T.C.

YEDITEPE UNIVERSITY

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DEPARTMENT OF CLINICAL PHARMACY

COMMON SIDE EFFECTS, ADHERENCE AND SATISFACTION OF PATIENTS USING BIOLOGICAL THERAPIES FOR RHEUMATOLOGIC DISEASES

MASTER THESIS

SELİN SARIKAYA, B. Pharm

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DECLARATION

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which has been accepted for the award of any other degree except where due acknowledgment has been made in the text.

Selin SARIKAYA

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURE

LIST OF SYMBOLS AND ABBREVIATIONS

ACR	American College of Rheumatology
ADA	Adalimumab
Anti-CCP	Anti-cyclic citrullinated peptide
ARA	American Rheumatology Association
AS	Ankylosing Spondylitis
BMQ	Brief Medication Questionnaire
CAPS	Cryopyrin associated periodic syndrome
CASPAR	Classification of Psoriatic Arthritis
CH	Crohn's Disease
CRP	C-reactive protein
CZP	Certolizumab Pegol
DIP	Distal interphalangeal joint predominant arthritis
DMARDs	Disease modifying antirheumatic drugs
ESR	Erythrocyte Sedimentation Rate
ETA	Etanercept
EULAR	European League Against Rheumatism
Fab	Fragment antigen binding
FADD	Fas associated death domain
Fc	Fragment crystallizable
FDA	Food and Drug Administration
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
GPA	Granulomatosis polyangiitis
GRAPPA	Group for Research and Assesment of Psoriasis and Psoritic Arthritis
HBV	Hepatitis B Virus
HLA	Human Leucocyte Antigen
ICAM-1	Intercellular Adhesion Molecule-1
Ig	Immunoglobulin

IGRA	Interferon gamma mediated test
IL	Interleukin
IL1RA	Interleukin-1 receptor antagonist
INF	Infliximab
INH	Isoniazid
IV	Introvenous
JIA	Juvenil Idiopatik Artrit
LT	Lymphotoxin
Mab	Monoclonal Antibody
MAPK	Mitogen Activating Protein Kinase
MIP-1	Macrophage inflammatory protein-1
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
NBD	Non-biological drug
NF	Nuclear Factor
NSAIDs	Non steroidal anti inflammatory drugs
PEG	Polyethylene Glycol
PS	Psoriasis
PsA	Psoriatic Arthritis
RA	Rheumatoid Arthritis
RANK	Receptor Activator of Nuclear Factor κB Ligand
RF	Rheumatoid Factor
RTX	Rituximab
SLE	Systemic Lupus Erytematosus
SSZ	Sulfasalazine
sTNF	Soluble Tumor Necrosis Factor
TACE	Tumor Necrosis Factor Alpha Converting Enzyme
TB	Tuberculosis
TCZ	Tocilizumab

TmTNF	Transmembrane tumor necrosis factor
TNF	Tumor necrosis factor
TNF-α	Tumor necrosis factor-alpha
TNF-β	Tumor necrosis factor-beta
TST	Tuberculin Skin Test
UC	Ulcerative Colitis
VCAM	Vascular cell adhesion molecule

ABSTRACT

Sarıkaya, S. (2021). Common Side Effects, Adherence and Satisfaction of Patients Using Biological Therapies for Rheumatologic Diseases. Yeditepe University Institute of Health Sciences, Department of Clinical Pharmacy, MSc Thesis, Istanbul.

Biological agents use have significantly improved the prognosis of rheumatologic diseases (RD). Despite great therapeutic effects, many patients may not adequately comply with these treatments. The aim is to study common side effects, adherence and its barriers during therapy.

A descriptive cross-sectional study was conducted using a questionnaire tool in the rheumatology service of a tertiary hospital. Patients diagnosed with one RD using a biological agent were enrolled in the study. The questionnaire was adopted and modified for the current study setting. Face validation was carried out following a forward backward translation to the Turkish language. A written consent form was acquired and the study design was approved by an ethical committee. Statistical analysis was carried using SPSS version 25.

80 patients with RD were invited of whom 60 patients responded (75%). Among responders, 76.7% were females with a mean age of patients 50.85 ± 1.7 years. The average duration of biological drug use was found significantly higher with infliximab (6.48 ± 0.78 years) than the others (p=0.017). Most patients (63.33%) used biological drugs for the first time. Of those who discontinued a biological therapy before; the most common reason was ineffectiveness (55%) followed by infusion reactions (24%). Common side effects include insomnia (18.33%), headache (15%), feeling restless (15%), muscle stiffness (13.33%), blurred vision (11.66%), and difficulty to move (11.66%).

In conclusion, findings indicate that biologic therapy has few tolerable side effects, and has a high rate of drug discontinuation mostly due to the ineffectiveness of the first agent used.

Keywords: Biological drugs, side effects, treatment satisfaction, discontinuation

ÖZET

Sarıkaya, S. (2021). Romatolojik hastalıklarda kullanılan biyolojik ilaçların yaygın yan etkileri, uyunç ve hasta memnuniyetlerinin değerlendirilmesi. Yeditepe Üniversitesi Sağlık Bilimleri Enstitüsü, Klinik Eczacılık ABD., Master Tezi. İstanbul

Biyolojik ajan kullanımı romatolojik hastalıkların (RD) prognozunu önemli ölçüde iyileştirmektedir. İyi terapötik etkilerine rağmen, aynı zamanda da birçok hasta bu tedavilere yeterince yanıt vermemektedir. Çalışmanın amaçı, biyolojik ilaçların yaygın yan etkilerinin, hasta memnuniyeti ve uyuncunun değerlendirilmesi ile tedavi sırasındaki engellerin gözlemlenmesidir.

Üçüncü basamak bir hastanenin romatoloji servisinde anket aracı kullanılarak tanımlayıcı, kesitsel bir çalışma yapılmıştır. Biyolojik ilaç kullanmakta olan ve bir RD tanısı konan hastalar çalışmaya dahil edilmiştir. Anket, mevcut çalışma ortamı içinde kabul edilip, değiştirilmiştir ve yüzyüze validasyon ile çift yönlü Türkçe-İngilizce çeviri yapılarak hazırlanmıştır. Çalışmanın etik kurul tarafından onayı alındıktan sonra başlanmış ve çalışma öncesinde hastalardan yazılı bir onam formu alınmıştır. İstatistiksel analiz SPSS versiyon 25 kullanılarak yapılmıştır.

Çalışmaya 80 hasta davet edilmiş ve çalışma sonunda 60 hasta (%75) dahil olmuştur. Çalışmaya katılan hastalardan %76.7'si kadındır ve hastaların ortalama yaşı 50.85 ± 1.7'dir. Ortalama biyolojik ilaç kullanım süresi, infliksimab kullanan hastalarda (6.48 ± 0.78 yıl) diğerlerine göre anlamlı derecede yüksek bulunmuştur (p=0.017). Hastaların çoğunluğu ise (%63.33) ilk kez biyolojik ilaç kullanmaktadır. Daha önce biyolojik ilaç tedavisini bırakanların en yaygın nedeni etkisizliktir (%55), bunu infüzyon reaksiyonları (%24) izlemektedir. Yaygın yan etkilerler; uykusuzluk (%18.33), baş ağrısı (%15), yorgun hissetme (%15), kas sertliği (%13.33), bulanık görme (%11.66) ve hareket etmekte güçlük (%11.66) şeklindedir.

Sonuç olarak, bulgular, biyolojik tedavinin tolere edilebilir ve yan etkilerinin az olduğunu, ayrıca biyolojik ajan bırakma oranın en fazla etkisizlik nedeni ile yaşandığını göstermektedir.

Anahtar kelimeler: Biyolojik ilaçlar, yan etki, tedavi memnuniyeti, ilaç bırakma

1. INTRODUCTION and PURPOSE

Rheumatologic diseases are autoimmune diseases with unknown etiopathogenesis but chronic inflammation in the pathogenesis (1). Rheumatologic diseases have a high morbidity and mortality rates, affects the life quality of patients, considering their chronicity, various organ involvement and comorbidities. The standard treatment relies on immunosuppression to control disease activity and reduce immune system overactivation. Conventional synthetic disease modifying antirheumatic drugs (DMARDs) and biological DMARDs have significantly improved the prognosis of rheumatologic diseases, but despite great therapeutic advances, many patients may not respond adequately to these treatments. Long-term drug therapy may be required for long-term remission (141). Still, biological drugs have begun to widely used in the treatment of rheumatologic diseases by enlightening the inflammation pathway and most of the immune system in the pathogenesis (2).

The treatment, which uses molecules in protein structure produced from living cells with biotechnological methods, is called "biological therapy" (3). Although they have widely used in the treatment of rheumatoid arthritis, they are using in other rheumatologic diseases such as ankylosing spondylitis, systemic lupus erythematosus psoriatic arthritis, juvenile idiopathic arthritis, Behcet’s disease, familial mediterranean fever (5).

Biological drugs inhibit disease activity by blocking specific pathways and signals of inflammation. Biological drugs used today to show these effects through 3 mechanisms. The first is to block the activities of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1), interleukin-6 (IL-6), which play an important role in inflammation. Others are suppressing inflammation by targeting T and B lymphocytes (3). In this way, biological drugs act on the pathogenesis of the disease by making a 'targeted therapy', not the entire immune system (3). However, biological drugs are used in patients resistant to standard therapy because of their not first-line therapy is the high cost and potential side effects of biologics (2,3,5).

The most common side effects during biological treatments are infusion reactions (dyspnea, high or low blood pressure, severe headache, vomiting, itching, urticaria), injection site reactions (itching, swelling, redness that can last up to a week), and

opporcunistic infections. One of the critical side effects that may occur during the use of biological drugs especially with anti TNF-α agents is mycobacterium tuberculosis infection. In addition, as biological drugs suppress the immunologic response, they can cause many infections such as upper respiratory tract infections, urinary tract infections and fungal infections (3,4).

Although, hepatotoxicity, lymphoma and malignancies, lupus-like disease, colon perforation, increased lipid levels, depression, suicidal tendency, vision problems, difficulty in walking and speaking are among the other uncommon side effects (3,4)

Many clinical studies have been conducted on the efficacy and safety of biological drugs to understand the side effects and patient concerns (5). According to the Cochrane network meta-analysis, patients who received biological therapy were more likely to discontinue treatment due to opportunistic infections, tuberculosis, drug side effects, and other side effects related to biological drugs (7). There are many studies about safety and effects of biological drugs, but the discontinuation and switching of biological drugs groups are big problem in the therapeutic period and the knowledge related to this topic are very limited in the lecture. Although many studies on the safety and pharmacologic effects of biological drugs are needed yet, there is no questionnaire study evaluating the satisfaction of drugs used by patients receiving biological therapy.

In the questionnaire, the first parts were adapted for the patients who are receiving biological treatment for their rheumatologic disease, based on the study named "Brief Medication Questionnaire". So, this questionnaire is one of use more frequently in the assessment of drugs, it was slightly modified according to the properties of biological drugs. In the last part, a table containing with biological drug side effects was prepared by evaluating general drug side effects.

In this study, we aimed to conduct a questionnaire study that evaluates the drug satisfaction, side effects and discontinuous of patients during chronic treatment period. Therefore, the goal of the study is to evaluate the satisfaction, discontinuation and safety of biological drugs with a survey study. It will be performed by the modified questionnaire and it use as an evaluation tool in rheumatology patients using biological drugs.

2. LITERATURE REVIEW

2.1. Biologics

The term biological agent "biological" concept comes from recombinant DNA technology, and living cells in the production of the agents are used instead of chemical synthesis. Monoclonal and polyclonal antibodies, peptides, oligonucleotides, therapeutic genes, recombinant proteins, DNA and recombinant vaccines are evaluated in the biological agent (8). The suffixes at the end of the drugs also provide information about their molecular structures. Such as, -mab is used for monoclonal antibodies and fragments, -cept is used for fusion proteins (2). Currently, biological agents are used in a variety of disorders and are also frequently used drugs in rheumatology practice.

After the discovery of cytokines such as endogenous pyrogen (IL-1) and interferon in the 1950s, the number of studies on cytokines in immunology began to increase. In 1974, the concept of "cytokine", which is a combination of the words "cyto" meaning cell and "quinine" meaning hormone, was introduced (9). In the 1970s and 80s, Skurkovich et al. Demonstrated that the interferon level in the circulation increased with immun deficiencies patients. They suggested that patients can be treated with interferon neutralization. Thus, they pioneered the idea of anti-cytokine therapy (9,10) In 1975, Köhler et al. Initiated the first studies of monoclonal antibody technology using immortalized cell cultures (11). Another breakthrough for anti-cytokine treatments was the demonstration of Beutler et al. In 1985 that the TNF antibody protected mice from bacterial septic shock (9,12).

The successive discoveries, helped clarify the roles of cytokines in autoimmune diseases. Studies on this subject accelerated after the 1990s. Rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), ankylosing spondylitis (AS), psoriatic arthritis (PSA), psoriasis (PS), Crohn's disease (CD) etc., considered under the title of chronic diseases of inflammatory and autoimmune. The roles of T and B cells, innate immune element cells, and cytokines released by these cells have been discovered (13).

Explaining the physiopathological mechanisms in RA, which is common in society, especially from autoimmune diseases, has been an important development in biological treatments (13). The determination of the roles of TNF-α and other similar cytokines in RA led to the idea of targeting these cytokines in treatment. Indeed, the use of soluble TNF receptor etanercept in 1998 and the chimeric monoclonal TNF antibody

infliximab began in 1999 for patients resistant to conventional therapies (Disease Modifying Antirheumatic Drugs-DMARDs). Additionally, the Food and Drug Administration (FDA) approved the treatment. After this date, other anti-cytokine therapies, anti B-cell therapies, T and B cell co-activation signal inhibitors rapidly came into use in the rheumatology clinic. Over time, these types of medications started to be used in diseases other than RA (14,15).

2.2. Tumor Necrosis Factors

Tumor Necrosis Factor (TNF) is a polypeptide cytokine that has an crucial role in innate and adaptive immun system, cell differentiation, and cell apoptosis. There are two types of TNF, TNF-alpha (TNF-α) released from active macrophages and TNF-beta (TNF-ß) released from active T cells (16). TNF alpha has a crucial role in the pathogenesis of RA, AS, PsA, CD, and many other systemic autoimmune diseases (4). TNF-α has two different types, transmembrane TNF (tmTNF) and soluble TNF (sTNF). First, TNF-α is synthesized in the cell and the precursor form, tmTNF, is released to the cell surface. tmTNF is converted by TNF alpha converting enzyme (TACE) into the biologically active of sTNF-alpha and thereby released from the cell. Although TNF alpha producing cells are mainly monocytes and macrophages, B and T cells, mast cells, and fibroblasts can synthesize TNF-α. The effects of TNF-α are provided by two structurally different receptors, TNF-R1; p55 and TNF-R2; p75. While p55 (55 kD) is commonly found on the surface of many cells, p75 (75 kD) is found much more frequently on hematopoietic and endothelial cell surfaces, however TNFRs are not found on erythrocytes (4,16). Both receptors can elicit antiapoptotic pro-inflammatory signals by activating nuclear factor (NF) κ-B or mitogen-activated protein kinase (MAPK) pathways. In addition, p55 can elicit apoptotic anti-inflammatory signals with the Fas-associated death domain (FADD) and caspase-8 (17). sTNF and tmTNF can bind to either receptors. However, p75 is characteristically found in immune cells and is exclusively stimulated by tmTNF (18).

TNF-α increases the phagocytosis capacity of macrophages, stimulates the release of various cytokines, enables adhesion molecules to come to the cell surface, and collect immune cells at the infection site. TNF-α is an essantial cytokines in the continuity of the granuloma structure. In short, TNF-alpha plays an important role in regulating the Th1

immune response against intracellular bacteria and viral infections and a potent stimulator of the inflammatory response, which is the main regulator of innate immunity (19,20).

2.2.1. TNF Inhibitors

Understanding the position of TNF alpha in inflammation, TNF antagonists have been used for diseases related with joint inflammation and destruction.

The biological effects of TNF-α are showed in *Table 2.1.* (3).

Table 2.1. The biological effects of TNF-α

Presentation of adhesion molecules (such as E-selectin and ICAM 1)
Synthesis of proinflammatory cytokines (IL-1, IL-6, GM-CSF)
Synthesis of chemokines (such as RANTES, IL-8, MIP-1)
Stimulation of T cell, B cell, and macrophages
Inhibition of regulatory T cells
Matrix metalloproteinase enzyme induction
Increased RANK ligand (RANK-L) presentation
Apoptosis induction
Anti-viral and anti-tumor effects

Note: ICAM-1; Intercellular Adhesion Molecule 1. GM-CSF; Granulocyte Macrophage Colony-Stimulating Factor. MIP-1; Macrophage inflammatory protein-1.RANK-L; receptor activator of nuclear factor κB Ligand.

The inhibition of the biological effects of TNF alpha explains most of the results obtained via anti-TNF treatment. For example, the reduce in the neutrophils is explained by the suppression of GM-CSF (granulocyte-macrophage colony-stimulating factor) as a result of TNF inhibition. Since VEGF (vascular endothelial growth factor) inhibition reduces edema and capillary leakage, the suppression of VEGF as a result of TNF inhibition provides rapid regression of swelling in the arthritic joint. The reason for the decrease in acute phase responses is the result of rapid inhibition of other proinflammatory cytokines as well as TNF inhibition (4).

