

Immunological profile in patients with rheumatoid arthritis and biological therapy

Anca E. Muşetescu, Paulina Ciurea, Anca Roşu

Department of Rheumatology, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania

Abstract. Objective: To assess the changes in autoantibody titres in patients with rheumatoid arthritis (RA) after treatment with anti-TNF- α agents and to correlate these variations with treatment response. Material and methods: In a prospective study we assessed 130 patients with established RA, diagnosed according to American College of Rheumatology criteria, eligible for treatment with infliximab, etanercept and adalimumab and followed for antibody production. Rheumatoid factor (RF), anti-cyclic citrullinated peptide (CCP) antibodies, antibodies against nuclear antigens (ANA), anti-double strand (ds) DNA and anticardiolipin (aCL) antibodies were monitored at baseline and regularly on a period of 24 months of treatment with TNF- α inhibitors. Results: Significant decrease in RF and anti-CCP titres were observed at 24 months correlated with disease activity ($p < 0.001$) while maintenance of high titres was observed in patients with unfavorable response. ANA positivity increased mostly in infliximab and in patients with unfavorable response. Although Anti-dsDNA and aCL antibody titre increased in dynamics, mean titre remained below the cut-off value for positivity and no relationship with response was found. Conclusion: TNF- α inhibitors induce significant decrease in RF and anti-CCP antibody correlated with treatment response and increase in ANA, anti-dsDNA and aCL antibodies.

Key Words: rheumatoid arthritis, anti-TNF- α therapy, autoantibody profile.

Copyright: This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Corresponding Authors: A. E. Muşetescu, e-mail: anca_musetescu@yahoo.com

Introduction

Rheumatoid arthritis (RA) is a systemic chronic autoimmune-inflammatory disease, with still uncertain etiopathogenesis characterized by inflammation of synovial joints with infiltrating-proliferative evolution, destructive and marked disabling potential involving tumor necrosis factor (TNF- α), a pivotal proinflammatory cytokine in inflammation and joint destruction. The research is focused in the last decade with the advance of biological response modifying therapies on the clinical benefit of anti-TNF α agents in RA and subsequent questions that arise upon the induction of autoantibody synthesis (Solomon 2013). Nevertheless the mechanism linking anti-nuclear antibodies (ANAs), anti-double stranded (ds)DNA and anticardiolipin (aCL) antibody production to treatment response, loss of efficacy (Yukawa et al 2011), immunogenicity, unfavorable clinical outcome mostly due to autoimmune complications such as drug-induced lupus (DIL) is still a matter of debate (De Bandt et al 2005). Numerous studies proved great advances in RA treatment using infliximab (IFX), etanercept (ETA) and adalimumab (ADA) that showed highly effective in most RA patients (Canhao et al 2012) thus still many patients have persistent active disease, high titres of rheumatoid factors (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies, specific markers for destructive joint disease. The inconsistencies in literature between the prevalence of several antibodies expressed in patients treated with anti-TNF- α inhibitors (Eriksson et al 2005; De Rycke et

al 2005), the profile of RF and anti-CCP antibodies throughout anti-TNF- α treatment (Alessandri et al 2004; De Rycke et al 2005) and the relationship between DAS28 (Disease Activity Score, evaluating 28 joints) and autoantibody titres encouraged us to undertake a prospective follow-up study on RA patients treated with infliximab, etanercept and adalimumab and follow the immunological profile.

Material and method

We carried out a prospective study on 130 patients with established RA according to ACR criteria, considered eligible for therapy with anti-TNF- α agents (infliximab N=44 patients, etanercept N=44 patients, adalimumab N=42 patients). The study aims the follow-up of patients with RA receiving anti-TNF- α therapy for a period of 24 months with complete evaluation at regular intervals by placing the immunological profile in a clinical and biological context, while monitoring treatment response according to EULAR response and improvement criteria. Patient monitoring regarding disease activity (DAS28) and treatment response according to EULAR was conducted periodically from the time of study entry (time T1), after 12 weeks (T2), at 24 weeks (T3) and then every 6 months (T4 – 12 months, T5 – 18 months, T6 – 24 months) up to 2 years (T6), when the study was completed. We used the expression $DASTiTi$ where $DASTiTi = DAST1 - DASTi$, $i = \{2-6\}$ to represent improvement from baseline DAS28. Autoantibody profile: rheumatoid factor,

