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Original Article

The Reported Adverse Effects Related to Biological Agents Used for the Treatment of Rheumatic Diseases in Turkey

Romatizmal Hastalıkların Tedavisinde Biyolojik Ajanların Kullanımına Bağlı Türkiye'de Bildirilmiş Yan Etkiler

Erkan KILIÇ,[1] Gamze KILIÇ,[1] Özgür AKGÜL,[1] Gürkan AKGÖL,[2] Salih ÖZGÖÇMEN[1]

[1]*Department of Physical Medicine and Rehabilitation, Medical Faculty of Erciyes University, Division of Rheumatology, Kayseri, Turkey*
[2]*Department of Physical Medicine and Rehabilitation, Bingöl State Hospital, Bingöl, Turkey*

Objectives: This study aims to review the reported adverse events related to the use of biological agents used for the treatment of rheumatic diseases in Turkey.

Patients and methods: Between January 2000 and January 2012, the literature was searched in English and Turkish for case reports and case series using the MedLine, Web of Science, and Scopus databases reporting adverse effects related to the use of biological agents including infliximab, etanercept, adalimumab, anakinra, rituximab which were used for the treatment of rheumatic diseases.

Results: A total of 53 patients (21 males, 32 females) with rheumatic disease who suffered from adverse effects related to the use of biological agents were reported in Turkey in the literature. The mean age was 39.0±15.6 years, while the mean disease duration was 10.6±8.2 years. The mean time from the initiation of the biological agents to the onset of the adverse events was 8.8±9.2 months. The most frequently seen biological agent-related adverse effects were observed in patients with ankylosing spondylitis (AS) and rheumatoid arthritis (RA). Tuberculosis (TB) was the most commonly reported adverse effect with in 14 patients (26.4%). Other adverse events included psoriasis (15.1%), solid tumors (7.6%), lymphoma (5.7%), drug-induced lupus (3.8%), and menstrual bleeding (3.8%). A total of 77.4% patients who suffered from adverse events discontinued biological therapies.

Conclusion: Biologic agents are relatively safe; however, they may rarely lead to serious adverse events. As tuberculosis is a moderate endemic disease in Turkey, patients who are scheduled for biological agents (anti-TNF and abatacept particularly) should be informed about the potential risks of biological therapy and monitored closely before and after the initiation of treatment.

Key words: Adalimumab; adverse event; biological agent; etanercept; infliximab; rheumatic disease; rituximab.

Amaç: Bu çalışmada Türkiye'de romatizmal hastalıkların tedavisinde kullanılan biyolojik ajanlara bağlı gelişen bildirilmiş yan etkiler derlendi.

Hastalar ve yöntemler: Ocak 2000 ile Ocak 2012 tarihleri arasında romatizmal hastalıkların tedavisinde kullanılan infliksimab, etanersept, adalimumab, anakinra, rituksimab dahil olmak üzere biyolojik ajanlara bağlı gelişen yan etkileri bildiren olgu ve olgu serileri MedLine, Web of Science ve Scopus veri tabanları kullanılarak İngilizce ve Türkçe dillerinde tarandı.

Bulgular: Literatürde Türkiye'den biyolojik ajana bağlı yan etki görülen romatizmal hastalıklı toplam 53 olgu (21 erkek, 32 kadın) bildirilmiştir. Yaş ortalaması 39.0±15.6 yıl ve ortalama hastalık süresi 10.6±8.2 yıl idi. Biyolojik ajanlara başlanması ile yan etkinin ortaya çıkması arasındaki geçen süre ortalama 8.8±9.2 aydı. Biyolojik ajan kullanımına bağlı olarak en sık görülen yan etki ankilozan spondilit (AS) ve romatoid artrit (RA) hastalarında gözlendi. En sık bildirilen yan etki 14 hastada (%26.4) tüberküloz idi. Diğer yan etkiler psöriyazis (%15.1), solid tümör (%7.6), lenfoma (%5.7), ilaca bağlı lupus (%3.8) ve menstrüel kanama (%3.8) idi. Yan etki gelişen olguların toplam %77.4'ünde biyolojik tedaviler sonlandırıldı.

Sonuç: Biyolojik ajanlar nispeten güvenli olmakla beraber, nadiren ciddi yan etkilere neden olabilir. Türkiye'de tüberküloz orta derecede endemik bir hastalık olması nedeniyle, biyolojik ajan tedavisi (özellikle anti-TNF ve abatasept) planlanan hastalar tedavi öncesinde ve tedaviye başladıktan sonra tedavinin olası riskleri açısından bilgilendirilmeli ve yakından takip edilmelidir.

Anahtar sözcükler: Adalimumab; yan etki; biyolojik ajan; etanersept; infliksimab; romatizmal hastalık; rituksimab.

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Correspondence: Erkan Kılıç, M.D. Erciyes Üniversitesi Tıp Fakültesi Fiziksel Tıp ve Rehabilitasyon Anabilim Dalı, Romatoloji Bilim Dalı, 38039 Talas, Kayseri, Turkey. Tel: +90 352 - 207 66 66 / 21276 e-mail: erkan1978@yahoo.com

In the last two decades, the use of biological agents which target the key molecules in the disease process has become increasingly more important in clinical practice. The current biological therapies for rheumatic diseases include the inhibition of tumor necrosis factor (TNF), interleukin (IL)-1, IL-6, co-stimulation blockade, and B cell depletion. Biologics usually have significant effects since they rapidly decrease the inflammatory process, improve clinical and laboratory signs, and retard the radiographic progression of the disease. These developments have even led to the new term "era of biologics" for the treatment of rheumatic diseases.

