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AUTHORS: Mehmet Ali UÇAR,Mehmet SAYARLIOGLU

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Effect of use of anti-TNF medications on development of urinary infections in patients with rheumatoid arthritis and ankylosing spondylitis

Romatoid artrit ve ankilozan spondilitli hastalarda anti-TNF ilaç kullanımının üriner enfeksiyon gelişimine etkisi

Mehmet Ali Uçar,[1] Mehmet Sayarlıoğlu[2]

[1]Department of Internal Medicine, Mersin University Faculty of Medicine, Mersin, Turkey
[2]Department of Rheumatology, Samsun University Faculty of Medicine, Samsun, Turkey

Abstract

Introduction: Our objective in this study is to investigate whether there is an increase in frequency of urinary infections in patients using anti-Tumor Necrosis Factor alpha (TNFα) compared to the patients using disease-modifying anti-rheumatic drugs (DMARD).

Methods: 29 patients with rheumatoid arthritis (RA) (F/M: 23/6) and 20 patients with Ankylosing Spondylitis (AS) (F/M: 3/17), for whom anti-TNF agents were initiated for the first time, and 30 healthy controls (F/M: 9/21) were included in the study. Additionally, in order to reveal effects of anti-TNF medications on development of urinary infections better, 29 RA (F/M: 26/3) and 20 AS (F/M: 6/14) patients using DMARDs were also included in the study.

Results: When the differences in age, gender and marital status among RA patients were eliminated, there was no significant difference in regard to frequency of development of urinary infections between patients with active disease before anti-TNF treatment for whom initiation of anti-TND treatment was considered and the patients without active disease who were using DMARDs, despite of differences in disease activity. When the AS patients using anti-TNF agents and DMARDs were compared with the healthy control group in regard to frequency of development of urinary infections; while there was no significant difference in the DMARD group, it was more frequently encountered in the anti-TNF group at 2nd and 3rd visits. When the differences in age, gender, marital status and disease activity among AS patients were eliminated, anti-TNF treatment was determined to pose an additional risk for frequency of development of urinary infections compared to DMARD treatment

Discussion and Conclusion: In conclusion, although anti-TNF treatment is quite effective in taking disease activity under control in RA and AS patients, it is always necessary to be alert due to increased risk for infection.

Keywords: Ankylosing spondylitis; anti-TNF; rheumatoid arthritis; urinary infections.

Özet

Amaç: Bu çalışmada hedefimiz, anti-Tümör Nekroz Faktörü alfa (TNFa) kullanan hastalarda hastalık modifiye edici anti-romatizmal ilaçlar (DMARD) kullanan hastalarla karşılaştırıldığında idrar enfeksiyonlarının sıklığında bir artış olup olmadığını araştırmaktır.

Gereç ve Yöntem: Anti-TNF ajanlarının ilk kez başlatıldığı 29 romatoid artritli (RA) hasta ve 20 adet Ankylosing Spondylitis (AS) hasta ve 30 sağlıklı kontrol çalışmaya dahil edildi. Ek olarak, anti-TNF ilaçlarının idrar enfeksiyonlarının gelişimi üzerindeki etkilerini daha iyi ortaya çıkarmak için DMARD kullanan 29 RA ve 20 AS hastası çalışmaya dahil edildi.

Bulgular: Anti-TNF tedavisine başlamadan önce aktif hastalığı olan ve anti-TNF tedavisine başlanan hastalar ile DMARD kullanan hastalar arasında üriner enfeksiyon gelişim sıklığı bakımından farklılıklara rağmen anlamlı bir fark yoktu. hastalık aktivitesinde. Anti-TNF ajanları ve DMARD kullanan AS hastaları idrar enfeksiyonlarının gelişim sıklığı açısından sağlıklı kontrol grubu ile karşılaştırıldığında; DMARD grubunda anlamlı bir fark bulunmazken, 2. ve 3. ziyaretlerde anti-TNF grubunda daha sık rastlandı. Anti-TNF tedavisinin, DMARD tedavisine kıyasla idrar yolu enfeksiyonlarının gelişme sıklığı için ek bir risk oluşturduğu tespit edildi.