anti-CCP antibodies, anti-nuclear antibodies, anti-dsDNA antibodies and anticardiolipin antibodies (aCL) were determined before treatment at study entry (T1), at 24 weeks (T3), at 12 months (T4) and 24 months (T6) at the end of the follow-up. The study protocol was designed according to the Declaration of Helsinki and all patients enrolled in the study signed an informed written consent before starting biological anti-TNF- α therapy. The research draft was validated and approved by the University Ethics Committee.

Demographic, clinical and biological data of the patients at study entry are presented in Table 1.

Laboratory analysis of the antibodies determined the presence and titre (where relevant) for the following: rheumatoid factor (RF) IgM by immunoenzymatic ELISA (Enzyme-Linked Immunosorbent Assay, Genesis Diagnostics Ltd, UK) with cut-off values for normal < 16 U/ml, equivocal 16-24 U/ml and positive > 24 U/ml, anti-CCP2 by "sandwich" ELISA (Inova Diagnostics Inc., San Diego, CA), with cut-off values for normal < 20 U/ml, equivocal between 20-39 U/ml and positive > 40 U/ml, antinuclear antibodies (ANA) detected by indirect immunofluorescence (IIF) with in-house HEP-2 cells slides according to the standard procedure, anti-dsDNA antibodies (anti-dsDNA) determined through ELISA (Inova Diagnostics Inc., San Diego, CA) with negative referent values <40 U/mL, equivocal between 40 and 60 U/mL and positive values > 60 U/ml, anticardiolipin antibodies (aCL, IgG) by ELISA with cut-off values for normal < 11 GPLU/ml, equivocal between 11 - 13 GPLU/ml and positive > 13 GPLU/ml.

Continuous variables were expressed as mean and standard deviation. In the analytical phase, "t" Student test or ANOVA analysis of variance were applied to compare averages. Comparison between groups was performed with t-test (parametric variables) or Mann-Whitney test (non-parametric variables) for continuous variables and chi-square, Mantel-Haenszel or Fisher's exact test for categorical variables, as needed. Correlations were determined by Spearman's correlation for non-parametric variables. All statistical analyses were performed with SPSS software. A p-value < 0.05 was considered significant.

Results

In terms of specific immunological markers for RA at study entry, both RF and anti-CCP antibodies were identified in high titres (RF - 87.18 ± 49.73 U/ml, anti-CCP antibodies 159.35 ± 72.24 U/ml) with no significant differences between therapy groups. These values drawn attention to the aggressiveness of the disease in the cohort studied, all patients included on biological therapy having an initial DAS28 > 5.1 as well as to the marked erosive and destructive potential. For both determinations, mean values were at least 3 times the cut-off value for positivity. A strong positive association was observed between the anti-CCP antibody titres and RF ($rT1=0.758$, $p=0.001$). We noted a strong positive association between RF titre and initial DAS28 values ($rT1=0.6$, $p<0.001$) as well as between anti-CCP antibody titres and initial DAS28 ($rT1=0.746$, $p=0.001$).

At the time of inclusion on anti-TNF- α therapy we identified a 3.8% ANA positivity, 1.53% anti-dsDNA antibody positivity and 2.30% aCL positivity while mean titres of anti-dsDNA antibodies and aCL antibodies have been found in normal range for the reference laboratory.

Analysis of the baseline immunological profile did not show significant differences between the three therapy study groups with high mean titres for RF and anti-CCP antibodies and normal values for anti-dsDNA and aCL antibodies (Table 2).

Dynamic evaluation of RF, anti-CCP, anti-dsDNA and aCL antibodies throughout the study showed changes generated by the anti-TNF- α treatment.

