Klinik pratikte ankilozan spondilitte anti tümör nekrosis faktör tedavisi

Anti tumor necrosis factor therapy of ankylosing spondylitis in clinical practice

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Abstract

Purpose: The aim of this study was to analize ankylosing spondylitis (AS) patients who were using tumor necrosis factor-alpha (TNF-α) blocking agents and present the data on the efficacy and safety of this treatment in clinical practice.

Materials and methods: AS patients using TNF-α blockers for at least six months were included in this retrospective study. Regular clinical observations were used to evaluate the efficacy and safety of the anti-TNF-α drugs. Adverse events were recorded. Reasons for discontinuation of treatment were also closely followed-up. All the patients had a baseline comprehensive rheumatologic assessment and were repeatedly monitored every three months in the routine clinic practice for AS spesific disease indexes as well as laboratory tests.

Results: A total of 41 patients with AS were reviewed of whom 26 were male and 15 were female, with a mean age of 43.22 years. The number of AS patients who were treated with etanercept was 18 (43.9%), adalimumab was 15 (36.6%), golimumab was 3 (7.3%) and finally infliximab was 5 (12.2%). Mean duration of the TNF-α bloker usage for AS patients was 39.56 months. 7 of the 11 (26.8%) AS patients who did not respond to the first anti-TNF-α therapy were switched to another anti-TNF-α agent. On the other hand 4 AS patients gave up anti-TNF-α therapy. AS spesific disease index scores and laboratory tests improved at the third and the sixth months when compared with the scores at the initiation of the TNF-α bloker therapy.

Conclusion: Follow-up of patients with AS in our clinical setting showed that anti-TNF therapy is an effective and safe way of treatment with good adherence rates.

Pam Med J 2014;7(3):218-224

Key words: Ankylosing spondylitis, tumor necrosis factor-alpha, biological therapy.

Özet

Amaç: Bu çalışmanın amacı, tümör nekrosis faktör-alfa (TNF-α) bloke edici ajanları kullanan ankilozan spondilitli (AS) hastaları tanımlamak ve klinik pratikte bu tedavinin etkinliği ve güvenliği ile ilgili verileri sunmaktı.

Gereç ve yöntem: Bu retrospektif çalışmaya, en az altı aydır TNF-α blokörleri kullanan AS'li hastalar dahil edildi. Anti-TNF-α ilaçların etkinliği ve güvenliğini düzenli klinik gözlemler ile değerlendirdik. Yan etkiler kaydedildi. Tedavi bırakma sebebleri de yakından takip edildi. Tüm hastalar ayrıntılı romatolojik değerlendirmeden geçirildi ve üç ayda bir AS özgü hastalık indeksleri yanı sıra laboratuar testleri ile rutin klinik pratikte izlendi.

Bulgular: Ortalama yaşları 43.22 yıl olan 26 erkek ve 15 bayan olmak üzere toplam 41 AS'li hasta gözden geçirildi. Etanersept ile tedavi edilen hasta sayısı 18 (%43.9), adalimumab ile 15 (%36.6), golimumab ile 3 (%7.3) ve son olarak infliximab ile 5 (%12.2) idi. AS'li hastalar için ortalama TNF-α blokör kullanım süreleri 39.56 ay idi. İlk anti-TNF-α tedavisi başarısız olan onbir (%26.8) hastanın yedisinde başka bir anti-TNF-α ajana geçildi. Diğer taraftan dört AS'li hasta anti-TNF-α tedaviyi bıraktı. AS özgü hastalık indeks ve laboratuar testleri üçüncü ve altıncı ayda TNF-α blokör başlangıcına göre düzelme gösterdi.

Sonuç: Klinik ortamımızda AS'li hastaların takibi anti-TNF tedavisinin iyi uyum oranları ile etkin ve güvenli bir tedavi yöntemi olduğunu göstermiştir.

Pam Tıp Derg 2014;7(3):218-224

Anahtar sözcükler: Ankilozan spondilit, tümör nekrosis faktör alfa, biyolojik tedavi.

