Advanced magnetic resonance imaging of the brain in patients treated with TNF-alpha blocking agents

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ABSTRACT

Objective. *Neurological symptoms have been reported in patients treated with anti-TNF-alpha. In a pilot study we evaluated the effect of anti-TNF-alpha on cerebral parenchyma using advanced Magnetic Resonance (MR) techniques.*

Methods. *Seven patients with a systemic inflammatory disease (5 rheumatoid arthritis, 2 psoriatic arthritis) had Magnetization Transfer Imaging, Diffusion Weighted Imaging (DWI) and Magnetic Resonance Spectroscopy (MRS) of the brain before and after administration of anti-TNF-alpha. Four patients were neuropsychologically evaluated.*

Results. *After treatment with TNF-alpha blocking agents the Magnetization Transfer Ratio histogram Peak-heights (MTR-Pht) of the white and gray matter decreased ($p < 0.01$ and $p < 0.05$ respectively). The Apparent Diffusion Coefficient for the white and gray matter and the metabolite ratios in the centrum semiovale did not significantly change after therapy. Neuropsychological assessment showed no difference before and after anti-TNF-alpha.*

Conclusions. *The decrease of the MTR-Pht after anti-TNF-alpha therapy suggests loss of parenchyma integrity; however, these changes could not be attributed to inflammation or demyelination based on our complementary DWI and MRS data. The decrease of the MTR-Pht did not result in decreased cognitive function.*

Introduction

TNF-alpha is an important cytokine in the pathogenesis of diseases such as rheumatoid arthritis (RA) and multiple sclerosis (MS) (1). Blockade of TNF-alpha is indeed effective in patients with RA and psoriatic arthritis (PA) (2). Despite high expectations, the use of anti-TNF-alpha in MS patients was disappointing and a randomized trial was adjourned prematurely because of an increase in exacerbations (3).

In patients treated with anti-TNF-alpha diverse neurological symptoms have been reported (4-6). In many patients the Magnetic Resonance (MR) findings were suggestive for demyelination or white matter injury as seen in MS patients (4), however, the number of patients with neurological symptoms did not exceed the number of MS patients in the general population. For this reason, amongst others, a direct link between the use of TNF-alpha blockade and demyelination is still under debate (4-6).

Advanced MR techniques are useful in the evaluation of brain parenchyma abnormalities. A decline of the Magnetization Transfer Ratio Peak-height (MTR-Pht), calculated from Magnetization Transfer Imaging (MTI), can detect and quantify gliosis, demyelination, oedema and/or inflammation (7, 8). The reproducibility of MTI is adequate as no significant changes were detected in healthy subjects after one year (9). In patients with MS as well as systemic lupus erythematosis, changes of the MTR-Pht is correlated with clinical symptoms (7, 10). Additional Apparent Diffusion Coefficient (ADC) calculated from the Diffusion Weighted Imaging (DWI) and the metabolite ratios derived by Proton MR Spectroscopy (MRS), can be helpful for further characterization of the histological changes in the brain (11, 12).

In order to detect possible alterations of the brain parenchyma, we performed MR scans before and after the administration of anti-TNF-alpha in patients with RA or PA.

Materials and methods

Patients

Seven patients from the department of Rheumatology of the Leiden University Medical Center were included: 5 RA patients, as defined by the American College of Rheumatology criteria (13), and 2 patients with psoriatic arthritis. All RA patients were rheumatoid factor positive, 4 had erosions and the median DAS_{28} score was 5.13 (range 3.7-5.59). Both PA patients had erosive joint destruction. The median age was 57 years (range 36-67) and median disease duration was 2.6 year (range 1.2-14.6). Except for one patient, who already used infliximab, all patients had active rheumatic disease despite previous disease modifying anti-rheumatic drug (DMARD) usage. The median number of (previous) used DMARDs was 3

(range 1-5). The current DMARDs were methotrexate (n = 5), sulphasalazine (n = 2), infliximab (n=1) and prednisone (n = 2). The patients had no obvious neurological co-morbidity such as stroke or MS. Written informed consent was obtained and the ethics committee approved the protocol.

Therapy

The TNF-α antagonist (infliximab (n = 1), etanercept (n = 3) or adalimumab (n = 3) were administered directly after the first scan. The second scan was performed 24 hours after the time of maximal plasma concentration in all patients corresponding with 1, 3 and 7 days after the first scan for infliximab, etanercept and adalimumab respectively.