In the entire study group there is a tendency to decrease of the RF under the influence of therapy, from the mean baseline value of 87.18 ± 49.73 U/ml to a final average of 22.63 ± 23.23 U/ml. The decrease is not statistically significant between treatments but between monitoring times ($T_i T_j$ $p<0.05$, $i=\{1,3,4\}$, $j=\{3,4,6\}$), demonstrating the effect of biological therapies to significantly reduce the RF titre, regardless of the anti-TNF- α preparation administered (Table 3).

There was a strong positive correlation between RF and DAS28 values, both at the start of the study ($r=0.605$ T1, $p<0.001$) and at its end ($r=0.751$ T6, $p<0.001$).

Twenty-four months analysis regarding RF profile on the three therapeutic regimens and depending on the type of DAS28 EULAR response demonstrates a significant progressive decrease between monitoring times (T1, T3, T4, T6) in patients with good EULAR response for all three therapeutic regimens to a mean value of 17.87 ± 6.208 U/ml, a progressive decrease to a mean value of 36.00 U/ml (above the cut-off value for the reference laboratory) for moderate response and an initial tendency to decrease up to T4 followed by a rise of the mean values to 85.25 ± 59.138 U/ml (three-times the cut-off values) at T6 in patients with unfavorable response for the three therapeutic regimens.

As with RF, there is a decreasing trend of anti-CCP antibodies. Although for the entire study group the mean approaches normal values, the average remains positive when treated with ETA (44.32 IU/ml) and IFX (44.35 IU/ml) (Table 4).

In the entire study group for patients in whom therapy was considered with good response we obtained a decrease of about 128 IU/ml of the anti-CCP antibody titre, representing 80% of the baseline value.

Twenty-four months analysis of anti-CCP antibody profile on the three therapeutic regimens and depending on the type of DAS28 EULAR response proved a significant progressive decrease between monitoring times (T1, T3, T4, T6) in patients with favorable response for all three therapeutic regimens to a mean value of 31.32 ± 12.32 U/ml (tending to approach normal values), a persistence of high titre of 137 U/ml after 24 months in patients with moderate response and an initial tendency to decrease up to T4 followed by a rise of the mean values up to 157.50 ± 50.951 U/ml (four-times the cut-off values) at T6 in patients with unfavorable response for the three therapeutic regimens.

During anti-TNF- α treatment the presence versus the absence of ANA showed statistically significant differences between treatments at times T3 ($p<0.001$), T4 ($p<0.001$) and T6 ($p<0.001$), manifested as a tendency to positivity, more striking in IFX therapy. In adalimumab study group we encountered the slightest tendency to positivity in 11.9% patients after 24 months of treatment, followed by etanercept 11.4% at 12 months and 15.9% at 24 months and the highest rate in infliximab patients 65.9%, respectively 61.4% at 12 and 24 months of treatment. Lack of response was encountered mostly in patients with ANA positivity.

Table 1. Demographic, clinical and biological data of the patients at study entry

Variable	Infliximab (N = 44)	Etanercept (N = 44)	Adalimumab (N = 42)
F/M	40/4	37/7	36/6
Mean age (years) ± SD	54.09±5.96	53.8±5.50	54.07±6.60
Urban/Rural origin%	56.8/43.2	52.3/47.7	59.5/40.5
Education level MH/L%	84.1/15.9	86.4/13.6	83.3/13.7
Occupation active/retired	45.5/54.5	59.1/40.9	52.4/47.6
Disease duration (years) ± SD	5.36±2.91	5.55±2.98	4.93±2.85
Corticosteroids (median dose 8 mg/day) %	34.1	40.9	38.1
ESR (mm/hour)	50.09±13.00	50.27±13.98	51.88±14.05
CRP (mg/l)	37.16±16.42	38.30±18.38	36.9±17.4
DAS28 baseline(T1)	6.892±0.833	6.923±0.834	6.916±0.834
DAS28 24months (T6)	3.24±1.200	3.13±0.95	2.91±0.43
Lost(T6) %	15.9	6.8	7.1
Response type according to DAS28 (T6)%			
good	75	84.1	90.5
moderate	0	2.3	0
no response	9.1	6.8	2.4

N – number of patients, F – female, M – male, age and disease duration are presented with mean value ± standard deviation, education level MH – medium, high, L – limited, ESR – erythrocyte sedimentation rate in mm/hour, CRP – C reactive protein in mg/l, DAS28 – disease activity score evaluating 8 joints, presented with mean value ± standard deviation, Lost – patients who did not complete the study due to abandon, lack of response or side effects.

