

THE OCCURRENCE RISK OF DEMYELINATING LESIONS IN PATIENTS WITH RHEUMATOID ARTHRITIS AND ANTI-TNF α BIOLOGICAL THERAPY

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Abstract

The aim of the study was to evaluate the occurrence risk of demyelinating lesions in rheumatoid arthritis patients treated with anti-TNF α biological therapy. The study was undertaken on 45 patients with rheumatoid arthritis distributed in two groups. The study group consisting of 25 patients received anti-TNF α therapy, while the control group consisting of 20 patients, received only conventional synthetic drugs. All patients were evaluated every two years using cranial magnetic resonance imaging (MRI) from the beginning of therapy for all 6 years of study. We noticed an increase in the number and dimensions of demyelinating lesions in the study group, but inactive, without gadolinium enhancement and without neurological clinical correspondence. Anti-TNF α biological therapy could be a favouring factor in the development of demyelinating brain lesions, but without any clinical correspondent and imaging inactive.

Rezumat

Articolul a avut drept scop evaluarea apariției leziunilor demielinizante cerebrale la pacienți cu poliartrită reumatoidă care primesc tratament biologic cu anticorpi anti-TNF α . Au fost luați în studiu 45 de pacienți cu poliartrită reumatoidă împărțiți în două grupuri. Grupul de studiu, constituit din 25 de pacienți, a primit tratament anti-TNF α , iar grupul control, care a cuprins 20 de pacienți, a primit doar tratament convențional de sinteză. Toți pacienții au fost evaluați imagistic prin rezonanță magnetică - IRM cranian de la începutul terapiei și pe parcursul celor 6 ani de studiu, la un interval de 2 ani. S-a constatat că la grupul de studiu leziunile demielinizante au fost mai multe și au crescut în dimensiuni, dar nu au fost active, nu au captat gadolinium, iar pacienții nu au prezentat elemente clinice. Terapia biologică anti-TNF α poate fi un factor favorizant în determinarea apariției de leziuni demielinizante cerebrale, însă fără a fi active imagistic și fără corespondent clinic.

Keywords: rheumatoid arthritis, anti-TNF α therapy, demyelinating lesions

Introduction

Biological therapy is a relatively new acquisition in the treatment of rheumatoid arthritis (RA) which requires careful monitoring of these patients regarding the disease activity and occurrence of adverse events. In certain instances, current literature is leaving free interpretation whether these events are associated with the therapeutic agent, with the disease itself or unlinked to either of them [18]. While research is targeted in the last decade on the extraordinary clinical benefits of anti-TNF α agents, subsequent questions arise upon their safety and induction of adverse reactions that can occur over time, such as cerebral demyelinating lesions with the risk of multiple sclerosis clinical framing. Multiple sclerosis (MS) is a chronic disease of the central nervous system characterized by episodes of inflammation and focal demyelination, disseminated

to multiple locations over time, through a process of axonal degeneration in a person with genetic susceptibility to the disease [3].

The diagnosis of MS is confirmed using McDonald criteria for dissemination in time and space, and uncertainty of the demyelinating lesions considering MS improbability criteria. MRI (magnetic resonance imaging) dissemination in time criteria include the presence of a demyelinating lesion or the addition of a new bright lesion in T2 sequence that occurs at any time, compared to a reference scan, while MRI dissemination in space criteria include MRI Dissemination in Space (DIS) as demonstrated by using Barkhof and Tintore criteria and adding the spinal cord lesions [4, 13, 14, 16]. To date, the new 2016 MAGNIMS recommendations include optic neuritis and the cortical location of demyelinating

lesions in the imaging diagnosis of multiple sclerosis in order to improve the McDonald DIS criteria [6].

Materials and Methods

Patients

We carried out a prospective study over six years, between 2009 and 2015.

Our study group included 25 patients (17 women and 8 men), aged between 18 - 67 years old, all of urban origin, diagnosed with RA and non-responsive to conventional synthetic drugs, whom according to the national protocol, were qualified for biological therapy with chimeric anti-TNF α antibodies (infliximab), fully humanized antibodies (adalimumab) and antibodies against the TNF α receptor – the dimeric fusion protein (etanercept).

