ANTIDRUG ANTIBODIES AND DISEASE ACTIVITY IN PATIENTS WITH RHEUMATIC DISEASES TREATED WITH TNF-A-BLOKERS IN THE BULGARIAN POPULATION

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Abstract: Rheumatic diseases have a vast social and economic impact due to the percentage of the disabilities and due to the price of the drugs, used for their treatment. The effects of the antidrug antibodies can be divided in two aspects: loss of effect from the treatment and development of side effects. Both of the times the result is discontinuation of the treatment or treatment with non-effective and at the same time very expensive drug. For the rheumatologist it will be extremely important to find and prove the factors that influence the production of these antidrug antibodies. In this study we pay attention to the production of these antibodies and their correlation to the loss of the effect and/or increase in the disease activity indexes.
Keywords: antidrug antibodies, TNF-alpha, etanercept, adalimumab, disease activity

INTRODUCTION

Treatment of the inflammatory diseases of the joints undergoes different stages- from symptomatic treatment in the past centuries, through Disease-modifying antirheumatic drugs (DMARDS) in the last century, to reach the biologic treatment used today.

Most often the modern treatment of Rheumatic diseases includes TNF-alpha blockers.

TNF-α found in 1975 is a cell mediated glycoprotein participating in the systemic inflammation and the immune response. It is produced by activated macrophages, NK-cells, neutrophils, mastocytes, eosinophiles and neurons. TNF-α has a key role in different immune and inflammatory processes- cell activation, proliferation and differentiation of immune cells, cell death through necrosis and apoptosis. Variety of experimental studies through the years have found a wide spectrum of biologic effects. On cellular level it has the ability to induce proliferation and differentiation as well as apoptosis and necrosis which predefines its participation in a variety of rheumatic, hematologic and oncologic diseases.

In 1993 the effect of the inhibitors of TNF-alpha in the prevention of joint damage was proven. The following newly synthesized drugs has shown significant effect in the treatment of the inflammatory joint diseases but due to the fact that they are foreign for the human organism they induce production of antidrug antibodies.

As inflammatory joint diseases are chronic conditions rheumatologist should have some target to achieve. In RA, AS and PsA this target is low disease activity and if possible-remission.

Treating rheumatoid arthritis (RA) with a goal or "treat to target" strategy is a therapeutic proposal taken from cardiovascular and endocrine literature. It proposes that the therapeutic target in RA should be a state of remission, or an alternative goal could be a low disease activity.

Biologic drugs are widely used nowadays and they are believed to be capable to achieve low disease activity and or remission. Despite the expectations some of the patients do not respond to therapy or they respond at first and later start to lose response to treatment. Being immunogenic makes the BA capable of triggering an immune reaction against them which results in production of anti-drug antibodies. Through the years it was proven that these ADA may alter the response to treatment and even cause unwanted side effects.

Through the years in different trials rheumatologist tried to find out what factors pose effect on the production of these ADA. There are some studies that implement that ADA may alter disease activity and cause worsening of the symptoms. On the other hand EULAR recommendations from 2016 state that presence of ADA in the serum of the patient does not affect the disease activity and therefore treatment should not be stopped.

OWN RESULTS

The aim of our study was to check and prove the dependence between the production of antidrug antibodies and the disease activity in the Bulgarian population.

MATERIALS AND METHODS

We included a total of 163 patients, divided in the following groups:

A: 92 patients treated with adalimumab aged 24-72 years, mean age 49.84±10.8

B:56 patient on treatment with etanercept aged 18 - 70 years, mean age 45.61±13.4

C:15 healthy controls aged 27-50 years, mean age 38.73±8.9

All the patients were followed-up on 3,6,12,24 month since treatment initiation. ADA were measured on each visit as well as CRP, ESR. Complete patient history and physical examination was taken. In order to calculate disease activity we used approved disease activity indexes:

For Rheumatoid arthritis (RA) DAS28- variables used are: number of swollen and tender joints, PtGADA, ESR/ CRP results . According to the results activity may be divided in the following groups: low ≤3.2, moderate 3.2 up to 5.1, high disease activity above 5.1.

For Psoriatic Arthritis (PsA) DAPSA- Here number of tender and swollen joints, patient Pain index, PtGADA and CRP are used. The disease activity is graded as follows : 5-14 low disease activity, 14-28 moderate and above 28 high disease activity

For Ankylosing spondylitis – BASDAI, consisting of different components graded 0-10, 0-no problem and 10 is highest imaginable severity of the symptom. This index is used to evaluate the 5 most common symptoms in AS- fatigue, back pain, joint pain/effusion, enthesitis, morning stiffness. The final score 0-50 is divided by 5 and a result from 0-10 is received. Score less than 4 is graded as low disease activity and score more than 4 is high disease activity.

Antibodies present in the serum of the patients was measured in Biochemistry Department in Medical University of Plovdiv. ELISA method and IDK® TNFα ELISA kits, produced by Immundiagnostik were used. All the data was statistically evaluated through SPSS v.25.

Results : On the third month of treatment in the adalimumab group no patients had ADA , on the 6th month 7 (7.6%) of them had, on the 12m-14 (15.21%) and on 24 month 26(28.26%)

For etanercept the results are as follows: 3m-0 patients, 6m-4 (7.1±3.46), 12 month 5 patients (8.9±3.83), 24 month 11 patients (19,64±5.35)

Table 1. Results from patients treated with adalimumab – Group A-patients without ADA, Group B patients with ADA (n/p% ±Sp).

