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ORIGINAL ARTICLE

Patients' concerns regarding biological agents in rheumatology

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Abstract

Objective: The potential side effects of biological agents may increase the anxiety levels of patients and influence not only their desire to use these therapies but also their concordance to treatment. This study aimed to determine the level and prevalence of drug-related concern in patients treated with biological agents and to acquire additional information regarding the related causes.

Materials and Methods: A total of 1134 patients who were using biological agents for at least 3 months with a diagnosis of rheumatic diseases were enrolled. General anxiety levels were evaluated using the State-Trait Anxiety Inventory (STAI).

Results: The most common cause for drug-related concerns was the potential side effects of the drugs (59.5%). Among the potential side effects, cancer risk was the most common cause for concern (40.1%), followed by the risk of tuberculosis activation (30.7%). Anxiety levels were higher in patients who experienced side effects than in other patients, and this difference was statistically significant ($P < 0.05$). STAI trait and state scores were moderately correlated with anxiety levels related to the drug ($P < 0.001$).

Conclusion: Anxiety related to biological agents may significantly affect the patients' anxiety levels. Awareness regarding the patients' concerns and expectations related to the drug is important to ensure drug adherence and concordance to treatment.

Key words: biological agents, patient, patients' concern, rheumatology.

INTRODUCTION

Anxiety, described as a neurosis, is characterized by anxious over-concern extending to panic and is frequently associated with somatic symptoms according to the *Diagnostic and Statistical Manual of Mental Disorders*.[1]

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Mood and anxiety disorders are common comorbid conditions in patients with rheumatic diseases.[2] In these patients, anxiety frequency was reported in varying proportions to be 30–70%.[3,4]

The presence of anxiety is correlated with quality of life and anxiety is an independent predictor of disease activity in patients with early arthritis.[3,5] Psychiatric comorbidity appears to be the most important independent predictor of work disability in patients with inflammatory rheumatic diseases.[6] Thus, concerns and