Study design

The control group included 20 patients with rheumatoid arthritis (12 women and 8 men) aged between 24 - 65 years old, 6 of rural and 14 of urban origin, in treatment only with conventional synthetic drugs.

The study protocol was designed according to the Declaration of Helsinki, validated and approved by the University Clinical Hospital of Craiova, Romania, Ethics Committees. Patients enrolled in the study signed an informed written consent before starting conventional synthetic or biological anti-TNF α therapy, also included in the Romanian Registry of Rheumatic Diseases and for the study entry.

All patients from the study group and the control group underwent brain MRI every 2 years, from the initiation of the biological therapy until 2015. At the time of study entry no patient had clinical features of brain damage. The distribution by the type of biological therapy was as follows: 14 patients were treated with etanercept, 6 patients with adalimumab and 5 with infliximab.

The study protocol included MRI interpretation and neurological evaluation performed every two years, starting from time (T) T-0 - before initiation of the biological therapy, T-1 - two years of treatment, T-2 - four years of treatment, T-3 - six years of biological treatment and more frequent rheumatologic evaluation, every six months, in order to reiterate the treatment indication.

Data analysis

Cerebral MRI interpretation included the evaluation of the involved regions (frontal, periventricular), the supra and infratentorial disposition of the demyelinating lesions, optic nerve neuritis, while in advanced forms of multiple sclerosis there were also registered demyelinating lesions that occur in the spinal cord.

In order to avoid bias, MRI evaluation was performed on the same device, with the same evaluator for all patients throughout the study period, blinded for the clinical frame.

Rheumatologic evaluation was performed according to EULAR recommendations using composite measuring tools in order to appreciate disease response to biological treatment after a complete physical examination. The DAS 28 index combines information relating to the number of swollen and tender joints on a count of 28 joints, in addition to a measure of pain - visual analogue scale from 0 to 100 (0 - no pain, 100 - maxim pain), and the acute phase response measured by C reactive protein, with a total score ranging from 0 to 9.4 and is used to evaluate a patient's response to treatment, with a value of < 3.2 defined as the threshold for a low disease activity state and < 2.6 as the threshold for remission. C reactive protein is the best predictor for joint inflammation; therefore it was included in DAS 28 index and was continuously monitored.

Neurological clinical evaluation included segmental muscle strength testing (0 to 5 - normal strength), examination of the cranial nerves, exteroceptive and proprioceptive sensitivity - quantified as normal, diminished or abolished. In some cases where the clinical signs were not clear, the modification of MS criteria can increase the safety zone for a correct diagnosis of multiple sclerosis [8, 14].

Results and Discussion

All patients receiving anti-TNF α therapy completed the study with no adverse events to impose treatment cessation over the six-year of monitoring. A good response to treatment evaluated through DAS 28 was recorded with a significant improvement of the disease activity every two years to a status of low disease activity - mean DAS 28 of 2.416 ± 0.323 at the end of the study (Table I).

Table I
DAS-28 follow-up

Evaluation	Number of patients	Mean	SD	Minimum	Maximum	p (t-test)*
T0 (initial)	25	6.952	0.308	6.3	7.5	
T1 (24 months)	25	4.02	0.824	2.5	5.4	< 0.00001
T2 (48 months)	25	3.14	0.631	2.3	4.2	< 0.00001
T3 (final)	25	2.416	0.323	2.1	3.5	< 0.00001

t-test between consecutive evaluations

In this composite index, C reactive protein has an important role in offering the value of the index,

through a quantitative determination in g/L and the normal values being considered between 0 - 5 g/L.

Monitoring C reactive protein (CRP) levels throughout the study period, a good response to therapy was recorded for the study group, with a significant decrease of the inflammatory marker, while it was maintained within normal values for the control group.

The study group started with a CRP average score of 13.9 g/L at T-0 with a prompt decrease to an average of 3.4 g/L at T-1. Evaluation at T-2 showed

an average within the normal range of 2.3 g/L, maintained at T-3 evaluation time.

A different behaviour could be observed for CRP in the control group, where at T-0 time the average score was 12.8 g/L with a decrease to 7.9 g/L at T-1 time. Measurements at T-2 and T-3 time revealed the maintaining of the CRP levels above the upper limit of the normal range, 6.7 g/L and respectively 6.8 g/L (Figure 1).