Table 2. The immunological profile at baseline differentiated on groups of treatment (T1)

Immunological profile	Infliximab (N = 44)	Etanercept (N = 44)	Adalimumab (N = 42)
RF (U/ml)	89.07±47.77	87.14±52.34	85.33±50.09
Anti-CCP abs (U/ml)	155.59±72.79	162.66±69.75	159.81±75.71
Anti-dsDNA abs (U/ml)	23.16±9.28	20.73±7.31	24.14±9.70
aCL abs (GPLU/ml)	5.11±2.27	5.77±1.89	5.12±2.12

RF – rheumatoid factor IgM, anti-CCP abs – anti-CCP antibodies, anti-dsDNA abs – anti – double strand DNA antibodies, aCL abs – anticardiolipin antibodies, expressed in mean value ± standard deviation

Table 3. RF throughout study monitoring

Therapy	RF T1	RF T3	RF T4	RF T6
Infliximab	89.07±47.77	53.58±26.82	36.74±18.19	21.46±19.22
Etanercept	87.14±52.34	54.70±28.37	35.07±16.91	28.15±33.38
Adalimumab	85.33±50.09	54.43±28.52	34.44±17.80	17.95±8.19
p-value	$p_{13}<0.001$	$p_{34}<0.001$	$p_{46}<0.001$	

RF – rheumatoid factor IgM, T1 – baseline, T3 – 24 weeks, T4 – 12 months, T6 – 24 months, expressed in mean value U/ml ± standard deviation, p - correlation between monitoring time

Table 4. Anti-CCP antibodies throughout study monitoring

Therapy	CCPT1	CCPT3	CCPT4	CCPT6
Infliximab	155.59±72.79	94.23±47.79	63.54±22.26	44.35±45.16
Etanercept	162.66±69.75	93.68±35.66	67.12±20.54	44.32±41.74
Adalimumab	159.81±75.71	97.14±50.09	67.95±18.84	33.90±20.73
p-value	$p_{13}<0.001$	$p_{34}<0.001$	$p_{46}<0.001$	

CCP– anti-CCP antibodies, T1 – baseline, T3 – 24 weeks, T4 – 12 months, T6 – 24 months, expressed in mean value U/ml ± standard deviation, p - correlation between monitoring times

Table 5. Anti-dsDNA antibodies during anti-TNF- α therapy over 24 months monitoring

Therapy	dsDNA T1	dsDNA T3	dsDNA T4	dsDNA T6
Infliximab	23.16 \pm 9.28	28.64 \pm 9.67	64.85 \pm 60.22	74.62 \pm 68.70
Etanercept	20.73 \pm 7.31	24.66 \pm 7.53	27.19 \pm 7.19	30.29 \pm 7.84
Adalimumab	24.14 \pm 9.70	26.73 \pm 8.61	29.28 \pm 8.71	31.38 \pm 8.72

dsDNA - anti-dsDNA antibodies, T1 – baseline, T3 – 24 weeks, T4 – 12 months, T6 – 24 months, expressed in mean value U/ml \pm standard deviation

Table 6. aCL antibodies during anti-TNF- α therapy over 24 months monitoring

Therapy	aCL T1	aCL T3	aCL T4	aCL T6
Infliximab	5.11 \pm 2.27	6.02 \pm 2.28	9.15 \pm 4.64	8.70 \pm 5.01
Etanercept	5.77 \pm 1.89	5.68 \pm 2.24	8.05 \pm 3.05	8.20 \pm 4.00
Adalimumab	5.12 \pm 2.12	5.98 \pm 2.21	8.26 \pm 3.83	8.31 \pm 4.56

p-value

p>0.05

aCL - anti-cardiolipin antibodies, T1 – baseline, T3 – 24 weeks, T4 – 12 months, T6 – 24 months, expressed in mean value U/ml \pm standard deviation

Significant differences were recorded for anti-dsDNA antibodies, presented as a tendency to positivity for all three therapies, stronger in patients treated with IFX at T6 mean titre of 74.62 \pm 68.705 U/ml (cut-off value for positivity 60 U/ml), for 29.54% patients, especially recorded after (T4) 12 months (p=0.002) and T6 (p<0.001) (Table 5).