Sonuç: Anti-TNF tedavisi, RA ve AS hastalarında hastalık aktivitesini kontrol altında tutma konusunda oldukça etkili olsa da, enfeksiyon riskindeki artış nedeniyle daima dikkatli olmak gerekir.

Anahtar Sözcükler: Ankilozan spondilit; anti-TNF; romatoid artrit; üriner enfeksiyonlar.

Corresponding *(İletişim)*: Mehmet Ali Uçar, Mersin Üniversitesi Tıp Fakültesi İç Hastalıkları Anabilim Dalı, Mersin, Turkey
E-mail *(E-posta)*: dr.mucar@hotmail.com
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Rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are inflammatory rheumatic diseases of whose etiology various factors have a role, which progress with inflammatory polyarthritis, and of whose treatment immunosuppressive agents are used.[1–4] Presence of Tumor Necrosis Factor Alpha (TNFα) in high concentrations within a rheumatoid joint, induction of other inflammatory cytokines by TNFα in the synovial cytokine network in in vitro experiments and suppression of arthritis through TNF inhibition in experimental models underlie the reason of why TNFα is targeted in treatment of RA.[5,6] It has been demonstrated that the T- lymphocytes and monocytes have increased in the biopsy material obtained from the sacroiliac joint in AS. Furthermore, local production of TNFα has been shown to increase. In many studies, serum TNFα and interleukin – 6 levels were also determined to have increased compared to healthy individuals.[2] This situation has raised the use of anti-TNF treatments in treatment of AS patients.

Disease-modifying anti-rheumatic drugs (DMARD) are generally used before anti-TNF agents in both RA and AS. Both groups of medications have advantages over each other in some fields. Their effects on the disease are known extensively. However, there are some uncertainties at some points in regard to complications. Development of an infection secondary to use of the medication may differ between both groups. For instance, while infection rate was 0.01–0.06/patient-year in those using DMARDs, it was determined to be 0.07–0.09/ patient-year in those receiving anti-TNF agents.[7,8] Some differences may be observed between the groups in regard to common localizations of infections.

Our objective in this study is, therefore, to determine whether there is an increase in frequency of urinary infections in patients receiving anti-TNF treatment compared to patients using DMARDs, whether there is an alteration in agents causing urinary infections, how these two conditions will change when major risk factors causing urinary system infections are eliminated and the effect of disease activity and functional index on development of urinary system infections.

Materials and Method

Study population

This study was conducted between 2009 and 2010 in Kahramanmaras Sutcu Imam University, Medical School Hospital, Clinic of Rheumatology.

29 patients with rheumatoid arthritis (RA) (F/M: 23/6) and 20 patients with Ankylosing Spondylitis (AS) (F/M: 3/17), for whom anti-TNF agents were initiated for the first time, and 30 healthy controls (F/M: 9/21) were included in the study. Additionally, in order to reveal effects of anti-TNF medications on development of urinary infections better, 29 RA (F/M: 26/3) and 20 AS (F/M: 6/14) patients using DMARDs were also included in the study.

Those experiencing recurrent urinary infections, patients with a risk factor for infection [cirrhosis, diabetes mellitus, urinary system stone diseases, chronic renal failure, chronic obstructive pulmonary diseases etc.], patients over 60 years of age, patients who had used antibiotics with renal excretion at a level that would have a post-antibiotic effect (with less than 48–72 hours after use), and patients with history of spermicides, diaphragms, having a new partner, multi-partners, anatomical abnormalities, bladder catheter, blockade of urinary tract (stone, prostatic pathology etc.), neurogenic bladder, pregnancy, vaginitis, cervicitis and pelvic inflammatory disease were not included in the study.

The whole population was evaluated in a total of 4 different visits: one in the beginning and 3 visits performed with 8-week intervals. Socio-demographical characteristics of the patients, including age, gender, duration of disease, age of diagnosis and marital status, were recorded from the files. The association with urinary infection was investigated between the patients using an anti-TNF agent and those receiving DMARD treatment, who had RA and AS. All patients included in the study and those in healthy control group underwent urinary ultrasonography in order to reveal the absence of any undiagnosed obstructive and chronic renal parenchymal disease.