TNF-α inhibition occurs by two mechanisms. First, a monoclonal antibody is created against TNF-α, and this biological agent inhibits its action by binding to TNF-α. While naming, the suffix -mab is added to the end. The other is to create a receptor fusion protein, which has the same structure as TNF receptors. Thus, the cytokine that binds to the receptor fusion protein cannot show the effects. While naming the biological agents, the suffix -sept is added to the end of the molecules (16).

2.2.2. TNF-α and Rheumatological Diseases

TNF alpha is an essential cytokine involved in the pathogenesis of many inflammatory and immunologic diseases as RA, AS, juvenile rheumatoid arthritis (JRA), PsA, psoriasis (PS), and Crohn's disease (CH). Therefore, anti-TNF agents can be used successfully in the treatment of these diseases. Indeed, the efficacy and safety of various TNF inhibitors have been demonstrated in several clinical research. Therefore, the success of TNF inhibitors in rheumatology practice leads and encourages other biological treatments (3,4).

2.2.3. Infliximab

In a 1993 study, the monoclonal anti-TNF antibody cA2 was developed and pioneered a new treatment method for RA patients (21). The molecule name later became infliximab and firstly approved for Crohn's disease in 1998 and then for RA treatment in 1999 (4).

Infliximab (INF) is a chimeric monoclonal antibody formed with combining the human IgG1κ constant region with the mouse antigen-binding region (22). The molecule is generated from the mouse myeloma cell line transfected with the DNA clone coding for cA2. Infliximab binds to either sTNF alpha and tmTNF alpha with high affinity, thus neutralizing its effect by inhibiting the binding of receptors to TNF alpha. Infliximab does not attach to TNF-ß. Due to TNF-α blockage, infliximab decreases the level of proinflammatory cytokines such as IL-6 and IL-1, prevents leukocyte migration by inhibiting endothelial cell permeability, inhibits the synthesis of adhesion molecules from endothelial cells and endothelial cells, and prevents eosinophil and neutrophil activation. INF, inhibits the bioactivity of fibroblasts, T and B lymphocytes, neutrophils, endothelial cells, and epithelial cells (4,23).

The half-life of infliximab is 7-12 days, and the dose is 3 mg / kg for RA patients, 5 mg / kg for AS and PsA patients, and doses are initially given every 0, 2, 6 weeks and then every 6-8 weeks. Because of the infusion reaction potency (dyspnea, high or low blood pressure, severe headache, vomiting, itching, urticaria), the first application is given as an i.v. infusion for 2 hours, if the patient can tolerate the subsequent applications, infusion can be reduced to 1 hour (3,13, 24).

Infliximab is FDA approved for RA with methotrexate (MTX), PsA, AS, CD, pediatric CD, and ulcerative colitis (UC) (13,24).

2.2.4. Etanercept

Etanercept (ETA) is a human TNF receptor p75-Fc fusion protein obtained by combining 2 human TNF receptor p75 and human IgG1-Fc protein produced by recombinant DNA technology. The molecule formed is a dimeric, soluble TNF-R binds to TNF-α and TNF-β known as, LT-α (lymphotoxin-alpha), with high affinity and specificity (16, 36).

The receptor on the TNF trimer binds to two of the three sites and prevents the proinflammatory response by blocking the functions of TNF. Due to these properties, ETA causes a decrease in tissue adhesion molecule expression and soluble adhesion molecule level and prevents inflammatory cell migration by blocking the stimulating effect of TNF-α on cells (4,16).

Approved for the treatment of RA, JIA, AS, psoriasis, and PsA. Etanercept is the first TNF inhibitor approved by the FDA to treat RA. The mean half-life of ETA is 102 ± 30 hours and is administered by subcutaneous (sc) injection of 25 mg twice a week or 50 mg once a week (3,24).

2.2.5. Adalimumab

Adalimumab (ADA) is a fully human IgG1 monoclonal anti-TNFα antibody. It is manufactured with phage-display technology and cannot be distinguished structurally or functionally from native human IgG1. Like other monoclonal anti-TNF agents, ADA binds both sTNF and tmTNF, shows high specificity and affinity for TNFα and does not bind to TNF-β (3,25,26).

By binding ADA to TNF-α, the interaction with the receptors attached to the membrane cannot occur and the biological function is neutralized. ADA activates the classical complement pathway by binding to TNF-α and initiates antibody-dependent cell-mediated cytotoxicity. Thus, ADA induces apoptosis in cells expressing TNF-α and causes cell destruction. Since studies have determined that there is a long half-life with 15 to 19 days (average 14 days), drug administration is applied every two weeks (27,28). Adalimumab is administered as sc injection of 40 mg every two weeks (24).

Approved for the treatment of RA, JIA, PsA, CD, severe AS, UC, and psoriasis by the FDA (13,24).

2.2.6. Golimumab

Golimumab is a TNF-alpha-specific human IgG1 kappa monoclonal anti-TNF-α antibody. In 2009, Golimumab was approved for the moderate to severe active RA with MTX, in the treatment of active PsA or active AS with or without MTX and other DMARDs. It binds to sTNF and tmTNF.

The half-life is about 2 weeks and the administration of the medication is subcutaneously or intravenously. On the same day every month, 50 mg sc once a month or 2 mg/kg IV at 0. and 4. weeks and then every 8 weeks. (29,30,31).

2.2.7. Certolizumab Pegol

Certolizumab pegol (CZP), a new anti-TNF alpha agent, is also known as CDP870. Like other monoclonal antibodies, certolizumab neutralizes by binding to both sTNFα and tmTNFα. CZP is a recombinant humanized anti-TNF-α monoclonal antibody and Fab (fragment antigen binding) pegylated with polyethylene glycol (PEG) (3,13).

Pegylation refers to the attachment of PEG groups to proteins by covalent bonds. Pegylation allows CZP to reach the inflamed area more easily and stay there longer. In addition, Pegylation decreases the renal clearance of CZP, increasing the duration of remain in circulation and thus its effectiveness. Since certolizumab consists of only a single Fab fragment, if not pegylated, it cannot remain in circulation for long periods and cannot be effective (32,33).

This new molecule has two properties that distinguish from the other TNF inhibitors. The first is the molecule is pegylated, the other is the Fc (Fragment

crystallizable) part is absent. The IgG molecule, which can be considered as the prototype of immunoglobulins (Ig), consists of two Fab and one Fc fragment, the function of the Fab regions is to bind the antigen and the Fc region to interact with complementary proteins. Unlike others, CZP does not have an Fc region. Therefore, in vitro complement-dependent or antibody-dependent cellular cytotoxicity mediated not cause. Another advantage provided by the lack of the Fc region is low potential immunogenicity (34, 35).

Certolizumab pegol is approved for the treatments of RA, CH, PsA, and AS. The adult dose of CZP is 400 mg at the 0, 2, and 4 weeks, and then 200 mg of SC injection every two weeks (24).

2.2.8. Adverse Effects

Common adverse effects of TNF alpha inhibitors are infusion reactions, injection site reactions, and infections.

Injection site reaction is common, especially in subcutaneous injectable drugs. Rarely, is severe enough to require discontinuation of the drug. This allergic reaction, which is seen as swelling, redness, itching, and pain in the application area, can last up to 7 days and generally does not require treatment.

Infusion reactions are also allergic side effects that can happen up to 24 hours after infusion, such as severe headache, shortness of breath, rapid or weak pulse, nausea, and vomiting. Sometimes, in severe cases, it can be seen as anaphylactic shock. The rapid infusion increases this risk of the side effect, it can be reduced by decreasing the infusion rate. To prevent mild reactions, paracetamol, antihistamines, and short-acting corticosteroids are given before the infusion.

The most important side effects include all types of infections, especially tuberculosis and fungal infections. TNF alpha is an important pro-inflammatory cytokine in body defense. Granulomatous infections and tuberculosis are particularly common in TNF-α deficiency, because TNF plays an crucial role in granuloma formation and maintenance (3, 24).

Therapy with the anti-TNF agents should not start in the active infection or patients with recurrent infections. Before starting treatment, screening for tuberculosis is done for patients. Patients whose tuberculin skin test (TST) is less than 5 mm or whose interferon gamma-mediated test (IGRA) is negative can be initiated without isoniazid

(INH) prophylaxis. Those with a TST of 5 mm or more or who are positive for IGRA are considered to have latent TB (tuberculosis) and INH treatment is started one month before the anti-TNF treatment and given for 9 months (3, 120, 121).

Long term use of TNF-α inhibitors can lead to cancer, especially skin cancer and lymphoma. In addition, demyelinating diseases may occur or exacerbated during treatment, especially multiple sclerosis has been reported. Patients with congestive heart failure should not use TNF-α inhibitors because they can make heart disease worse (3, 122).

2.3. B-Cell Inhibitors

The most vital part of humoral immunity and an important component of the adaptive immune system are B lymphocytes that can activate the functions of antigen-presenting cells as well as direct antigen presentation. They have also a regulatory role in activation and differentiation of T cell, differentiation of follicular dendritic cells, and the organization of germinal center-like structures in the RA synovium. Since B lymphocytes are the precursor cells of plasma cells, they are also responsible for antibody production (38).

However, B lymphocytes can also be pathogenic and are responsible for the etiopathogenesis of many rheumatologic diseases such as SLE and RA. (38) For example, unlike normal individuals, B cells hyperactivity occur spontaneously produce large amounts of immunoglobulin in SLE patients. As the hyperactivity of B cells is characteristic of many autoimmune diseases, with targeting b cell-specific antigens such as CD20 depletion of b cells can be achieved (1).

B cells provide immune response through secretion of cytokines, antigen presentation, autoantibody production, and co-stimulation of T cells. Therefore, the discovery of new B-cell-targeted biological therapies is increasing (37).

2.3.1. Rituximab

The most widely used approach for B cell depletion today is targeting B cell surface molecule, CD20 which is a hydrophobic transmembrane protein found on the mature B-lymphocytes and B-cell precursors.

Rituximab (RTX) is a chimeric mouse / human IgG1 monoclonal antibody raised for the CD20 protein. The Fab domain of rituximab binds to the CD20 antigen, and the Fc domain mediates immune effector functions mediating in vitro B-cell lysis (39,40).

RTX causes the depletion of the B cell by binding to the surfuce molecule CD20 with three different mechanisms, induction of apoptosis, complement dependent and antibody-dependent cellular cytotoxicity. Thus, inflammation is reduced by decreased antigen presentation to T lymphocytes and inhibition of the production of proinflammatory cytokines (41).

Rituximab is approved by the FDA in 2006 for moderate to severe RA with MTX (or other DMARDs) who have inadequate response to TNF-α inhibitors. RTX is also option for treat microscopic polyangiitis, granulomatosis polyangiitis (GPA, Wegener granulomatosis), and non-Hodgkin lymphoma (38,42).

Treatment is done in cures. RTX is administered as 1000 mg IV infusion at 1. and 15. days, then if necessary, the cure can be repeated every 6-9 months. Because of the risk of infusion-related reactions, RTX should be given by slow infusion, and paracetamol, antihistaminic or intravenous corticosteroid (usually 100 mg methylprednisone) should be given 30 minutes before treatment (24,41).

2.3.2. Adverse Effects

The most common adverse effects of RTX is infusion- related reactions with a 30 percent frequency and can include itching, urticaria, fever, throat irritation, nausea, headache, hypotension, or hypertension. These symptoms can arise because of B cell lysis. In the second cure, the frequency drops to about 10 percent, partly due to the reduction of B cells in the first infusion. Anaphylaxis is rare. Pre-medication is given to the patient because it reduce the risk of an infusion reaction. Therefore, patient monitoring is required during the application (3,39,41).

B cell inhibitors are not given in the presence of active infection and before treatment serology for Hepatitis B virus (HBV) should be done because HBV reactivation is likely to occur. After repeated treatments, immunoglobulin levels, especially IgM and IgG, decrease, although this may cause serious infections, its direct relationship with immunoglobulins is not clear. In rituximab treatment, reactivation of tuberculosis is uncommon. Progressive multifocal leukoencephalopathy (JC virus) is not a common

complication of RTX, although it is commonly in patients receiving multiple immunosuppressive therapy. There is no effective treatment and usually fatal (41,42,43).

2.4. Interleukin-1 Inhibitors

Interleukin-1 causes the increase of inflammatory mediators such as prostaglandins by stimulating synoviocytes and osteochondrocytes, and cartilage destruction and bone erosion by matrix metalloproteases (44).

There are three ligands in the IL-1 family, namely IL-1α, IL-1β, and IL-1 receptor antagonist (IL-1Ra). In the inflammatory response, IL-1α and IL-1β the ligands (IL-1β and L-1α) play a critical role with an agonistic activity (3).

According to study conducted on mice, has been shown that the stimuli causing the erosive, chronic arthritis are insufficient in mice with interleukin-1β deficiency, and autoimmunity and arthritis develop spontaneously in mice with IL1Ra deficiency (45).

2.4.1. Anakinra

Interleukin-1 receptor antagonist is important for the IL-1 activity regulation because the imbalance between interleukin-1 and IL-1Ra results in inflammation. Anakinra is the human recombinant form of IL-1Ra. The half-life is 4-6 hours, and it should be applied every day due to the short half-life. Its clearance is reduced in renal failure (creatinine clearance is 75% in patients with <30 ml / min). The daily dose is 100 mg/kg subcutaneously and anakinra can be used in combination with methotrexate but not recommended for use with anti-TNF agents (44).

In rheumatology, used in adult-onset JIA, cryopyrin-associated periodic syndrome (CAPS), and Behçet's Disease (41).

MTX-resistant RA patients are approved for use with anakinra, but it is less effective than other biological drugs and no longer recommeded in the American College of Rheumatology (ACR) treatment procedure (46).

2.4.2. Adverse Effects

Interleukin inhibitors are a relatively safe therapy. The most common adverse effects are prone to infections, usually upper respiratory tract infections (3).

Injection site reactions such as itching, swelling and redness, are seen more frequently in the treatment of anakinra and is hardly associated with tuberculosis (1).

2.5. Interleukin-6 Inhibitors

Interleukin-6 is proinflammatory cytokine. IL-6 is released by monocytes, keratinocytes, B cells, T cells, endothelial cells, fibroblasts, mesenchymal cells, and some tumor cells. IL-6 has a many biological activities on the immune system and hematopoiesis, regulation response, inflammation, and oncogenesis. (3,47)

IL-6 and IL-6 receptors show a critical part in the initiation and progression of immune system dysfunction. Apart from its part in the inflammation response and the pathogenesis of arthritis, IL-6 is also part of the inflammatory pathogenesis of gastrointestinal system diseases, cardiac diseases, and visual disorders (48). Disruption of the balance between IL-6 and soluble receptor of IL-6 causes an increase the cell surface receptors' number, intracellular signaling, and an increase in cytokine production and release (49).

2.5.1. Tocilizumab

Tocilizumab (TCZ) is a human monoclonal antibody developed against the IL-6 receptor. While inhibiting the binding of IL-6 receptors, TCZ does not inhibit other cytokines of the IL-6 family. Although it blocks IL-6 activity, not extends the half-life of IL-6 that cannot bind to its receptors. Despite TCZ is an IgG1 antibody, not cause antibody-mediated or complement-mediated cellular cytotoxicity in cells presenting IL-6R (50).

The FDA licenced TCZ for use of rheumatoid arthritis and systemic JIA. TCZ can be given with MTX or other DMARDs for RA or can be given as monotherapy in patients with intolerance or contraindication. For RA therapy, TCZ is given as 1-hour infusion every four weeks, at a dose of 4 mg/kg initially and in case of clinical unresponsiveness, 8 mg/kg. In rheumatoid arthritis cases, the half-life is concentration-dependent, and

approximately 11 days for the 4 mg/kg dose given every four weeks and 13 days for the 8 mg/kg dose (47,51).

2.5.2. Adverse Effects

The most common adverse effects are upper respiratory tract infections, nasopharyngitis, headache, increased transaminases, and abdominal pain (47-50).

As the duration of TCZ use increases, the incidence of infection does not increase and remains stable. Serious opportunistic infections such as tuberculosis can be seen rarely. As with anti-TNF agents, screening for latent TB should be performed in accordance with the guideline and the rules stated in the guideline should be followed.

Although rare, there is a risk of developing diverticular perforation in the colon in TCZ treatment. Considering the possibility of diverticulitis and colon perforation, the frequency of serious infections is more common in patients over 65 years of age and more caution should be exercised in elderly patients.

After TCZ treatment, elevated transaminases, neutropenia and thrombocytopenia, and increased cholesterol and triglyceride levels can be seen. Therefore, serology should be checked every 4-8 weeks.

During the infusion, a decrease or increase in blood pressure, headache, and skin reactions occurs within the first 24 hours, known as an infusion reaction. Anaphylactic reactions can be seen rarely (3,47).

2.6. Interleukin-17 Inhibitors

Interleukin-17 (IL-17) inhibitors are current therapeutic agents that act by inhibiting cytokines released from Th 17 cells or blocking the receptor binding.

IL-17 family has six members named from A to F, and the most important ones are IL-17A. IL-17A is produced specifically by the Th17 cell subgroup. IL-17 receptors are found in fibroblasts, macrophages chondrocytes, monocytes, and osteoblasts (51).

