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How Useful is Anti-TNF Serum Level and Anti-drug Antibodies Detection in Evaluating Patients with Spondyloarthritis?

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Abstract

Objective: The aim of this study was to assess whether infliximab and adalimumab drug serum levels and the detection of anti-drug antibodies (ADA) can be of use in better observing disease activity in patients with spondyloarthritis, besides classical tools such as BASDAI, ASDAS and inflammatory markers. We proposed to evaluate the influence of ADA in non-responders and in drug-related adverse events.

Methods: Over one year, we enrolled 115 patients with SpA, treated with infliximab (IFX) or adalimumab (ADL). Patients who delayed prescribed drug administration were excluded from the study cohort. The population comprised 69 patients - 33 on IFX and 35 on ADA. NSAID administration was recommended "on demand". Demographic, clinical (BASDAI, ASDAS) and laboratory (ESR, CRP) data was collected together with drug serum level and anti-drug antibodies using ELISA. The statistical analysis was performed using the SPSS software, version 20.0 with the aid of Student t-test, Spearman and Pearson tests.

Results: Detectable IFX serum levels were identified in 60% of patients while 40% had undetectable drug titers. The IFX-negative had significantly higher disease activity scores: BASDAI (P=0.023), ASDAS-ESR (P<0.001) and ASDAS-CRP (P<0.001). Significant differences were found in the same subgroups regarding inflammatory markers, with higher ESR (P<0.001) and CRP (P=0.032) in patients with undetectable IFX levels. When measuring ADL serum levels, 82% had detectable drug concentrations, with lower BASDAI (P<0.001), ASDAS-ESR and ASDAS-CRP (P<0.001) and higher ESR and CRP at collection time when compared to ADL-negative patients. NSAID consumption correlated to undetectable levels of IFX and ADL as well as with anti-drug antibodies for both IFX and ADL positivity. All patients who experienced drug related adverse events on both IFX and ADL had positive anti-drug antibodies.

Conclusion: Serum drug level measurement and anti-drug antibody detection can be used as a completion of a clinician's tools in assessing disease activity, leading to an optimal patient management.

Keywords: Spondyloarthritis; Anti-TNF therapy; Drug serum level; Immunogenicity

Abbreviations: IFX: Infliximab; ADL: Adalimumab; ADA: Anti-drug Antibodies; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; TNF: Tumor Necrosis Factor; SpA: Spondyloarthritis; NSAID: Non-steroidal Anti-inflammatory Drugs; ELISA: Enzyme Linked Immunosorbent Assay; ESR: Erythrocyte Sedimentation Rate; CRP: C Reactive Protein; ETN: Etanercept; AIA: Anti-Infliximab Antibodies; AAA: Anti-Adalimumab Antibodies; dpw: days per week

Introduction

Spondyloarthritides, a heterogeneous group of chronic, inflammatory disorders with overlapping organ and joint targeting, share the same therapeutic approach in regard to biological therapy [1-3]. Anti-tumor necrosis factor (anti-TNF) agents, such as adalimumab (ADL), infliximab (IFX) or etanercept (ETN), golimumab and certolizumab have proved their efficacy in diminishing signs and symptoms as well as lowering overall disease activity [4]. Since their appraisal as a second line therapeutic option, patients' prognosis has valuably improved [5].

Patients' response to biological therapy is relatively high, reaching a rate of 60-70% [6,7]. However, a third of the individuals considered initially as responders, fail to maintain their treatment response or experience adverse events, leading to anti-TNF discontinuation [7,8].

Immunogenicity is currently a matter of debate, as the main responsible mechanism underlying the non-responder status [9].

One of the main mechanisms underlying failure to anti-TNF agents is immunogenicity. Loss of response to TNF-inhibitors in spondyloarthritis (SpA) patients might be due to undetectable drug serum level. This may result from anti-drug antibody (ADA) formation that bind the medication into immune complexes and prevent its functional part from acting. The factors that are involved in drug immunogenicity are multiple, including the structure of the product and its mode of action as well as the administration route [8-15]. Patient's individual features were also suggested to influence immune reactions [11-15].