The effect of the anti-TNF- α treatment on the anticardiolipin antibodies revealed a tendency to increase in titre mostly in patients with IFX (p>0.05) thus with a mean of 8.39 \pm 4.493GPLU/ml, below the positivity threshold (cut-off 13GPLU/ml) for the entire study group as well as differentiated on therapy groups. 10.28% of patients proved positivity for aCL for the entire study group, without differences between the therapies used. Individual variability distorts the series of values with a variation between 2 and 25 U/ml (Table 6) and no correlation was found with response type.

Therapy was discontinued in a total of 23 patients, non-responders (five patients), who lost response (9 patients, assessed at the end of follow-up), abandonment (1 patient - ADA) or adverse effects (8 patients - two cases of reactivation of tuberculosis on IFX, a pulmonary embolism in a patient with etanercept, a lupus-like syndrome - IFX, two cases of severe hepatocytolysis ETA and IFX, two allergic reactions - IFX). Most side effects were recorded at IFX therapy.

Discussion

Regarding specific immunological markers for RA, the erosive nature and unfavorable prognosis for long-term joint destruction both rheumatoid factor and anti-cyclic citrullinated peptide were identified in elevated titres at baseline, before initiation of anti-TNF- α treatment (Bongi *et al* 2004) with no significant differences between the three study groups. High titre of these antibodies correlates with the disease activity before anti-TNF- α treatment. Data from several studies did not find a correlation between anti-CCP and disease activity (Serdaroglu *et al* 2008) and we consider the differences in results due to the indication of anti-TNF- α therapy according to the protocol in our country, addressed to more severe RA cases non-responsive to at least two conventional disease modifying anti-rheumatic drugs.

Dynamic immunological profile analysis showed a significant decrease at two years of treatment for RF and anti-CCP antibodies titres regardless of the anti-TNF therapy administered (p<0.001) correlated with disease activity (Atzeni *et al* 2006), similar data being found in literature with differences regarding monitoring time (Benucci *et al* 2006; Vis *et al* 2008). We found rheumatoid factor titre normalization of the cohort analyzed at 24 months of biological therapy with persistent high titre in patients with unfavorable response. Regarding the anti-CCP antibody titre although a significant decrease was registered during 24 months of follow-up mean values remain above the upper limit of normal, especially in patients with infliximab and etanercept, the increase in dynamic being associated with unfavorable response. Although decrease in RF and anti-CCP titre was found in IFX treated patients changes in IgM-RF and anti-CCP failed to correlate with treatment response in a study by Bruns *et al* (2009). Similar data to our findings were published by Cuchacovich *et al* (2008) and Bos *et al* (2008). Several studies in literature report a significant decrease of the titre for anti-CCP antibodies as a response to anti-TNF- α therapy although recent data from a meta-analysis of large study groups refute this hypothesis, indicating that the status of RF and anti-CCP is not associated with the clinical response to anti-TNF- α treatment in RA patients (Qianwen *et al* 2014), thus anti-CCP being an independent predictor of radiological damage and progression in RA patients (Berglin *et al* 2006) in general associated with a worse prognosis. Heterogeneity of the groups under study in terms of demographic and biological characteristics, type of TNF- α blocker therapy used, lack of a placebo comparator, different inclusion protocols in each country create certain bias that must be analyzed in the future.

To all TNF- α antagonists were described lupus-like syndrome, autoimmune serology conversion, with the emergence of human anti-chimeric, ANA, anti-dsDNA (Bacquet-Deschryver *et al* 2008) and anticardiolipin antibodies (Jondosttir *et al* 2004), without knowing the precise impact of the occurrence of these antibodies on efficacy, therapeutic effect or increased toxicity (De Bandt *et al* 2005).