2.6.1. Secukinumab and Adverse Effects

Secukinumab is a selectively targeted interleukin 17A monoclonal antihuman antibody of IgG1/kappa isotype, and inhibits the relationship with IL-17RA (52). In this way, secukinumab inhibits the release of tissue damage mediators, chemokines, and proinflammatory cytokines (53).

Secukinumab was licenced by the FDA for plaque psoriasis in 2015, psoriatic arthritis, and AS in 2016 (52). Secukinumab shows rapid response and continuous symptom reduction in AS, RA, and PsA (54). Initial loading doses are 150 mg subcutaneous injection at 0, 1, 2, 3, and 4 weeks, then 150-300 mg monthly.

Used in therapeutic doses, secukinumab can completely neutralize IL-17A without neutralizing IL-17F, affecting Th1 pathway or Th17 functions. Thanks to target specification of secukinumab cause less side effects than alternative therapies (55). As with other biologic, infection is a common side effect. TB status should be evaluated before treatment (41).

2.7. Rheumatological Diseases

2.7.1. Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a disease that cause progressive damage to the tissues around the joints, especially affecting the synovial joints and synovial tendon sheaths. The most prominent feature of the disease is inflammatory synovitis that keeps the peripheral joints in shape (56,57).

The incidence of the disease is 1% on average worldwide (59). In a new series reported from Turkey, the prevalence of RA was determined as 0.32% (58).

The disease is associated with age and gender. Womans are more likely to RA, like many other autoimmune diseases. The average female / male incidence rate can be considered as 3/1. As the age progresses, the incidence of women/men decreases (60,61)

Genetic and environmental factors display an essential role in the pathogenesis. However, the higher incidence in women compared to men is thought to be due to hormonal factors (62). Oral contraceptives and pregnancy have a protective effect on development of RA. During pregnancy, 75% of RA patients go into remission. However, exacerbations usually begin after birth (63).

Human Leucocyte Antigen (HLA) genotype determination has an essantial role in determining the response to treatment, risk and disease severity. While the disease is milder in DR1 gene positive cases in RA patients, the disease is more severe in HLA DR4 gene positive cases (63,64)

2.7.1.1. Pathogenesis

In rheumatoid arthritis, plasma cells, T and B lymphocytes, mast cells, macrophages, and synovial fibroblasts, activated stromal cells, and damaged extracellular matrix is densely found in synovial tissue (56). The fact that these cells infiltrate the synovial environment creates excessive TNFα expression, which displays an important role in the inflammation cascade. TNFα has a role in both synovial inflammation formation and joint damage. Through TNFα, T and B lymphocyte, macrophage, and synovial fibroblast activation is maintained. Another increasing mediator in the environment is IL6. Like TNFα, IL-6 maintains the continuation of inflammation and joint damage. IL-1, one of the other proinflammatory cytokines, is less effective than IL-6 in pathogenesis of RA but is effective in pathogenesis of juvenile rheumatoid arthritis and Still's disease. In rheumatoid arthritis, the most affected cells in the joints are synovial and cartilage cells. It is believed that increased proinflammatory cytokines in the environment differentiate synovial cells into fibroblast-like and macrophage-like cells. Fibroblast-like synovial cells have been found to attack the cartilage tissue in experimental models of RA. Otherwise, the receptor activataion of the nuclear factor κ B ligand (RANKL) expressed by T and B lymphocytes also fibroblasts increases osteoclast transformation and activity with binding to its receptor (RANK) on pro-osteoclasts. Thus, due to increased osteoclast activity in the bone tissue erosions develop. (57,65) It is thought that joint damage develops when all these come together. It is not yet clear which is the first mechanism to be triggered in this chain of events. In some sources, argued that fibroblast-like synovial cells are the factor initiating joint damage (57).

2.7.1.2. Clinical Presentation

In 3/4 of the patients, the disease starts slowly and insidiously. Swelling and morning stiffness occur in joints within weeks or months. Joint pain, low-grade fever, fatigue, and loss of appetite, begin to appear. Joint stiffness tends to be symmetrical also

affects the small joints of the ankles, hands, and feet. The number of joints involved increases over time. Joint stiffness usually worsens in the morning and lasts up to 30 minutes and can last all day. Acute or subacute onset is seen in 1/4 of the patients. Metacarpophalangeal, wrists, and proximal interphalangeal joints are more frequently affected. Knees, elbows, and metatarsophalangeal joints are also highly clinical. In particular, cervical C1 and C2 joints may be involved in the hips and shoulders, ankles, and cervical region. It is not unusual for dorsal and lumbar vertebrae, sacroiliac joints and distal interphalangeal joints to be involved in RA. Hip joints are also rare. In RA, all organ systems can be affected. In general, the number and severity of the features of extra-articular findings vary according to the severity and duration of the disease. In addition, it is known that mortality is increased in patients with extra-articular involvement. Extra-articular findings are more common in seropositive patients (46,67,68).

2.7.1.3. Laboratory

For the RA diagnosis, there is no specific test. However, rheumatoid factor (RF) is the classic auto-antibody in RA and occurs against the Fc fragment of human IgG molecules. RF is positive in 60-80% of patients but is not specific. RF positivity can seen with 5% of healthy people. In addition, RF can be detected in the blood in other rheumatological diseases such as Sjogren's Syndrome, sarcoidosis, SLE and infective diseases as hepatitis B, tuberculosis, and infectious mononucleosis (69).

In addition, Anti-Cyclic citrullinated peptide (Anti-CCP) types are also increasing in importance. Anti-CCP is one of the autoantibodies against citrulline peptides and is more sensitive and specific in the RA diagnose (57,69).

2.7.1.4. Diagnosis

Classification criteria have been established in order to determine the stage of RA and to arrange the therapy accordingly.

First, in 1956, the American Rheumatology Association (ARA) developed criteria for diagnosing rheumatoid arthritis. As studies increased, the content and number of criteria changed, including revising the duration of joint complaints. Criteria were developed several times by the committees, including 1958, 1966, and 1983. The ARA criteria in 1987 remained valid until 2010.

In 2010, ACR and European League Against Rheumatism (EULAR) jointly regulated the final classification criteria for rheumatoid arthritis. 2010 criteria; Contrary to the 1987 ARA criteria, also includes patients with early rheumatoid arthritis and different arthritis patterns.

Patients with synovitis and no other symptoms are candidates for evaluation. The criterion that the patient has definite RA is considered a score of 6 or more out of 10 according to the scoring system.

Although the 2010 ACR / EULAR criteria are evaluated more effectively RA, there is not enough data to predict disease development. But, in the studies performed, anti-CCP (30-50%) and rheumatoid factor (RF) (20-50%) positivity were found in some of the cases in about 2-4 years before the development of rheumatoid arthritis. Also; 3 times the female gender, 5 times the CRP value above 50 mg/dl, and 1.5 times the presence of polyarthritis, and smoking and HLADRB1 gen have been shown to increase the risk (70,71,72).

2.7.1.5. Non-pharmacologic Treatment

Patients should be given physical therapy exercises to protect their joint structures. If the patient is overweight, they should lose weight. The use of assistive devices can reduce disease complaints, and the patient should have adequate rest.

Surgical procedures such as tenosynovectomy and joint replacement are beneficial in severe diseases (46).

2.7.1.6. Pharmacologic Treatment

Drugs that reduce RA symptoms and prevent joint damage are divided into traditional synthetic DMARDs and biologic DMARDs (Biologicals). ACR guidelines consider tofacitinib separately in 2015.

Biologics are divided into IL-inhibitors, B cell inhibitors, TNF inhibitors, and selective co-stimulation modulators according to their mechanism of action. The effectiveness of biologics has been proven for insufficient DMARDs therapy (46).

DMARD treatment is started within the first 3 to 6 months of the disease. Treatment guidelines recommend that most patients be initiated with a DMARD, preferably methotrexate (MTX), regardless of clinical disease activity. Patients with

moderate to severe disease activity despite theray should switch to another DMARD, biologic agent, or DMARD combination therapy (46,73).

The ACR guidelines recommend the anti-TNF biologics in combination with monotherapy or MTX with moderate to high disease activity after DMARD therapy. Biological drugs combined with MTX is more effective than biologic monotherapy. The dual biologic usage is not recommended due to the risk of infection due to immune system suppression (46).

Non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are used for symptomatic treatment for necessary. NSAIDs do not decelerate the progression of the disease.

Corticosteroids are used to control pain until DMARDs take effect (bridging therapy). When DMARD therapy begins to show its effectiveness, the corticosteroid dose is reduced and discontinued. Long-term use of systemic corticosteroids is not recommended due to the side effects. In addition, high-dose oral or IV steroids are used for a few days to suppress disease exacerbations.

Since DMARDs, biologics, and some corticosteroids cause immunosuppression, vaccination can be performed against vaccine-preventable infections before starting treatment.

Some biologics are contraindicated in hepatitis C and malignancy due to immunosuppression (46).

2.7.1.7. Patient Education

Patients should be informed about chronic disease and that requires regular joint examinations and laboratory monitoring. In addition, patients must be educated about the life changes related to RA. If patients are not at the ideal weight, they should be supported to lose weight.

The patient should be informed about drug use. The drugs administered by the patient himself/herself, such as subcutaneous drugs, should be explained in detail. Patients should be educated about side effects of the drug and what to do during serious side effects (46).

2.7.2. Ankylosing Spondylitis

Ankylosing spondylitis is a chronic inflammatory disease, usually causing inflammation in the sacroiliac joints at an early stage and may affect the axial spine as the disease progresses but unknown etiology. The disease lead to inflammatory low back pain with functional and structural insufficiency and can cause decrease in life quality (74).

Ankylosing spondylitis is effects young population and usually occurs around the 26 ages. Male population is affected more than women, the male-female ratio is 2: 1. While 80% of the patients' symptoms start below the 30s, less than 5% give the first symptom after the 45s (75). There is a positive relationship between the prevalence of AS and the HLAB27 antigen and it’s prevalence is 90% in Northern European populations, whereas it is around 70% in the Turkish population (76). In an epidemiological study conducted in Izmir, the prevalence of Turkey is reported as 0.49% and equal to the RA in the population (77).

2.7.2.1. Pathogenesis

The fact that many HLA and non-HLA genes have been investigated in the pathogenesis of AS shows that genetic factors have an important role. The gene that has the most important role in etiopathogenesis is HLA B27. This antigen is a class-I MHC molecule. (78). However, the underlying molecular mechanism has not been fully explained yet. Although the genes of the HLA locus are found in every cell, it is known to be more common in antigen presenting cells (79).

2.7.2.2. Clinical Presentation

The first symptom of AS is morning stiffness and low back pain. The characteristic of this complaint, starts gradually and continues at least three months, the stiffness is more in the morning or after resting, and the complaints decrease with exercise and movement. Morning stiffness can last up to three hours and most patients may not be able to distinguish between stiffness and back pain. Good response to non-steroidal anti-inflammatory drugs (NSAIDs) and recovery with exercise are the most important characteristics of AS (80).

Spinal inflammation causes back pain and mobility stiffness. Spinal inflammation can manifest as spondylitis, spondyloarthritis or spondylodiscitis. In addition, inflammation can be seen in other locations. For example, inflammation in the peripheral arthritis axial skeleton, anterior uveitis and enthesitis can be seen (81,82). Effecting of other organs such as the heart is rare (83).

2.7.2.3. Laboratory

C reactive protein (CRP) and erythrocyte sedimentation rate (ESR) increase in only 50-70% of the patients and their place in determining the disease activity is limited. Mild normochromic and normocytic anemia may be present. Elevated serum IgA levels are common, and elevated alkaline phosphatase levels are also seen in severe disease. (75, 84, 85).

2.7.2.4. Diagnosis

In 1984, Modified New York criteria, which are still widely used, were developed and are still in use (Table2.2.) (123). Inflammatory back pain has been added to these new criteria. A radiological finding (bilateral stage 2 and unilateral stage 3 sacroiliitis) in addition to a clinical criterion is sufficient for the diagnosis of AS (86).

None of the criteria are helpful in early diagnosis but are guiding in classifying the disease. With the development of the magnetic resonance imaging (MRI) technique, sacroiliitis can now be detected at an early stage. Detection of active sacroiliitis in MRI has been shown to emerge over time, also indirect radiography (87). The detection of sacroiliitis with MRI in AS patients with inflammatory low back pain but normal direct radiography is very essantial for determining the early stage of disease, and it is accepted that radiographic sacroiliitis becomes prominent in time and meets the Modified New York criteria (79).

Table 2.2. Modified New York Criteria (1984) for Ankylosing Spondylitis

Clinical criteria
• Low back pain and stiffness which improves with activity for more than three months
• Limited range of motion of the lumbar spine in both forward and lateral bending.
• Limitation of chest expansion relative to normal values correlated for age and sex
Radiological criteria
• Sacroiliitis grade ≥2 bilaterally
• Sacroiliitis grade 3 to 4 unilaterally

Note: Diagnosis of AS is made if the patient fulfills at least one radiological and one clinical criteria. Source: Copyright © 1984 American College of Rheumatology. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum.* 1984;27(4):361–368.

2.7.2.5. Non-pharmacologic Treatment

The aim of the applied treatments is to relieve stiffness and joint pain, slow down structural damage, and, if possible, prevent it. Patient education and exercise are crtical for the therapy and are used as a complement to pharmacological treatments. Physical Therapy and Rehabilitation is the most crucial approach in the therapy of AS with proven effectiveness.

The most important goals are regular exercise to reduce or slow down spinal limitation, maintain functional status, and reduce pain and stiffness (88). Group exercise for this purpose is more beneficial than individual home exercise (74).

2.7.2.6. Pharmacologic Treatment

Commonly prescribed NSAIDs have proven efficacy for first-line therapy in peripheral and axial complaints (including arthritis and enthesitis). In a relatively short period such as 48-72 hours, show the effect on the symptoms of pain and stiffness (89). The positive response to NSAIDs has been accepted as an indicator that low back pain has an inflammatory character, and included in many classification criteria. Pain and stiffness symptoms decreased after NSAID use in 70-80% of A.S patients. In cases of

active disease, it may be necessary to use a single NSAID at the highest tolerated dose (90).

Although systemic corticosteroids have dramatic and important effects in RA or SLE, these effects are not in question for treatment of AS (89).

DMARDs have not as effectiveness in AS as in RA. It is known that using of the drugs cannot prevent progression of AS in axial skeletal involvement and that their benefit is limited in patients with peripheral involvement (91).

Sulfasalazine (SSZ) is the most studied DMARD in the treatment of AS. In a recently published Cochrane review, SSZ was effective only on morning stiffness and peripheral joint complaints compared to placebo (92). According to a meta-analysis published in 2006, there was no evidence of its effect (93). In a recently published and well-designed study, the effectiveness of MTX treatment with subcutaneous 20 mg/week dose was not demonstrated during 16 weeks of treatment (94).

Despite adequate standard therapy, the use of biological agents has been recommended in active AS patients. The anti-TNF effect starts rapidly, stopping treatment causes relapse in the first six months when patients are almost completely. TNF inhibitors not only improve clinical symptoms, but also physical, function, and life quality, normalize the increased acute phase response, and suppress acute inflammatory signals seen in MRI. Studies shows that, TNF inhibitors have more efficacy with high CRP and ESR values before treatment and in patients with significant spinal inflammation in MRI (95,96). In a systematic review and meta-analysis published in 2014, therapy with TNF inhibitors improves the functional status and disease activity (97).

With a higher dose than RA, INF is used at a dose of 5 mg / kg, and ETA and ADA at the same doses (24).

2.7.3. Psoriatic Arthritis

Psoriatic arthritis (PsA) is known as inflammatory arthritis, a type of psoriasis associated with RF negativity. The ACR approved PsA as a separate disease in 1964. The ACR emphasized that PsA should be examined within seronegative spondyloarthritis. The condition in which PsA is associated with psoriasis and erosion and RF is negative is expressed as PsA. In addition, DIP (distal interphalangeal) joint and sacroiliac involvement, and asymmetric arthritis have been described (98,99).

While the general prevalence of PsA is 0.02-0.1%, the incidence of PsA with psoriasis varies between 7-40% (100).

2.7.3.1. Pathogenesis

As with most rheumatological diseases, the cause of PsA is not known exactly, but genetic, immunological, and environmental factors play a role in the pathogenesis (101).

Due to the increased frequency of PsA, genetic factors may important in the etiology was emphasized, and it was found that the possibility of developing PsA in family members of a patient with PsA increased 20-55 times (102).

Studies shows that, T cells are critical for immunogenic pathogenesis. In addition, both CD4 + and CD8 + T lymphocytes increased in skin and joints. Recognizing the role of T cells and cytokines in the pathogenesis has brought up the use of agents opposing these molecules in treatment (104). Increase in proinflammatory cytokines such as p40 (IL-12 and 23 common subunits), IL-1, IL-6, IL-8, TNF-α in the joint, by stimulating adhesion molecules such as vascular cell adhesion molecule (VCAM) -1 and ICAM-1 that accelerates the chemotaxis of T cells to the synovium (103).

Trauma is the leading environmental factor. The formation of inflammation in the joint after physical trauma is called "deep Koebner". The situation here is the chemotaxis of inflammatory cells to damaged tissue after trauma and the secretion of substance P from the nerve endings (105). Another factor is psychogenic stress, plays a triggering role in both psoriasis and PsA (106).