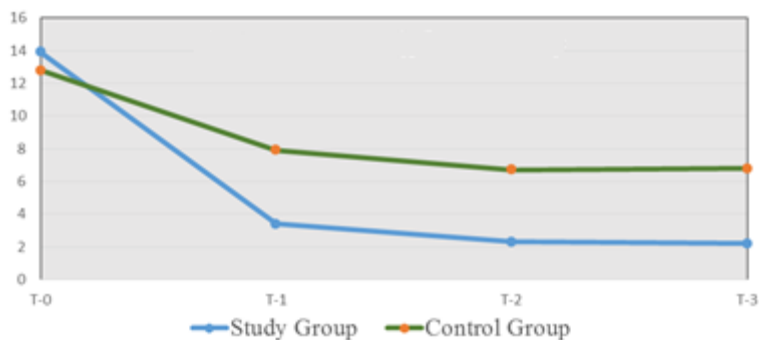


Figure 1.
C Reactive Protein follow-up (g/L)

The CRP levels decreased faster in the first two years (period T-1) for the study group with a CRP annual rate of 5.25 g/L, compared to the annual decrease rate for the control group of 2.45 g/L.

For the next two years (period T-2) the CRP annual decrease rate was similar for both groups (0.55 g/L study group *versus* 0.6 g/L control group) and for the last two years (period T-3) the CRP annual decrease rate was approximately zero (Figure 2).

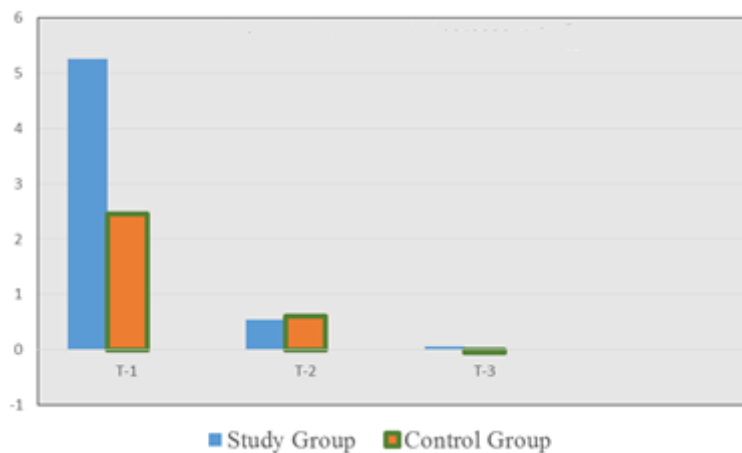


Figure 2.
C Reactive Protein - annual decrease rate (g/L)

MRI images were interpreted for demyelinating lesions disposal in the periventricular, cortical–juxtacortical, infratentorial, spinal cord and optic nerve areas, their number, the growth rate of injuries and the formation rate of new demyelinating lesions. Lesions were quantified in terms of their activity through the enhancement of gadolinium.

Initial MRI evaluation performed at T-0 revealed in the study group two patients, each one with one demyelinating lesion of 1 mm, respectively of 2 mm,

before initiation of biological therapy. The observed lesions were non-enhancing for gadolinium, considered as neurologically inactive, subsequently with an occurrence rate of $(2/25) \times 100 = 8\%$. None of these two patients presented clinical neurologic signs of MS.

In the control group we identified one patient with a 1 mm demyelinating lesion, non-enhancing as well, representing an occurrence rate of $(1/20) \times 100 = 5\%$. T-1 evaluation after two years of treatment showed a multiplication rate of 0% in the study group with

biological treatment (number of patients with new demyelinating lesions) and of 5% in the control group – one patient $((1/20) \times 100)$ that generates a disease rate of 10% (patients with lesions)

To note, in the sagittal T2-FLAIR weighted sections, MRI showed hypointense lesions tangential parasagittal without gadolinium enhancement and a parietal lesion in a patient with etanercept for 2 years and after 2 years of treatment, for the same patient, same sections, device and imaging evaluator noticed parietal bilateral demyelinating lesions without tendency to merge, focal, isolated. The same lesion was tangential to the lateral ventricle. No lesion was gadolinium-enhanced.