Presence of a urinary infection was considered in case of I) a positive culture (100.000 colony-forming bacteria/ml), II) observation of one or more bacteria within each field under immersion objective in a gram-stained sample obtained from fresh and centrifuged urine dripped on a microscope slide, and III) detection of 4–5 leukocytes within each magnification field in centrifuged urinary sediment.

Written informed consents were obtained from all patients and the control group. Our study was approved by Kahramanmaras Sutcu Imam University, Committee on Medical Ethics on the date 07.05.2009 with the decision numbered 05–2009/10.

Laboratory measurements

At each visit patients were investigated about dysuria, frequency of urination, sensation of urinary incontinence, abdominal pain, flank pain, nausea, vomiting, presence of fever, intermittent urine stream and foul-smelling urination. In order to minimize the level of bacterial contamination during obtaining urinary cultures, patients' urethral meatus or its mucosa were cleaned locally with a disinfectant without foaming with an antiseptic solution (this area was cleaned with a sterile cloth in order to prevent mixing of urine with the antiseptic solution). As the initial urine sample reflected urethral contamination of the initial urine stream, mid-stream urine was sent to the laboratory. Urine samples were sent immediately to the bacteriology laboratory because of the risk of growth of bacteria within hot, fresh urine and consequent increment of number of bacteria. During routine controls of the patients; blood samples for erythrocyte sedimentation rate (ESR), c-reactive protein (CRP) and complete blood count, as well as urinary samples for total urinalysis and urine microscopy were collected. ESR was measured by using Westergreen method and CRP was measured by using turbidimetric method.

Table 1. Demographical characteristics of the patients

Variables	RA n=58			AS n=40		
	DMARD n=29	anti-TNF n=29	p	DMARD n=20	anti-TNF n=20	p
Age (years)	45.2±9.8	44.8±11.1	0.971	37.8±0.8	36.1±8.9	0.450
Gender						
Male	3 (10.3%)	6 (20.7%)	0.468	14 (70.0%)	17 (85.0%)	0.999
Female	26 (89.7%)	23 (79.3%)		6 (30.0%)	3 (15.0%)	
Duration of Disease (years)	7.3±5.9	9.4±5.5	0.075	9.9±6.7	12.7±7.0	0.187
Age of Disease Onset (years)	37.9±10.6	35.4±10.1	0.450	27.9±9.9	23.4±8.6	0.189
Age of Diagnosis	40.5±10.7	39.2±10.8	0.708	32.7±9.6	30.2±8.3	0.372
Duration of steroid use (month)	45.5±38.7	64.5±38.6	0.031*	19.8±14.9	28.8±23.0	0.249
Duration of MTX use (month)	20.8±12.8	41.3±25.3	<0.001*	19.5±23.3	4.7±3.5	0.411
Duration of SZP use (month)	31.4±36.9	46.0±29.5	0.004*	47.4±34.9	50.0±35.6	0.827

Numerical variables were represented asmean±standard deviation; Categorical variables were represented as count (%). *p<0,05 indicates statistical significance; RA: Rheumatoid arthritis; AS: Ankylosing spondylitis; DMARD: Disease modifying anti-rheumatic drug; MTX: Methotrexate; SZP: Salazopyrin.

Clinical measurements

For assessment of disease activities of the patients; HAQ20 and DAS28 were used for RA patients and BASDAI and BASFI scorings were used for AS patients.

Health assessment questionnaire (HAQ20) isa questionnaire evaluating the level of patient having difficulties while he/she is performing daily routine activities and the functional status for last 1 week. It is comprised of 8 questions and each question is scored between 0 and 3.

Disease activity score (DAS28) is an assessment in which number of swollen and tender joints among 28 pre-determined joints, general medical condition of the patient, scoring at visual analog scale ranging 0-100 and ESR or CRP are used and calculated commonly via appropriate calculators or computer programs.

Bath ankylosing spondylitis disease activity index (BASDAI) includes 6 visual scales concerning fatigue, spine pain, peripheral joint swelling, severity or duration of morning stiffness. Each question is scored by the patient from 0 to 10. By averaging the total score, BASDAI is calculated.

Bath ankylosing spondylitis functional index (BASFI) includes 10 visual analog scales concerning daily routine activities.