Patients	3m	6m	12m	24m
Group A-without ADA	92 (100%)	85 (92,39±2,77)	78 (84.78±3.76)	66 (71.74±4.72)
Group B-with ADA	0 (0%)	7 (7,6±2,77)	14 (15.21±3.76)	26 (28.26±4.72)
U-criteria		u=21,68	u=13.10	u=8.18
Significance level	0.00001	0.0001	0.0001	0.0001

P – significance between patients from group A and group B divided by months

28,26% of the patients have ADA on 24th month of the treatment which is significantly higher than the previous months and clearly shows the tendency for increase of this percentage in time .

Table 2. Results from patients on etanercept treatment- Group A-patients without ADA, Group B-patients with ADA.

Patients	3m	6m	12m	24m
Group A-without ADA	56(100 %)	52 (92,85±3.47)	50 (89.28±4.17)	45(80.35±5.35)
Group B-with ADA	0 (0%)	4(7,15±3.47)	6 (10.72±4.17)	11 (19.65±5.35)

U-criteria **Significance level**	0.0000 1	u=23.03 0.0001	u=20.86 0.0001	u=2.83 0.0001

25 of the patients in Group A are with low disease activity, 64- with moderate and only 3- with high disease activity. During the next months there is significant increase in the number of patients with low disease activity. There is no significant difference between the patients with low disease activity during month 12 and month 24. (U=0,67, p>0.05). The difference between the number of patients with moderate disease activity during month 12 and 24 in group A is not significant, as well. (U=1,25, p>0.05).

In group B there are no patients with low disease activity throughout the whole study. By analysing the data it is proven that patients from Group B have significantly higher disease activity on month 12 (U=3,51, p=0,001) and 24 (U=19,29, p=0,0001)

Table 3. Distribution of patients treated with adalimumab according to disease activity and presence of ADA (n/p% ±Sp).

Patient Group	**Disease activity**	**3m n=92**	**6m n=92**	**12m n=92**	**24m n=92**
Group A-without ADA	**Low activity**	25(27.17±4.66)	28(30.43±4.82)	51(55,43±5,21)	46(50,0±5,24)
	Moderate activity	64(69.56±4.79)	55(59.78±5.14)	27(29,34±4.77)	19(20,65±4,24)
	High activity	3(3,26±1.86)	2 (2.17±1.52)	0	1(1.08±1.08)
Group B-with ADA	**Low activity**	0	0	0	0
	Moderate activity	0	3 (3.26±1.86)	3 (3.26±1.86)	6 (6.52±2.58)
	High activity	0	4 (4.34±2.13)	11(11.95±3.4)	20(21.73±4,32)

Table 4. Distribution of patients treated with etanercept according to disease activity and presence of ADA (n/p% ±Sp).

Patient Group	**Disease activity**	**3m n=56**	**6м n=56**	**12м n=56**	**24м n=56**
Group A-without ADA	**Low activity**	22(39.28±6.58)	24(42.85±6.67)	31(55,35±6.70)	32(57.14±6.67)
	Moderate activity	32(57.14±6.67)	26(46.42±6.72)	18(32.14±6.29)	13(23.21±5.69)
	High activity	2(3,57±2.50)	2(3,57±2.50)	0	0
Group B-with ADA	**Low activity**	0	0	0	0
	Moderate activity	0	1(3.26±1.86)	2(3,57±2.50)	4(11.95±3.4)
	High activity	0	3(4.34±2.13)	4(11.95±3.4)	7(12.5±4,45)

DISCUSSION

Our results show that the number of patients, treated with adalimumab, and producing antidrug antibodies are 0 on month 3, 7,6%±2,77% on month 6, 15.21%±3.76% on 12 and 28.26%±4.72% on month 24. This coincides with Mok C et al finding who find ADA in 31% of the patients treated with adalimumab. Wolbink G.J. studied 51 patients with PsA , treated with infliximab. In 22 of them they found ADA. Most of them had decreased treatment response. Ducourau E. et al studied 108 patients treated with biologics-17 with RA and 91 with spondyloarthropaties- AS, PsA. In 21 of them (19%) ADA were positive, the mean period for their production was around 3.7 months. Their presence corresponded to decreased effect to the treatment and low concentration of the biologic agent in the serum.

Disease activity significantly depends on the presence of the antidrug antbodies which coincides with the literatutre (Rudalweit et al, Anderson et al.) and which we believe is credible. Bartelds et al believes that there is connection between the production of ADA and drug concentration in serum. He believes that decreased drug concentration affects therapeutic response and the disease activity. According to EULAR recommendations from 2016 the presence of ADA not always predicts change in the disease activity and effect of the therapy. Therefore therapy should not be discontinued if ADA are present in patient`s serum.

Rheumatic diseases have enormous social and economic impact both due to the big percentage of disabilities caused by them and due to their expensive price. The effects of the antidrug antibodies can be divided in two aspects: loss of effect from the treatment and development of side effects. Both of the times the results is discontinuation of the treatment or treatment with non-effective and at the same time very expensive drug.

CONCLUSIONS

Algorhytms for treatment initiation should be created and they should include taking precise patient history, bad habits, disease activity. Dynamic ADA detection should become part of the treatment follow up and this may help minimize cases with therapy resistance- primary or secondary and at the same time will lead to maximum effect from treatment.

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