Table 1 Demographic data and group differences between anxiety scores

	n (%) *N* = 1134	Drug-related concern (VAS)	STAI-S score	STAI-T score
Sex				
Female	612 (54%)	4.4 ± 3.2	42.6 ± 10.4	47.2 ± 8.5
Male	522 (46%)	3.5 ± 2.7	38.5 ± 10.9	42.9 ± 8.5
P-value		0.001	0.000	0.000
Marital status				
Single	185 (16.3%)	3.6 ± 2.8	38.8 ± 10.8	42.9 ± 8.8
Married	880 (77.6%)	4.1 ± 3.0	40.9 ± 10.8	45.6 ± 8.7
Divorced	38 (3.4%)	3.8 ± 3.1	45.4 ± 10.4	47.9 ± 7.4
Widowed	31 (2.7%)	3.0 ± 3.0	40.7 ± 9.9	46.4 ± 9.1
P-value		0.029	0.005	0.000
Disease				
RA	429 (37.8%)	4.1 ± 3.1	42.1 ± 10.9	46.4 ± 8.4
AS	561 (49.5%)	3.9 ± 2.9	38.9 ± 10.8	43.9 ± 8.9
PsA	70 (6.2%)	4.1 ± 2.9	41.0 ± 9.9	46.3 ± 8.9
Behçet's	8 (0.7%)	2.6 ± 2.5	37.8 ± 13.7	46.0 ± 15.5
Other	66 (5.8%)	4.1 ± 2.5	47.2 ± 8.1	47.5 ± 6.3
P-value		0.655	0.000	0.000
Drug				
Adalimumab	227 (20.0%)	4.23 ± 3.21	40.9 ± 10.9	45.9 ± 9.2
Etanercept	252 (22.2%)	3.65 ± 3.12	38.4 ± 11.1	44.2 ± 9.6
Golimumab	99 (8.7%)	4.30 ± 2.83	39.7 ± 11.6	43.6 ± 8.6
Infliximab	292 (25.7%)	4.05 ± 2.95	39.7 ± 10.5	44.2 ± 8.5
Rituximab	171 (15.1%)	3.96 ± 2.63	44.7 ± 10.2	47.7 ± 7.4
Abatacept	40 (3.5%)	3.78 ± 3.71	40.2 ± 8.9	46.7 ± 9.1
Tocilizumab	35 (3.1%)	3.83 ± 2.82	43.2 ± 8.8	45.9 ± 7.2
Anakinra	18 (1.5%)	4,33 ± 2.16	50.89 ± 5.2	48.7 ± 2.5
P-value		0.321	0.000	0.000
Working status				
Working	421 (37.1%)	4.0 ± 2.8	39.7 ± 10.7	43.9 ± 8.3
Not working	713 (62.9%)	3.9 ± 3.1	41.3 ± 10.9	46.1 ± 8.9
P-value		0.907	0.014	0.000
Education level				
Illiterate	86 (7.6%)	3.6 ± 2.9	44.6 ± 10.7	47.5 ± 7.5
Primary school	476 (42.0%)	3.8 ± 3.2	40.5 ± 11.9	45.7 ± 9.4
Middle school	147 (13.0%)	4.2 ± 2.9	42.2 ± 9.8	46.6 ± 7.7
High school	266 (23.5%)	4.3 ± 2.8	41.1 ± 10.9	44.9 ± 8.2
University	159 (14.0%)	4.1 ± 2.7	37.4 ± 10.8	41.9 ± 8.6
P-value		0.122	0.000	0.000
Comorbid disease				
Yes	381 (33.6%)	4.1 ± 2.9	41.1 ± 10.9	45.1 ± 8.8
No	753 (66.4%)	3.7 ± 3.1	40.0 ± 10.8	45.6 ± 8.7
P-value		0.026	0.121	0.305
Disease activity				
Asymptomatic	87 (7.7%)	3.2 ± 3.1	33.4 ± 10.7	41.0 ± 9.7
Mild	386 (34.0%)	3.7 ± 2.9	39.0 ± 10.6	43.8 ± 8.3
Moderate	475 (41.9%)	4.3 ± 2.9	41.9 ± 10.2	46.2 ± 8.3
Severe	154 (13.6%)	4.5 ± 3.2	44.1 ± 11.1	47.9 ± 9.2
Very severe	32 (2.8%)	3.9 ± 3.1	46.7 ± 9.9	47.6 ± 9.9
P-value		0.000	0.000	0.000

AS, ankylosing spondylitis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; STAI-S, State-Trait Anxiety Inventory-state; STAI-T, State-Trait Anxiety Inventory-trait; VAS, visual analog scale.

anxiety are important health problems in rheumatic diseases and may increase the disease burden.

Patients may have many concerns regarding a disease (e.g., pain, shortened life expectancy, disability), distrust toward the medical profession and anxiety regarding their medications.[7] Some patients have concerns because of various beliefs regarding their medications. Moreover, beliefs concerning medication were found to be essentially related to drug adherence.[8]

With the invention of biological agents (e.g., anti-tumor necrosis factor [TNF], other cytokines, and T- and B-cell-targeted therapies), there have been many important advances in the treatment of rheumatic disease in the past 10 years.[9] These new drugs can decrease pain and control disease activity and improve the quality of life and functionality.[10,11] In addition, they may aid in reducing the frequency of anxiety and mood disorders, increase the positive outlook on life, and improve the patient's social life and work productivity.[2,12,13] However, there is also a risk of serious adverse effects (e.g., the reactivation of tuberculosis and severe infections), and although it remains controversial, there is an increased theoretical risk of malignancy.[14–16]

Because of medico-legal rules in our country, informed consent forms, which contain the list of potential side effects, must be signed by patients while initiating biological agents and at regular intervals during treatment. Although the objective of this consent form is to inform patients regarding the potential side effects, patients often commence treatment with anxieties regarding side effects before experiencing any of the positive effects of the drug. Furthermore, patients may sometimes refuse to use the medication. Ribeiro *et al.*[17] observed that among all the patients studied, depression, anxiety and suicidal ideation levels were high in patients with rheumatoid arthritis (RA) who were taking biological disease-modifying antirheumatic drugs (DMARDs).