The United States Food and Drug Administration (FDA) has currently approved five TNF inhibitors for the treatment of several rheumatic diseases, and in Turkey, patients using etanercept, infliximab, and adalimumab to treat several rheumatic diseases can be reimbursed for these medications. Infliximab, the first marketed anti-TNF in Turkey, is a chimeric monoclonal antibody (mAb) directed against TNF which is administered via intravenous infusion every six or eight weeks.[1] Etanercept is a soluble p75 TNF receptor fusion protein that is subcutaneously administered once or twice a week, and adalimumab is a recombinant human mAb which is given subcutaneously every other week.[1]

Two relatively new options are also available for treatment for rheumatoid arthritis (RA) in Turkey, and reimbursement is also possible. Abatacept is a soluble fusion protein comprised of the cytotoxic T lymphocyte antigen 4 (CTLA-4) and the Fc portion of immunoglobulin G1 (IgG1) that prevents CD28 from binding to its counter-receptor, CD80/CD86, due to its higher affinity for CD80/CD86. It is administered via intravenous infusion approximately every four weeks.[2] Rituximab is a human/mouse chimeric B cell-depleting monoclonal anti-CD20 antibody that is administered via intravenous infusion every six months.[2] Approval of these drugs is relatively new compared with the anti-TNF drugs which have been on the market for nearly 10 years in our country.

In Turkey, patients can be reimbursed for all of these drugs for the treatment of approved rheumatic diseases if they are prescribed by a rheumatologist or physiatrist working in a tertiary center and indications are in accordance with internationally accepted guidelines or recommendations (but with minor changes on them). In addition, the Ministry of Health has welcomed them for off-label use for special indications such as Behçet's disease (BD), familial Mediterranean fever (FMF), and adult Still's disease. Furthermore, they have also been approved for treating vasculitis if the patient failed to respond to conventional treatments.

The use of anti-TNFs has revolutionized the treatment of rheumatic diseases, even though they may cause various adverse events since TNF-α also has various physiological effects since it is utilized to fight against infectious agents and malignant cells and regulate apoptosis. Thus, a TNF-α blockade may have a tendency to cause infectious diseases, malignancies, and autoantibody production.[3,4] One of the most important infections associated with anti-TNF therapy is tuberculosis (TB), as several studies have proven that the risk for this disease increases during treatment with anti-TNF agents.[5-8] Animal studies have also shown that TNF-α plays a key role in the formation and maintenance of granuloma. Additionally, numerous studies have shown that fatal reactivation occurred in animals infected with TB who received a subsequent blockade of TNF-α.[9] Other frequently reported side effects include respiratory infections and injection site reactions associated with the use of anti-TNF agents.[10,11] Skin lesions, such as cutaneous vasculitis, psoriasis, erythema multiforme (EM), or subcutaneous lupus erythematosus (SLE), have also been frequently reported in patients with RA who are being treated with anti-TNFs.[12-14] Furthermore, serious skin infections, for example folliculitis perforans, cellulitis, and necrotizing fasciitis have also been reported.[12,15-17] Biologics have been used for the treatment of rheumatic diseases for nearly ten years in Turkey, and there have been reported adverse events that have been associated with their use. However, the lack of a reliable, frequently updated, formal data registry poses some difficulty for comparing our data regarding these adverse events with other countries. Thus, the aim of our study was to collect data on reported adverse effects associated with biological agents during the treatment of rheumatic diseases in Turkey.

PATIENTS AND METHODS

We searched the MedLine, Web of Science, and Scopus databases for relevant case reports published between January 2000 and January 2012 and used "Turkey" plus synonyms and combinations of the following terms: "anti-tnf", "tnf", "biologics", "adalimumab", "etanercept", "infliximab", "anakinra", "rituximab", or "abatacept". In addition we manually scanned

the references of the reviewed articles for other relevant studies. We also limited our literature search to articles that involved human subjects that were published in either English or Turkish.

Four reviewers screened each title and abstract for relevance, and case reports or case series were manually selected from the papers. The reviewers excluded articles based on an abstract review if the report was a review article or meta-analyses, if the biological agents w ere not used for a rheumatic disease, or if the article and cases did not report the adverse effects of biological agents. Those that met our criteria were then reviewed, and key elements were noted.

Statistical analysis

All data was analyzed on a personal computer using SPSS for Windows version 15.0 (SPSS Inc., Chicago, IL, USA), and the mean values, standard deviations, and percentages were calculated.

RESULTS

A flow chart with the entire selection process is shown in Figure 1. All of the reported adverse effects were related to the anti-TNFs, with none being connected to other biologics. The characteristics of these cases are shown in Tables 1 and 2. We identified 53 patients (21 males, 32 females; mean age 39.0±15.6 years; range 7-72 years) with rheumatic disease who had adverse effects due to biologics. The mean disease duration was 10.6±8.2 years (range 1-40), and the mean elapsed time between the initiation of the biological agents and the onset of adverse events was 8.8±9.2 months (range 0-48). There were 23 patients (43.4%) with ankylosing spondylitis (AS), 19 (35.7%) with rheumatoid arthritis (RA), four (7.6%) with spondyloarthropathy (SpA), three (5.7%) with juvenile idiopathic arthritis (JIA), two (3.8%) with Behçet's disease (BD), one (1.9%) with juvenile AS, and one (1.9%) with seronegative arthritis.

Table 3 summarizes the information of all 53 cases together. The most common adverse event was TB in 14 patients (26.4%), and five of these were treated with infliximab, two with etanercept, and one with adalimumab. Six others were reported as "treated with TNF inhibitors". Furthermore, 12 (22.6%) of the 14 had pulmonary TB while two (3.8%) had extrapulmonary TB. In addition, we discovered that chemoprophylaxis was administered for eight (57.1%) of the 14 TB patients.