It was calculated by averaging the total score obtained by scoring of questions asked to a patient on a visual analog scale from 0 to 10. Presence of BASDAI >4/10 and DAS28 >5.1 was considered as active disease.

Statistical analysis

Statistical evaluation was performed by using Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, IL) program. Normal distribution of the data was evaluated by using Kolmogorov-Smirnov test. Numerical variables were represented as mean±standard deviation.Categorical variables were defined as count and percentage. Intergroup difference of numerical variables exhibiting normal distribution was evaluated by ANOVA test and intergroup difference of numerical variables that did not exhibit normal distribution was evaluated by Kruskal Wallis Test, Bonferoni correction was used for paired comparisons. For comparison of categorical data, Chi-Square and Fisher's Exact Chi-Square Tests were used. Alteration in laboratory and clinical activity scores by follow-up durations was evaluated by using therepeated measures ANOVA test (post hoc: Benforroni test). In statistical analyses, values p<0.05 were considered to be significant.

Result

In Table 1, clinical and demographical findings of the study population are summarized. Among RA patients, mean duration of steroid use, mean duration of methotrexate use and mean duration of Salazopyrin use were determined to be higher in patients using anti-TNF agents compared to those using DMARDs (p<0.05). No such difference was determined in the AS group.

In patients diagnosed with RA who were using DMARD and anti-TNF agents, a significant decrement in mean leukocyte count was determined at the 3rd visit compared to other visits (p=0.045; p=0.031, respectively), however, the change in visit values did not differ significantly by treatment groups (Δp=0.650). In patients diagnosed with SA who were using DMARDs, no significant difference was determined in mean leukocyte count during the follow-up duration (p=0.460), in patients using anti-TNF agents, however, mean leukocyte count was determined to be higher compared to the basal values in other follow-up durations (p=0.048), at 1st-3rd visits, however, leukocyte count did not differ significantly. During the follow-up duration, the increment in mean leukocyte count was determined to be significantly higher in patients diagnosed with SA who were using anti-TNF agents compared

Table 2. Laboratory findings by treatment of diseases

Laboratory findings	Disease	Treatment	Basal	1st visit	2nd visit	3rd visit	p	Δp
Leukocyte count	RA	DMARD	5.9±10.9	9.1±15.4	5.6±11.6	**2.9±2.2**	0.045*	0.650
		anti-TNF	7.7±13.2	9.5±21.4	6.0±7.9	**4.4±4.5**	0.031*	
	AS	DMARD	2.7±3.2	2.1±1.1	2.4±1.9	2.1±0.8	0.460	0.010*
		anti-TNF	**3.9±6.6**	4.7±5.3	5.6±5.3	6.2±6.4	0.048*	
Sedimentation	RA	DMARD	27.8±15.7	26.6±14.6	30.2±16.1	35.3±18.2	0.548	0.145
		anti-TNF	38.9±26.9	37.0±24.9	27.2±22.7	33.2±31.1	0.270	
	AS	DMARD	21.2±21.3	**18.0±13.9**	28.6±18.2	21.4±10.2	0.045*	0.020*
		anti-TNF	21.4±12.7	15.7±13.1	15.7±16.3	14.7±9.5	0.030*	
CRP	RA	DMARD	9.9±11.7	13.9±28.4	14.8±27.0	10.5±13.9	0.210	0.001*
		anti-TNF	**30.9±39.1**	15.3±24.0	**8.4±7.6**	17.8±25.8	0.006*	
	AS	DMARD	14.0±25.8	11.0±18.6	12.0±15.4	**7.5±6.2**	0.005*	0.013*
		anti-TNF	19.5±24.1	10.1±10.9	**4.4±3.4**	**4.5±2.5**	0.001*	
Positive urinary culture	RA	DMARD	1 (3.4)	3 (10.3)	2 (6.9)	1 (3.4)	0.045*	0.120
		anti-TNF	7 (24.1)	8 (27.6)	5 (17.2)	5 (17.2)	0.040*	
	AS	DMARD	–	–	–	–	–	<0.001*
		anti-TNF	1 (5)	2 (10)	1 (5)	5 (25)	0.012*	

