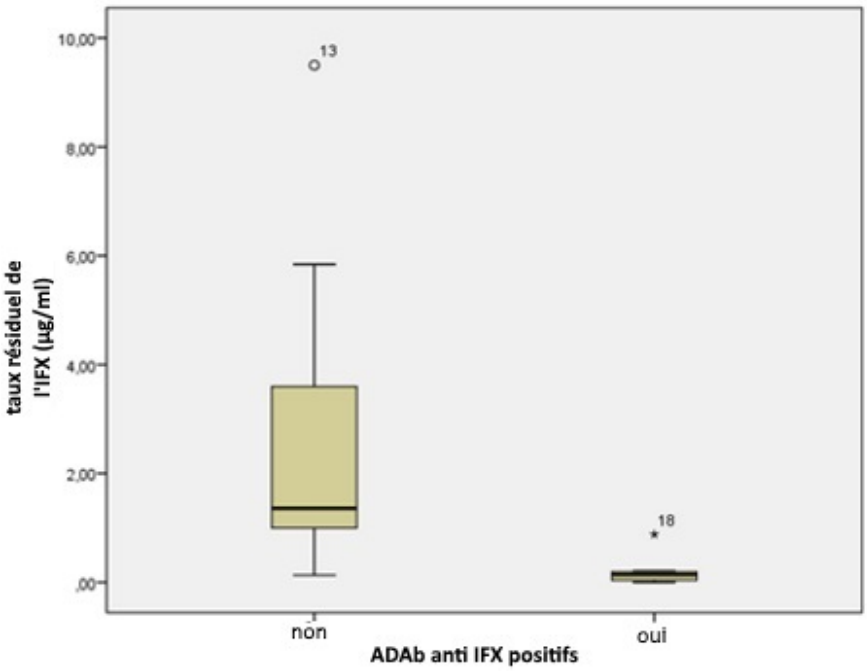
*Abbreviations: RA: rheumatoid arthritis; SPA: Spondyloarthritis; CD: Crohn's disease; TNF: tumor necrosis factor; IFX: infliximab; ADA: adalimumab; MTX: methotrexate; AZA: azathioprin*Table 3: ADAbs and drug levels assessment

	RA (n=37)	SpA (n=53)	CD (n=47)
Positive total ADAbs, n (%)	13 (35)	21 (39)	10 (21)
Positive ADAbs anti IFX, n	8	11	8
Positive ADAbs anti ADA, n	5	10	2
Mean anti-IFX ADAbs rate (UI/ml)	15.7 [0-200]	60.5 [0-200]	0.7 [0-200]
Mean anti-ADA ADAbs rate (UI/ml)	5.61 [0.64-111]	6.5 [0-405]	5.69 [0-405]
Mean IFX residual dose rate (µg/ml)	0.43 [0.23-3]	0.54 [0-9.5]	1.5 [0-5.67]
Mean ADA residual dose rate (µg/ml)	5.06 [0-8]	5.9 [0-9.32]	4.85 [0-7.85]

Note: Data presented median and interquartile range (IQR)

Abbreviations: ADAbs: anti-drug antibodies; RA: rheumatoid arthritis; SPA: Spondyloarthritis; CD: Crohn's disease; IFX: infliximab; ADA: adalimumab

Figure 1a: IFX levels (µg/ml) in ADAbs+ Figure 1b: ADA levels (µg/ml) in ADAbs+ *versus* ADAbs- patients in RA *versus* ADAbs- patients in RA