The second most commonly reported adverse event was psoriasis, which was found in eight patients (15.1%). Five of these were treated with infliximab, two with etanercept, and one with adalimumab. Solid tumors were reported in four cases (7.6%), and all of them were treated with etanercept. In addition, there were three cases of lymphoma (5.7%). Two were treated with etanercept and one with infliximab.

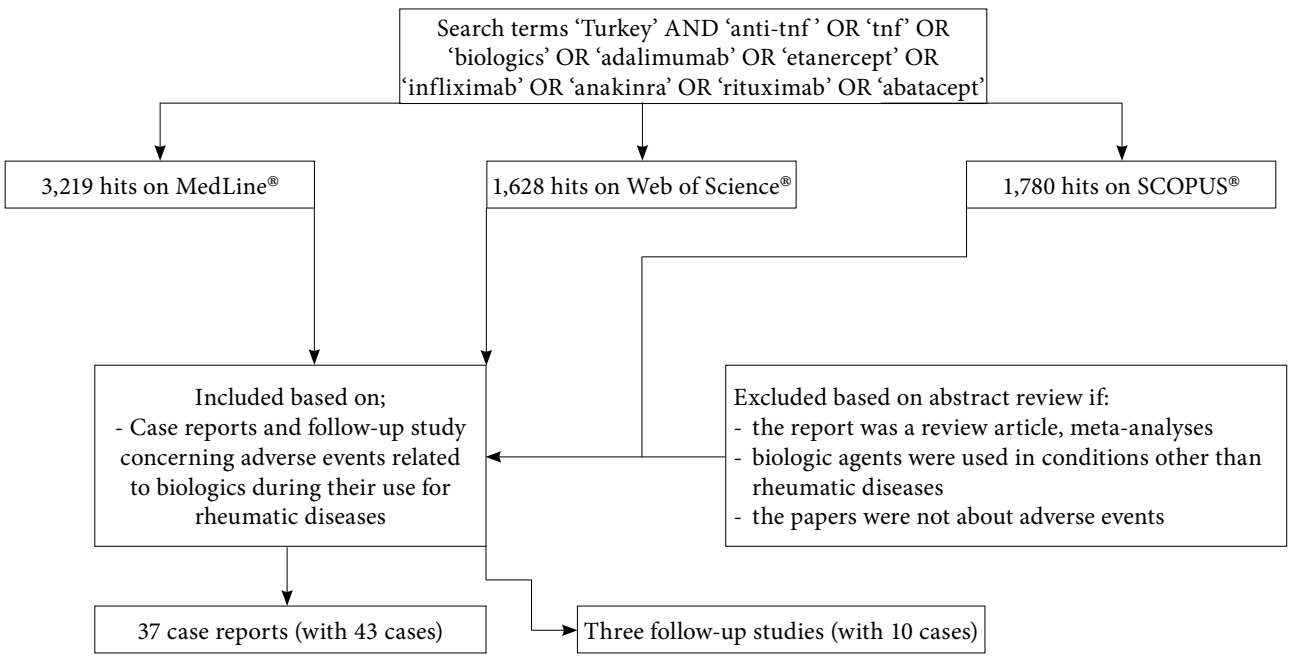

Figure 1. Flow chart.

Table 1. Characteristics of the reported cases

	n	%	Mean±SD	Range
Age (years)			39.0±15.6	7-72
Gender				
Male	21	39.6		
Female	32	60.4		
Primary disease				
Ankylosing spondylitis	23	43.4		
Rheumatoid arthritis	19	35.7		
Juvenile rheumatoid arthritis	3	5.7		
Unclassified spondyloarthropathy	2	3.8		
Psoriatic arthritis	2	3.8		
Behçet's disease	2	3.8		
Juvenile ankylosing spondylitis	1	1.9		
Seronegative arthritis	1	1.9		
Duration of underlying disease (years)			10.6±8.2	1-40
Time elapsed between the start of biologics and the onset of adverse event (months)			8.8±9.2	0-48
Biological therapy				
Infliximab	20	37.8		
Etanercept	19	35.8		
Adalimumab	7	13.2		
Anti-TNFs (not specified)	7	13.2		
Discontinuation of biologics after adverse events				
Yes	41	77.4		
No	3	5.6		
Not mentioned	9	17.0		
Switch of biologics				
No	48	90.6		
Yes	5	9.4		
ETA: 2; INF: 1; ADA: 1; RTX: 1				
INH chemoprophylaxis in patients who developed TB				
Yes	8	57.1		
No	6	42.9		

SD: Standard deviation; TNF: Tumor necrosis factor; ETA: Etanercept; INF: Infliximab; ADA: Adalimumab; RTX: Rituximab; INH: Isoniazid; TB: Tuberculosis.

Furthermore, there were two cases of drug-induced lupus (3.8%), with one having been treated with etanercept and one with infliximab). There were also two cases of serious menstrual bleeding (3.8%), and adalimumab was used with both patients. In addition, treatment with biological agents was discontinued