T-2 evaluation after four years of treatment revealed a multiplication rate for two patients in the control group of $(2/20) \times 100 = 10\%$ that determined a rate of illness of $10\% + 10\% = 20\%$. Instead, for the study group we detected in two patients a multiplication rate of $(2/25) \times 100 = 8\%$ and a rate of illness of $8\% + 8\% = 16\%$.

At T-3 evaluation time, after six years of treatment, a multiplication rate of $(3/25) \times 100 = 12\%$ has been found for the study group (three patients) that determined an illness rate of $16\% + 12\% = 28\%$ while for the control group, a multiplication rate of $(0/20) \times 100 = 0\%$ to a stagnating illness rate of 20% (Figure 3).

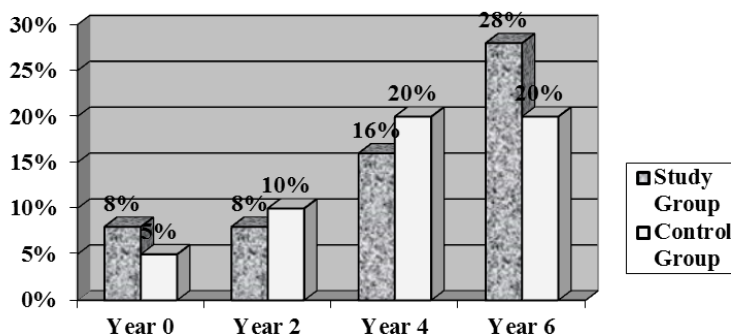


Figure 3.

Illness rate for the study and control group over the monitoring time

Taking into consideration the increase in the number and dimension of the lesions in patients with demyelinating lesions from the study group we can consider that: $(5/25) \times 100 = 20\%$ of the patients with demyelinating lesions from the study group presented an increased risk of augmentation in number and size of the lesions; $(3/8) \times 100 = 37.5\%$ of the patients from the study group presented a lower risk of increase of the number and size of the lesions; $(5/8) \times 100 = 62.5\%$ of the patients from the study group presented an increased risk of augmentation in number and size of the lesions (Figure 4).

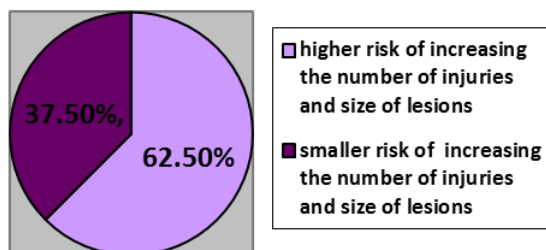


Figure 4.

The distribution rate of evaluation of the number and size of lesions

The analysis of the rate of illness in the study group demonstrated that it doubled after four years of treatment with anti-TNF α agents, starting from 8%

to 16%. After another two years we have noticed an increase in the rate of demyelinating lesions from 16% to 28%, than can suggest that the lesions disseminated in space and time, while for the control group, a multiplication rate from $(0/20) \times 100 = 0\%$ to 20% was noticed. We remarked that apparently the lesions have increased in number and size after 6 years of treatment with TNF α blocker.

A strict correlation could not be done between the occurrence rate and the age of the patients, as in the younger patients it hasn't been noticed an increase in the demyelinating lesions compared to those seen in patients over 45 years. Also, as conventional MRI is not sensitive to early alterations of microstructural structure in the normal appearing white matter, possible changes associated to Binswanger's disease in the elderly, with demyelinating lesions similar in imaging expression to those observed in patients with biological therapy, are very difficult to assess [12].

We considered another statistic method to demonstrate the significance of this study. Odd ratio (OR) is a measure of association between two particular properties (A and B) in a group/population. This ratio determines the relative odds that property B (e.g. disease) will occur in the presence of property/exposure to A (e.g. risk factor/medical history).

OR = 1 Exposer has no effect on the odds of outcome.

OR > 1 Exposure means higher odds of outcome.

OR < 1 Exposure means lower odds of outcome.

For this reason we used ODD Ratio [19] in order to show that the study is not statistically significant due to the small number of patients included. ODDS for the study group in exposed patients (to have lesions as exposed) were 7/18. ODDS for the control group in non-exposed were 4/16. ODDS RATIO, (ratio ODDS Exposed/ODDS non-exposed): $(7/18)/(4/16) = 1.5556$ (Table II).

