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ANKİLOZAN SPONDİLİTLİ HASTALARDA ANTİ-TNF-ALFA TEDAVİ ÖNCESİ VE SONRASI SAKROİLİAK EKLEMLERİN MANYETİK REZONANS İLE GÖRÜNTÜLENMESİ

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ÖZET

AMAÇ: Çalışmanın amacı, dirençli AS'li hastalarda, anti-TNF-alfa ilaçların etkinliğini ve güvenirliğini yanısıra, manyetik rezonans (MR) görüntüleme ile tedavi öncesi ve sonrası sakroiliak eklem değişiklerini tespit etmektir.

GEREÇ ve YÖNTEM: Modifiye New York tanı kriterlerine göre AS tanısı almış, 27 hasta çalışmaya dahil edildi. Sakroiilitis bulguları, anti-TNF-alfa tedavi öncesi ve sonrası, Gd-MR ile tespit edildi. Sekiz hastaya, 4 haftada bir İnfliximab 4 mg/kg i.v. infüzyon verildi. Diğer 19 hastaya ise Etanercept 2x25 mg/hafta s.c. verildi. Değerlendirilen klinik ve laboratuvar parametreler; BASDAİ, BASFİ, ağrı (VAS skoru), Schöber testi, göğüs ekspansiyonu, C-reaktif protein (CRP), eritrosit sedimentasyon hızı (ESH).

BULGULAR: Hastaların çoğu, anti-TNF-alfa tedavilerine iyi yanıt verdi. 24. haftanın sonunda, takip edilen tüm parametrelerde iyileşme gözlendi. MR görüntüleme çalışmalarında, anti-TNF-alfa tedavi sonrası sadece 3 hastanın sakroiliak eklem inflamasyonunda gerileme gözlendi.

SONUÇ: Aktif AS'li hastalarda, 24. hafta sonunda anti-TNF-alfa ilaçları güvenilir ve etkin bulundu. BASDAİ, BASFİ, ağrı skorlarında belirgin düşüş gözlendi. Fakat, sakroiliak eklemin akut inflamatuvar bulgularında, MR görüntüleme ile herhangi bir gerileme tespit edilmedi.

Anahtar sözcükler: Ankilozan spondilit, anti-TNF-α ilaçlar, manyetik rezonans görüntüleme, sakroiliak eklem

Magnetic Resonance Imaging of the Sacroiliac Joints in Ankylosing Spondilitis Before and After Therapy with Anti-Tumor Necrosis Factor Alpha

SUMMARY

OBJECTIVE: The goal of this study is to assess the changes in the sacroiliac joints (Sİ) by magnetic resonance imaging (MRI) in a 24-week follow-up period and to determine the efficacy and safety of anti-TNF-α therapies for refractory AS.

MATERIALS and METHODS: Twenty-seven patients who met the modified New York criteria for AS were enrolled in this study. Activity of sacroiliitis was determined by Gd-MRI scan before and after anti-TNF-α treatment. Eight patients received infliximab at a dose of 4mg/kg by intravenous infusion over 2 hours at every 4 week. Other patients (n=19) were treated with 25mg subcutaneous etanercept twice weekly. Total observational period was 24 weeks. The clinical and laboratory variables included: Bath AS Disease Activity Index (BASDAI), Bath AS Functional Index (BASFI), pain on a visual analog scale, Schober's index, chest expansion, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR).

RESULTS: Most patients responded well to treatment of anti-TNF-α antagonists. At 24 weeks, there was an improvement in all of the measures followed. Imaging studies showed decreased inflammation of the SI joints after 24 weeks of treatment with anti-TNF-α therapies in 3 patients only.

CONCLUSION: The anti-TNF-α therapy was found to be safe and effective in treating patients with active AS during 24-week study period. The BASDAI, BASFI, VAS of pain were decreased significantly, however we could not determine any regression of acute inflammatory changes of the SI joints as depicted by MRI.

