

Anti-TNF-alpha does not cause acute demyelination.

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Introduction: TNF- α is an important proinflammatory cytokine in the pathogenesis of rheumatoid arthritis (RA) and psoriatic arthritis (PA). Blockade of TNF- α is very effective in patients with RA and PA. In patients treated with anti-TNF- α neurological symptoms have been reported including optic neuritis, confusion apraxia, paraplegia, weakness and dysarthria (1). The neurological complaints originated after a time period varying from one gift to more than one year. MR findings suggested that these symptoms were the result of demyelination or white matter injury. Quantitative magnetic resonance (MR) techniques, like magnetization transfer imaging (MTI) diffusion weighted imaging (DWI) or proton magnetic resonance spectroscopy (MRS), can be used to detect brain parenchyma abnormalities. We assumed that quantitative MRI could detect possible alterations in the brain parenchyma induced by TNF- α blocking agents. We performed MRI before and after the administration of anti-TNF- α in patients with RA or PA.

Methods: Seven patients from the department of rheumatology of our institution were selected. Except for one patient, who was already using infliximab, all patients had active rheumatic disease despite previous DMARD usage and started anti-TNF- α therapy. The patients had no obvious neurological involvement such as stroke or MS. The MR, MTI, DWI and MRS scans were performed before and after the administration of one the TNF- α antagonists infliximab, etanercept or adalimumab. The drug was administered directly after the first scan. The second scan was performed 24 hours after the time of maximal plasma concentration (T_{max}) in all patients. All patients were subjected to T2 weighted (TR/TE 2500/120 ms) and FLAIR (TR/TE/TI 8000/120/2000 ms) with 6 mm slice thickness, 0.6 mm interslice gap and 22 slices. MTI was performed using a 3D gradient-echo sequence with a TR/TE of 106/6 ms, 5 mm slice thickness, no slice gap. All scans were performed with 220mm field of view and a 256 x 256 matrix. DWI was performed with a TR/TE 2000/114 ms, a b factor of 800 sec/mm², 256 x 128 matrix and 20 axial sections of 6 mm with an intersection gap of 1 mm. Single voxel ¹H-MRS was performed with a double spin-echo PRESS sequence. The volume-of-interest (size AP/LR/CC: 40/15/10 mm) was selected in the left centrum semi-ovale of each subject. Special care was taken to exclude gray matter and CSF. Measurement parameters were: TR/TE 2000/136 ms, 2048 time domain data points, 2000Hz spectral width and 128 signals acquired. MRI data were segmented into white matter, gray matter and CSF using SNIPER (Software for Neuro-Image Processing in Experimental Research, Division of Image Processing, Department of Radiology, LUMC). MTI data of the gray and white matter are expressed as normalized histogram peakheight. DWI data of the gray and white matter are expressed as mean ADC. For MR spectroscopy NAA/choline, NAA/creatine and choline/creatine were calculated. To test for changes due to the use of anti-TNF- α , paired t-tests were used.

Results: Of the 7 patients that were included 5 were RA patients, as defined by the American College of Rheumatology (ACR) 1987 criteria (5), and 2 were psoriatic arthritis patients (6).

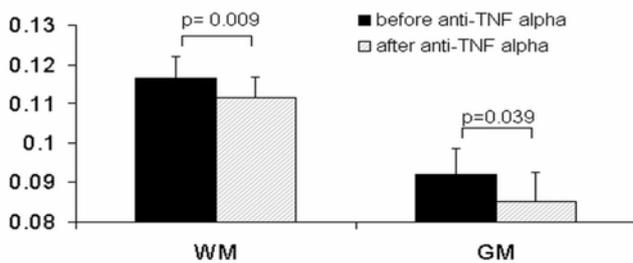
The median age was 57 years (range 36-67) and disease duration of all 7 patients was 2.6 years (range 1.2-14.6). The T1/T2 weighted scans did not show any brain abnormalities. The MTR-peakheight of the white and gray matter both demonstrated a significant decrease after the use of anti-TNF- α . The ADC for both the gray and white matter did not show any changes after the administration of anti-TNF- α (middle graph). The NAA/choline, NAA/creatine and creatine/choline ratios of the centrum semiovale did not change after treatment with TNF- α (bottom graph).

Conclusion: During treatment with TNF- α blockade a decline of the MTR peakheight occurs, suggesting impaired parenchymal integrity. However since no changes were observed in either the ADC or metabolite ratios, the observed cerebral changes directly after treatment with anti-TNF- α are not likely to be caused by (vasogenic) edema nor demyelination. Still, the finding that MTR peakheight decreases after the use of anti-TNF- α could be of interest for the possible link between TNF- α blocking agents and neurological symptoms.

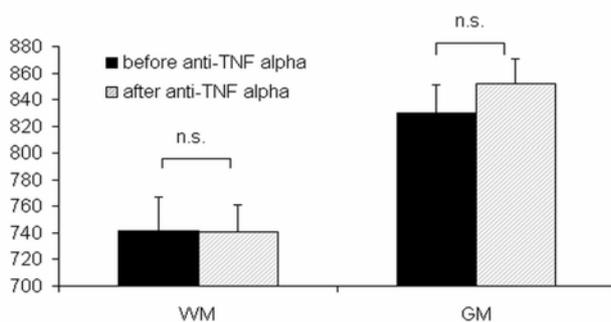
References:

1. Mohan, N., et al.. Demyelination Occurring During Anti-Tumor Necrosis Factor Alpha Therapy for Inflammatory Arthritides. *Arthritis Rheum.* 2001;44(12):2862-9.
2. Arnett et al. The American Rheumatism Association 1987 Revised Criteria for the Classification of Rheumatoid Arthritis. *Arthritis Rheum.* 1988;31(3):315-24.

Mean MTR peak height before and after anti TNF alpha



Mean ADC before and after anti TNF alpha



Spectroscopy before and after anti-TNF alpha