Table II

Odd ratio calculator

Odds ratio	1.5556
95% CI	0.3832 to 6.3142
Z statistic	0.618
Significance level	p = 0.5365

Finally the ODDS to have lesions in the study group are 1.5556 higher than the ODDS to have lesions in the control group (not-significant).

The common element of demyelinating diseases is the status of immune dysregulation, overstressed by the biological therapy. MS and RA share a common genetic background related to the Human Leukocyte Antigen – antigen D Related (HLA DR) of the major histocompatibility complex (MHC) located on chromosome 6, as the existence of HLA DR3 and DR4 alleles can be a common feature and could explain the occurrence of *de novo* demyelinating lesions of the brain in these patients before the initiation of the biological therapy [7, 9]. There are two forms of TNF α : a transmembrane protein (Tm TNF) and a soluble form (sTNF) each one responsible of different actions according to the bound receptor. Both forms interact with these receptors but the soluble form has an increased affinity for the TNFR1 (TNF-receptor 1), responsible for cell apoptosis, while TNFR2 (TNF-receptor 2) function is less known as it could promote both cell proliferation and programmed cell death [2]. TNF α plays an essential role in oligodendrocytes and myelin damage, early in the disease being involved in demyelination and essential for remyelination in more advance stages of the disease [1]. It is possible that adding to the gene (HLA DR) and immune (T lymphocyte) profile, the biological therapy to be just one favouring factor for the development of demyelinating lesions of the brain or maybe the anti-TNF alpha agents act as main drivers in patients genetically predisposed to MS. The subsequent follow up in patients with TNF α blockers should highlight the evolution of brain demyelinating lesions and if there is a risk of becoming active [11, 16].

A recent analysis of Fernandez Espartero *et al.* in Spain compared literature studies from a systematic literature review with the Spanish Biological Registry BIOBADASER (Spanish Registry of Biological Therapies in Rheumatic Diseases) and FEDRA (Spanish Pharmacosurveillance Database of Adverse

Drug Reactions) and failed in finding a positive association between the use of anti-TNF agents in inflammatory diseases and the occurrence of demyelinating disorders. The incidence of MS in Spanish population (0.022 - 0.038) did not differ from that observed in anti-TNF treated patients (0.01 - 0.33) [5].

Quite different from our study that proved no clinical signs and demyelinating MRI lesions detected after a mean period of four years of treatment, several literature studies report a mean of 7.5 months from biological therapy initiation and the debut of the neurological symptomatology, with significant improvement after biological treatment cessation and specific neurological treatment [10, 16, 20]. The *Journal of Neurology and Neuroscience* reported only 2 cases out of 15 with MRI suggestive proof of demyelination [11], after anti-TNF α therapy, and the Department of Rheumatology in Carilion, Virginia, USA, shows only 3 cases in 476 patients with intramedullary demyelinating lesions [13].

By observing the persistence of demyelination after stopping the anti-TNF α treatment, it has been suggested the fact that these therapeutic agents may only be a trigger in starting the demyelinating process with further evolution of this process being independent from that point on. So, the management of these patients, after the interruption of anti-TNF, should be identical to those with idiopathic demyelinating diseases.

In our study appears the well-known isolated radiological syndrome (IRS), proven on different groups of patients to be the clinical precursor for MS, or other neurological diseases with a demyelinating substrate [12].

Conclusions

The presence of demyelinating lesions that appeared before the initiation of biological therapy may be possible on a degenerative aging background, hypothesis confirmed in the control group.

Following the imaging assessment, although demyelinating lesions appeared, which have grown in number and dimension, criteria of multiple sclerosis or other demyelinating disease were not met, and furthermore, patients were not neurologically by symptomatic.

We cannot say that demyelinating lesions may be favoured by the HLA DR genetic background as we recorded them in both groups with rheumatoid arthritis, or be the consequence of biological therapy on the cerebral vascular wall, but we can appreciate that are imaging inactive and without clinical expression.

The anti-TNF alpha therapy could be a promoter in developing demyelinating lesions with or without

neurological manifestations, but it was not a determining factor for the disease itself.

Further monitoring over longer periods of time on significant number of patients should be of valuable interest in evaluating the impact of biological anti-TNF α therapy on demyelinating lesions.

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