Key words: Ankylosing spondylitis, anti-TNF-α therapies, magnetic resonance imaging, sacroiliac joints

Ankylosing spondylitis (AS), the prototype of spondyloarthritis, is a chronic inflammatory rheumatic diseases, leading to progressive spinal ankylosis and deformity [1]. Its pathogenesis is incompletely understood [2]. The fırst symptoms normally occur in the second and thırd decade of life. AS most offen starts with inflammation of the sacroiliac joints (SI) and affect mainly the axial skeleton [3,4]. Until recently, non-steroidal anti-inflammatory drugs(NSAIDs) and physical therapy were the only accepted treatment. The only disease modifying antirheumatic drug (DMARDs) that has been demonstrated to be useful for AS is sulfasalasine (SSZ), which has a proven beneficial effect for peripheral arthritis and enthesitis and nearly imperceptible for spondylitis [5,6].

Tumor necrosis factor-alpha (TNF-α) has been determined in sacroiliac joints of patients with AS. TNF-α mRNA and protein have been identified in the sacroiliac joint (SI) biopsies of patients with active disease suggesting a role for this cytokine in the target organ inflammation [7]. Over the past few years several placebo controlled and open trials have shown a dramatic response in active AS to TNF-α blocking agents [8-10]. Studies on magnetic resonance imaging (MRI) of SI joints in AS indicate that MRI enables

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early diagnosis of sacroiliitis [11]. Dynamic MRI has been shown to be useful in the detection of both early SI joint and spinal inflammation in AS [12,13].

In this study, our aim was to determine the efficacy and safety of anti-TNF-α therapies for refractory AS and to assess the changes in the SI joints by MRI in a 24- week follow-up period before and after treatment.

MATERIALS and METHODS

Twenty-seven (18 men and 9 women) who met the modified New York criteria for AS and anti-TNF-alpha naive patients were enrolled in this 24- week study. All patients gave written informed consent. Before study entry, all patients were evaluated for latent tuberculosis by a tuberculin test and chest radiographs. Despite treatment with methotrexate (MTX) at least 10 mg/week, sulfasalazine (SSZ) 3 g/day, corticosteroid 4 mg/day, nonsteroid antiinflammatory drugs (NSAIDs), at the time of enrollment, all patients had active disease. Disease modifying drugs, such as SSZ, MTX were not allowed during the study. Patients were allowed to continue NSAIDs and/or corticosteroids (<10 mg/day prednisolone), provided that the dosage and schedule regiment were stable at least 4 weeks prior to baseline and troughout the study. Eight patients received infliximab at a median dose of 4 mg/kg by intravenous infusion over 2 hours at every 4 week. Other 19 patients were treated with 25 mg subcutaneous etanercept twice weekly. The total observational period was 24 weeks. The clinical variables included: Bath AS Disease Activity İndex (BASDAI), Bath AS Functional Index (BASFI), pain on a visual analog scale The laboratory variables for activity of disease included: C-reactive protein(CRP), erythrocyte sedimentation rate (ESR). All the above variables (clinical and laboratory) were evaluated at week 0, 4, 8, 16, 24. Furhermore, a complete blood count and biochemical measurements were obtained at each patient visit.

Activity of sacroiliitis was determined by Gd-MRI scan before and after anti-TNF-alpha treatment. The following sequences were used: T1 weighted spin echo (SE), short tau inversion recovery (STIR), T2 weighted fast SE with fat saturation and T1 weighted SE with fat suppression after the intravenous administration of contrast medium (gadolinium diethylenetriaminepentate, 0.1 mmol/kg body weight). Inflammation was scored for each sacroiliac joint in the joint space, subchondral bone, bone marrow, ligaments, and joint capsule. Inflammation was defined as a low signal intensity on T1, with enhancement after gadolinium administration, and/or high signal intensity on STIR, and/or T2 fast SE. Inflammation in ligaments was defined as areas of low signal intensity running through high signal intensity tissue on T1, which reflects interosseous ligaments crossing juxtaarticular fatty tissue. Structural changes (erosions, sclerosis, ankylosis) were scored in joint space, subchondral bone, and bone marrow.

Statistical analysis

SPSS was used to analyze the data. Data were summarized as frequency and percentages. t-test was used for comparison of numerical variables. The level of significance was accepted as $p < 0.05$.