Numerical variables were represented as mean±standard deviation; Categorical variables were represented as count (%); Bold characters represent visits exhibiting significant difference; *p<0,05 indicates statistical significance; Δp: DMARD vs anti-TNF; RA: Rheumatoid arthritis; AS: Ankylosing spondylitis; DMARD: Disease modifying anti-rheumatic drug; CRP: C reactive protein.

to the patients using DMARDs (Δp=0.010). In patients diagnosed with RA who were using DMARD and anti-TNF agents, mean ESR value did not differ significantly by visits (p=0.548; p=0.270, respectively). In patients diagnosed with SA who were using DMARD, mean ESR values were determined to be higher at the 2nd visit compared to other visits (p=0.045), in patients diagnosed with SA who were using anti-TNF agents, however, a significant decrement in mean ESR values was determined compared to basal values in other follow-up durations (p=0.030), at 1st-3rd visits, however, mean ESR values did not differ significantly. A more decrement in mean ESR value was determined in patients diagnosed with SA who were using anti-TNF agents compared to those using DMARD during the follow-up duration (Δp=0.020) (Table 2).

In patients diagnosed with RA who were using DMARD, mean CRP values did not differ significantly by visits (p=0.210), in patients diagnosed with RA who were using anti-TNF agents, however, a significant decrement in mean CRP level was determined compared to basal values in other follow-ups (p=0.006). In patients diagnosed with RA who were using anti-TNF agents, more decrement in mean CRP values was determined compared to those using DMARD (Δp=0.001). In patients diagnosed with SA who were using DMARD, mean CRP values did not differ significantly by visits (p=0.210), in patients diagnosed with SA who were using anti-TNF agents, however, a significant decrement in mean CRP level was determined at 2nd-3rd visit follow-up values compared to the basal and 1st visit values (p=0.001). A more decrement in mean CRP values was determined in patients diagnosed with SA who were using anti-TNF agents compared to those using DMARD during the follow-up duration (Δp=0.013) (Table 2).

In patients diagnosed with RA who were using DMARD, ratio of patients with positive urinary culture was determined to be higher at the 2nd visit compared to the basal visit, and a significant decrement in positive culture rate was determined in other follow-ups (p=0.045), in patients diagnosed with RA who were using anti-TNF agents, however, ratio of patients with positive urinary culture exhibited a significant decrement in other visits compared to basal and 1st visit values (p=0.040). Among patients diagnosed with RA, the change in ratio of patients with positive urinary culture did not differ significantly between those using DMARD and anti-TNF agents (Δp=0.120). In patients diagnosed with SA who were using DMARD, no patient with positive urinary culture was determined during all follow-ups. In patients diagnosed with SA who were using anti-TNF agents, however, ratio of patients with positive urinary culture at the 3rd visit was determined to be higher compared to other follow-ups (p=0.012) (Table 2).

Distribution of urinary cultures during follow-up duration by disease and treatment groups is represented in Table 3.

In patients diagnosed with RA who were using DMARD, mean HAQ20 score did not differ significantly by visits (p=0.115), in patients diagnosed with RA who were using anti-TNF agents, however, a significant decrement in mean HAQ20 score was determined in other follow-ups compared to the basal values (p=0.011). A more decrement in mean HAQ20 score was determined in patients diagnosed with RA who were using anti-TNF agents compared to those using DMARD during the follow-up duration (Δp=0.005). In patients diagnosed with RA who were using DMARD, mean DAS28 score exhibited a significant decrement at 1st and 2nd visits compared to the basal