Table 2. Characteristics of reported cases by diagnosis

Primary diagnosis	Patient	Female		Age (years)	Disease duration (years)	ETN		INF		ADA		Anti-TNF (not specified)		Adverse events (months)
	n	n	%	Mean±SD	Mean±SD	n	%	n	%	n	%	n	%	Mean±SD
Ankylosing spondylitis	23	11	47.8	37.70±9.6	12.8±8.8	5	21.7	12	52.2	4	17.4	2	8.7	10.9±11.6
Rheumatoid arthritis	19	17	89.5	49.3±15.0	10.8±8.1	10	52.6	3	15.8	2	10.5	4	21.1	7.7±6.0
Juvenile idiopathic arthritis	3	1	33.3	12.67±7.6	6.3±7.6	2	66.7	1	33.3	–	–	–	–	6.20±10.2
Spondyloarthropathies other than PsA and AS	2	0	0	18.50±3.5	5.0±2.8	1	50	1	50	–	–	–	–	4.10±4.1
Psoriatic arthritis	2	1	50	46.00±22.6	17.5±3.5	1	50	1	50	–	–	–	–	12.13±16.8
Behçet's disease	2	0	0	25.50±0.7	2.5±2.1	–	–	2	100	–	–	–	–	6.40±6.5
Juvenile AS	1	0	0	20.00±0.0	5.0±0.0	–	–	1	100	–	–	–	–	2.00±0.0
Seronegative arthritis	1	1	100	25.00±0.0	3.0±0.0	–	–	–	–	–	–	1	100	10.00±0.0

ETN: Etanercept; INF: Infliximab; ADA: Adalimumab; NA: Not available; SD: Standard deviation; PsA: Psoriatic arthritis; AS: Ankylosing spondylitis.

Table 3. Summary of 53 cases

Authors	Age (years)/ gender	Primary disease	Disease period (years)	Biologics used	Time to adverse event (months)	Adverse event	Cessation of biologics	Switch	TB prophylaxis	Follow-up
Altındağ et al.[73]	65/F	RA	10	ADA	12	Bullous pemhigoid	Yes	–		A reduction in skin lesions was observed after two weeks of prednisolone therapy.
Deniz et al.[74]	52/F	RA	21	ETN	6	Cellulitis causing tissue defect	Yes	–		Total healing after the surgery. Methotrexate (15 mg) was administered per week.
Dagcı et al.[75]	30/M	PsA	15	ETN	0.2	Myiasis	Yes	–		Larva removed from the wound site. Final status unknown.
Çay et al.[70]	36/M	AS	15	ETN	6	Demyelination of cervical spinal cord	Yes	–		Intravenous methylprednisolone 1 g/day for five days; total resolution of the demyelinating lesion on MRI at the third month.
Şendur et al.[76]	59/F	RA	8	ETN	4	Angioedema	Yes	–		Improved after therapy with volume expanders, 0.25 mg subcutaneous adrenaline, intravenous antihistamine, and 40 mg of intravenous methylprednisolone. DMARD therapy was resumed.
Sarı et al.[77]	30/F	RA	3	ETN	2	Psoriasis	Yes	INF		Psoriatic lesions resolved completely after the drug was discontinued. No such adverse skin reaction occurred after switching therapy to INF.
Sarı et al.[27]	20/M	JAS	5	INF	2	Atypical infectious mononucleosis	Yes	ADA		Three months after the EBV infection, ADA was added to the treatment. Over a two-year follow-up period, there was no recurrence.
Tutar et al.[78]	10/F	JIA	3	INF	0.3	Delayed maculopapular, urticarial rash	No	–		Corticosteroids were added to INF for three months. Similar cutaneous eruptions have not recurred.
Tutar et al.[78]	16/M	JIA	7	INF	1.2	Delayed maculopapular, urticarial rash	No	–		Corticosteroids were added to INF for three months. Similar cutaneous eruptions have not recurred.
Yazisiz et al.[79]	23/M	AS	6	ETN	6	Crohn's disease	Yes	–		Six months later, ulceration and substenotic inflammation had disappeared with oral steroids and sulfosalazine (2 g/ day).
Korkmaz and Kaşifoğlu[25]	25/F	RA	5	ETN	4	Recurrent pseudo septic arthritis	Yes	–		Except for ETN, the other drugs were continued, and the prednisolone dosage was increased to relieve pain. The patient has remained in a remission for over six months.
Ekici et al.[80]	7/M	JIA	1	ETN	0.3	Encephalopathy	Yes	–		Cranial magnetic resonance images revealed the complete regression of restricted diffusion and the development of severe cortical atrophy in the left temporal lobe and left insula.
Akgül and Özgöçmen[28]	57/M	RA	3	INF	3.5	Brucellosis	Yes	–		A combination of rifampicin (600 mg daily) and doxycycline (100 mg twice a day) was initiated. The patient responded well to the treatment. In the fourth month, the antibiotics were stopped.
Bodur et al.[81]	62/F	AS	40	INF	4	Drug induced lupus	Yes	–		Methylprednisolone (16 mg) was started. One month after the patient's lupus findings completely resolved, the dosage was gradually decreased at the follow-up.
Çapkın et al.[82]	29/F	AS		INF	4	Palmoplantar psoriasis	Yes	–		Oral administration of methotrexate and topical treatment with corticosteroids were initiated, and the skin lesions improved after two months. However, the complaints of low back pain returned, she did not accept a new treatment plan with different biologics.
Bavbek et al.[66]	28/M	AS		ADA	13	Injection site reactions	Yes	ETN		A desensitization protocol was initiated. Once the desensitization was completed, the patient was maintained ETN injection on twice weekly.
Altındağ et al.[64]	45/F	RA	12	ETN	11	Drug induced lupus	Yes	–		Eight weeks after the patient's lupus findings resolved, corticosteroids and methotrexate were initiated for RA treatment.
Aksu et al.[54]	45/M	AS	9	ETN	11	NHL	Yes	–		Chemotherapy was initiated and was four times every 21 days. After treatment, the control CT findings were normal. The patient is still in follow-up and in remission