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Gönderilme tarihi: 15.04.2014 Kabul tarihi: 04.06.2014

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease that primarily affects the axial skeleton [1]. Treatment options for AS patients have been relatively few. Non-steroidal anti-inflammatory drugs (NSAIDs) are currently recommended as the first choice of medical treatment, and there is also a clear role for regular exercise and physical therapy in order to preserve and prevent loss of spinal mobility in patients with AS. Sulfasalazine is the best studied disease-modifying anti-rheumatic drug in AS, but its efficacy remains unclear. None of these treatments has been shown to alter the progression of the disease, but they may offer palliation of pain and symptoms [2].

Tumor necrosis factor-alpha (TNF-α) is a critical cytokine with both beneficial and pathologic effects. Elevated levels of TNF-α have been implicated in several inflammatory rheumatic diseases, including spondylarthritis [3]. This has prompted the development of TNF inhibitors that are effective in the treatment of inflammatory rheumatic diseases. The introduction of TNF-α blockers has revolutionized the management of AS over the last decade [4]. However, anti-TNF-α therapy is not indicated for all patients with AS, and is only used in cases refractory to conventional therapy [5]. Nowadays, the drug survival duration is considered to be an important measure of performance of biological agents. Registries of patients treated with biological therapy represent the most important source of information on drug survival of patients as well as efficacy and safety of TNF-α blockers. To analyse the long-term safety of TNF-α blockers there were several registries reported in the literature [6–9], however only one registery was found in our country [10]. Clearly, data from international studies may not always be extrapolated to the Turkish population. To our knowledge there is no biologic treatment registry reported in our country up to date.

The aim of this study was to describe AS patients using TNF-α blocking agents and present the data on the efficacy and safety of this treatment in clinical practice.

Materials and Methods

Subjects

AS patients using TNF-α blockers for at least six months were included in this retrospective study. A total of 41 AS patients who were administered anti-TNF-α therapy for at least six months and followed-up in a university Physical Medicine and Rehabilitation Clinic were enrolled in this study. All patients had to fulfill the following criteria for treatment of AS with anti-TNF-α drugs; high disease activity assessed with Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (BASDAI higher than 5), and higher C-reactive protein (CRP) or elevated erythrocyte sedimentation rate (ESR) or active sacroiliitis on magnetic resonance imaging, with failure to respond to conventional therapy. The response to anti-TNF-α treatment is defined as a reduction in BASDAI of at least 50% or 2 units [5]. Anti-TNF-α treatment was administered on the basis of patient's clinical characteristics and patient's request individually. Standard doses of TNF blocking agents were used as described; 5 mg/kg infliximab intravenously in the intervals of 0, 2nd and 6th weeks and after induction every 6 or 8 weeks, 50 mg etanercept subcutaneously once a week and 40 mg adalimumab subcutaneously every two weeks and 50 mg golimumab subcutaneously once a month. This retrospective study analysed the anti-TNF-α drugs' efficacy and safety via regular clinical observations. Adverse events were recorded. Reasons for treatment discontinuation were also closely followed. Screening for latent tuberculosis and serious infection as well as hepatitis was carried out prior to the start of treatment. All patients received a comprehensive rheumatologic assessment at baseline and were monitored in every three months in routine clinical practice with AS specific disease indexes as well as laboratory assay including CRP and ESR.

Assessment of patients with AS

The BASDAI was used to evaluate disease activity using six self-reported questions pertaining to fatigue, spinal and peripheral joint pain, localized tenderness and morning stiffness [11]. On the other hand the Bath Ankylosing Spondylitis Functional Index (BASFI) was used to determine the degree of functional limitation in patient with AS [12]. The Turkish versions of the BASDAI and BASFI were shown to be reliable and valid [13,14]. Moreover the Bath Ankylosing Spondylitis Metrology Index (BASMI) was used to grade the mobility of the spine and hip by measuring the distance from the tragus to the wall, lumbar flexion, cervical rotation, lumbar side flexion and intermalleolar distance [15]. Furthermore health related quality of life was evaluated by the Ankylosing Spondylitis quality of life (ASQoL) which is a disease-specific instrument in patients with AS [16]. It was shown that the Turkish versions of the ASQoL was reliable and valid [17].