Table 3. Distribution of urinary cultures by treatment of diseases

Disease	Treatment	Group	Basal	1st visit	2nd visit	3rd visit
RA	DMARD	None	16 (55.2)	22 (75.9)	24 (82.8)	22 (75.9
		No growth	9 (31)	4 (13.8)	2 (6.9)	6 (20.7)
		Contamination	3 (10.3)	–	1 (3.4)	–
		E. coli.	1 (3.4)	2 (6.9)	2 (6.9)	1 (3.4)
		gr (+) enterococcus	–	–	–	–
		pseudomonas	–	1 (3.4)	–	–
	anti–TNF	None	17 (58.6)	16 (55.2)	18 (62.1)	20 (69)
		No growth	4 (13.8)	5 (17.2)	5 (17.2)	3 (10.3)
		Contamination	1 (3.4)	–	1 (3.4)	1 (3.4)
		E. coli.	4 (13.8)	6 (20.7)	3 (10.3)	4 (13.8)
		gr (+) enterococcus	3 (10.3)	2 (6.9)	2 (6.9)	1 (3.4)
		pseudomonas	–	–	–	–
AS	DMARD	None	18 (90)	19 (95)	19 (95)	19 (95)
		No growth	1 (5)	1 (5)	0	1 (5)
		Contamination	1 (5)	–	1 (5)	–
		E. coli.	–	–	–	–
		gr (+) enterococcus	–	–	–	–
		pseudomonas	–	–	–	–
	anti–TNF	None	18 (90)	14 (70)	12 (60)	11 (55)
		No growth	1 (5)	4 (20)	6 (30)	4 (20)
		Contamination	–	–	1 (5)	–
		E. coli.	1 (5)	1 (5)	–	4 (20)
		gr (+) enterococcus	–	1 (5)	1 (5)	1 (5)
		pseudomonas	–	–	–	–

Categorical variables were presented as count (%); RA: Rheumatoid arthritis; AS: Ankylosing spondylitis; DMARD: Disease modifying anti–rheumatic drug; CRP: C reactive protein.

values, a similarity was determined with the basal values at the 3rd visit (p=0.045). In patients diagnosed with RA who were using anti-TNF agents, however, a significant decrement in mean DAS28 score was determined in other follow-ups compared to basal values (p=0.009). A more decrement in mean DAS28 score was determined in patients diagnosed with RA who were using anti-TNF agents compared to those using DMARD during the follow-up duration (Δp=0.016). In patients diagnosed with SA who were using DMARD, mean BASDAI score did not differ in other follow-ups compared to basal values (p=0.133). In patients diagnosed withSA who were using anti-TNF agents, however, a significant decrement in mean BASDAI score was determined in other follow-ups compared to basal values (p=0.006). A more decrement in mean BASDAI score was determined in patients diagnosed with SA who were using anti-TNF agents compared to those using DMARD during the follow-up duration (Δp=0.001). In patients diagnosed with SA who were using DMARD, mean BASFI score did not differ in other follow-ups compared to basal values (p=0.340). In patients diagnosed with SA who were using anti-TNF agents, however, a significant decrement in mean BASFI score was determined in other follow-ups compared to basal values (p=0.001). A more decrement in mean BASFI score was determined in patients diagnosed with SA who were using anti-TNF agents compared to those using DMARD during the follow-up duration (Δp=0.001) (Table 4).

Discussion

In our study, when the differences of age, gender and marital status among RA patients were eliminated, there was no significant difference in regard to frequency of development of urinary infections between patients with active disease before anti-TNF treatment for whom initiation of anti-TND treatment was considered and the patients without active disease who were using DMARDs, despite of differences in disease activity. When the AS patients using anti-TNF and DMARDs were compared with the healthy control group in regard to frequency of development of urinary infections; while there was no significant difference in the DMARD group, it was more frequently encountered in the anti-TNF group at 2nd and 3rd visits. When the differences of age, gender, marital status and disease activity among AS patients were eliminated, anti-TNF treatment was determined to pose an additional risk for frequency of development of urinary infections compared to DMARD treatment.

In a study involving 10,755 patients conducted by Dixon and colleagues in which severe infections that developed follow-

Table 4. Laboratory findings by treatment of diseases

Disease	Treatment	Clinical activity scores	Basal	1st visit	2nd visit	3rd visit	p	Δp
RA	DMARD	HAQ20	1.6±0.4	1.6±0.5	1.5±0.5	1.7±0.4	0.115	0.005*
	anti-TNF		**3.9±0.4**	1.3±0.3	1.1±0.3	1.4±0.5	0.011*	
	DMARD	DAS28	3.8±0.6	**3.5±0.6**	**3.5±0.6**	3.9±0.5	0.045*	0.016*
	anti-TNF		**5.8±0.4**	3.4±0.8	3.2±0.7	3.2±1.2	0.009*	
SA	DMARD	BASDAI	1.8±0.3	1.8±0.2	2.0±0.4	1.9±0.2	0.133	0.001*
	anti-TNF		**4.8±0.4**	1.5±0.5	1.3±0.6	1.4±0.7	0.006*	
	DMARD	BASFI	3.2±0.6	3.1±0.5	3.5±0.9	3.3±0.4	0.340	0.001*
	anti-TNF		**7.9±1.1**	2.5±1.0	2.7±1.0	2.8±1.2	0.001*	