2.7.3.2. Clinical Presentation

Psoriatic is among the SpA according to the arthritis clinic and laboratory (101). 5 clinical involvement types were defined by Moll and Wright (107) in 1973 and are shown in Table 2.3. (124). There is overlap between the categories within this classification and therefore there are limitations in practice.

There are no specific laboratory findings for psoriatic arthritis. RF positivity is reported in 5-10% of patients. Antinuclear antibody positivity is detected in 10-14% for PsA. Hyperuricemia is detected in 10-20% of the patients, which is assosiated with severity of the skin disease (108).

Table 2.3. Joint involvements in psoriatic arthritis

Moll and Wright subgroups for PsA
Distal interphalangeal joint predominant arthritis (DIP) 5%
Asymmetrical oligoarticular arthritis 70%
Symmetrical polyarthritis 15%
Arthritis mutilans 5%
Predominant spondylitis 5%

2.7.3.3. Diagnosis

The Classification of Psoriatic Arthritis (CASPAR) group developed a new classification after their study in 2006. According to the CASPAR criteria, the presence of psoriasis is not mandatory for the diagnosis of PsA. To meet the criteria for PsA 2006 CASPAR, patients must score 3 according to the scoring indicated in parentheses from other criteria in addition to inflammatory articular disease. The specificity of the criteria is 98.7%, sensitivity is 91.4% (98, 109).

2.7.3.4. Treatment

The disease is mostly chronic and progressive and can cause permanent disability in many patients. Despite treatment, destruction and deformations develop in 20% of patients. Therefore, treatment is recommended continuously, not intermittently (110).

In mild disease, NSAIDs, analgesics, low-dose corticosteroids, or intraarticular steroid injections can be used. Among the DMARDs, methotrexate is the widely using in moderate-severe PsA (111). Another agent that can be used is sulfasalazine, is particularly effective in peripheral arthritis. However lack of effect of the psoriasis lesions, gastrointestinal side effects are significant disadvantages. Leflunomide, a pyrimidine antagonist, is an effective agent used for PsA (112).

Anti-TNF agents can be used for DMARD resistant cases (113). When the synovium and joint fluid of patients with PsA were examined, anti-TNF treatment in PsA came to the fore with a high level of TNF-α. Anti-TNF agents have been shown to reduce

joint symptoms and psoriatic lesions, and inhibit radiological progression (114, 115). ADA (40 mg every 2 weeks) and ETA (50 mg per week) are used in doses similar to RA, while INF is used at a similar dose (5 mg/kg) to AS (24).

Apart from anti-TNF agents, biological agents such as Ustekinumab (anti-IL-12/23) and Secukinumab (anti-IL-17A) are also used in the treatment of PsA.

Due to the clinical heterogeneity of psoriatic arthritis, treatment options are variable. International groups such as GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis) and EULAR published treatment recommendations in 2015. There are certain differences between these two guidelines.

Non-pharmacological applications, rehabilitation, and reconstructive surgical interventions are also used in addition to drug therapy (116-119).

3. MATERIALS AND METHODS

3.1. Study Desing and Population

This questionnaire was planned to apply to volunteers who are undergoing biological drug treatment at the Istanbul "Fatih Sultan Mehmet Training and Research Hospital" Rheumatology Service for 6 months.

Prior to conducting the study, an ethical committee approval was obtained from the Yeditepe University Clinical Research Ethics Committee on 30 December 2019, with the desicion number; 1142 and the approval from the head of the Rheumatology department of the Istanbul Fatih Sultan Mehmet (FSM) Training and Research Hospital was obtained.

Sample size calculation was calculated using Raosoft software (66). Assuming the population of patient with RD in the turkish population to be large (1-2%) at 90% confidence level, the expected presence of side effects was calculated as p = 50% and for 10% deviation, the minimum sample size calculated was 68.

Despite this study was carried during the COVID19 pandemic restrictions and thus contact with patients should been held minimum, 80 patients matching inclusion criteria were approached during the study duration.

3.1.1. Inclution Criteria

- Patients diagnosed with any rheumatological disease.
- Patients who use at least one of the following biological drug;
    - 1.Humira 2.Orencia 3.Simponi 4.Remicade 5.Mabthera 6.Amgevita 7.Enbrel 8.Cimzia 9.Remsiva 10.Redditux 11.Kineret 12.Prolia 13.Actemra 14.Stelara 15.Benlysta 16.Ilaris 17.Verxant 18.Copellor
- Patients having received at least one previous dose of the biological drug.
- Patients using these biological drugs while aged 18 and over.
- Patients who have accepted to participate and signed the study's written consent form voluntary.

3.1.2. Exlution Criteria

- Patient with mentally unstable.
- Patients unable to comprehend study question and patients who didnot complete their interviews were excluded.

3.2. Questionnaire

In this study, we conducted a by face to face interview questionnaire study that evaluates the discomfort or satisfaction of patients with the drug during their treatment and asks about the side effects they see. The first section collects patient's demographic information along disease and medication history. The second part of the questionnaire was developed using the "Brief Medication Questionnaire" (BMQ) (6) questionnaire modified slightly to fit biological drugs used in rheumatological disease. The third part collects the occurance of side effects associated commonly with biological agents use (144,145).

BMQ is a tool designed to determine patients' compliance with medication and, if any, the causes of incompatibilities. It has a version previously prepared for hypertension drugs. The tool was revised and adopted to biological drugs by two experts (a physician and a pharmacist).

By the questionnaire, the patients used biological medications were evaluated whether there were some side effects due to the biologic medication they used. Side effects were analysed in seven sections. These sections include; general drug side effects, side effects related to muscle and mobility, psychological side effects, injection site reactions, infusion-related reactions, infection related side effects, and allergic reaction. These adverse effects were evaluated according to generic name of biological drugs separately.

To summarize, in this three-part questionnaire study, in the first part, there is information obtained about the demographic characteristics of the patients, the drugs they used and discontinued, and the infections they have had during this period. In the second part, there are questions that we expect the patient to evaluate by themselves in terms of whether the biological drug treats the disease and the discomfort of the patient. The first

and second parts were adapted for the patients who are receiving biological treatment for their rheumatologic disease, based on the "Brief Medication Questionnaire" (6). In the last part, a table containing biological drug side effects present of drug leaflet was prepared by evaluating general drug side effects, and patients are expected to mark the side effects they see. The questionnaire is presented in the ‘Appendices’.

3.3. Data Collection

Patients were given an appointment by the nurses according to the periods of the biologic dose application. Patients who come for an appointment were also being examined by the doctors. A maximum of 4 patients were given an appointment a day.

Throughout the study, the hospital was visited according to the appointments of the patients. After the thesis study and its purpose were explained to the patients who were on at least the second dose and who were 18 years old and above, they were asked to sign an informed consent form if they volunteered. The questionnaire was read aloud to the patients and marked by the researcher, the patients who requested it filled in the questionnaire themselves.

The survey data was entered by the researcher into the SPSS software (Statistical Package for Science Service) version 25.

3.4. Statistical Analysis

Data were analyzed using SPSS software version 25 in this study. Descriptive analysis is expressed using means and ± standard deviations for continuous data and frequencies and percentages for categorical data. Non-parametric tests were used for the data that did not normally distributed and for the data with small sample size. Relationships between categorical and nonparametric variables were analyzed using Pearson's chi-square test. Besides, the two-tailed Pearson correlation test was used to evaluate the relationship between normally distributed variables. One-way ANOVA followed by the Post-Hoc Tukey test was used to analyze the statistical significance of independent groups (nonparametric test, Kruskal Wallis of variance analysis). P values <0.05 were considered as statistically significant.

4.RESULTS

4.1. Demographics and Characteristic Patients Information

Among patients matching the studies inclusion criteria, 80 patients were approached and invited to the study, only 60 patients have accepted to participate and fully completed their interviews. Additionally, the number of patients in the study had to be limited due to the Covid -19 pandemic. Among the 60 patients, 46 (76.7%) were female and 14 (23.3%) were male. The mean age of the patients applied quetinaire was 50.85 ± 1.7 years. There is no difference the between the mean of ages female and male groups.

The educational status of the patients was 30 (50%) elementary-school graduates, 7 (11.7%) middle-school graduates, 13 (21.7%) high-school graduates, and 10 (16.7%) university graduates.

Table 4.1. Demographics and Characteristic Patients Information

Demographics	TOTAL (n:60)	INF (n:27)	TCZ (n:14)	RTX (n:9)	SECU (n:4)	ETA (n:3)	Other(n:3)
Age (years) mean ± SD	50.9 ± 1.7	49.7 ± 10.5	49.5 ± 14	56.3 ± 14.7	38 ± 11.7	65 ± 15	53.7 ± 17
Gender total%							
Female (76.7%)	46	21	13	6	1	2	3
Male (23.3%)	14	6	1	3	3	1	0
Education total%							
Elementary (50%)	30	12	6	7	1	2	2
Middle-School (11.7%)	7	3	1	1	2	0	0
High-School (21.7%)	13	9	1	1	0	1	1
University (16.7%)	10	3	6	0	1	0	0

4.2. Patients Information Related to Diagnose

Since the thesis study was conducted by an observational questinaire in the rheumatology service in the hospital, the distribution of the diseases was as follows; 39 (65%) patients with RA, 7 (11.7%) patients with SLE, 6 (10%) patients with AS, 6 (10%) patients with PsA, and 2 (3.8%) patients with Behçet's disease (Figure 4.1.).

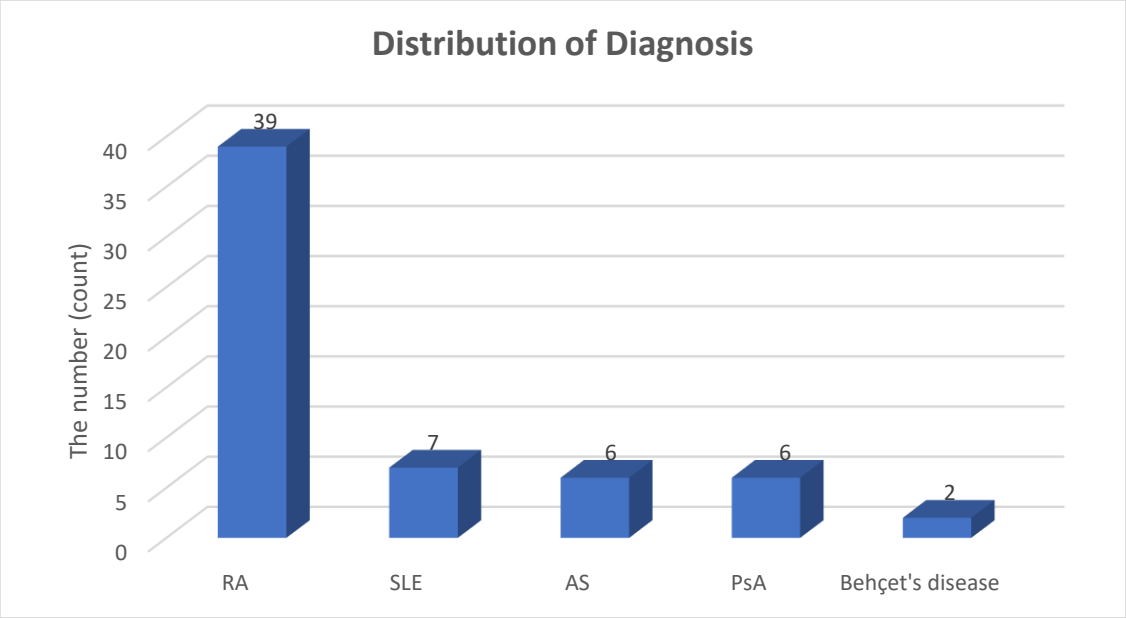

Figure 4.1. Distrubiton of the diseases

4.2.1. Relationship between Diagnosis and Treatment Duration

The treatment duration of the patients participating in the questionnaire is 14.36 ± 1.46 years for RA patients, 8.14 ± 1.7 years for SLE patients, 15.17 ± 3.15 years for AS patients, 21.50 ± 4.08 years for PsA patients, and 19 ± 1.20 years for Behçet's disease patients.

There is no statistical significance between diseases and duration of treatment with one-way ANOVA and Post-Hoc Tukey tests. (F(55.4)=1.902 P=0.12>0.05) (Table 4.1.). although the treatment duration of PsA and Bechet's disease are long than the other diseases, Post-hoc tests not showed a difference in the treatment duration of PsA and Bechet's disease.

Table 4.2. Mean duration of treatment

Diagnose	N	MEAN	± SD
SLE	7	8.14	1.70
RA	39	14.36	1.46
AS	6	15.17	3.15
Behçet's D.	2	19.00	1.20
PsA	6	21.50	4.08

a. Uses Harmonic Mean Sample Size = 4,991.

4.3. Relationship between Diagnosis and Treatment Duration

The distribution of biologic medication uses among 60 patients participating in the questionnaire is as follows, 27 (45%) patients was using infliximab, 14 (23.3%) patients tocilizumab, 9 (15%) patients rituximab, 4 (6.7%) patients secukinumab, 3 (5%) patients etanercept and the other three patients were adalimumab, anakinra, and certolizumab pegol, respectively. These last three drugs have been determinate as 'others' and represent 5% of patients. Infliximab, tocilizumab and rituximab are more used biological drugs in this study.

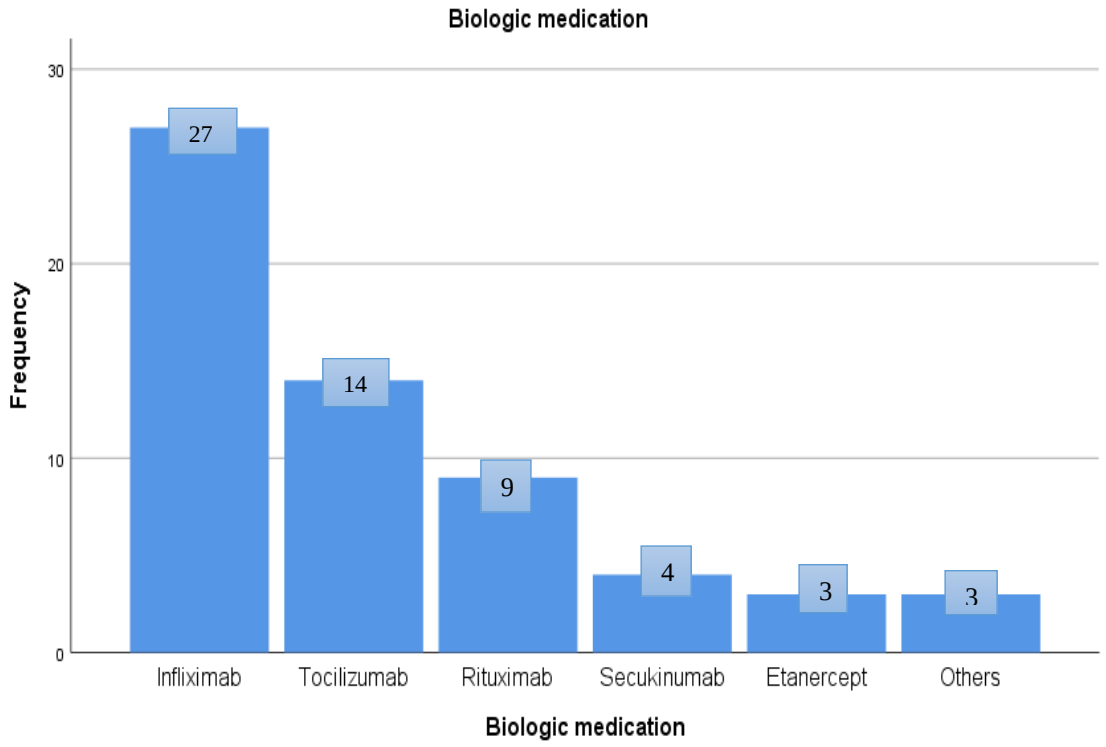

Figure 4.2. Biologic medication distrubition

4.3.1. Distribution of Diseases According to Using Biological Medication

To evaluate **t**he frequent use of biological drugs according to disease types, biological drug distribution was analyzed as follows. Of the 27 patients using infliximab, 18 (67%) were using for RA treatment, 4 (15%) for AS, 3 (11%) for PsA, and 2 (7%) for Behcet's disease**.** Of the 14 patients using tocilizumab, 11 (78%) were treated for RA treatment and 3 (22%) for SLE. Of the 9 patients using rituximab, 5 (56%) were treated for RA treatment and 4 (44%) for SLE. Of the 4 patients using secukinumab, 2 (50%) for AS and 2 (50%) for PsA treatment. Of the 3 patients using etanercept all of them were using for RA treatment. In addition, other medication which adalimumab and anakinra using for RA treatment while certolizumab pegol for PsA treatment.