We noticed in the analyzed group a tendency to positivity for ANA significant (p<0.001) after 6 months of treatment, stronger

in IFX study group where more than half of the patients were ANA positive at 12 and 24 months, most patients ANA positive showing no response. A retrospective study of infliximab (Yukawa *et al* 2011) proved that positivity for ANA significantly increased to 40% and was associated with lack of efficacy. Similar data were reported in psoriasis (Hoffmann *et al* 2011) where induction of ANAs and anti-dsDNA antibodies was associated with lack of response and induction of anti-IFX antibodies. Anti-dsDNA antibodies showed an increasing trend for all three therapies significant at one year ($p=0.002$), positivity occurring in 11.21% of patients, mostly in the IFX group (29.54%), being recorded a single lupus-like syndrome associated with the increase of these antibodies (Favalli *et al* 2002; Benucci *et al* 2005). Lupus-like syndromes were described in literature not only to infliximab but also after etanercept (Shakoor *et al* 2002) and adalimumab (van Rijthoven *et al* 2006). We have not found statistically significant correlations with the response type in none of the three studied groups and also between the increase in titre and lack of effectiveness. A recent survey of the literature shows positivity up to 26% of anti-dsDNA antibodies in a group of 111 patients with IFX (Yukawa *et al* 2011) positivity being considered a marker for lack of response.

Anticardiolipin antibodies as well expressed a tendency to increase to the entire study group with positivity frequency of 10.28% mostly in IFX patients though with a mean within the normal references. No correlation was found with the type of response. There are several publications relating the occurrence of aCL in RA patients treated with infliximab with an incidence of 21–47% after initiation of treatment (Morris *et al* 2001; Ferraro-Peyret *et al* 2004; Jonsdottir *et al* 2004). In the Ferraro-Peyret *et al* study on infliximab, the researchers found 21% of new aCL IgM antibodies with no significant relationship with infusion side effects, while Jonsdottir reported a significantly lower number of patients treated with infliximab aCL positive who met ACR20 criteria as well as more frequent serious infusion reactions. Our data is similar to those published by Visvanathan *et al* (2006) who reported a low 11.6% incidence of the development of IgM aCL in patients with early active RA treated with infliximab plus methotrexate, with higher frequency of infections in IFX-treated patients not reflective of differences in aCL status. In our study the thromboembolic event occurred in a patient with etanercept without aCL positive antibodies. Literature data available regarding aCL profile in RA under anti-TNF- α treatment is relatively limited due to multiple biases generated by the study population, follow-up period and laboratory methods of analysis for aCL.

Conclusions

Anti-TNF- α treatment in patients with RA showed a marked influence on antibody profile monitored in dynamics. After 24 months of treatment a significant decrease of rheumatoid factor and anti-CCP antibody titre was registered correlated with disease activity and treatment response. A marked increase in ANA positivity especially in the infliximab treated group was associated with unfavorable response. Although an increase in titre of anti-dsDNA and anticardiolipin antibodies was detected mean values remained within the normal range and no significant correlation was found with treatment response.

Acknowledgements

All authors contributed equally to the study.