This study aimed to determine the level and prevalence of drug-related anxiety in patients treated with biological agents and to gain information regarding the related causes.

MATERIALS AND METHODS

This multicenter study included 1134 individuals who had RA, ankylosing spondylitis (AS), psoriatic and enteropathic arthritis, Behçet's disease, or other rheumatic diseases and who were using biological agents (e.g., adalimumab, etanercept, infliximab, golimumab, rituximab, abatacept, anakinra or tocilizumab) for at least 3 months from six different rheumatology centers. Patients who were accepted were informed regarding the study, and written informed consent was obtained

Table 2 Patient thoughts and beliefs about the biological agents

Thoughts regarding biological agents	Agree *n* (%)	Undecided *n* (%)	Disagree *n* (%)
I am worried about the long-term side effects of the drug	721 (63.6%)	167 (14.7%)	246 (21.7%)
I do not want to use this drug because of its side effects	375 (33.1%)	235 (20.7%)	524 (46.2%)
I think I'm vulnerable to infections	625 (55.1%)	170 (15%)	339 (29.9%)
There are no other treatment options that can be used for my disease	544 (48%)	349 (30.9%)	241 (21.3%)
I am afraid if I cannot get the drug anymore	651 (57.4%)	142 (12.5%)	341 (30.1%)
Sometimes I hide the side effects of the drug from my doctor	187 (16.5%)	79 (7%)	868 (76.5%)
I would like to get more information about the drug	813 (71.7%)	119 (10.5%)	202 (17.8%)
Too much information about the side effects of drugs worries me	555 (48.9%)	161 (14.2%)	418 (36.9%)
I want to use this drug	894 (78.9%)	140 (12.3%)	100 (8.8%)
My current health is related to my drug	1005 (88.6%)	73 (6.4%)	57 (5.0%)
My drug has more benefits than side effects	909 (80.2%)	107 (9.4%)	118 (10.4%)

from each participant. The local ethics committee approved the study.

Demographic characteristics, such as age, gender, working and marital status, education level, and information regarding the disease (e.g., disease duration), commencement date of the biological agent, and drugs formerly used (if available) were recorded.

A global assessment of the disease activity was determined according to a five-level grading scale (1, asymptomatic; 2, mild; 3, moderate; 4, highly active; and 5, very highly active) and using a 10-cm visual analog scale (0, none; 10, very much) by follow-up physicians.

Thoughts and concerns regarding the drug and its side effects were assessed by multiple choice questions (questions about side effects were obtained from the informed consent form, which contains the list of potential side effects, must be signed by patients while initiating biological agents and at regular intervals during treatment) and a closed-ended questionnaire with answers that included agree, undecided and disagree. The feelings of patients when the drug was first administered and the details that patients wished to know regarding the drug were gathered using open-ended questions.

Concern levels regarding the possible side effects of the drug were determined using a 10-cm visual analog scale (0, none; 10, very much). Anxiety levels of patients were assessed using the Turkish version of the self-assessment questionnaire State-Trait Anxiety Inventory (STAI) Form TX-1. STAI was developed by Spielberger *et al.* in 1970 and adapted to Turkish populations by LeCompte *et al.* in 1976 and confirmed for reliability and validity by Oner in 1977.[18] STAI is a 40-item questionnaire and in two parts, state and trait. The State STAI (STAI-S) consists of 20 questions (between 1–20 items) and determines how the individual felt in specific conditions at a specific time. The Trait STAI (STAI-T) consists of 20 questions (between 21–40 items) and determines how they feel in general. Each item was rated using a 1–4 scale, which are: 1, none; 2, some; 3, a lot of; and 4, entirely, for every question. The score taken from each scale ranges between 20–80. Higher scores indicate higher levels of anxiety. The internal consistency alpha coefficients of the State portion range from 0.86 to 0.92.[18,19]

The drug adherence status was assessed and identified as active concordance, passive concordance, resistance or clearly rejecting. The patients were also questioned regarding whether they had sufficient information about the drug they had been using and the source of the information they had obtained.