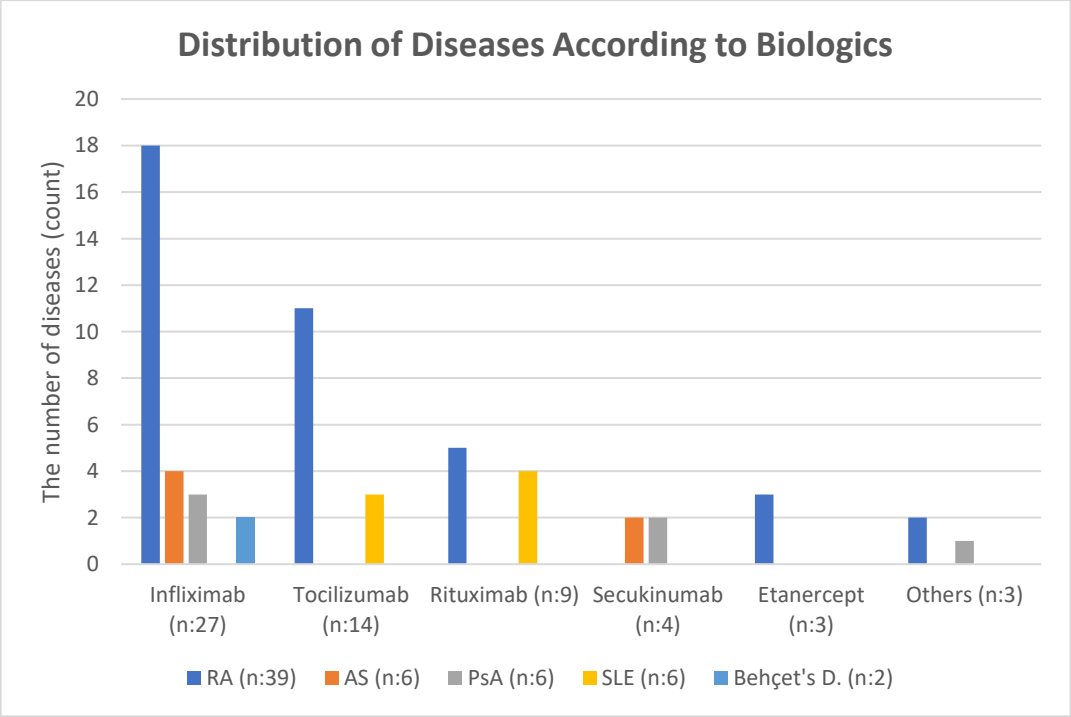

Figure 4.3. Distribution of Diseases for Using Biological Medication

4.3.2. Findings About Duration of Biologic Medications

The average duration of biologic drug use of patients was analyzed by ANOVA and found as follows; 6.48 ± 0.78 years for patients using infliximab, 4.14 ± 0.38 years for tocilizumab, 4.11 ± 1.59 years for rituximab, 2.5 ± 1.50 years for secukinumab, 1.33 ± 0.33 years for etanercept and 1 year for others.

Infliximab is used longer than other biological drugs. There is statistical significance according tests; one-way ANOVA and Post-hoc Tukey's ($F(59.4)=3.058$ $p=0.017<0.05$).

Table 4.3. Mean duration of biological drugs

Biological Drugs	N	MEAN	±SD
Others	3	1.00	0
Etanercept	3	1.33	0.33
Secukinumab	4	2.50	1.50
Rituximab	9	4.11	1.59
Tocilizumab	14	4.14	0.38
Infliximab*	27	6.48*	0.78

a. Uses Harmonic Mean Sample Size =5,281.

4.3.3. The Duration of Biologic Drug Changes according to the Patients' Diagnosis

The using duration may be changed in the biologic drugs according to the patients' diagnosis. So, the changes of duration are presented as follows; 4.62 ± 0.56 years for RA patients, 8.17 ± 2.37 years for AS patients, 5.83 ± 1.58 years for PsA patients, 3 ± 0.65 years for SLE patients, and 1 year for Behçet's disease patients. ANOVA was showed significantly long duration in AS treatment than SLE ($p<0.05$).

According to Post-Hoc Tukey's test, there is relationship between medication duration and diagnose ($F(55.4)=2.428$ $P<0.05$).

Table 4.4. Mean duration of biologics according to diseases

Diagnose	N	Mean	±SD
Behçet's D.	2	1.00	0
SLE*	7	3.00	0.65
RA	39	4.62	0.56
PsA	6	5.83	1.58
AS*	6	8.17	2.37

4.3.4. The Relationship between the Duration of Disease and Biological Drug Use

To evaluate whether the dissatisfaction and discontinuous related with disease or treatment duration, two-tailed Pearson Correlation analysis was performed. There is a significant linear relationship between duration of trearment and duration of biologic treatment, by the two-tailed Pearson Correlation (r=0.267, p=0.04).

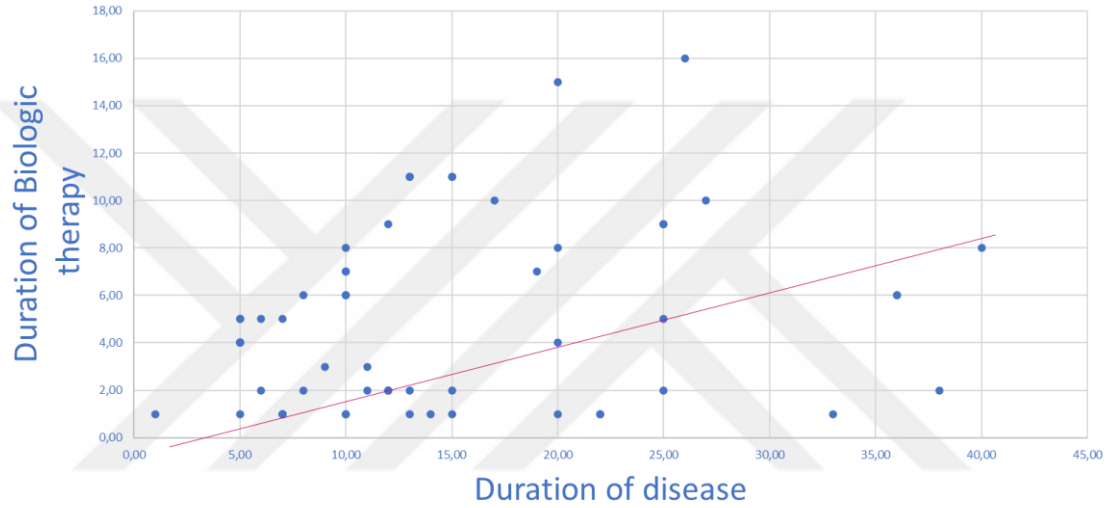

Figure 4.4. The Relationship between the Duration of Disease and Biologic therapy

4.4. Other Medications Used with Biological Medication

Other medications may be affected the clinical and pharmacological profiles of biological drugs. Therefore, in the questionnaire study, it was asked, whether the patient used any drug other than biological drug. It was observed that 16 different group of drugs were used, except for biological drugs. These are, DMARDs, antimalarials, PPIs, food supplemants, antidiabetics, antihypertensives, antiasthmatic and antidepressant drugs.

The number of using non-biological drugs (NBD) was observed to be approximately 4.44 ± 2.23. This NBD numbers changes with every biological drug. The number of NBD drugs, are as follows; 4.11 ± 2.08 for the patients using infliximab, 5.57 ± 2.21 for the patients using tocilizumab, 4.46 ± 2.78 for the patients using rituximab, 2.5 ± 1.73 for the patients using secukinumab, 6.67 ± 1.53 for the patients using etanercept and 3.33 ± 3.05 for the patients using other biologic drugs.

In addition, the number of rheumatologic NBD are also checked. The rheumatologic NBD means drugs using only related to the rheumatological disease. The numbers are as follows, 1.93 ± 1.49 for the patient using infliximab, 2.93 ± 1.07 for the patient using tocilizumab, 2.11 ± 1.67 for the patient using rituximab, 1.75 ± 1.26 for the patient using secukinumab, 3.33 ± 0.58 for the patient using etanercept and 1.33 ± 1.15 for the patient using other biologic drugs.

Table 4.4. Mean number of non-biologic drugs

Biological Drugs	Number of NBD	Number of Rheumatologic NBD
Infliximab (n:27)	4.11± 2.08	1.93 ± 1.49
Tocilizumab (n:14)	5.57 ± 2.21	2.93 ± 1.07
Rituximab (n:9)	4.46 ± 2.78	2.11 ± 1.67
Secukinumab (n:4)	2.5 ± 1.73	1.75 ± 1.26
Etanercept (n:3)	6.67 ± 1.53	3.33 ± 0.58
Others (n:3)	3.33 ± 3.05	1.33 ± 1.15

NBD: non-biological drugs

4.4.1. The Relationship Between the Number of NBD and Rheumatic NBD

According to the two-tailed Pearson Correlation analysis, as the number of NBD increases, rheumatologic NBD also increase. There is a significant linear relationship between the number of NBD and rheumatic NBD (r=0.738, p=0.01).

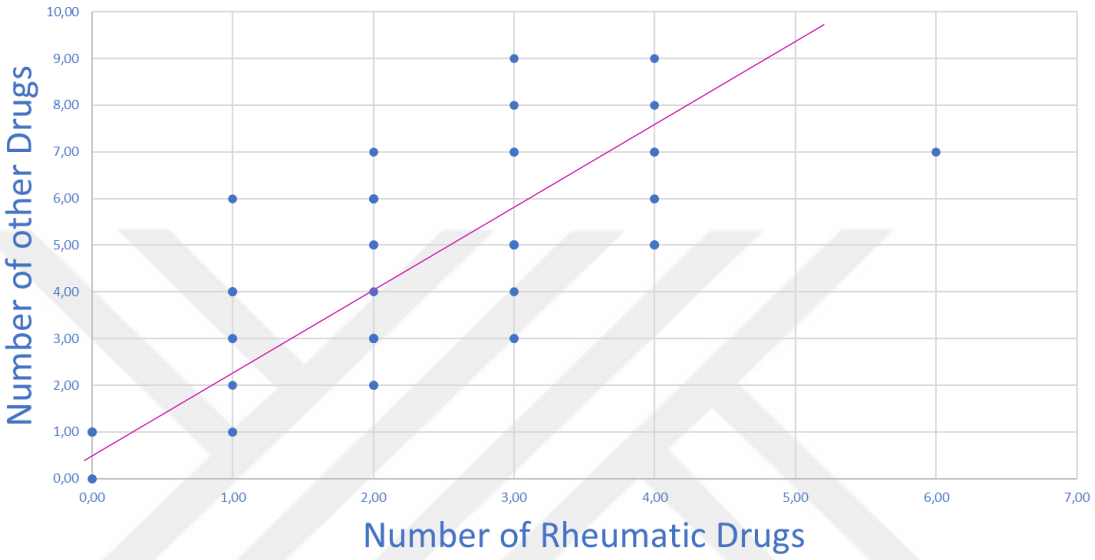

Figure 4.5. The relationship between the number of NBD and rheumatic NBD

4.4.2. The Relationship Between the Numbers of Non-biologic Drugs and Diseases

The one-way ANOVA test showed an increased NBD use in RA diease groups. $F(59.4)= 4.055$ $p=0.006<0.05$. NBD was decreased in the other disease types, but not signifcant. The NBD in RA patients is 4.77 ± 0.36 and 1.33 ± 0.21 in AS patients. According to the post-hoc Tukey's test, there is only a significance in NBD between RA and AS. RA patients are using more medication than AS patients ($p=0.003$).

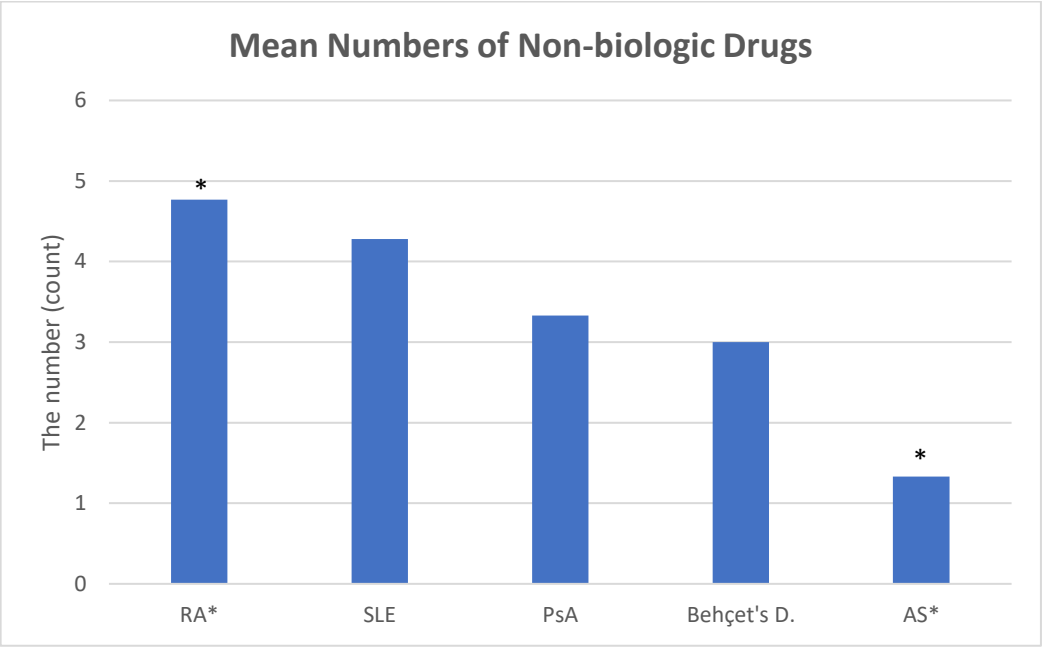

Figure 4.6. Mean numbers of non-biologic drugs according to diseases

4.5. Findings About Discontinuous of Biological Drugs

Throughout the diseases, it is important to be able to maintain and quey rational drug use for recovery. Because that, the patients were evaluated whether they used biological drugs before or not. 22 (36.67%) of the patients stated that they had used at least one biological drug before, other 38 (63.33%) patients stated that they had not used biological drugs before.

7 (25.92%) of the patients using infliximab (n=27), 7 (50%) of the patients using tocilizumab (n=14), 1 (11,11%) of the patients using rituximab (n=9), 1 (25%) of the patients using secukinumab (n=4), 3 (100%) of the patients using etanercept(n=3), and 3 (100%) of the patients using other biologics (n=3) had previously used another biological drug.

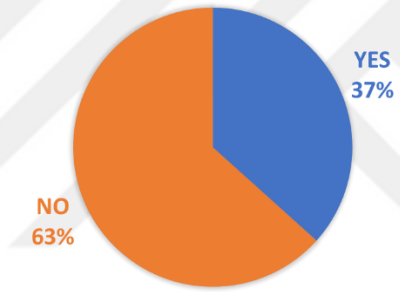

Figure 4.7. Discontinuous of Biological Drugs

Table 4.5. The number of patient who used biological medication before

Usage of Another Biologic Before	YES (22/60)	NO (38/60)
Infliximab (n:27)	7	20
Tocilizumab (n:14)	7	7
Rituximab (n:9)	1	8
Secukinumab (n:4)	1	3
Etanercept (n:3)	3	0
Others (n:3)	3	0

Some of patients used more than one biologic drug during treatment period. 38 out of 60 (63.33 %) patients have not used biologic medication before, so, they are currently on the first biologic therapy. The number of patients on the second biologic therapy was 17 (28.33%), on the third biologic therapy was 3 (5%), and on the fourth biologic therapy was 2 (3.33%). Data not analyzed statically due to the number of patients or distribution but it presented in table 4.6.

Table 4.6. The number of patients according to their biological therapy

	1. Biologic Therapy	**2. Biologic Therapy**	**3. Biologic Therapy**	**4. Biologic Therapy**
Infliximab (n:27)	20	5	2	0
Tocilizumab (n:14)	7	5	0	2
Rituximab (n:9)	8	1	0	0
Secukinumab (n:4)	3	1	0	0
Etanercept (n:3)	0	3	0	0
Others (n:3)	0	2	1	0
TOTAL	**(%63,33) 38**	**(%28.33) 17**	**(%5) 3**	**(%3.33) 2**

The reason of discontinuous or interruption of biologic drugs is very important to understand and to solve clinical treatment problems. Previously used medications are as follows; infliximab was used 11 times, etanercept 6 times, adalimumab 4 times, tocilizumab 3 times, golimumab 2 times, secukinumab 1 time, rituximab 1 time, certolizumab pegol 1 time. Also, not analysed statically due to the number of patients or distrubution.

The biologic medications in last period are shown in detail in the table 4.7- 4.8 according to the currently using biologics. Also, not analyzed statically due to the number of patients or distribution.

Table 4.7. The number of patients' older biologic medications-1

	Etanercept (n:6)	Infliximab (n:11)	Adalimumab (n:4)	Golimumab (n:2)
Infliximab (n:27)	2	3	3	1
Tocilizumab (n:14)	2	3	1	1
Rituximab (n:9)	0	1	0	0
Secukinumab (n:4)	0	1	0	0
Etanercept (n:3)	0	2	0	0
Others (n:3)	2	1	0	0

Table 4.8. The number of patients' older biologic medications-2

	Certolizumab (n:1)	Rituximab (n:1)	Tocilizumab (n:3)	Secukinumab (n:1)
Infliximab (n:27)	0	0	0	0
Tocilizumab (n:14)	1	0	3	0
Rituximab (n:9)	0	0	0	0
Secukinumab (n:4)	0	0	0	0
Etanercept (n:3)	0	1	0	0
Others (n:3)	0	0	0	1

4.5.1. The Reasons of Discontinuous of Biological Drug

During biological drug therapy, some medications was discontinued, while some were interrupted for some clinical reasons. The frequency of the reasons for discontinuation or interruption of biological drugs are as follows: 16 patients were discontinued due to ineffectiveness, 7 patients due to infusion reaction, 3 patients due to unadherance, 2 patients due to allergic reaction, and 1 patient due to injection site reaction.