MR Imaging protocol

All MR scans were carried out on a Philips Gyroscan 1.5T MR scanner (Philips, the Netherlands). Scans covered the whole brain in all sequences. All patients were subjected to T2 weighted and FLAIR MR of the brain. *MTI* was performed using a 3D gradient-echo pulse sequence. *DWI:* Diffusion-weighted echo-planar imaging also covering the entire brain was performed. From the DWI images an average DWI was calculated and secondary the Apparent Diffusion Coefficient (ADC) was calculated. *MRS:* ^{1}H-MRS was performed with a double spin-echo PRESS sequence. The volume-of-interest was selected in the left centrum semi-ovale of each subject. N-acetyl-aspartate (NAA), choline and total creatine peaks were quantified. The following ratios were calculated from the obtained metabolites: NAA/choline, NAA/creatine and choline/creatine.

Image processing

The ADC and MTR images were segmented to select the brain parenchyma as well as white and gray matter voxels.

Neuropsychological assessment

In this pilot study 4 patients performed a short neuropsychological test battery prior to the first and second scan. The first 3 patients were not tested because neuropsychological assessment was added during the study period. The following tests, covering global cognitive functioning, memory, executive functioning and attention, were used(14): Mini-Mental State Examination, Hopkins Verbal Learning Test, Stroop Colour-Word test, Symbol-Digit Modalities test and Bourdon.

Statistical analyses

We used the paired samples student's t-test to test for significant differences between the results of MTI, DWI and MRS before and after therapy. Statistical analyses were performed using SPSS 12.0.1 statistical analysis software.

Results

MR: T1/T2 weighted scans performed before and after the use of a TNF-α blocking agent did not show any brain abnormalities on visual inspection.

MTI: After therapy the mean MTR-Pht of the *white* matter decreased significantly (p = 0.009) from 0.117 (standard deviation (SD) 0.0055) to 0.112 (SD 0.0053) (Fig. 1). Also the decline of the MTR-Pht of the *gray* matter was significant (p = 0.039) from 0.0921 (SD 0.0065) to 0.0852 (SD 0.0073). The mean MTR value determined in the *white* and *gray* matter before therapy was 36 (SD 0.68) and 33.06 (0.56) and after therapy 35.94 (SD 0.79) and 32.66 (0.92) respectively.

DWI: Although an increase of the mean ADC in the *gray* matter was detected (before 830 (SD 21) and after 852 (SD 18)), the changes were not significantly different (Fig. 2).

MRS: The NAA/choline, NAA/creatine and creatine/choline ratios did not change (Fig.3).

Neuropsychological assessment: In the 4 patients who were neuropsychologically tested, the test results were within the normal range and did not alter after the administration of anti-TNF-alpha.

Discussion

Our observational study demonstrated a decrease of the mean MTR-Pht in the normal appearing white and gray matter in patients with a systemic inflammatory disease following anti-TNF-alpha administration. A decline in the MTR-Pht suggests loss of parenchymal

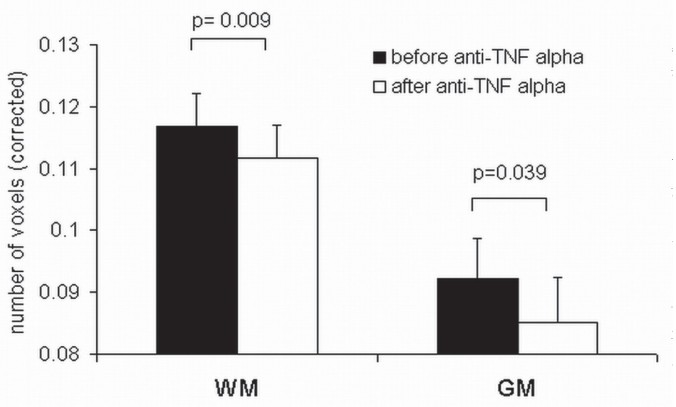

Fig. 1. Mean MTR-Pht before and after anti-TNF-alpha.

GM: gray matter; WM: white matter

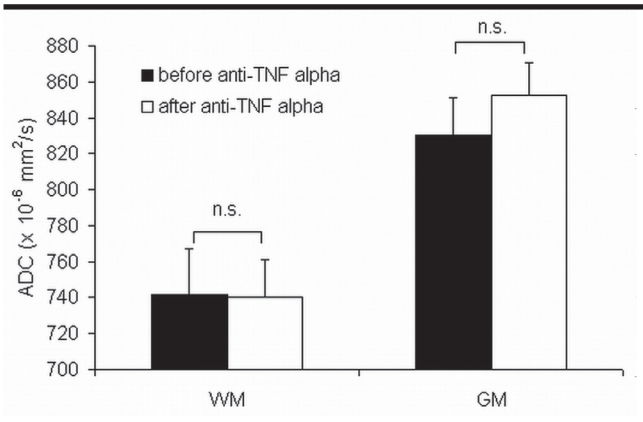

Fig. 2. Mean ADC before and after anti-TNF-alpha.