RESULTS

The mean age was 46,3±12,3 years (range 20-70) and mean disease duration was 12,1±3,4 years (range: 5-20). Ten patients were HLA-B27 positive. Nine patients had peripheric arthritis and 8 patients had enthesitis. Five patients had a prior history of anterior uveitis (Table1). All 27 patients responded well to treatment of anti TNF-alpha agents. At 24 weeks, there was an improvement in all of the following measures: BASDAI, BASFI, patient global assessment, physician global assessment, pain scores. For BASDAI, there was a reduction from 6,3 at baseline to 3,5 at 24 weeks. ESR and CRP showed significant improvement at 6 weeks and were maintained to the 24 week assessment point. The mean baseline scores for inflammatory markers in the peripheral blood were 53,4 mm/h for ESR(reference range 0-15), 3,5 mg/dl for CRP (reference range < 0,5 mg/dl). At week 24, there was an improvement in inflammatory markers (median ESR were 16,2 mm/h, median CRP were 0,4 mg/dl respectively). Also peripheral arthritis, enthesitis and spinal symptoms improved. There was a improvement in Schober's index and chest expansion at 24 weeks, but there was not statistically significant (Table2). Imaging studies before and after 24 weeks of treatment with anti-TNF-α was performed in 22 patients. Active inflammation depicted by MRI was seen in 20 patient (Table3). Among these patients, 12 had bilaterally sacroiliitis. Inflammation of the subchondral region and the bone marrow was the most frequently observed finding. Only one patient had inflammation excluding the bone marrow and subchondral bone. The pathological

Table 1. Demographic data of 27 patients with ankylosing spondylitis.

Characteristic	Patients
Age/years/mean	46.3±12.3
Disease duration/years	12.1±3.4
Sex/male	18(66.6%)
History of anterior üveitis	5(18.5%)
Peripheric arthritis	9(33.3%)
Enthesitis	8(29.6%)
HLA B-27 positivity	10(37%)

findings were mostly scored as grade 2, representing moderate involvement. Structural changes was seen in all 22 patients. Similarly to inflammation, about one half of the patients with structural changes showed these changes bilaterally. Furthermore, after 24 weeks of continuous treatment of 22 patients with AS with anti-TNF-α agents there was a slight but not significant decrease of the mean score for active inflammatory lesions in the SI joints. MRI showed decreased inflammation of the SI joints in only 3 patients. Among these 3 patients, 2 were women and all of them has been treated with etanercept. All of these 3 patients had positivity for HLA-B27 antigen. Also no difference in chronic changes was found among the patients with AS after 24 weeks of treatment with anti-TNF-α drugs. Despite clinically and laboratory improvement there are no showed regression of inflammatory findings of sacroiliac joints. During follow-up of the treatment, 3 patients developed headache, one patient developed allergic reaction during the infusion. Infections was developed in 4 patients (one pneumonia, 3 urinary tract infection). No patient developed ANA or anti-dsDNA antibodies. No clinical events occured to suggest a lupus-like illness in any patient.

DISCUSSION

Our study shows that treatment of patients with active AS with anti-TNF-α agents are not associated with a significant reduction of active inflammatory changes of the sacroiliac joints as depicted by MRI. Active inflammatory findings as bone marrow oedema and enhancement of the contrast agent was persisted after 24 week follow period. Only 3 patients had regression of acute inflammatory findings depicted by MRI. During the study, no progression occurred of chronic changes of the SI joints as depicted by MRI. Results of studies of the influence of anti-TNF-α treatments on spinal and sacroiliac joints

Table 3. MRI findings of sacroiliac joints in 22 patients with AS before and after anti-TNF-α treatment.