The most common reasons for discontinuation of biologic drugs are as follows; Ineffectiveness ratio for infliximab were observed in 7 (63.63%) patients, for etanercept were observed in 3 (50%) patients, for golimumab were observed in 2 (100%) patients, for certolizumab pegol were observed in 1 (100%) patient, for rituximab were observed in 1 (100%) patient. Allergic reaction ratio for adalimumab were observed in 2 (50%) patients. Lastly, infusion reaction ratio for tocilizumab were observed in 3 (100%) patients. In addition, other reasons for drug quitting are shown in the *table 4.9*. Also, not analyzed statically due to the number of patients or distribution.

According to questionnaire results, all class of biologic medication quitted once before.

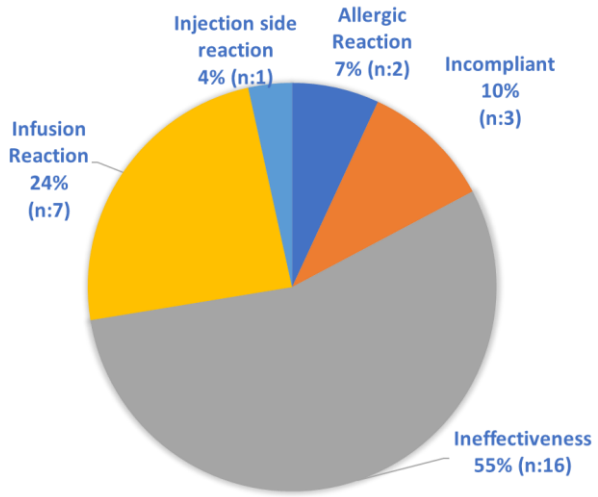

Figure 4.8. Distribution of reason for discontinuation

Table 4.9. The number of reasons for discontinuation of biological drugs

Reasons of Discontinuation	Ineffectiveness	Infusion Reaction	Nonadherence	Allergic Reaction	Injection side reaction
Etanercept (n:6)	3	1	1	0	1
Infliximab (n:11)	7	3	1	0	0
Adalimumab (n:4)	1	0	1	2	0
Golimumab (n:2)	2	0	0	0	0
Certolizumab (n:1)	1	0	0	0	0
Rituximab (n:1)	1	0	0	0	0
Tocilizumab (n:3)	0	(%100) 3	0	0	0
Secukinumab (n:1)	1	0	0	0	0
TOTAL	(%55.17) 16	(%24.14) 7	(%10,34) 3	(%6,9) 2	(%3.45) 1

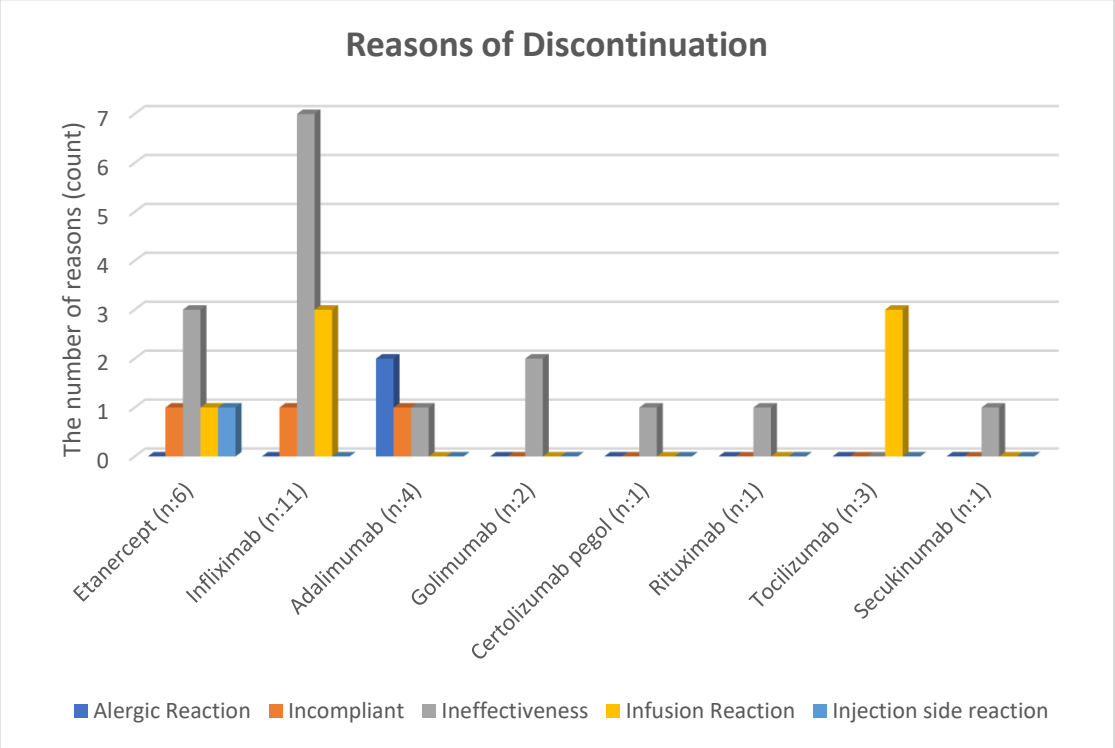

Figure 4.9. Distribution of reason for discontinuation according to biologics

4.6. The findings about Patients' Infections, Antibiotic Usage and Vaccination

During biological therapy, the infections, antibiotic usage and vaccination of patients might change or affect the clinical responsive of biological therapy and recovery of disease. Evaluating by questionnaire whether they had any infections in the last 6 months are crucial to maintain the therapy. The results of questionnaire showed that 43 patients did not have infection, and 17 patients had an infection. Among the patients with infections, 8 patients had urinary tract infections, 5 patients had upper respiratory tract infections, 2 patients had fungal infections, and 2 patients had tuberculosis.

Dramatically, 2 (100%) tuberculosis infection and 5 (62.5%) urinary tract infection were observed in the patients using infliximab. Infections seen in patients using other biologics are also detailed in the table 4.10.

Table 4.10. The number of patients according to the infections

Infections	Urinary I. (n:8)	Upper Respiratory I. (n:5)	Tuberculosis (n:2)	Fungal I. (n:2)
Infliximab (n:27)	5	1	2	1
Tocilizumab (n:14)	1	2	0	1
Rituximab (n:9)	2	0	0	0
Secukinumab (n:4)	0	2	0	0
Etanercept (n:3)	0	0	0	0
Others (n:3)	0	0	0	0

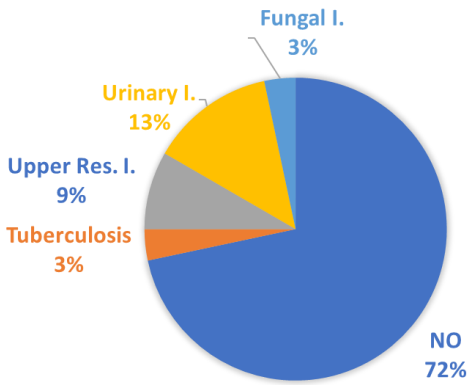

Figure 4.10. Distribution of infections

Also, they were asked whether they used antibiotics and whether they were vaccinated in the last 6 months to evaluate immune system and clinical history of patients.

The ratio of patients used antibiotics is 27, patients not used antibiotics is 33, vaccinated patients is 5 and non-vaccinated patients is 55. All vaccinated patients were vaccinated for hepatitis B treatments.

Antibiotic usage and vaccination detailed in the table 4.11. and 4.12.

Table 4.11. The number of patients according to the antibiotic usage

Antibiotic Usage	Yes (n:27)	No (n:33)
Infliximab (n:27)	15	12
Tocilizumab (n:14)	4	10
Rituximab (n:9)	4	5
Secukinumab (n:4)	2	2
Etanercept (n:3)	2	1
Others (n:3)	0	3

Table 4.12. The number of patients according to the vaccination

Vaccination	Yes (n:5)	No (n:55)
Infliximab (n:27)	2	23
Tocilizumab (n:14)	1	13
Rituximab (n:9)	2	7
Secukinumab (n:4)	0	4
Etanercept (n:3)	0	3
Others (n:3)	0	3

4.7. Patient Satisfaction about Biological Therapy

The patients were evaluated whether they benefited from the biologic therapy and bothered using the biologic therapy in this study. According to questionnaire results, 43 (71.7%) of the patients stated that they benefited from the biologcal treatment and 17 (28.3%) patients did not. However, 55 (91.7%) patients stated that they not bothered using the biologic drugs, and 5 (8.3%) patients stated that they bothered using it. Ratio of benefit and bathering changed in this patient population using biological thaerapy.

Although there were 17 patients who indicated that they did not benefit from the biological therapy, 13 of these patients stated that they not bothering and the continuated to the use of biological drugs. Only 4 of these patients stated that they bothered and not benefited. And, one of the 5 patients who bothered using the drug finds the drug beneficial at the same time.

According to the results of questianaire data, those who stated the drug as beneficial and who are bothering with the drug using are given in the Table 4.13 and 4.14 in detail.

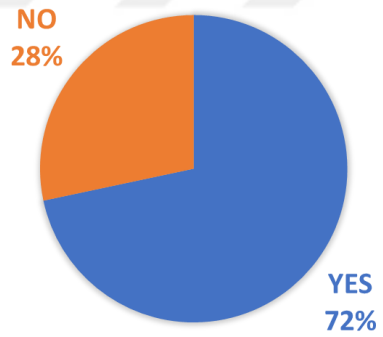

Figure 4.11. Distribution of benefit

Table 4.13. The number of patients according to the benefit from the biological drugs

BENEFIT	Yes (n:43)	No (n:17)
Infliximab (n:27)	20	7
Tocilizumab (n:14)	9	5
Rituximab (n:9)	8	1
Secukinumab (n:4)	3	1
Etanercept (n:3)	1	2
Others (n:3)	2	1

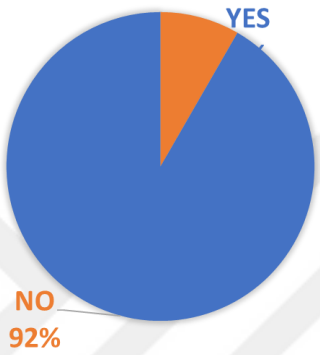

Figure 4.12. Distribution of bothering

Table 4.14. The number of patients according to biological drug bothering

BOTHER	Yes (n:5)	No (n:55)
Infliximab (n:27)	3	24
Tocilizumab (n:14)	1	13
Rituximab (n:9)	0	9
Secukinumab (n:4)	0	4
Etanercept (n:3)	1	2
Others (n:3)	0	3

4.7.1. Patient's Other Concerns about Biological Therapy

To understand the other concerns related with the satisfactions and dicontinous of biological drugs, the patients were evaluated to rate 6 concerns they might have with the drug they used. The concerns are hard to remember the doses, hard to apply doses, medication gives pain, medication hard to pay, having unwanted side effects, worrying long-term side effects and their answers of patients were scored as none, a little, and a lot.

More of patients did not have concerns such as hard to remember the doses (n=55), hard to apply doses (n=57), medication gives pain (n=57), medication hard to pay (n=59), having unwanted side effects (n=59) and worrying long-term side effects (n=43) during biological therapy. The frequences of patient concerns analysed and shown separately *(Table 4.15).*

The answers to these problems were as follows; 2 patients stated that the doses were very hard to remember, 1 patient found a little hard, and 55 patients did not find it hard at all. 3 patients stated that they found the drug a little hard to apply, 57 patients stated that they did not find it hard. 3 patients stated that the administration of the drug gives pain a little, 57 patients stated that it did not give pain to them. There was 1 patient who found medication a little hard to pay, 59 patients stated that they did not find it hard to pay. There was 1 patient who stated that the drug had unwanted side effects, 59 patients stated that they did not experience any unwanted side effects. There were 3 patients who stated that they were a lot worried about the long-term effects of the drug, there were 14 patients who stated that they were a little worried, and 43 patients who said they did not worry at all.

The distributions of corcern according to the biologics is shown in Table 4.16.

Table 4.15. General distribution of concerns about biological drugs.

CONCERNS ABOUT BIOLOGIC	None	A little	A lot
Hard to remember the doses	55	3 (5%)	2 (3.33%)
Hard to apply doses	57	3 (5%)	-
Medication gives pain	57	3 (5%)	-
Medication hard to pay	59	1 (1.67%)	-
Having unwanted side effects	59	-	1 (1.67%)
Worrying long term side effects	43	14 (20,33%)	3 (5%)

Table 4.16. Distribution of cornerns about biological drugs

	Infliximab(n:27)			Tocilizumab (n:14)			Rituximab (n:9)			Secukinumab (n:4)			Etanercept (n:3)			Others (n:3)		
	None	A little	A lot	None	A little	A lot	None	A little	A lot	None	A little	A lot	None	A little	A lot	None	A little	A lot
Hard to remember the doses	23	3	1	13	0	1	9	0	0	4	0	0	3	0	0	3	0	0
Hard to apply doses	24	3	0	14	0	0	9	0	0	4	0	0	3	0	0	3	0	0
Medication gives pain	24	3	0	14	0	0	9	0	0	4	0	0	3	0	0	3	0	0
Medication hard to pay	26	1	0	14	0	0	9	0	0	4	0	0	3	0	0	3	0	0
Having unwanted side effects	26	0	1	14	0	0	9	0	0	4	0	0	3	0	0	3	0	0
Worrying long term side effect	17	9	1	12	1	1	7	1	1	2	2	0	2	1	0	3	0	0
Any other concerns	27	0	0	14	0	0	9	0	0	4	0	0	3	0	0	3	0	0

4.8. Patients's Adverse Effects

By the questionnaire, the patients used biological medications were evaluated whether there were some side effects due to the biologic medication they used. Side effects were analysed in according to side effects frequency. No adverse effect (AE) were observed in approximately half of the patients (47%); 1 AE (n:6), 2 AE (n:5), 3 AE (n:3), 4 AE (n:6) and 5 AE (n:2) etc. The frequencies of adverse effects were shown in table 4.17. and adverse effects according to generic name of biological drugs separately in tables, respectively.

Adverse Effects (number)	Adverse Effects (frequency)
0	28
1	6
2	5
3	3
4	6
5	2
6	2
7	4
9	3

Table 4.17. The Adverse Effects Observed in Biologics

Common side effects include insomnia (18.33%), headache (15%), feeling restless (15%), muscle stiffness (13.33%), blurred vision (11.66%), and difficulty to move (11.66%).

Among the most common drug side effects, insomnia were observed in 11 patients (infliximab 5, tocilizumab 2, rituximab 3 and etanercept 1), 9 patients for headache (infliximab 6, tocilizumab 2, rituximab 1), 9 patients for feeling restless (infliximab 5, tocilizumab 1, secukinumab 2, and etanercept 1), 8 patients for muscle stiffness (infliximab 3, tocilizumab 2, secukinumab 2, and etanercept 1), 7 patients for blurred vision (infliximab 3, tocilizumab 1, rituximab 2, and etanercept 1), 7 patients for trouble to move (infliximab 3, tocilizumab 1, secukinumab 2, and etanercept 1). The side effects of biologics is shown in *Table 4.17*.

Unable to sit was observed in 6 patients (infliximab 3, tocilizumab 1, rituximab 1 and etanercept 1), 6 patients for rash and swelling (infliximab 2, tocilizumab 1, and rituximab 3), 6 patients for weight gain (infliximab 4, and secukinumab 2), 5 patients for easily tired (infliximab 2, tocilizumab 1, and etanercept 2), 4 patients for diarrhe (infliximab 4), 4 patients for anxiety (infliximab 4). The side effects of biologics is shown in *Table 4.18.*

According to the Pearson chi-square test, easily tired is significant (x^2 =14.874 p=0.011).

Dyspnea was observed in 4 patients patients (infliximab 3, and etanercept 1), 4 patients for allergic reaction (rituximab 4), 3 patients for constipation (infliximab 2, and tocilizumab 1), 3 patients for salivation (tocilizumab 1, and secukinumab 2), 3 patients for mounth dryness (rituximab 1, and secukinumab 2), 3 patients for hypotension (infliximab 3). The side effects of biologics is shown in *Table 4.19*.

According to the Pearson chi-square test, allergic reaction was seen statistically significant for 4 patients using only rituximab, (x^2= 24.286, p<0.001), salivation was seen statistically significant (x^2= 19.398, p=0.002) and dry mouth was seen statistically significant (x^2= 20.234, p=0.001).

Fever was observed in 3 patients (infliximab 2, and tocilizumab 1), 2 patients for polyuria (secukinumab 2), 2 patients for nausea (rituximab 2), 2 patients for weight loss (infliximab 2), 2 patients for tachycardia (infliximab 1 and rituximab 1), 2 patients for muscle trempling (tocilizumab 1, and etanercept 1). The side effects of biologics is shown in *Table 4.20*.

According to the Pearson chi-square test, nausea was only seen in 2 of 9 patient using rituximab and it is statistically significant (x^2= 11.724, p=0.039).