Determining biologic agent serum levels in SpA patients and adjusting dose or interval administration in a personalized manner together with identifying the presence of ADA might lead to a better disease management. This immunogenic profile analysis becomes of increasing interest considering recent studies suggesting that therapeutic failure to a first anti-TNF agent, due to ADA occurrence, predicts a better clinical response when switching to a second TNF inhibitor [16-20].

Acknowledging the rather scarce data of TNF immunogenicity in SpA, our purpose was to measure IFX and ADL serum level concentrations in this patient category together with establishing ADA presence and to assess their relationship with disease activity through inflammatory markers (erythrocyte sedimentation rate ESR and C-reactive protein CRP), specific disease activity scores (Bath Ankylosing Spondylitis Disease Activity Index - BASDAI and Ankylosing Spondylitis Disease Activity Score - ASDAS). Frequency of non-steroidal anti-inflammatory drug (NSAID) consumption in these patients was also evaluated.

Methods

Over a period of one year (from May 2014 to June 2015), we enrolled a number of 115 patients previously diagnosed with SpA, according to the latest ASAS criteria, under ongoing therapy with a TNF inhibitor, namely adalimumab or infliximab. This study included patients with both axial and peripheral form of SpA with no differentiation when performing statistical analysis. Patients were included in order of admission to our Rheumatology Department of "Sfânta Maria" Clinical Hospital in Bucharest, Romania, while on hospital visit for treatment administration or for regular physician follow-up. Their treatment plan followed local guidelines, regarding dosage and interval of administration. Patients representing therapy "drop-offs" or presenting delays in drug administration, either on purpose (not presenting to hospital visit on scheduled time) or due to concomitant infection were excluded from this study. To minimize study bias related to immunogenicity, we excluded patients in concomitant treatment with sulfasalazine or methotrexate for peripheral manifestations of SpA.

The study was approved by the hospitals' Ethics Committee and all patients gave their written informed consent before proceeding with study procedures.

Demographic (age, sex and race) and clinical data were gathered. The latter included spinal mobility measures, namely the Schober test, occiput-wall, chin-chest and finger-to-floor distances) and patients were asked to complete both disease activity scores (BASDAI and ASDAS). BASDAI scores of 4 or greater indicate an active disease status with a suboptimal control of the disease. According to the ASAS group recommendations [21], an ASDAS score of less than 1.3 corresponds to an "inactive disease", greater or equal to 1.3 and less than 2.1 defines "moderate disease activity", ASDAS values between 2.1 and 3.5 relates to "high disease activity", whereas ASDAS greater than 3.5 reflects "very high disease activity".

History of magnetic resonance imaging (MRI) performing at disease onset was investigated in order to identify non-radiographic forms of SpA.

Laboratory inflammatory markers (ESR with laboratory reference values ranging from 2 to 20 mm/h and CRP with normal values between 0 to 5 mg/L) were collected.

Biologic serum level concentrations and anti-drug antibody levels were measured using PROMONITOR® kits (Promonitor® -IFX, Promonitor® -ANTI-IFX, Promonitor® -ADL, Promonitor® -ANTI-ADL) that are enzyme-linked immunosorbent assays (ELISA) capable of a quantitative detection of the above mentioned in human serum. As a cross-sectional study, the drug serum determinations were measured only once in each patient during their follow-up visit.

When interpreting results, the kit protocol states that a value of equal or under 0.035 μg/mL of IFX indicates that no IFX is detected, while a level greater than 0.035 μg/mL signifies positivity for IFX detection; the same technique applies to ADL determination, using 0.024 μg/mL as bound limit. The antibody detection has a set-up limit of equal or lowers 5 AU/mL for negative anti-IFX-antibodies (no anti-IFX antibodies were found) or greater than 5 AU/mL when the patient is positive for anti-IFX antibodies. A value greater than 10 AU/mL reports that the patient has anti-ADL antibodies, whereas under this cut-point there are no anti-ADL antibodies detected. These values were validated as cut-offs by the Promonitor kits by performing a statistical evaluation of samples in different rheumatic pathologies. All patient samples were collected respecting the optimum collection time, which is immediately before drug administration.