References

- Alessandri C, Bombardieri M, Papa N, *et al*. Decrease of anti-cyclic citrullinated peptide antibodies and rheumatoid factor following anti-TNF α therapy (infliximab) in rheumatoid arthritis is associated with clinical improvement. *Ann Rheum Dis* 2004;63:1218-21.
- Atzeni F, Sarzi-Puttini P, Dell'Acqua D, de Portu S, Cecchini G, Cruini C, *et al*. Adalimumab clinical efficacy is associated with rheumatoid factor and anti-cyclic citrullinated peptide antibody titer reduction: a one-year prospective study. *Arthritis Research & Therapy* 2006;8:R3
- Bacquet-Deschryver H, Jouen F, Quillard M, Ménard JF, Goëb V, Lequerré T, *et al*. Impact of three anti-TNF α biologics on existing and emergent autoimmunity in rheumatoid arthritis and spondylarthropathy patients. *J Clin Immunol* 2008;28:445-455.
- Benucci M, Turchini S, Parocchi P, Boccaccini P, Manetti R, Cammelli E, Manfredi M. Correlation between different clinical activity and anti-CCP (anti-cyclic citrullinated peptide antibodies) titres in rheumatoid arthritis treated with three different tumor necrosis factors TNF- α blockers, *Recenti Orog Med* 2006;97(3):134-9.
- Benucci M, Li Gobbi F, Fossi F, Manfredi M, Del Rosso A. Drug induced lupus after treatment with infliximab in rheumatoid arthritis. *J Clin Rheumatol.* 2005;11(1):47-9.
- Berglin E, Johansson T, Sundin U, Jidell E, Wadell G, Hallmans G, *et al*. Radiological outcome in rheumatoid arthritis is predicted by presence of antibodies against cyclic citrullinated peptide before and at disease onset, and by IgA-RF at disease onset. *Ann Rheum Dis* 2006;65(4):453-8.
- Bongi SM, Manetti R, Melchiorre D, Turchini S, Boccaccini P, *et al*. Anti-cyclic citrullinated peptide antibodies are highly associated with severe bone lesions in rheumatoid arthritis anti-CCP and bone damage in RA. *Autoimmunity* 2004;37:495–501.
- Bos WH, Bartelds GM, Wolbink GJ, de Koning MHMT, van de Stadt RJ, *et al*. Differential response of the rheumatoid factor and anticitrullinated protein antibodies during adalimumab treatment in patients with rheumatoid arthritis. *Journal of Rheumatology* 2008;35:1972–1977.
- Bruns A, Nicaise-Roland P, Hayem G, Palazzo E, Dieude P, *et al*. Prospective cohort study of effects of infliximab on rheumatoid factor, anti-cyclic citrullinated peptide antibodies and antinuclear antibodies in patients with longstanding rheumatoid arthritis. *Joint, Bone, Spine: Revue du Rhumatisme* 2009;76:248–253.
- Canhao H, Rodrigues AM, Mourao AF, Martins F, Santos MJ, *et al*. Comparative effectiveness and predictors of response to tumour necrosis factor inhibitor therapies in rheumatoid arthritis. *Rheumatology Oxford* 2012;51:2020–2026.
- Cuchacovich M, Catalan D, Wainstein E, Gatica H, Soto L, *et al*. Basal anti-cyclic citrullinated peptide (anti-CCP) antibody levels and a decrease in anti-CCP titres are associated with clinical response to adalimumab in rheumatoid arthritis. *Clinical & Experimental Rheumatology* 2008;26:1067–1073.
- De Bandt M, Sibilia J, Le Loët X, Prouzeau S, Fautrel B, Marcelli C, *et al*, the Club Rhumatismes et Inflammation: Systemic lupus erythematosus induced by anti-tumour necrosis factor alpha therapy: a French national survey. *Arthritis Res Ther* 2005;7:R545-551.
- De Bandt M, Sibilia J, Le Loët X, Prouzeau S, Fautrel B, Marcelli C, *et al*, the Club Rhumatismes et Inflammation. Systemic lupus erythematosus induced by anti-tumour necrosis factor alpha therapy: a French national survey. *Arthritis Res Ther* 2005;7:R545–551.