Memory loss was observed in 2 patients (rituximab 2), 2 patients for pain in injection (infliximab 2), 2 patients for sweating (infliximab 1 and tocilizumab 1), 2 patients for sore throat (infliximab 1 and tocilizumab 1), 2 patients for cough (infliximab 1 and tocilizumab 1). The side effects of biologics is shown in *Table 4.21*.

According to the Pearson chi-square test, memory loss was also seen in only patient using rituximab (2 of 9 patients) and it is statistically significant (x^2=11.724, p=0.039).

Feeling restless was observed in 2 patients (infliximab 1 and tocilizumab 1), 1 patient for low urination (rituximab 1), 1 patient for loss of concentration (etanercept 1), 1 patient for low motivation (infliximab 1). The side effects of biologics is shown in *Table 4.22*.

According to the Pearson chi-square test, loss of concentration was only seen in patient using etanercept (1 of 3 patient), and it statistically significant (x^2=19.322, p=0.002).

In addition, unseen side effects are, vomitting, sexual disfunction, suicadal thoughts, nausea after biologic, vomitting after biologic and hypertension.

Table 4.18. Distribution of adverse effects by biological drugs-1

Adverse Effects	Insomnia	Headache	Feeling Restless	Muscle Stiffness	Blurred Vision	Trouble to Move
Infliximab (n:27)	5	6	5	3	3	3
Tocilizumab (n:14)	2	2	1	2	1	1
Rituximab (n:9)	3	1	0	0	2	0
Secukinumab (n:4)	0	0	2	2	0	2
Etanercept (n:3)	1	0	1	1	1	1
Others (n:3)	0	0	0	0	0	0
TOTAL	**11**	**9**	**9**	**8**	**7**	**7**

Table 4.19. Distribution of adverse effects by biological drugs-2

Adverse Effects	Unable to Sit	Rash Swelling	Weight Gain	Easily Tired*	Diarrhea	Anxiety
Infliximab (n:27)	3	2	4	2	4	4
Tocilizumab (n:14)	1	1	0	1	0	0
Rituximab (n:9)	1	3	0	0	0	0
Secukinumab (n:4)	0	0	2	0	0	0
Etanercept (n:3)	1	0	0	2	0	0
Others (n:3)	0	0	0	0	0	0
TOTAL	**6**	**6**	**6**	**5**	**4**	**4**

Table 4.20. Distribution of adverse effects by biological drugs-3

Adverse Effects	Dyspnea	Allergic Reaction**	Consptitation	Salivation*	Mouth Dryness**	Hypotension
Infliximab (n:27)	3	0	2	0	0	3
Tocilizumab (n:14)	0	0	1	1	0	0
Rituximab (n:9)	0	4	0	0	1	0
Secukinumab (n:4)	0	0	0	2	2	0
Etanercept (n:3)	1	0	0	0	0	0
Others (n:3)	0	0	0	0	0	0
TOTAL	**4**	**4**	**3**	**3**	**3**	**3**

Table 4.21. Distribution of adverse effects by biological drugs-4

Adverse Effects	Fever	Polyuria	Nausea*	Weight Loss	Tachycardia	Muscle Trempling
Infliximab (n:27)	2	0	0	2	1	0
Tocilizumab (n:14)	1	0	0	0	0	1
Rituximab (n:9)	0	0	2	0	1	0
Secukinumab (n:4)	0	2	0	0	0	0
Etanercept (n:3)	0	0	0	0	0	1
Others (n:3)	0	0	0	0	0	0
TOTAL	**3**	**2**	**2**	**2**	**2**	**2**

Table 4.22. Distribution of adverse effects by biological drugs-5

Adverse Effects	Memory Loss*	Pain in Injection	Sweating	Sore Throat	Cough
Infliximab (n:27)	0	2	1	1	1
Tocilizumab (n:14)	0	0	1	1	1
Rituximab (n:9)	2	0	0	0	0
Secukinumab (n:4)	0	0	0	0	0
Etanercept (n:3)	0	0	0	0	0
Others (n:3)	0	0	0	0	0
TOTAL	**2**	**2**	**2**	**2**	**2**

Table 4.23. Distribution of adverse effects by biological drugs-6

Adverse Effects	Feeling Restless	Low Urination	Loss of Concentration*	Low Motivation
Infliximab (n:27)	1	0	0	1
Tocilizumab (n:14)	1	0	0	0
Rituximab (n:9)	0	1	0	0
Secukinumab (n:4)	0	0	0	0
Etanercept (n:3)	0	0	1	0
Others (n:3)	0	0	0	0
TOTAL	**2**	**1**	**1**	**1**

5. DISCUSSION AND CONCLUSION

In the thesis that conducted as a questionnaire study by including 60 patients, it was demosntrate that, patient satisfaction of biological therapy is high, therapy discontinuation can be preferable but usually not related with side effect and during therapy period there is no severe side effect. Otherwise, some patients are worried about the long-term side effects of biologics. The evaluation of patient satisfaction, discontuniation the biological therapy and safety of biological drugs are also related to patients' demographic characteristics, disease, duration of treatment, number of other medications further the comorbid disease.

According to study, the average age was 50.85 ±1 and biological drug using ratio was more common in women (76.7%). They were more common in all diseases except AS patients. According to the literature, ankylosing spondylitis incidence in men is 2:1 and rheumatoid arthritis in women is 3:1 (60,61,75). In the study, 66.6% of AS patients were men and 80.85% of RA patients were women. In addition, the most common disease treated with biological drug was RA (65%) which also has the highest incidence among rheumatologic diseases (137). Besides, %50 of patients were elementary school graduates. According to Sharon J. et al., educational status may be one of the factors affecting patient compliance and thus therapy effectiveness (138).

Patients' mean treatment duration was range from the 8.14 ± 1.70 and 21.50 ± 4.08 years according to diseases but study shown that there was no relation of diseases' duration. Biological therapy duration was range from the 1 to 8.17 ± 2.37 years and there was relation, biological therapy in AS patients (8.17 ± 2.37) significantly had longest duration of time ($F= 2.43$, $p<0.05$). According to study related with patient biological therapy response, the rheumatological disease duration range was 1–42 years, and biological therapy duration range was 0.25–10 years (140). In the study, patients' biological drug usage time vary between 1 to 6.48 ±0.78 years and infliximab had significantly the longest duration of time (6.48 ±0.78) among the other biologicals ($F= 3.06$, $p=0.017$). Cruyssen B. et. al. conducted a seven-year infliximab follow-up study in RA patients, that shown, of the 441 patient received infliximab, 160 (36%) were still on the therapy after seven years (142).

Almost all patients have been treated for a relatively long time also have comorbid diseases. Most patients have diabetes and hypertension, and other diseases include asthma, anemia, depression, cardiovascular diseases, gastrointestinal ulcers, osteoarthritis, bacterial or viral infections, and hepatitis B. Comorbid diseases affect the variety of other drugs patients use. Patients were using approximately 4.44± 2.23 non-biologic drugs (NBD) and 2.23± 1.20 rheumatological NBD drugs. The study determinated that correlation, the number of NBD and the number of rheumatologic NBD was increasing proportionally (P=0.738, p<0.001). In addition, there was no relation between the NBD and the biological drug. Otherwise, when the duration of biological therapy increase number of rheumatologic NBD decrease there was inverse relationship (P=-0.304, p=0.18). Also, patients with RA were significantly using the highest number of NBD (4.77± 0.36) and AS patients were using the lowest (1.33± 0.21) (F=4.05, p=0.003). There is no data about non-biological drugs ratio during the biologic therapy but literatures shown that patients with RA have approximately 1.6 comorbid diseases and the number increases with age. This affect the number of drug, progression of the disease, the effectiveness of the treatment, and make treatment decisions more difficult for the practitioner. Patients whose quality of life is affected will also change their treatment satisfaction (137)

The most using biological drug was infliximab (45%), a TNF-α inhibitor. The second one was tocilizumab (23%), an IL-6 inhibitor and the third most using one was rituximab (15%), B-cell inhibitor. These three commonly used biologics were also using mostly in the rheumatoid arthritis (RA) treatment. In particular, these three biologics are essential in the treatment of RA as the most preferred biologic DMARD (125). In a meta-analysis revealing the efficacy of interleukin-17 inhibitors in rheumatologic diseases, the efficacy was found to be high in the treatment of PsA and AS (126). Also in the study, the secukinumab (IL-17A inh.) is only used for AS and PsA. Further, etanercept, which is the first-line biological group in RA treatment (127). In the study, is also preferred only for RA treatment but for the second-line biological therapy.

During the clinical practice of biological drugs, discontinuation or switching the therapy is often observed (135). ACR and EULAR have recommendation guidelines about switching the biological therapy, first-line and second-line therapy options (125). The studies determined that the most common reason is inadequate response to treatment

(136). In this study, 38 patients were in first biologic therapy, 17 patients were in second biologic therapy, 3 patients were in third biologic therapy and 2 patients were in fouth biologic therapy. The most common reason for discotinuation the therapy or stopping treatment for a certain period of time was due to ineffectiveness (55.17%). The other common reason was infusion reaction (24.14%), but generally re-start the treatment with same biologics (4 of 7 patients). The third reason was (10.34%). The fourth reason was allergic reaction (6,9%). This patients was using the TNF-α inhibitor adalimumab. The last reason was injection site reaction (3.45%), a patient using etanercept. Strand V. et. al. were conducted a study with 6209 RA patients using biological DMARDs, they shown that the most common reason for biological drug discontinuation was ineffectiveness (136).

Infliximab, a TNF-α inhibitor, was the most used drug, as well as the most used drug among discontinued drugs. Also, commonly used for RA treatment. The majority of the reason for switching the drug was ineffectiveness with 7 out of 11 patients. ACR and EULAR recommends a TNF-α inhibitors as a first-line biologics therapy in RA treatment, if first-line biologic failure there is no clear agreement to swicthing to non-TNF biologics or another TNF inhibitors (125). Also, the seven years infliximab follow up study shown that, the patient were stopping the therapy commonly because of ineffectiveness (142).

During biological therapy susceptibility to opportunistic infections is increased especially tuberculosis beacuse of biological drug mechanisim of action is to suppressing the immune system and reducing the inflammation thus getting harder for the immune system to fight off infections (7). In the study, urinary tract infection (URT) was the most common infection among 8 patients and 5 of themwere using infliximab. Other infections were not observed usual, 2 patients using infliximab had tuberculosis, 5 patients had upper respiratory tract infection, 2 patients had fungal infection, and 44 patients stated that there was no infection in the last 6 months. Despite 10 patients stated that they had no infections, they used antibiotics. In addition, during biological therapy, the risk of infection is taken into consideration and patients are examined regularly. All classes of biological drugs can cause serious infections such as tuberculosis and also other opportunistic infections. Although, TNF-α inhibitors have high impact on the tuberculosis and have a treatmeant protocols for starting to therapy, screenings are also performed in

all biological treatments (134). In addition, according to clinical studies, URT is common side effects (8%) for infliximab (128).

Except the infectious, infusion reactions, injections side reactions and headache are the major side effects of biological drugs. In the study, most common side effects were insomnia (n=11), headache and feeling restless (n=9), muscle stiffness (n=8), blurred vision and trouble to move (n=7). Other side effects were very rare. Side effects related to muscle and mobility could be related to disease progress and inadequate response to therapy because there is no enough data for these side effects. In addition, there is not enough data for the insomnia, the most common side effect for the study, it was revealed in every class of biological drugs. The second common side effect was headache, 6 of them were using infliximab. According to clinical studies, headache is very common adverse effect that is reported in 18% for infliximab therapy (128). Blurred vision, was also seen in almost every biological drug classes. Ocular effects with the use of biologics are the commonly reported side effects, especially the side effect is related with infection (129). So, blurred vision may be a symptom of infection, although it is not directly mentioned adverse effects. Moreover, temporary vision loss has been reported for infliximab after infusion (128). Another adverse effect is rash and swelling at the injection site, 3 of these were using rituximab. However, there is not enough data to show that injection site reactions are frequent for rituximab, this adverse effect is already common in subcutaneous (s.c.) applications (24). In the study, most of the biologics were administered in i.v infusion. Therefore, the application methods of drugs should be taken into consideration while evaluating the adverse effects of biologicals.

Some adverse effects have been seen in only one biologics. The adverse effects observed in only infliximab, TNF inhibitor, were as follows; diarrhea and anxiety (n=4), post-infusion hypotension (n=3), pain in the injection site and weight loss (n=2), and also 3 of 4 patients had post-infusion dyspnea. The frequency of infusion-related reactions for infliximab is 18% according to clinical studies. Severe infusion reaction rate is less than 1% (128). Studies show that premedication with paracetamol, antihistamines or hydrocortisone decreases rates, generally reactions got under controlled and did not result in discontinuation of treatment. (131). In recent years, there are even studies showing that the infusion reaction is rare (130). There are insufficient data on other adverse effects, diarrhe, anxiety and weigh loss, seen with infliximab alone.

Only the side effects seen with the B-cell inhibitor, rituximab was as follows, allergic reactions (n=4), memory loss and nausea (n=2). Hypersensitivity reactions are frequently seen with rituximab use, particularly highly associated with infusion reactions, and also type I (IgE / non-IgE), mixed, type III, and type IV reactions are seen. According to clinical studies, the rate of infusion-related reaction with the first dose is 12% to 77% and decreases with s.c. administration. In addition, angioedema was reported to be 11% which is also a common hypersensitivity reaction (128,132). In the study, it was statistically significant (x^2=24.286, p<0.001) that 4 out of 9 patients using rituximab had an allergic reaction. There are insufficient data on memory loss, but the incidence of nausea was 8% and 23%, (133) which was also statistically significant (x^2=19.322, p <0.005).

There were no frequent adverse effects for tocilizumab, an IL-6 inhibitor, and secukinumab, an IL-17A inhibitor. And also, there are no specific adverse effects reported for etanercept and other biologics namely, adalimumab, anakinra, and certolizumab pegol.

When evaluating the patient satisfaction, it is essantion to patients response to benefit from the therapy and bothering from the therapy (8%). Among the participants, 43 patient found beneficial the therapy (72%) and 55 not bothered from the therapy (92%). In particular, patients who were bothering from the treatment and did not benefit from the treatment were examined.

Regarding tocilizumab, patients did not report significant side effects and although there was no drug switching who used tocilizumab before, However, 5 of 14 patients did not find the therapy beneficial, and 1 patient who at the 4th biological therapy stated the therapy is bothering. 1 of the 5 patients who found not beneficial the therapy was on the 4th biological therapy and 1 patient was on the 2nd therapy. In addition, 2 of 3 patients who previously discontinued tocilizumab treatment and later re-started did not find the therapy beneficial. Additionally, all of these patients are receiving treatment for RA. Regarding etanercept, 2 of 3 patient did not find the treatment beneficial and 1 of them found the therapy bothering. The most common side effects of etanerccept were related to muscle and mobility, and all of was using for RA treatment. Moreover, 3 of 6 patients who had previously used etanercept discontinued treatment due to ineffective.

According to the study, ineffectiveness was observed in the treatment of etanercept and not the first option for practitioners, all of them were used as second-choice biological therapy. In addition, 1 patient was using anakinra for RA treatment stated that the therapy not beneficial and also the patient was on the second biologic therapy. Further, 2 patients who were treated with infliximab for Behçet's disease, did not benefit from the therapy.

As a result, the satisfaction about biological therapy was high, but the patients with severe disease and generally the patients who discontunuated the biologic before due to ineffectiveness, do not find the treatment beneficial. Jiang N. et. al. conducted two consecutive survey study about patient satisfaction with RA treatment, as a results, they found education, age, communication with the physician, disease severity, and treatment costs were affect satisfaction. Especially, the disease severity were inversely affect satisfaction (143, 144).

To understand the other concerns related with the satisfactions and dicontinous of biological drugs, the patients were evaluated to rate 6 concerns they might have with the drug they used. Patients did not have such concers; 55 patient did not find hard to remember the doses, 57 patients did not find hard to apply the doses and did not agree the medication gives pain, 59 patients did not find medication hard to apply and did not agree to having unwanted side effects but 17 patients worrying about long-term side effects (25,33%). Patients worrying about long-term side effects because of the ‘informed consent form’, this form must be obtained before treatment, and patients are particularly informed about possible side effects. For this reason, a patient using every class of biological drugs has stated concern in this regard. Regular appointments are made for the patients and their medications are administered at the clinic. Patients stated that they had difficulty to remembering the doses due to the long time between doses and these patients were using infliximab and tocilizumab. Three patients who stated that drug administration was difficult and painful, were using infliximab. Since these drugs are administered as i.v infusion, they are given as slow infusion to prevent infusion reactions and administration takes a relatively long time (24). 2 of 3 patients also had symptoms of hypotension, redness and swelling after infusion. These 2 patients stated that they experienced infusion reaction. There was only 1 patient who found medications hard to pay' and stated that it is about to transportation to the hospital. Payment for biological drugs in Turkey is made by the social security institution (SGK), so patients do not have payment difficulties. In

addition, there was only 1 patient who stated 'having unwanted side effects', that patient was on the third biologic therapy for Behçet disease. In conclusion, patient's satisfaction with biologic therapy is high, and their concern with the medications is unremarkeble, except that they are concerned about long-term side effects.