The SPSS software for Windows (version 22.0; IBM, Armonk, NY, USA) was used for the analyses. Descriptive statistics are given as the mean ± SD and frequency (percentage). Kolmogorov–Smirnov test was used for defining the distribution of the variables. Analysis of variance was used to compare the variables between groups. The correlation between the variables was tested using Spearman's correlation coefficients. A *P*-value of < 0.05 was considered to be statistically significant.

RESULTS

A total of 1134 patients (612 female [54%] and 522 male [46%]) were enrolled. The mean age was 43.5 ± 13.2 years. Patients were using biological agents (e.g., adalimumab, etanercept, golimumab, infliximab, rituximab, abatacept, tocilizumab and anakinra) with diagnoses of RA ($n = 429$, 37.8%), AS ($n = 561$, 49.5%), psoriatic arthritis ($n = 70$, 6.2%), Behçet's disease ($n = 8$, 0.7%) and other rheumatic diseases ($n = 66$, 5.8%). The mean duration of disease was 109.70 ± 85.28 months and mean biological drug usage duration was 39.92 ± 29.72 months. Socioeconomic status such as empolyment and education, and

Table 3 Correlation between anxiety levels and demographic data

	STAI-T		STAI-S		Drug-related concern	
	r	*P*	*r*	*P*	*r*	*P*
Age	**0.069**	**0.021**	0.016	0.594	−0.052	0.082
Disease duration	0.033	0.274	**−0.099**	**0.001**	**0.062**	**0.038**
Biological agent usage duration	0.036	0.222	−0.017	0.562	0.054	0.069
Total drug number except biological agent	**0.092**	**0.002**	0.057	0.057	0.010	0.728
Drug-related anxiety	**0.297**	**0.000**	**0.302**	**0.000**	–	–
Disease activity	**0.224**	**0.000**	**0.246**	**0.000**	**0.130**	**0.000**

STAI-S, State-Trait Anxiety Inventory-state; STAI-T, State-Trait Anxiety Inventory-trait. The statistically significant values have shown as bold.

the severity of the disease reported by the patients, were questioned (Table 1).

Concern regarding biological drugs was reported by 82.2% of patients (n = 931). The mean anxiety level was 3.9 ± 3.0, mean STAI-S (state) score was 40.7 ± 10.9, and STAI-T (trait) score was 45.2 ± 8.8. Moreover, only 17.8% of patients did not have concerns regarding biological agents. The most common causes of concern were as follows: side effects, 59.5%; addiction risk to the drug, 22.9%; possible effect on reproductive functions, 10.1%; ideas that biological agents can interact with other drugs used by patients, 9.3%; and fear of injection, 7.6%.

Concerns regarding the side effects included: the risk of cancer (40.1%); tuberculosis reactivation (30.7%); infection (11.6%); allergy (7.6%); heart failure (6.5%); neurological disorders (6.0%); and a decrease in blood parameters (3.7%). The patients' thoughts and beliefs regarding biological agents are presented in Table 2.

Higher anxiety levels were observed in patients with negative feelings than those with positive (n = 0.001) or neutral (n = 0.001) feelings. Compared with other patients, those who experienced side effects had higher anxiety levels, and this difference was statistically significant (n = 0.001). STAI-T and STAI-S scores were fairly correlated with drug-related concern levels (P = 0.001, r = 0.297 and P = 0.001, r = 0.302, respectively). In patients with high drug-related concern levels, either state or trait anxiety levels were high.