The statistical analysis was performed using the SPSS statistical software, version 20.0, with a standardized p value of 0.05. Data was expressed as mean value ± standard deviation (SD). Differences between groups were recorded with the aid of Student t-test, whereas Spearman and Pearson tests were used for correlations.

Results

The study included 115 patients with established spondyloarthritis. After applying the above-mentioned exclusion criteria, 68 patients remained in the study. 48% (33 patients) were under IFX treatment, while 52% (35 patients) had ADL prescription. All patients in the study lot were Caucasian.

Results in the infliximab-treated subgroup

Out of the 33 enrolled patients currently under IFX treatment, 90% were males. The mean age was 37.8 years old and their mean disease duration was 89 months ± 56. All patients in the IFX cohort presented HLA B27 antigen positivity. At the time of diagnosis, 39% of patients required an MRI of the sacroiliac joints and these patients were identified with higher IFX serum levels (R=0.5, P=0.003). Regarding screening for tuberculosis, 27% of patients tested positive for Quantiferon Gold and were given prophylactic antibiotherapy before initiation of biologic therapy, according to local guidelines.

Detectable IFX serum levels were identified in 60% of patients (20 patients) while 40% (13 patients) had undetectable drug titers. There were no clinically relevant differences between the two subgroups regarding results of specific mobility tests, as seen in Table 1.

Concerning inflammatory markers, patients with undetectable IFX drug level had significantly higher ESR (P<0.001) and CRP (P=0.03). Patients with undetectable drug level had significantly higher disease activity scores such as BASDAI (P=0.02), ASDAS-ESR (P<0.001) and ASDAS-CRP (P<0.001) when compared to patients with detectable serum drug (mean score values in the above stated order were 1.52, 1.39 and 1.34 respectively), as shown in Table 2. Interestingly, serum IFX detection correlated to ASDAS scores (r= -0.58, P <0.001for ASDAS-ESR; r= -0.51, P=0.002 for ASDAS-CRP) but not to BASDAI. Detectable IFX levels also correlated to inflammatory biomarkers (r= -0.6 P<0.001 for ESR; r= -0.57 P<0.001 for CRP).

Mobility tests	Undetectable IFX serum level (mean±SD)	Detectable IFX serum level (mean±SD)	P
Schober test	4.49 ± 1.14	4.05 ± 2.19	0.5
Occiput-wall distance	1.23 ± 2.80	3.40 ± 5.31	0.01
Chin-chest distance	1.23 ± 1.58	3.20 ± 3.36	0.05
Finger-to-floor distance	14.08 ± 11.13	17.60 ± 14.61	0.46

Table 1: Mobility test results in patients with undetectable IFX serum level versus patients with detectable IFX serum level. IFX=infliximab, SD=standard deviation.

	Undetectable IFX serum level (mean ± SD)	Detectable IFX serum level (mean ± SD)	P
NSAID (days/week)	2.62 ± 1.85	1.7 ± 2.27	0.23
BASDAI	3.01 ± 2.24	1.52 ± 1.34	0.02
ASDAS-CRP	2.48 ± 1.13	1.34 ± 0.63	<0.001
ASDAS-ESR	2.77 ± 1.12	1.39 ± 0.63	<0.001
ESR (mm/h)	37 ± 27.67	9.5 ± 8.82	<0.001
CRP mg/dl	25.08 ± 41.58	4.06 ± 6.38	0.03
Dose (mg/kg)	5.11 ± 0.33	5 ± 0.077	0.49

Table 2: Differences in detectable versus undetectable IFX serum level patients regarding NSAID ingestion, inflammatory markers, BASDAI and ASDAS scores and IFX dose regimen. IFX=Infliximab, SD=Standard Deviation, NSAID=Non-Steroidal Anti-Inflammatory Drugs, BASDAI=Bath Ankylosing Spondylitis Disease Activity Index, ASDAS=Ankylosing Spondylitis Disease Activity Score, ESR=Erythrocyte Sedimentation Rate, CRP=C-reactive Protein.