Table 3. Continued

Authors	Age (years)/ gender	Primary disease	Disease period (years)	Biologics used	Time to adverse event (months)	Adverse event	Cessation of biologics	Switch	TB prophylaxis	Follow-up
Kalyoncu et al.[30]	59/F	RA	7	ADA	3	Pneumocystis carinii pneumonia	Yes	–		The patient was hospitalized, and methotrexate and ADA were discontinued. Antibiotics were initiated for four weeks. Control chest X-ray was normal.
Bal et al.[83]	28/M	AS	10	INF	9	Psoriasis vulgaris	Yes	–		Methotrexate and topical corticosteroids were initiated for both AS and psoriasis. Within one month of the withdrawal of INF, the psoriatic skin lesions had disappeared completely and there was no recurrence.
Sarpel et al.[84]	31/M	AS	3	INF	0.5	Psoriasis	Yes	ETN		Both INF and ETN caused skin lesions. After withdrawing the biologics, clear recovery was observed.
Sarpel et al.[84]	53/F	RA	31	ETN	2	Psoriasiform dermatitis	Yes	–		Although treatment cessation was not recommended, the patient did not want to continue. The lesions recovered fully after treatment was stopped.
Sarpel et al.[84]	34/F	AS	16	INF	10	Palmar pustulosis	Yes	–		Topical treatment was started for the patient. Infliximab treatment was stopped at the patient's request, and the lesions fully recovered.
Sarpel et al.[84]	40/F	AS	15	INF	26	Palmoplantar psoriasis	No	–		Topical treatment was started for psoriasis. The cessation of infliximab treatment was not suggested. No increase in the lesions was observed during follow-up.
Nalbant et al.[85]	72/F	RA	10	ADA	NM	Pulmonary and extra-pulmonary TB	Yes	–	No	Triple anti-tuberculosis treatment was given. At the end of the first month of treatment, knee joint circumference regressed.
Bes and Soy[86]	41/F	AS	12	ADA	6	Serious menstrual bleeding	Yes	–		The patient was transfused with two units of erythrocyte suspension, and norethisterone was given. The patient's bleeding ceased three days after the therapy, and there has been a normal menstrual cycle for three months.
Bes and Soy[86]	31/F	AS	5	ADA	4	Serious menstrual bleeding	Yes	–		Bleeding ceased three or four days after giving a drug containing estradiol. She still experiencing normal menstrual cycles.
Cansu et al.[49]	45/F	AS	19	ETN	48	Primary cutaneous adenoid cystic carcinoma	Yes	–		Extended tumor resection was performed, and there was no evidence of metastatic disease.
Akoğlu et al.[87]	36/M	AS	NM	INF	0.5	Tuberculosis pleurisy	Yes	–	No	Anti-tuberculosis therapy with isoniazid, rifampicin, ethambutol, and pyrazinamide was used for six months.
Akgül et al.[88]	33/M	AS	13	ADA	12	Palmoplantar psoriasis	Yes	–		A topical steroid was administered for the psoriasis lesions, and they disappeared completely within a couple of weeks. The patient was followed up with meloxicam (15 mg daily).
Maraklı et al.[89]	43/M	AS	19	INF	0.5	Dermatitis herpetiformis	Yes	–		Dapsone (50 mg/day) was applied for two months while the patient was on a gluten-free diet. Two months after the cessation of the dapsone therapy, there was no recurrence.
Şimşek et al.[50]	21/M	SpA undif	3	ETN	7	Atypical carcinoid tumor of the thymus with ectopic ACTH production	Yes	–		The tumor was removed surgically, and a histological examination revealed an atypical thymic carcinoid tumor.
Sarı et al.[29]	25/M	BD	4	INF	1.8	Cytomegalovirus colitis	Yes	–		Ganciclovir (600 mg/d IV) was initiated. On the 14th day of treatment, repeated colonoscopy revealed edematous mucosa without ulcers. The ganciclovir was continued for an additional 14 days. No recurrence of the colitis symptoms was seen at the 30-month follow-up.
Erten[51]	62/F	PsA	20	ADA	24	Endometrium cancer	Yes	-		A total abdominal hysterectomy with bilateral salpingo-oopherectomy was performed.
Aksu et al.[53]	44/M	AS	6	ETN	6	Hodgkin's lymphoma	Yes	-		Chemotherapy and localized radiotherapy were started. The clinical response was very good even after the first chemotherapy session. However, the remission lasted for only one year. The chemotherapy was changed, and stem cell transplantation was planned.