There was a weak correlation between anxiety scores and disease activity and also drug-related concerns ($P < 0.05$). In addition, there was no correlation between anxiety levels and disease duration, biological agent usage duration, and some other non-biological agents ($P > 0.05$) (Table 3).

There was no significant relationship between the patients' concordance to treatment and anxiety scores ($P > 0.05$). Anxiety scores and drug-related concern levels were high in patients who had a habit of reading drug leaflets ($P < 0.05$). In addition, patients who tended to discontinue drugs without consulting with physicians had high anxiety levels ($P < 0.05$). Patients also indicated concerns related with biological agents, and those who had anxiety regarding the side effects, addiction risk, cancer and tuberculosis risk, had high anxiety levels and scores ($P < 0.05$). Moreover, anxiety levels and STAI-S scores were significantly high in patients who believed that biological agents may affect their reproductive function ($P < 0.05$). Patients who have a history of adverse effects with biological agents and have knowledge regarding other patients who experienced side effects had high anxiety levels and scores ($P < 0.05$). Table 1 shows the differences between the groups regarding drug-related concerns and demographic and other characteristics of our study groups.

DISCUSSION

Accompanying anxiety may be a significant comorbid condition of chronic rheumatic diseases because they are associated with severe pain and affect the general quality of life. Anxiety may be associated with the disease itself, but it can also be related to concerns regarding the treatment.[8] This study aimed to determine the severity of anxiety and causes of drug-related concerns in patients using biological agents because of various chronic rheumatic diseases. In our study, we found that although most patients had concerns regarding potential side effects of biological agents, anxiety levels related to these side effects were not high. The majority of patients indicated that they were willingly using the drug, despite the worrying side effects, and that they owe their current health condition to their medications.

The major reason for concerns regarding the biological agents was the potential side effects, which were stated in the informed consent. Furthermore, some patients were concerned regarding the beliefs that the drugs may cause an addiction and have a potentially negative impact on reproductive functions. Cancer risk was the most common cause of drug-related concerns. Arkell *et al.*[20] also reported that concerns regarding cancer were common among patients and the patients saw themselves as having an ongoing risk of cancer while using anti-TNF drugs.

Although the potential side effects of the drugs can cause anxiety, patients wanted to receive more information regarding the beneficial and adverse effects of their drugs.[21] Ziegler *et al.*[22] reported that 76.2% of patients wished to receive information regarding all the possible adverse effects of the drugs. In the same study, 73.4% of the patients opined that their physician was never justified in withholding any information. O'Brien *et al.*[23] found that the most likely cause of adverse drug reactions was attributed to insufficient information regarding the drug administered to the patients. In our study, the patients desired to obtain more information regarding the drugs, but they also stated that too much information regarding the side effects would cause apprehension. The additional information most often requested by the patients was how long the treatment would continue. Studies also revealed that most

patients want only limited information regarding the side effects of the drugs. Arkell *et al.*[20] found that the desire to obtain information regarding anti-TNF drugs was related to diversity, and many participants stated that they required a balance between too little and too much knowledge.

In our study, we found high drug-related anxiety levels in patients who had a habit of reading the drug leaflet ($P < 0.05$). The drug leaflet reading rate was reported to be 51.5% in a previous study; 34.9% of patients who read the leaflet experienced an increase in anxiety and drug adherence was observed to decrease by 9.7%. After reading the drug leaflet, many patients choose to search for other sources of information.[24] In our study, although the majority of patients reported that they had received basic information regarding the beneficial and adverse effects of the drug from the doctor, some patients reported that they also referred to information outside of the healthcare team. The primary preferred information source apart from the healthcare team was the informed consent form that was signed every 3 months. However, the explanation of potential complications or side effects to patients may induce a nocebo effect, which is the mirror phenomenon of the placebo effect, and negative expectations may cause exacerbations of symptoms.[25] The informed consent that is used in our country, which is an ethical and legal requirement for the prescription of biological agents, mainly specifies the potential side effects; however, the positive effects on disease activity, pain, and the quality of life are not mentioned.[26]