Statistics

All statistical analyses were performed using SPSS version 17.0 for Windows (Statistical Package for the Social Sciences Inc, Chicago, IL, USA). Descriptive statistics were used to describe demographic characteristics. Because the distributions were not normal, nonparametric tests were used in statistical evaluation. For AS disease specific variables, and acute phase reactants the significance of the differences between baseline assessment and control assessments were analysed using Friedman test. In case of a statistically significant difference was detected between overall results, Wilcoxon signed-rank test was used to determine the difference between each evaluations. In all analyses, *p* values <0.05 were considered as statistically significant.

Results

A total of 41 patients with AS were reviewed of whom 26 were male and 15 were female, with a mean age of 43.22 years ranging from 23 to 66 years. The disease duration of the AS patients was between 12 and 416 months with a mean of 137.6 months. Manifestations of extraarticular involvement and positive family history were found in approximately one third of AS patients. A total of 13 (31.7%) patients had extraarticular involvement of whom eleven patients had history of uveitis, one had renal amyloidosis and the other had cardiac involvement. The prevalence of peripheral arthritis was 22%. Demographic and clinical characteristics of AS patients included in this study are given in Table 1.

Table 1. Demographic characteristics of ankylosing spondylitis patients using tumor necrosis factor blocking agents

	Ankylosing Spondylitis (n=41)
Gender, n (%)	
Men	26 (63.4%)
Women	15 (36.6%)
Age (years) (mean ± SD)	43.22 ± 11.11
Disease duration (month) (mean ± SD)	137.61 ± 96.41
Marital Status, n (%)	
Married	36 (87.8%)
Single	3 (7.3%)
Widow(er)	2 (4,9%)
Educational level, n (%)	
Primary	26 (63.4%)
High	6 (14.6%)
University	9 (22%)
Occupation, n (%)	
Government official	10 (24.4%)
Employee	8 (19.5%)
Retired	4 (9.8%)
Home-maker	12 (29.3%)
Unemployed	7 (17.1%)
Family history, n (%)	
No	28 (68.3%)
Yes	13 (31.7%)
Peripheral involvement, n (%)	
Absent	32 (78%)
Present	9 (22%)
Extraarticular findings, n(%)	
Absent	28 (68.3%)
Present	13 (31.7%)

The number of AS patients who were treated with etanercept was 18 (43.9%), adalimumab was 15 (36.6%), golimumab was 3 (7.3%) and finally infliximab was 5 (12.2%). Duration of the TNF-α blocker usage for AS patients was between 6 and 120 months with a mean of 39.56 months. Seven of 11 (26.8%) AS patients who failed first anti-TNF-α therapy were switched to a second anti-TNF-α agent; one from infliximab, two from adalimumab and four from etanercept group. On the other hand four AS patients gave up anti-TNF-α therapy; three because of patients' preference and one due to hepatitis B infection. Despite being on anti-TNF-α therapy, approximately a third of AS patients were using NSAIDs when needed. The prevalence of adverse events were 19.5%. One had mild urinary tract infection and another had hepatitis B in adalimumab, on the other hand a patient had hidraadenitis supurativa, the other one zona and three patients had mild allergic reaction in etanercept, only a patient had mild respiratory infection in infliximab group. The majority of patients (85.4%) had received isoniazid prophylaxis for tuberculosis as shown in Table 2.

Upon the start of anti-TNF-α treatment, the mean BASDAI value was 6.61. Compared with baseline, disease activity scores were reduced by close to 2.5 BASDAI points at three months and approximately 3 points at six months following initiation of anti-TNF-α therapy. Moreover other AS disease specific intruments such as BASFI, BASMI and ASQoL scores were reduced at third and sixth months as well as CRP and ESR values when compared with baseline scores at the initiation of TNF-α blocker treatment (Table 3, $p<0.001$).