We assessed the cohort's drug persistence expressed in months that is the time of continuous treatment from initiation to current point of study. In the IFX-positive group, mean drug persistence was 64 months ± 32.5, significantly lower (P=0.06) compared to patients with undetectable IFX level (45 ± 21 months). The time frame positively correlated to drug detection (r=0.352, P=0.04). Treatment persistence also correlated to disease duration (r=0.71, P<0.001). Patients with detectable and undetectable drug level did not differ in their dosage regimen (P=0.49) and the maintenance drug administration interval, whether at 6 or 8 weeks, positively correlated to quantitative serum IFX levels. Regarding previous biologic treatment, 9% of patients benefited from previous drug switch, two thirds had adalimumab prior to IFX treatment and one third had both adalimumab and etanercept prescription preceding IFX current therapy. IFX levels were lower in patients who had been switched from another anti-TNF agent (r -0.35, P=0.04).

Anti-IFX antibodies (AIA) were detected in 48% of IFX-treated patients. Patients with AIA had significantly higher disease activity scores than the AIA-negative patients (BASDAI P=0.002, ASDAS-ESR P=0.01 and ASDAS-CRP P=0.01). Higher mean ESR (27.5 ± 28.05) and CRP (21.24 ± 38.52) were detected in AIA positive patients. However the difference between the two groups did not reach statistical significance (P=0.007 and P=0.02, respectively). However, IFX antibody detection positively correlated to CRP values (r =0.38, P=0.02), but not to ESR levels (Table 3).

Out of the patients with detectable serum IFX, 75% had no positive anti-drug antibodies, while 25% were identified with positive AIA. 85% of patients with positive anti-IFX antibodies had undetectable serum drug, while 15% with no detectable biologic drug at determination had no identified antibodies.

Out of the anti-IFX antibodies positive patients, 18% (3 patients) had had previous exposure to one or two anti-TNF products (adalimumab and etanercept).

Regarding dose regimen, patients with AIA received a higher dose

when compared to AIA-negative patients (P=0.01). The presence of anti-IFX antibodies correlated with undetectable IFX drug levels. AIA presence negatively correlated to IFX drug serum titers (r=0-.493, P=0.004) and with the administration interval, every 6 or 8 weeks accordingly (r=0-.639, P<0.001). Mean drug persistence for AIA positive patients was 51.4 months ± 30.3 in comparison to the AIA-negative group (62 months ± 29.6, P=0.32). The presence of drug antibodies did not correlate with disease duration. Eighteen percent of patients with AIA suffered from infusion adverse reactions, exhibiting hypotension or cutaneous phenomena.

NSAID administration, expressed as number of days per week, positively correlated with BASDAI score in the study group (r=0.53 P=0.002) as well as with the 6-week regimen administration (r=0.43, P=0.01). NSAID use correlated inversely to serum IFX levels (r= -0.4 P=0.01) and positively correlated to AIA presence (r=0.44, P=0.009).

Results in the adalimumab-treated subgroup

The ADL cohort comprised of 35 patients, with 74% being of male gender. Their mean age was 40 years old, with disease duration of 102 months. HLA B27 antigen was positive in 91% of patients and 28% of them required MRI of the sacroiliac joints for diagnosis. Concerning Quantiferon tuberculosis screening, 28% of patients tested positive and needed treatment prophylaxis before initiation of biologic therapy. Twenty-two percent of patients presented a positive history of uveitis at disease onset, out of which 9% (2 patients) suffered recurrent ocular events while on ADL treatment.

When measuring ADL serum levels, 82% (29 patients) had detectable drug concentrations while 17% were ADL-negative. There were notable differences between the two subgroups, regarding disease activity assessed through BASDAI score that was significantly higher in patients with non-detectable drug level (P<0.001), with an elevated mean value of 6.3. Similarly, ASDAS-ESR and ASDAS-CRP were higher in these patients (P<0.001). Patients who tested negative for serum ADL proved a higher frequency of NSAID administration per week (Table 4).