Concerns regarding these drug-related side effects can also affect the patient's concordance to treatment and their willingness to start and continue the treatment.[8,20] Many patients are concerned regarding the potential toxicity of the drugs. However, the deterrence of potential risks were observed to decrease the experience of adverse effects.[27] Fraenkel *et al.*[27] reported that patients who experienced adverse events are more inclined to accept the major toxicities of DMARDs compared with those who did not have any experience. However, in our study, patients who experienced drug-related adverse events had higher anxiety levels and STAI-T scores than those who did not experience adverse events ($P < 0.05$). Moreover, the majority of drug-related side effects reported by patients were not related to the drug. Thus, patients who are more concerned regarding the drugs may be more prone to attribute any physical symptoms as the side effects of the drugs.

Mood and anxiety disorders often accompany RA, and psychiatric disorders are less common in patients with RA who use anti-TNF drugs than those who do not use anti-TNF drugs. TNF-α appears to be associated with many psychiatric disorders, particularly with depression, in patients with RA. Anti-TNF drugs may decrease anxiety and depressive symptoms by affecting the increased release of TNF-α-induced neurotransmitter or functional changes.[2] Moreover, a positive correlation between anxiety and depression and interleukin (IL)-6, IL-8 and TNF-α was observed in patients with colorectal cancer. Circulating proinflammatory cytokines may play roles in anxiety and depression pathogenesis.[28] Tuglu *et al.*[29] observed significantly higher serum TNF-α levels in patients with major depressive disorders than in control subjects. In addition, after an anti-depressant therapy, TNF-α levels were observed to be decreased to similar levels as the control group. Arisoy *et al.*[30] suggested that TNF-α inhibitors appeared to have potential anti-depressant effects; this appears to be independent from their anti-inflammatory effect. Based on this information, patients who use anti-TNF drugs can be expected to have less anxiety than patients who do not use the drugs; however, drug-related concerns can reduce this impact.

State-Trait Anxiety Inventory, a self-reported scale developed by Spielberg, aims to assess state and trait anxieties, and indicates the intensity of the anxiety, and distinguishes between state and trait anxieties.[31] State anxiety is related to the anxiety experienced at a certain time, whereas trait anxiety is the tendency toward feeling anxious.[32] High scores are associated with higher anxiety levels. However, there is no determined and validated cut-off score for STAI, and several studies have used various different cut-off scores. For example, Devier *et al.*[33] used 30 as the reference, while Kvaal *et al.*[34] used 39/40 values as the reference.

In our study, the average STAI-S score was 40 and the average STAI-T score was 45 in patients treated with biological agents. When compared with the studies by Parker *et al.*[35,36] the average anxiety levels in our study was higher than in general patients with RA (33/36) but lower than in patients with RA having depression (46/48).

This study has further limitations to be considered. One of the limitations of this study was that anxiety levels were not compared between the age-matched healthy controls and patients who were treated with conventional DMARDs. Additionally, patients in whom biological agents were previously initiated but their treatment was suspended because of various reasons were not included in the study. Although the general evaluation questionnaire was used for anxiety assessment, an extensive diagnostic assessment for detecting

anxiety disorders was not performed. The disease activity indices specific to each disease could not be used because the patient populations were different from each other. Disease activity was determined by a single method (VAS) based on physician assessment.

In conclusion, potential side effects of biological agents that are used in rheumatology practice may increase patient anxiety levels. Most anxiety disorders substantially increase the risk of secondary depression.[37] Therefore, determining anxiety symptoms in patients with a rheumatic disease treated with biological agents may help in preventing the progression to depression. Awareness of concerns, anxiety and expectations regarding the drug therapy is important to increase drug adherence and the effectiveness of treatment. Providing detailed information regarding the most common causes of drug-related concerns (i.e., cancer and tuberculosis risk in our study) may significantly reduce the patient anxiety. Information obtained from this study may help in increasing knowledge regarding the patient concerns about treatment with biological agents, thereby enabling a more careful assessment of anxiety in new patients who start biological treatment. This will help in establishing more effective communications with patients and increasing patients' confidence in their physicians.