Table 2. Tumor necrosis factor blocking agents usage ın patients with ankylosing spondylitis

	Ankylosing Spondylitis (n=41)
First TNF Blocking Agent, n (%)	
Etanercept	18 (43.9%)
Adalimumab	15 (36.6%)
Golimumab	3 (7.3%)
Infliximab	5 (12.2%)
First TNF Blocking Agent Usage, n (%)	
Continue	30 (73.2%)
Switch to another	7 (17%)
Discontinue	4 (9.8%)
Adverse Events, n (%)	
Absent	33 (80.5%)
Present	8 (19.5%)
Duration of TNF Blocking Agent Usage (month) (mean ± SD)	39.56±34.32 (min:6, max:120)
Isovit prophylaxis, n (%)	
No	6 (14.6%)
Yes	35 (85.4%)
NSAID Usage with TNF Blocking Agent, n (%)	
No	27 (65.9%)
Yes	14 (34.1%)

TNF: Tumor necrosis factor; **NSAID:** nonsteroidal anti-inflammatory drug

Table 3. Efficacy of biologic agents ın patients with ankylosing spondylitis

	First Assessment (mean ± SD)	Second Assessment (mean ± SD)	Third Assessment (mean ± SD)	*p**	*p***
BASDAI	6.61 ± 1.53	4.12 ± 1.79	3.52 ± 1.74	<0.001	First >Second, *p*<0.001 First>Third, *p*<0.001 Second>Third, *p*<0.001
BASFI	5.18 ± 2.63	4.11 ± 2.53	3.54 ± 2.47	<0.001	First >Second, *p*<0.001 First>Third, *p*<0.001 Second>Third, *p*<0.001
BASMI	4.01 ± 2.90	3.90 ± 2.95	3.76 ± 2.99	<0.001	First >Second, *p*=005 First>Third, *p*<0.001 Second>Third, *p*=0.014
ASQoL	12.00 ± 3.51	10.10 ± 4.08	8.39 ± 3.83	<0.001	First >Second, *p*<0.001 First>Third, *p*<0.001 Second>Third, *p*<0.001
CRP	1.91 ± 1.64	0.96 ± 1.89	0.52 ± 0.87	<0.001	First >Second, *p*<0.001 First>Third, *p*<0.001 Second>Third, *p*<0.001
ESR	41.20 ± 19.68	21.88 ± 14.70	18.17 ± 13.54	<0.001	First >Second, *p*<0.001 First>Third, *p*<0.001 Second>Third, *p*=0.004

p:* Friedman ***p****:* Wilcoxon
BASDAI: Bath Ankylosing Spondylitis Diseases Activity Index
BASFI: Bath Ankylosing Spondylitis Functional Index
BASMI: Bath Ankylosing Spondylitis Metrology Index
ASQoL: Ankylosing Spondylitis Quality of Life
CRP: C-reactive protein **ESR:** Erythrocyte sedimentation rate

Discussion

In this retrospective study, we investigated long term efficacy and safety of anti-TNF-α treatment in patients with AS. Our results demonstrated that TNF-α blockers were effective and safety drugs in AS patients with acceptable adverse events in the routine clinic practice. Moreover, AS patients demonstrated good adherence to TNF-α blockers and good tolerability with higher compliance.

National and international registries and other types of large databases are relevant sources for providing complementary evidence regarding the short and long term safety of biologics. In a recent registry, it was concluded that AS patients treated with anti-TNF agents perform good efficacy with low frequency of adverse events and good adherence to therapy [7]. In the Leeds cohort of 84 males and 29 females of total 113 AS patients treated with anti-TNF the mean age was 45 years and the median disease duration was 16 years. The majority of patients (79%) showed a sustained response to anti-TNF therapy with only 13% being non-responders and 8% changing anti-TNF therapy due to adverse effects [8]. In another cohort of AS patients from the Finland registry, patients with severe disease of long duration were followed up for 24 months. In this registry seventy-nine percent of the patients were ASAS 20 responders. The first biological drug was discontinued in only 7% due to lack of efficacy and in 6% due to adverse events [9]. In accordance with these registries, we also had similar discontinue ratios for the first TNF-α blocking therapy. In the British Society for Rheumatology Biologics Registry, the majority of patients receiving anti-TNF therapy for AS during routine care demonstrated an

improvement in disease activity. At 6 months, the mean improvements in BASDAI and BASFI were 3.6 and 2.6 points respectively [18]. Similar to this registry we also demonstrated significant improvements in AS specific measurements at sixth month.