Table 3. Continued

Authors	Age (years)/ gender	Primary disease	Disease period (years)	Biologics used	Time to adverse event (months)	Adverse event	Cessation of biologics	Switch	TB prophylaxis	Follow-up
Sarı et al.[90]	21/M	JIA	15	ETN	18	Thymic enlargement and constitutional symptom	Yes	–		The constitutional symptoms and fever completely resolved within one month of discontinuing MTX and ETN. He was discharged with a regimen of prednisolone (7.5 mg/day) and diclonenac (150 mg/day). He experienced a relapse in his arthritic symptoms nearly three months after the initial presentation, and MTX (20 mg/week) and leflunomide (20 mg/week) were begun. His prednisolone was also increased to 15 mg/day. A thoracic CT was repeated six months later which showed a regression of the anterior chest mass and complete resolution of the mediastinal LAP. No relapse of the mass lesion has occurred during two and a half years of follow-up, and he is currently being treated with MTX, leflunomide, and prednisolone.
Özgüneş et al.[91]	26/M	BD	1	INF	11	Pulmonary TB	Yes	–	Yes	Azathioprine and colchicine were continued, and anti-tuberculosis treatment was given. Six months later, the CT imaging was normal.
Elbek et al.[92]	32/F	AS	NM	INF	7	Pulmonary TB, peritoneal TB	Yes	–	Yes	Anti-tuberculosis therapy with isoniazid, rifampicin, ethambutol, and pyrazinamide was started. She has been under regular follow-up which has been uneventful.
Elbek et al.[92]	60/F	RA	NM	ETN	5	Pulmonary TB	Yes	–	Yes	Isoniazid, rifampicin, ethambutol, and pyrazinamide were started. She died four months after the diagnosis.
Korkmaz et al.[93]	62/F	RA	NM	INF	1.5	Acceleration of left-ventricular diastolic dysfunction and pulmonary hypertension	Yes	–		Sulfasalazine was added to the MTX therapy. Twenty days later, the patient was hospitalized for interstitial nephritis, and hemodialysis was started. Unfortunately, the patient died of septic shock due to catheter infection.
Pamuk and Harmandar[52]	70/F	RA	8	ETN	18	Benign meningioma	Yes	–		The quadriparesis partially regressed following surgery. Two months later, the patient had RA flare-up. Sulfasalazine was added to the therapy, and the doses of steroids and NSAIDs were increased. Unfortunately, the patient died four months after surgery because of gastrointestinal perforation and hypovolemic shock.
Şimşek et al.[94]	31/F	RA	4	INF	4.3	Optic neuritis	Yes	–		The treatment with INF and isoniazid was terminated, and pulse corticosteroids (daily) for three consecutive days, were prescribed followed by oral prednisolone. One month after the cessation of the offending drugs and the initiation of the prednisolone, there was complete resolution of the visual field defects in the affected eye.
Şanlı et al.[55]	32/M	AS	NM	INF		NHL	Yes	–		–
Hanta e al.[95]	48/F	AS	NM	INF	2	Extrapulmonary TB	NM	–	No	NM
Hanta e al.[95]	44/F	RA	NM	ETN	8	Pulmonary TB	NM	–	No	NM
Hanta e al.[95]	53/F	AS	NM	INF	30	Extrapulmonary TB	NM	–	No	NM
Çağatay et al.[96]	24/F	RA	4	TNF-i	7	Pulmonary TB	NM	–	No	NM
Çağatay et al.[96]	50/F	RA	23	TNF-i	4	Pulmonary TB	NM	–	Yes	NM
Çağatay et al.[96]	46/F	RA	17	TNF-i	18	Pulmonary TB	NM	–	Yes	NM
Çağatay et al.[96]	26/M	AS	6	TNF-i	10	Pulmonary TB	NM	–	Yes	NM
Çağatay et al.[96]	47/F	AS	10	TNF-i	24	Pulmonary TB	NM	–	Yes	NM
Çağatay et al.[96]	25/ F	SNA	3	TNF-i	10	Pulmonary TB	NM	–	Yes	NM
Abadoglu et al.[67]	32/F	RA	7	ETN ADA INF		Anti-TNF hypersensitivity	Yes	RTX		She developed hypersensitivity to four biologics. Desensitization was performed successfully for RTX, and it was than continued.

ADA: Adalimumab; RA: Rheumatoid arthritis; ETN: Etanercept; PsA: Psoriatic arthritis; AS: Ankylosing spondylitis; DMARD: Disease modifying anti-rheumatic drug; JAS: Juvenile ankylosing spondylitis; INF: Infliximab; EBV: Epstein–Barr virus; JIA: Juvenile idiopathic arthritis; NHL: Non-Hodgkin's lymphoma; CT: Computed tomography; NM: Not mentioned; SpA: Spondyloarthropathy; ACTH: Adrenocorticotropic hormone; BD: Behçet's disease; TB: Tuberculosis; MTX: Metotreksat; NSAIDs: Non-steroidal anti-inflammatory drugs; TNF-i: TNF-inhibitors; SNA: Seronegative arthritis; RTX: Rituximab.

in 41 patients (77.4%) and continued in three others (5.6%), two of whom had a maculopapular rash and one had palmoplantar psoriasis that was treated with infliximab. Data was not available for nine patients (17.0%), and five (9.5%) switched to another anti-TNF agent.

Infliximab was used to treat 20 patients (37.7%) while etanercept was used for 19 others (35.8%). Adalimumab was the treatment of choice for seven more (13.2%). However, which anti-TNF was used has not been specified in seven patients (13.2%). Patients with RA reported more adverse effects when taking etanercept, whereas AS patients had more problems with infliximab. The elapsed time between the initiation of the biologics and the onset of adverse events was 10.9±11.6 months for patients with AS and 7.7±6.0 months for those with RA.

DISCUSSION

Herein, we collected data on the reported adverse effects of biological agents used in the treatment of rheumatic diseases in Turkey. Although it could not be generalized, it provided vital knowledge regarding the common adverse events associated with the use biologics in patients of rheumatic diseases.

A Cochrane review showed that patients treated with these drugs developed a significantly higher risk for the total number of adverse events [odds ratio (OR) 1.28], serious infections (OR 1.37), and TB reactivation (OR 4.68) compared with the control group at standard doses.[18] However, the rates of serious adverse events, lymphoma, and congestive heart failure were not statistically significantly different between the groups.[18]

Infections

A higher rate of upper respiratory infections was observed with anti-TNFs with in clinical trials when compared with placebos. In a study by İnanç and Direskeneli,[19] 178 patients with RA [130 took disease modifying antirheumatic drugs (DMARDs); 48 took anti-TNFs] were analyzed for the incidence of infections. The rate of serious infections was 8.6/100 patient years in those treated with DMARDs, but this rate rose to 17/100 patient years during therapy with TNF antagonists. Leombruno et al.,[20] reported in a meta-analysis of 8,800 RA subjects treated over an average of 0.8 years that there was no increased risk of serious adverse events when they took the recommended doses of their medication. However, they found that high-dose anti-TNF therapy was associated with a two-fold increase in the risk of serious infections. In addition, the overall infection rate was noted as 13% in a German biologics registry between 2001 and 2003.[21] This registry also reported that upper respiratory tract infections were seen 32 patients (3.4%) while TB was seen in only one (0.1%). These results suggest that patients treated with anti-TNFs have a higher a priori risk of infection.[21] Furthermore, a Spanish biologics registry identified the most common sites of severe infection as being the lower respiratory tract (39%), the blood (bacteremia/sepsis) (20%), and the urinary tract (16%).[22]