Both ESR and CRP values were elevated in ADL-negative patients at the time of sample collection (P=0.002 and P=0.003, respectively).

The ADL serum concentration strongly correlated to the above mentioned scores (BASDAI-r= -0.612, P<0.001, ASDAS-ESR-r= -0.55, P=0.001, ASDAS-CRP-r= -0.561, P<0.001), NSAID utilization (r= -0.66, P<0.001) and inflammatory markers (ESR-r= -0.54, P=0.001, CRP-r= -0.52, P=0.001) but also to disease duration (r=0.636, P<0.001).

Within the detectable serum ADL subgroup, 86% of patients

	Anti IFX negative (mean ± SD)	Anti IFX positive (mean ± SD)	P
NSAID (days/week)	1.65 ± 2.34	2.50 ± 1.86	0.25
BASDAI	1.17 ± 0.88	3.1 ± 2.14	0.002
ASDAS-CRP	1.35 ± 0.63	2.25 ± 1.17	0.01
ASDAS-ESR	1.49 ± 0.69	2.40 ± 1.24	0.01
ESR (mm/h)	13.59 ± 14.02	27.50 ± 28.05	0.07
CRP mg/dl	3.96 ± 4.21	21.24 ± 38.52	0.07
Dose (mg/kg)	4.90 ± 0.30	5.19 ± 0.32	0.01

Table 3: Differences in patients with positive anti-IFX antibodies versus negative anti-IFX antibodies patients regarding NSAID ingestion, inflammatory markers, BASDAI and ASDAS scores and IFX dose regimen. IFX=infliximab, SD=standard deviation, NSAID=non-steroidal anti-inflammatory drugs, BASDAI=Bath Ankylosing Spondylitis Disease Activity Index, ASDAS=Ankylosing Spondylitis Disease Activity Score, ESR=erythrocyte sedimentation rate, CRP=C-reactive protein.

	Undetectable ADL serum level (mean ± SD)	Detectable ADL serum level (mean ± SD)	P value
NSAIDs (days per week)	4 ± 2.09	0.31 ± 0.76	<0.001
BASDAI	6.30 ± 3.21	1.57 ± 2	<0.001
ASDAS-CRP	4.80 ± 2.20	1.54 ± 1.59	<0.001
ASDAS-ESR	4.58 ± 2.38	1.46 ± 1.47	<0.001

Table 4: Differences in detectable versus undetectable ADL serum level patients regarding NSAID ingestion, BASDAI and ASDAS scores. ADL=Adalimumab, SD=Standard Deviation, NSAID=Non-Steroidal Anti-Inflammatory Drugs, BASDAI=Bath Ankylosing Spondylitis Disease Activity Index, ASDAS=Ankylosing Spondylitis Disease Activity Score, ESR=Erythrocyte Sedimentation Rate, CRP=C-Reactive Protein.

	AAA negative (mean ± SD)	AAA positive (mean ± SD)	P value
NSAIDs (days per week)	0.31 ± 0.78	2.78 ± 2.48	<0.001
BASDAI	1.28 ± 1.86	5.56 ± 2.87	<0.001
ASDAS-CRP	1.38 ± 1.52	4.18 ± 2.17	<0.001
ASDAS-ESR	1.29 ± 1.43	4.02 ± 2.11	<0.001
ESR (mm/h)	11.12 ± 18.01	43.89 ± 28.89	0.01
CRP mg/dl	7.67 ± 12.97	38.94 ± 30	0.001

Table 5: Differences in patients with positive anti-ADL antibodies versus negative anti-ADL antibodies patients regarding NSAID ingestion, inflammatory markers, BASDAI and ASDAS scores. AAA=anti-adalimumab antibodies, ADL=adalimumab, SD=standard deviation, NSAID=non-steroidal anti-inflammatory drugs, BASDAI=Bath Ankylosing Spondylitis Disease Activity Index, ASDAS=Ankylosing Spondylitis Disease Activity Score, ESR=erythrocyte sedimentation rate, CRP=C-reactive protein.

had negative anti-drug antibodies and 14% were found positive for antibodies. 83% of patients with no detectable serum drug had positive anti-ADL antibodies, while 17% had no anti-drug antibodies.