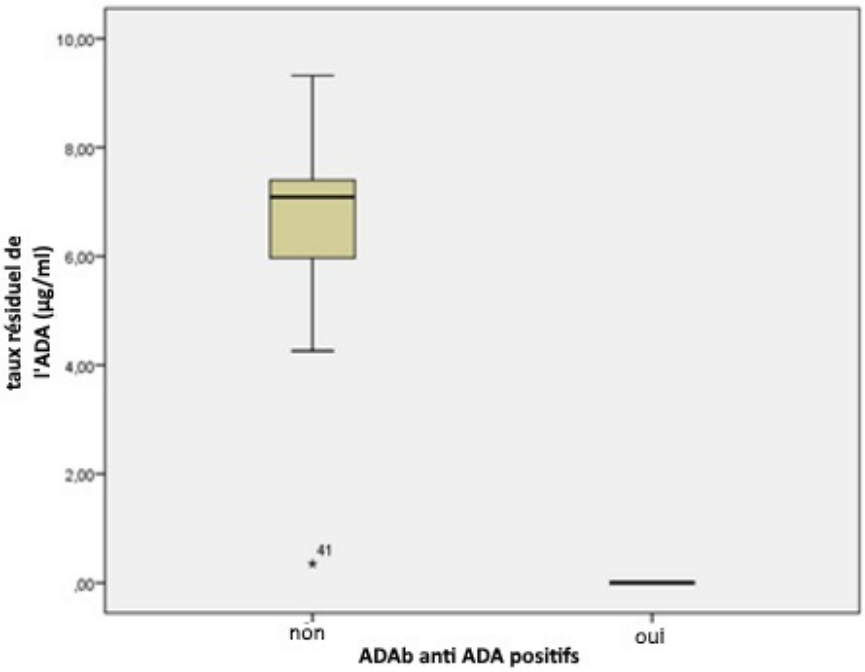


Figure 2a: IFX levels (µg/ml) in ADAbs+ patients in SpA *versus* ADAbs- patients in SpA

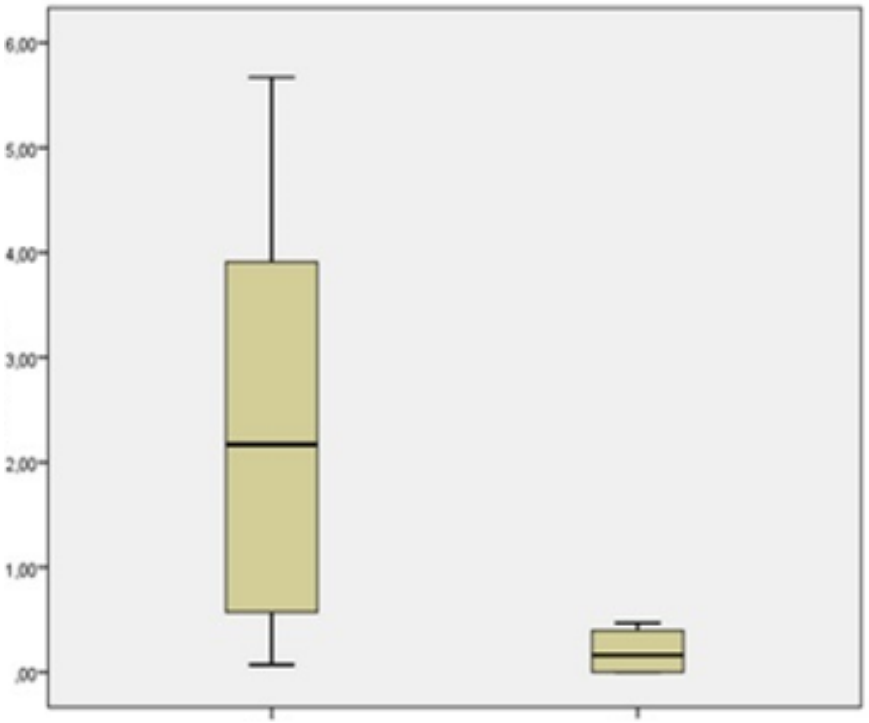


Figure 2b: ADA levels (µg/ml) in ADAbs+ *versus* ADAbs- patients in SpA

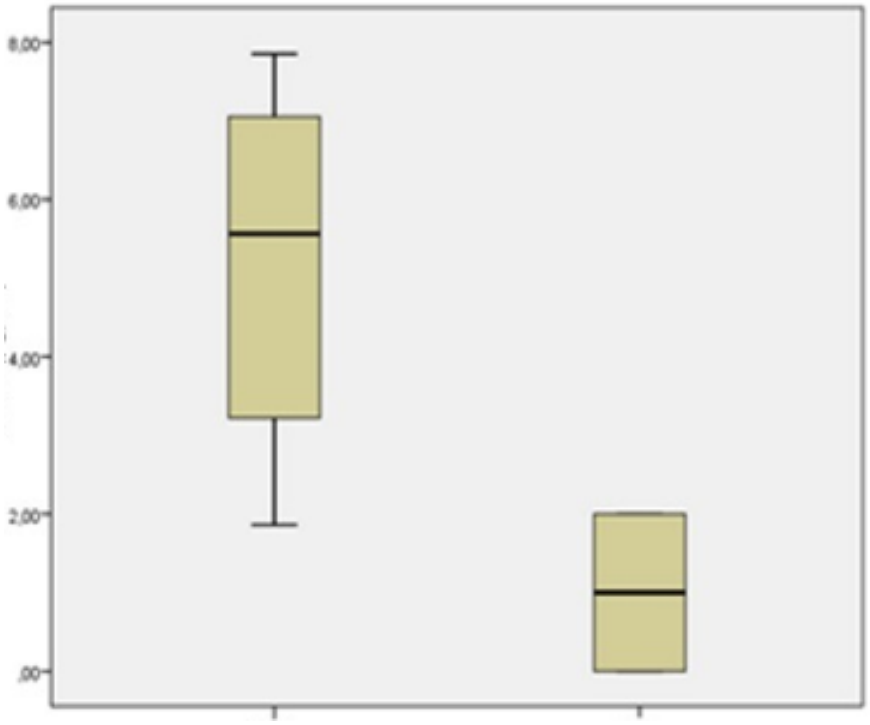


Figure 3a: IFX levels (µg/ml) in ADAbs+ Figure 3b: ADA levels (µg/ml) in ADAbs+ *versus* ADAbs- patients in CD *versus* ADAbs- patients in CD