The incidence of septic arthritis in the general population varies from 4-10/100,000 patient years.[23] In a British registry, the risk of septic arthritis in 11,881 patients with RA who were treated with anti-TNFs was as high as 4.2/1,000, and the authors suggested that the anti-TNF therapy doubled the risk of getting this disease.[24] However, our search yielded only one report related to pseudoseptic arthritis.[25]

Opportunistic infections were reported with the use of anti-TNFs,[26] including histoplasmosis, listeriosis, pulmonary aspergillosis, and *Pneumocystis (carinii)* jiroveci pneumonia. We identified three patients in Turkey with infections related to adverse events who were treated with infliximab and one who was treated with adalimumab.[27-30]

Tuberculosis

Patients treated with anti-TNF therapy have an increased risk for developing TB and reactivating latent TB because TNF-α is the main cytokine in the immune response against *Mycobacterium tuberculosis* and granuloma formation.[5,31,32] Moreover, *Mycobacterium tuberculosis* is the most common granulomatous infection after the use of TNF antagonists.[26] The incidence of TB varies from 9.3 to 449/100,000 in patients treated with anti-TNFs; however, it can differ according to the country, length of the follow-up period, and type of TNF antagonist used.[33] Disseminated TB was more common with monoclonal antibodies.[33] Additionally, the reactivation of latent TB infection leads to significant morbidity and mortality, especially in immunosuppressed patients.[34]

According to a result from a British biologics registry, 40 cases of TB were reported out of the 10,712 patients with RA through April 2008. The adjusted incidence rate (AIR) ratio compared with

etanercept-treated patients was 3.1 [95% confidence interval (CI) 1.0-9.5] for infliximab and 4.2 (95% CI 1.4-12.4) for adalimumab.[35]

In a French biologics registry, 69 cases of TB were identified in the patients treated with anti-TNFs, but none of the cases received the correct chemoprophylaxis. The gender- and age-adjusted incidence rate of TB was 116.7/100,000 patient years. Compared with the general population, the standardized incidence ratio (SIR) of TB was 12.2 (95% CI 9.7-15.5), but it was higher for therapy with infliximab a SIR of 18.6 (95% CI 13.4-25.8) and adalimumab with a SIR of 29.3 (95% CI 20.3-42.4) than for therapy with etanercept with a SIR of 1.8 (95% CI 0.7-4.3). The authors of this registry concluded that the risk of TB was higher for patients receiving monoclonal antibodies than for those receiving soluble TNF receptor therapy.[36]

In a prospective study from the US, the incidence of TB in RA patients treated with infliximab was 52.5/100,000 patient years,[7] whereas the Ministry of Health of Turkey reported it as 25.8/100,000 between 2007 and 2008.[37]

A study from Turkey by Elbek et al.[38] assessed the risk of TB development in 240 patients with rheumatic disease who were being treated with anti-TNF, and they found that the duration of anti-TNF treatment was 17.1±11.7 months. Of these 240 patients, only two developed active TB during the follow-up period (13.6±6.5 months). The incidence of TB in this cohort was estimated at 833/100,000. Based on these results, the authors suggested that anti-TNF therapy increased the risk of TB, despite treatment for latent infections. The rate of latent TB in this study was 77.6%. The British Thoracic Society (BTS) suggested that six months of isoniazid treatment is effective and can reduce the risk of developing TB by 60%.[39] In our study, 14 patients had TB, although eight received isoniazid chemoprophylaxis.

Malignancies

Because TNF has a tumor-reducing capacity, treatment with anti-TNFs might theoretically promote the formation of tumors[40,41] We found several reports that focused on the risk of lymphoma in patients with RA who were treated with anti-TNF agents.

One Turkish study assessed the association between anti-TNF therapy and the development of tumors among patients in this country with rheumatological diseases.[42] A total of 2,199 patients [943 with AS, 931 with RA, 132 with PsA, 127 with juvenile chronic arthritis (JCA), and 66 with other diseases] were collected from 26 different rheumatology centers in Turkey. Fifteen patients had developed malignancies, including 13 with solid cancers and two with lymphoproliferative disorders (SIR: 1.26; 95% CI 0.70-2.08). The authors stated that the risk of malignancy might differ according to the primary disease (i.e., RA, SpA) and whether an anti-TNF agent was used.[42] From 2001 to 2009, five cases of malignancy (non-Hodgkin's lymphoma, Hodgkin's lymphoma, thyroid carcinoma, yolk sac carcinoma, and cervical dysplasia) were documented in a German juvenile idiopathic arthritis biologics registry which contained 1,260 patients.[2]

We found different results regarding the association between malignancies and the use of anti-TNFs. Geborek et al.[43] suggested that the overall incidence of cancer did not increase in patients with RA treated with anti-TNF agents, and that overall, patients with RA have the same increased risk for lymphoma and leukemia. Furthermore, Askling et al.[44] reported that patients with RA who were treated with anti-TNFs did not have a higher risk for lymphoma than those with RA who are treated with DMARDs. In a meta-analysis concerning the safety of biological treatments for RA, no increased risk for lymphoma, melanoma, or non-melanoma skin cancers when patients took the recommended doses was reported. However, the CIs for the risk estimates had quite a wide range.[20]

In a large cohort by Chakravarty et al.,[45] they found that the use of anti-TNFs and prednisone was associated with an increased risk of non-melanoma skin cancer in patients with RA. Furthermore, a case-control study by Baecklund et al.[46] showed that there was a strong association between disease activity and the risk for developing lymphoma in patients with RA.