REFERENCES

1 American Psychiatric Association (2013) *Diagnostic and Statistical Manual of Mental Disorders*, 5th edn. American Psychiatric Association, Arlington, VA.

2 Uguz F, Akman C, Kucuksarac S, Tufekci O (2009) Anti-tumor necrosis factor-alpha therapy is associated with less frequent mood and anxiety disorders in patients with rheumatoid arthritis. *Psychiatry Clin Neurosci* **63**, 50–5.

3 Anyfanti P, Gavriilaki E, Pyrpasopoulou A *et al.* (2016) Depression, anxiety, and quality of life in a large cohort of patients with rheumatic diseases: common, yet undertreated. *Clin Rheumatol* **35**, 733–9.

4 el-Miedany YM, el-Rasheed AH (2002) Is anxiety a more common disorder than depression in rheumatoid arthritis? *Joint Bone Spine* **69**, 300–6.

5 Xiong H (2014) Anxiety is an independent predictor of disease activity at three months after initiating treatment with disease modifying antu-rheumatic drugs (DMARDs) in early arthritis patients [Internet]. Bachelor scripties (iBMG) Available from URL: http://hdl.handle.net/2105/16458

6 Löwe B, Willand L, Eich W *et al.* (2004) Psychiatric comorbidity and work disability in patients with inflammatory rheumatic diseases. *Psychosom Med* **66**, 395–402.

7 Teutsch C (2003) Patient-doctor communication. *Med Clin North Am* **87**, 1115–45.

8 Horne R, Weinman J (1999) Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. *J Psychosom Res* **47**, 555–67.

9 Isaacs JD (2015) Decade in review-clinical rheumatology: 10 years of therapeutic advances in the rheumatic diseases. *Nat Rev Rheumatol* **11**, 628–30.

10 Bowen CJ, Edwards CJ, Hooper L *et al.* (2010) Improvement in symptoms and signs in the forefoot of patients with rheumatoid arthritis treated with anti-TNF therapy. *J Foot Ankle Res* **3**, 10.

11 van der Heijde D, Breban M, Halter D *et al.* (2015) Maintenance of improvement in spinal mobility, physical function and quality of life in patients with ankylosing spondylitis after 5 years in a clinical trial of adalimumab. *Rheumatology (Oxford)* **54**, 1210–9.

12 Stockdale J, Goodacre L (2009) "It's magic stuff": the experiences of patients with ankylosing spondylitis taking anti-TNF-alpha medication. *Musculoskeletal Care* **7**, 162–77.

13 Maksymowych WP, Gooch KL, Wong RL, Kupper H, van der Heijde D (2010) Impact of age, sex, physical function, health-related quality of life, and treatment with adalimumab on work status and work productivity of patients with ankylosing spondylitis. *J Rheumatol* **37**, 385–92.

14 Singh JA, Wells GA, Christensen R *et al.* (2011) Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev* **16**, CD008794.

15 Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V (2006) Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* **295**, 2275–85.

16 Strangfeld A, Hierse F, Rau R *et al.* (2010) Risk of incident or recurrent malignancies among patients with rheumatoid arthritis exposed to biologic therapy in the German biologics register RABBIT. *Arthritis Res Ther* **12**, R5.

17 Pinho de Oliveira Ribeiro N, Rafael de Mello Schier A, Ornelas AC, Pinho de Oliveira CM, Nardi AE, Silva AC (2013) Anxiety, depression and suicidal ideation in patients with rheumatoid arthritis in use of methotrexate, hydroxychloroquine, leflunomide and biological drugs. *Compr Psychiatry* **54**, 1185–9.

18 Öner N, Le Compte A (1985) *State-Trait Anxiety Inventory Manual*. Bogazici University Press, Istanbul.