Out of the study population, 25% had positive ADL-antibodies. Patients with no anti-ADL antibodies had lower disease activity scores, namely BASDAI, ASDAS-ESR and ASDAS-ESR (P<0.001) as well as a decreased NSAID ingestion (P<0.001). As expected, values of ESR and CRP were greater in patient with present serum drug antibodies (P=0.01 and P<0.001) (Table 5). Drug serum level inversely correlated to the presence of antibodies (R=-0.36, P=0.03).

Mean values of BASDAI and ASDAS scores showed an inadequate disease control, indicating a highly active disease. ESR value was two times the upper limit of normal laboratory ranges and CRP level was approximately seven times higher. There were no significant differences in comparing mobility test results between the two groups, as shown in Table 6.

The presence of anti-drug antibodies correlated with BASDAI (r=0639, P<0.001) and both ASDAS-ESR (r=0.65, P<0.001) and ASDAS-CRP (r=0.58, P<0.001). It also associated with NSAID administration (r=0.67, P<0.001) and with CRP level but not with ESR (R=0.3, P=0.07).

The patient that experienced reaction at the injection site tested positive for anti-ADL antibodies.

As previously expressed, NSAID prescription was recommended as an "on demand" therapy between follow-up visits and frequency was expressed as days per week (dpw). Sixty-eight percent of patients had no NSAID ingestion during the week, while 6% had no more than one administration per week. Eleven percent used NSAID two times per week and 6% used regularly NSAID for three dpw. More frequent

usage (4, 6 and7 dpw) was related each by 3% of patients in this study. No patient reported consumption of 5 dpw.

When categorizing patients according to ASAS cut-offs for the ASDAS score, we note that 60% corresponded to "inactive disease", while 14% had a moderate disease state. Twenty four percent of patients fit in the "high" and "very high disease activity" category.

Neither the drug serum levels nor the presence of antidrug antibodies correlated to adalimumab dose per kilogram (r= -0.06, P=0.69 and r=0.13, P=0.43), or with previous anti-TNF administration (r= -0.25, P=0.13 and r=0.21, P=0.2), in patients who had switched biologic therapy. Twenty-two percent of patients on current ADL experienced prior anti-TNF treatment (either infliximab or etanercept), out of which 37% (3 patients) were confirmed as anti-IFX antibodies positive. Mean disease duration on the first anti-TNF agent was estimated at 42 months, while the second product had an 11 month drug persistence. All patients in this category were declared as secondary non-responders.

Discussions

There is no written consensus as to whether unique measurement or regular monitoring of anti-TNF serum levels and detection of anti-drug antibodies is of use in patients with spondyloarthritis, as opposed to rheumatoid arthritis where data stands in a satisfactory point [6,22-24]. There are studies on both IFX and ADL that indicate a higher failure occurrence rate in patients testing positive for ADA, leading to the hypothesis that developing ADA is the reason behind non-responsiveness [9,10,16,25,26]. However other researchers who found no relation between response to therapy and the presence of ADA suggest that this determination is not clinically relevant [25,27]. These controversial results might be due to the detection method or the timing of the sample collection [11,28,29]. Moreover the rate of ADA presence varies among studies and is estimated at 25% of SpA patients, relatively close to rheumatoid arthritis patients (33%) [30,31].

In this article we aimed to establish whether the above mentioned analysis can be an appropriate tool in assessing disease activity together with the traditional disease scores (BASDAI and ASDAS), in confirming non-responder patients or avoiding future drug-related adverse events.