Mercer et al.[47] in an evaluation of data from a British biologics registry revealed that the SIRs for skin cancer were increased for both anti-TNFs (1.72; 95% CI 1.43-2.04) and non-biological DMARDs (1.83; 95% CI 1.30-2.50). In addition, they discovered that the rate of skin cancer increased among patients with RA who were treated with either DMARDs or biologics. The authors underscored that there was no evidence that anti-TNF therapy exacerbated the risk of skin cancer, although this could not be completely excluded. The fact that many cancers develop very slowly and the risk of cancer being associated with the use of biological agents should be further

examined as experience with these drugs continues to accumulate.[48] In our search of the literature, we found four solid tumors and three lymphomas.[49-55]

Skin diseases

Dermatological adverse events associated with anti-TNF therapy include injection site reactions, allergic rashes, cutaneous infections, psoriasis, drug-induced lupus, erythema multiforme (EM), and cutaneous vasculitis.[56] These are not rare and were reported in 23-25% of patients with rheumatic diseases who were treated with anti-TNF treatments.[12,57]

In a review by Ko et al.,[58] 127 anti-TNF-related cases of psoriasis were identified. Seventy of these were treated with infliximab (55.1%), 35 with etanercept (27.6%), and 22 with adalimumab (17.3%). The psoriasis was resolved in 64% of the patients after they stopped using the anti-TNFs and starting systemic therapy. Harrison et al.[59] reported 25 cases of psoriasis in a British biologics registry of 9,826 patients with RA who received anti-TNF-α therapy between January 2001 and July 2007. The authors suggested that the incidence of psoriasis increased in patients who had been treated with anti-TNFs.

Anti-TNF agents can induce lupus-like symptoms. During an eight-year period at the Mayo Clinic, anti-TNF-induced lupus was identified in 14 cases.[60] We also noted that etanercept and infliximab were the two most common causative agents for anti-TNF-induced lupus.[60,61] Katz and Zandman-Goddard[62] hypothesized that there is always the possibility of latent idiopathic SLE being triggered by anti-TNF drugs. Furthermore, in drug-induced lupus, regression of the symptoms is expected if the causative drug is withdrawn.[62] We discovered two reported cases of patients with rheumatic diseases that also had drug-induced lupus in Turkey.[63,64]

Others

Hypersensitivity reactions may occur in patients who are treated with biological agents, but these can be managed by switching to other biological agents or desensitization.[65] In addition, our review found that desensitization was used in a patient with AS who developed an injection site reaction just after using adalimumab and then etanercept. However, after desensitization, the patient could continue to use etanercept without side effects.[66] Desensitization was also achieved in one case with RA who had a hypersensitivity to four different biological agents.[67]

Demyelinating disease was associated with the use of anti-TNFs in some patients with underlying neurological symptoms prior to the initiation of the therapy.[68] Thus, for patients with preexisting neurological diseases, for example multiple sclerosis (MS), anti-TNF treatment should be avoided, or if such symptoms develop, anti-TNF therapy should be stopped immediately.[68] In a Spanish biologics registry, the incidence rate of demyelinating disease in patients with rheumatic diseases exposed to anti-TNFs was 0.65/1,000 patient years (95% CI: 0.39-1.1).[69] A patient who had cervical spinal demyelinating disease after etanercept therapy was also reported in Turkey.[70]

Safety and efficacy

We found many papers related to the safety and efficacy of anti-TNF therapies. According to one comparative trial, abatacept and infliximab demonstrated similar efficacy with RA, but abatacept had a relatively more acceptable safety and tolerability profile with fewer adverse events.[71] In addition, discontinuations due to adverse events were lower with abatacept than with infliximab (3.2% vs. 7.3%, respectively).[71] The data from a British biologics registry revealed that treatment with anti-TNFs was not associated with an increase in mortality when compared with standard DMARD therapies.[72] A regularly updated consensus statement (last updated in 2011) is available in which all of the safety and efficacy data is evaluated by an expert panel.[2]

Case reports usually provide weak evidence of causality because they are particularly prone to bias; therefore, the results derived from our review of case reports cannot be generalized. However, it does provide useful information regarding the adverse events related to the use of biologics in Turkey. The results should be carefully evaluated since the vast majority of adverse events probably were not published. In fact, the reported adverse effects were related only to the use of anti-TNFs, but this may be explained by the subsequent approval and inclusion on the reimbursement list of other biologics (i.e., abatacept or rituximab). In fact, the number of reported cases was parallel to the order of approval and reimbursement in Turkey. Infliximab was the first anti-TNF for which patients could be reimbursed for the treatment of RA and AS and was soon followed by etanercept and then adalimumab. Additionally, golimumab has been approved for the

treatment of RA and AS, but it is not yet reimbursable. Rituximab and abatacept are also newly approved and reimbursable drugs in Turkey for the treatment of RA, but it may be too early to see any reported adverse events related to these drugs in the literature. As expected, the off-label prescription of biologics is also small in this country.

In conclusion

With the introduction of TNF inhibitors and other biological agents, we have gained effective new treatment options for various rheumatic diseases. Although studies exist which present the safety data related to these biologics, clinicians should be careful and watch for potential adverse events which can be severe. Patients should be informed about this potential risk and monitored closely for any signs of adverse effects associated with their biological treatments. In particular, patients should be screened for TB prior to treatment, especially in countries with a high risk of latent TB like Turkey.

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