	MRI findings(R/L)			
	Active inflammation(R/L)		Chronic changes(R/L)	
Pts	before treatment	after treatment	before treatment	after treatment
1	+/+	+/+	+/+	+/+
2	-/+	-/+	+/+	+/+
3	+/+	+/+	-/+	-/+
4	+/+	-/-	+/-	+/-
5	+/+	+/+	+/+	+/+
6	-/+	-/+	+/+	+/+
7	-/+	-/+	-/+	-/+
8	+/+	-/-	+/+	+/+
9	+/+	+/+	+/+	+/+
10	-/+	-/+	+/-	+/-
11	+/+	+/+	+/+	+/+
12	+/+	-/-	-/+	-/+
13	-/+	-/+	-/+	-/+
14	+/+	+/+	+/+	+/+
15	+/-	+/-	-/+	-/+
16	-/+	-/+	+/+	+/+
17	-/+	-/+	+/+	+/+
18	+/+	+/+	+/+	+/+
19	+/+	+/+	-/+	-/+
20	-/-	-/-	-/+	-/+
21	+/+	+/+	-/+	-/+
22	-/-	-/-	+/-	+/-

Table 2. Clinical and laboratory follow-up of patients with AS during anti-TNF-α treatment.

Follow-up	BASDAI 0-10cm Median	BASFI 0-10cm median	ESR mm/h median	CRP mg/dl median	Pain 0-10cm median	Schober cm median	Chest expansion cm median
Baseline	**6.3*±0.93**	**6.5*±0.97**	**53.4*±2.12**	**3.5*±0.74**	**7.2*±0.80**	**2.1±0.89**	**3.1±0.75**
8.week	**3.0±1.03**	**2.5±0,58**	**17.4±1.97**	**0.6±0.93**	**3.1±1.01**	**3.5±0.74**	**4.0±1.29**
24.week	**3.5*±0.74**	**2.8*±1.26**	**16.2*±1.93**	**0.4*±0.57**	**3.4*±0.77**	**4.1±1.27**	**5.2±1.33**

*t-test was performed, $p<0.05$ was accepted as significance

inflammation in AS are promising. Rudwaleit et all. showed that etanercept treatment in patients with active AS and uSpA leads to regression of active inflammatory lesions of the spine as depicted by MRI [14]. In this study, there was only a trend for a decrease of active inflammatory lesions of the SI joints. Braun et all. showed clinical improvement in patients with active AS who were treated with infliximab and significant regression of spinal inflammation by using the MRI activity scores [15]. Won-Hee Jee et all showed that synovial enhancement at MR imaging could correlate disease activity as measured by laboratory inflammatory markers in ankylosing spondylitis [16].

By investigating results of sacroiliac biopsies demonstrated that there is a fair correlation between MRI activity and histologic scores of inflammation [17]. Thus, we are not surprised that infliximab and etanercept, a potent inhibitors of major proinflammatory cytokine TNF-α, are able to reduce spinal inflammation, especially because spinal inflammation in AS is associated with new blood vessel formation. This may be a factor that most likely contributes to the enhancement seen after application of contrast agent. Therefore, improvement in spinal inflammation induced by anti-TNF-α therapies will lead to a reduction of blood vessels at inflamed sites. These data suggest that regression of bone marrow edema appears to be a sensitive sign of improvement of spinal inflammation in AS [18]. In our study despite of clinically and laboratory improvement of patients there are not radiologically regression on MRI. Active inflammatory lesions of the SI joints showed only moderate and non-significant regression of such lesions upon treatment with anti-TNF-α agents. In only 3 patients noted some decrease of active inflammatory lesions after 24 weeks. Thus, one possible explanation is that the scoring method applied for the SI joints is not sufficiently sensitive to change. Whether semiaxial planes in addition to the conventional semicoronal planes of the SI joints would have added further information on the change in the SI joints is unknown, but unlikely. Further studies on MRI examination of the SI joints will provide more information on this issue.

The relatively small size of the present study group limits our ability to draw extensive conclusions.

According to our data, anti-TNF-α therapies has strong clinical efficacy on many aspects of active AS and leads to significant regression of active inflammatory markers. But we could not determine any regression of acute inflammatory changes of the SI joints as depicted by MRI. Some effects on the SI joints were also detected, but this was not statistically significant, possibly indicating that the scoring method used lacks sensitivity to change. However, further clinical studies are needed to shows the efficacy of anti-TNF-α agents on active inflammatory changes of sacroiliac joints.

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