Numerical variables were represented as mean±standard deviation; Bold characters represent visits exhibiting significant difference; *p<0,05 indicates statistical significance; Δp: DMARD vs anti-TNF; RA: Rheumatoid arthritis; AS: Ankylosing spondylitis; DMARD: Disease modifying anti-rheumatic drug; HAQ: Health assessment questionnaire; DAS28: Disease activity score; BASDAI: Bath ankylosing spondylitis activity index; BASFI: Bath ankylosing spondylitis functional index.

ing anti-TNF treatment in RA patients, patients' age, gender (female: 72%) and duration of the disease (mean DMARD/anti-TNF: 7/12 years) were similar to those in our study. HAQ20 (anti-TNF/DMARD: 2.1/1.5) and DAS28 (anti-TNF/DMARD: 6.6/5) scores, which are disease activity scores, were similar to the activity scores we obtained in our study. In this study conducted by Dixon and colleagues, it was shown that, although cumulative incidence of infections was higher in patients receiving anti-TNF treatment compared to the patients using DMARD, all of the severe infections did not increase following anti-TNF treatment.[8] In our study, no statistically significant difference was determined between RA patients using anti-TNF agents and DMARD in regard to development of urinary infections; although anti-TNF treatment may pose a risk for development of severe infections, it may not pose a risk for development of urinary system infections in RA patients due to recovery of disease activity and absence of accompanying chronic diseases.

In a study conducted by Daniel and colleagues in which the studies published between 1990 and 2008 were reviewed, and biological treatments (infliximab, etanercept, adalimumab, abatacept, anakinra) as well as their risk for infections were investigated, it was revealed that there was an increment in risk for severe and non-severe infections in controlled studies in which patients using anti-TNF agents and those using DMARDs were compared.[9] In our study, although no statistically significant difference was determined between RA patients using DMARD and anti-TNF agents in regard to frequency of urinary infections, rate of bacterial growth in urinary cultures collected from the patients with urinary infections were higher at the 4th visit in patients using anti-TNF agents compared to the patients using DMARD. In our study, the statistically significant improvement in HAQ20 and DAS28 scores, which are disease activity scores, among RA patients may be one of the causes leading to this outcome.

In a 4-year ARMADA study in which long-term effectiveness and safety of adalimumab added in addition to methotrexate among RA patients,[10] patients' age, gender (female: 76%) and duration of disease (12.4 years) were similar to those in our study. In the ARMADA study, DAS28 score regressed from 5.3 to 3 by the end of 4 years, HAQ20 score, however, regressed from 1.5 to 0.7, and CRP value regressed from 25 mg/dl to 7 mg/dl. In our study, however, DAS28 score regressed from 5.8 to 3.2, HAQ20 score regressed from 3.9 to 1.1 and CRP value, however, regressed from 30.9 mg/dl to 8.4 mg/dl. In the ARMADA study, ratio of severe infections (pneumonia, urinary tract infections, septic arthritis, tuberculosis) determined in the patients was similar between both groups (2.30/100 patient-year, 2.03/100 patient-year).[10] Also in our study, no statistically significant difference was determined between the patients using anti-TNF agents and those using DMARD in regard to frequency of urinary tract infections. Functional recovery, taking disease activity under control and improvement in acute phase response achieved through anti-TNF treatment may have a preventive role for development of urinary infections in RA patients.[8]