19 Ozguven IE (1994) *Stress and Anxiety Scales and Sociometric, Psychologic Tests*. Dogus Press, Yeni Ankara (In Turkish).

20 Arkell P, Ryan S, Brownfield A, Cadwgan A, Packham J (2013) Patient experiences, attitudes and expectations towards receiving information about anti-TNF medication–"It could give me two heads and I'd still try it!". *BMC Musculoskelet Disord* **14**, 165.

21 Berry DC, Gillie T, Banbury S (1995) What do patients want to know: an empirical approach to explanation generation and validation. *Expert Syst Appl* **8**, 419–28.
22 Ziegler DK, Mosier MC, Buenaver M, Okuyemi K (2001) How much information about adverse effects of medication do patients want from physicians? *Arch Intern Med* **161**, 706–13.
23 O'Brien BJ, Elswood J, Calin A (1990) Perception of prescription drug risks: a survey of patients with ankylosing spondylitis. *J Rheumatol* **17**, 503–7.
24 Vinker S, Eliyahu V, Yaphe J (2007) The effect of drug information leaflets on patient behavior. *Isr Med Assoc J* **9**, 383–6.
25 Cohen S (2014) The nocebo effect of informed consent. *Bioethics* **28**, 147–54.
26 Drug Safety Monitoring Forms (2016) Turkey Drugs and Medical Devices: Ministry of Health, Republic of Turkey. [2016 Apr 14]. Available from URL: http://www.titck.gov.tr/PortalAdmin/Uploads/UnitPageAttachment/nczKNagk.pdf
27 Fraenkel L, Bogardus S, Concato J, Felson D (2002) Unwillingness of rheumatoid arthritis patients to risk adverse effects. *Rheumatology (Oxford)* **41**, 253–61.
28 Oliveira Miranda D, Soares de Lima TA, Ribeiro Azevedo L, Feres O, Ribeiro da Rocha JJ, Pereira-da-Silva G (2014) Proinflammatory cytokines correlate with depression and anxiety in colorectal cancer patients. *Biomed Res Int* **2014**, 739650.
29 Tuglu C, Kara SH, Caliyurt O, Vardar E, Abay E (2003) Increased serum tumor necrosis factor-alpha levels and treatment response in major depressive disorder. *Psychopharmacology* **170**, 429–33.
30 Arısoy O, Bes C, Cifci C, Sercan M, Soy M (2013) The effect of TNF-alpha blockers on psychometric measures in ankylosing spondylitis patients: a preliminary observation. *Rheumatol Int* **33**, 1855–64.
31 Spielberger CD, Gorsuch RL, Lushene RE (1970) *Test Manual for the State Trait Anxiety Inventory*. Consulting Psychologists Press, Palo Alto, CA.
32 Lader M, Bruce M (1986) States of anxiety and their induction by drugs. *Br J Clin Pharmacol* **22**, 251–61.
33 Devier DJ, Pelton GH, Tabert MH *et al.* (2009) The impact of anxiety on conversion from mild cognitive impairment to Alzheimer's disease. *Int J Geriatr Psychiatry* **24**, 1335–42.
34 Kvaal K, Macijauskiene J, Engedal K, Laake K (2001) High prevalence of anxiety symptoms in hospitalized geriatric patients. *Int J Geriatr Psychiatry* **16**, 690–3.
35 Parker JC, Smarr KL, Buckelew SP *et al.* (1995) Effects of stress management on clinical outcomes in rheumatoid arthritis. *Arthritis Rheum* **38**, 1807–18.
36 Parker JC, Smarr KL, Slaughter JR *et al.* (2003) Management of depression in rheumatoid arthritis: a combined pharmacologic and cognitive-behavioral approach. *Arthritis Rheum* **49**, 766–77.
37 Wittchen HU, Kessler RC, Pfister H, Lieb M (2000) Why do people with anxiety disorders become depressed? A prospective-longitudinal community study. *Acta Psychiatr Scand Suppl* **406**, 14–23.