An undetectable IFX serum level was found in 40% of patients and 68% of them presented positive anti-IFX antibodies. This percentage which shows that not all IFX-negative patients are AIA-positive may imply that the ELISA detection fails to identify drug immunocomplexes. This "immuno-serological" state correlated to BASDAI and ASDAS scores, with high-level CRP at the moment of serum drug detection and to an increased NSAID administration, which was prescribed "on demand" between follow-up visits., thus reflecting a subtherapeutic case. It has been previously mentioned that the presence of AIA leads to a shorter drug survival. Our study also showed that drug persistence was higher in patients with no AIA reflecting once again that anti-drug

Mobility tests	Undetectable ADL serum level (mean ± SD)	Detectable ADL serum level (mean ± SD)	P value
Schober test	3.266 ± 1.94	4.40 ± 1.92	0.19
Occiput-wall distance	2.833 ± 3.92	3.44 ± 4.69	0.76
Chin-chest distance	1.833 ± 2.71	2.05 ± 2.45	0.84
Finger-to-floor distance	15.16 ± 14	14.48 ± 12.32	0.9

Table 6: Mobility test results in patients with undetectable ADL serum level versus patients with detectable ADL serum level. ADL=adalimumab, SD=standard deviation.

antibodies play a major role in secondary non-responder patients. The fact that IFX antibody detection positively correlated to CRP values but not to ESR levels raises the question of which inflammatory marker would be the most prompt and precise in reflecting non-responsiveness to anti-TNF therapy. Patients with AIA received a higher total dose when compared to AIA-negative patients but we believe it is likely improbable that an increase in dose regime changes the outcome of AIA confirmed patients. However a French study [32] proved that higher IFX dose at initiation leads to lower AIA development, so AIA detection should be done early after biologic initiation.

All patients with previous IFX switch on other anti-TNF agents had positive anti-IFX antibodies, thus suggesting that switching did not improve their response to this type of biologics.

Eighty-two percent of patients with ADL treatment had detectable drug concentrations, while 17% were ADL-negative. Undetectable serum ADL correlated to the presence of ADL-antibodies thus highlighting the impact of immunogenicity in non-responder patients. Similarly to IFX observations, both determinations correlated to increased disease activity evaluated with BASDAI and ASDAS scores, inflammatory markers indicating insufficient disease control. Increased administration of NSAIDs also stands as evidence for the inadequate symptom control. Although 63% of patients with previous anti-TNF failure presented a good response to current ADL treatment with negative anti-IFX antibodies detection, we cannot estimate whether they were interrelated as suggested by the study of Plasencia et al. The latter found that failure to the first anti-TNF product attributable to the presence of ADA may predict a better response when switching to a second anti-TNF drug in patients with spondyloarthritis.

The present study shows that low drug serum concentrations and the presence of ADA are highly indicative of the patients' disease activity and it stands in line with previous studies that recommend including this detection in the regular clinical practice, at the very base of the therapeutic approach. Acknowledging that a patient has developed ADA together with the clinical assessment may lead to a faster drug switch and a better disease response. Furthermore, all patients who experienced drug related adverse events on both IFX and ADL were identified as ADA-positive, thus confirming other published studies [32,33].

One of the study limitation is that drug levels are quantified in a highly specific manner, using monoclonal antibodies to TNF alpha and to biologic product that are non-competitive when binding to the drug. Thus the kit is able to provide us with the product's bioavailability which is the fraction of the free drug reaching systemic circulation. Anti-drug antibodies are assessed using bridging ELISA that detects free neutralizing anti-idiotypic antibodies in the circulation. It does not measure immunocomplexes formed between the biologic drug and ADA [34].

Unfortunately the study cohort included a relatively small number of patients with a single determination of serum drug and anti-drug antibodies. Moreover, patients were not classified according to their disease form – axial or peripheral.

The literature on this particular topic does not offer subsets of drug level cut-off values therefore this issue still remains to be established in patients with SpA. Further studies are needed to identify the predictive value of these cut-offs so that we can categorize patients in therapeutic or subtherapeutic levels of active substance.

Conclusion

We hereby support the idea of drug level measurement and anti-drug antibody detection as a completion of a clinician's tools in assessing disease activity. This information can help optimizing drug therapy by switching it faster in non-responder patients and avoiding continuous administration in patients experiencing adverse events. Data still remains to be collected in patients with SpA regarding other anti-TNF drugs and the cost-effectiveness of this determination.

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