In a retrospective cohort study conducted by Michele F. Doran and colleagues in which 609 RA patients were reviewed and determinants of infection in RA were investigated, mean age was determined to be 58, female ratio to be 73.1% and duration of disease to be 7.7 years;a strong correlation was determined between RA patients with severely progressing disease (RF positivity, rheumatoid nodule, extra-articular findings, increased sedimentation, loss of functional status) and development of infections in the study; at the end of the study, it was revealed that there was a strong correlation between RA patients and particularly disease activity, advanced age, leucopenia and accompanying chronic diseases, as determinants of infections.[11] Although there were similar gender and duration of disease factors in our study, the population (mean age: 45) was comprised of younger patients; that those with recovery of disease activity achieved via anti-TNF and DMARD treatments (HAQ20: 1.4–1.7, DAS28: 3.2–3.9, respectively) and accompanying chronic diseases were not included in the study may have played a preventive role for the development of urinary infections in our study.

In a study conducted by Martinez and colleagues in which the correlation between disease activity and infection in patients with spondyloarthropathies was investigated in 95 patients

with spondyloarthropathies (52 AS); AS patients'mean age was determined to be 26.7, ratio of male patients was determined to be 76% and duration of disease was determined to be 9.7 years. An infection was detected in 50% of the AS patients and these infections were comprised of gastrointestinal system, respiratory system and genitourinary infections, respectively. An infection was detected in 82% of the AS patients with active disease and 11% of this was comprised of genitourinary system infections; in this study,prevalence of the correlation between disease activity and infections was determined to be high, they were primarily AS and prevalence of enteric and genitourinary tract infections were determined to be higher in those with active disease.[12] Also in our study age, gender and duration of disease were similar. Disease activity in patients for whom anti-TNF treatment was considered to be initiated was determined to be higher at the initial visit and disease activity following anti-TNF treatment was similar to that of the group using DMARD; however, despite of the improvement in disease activity, rate of urinary tract infections was determined to be higher in the group using anti-TNF agents compared to the group using DMARD. Anti-TNF treatment may be a risk factor for development of urinary infections, independent from age, gender, duration of disease and disease activity.

In a study on bacterial and opportunistic infections during anti-TNF treatment which was conducted by Strangfeld A. and colleagues, RA and AS patients using anti-TNF treatment were under greater risk of infection and especially rates of granulomatous infections were determined to be more commonly encountered. Furthermore, patients receiving anti-TNF treatment were determined to be those with more active progression.[7] Also in our study, frequency of development of urinary infections were determined to be higher in AS patients receiving anti-TNF treatment compared to the group receiving DMARD. Disease activity was higher in the anti-TNF group at the beginning of treatment; under the light of data obtained in our study, anti-TNF treatment may increase not only the risk of granulomatous infections but also the risk of urinary system infections.

In a study on AS and genitourinary system infections which was conducted by Lange U. and Teichmann J.,[13] in majority of patients with genitourinary system infections, chlamydia trachomatis was isolated. Most of these patients were shown to be comprised of HLA-B27 (+) patients and in conclusion of this study, genitourinary system infections caused by chlamydia trachomatis were shown to be more common in female and male AS patients compared to female and male HLA-B27 (+) AS patients.[13] Also in our study, *E. coli*, which is the most commonly responsible pathogen in etiology of urinary system infections, was observed more commonly. Based on the result we obtained, *E. coli* which is the most commonly isolated pathogen in normal population may cause urinary system infections more frequently in these patients because of the increased risk for infection caused by anti-TNF treatment.

TNFα is an important cytokine for defense against bacterial infections and patients receiving anti-TNF treatment are at high risk for granulomatous infections; in addition to this, these patients have more active progression and their predisposition to infection is higher. Infections can be caused by atypical pathogens in addition to the typical pathogens. Macrophage/granulomatosis-dependent opportunistic infections may occur after anti-TNF medications but their incidence is extremely low. Thus, inhibition of TNFα may increase the risk for severe/non-severe infections.[14–17]

In conclusion, although anti-TNF treatment is quite effective in taking disease activity under control in RA and AS patients, it is always necessary to be alert due to increased risk for infection; it was revealed in this study, which attracted attention on urinary infections commonly encountered particularly in normal population, that although anti-TNF treatment increases this risk, underlying disease on its own, activity of the disease, degree of disability and other accompanying diseases may be factors that may cause predisposition to infections, and conduction of more large-scale studies is required in order to better clarify this matter.

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