Table 4: Comparison between ADAbs+ and ADAbs- patients

	Disease	ADAbs + (n=25)	ADAbs – (n=52)	p
Age, years	RA SpA CD	55.5 42.85 41.17	51.64 42.9 38.42	NS NS NS
Sex ratio	RA SpA CD	0.2 3.3 1	0.3 5.6 1.3	NS NS NS
BMI, kg/m^2 (mean ± SD)	RA SpA CD	33 ± 1.2 22 ± 0.8 21.8 ± 0.3	26.5 ± 1.7 19.71 ± 0.9 20.58 ± 1.3	**0.04** NS NS
Mean age at disease onset, years (mean ± SD)	RA SpA CD	39.33 ± 3.5 31.23 ± 2.8 30.83 ± 1.9	36.82 ± 2.8 33.25 ± 0.6 28 ± 3.1	NS NS NS
Disease duration, years (mean ± SD)	RA SpA CD	9.08 ± 3.2 7.3 ± 2.1 17.17 ± 4.2	3.05 ± 1.1 6.3 ± 1.9 23.14 ± 4.8	NS NS NS
Duration of TNF alpha blockers therapy, months (mean ± SD)	RA SpA CD	51.83 ± 7.9 26.46 ± 6.9 5.17 ± 1.1	32.36 ± 11.2 39.9 ± 9.9 4.4 ± 1.3	NS NS NS
Concomitant use of MTX, n	RA SpA CD	9 5 0	12 6 3	NS NS **0.04**
Mean dose of MTX, mg/week	RA SpA CD	10 ± 2.5 15 ± 2.3	13.5 ± 2.8 16.5 ± 2.9 20	**0.04** NS **0.005**
Concomitant use of AZA, n	RA SpA CD	0 0 12	0 0 21	**- -** NS

	Disease	ADAbs + (n=25)	ADAbs – (n=52)	p
Mean dose of AZA, mg/kg/day	RA SpA CD	0 0 2,5 ± 0.9	0 0 2 ± 0.2	- - NS

Note: Data presented mean ± standard deviation (SD)

Abbreviations: ADAbs: anti-drug antibodies; RA: rheumatoid arthritis; SPA: Spondyloarthritis; CD: Crohn's disease; BMI: body mass index; TNF: tumor necrosis factor; MTX: methotrexate; AZA: azathioprine; NS: not significant

Table 5: Comparison of disease activity parameters between ADAbs+ and ADAbs- patients:

Disease activity parameters	Disease	ADAbs+	ADAbs-	p
ESR (mean ± SD)	RA SpA CD	32.67 ± 9.6 32 ± 6.9 4 ± 1.1	33.5 ± 7.3 21 ± 4.4 17 ± 3.2	NS NS NS
CRP (mean ± SD)	RA SpA CD	4.67 ± 1.1 16.6 ± 5.2 5.5 ± 2	21.82 ± 6.6 12.3 ± 5.7 19.3 ± 6	NS NS NS
DAS28 (mean ± SD)	RA SpA CD	3.51 ± 0.8 NA NA	4.67 ± 1.3 NA NA	NS - -
BASDAI (mean ± SD)	RA SpA CD	NA 3.5 ± 0.9 NA	NA 3.2 ± 0.8 NA	- NS -
ASDAS (mean ± SD)	RA SpA CD	NA 2.5 ± 0.3 NA	NA 1.4 ± 0.1 NA	- NS -
HBI (median, IQR)	RA SpA CD	NA NA 6 [3-9]	NA NA 6 [3-11]	- - NS

Note: Data presented mean ± standard deviation (SD) or median and interquartile range (IQR)

Abbreviations: ADAbs: anti-drug antibodies; ESR: erythrocyte sedimentation rate; RA: rheumatoid arthritis; SPA: Spondyloarthritis; CD: Crohn's disease; CRP: C-reactive protein; DAS28: disease activity score; BASDAI: bath ankylosing spondylitis disease activity index; ASDAS: ankylosing spondylitis disease activity score; HBI: Harvey Bradshow index; NS: not significant

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