GM: gray matter; WM: white matter

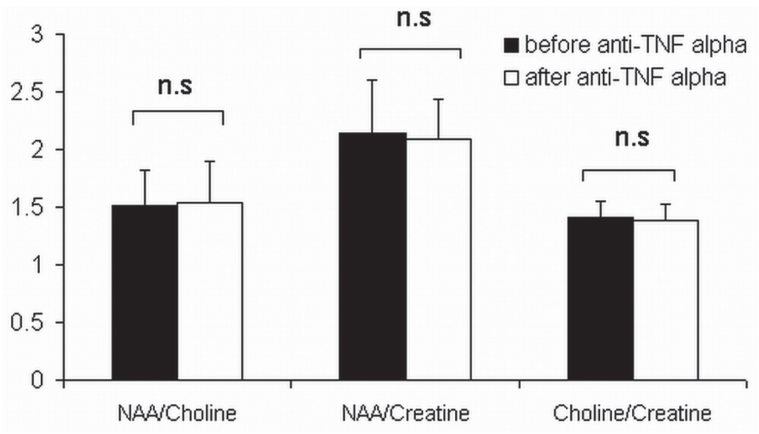

Fig. 3. Spectroscopy before and after anti-TNF-alpha.
GM: gray matter; WM: white matter.

integrity; however, the stable ADC and metabolite ratios did not advocate inflammation or demyelination.

In literature, several patients have been reported with neurological symptoms during anti-TNF-alpha therapy (4-6). Besides the time relationship, the link between the use of TNF-alpha blocking agents and neurological symptoms is even more suggestive as some patients had a (partial) resolution of symptoms after interrupting therapy and even one patient had a relapse after re-challenge (4). In some patients qualitative T1 and T2 weighted MR scans demonstrated visible abnormalities corresponding with demyelination. Several theories have been postulated concerning the mechanism causing demyelination (4, 5). The stable metabolite ratios in our patients did not support the significance of inflammation as proposed in these theories.

In general, a decline of the MTR-Pht can be explained by gliosis, demyelination, oedema and/or inflammation (7, 8). In MS patients several abnormalities can be detected by advanced MR techniques. The MTR-Pht is slightly decreased in inflammatory lesions and demyelination induces even a more prominent decrease. In normal-appearing white and gray matter MTR-Pht can also be reduced (7). Besides changes in the MTR, in MS plaques the increased membrane phospholipids metabolism resulted in increased choline/creatine ratios and also in normal appearing white and gray matter a rise of this ratio can be detected (11).

In our population the stable metabolite ratios did not provide evidence for neural loss and/or inflammation as reported before (11).

The advanced MR could not clarify the aetiology of the MTR-Pht decline, although, in our patients the moderate, but not significant, increase of the mean ADC value of the gray matter may represent a subtle alteration of the brain integrity. The increase of the ADC may reflect oedema and oedema has been reported before in one patient with neurological symptoms during anti-TNF-alpha therapy (4).

In the patients developing neurological symptoms during TNF-alpha blocking therapy the time interval between the start of therapy and symptoms ranged from 1 gift to many years (4). Remarkable is the development of symptoms within the first month of treatment in some of these patients. Maybe the alterations of the brain integrity induced clinical symptoms in those patients who had pre-existent abnormalities such as (non-symptomatic) demyelination or white matter injury (5). This could be the reason for the exacerbation of symptoms in MS patients treated with the TNF-α blocking agents despite the important role of TNF-α in the pathogenesis of MS (3).

Short neuropsychological assessment in 4 of our patients was within the normal range before therapy. This is in accordance with Appenzeller and coworkers (15) who found no difference in the MMSE between healthy controls and RA patients, although, the logic and short memory domains were disturbed. The alterations in MTR-Pht was not associated with cognitive impairment in our patients as was previously found in SLE patients (10).

In conclusion, during treatment with TNF-alpha blocking agents a decline of the MTR-Pht can be detected indicating changes in parenchymal integrity. The stable metabolite ratios and ADC plead against acute inflammation or demyelination. The small number of patients evaluated in this pilot study and the lack of controls limits the significance of our observation and further conformation in a more extensive controlled study is needed.

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