- De Rycke L, Baeten D, Kruithof E, Van den Bosch F, Veys EM, De Keyser F. Infliximab, but not etanercept, induces IgM anti-double-stranded DNA autoantibodies as main antinuclear reactivity: biological and clinical implications in autoimmune arthritis. *Arthritis Rheum* 2005;52:2192-2201.
- De Rycke L, Verhelst X, Kruithof E, et al. Rheumatoid factor, but not anticyclic citrullinated peptide antibodies, is modulated by infliximab treatment in rheumatoid arthritis. *Ann Rheum Dis* 2005;64:299-302.
- Eriksson C, Engstrand S, Sundqvist K-G, Rantapaa-Dahlqvist S. Autoantibody formation in patients with rheumatoid arthritis treated with anti-TNF α . *Ann Rheum Dis* 2005;64:403-7.
- Favalli EG, Sinigaglia L, Varenna M, Arnoldi C. Drug-induced lupus following treatment with infliximab in rheumatoid arthritis. *Lupus* 2002;11:753-5.
- Ferraro-Peyret C, Coury F, Tebib JG, Bienvenu J, Fabien N. Infliximab therapy in rheumatoid arthritis and ankylosing spondylitis-induced specific antinuclear and antiphospholipid autoantibodies without autoimmune clinical manifestations: a two-year prospective study. *Arthritis Res Ther* 2004;6:R535-43.
- Hoffmann JH, Hartmann M, Enk AH, Hadaschik EN. Autoantibodies in psoriasis as predictors for loss-of-response and anti-infliximab antibody induction. *Br J Dermatol* 2011;165:1355-1358.
- Jondostir T, Forslid J, Van Vollenhoven A, Harju A, Brannemark S, Klareskog L, et al. Treatment with tumor necrosis factor α antagonists in patients with rheumatoid arthritis induces anticardiolipin antibodies. *Ann Rheum Dis* 2004;63:1075-8.
- Lv Q, Yin Y, Li X, Shan G, Wu X, Liang D, et al. The status of rheumatoid factor and anti-cyclic citrullinated peptide antibody are not associated with the effect of anti-TNF α agent treatment in patients with rheumatoid arthritis: a meta-analysis. *PLoS One* 2014;9(2):e89442.
- Morris A, Morris C, Hernandez C. Anticardiolipin antibodies developing during infliximab therapy. *Arthritis Rheum* 2001;44:S373.
- Serdaroglu M, Cakirbay H, Deger O, Cengiz S, Kul S. The association of anti-CCP antibodies with disease activity in rheumatoid arthritis. *Rheumatol Int* 2008;28:965-970.
- Shakoor N, Milchalska M, Harris CA, Block JA. Drug-induced systemic lupus erythematosus associated with etanercept therapy. *Lancet* 2002;359:579-80.
- Solomon G. Immunogenicity: implications for rheumatoid arthritis treatment. *Bull Hosp Jt Dis* 2013;71(3):200-3.
- van Rijthoven AWAM, Bijlsma JWJ, Canninga-Van Dijk M, Derksen RHW, Van Roon JAG. Onset of systemic lupus erythematosus after conversion of infliximab to adalimumab treatment in rheumatoid arthritis with a pre-existing anti-dsDNA antibody level. *Rheumatology* 2006;45:1317-19.
- Vis M, Bos WH, Wolbink G, et al. IgM-rheumatoid factor, anti-cyclic citrullinated peptide, and anti-citrullinated human fibrinogen antibodies decrease during treatment with the tumor necrosis factor blocker infliximab in patients with rheumatoid arthritis. *J Rheumatol* 2008;35(3):425-8.
- Visvanathan S, Wagner C, Smolen J, et al. IgG and IgM anticardiolipin antibodies following treatment with infliximab plus methotrexate in patients with early rheumatoid arthritis. *Arthritis Rheum* 2006;54(9):2840-44.
- Yukawa N, Fujii T, Kondo-Ishikawa S, et al. Correlation of antinuclear antibody and anti-double stranded DNA antibody with clinical response to infliximab in patients with rheumatoid arthritis: a retrospective clinical study. *Arthritis Res Ther*. 2011;13(6):R213.

Authors

- Anca E. Muşetescu, Department of Rheumatology, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, 2-4 Petru Rareş Street, 200349, Craiova, Romania, EU, e-mail: anca_musetescu@yahoo.com
- Paulina Lucia Ciurea, Department of Rheumatology, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, 2-4 Petru Rareş Street, 200349, Craiova, Romania, EU, e-mail: ciurea_paulina@yahoo.com
- Anca Roşu, Department of Rheumatology, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, 2-4 Petru Rareş Street, 200349, Craiova, Romania, EU, e-mail: rosuanca61@yahoo.com

Citation Muşetescu AE, Ciurea P, Rosu A. Immunological profile in patients with rheumatoid arthritis and biological therapy. *HVM Bioflux* 2015;7(1):11-16.

Editor Stefan C Vesa

Received 14 December 2014

Accepted 29 December 2014

Published Online 29 December 2014

Funding None reported

**Conflicts/
Competing
Interests** None reported