To investigate the long-term response and toxicity to biological therapies in a real life clinical setting, international recommendations encourage rheumatologists using biological treatments to register patients in national registries [5]. TRASD-IP is the unique registry designed for AS in Turkey. A total of 1381 patients with AS of whom 1038 were male (75.2%) were included in this registry from 41 centers between October 2007 and February 2009. In this registry the mean age of AS patients was 39.5 years with a mean disease duration of 12.1 years [10]. In 51.7% of AS patients in this registry, the BASDAI was ≥4, however the authors concluded that since their patients consisted of the ones with more severe disease who referred to the tertiary centers therefore these patients may not represent the general AS population. In contrast to the high proportion of AS patients with active disease, only 16.4% of patients with AS were using anti-TNF agents. In accordance with this registry, our AS patients had similar mean disease duration and age. On the other hand we only included patients using anti-TNF agents to our study. In contrast to this registry, all patients who had higher disease activity with failure to respond to conventional therapy had received TNF-α blockers in our study.

TNF-α antagonism is an important treatment strategy in patients with AS, however there are several side effects reported in patients with anti-TNF-α therapy. In a recent systematic review and meta-analysis, it was concluded that the incidence of adverse events was not significantly different between anti-TNF blockers and the safety profiles of these drugs do not significantly restrict their use [19]. In Finland national registry, only 11% of the 229 AS patients were reported as having experienced an adverse events due to biological treatment [9]. This is a relatively small and apparently represents under-reporting of milder adverse events in longitudinal registers. In our population 19.5% patients reported adverse events. Because anti-TNF therapy suppresses the immune system, serious infections were the most frequently reported serious adverse events. We recorded only two serious infection one hepatitis B and the other one zona. In particular, the reactivation of tuberculosis is a recognized risk of therapy with anti-TNF therapy and national guidelines have been developed for screening of patients prior to treatment initiation. No active tuberculosis was seen in our patients with AS. Since latent tuberculosis infection screening and prophylaxis was implemented in 2005 the rate has decreased. In addition no malignancy was observed in our clinical database. In present study, safety profile was consistent with known information about the anti-TNF therapy.

It is recognized that a proportion of patients will have to stop their first TNF-α blocking therapy due to inefficacy or side effects. There is evidence to support switching patients to alternative anti-TNF therapies in the case of adverse events or non-response. Reduced response is seen more frequently in the cases switched because of inefficacy when compared with patients who switched due to adverse events. During our follow up seven patients switched first TNF-α blocking therapy to another and four patients discontinue.

A potential limitation of the present study is that data on efficacy and safety of anti- TNF-α were collected retrospectively with relatively small sample size. Moreover, the present study was performed only in one clinic, therefore the sample may not be representative of the general population. Finally, further registry data of AS patients treated with anti-TNF and larger sample size that represents multicenter clinics are needed for sufficient evidence about efficacy and safety of biologic treatments. Establishing regional biologics registries will be helpful to assess and evaluate various parameters such as safety, efficacy, drug survival, and quality of life with long term use of anti-TNF agents in AS.

In conclusion, follow-up of patients with AS in our clinical setting showed that anti-TNF therapy is an effective and safe way of treatment with good adherence rates in patients failed to respond to conventional therapy. It may be concluded that AS patients treated with anti-TNF agents confirm a very good adherence to therapy with low occurrence of adverse events.

Conflict of interest: We have no conflicts of interest and also this study has no financial support.

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