There are limitations to consider in relation to our current findings. One of the most important limitations was the number of patients. Due to the Covid-19 pandemic, the questionnaire had to be paused after a very short time of starting the study, and when the study started again, a very limited time was allowed. At the same time, in this period, the admissions of the patients to the hospital were reduced in a controlled manner about pandemic so, the number of patients reached 65, while 5 could not be included because of exclusion criteria. In addition to the need to increase the number of patients in the study, the clinical diversity should also be increased. Since there may be bias of practitioners in treatment, different practitioners should be observed to eliminate this bias. In addition, although the thesis was planned as a questionnaire study, the information obtained from the patients should be verified. The patients generally stated that they did not know the comorbid diseases, other drugs, and the biological drugs they discontinued and the reasons. Thanks to the assistance of the responsible nurses throughout the study, some missing information was completed, but it was not sufficient.

Despite its limitations, it is an distinctive study, open to improvement and can yield beneficial results. The research can be improved with a larger number of patients and further specificizing the study, for example by reducing it to a single rheumatologic disease such as RA.

In conclusion, biological therapies are started to widely used for rheumatologic diseases, by enlightening the inflammation pathway and most of the immune system in the pathogenesis. Their importance in treatment is getting an increased and safety of therapy, discontuniation and patient satisfaction need to be evaluated. In the study, findings indicate that biologic therapy is beneficial, has few side effects, and has a high rate of drug discontinuation, it is generally not associated with side effects but with ineffectiveness of treatment. On the other hand, although patients report that they did not experience any severe adverse effects, they were concerned about the long-term adverse effects of the biological therapy. There are other factors that effects the safey,

discontuniation and satisfaction, these are; gender, age, rheumatologic disease and disease severity, duration of treatment, comorbidities, and other medicines they use, even the educational status. In addition, studies about safety of biological drug and discontuniation and patient satisfaction of these drugs need to be increased, further.

6. REFERENCES

1. Shirota Y, Illei GG, Nikolov NP. Biologic treatments for systemic rheumatic diseases. Oral Dis. 2008;14(3):206-216.

2. Johnston SL. Biologic therapies: what and when? J Clin Pathol. 2007;60(1):8-17.

3. Gülbezer, E. E., & Keser, G., Biyolojik tedaviler. RAED Journal/RAED Dergisi, 2017. 9(1-2): p. 11-31.

4. Taylor PC., Tumor necrosis factor-blocking therapies in Rheumatology. 5th ed. Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH: Philadelphia. 2015.p. 492–510.

5. Tugwell P, Singh JA, Wells GA. Biologicals for rheumatoid arthritis. BMJ. 2011;343:d4027.

6. Svarstad BL, Chewning BA, Sleath BL, Claesson C. The Brief Medication Questionnaire: a tool for screening patient adherence and barriers to adherence. Patient Educ Couns. 1999;37(2):113-124.

7. Singh JA, Wells GA, Christensen R, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev.;2011(2)

8. Dobler CC. Biologic Agents and Tuberculosis. Microbiology Spectrum. 2016 Dec;4(6).

9. Tayal V, Kalra BS: Cytokines and anti-cytokines as therapeutics--an update. Eur J Pharmacol 2008, 579 (1-3): 1-12.

10. Skurkovich S., Skurkovich B., Development of autoimmune disease is connected with the initial disturbance of IFN synthesis in the cells. J IFN Res 1989, 9 (suppl 2): S305.

11. Köhler G, Milstein C. Continuous cultures of fused cells secreting antibody of predefined specificity. Nature. 1975;256(5517):495-497.

12. Beutler B, Milsark IW, Cerami AC. Passive immunization against cachectin/tumor necrosis factor protects mice from lethal effect of endotoxin. Science. 1985;229(4716):869-871.

13. Kuek A, Hazleman BL, Ostör AJ. Immune-mediated inflammatory diseases (IMIDs) and biologic therapy: a medical revolution. Postgrad Med J. 2007;83(978):251-260.

14. Miller AV, Ranatunga SK. Immunotherapies in rheumatologic disorders. Med Clin North Am. 2012;96(3):475-x.

15. Ishii M. Immunology proves a great success for treating systemic autoimmune diseases - a perspective on immunopharmacology: IUPHAR Review 23. Br J Pharmacol. 2017;174(13):1875-1880.

16. Tracey D, Klareskog L, Sasso EH, Salfeld JG, Tak PP. Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. Pharmacol Ther. 2008;117(2):244-279.

17. Wajant H, Pfizenmaier K, Scheurich P. Tumor necrosis factor signaling. Cell Death Differ. 2003;10(1):45-65.

18. Harris J, Keane J. How tumour necrosis factor blockers interfere with tuberculosis immunity. Clin Exp Immunol. 2010;161(1):1-9.

19. Kollias G, Kontoyiannis D. Role of TNF/TNFR in autoimmunity: specific TNF receptor blockade may be advantageous to anti-TNF treatments. Cytokine Growth Factor Rev. 2002;13(4-5):315-321.

20. Pfeffer K. Biological functions of tumor necrosis factor cytokines and their receptors. Cytokine Growth Factor Rev. 2003;14(3-4):185-191.

21. Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to tumor necrozis factor alpha. Arthritis rheum. 1993;36:1681-90.

22. Winterfield LS, Menter A. Infliximab. Dermatol Ther. 2004;17(5):409-426.

23. Centocor Inc. Prescribing information for Remicade for IV injection. Malvern (PA), USA. 1999;14:245-89.

24. Assessing, managing and monitoring biologic therapies for inflammatory arthritis: RCN guidance for rheumatology practitioners Fourth edition London, UK: Royal Collage of Nursing; 2017

25. Papoutsaki M, Chimenti MS, Costanzo A, Talamonti M, Zangrilli A, Giunta A, at al. Adalimumab for severe psoriasis and psoriatic arthritis: An open-label study in 30 patients previously treated with other biologics. J Am Acad Dermatol. 2007;57:269- 275.

26. Wiesman MH, Moreland LW, Furst DE, Weinblatt ME, et al. Efficacy, pharmacokinetic, and safety assessment of adalimumab, a fully human anti-tumor necrosis factor-alpha monoclonal antibody, in adults with rheumatoid arthritis receiving concomitant methotrexate: A pilot study. Clinical Therapeutics. 2003;25(6):1700-1721.

27. Shen C, Assche GV, Colpaert S, Maerten P, Geboes K, Rutgeerts P, et al. Adalimumab induces apoptosis of human monocytes: A comparative study with infliximab and etanercept. Aliment Pharmacol Ther. 2005;21:251-258.

28. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy. Arthritis&Rheumatism. 2004;50(5): 1400-1411.

29. Voulgari PV. Golimumab: a new anti-TNF-α agent for rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. Expert review of clinical immunology. 2010;6(5):721-33.

30. Lonberg N. Fully human antibodies from transgenic mouse and phage display platforms. Current opinion in immunology. 2008;20(4):450-9.

31. Boyce EG, Halilovic J, Stan-Ugbene O. Golimumab: review of the efficacy and tolerability of a recently approved tumor necrosis factor-α inhibitor. Clinical therapeutics. 2010;32(10):1681-703.

32. McDonnell T, Ioannou Y, Rahman A. PEGylated drugs in rheumatology – why develop them and do they work? Rheumatology (Oxford) 2014;53:391–6.

33. Pasut G. Pegylation of biological molecules and potential benefits: pharmacological properties of certolizumab pegol. BioDrugs 2014; 28(1):15–23.

34. Deeks ED. Certolizumab pegol: a review of its use in the management of rheumatoid arthritis. Drugs 2013;73:75–97.

35. Weir D, Athwal D, Brown D, et al. A new generation of highaffinity humanized pegylated Fab fragment anti-tumor necrosis factor-α antibodies. Therapy 2006;3:535–45.

36. Lim LL, Fraunfelder FW, Rosenbaum JT. Do tumor necrosis factor inhibitors cause uveitis? A registry-based study. Arthritis Rheum. 2007;56(10):3248-3252.

37. Ureyen S, Terzioğlu E, B Hücre Hedefli İlaçlar, Turkiye Klinikleri J Rheumatol, 2015;8(3):51-61

38. Sağ S, Nas K. Romatolojide Biyolojik Ajanların Kullanımı. Online Türk Sağlık Bilimleri Dergisi, 2017;2(2):34-45.

39. Shord SS, Cordes LM. Cancer Treatment and Chemotherapy. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. eds. Pharmacotherapy: A Pathophysiologic Approach, 10e. McGraw-Hill; 2017.

40. Edwards JC, Szczepanski L, Szechinski J, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med. 2004; 350(25):2572-2581.

41. Negm AA, Furst DE. Nonsteroidal Anti-Inflammatory Drugs, Disease-Modifying Antirheumatic Drugs, Nonopioid Analgesics, & Drugs Used in Gout. In: Katzung BG. eds. Basic & Clinical Pharmacology, 14e. McGraw-Hill; 2018.

42. Lake DF, Briggs AD. Immunopharmacology. In: Katzung BG. eds. Basic & Clinical Pharmacology, 14e. McGraw-Hill; 2018.

43. Molloy ES, Calabrese LH. Progressive multifocal leukoencephalopathy associated with immunosuppressive therapy in rheumatic diseases: evolving role of biologic therapies. Arthritis Rheum. 2012;64(9):3043-3051.

44. Petty RE, Laxer R. Textbook of Pediatric Rheumatology. 7th ed. Elsevier; 2016.

45. Saijo S, Asano M, Horai R, Yamamoto H, Iwakura Y. Suppression of autoimmune arthritis in interleukin-1-deficient mice in which T cell activation is impaired due to low levels of CD40 ligand and OX40 expression on T cells. Arthritis Rheum. 2002;46(2):533-544.

46. Celik T., ed. Farmakoterapi El Kitabı. 10th ed. Gunes Tıp Yayınevi; 2019.

47. Keystone E, Omair MA. Interleukin-6 inhibition. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology. 5th ed. Philadelphia, PA: Mosby, Elsevier; 2015:485–91.

48. Malemud CJ. Recent advances in neutralizing the IL-6 pathway in arthritis. Open Access Rheumatol. 2009;1:133-150.

49. Choy E. Clinical experience with inhibition of interleukin-6. Rheumatic Diseases Clinics of North America. 2004; 30(8): 405-15.

50. Schiff MH, Kremer JM, Jahreis A, Vernon E, Isaacs JD, van Vollenhoven RF. Integrated safety in tocilizumab clinical trials. Arthritis Res Ther. 2011;13(5):141.

51. Davies R, Choy E. Clinical experience of IL-6 blockade in rheumatic diseases-implications on IL-6 biology and disease pathogenesis. Semin Immunol. 2014;26(1):97-104.

52. Frieder J, Kivelevitch D, Menter A. Secukinumab: a review of the anti-IL-17A biologic for the treatment of psoriasis. Ther Adv Chronic Dis. 2018;9(1):5-21

53. Atakan N. Sekukinumab. Türkderm-Deri Hastalıkları ve Frengi Arşivi Dergisi 2016;50(1):46-7.

54. Patel DD, Lee DM, Kolbinger F, Antoni C. Effect of IL-17A blockade with secukinumab in autoimmune diseases. Ann Rheum Dis. 2013;72(2):116-123.

55. Koyun B. Ozalp E. Romatolojik ve otoimmün hastalıklarda interlökin 23/tip 17 yardımcı T hücreleri yolağı için etkili güncel tedavi yöntemleri. FNG & Demiroğlu Bilim Tıp Transplantasyon Dergisi, 2018;3(1-2):25-30

56. McInnes, I. B., & Schett, G., Pathogenetic insights from the treatment of rheumatoid arthritis. Lancet (London, England), 2017; 389(10086), 2328–2337.

57. Scott D. L, Wolfe F, Huizinga T. W. J. Rheumatoid arthritis. Lancet 2010; 376: 1094– 1108

58. Cakır, N., Pamuk, Ö. N., Derviş, E., Imeryüz, N., Uslu, H., Benian, Ö., Elelçi, E., Erdem, G., Sarvan, F. O., & Senocak, M. The prevalences of some rheumatic diseases in western Turkey: Havsa study. Rheumatology international, 2012;32(4), 895–908.

59. Davis JC, van der Heijde DM, Braun J, et al. Sustained durability and tolerability of etanercept in ankylosing spondylitis for 96 weeks. Ann Rheum Dis. 2005;64(11):1557-1562.

60. Ergin S. Romatoid artritte etyopatogenez ve patoloji. In: Ataman Ş, Yalçın P ed. Romatoloji. Ankara: Nobel Kitabevi, 2012: p.457-468.

61. Cutolo M., Androgens in rheumatoid arthritis: when are they effectors?. Arthritis research & therapy, 2009; 11(5), 126.

62. Okamoto, H., Cujec, T.P., Yamanaka, H. and Kamatani, N, Molecular aspects of rheumatoid arthritis: role of transcription factors. The FEBS Journal, 2008; 275: 4463-4470

63. Özsoy M H, Altınel L, Başarır K, Çavuşoğlu A T, Dinçel V C. Romatoid Artritte Eklem Hastalığının Patogenezi. Türk Ortopedi ve Travmatoloji Birliği Derneği Dergisi 2006; 5:3-4.

64. Stastny P. Association of the B-cell alloantigen DRw4 with rheumatoid arthritis. The New England journal of medicine, 1978; 298(16), 869–871.

65. Smolen, J. S., Aletaha, D., & McInnes, I. B. Rheumatoid arthritis. Lancet, 2016; 388(10055), 2023–2038.

66. Smolen, J. S., Aletaha, D., Koeller, M., Weisman, M. H., & Emery, P. New therapies for treatment of rheumatoid arthritis. Lancet, 2007; 370(9602), 1861–1874.

67. Grassi W, De Angelis R, Lamanna G, Cervini C. The clinical features of rheumatoid arthritis. Eur J Radiol. 1998;27 Suppl 1:S18-S24.

68. Cojocaru M, Cojocaru IM, Silosi I, Vrabie CD, Tanasescu R. Extra-articular Manifestations in Rheumatoid Arthritis. Maedica (Bucur). 2010;5(4):286-291.

69. Lipsky P. E. Romatoid artrit. Akkoç N, Biberoğlu K. ed. Harrison's Principles of Internal Medicine 2th ed. İstanbul: Nobel Tıp Kitabevleri; 2013.

70. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569-2581.

71. Yıldırım R, Yazıcı Y. Romatoid artritte erken tedavi. J Turk Soc Rheumatol 2012;4:59-67.

72. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31(3):315-324.

73. Oliver AM. Clair EW. Rheumatoid arthritis. Treatment and assessment. In: Klippel JH, Stone JH, Crofford LJ, White PH. Primer on the Rheumatic Diseases. 13th ed.Springer, NY 2008; Chapter 6, p:133-41

74. Elbey B. Ankilozan spondilitli hastalarda güncel tedavi yaklaşımları. Dicle Tıp Dergisi, 2015; 42 (1): 123-127.

75. Feldtkeller E, Khan MA, van der Heijde D, van der Linden S, Braun J. Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. Rheumatol Int. 2003;23(2):61-66.

76. Gunal EK, Sarvan FO, Kamali S, et al. Low frequency of HLA-B27 in ankylosing spondylitis patients from Turkey. Joint Bone Spine. 2008;75(3):299-302.

77. Onen F, Akar S, Birlik M, et al. Prevalence of ankylosing spondylitis and related spondyloarthritides in an urban area of Izmir, Turkey. J Rheumatol. 2008;35(2):305-309.

78. Brophy S, Taylor G, Blake D, Calin A. The interrelationship between sex, susceptibility factors, and outcome in ankylosing spondylitis and its associated disorders including inflammatory bowel disease, psoriasis, and iritis. J Rheumatol. 2003;30(9):2054-2058.

79. Rudwaleit M. Classification and epidemiology of spondyloarthritis. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, eds. 5th Edition Rheumatology vol.2. Philadelphia: Mosby, Elsevier; 2011, p.1123-27.

80. Taggard DA, Traynelis VC. Management of cervical spinal fractures in ankylosing spondylitis with posterior fixation. Spine (Phila Pa 1976). 2000;25(16):2035-2039.

81. McGonagle D, Gibbon W, Emery P. Classification of inflammatory arthritis by enthesitis. Lancet. 1998;352(9134):1137-1140.

82. Martin TM, Smith JR, Rosenbaum JT. Anterior uveitis: current concepts of pathogenesis and interactions with the spondyloarthropathies. Curr Opin Rheumatol. 2002;14(4):337-341.

83. Lautermann D, Braun J. Ankylosing spondylitis--cardiac manifestations. Clin Exp Rheumatol. 2002;20(6-28):11-15.

84. Feldtkeller E, Erlendsson J. Definition of disease duration in ankylosing spondylitis. Rheumatol Int. 2008;28(7):693-696.

85. Khan MA. Ankylosing spondylitis: introductory comments on its diagnosis and treatment. Ann Rheum Dis. 2002;61(3):3-7.

86. Oostveen J, Prevo R, den Boer J, van de Laar M. Early detection of sacroiliitis on magnetic resonance imaging and subsequent development of sacroiliitis on plain radiography. A prospective, longitudinal study. J Rheumatol. 1999;26(9):1953-1958.

87. Korkmaz C, Ozcan A, Akçar N. Increased frequency of ultrasonographic findings suggestive of renal stones in patients with ankylosing spondylitis. Clin Exp Rheumatol. 2005;23(3):389-392.

88. Dagfinrud H, Kvien TK, Hagen KB. Physiotherapy interventions for ankylosing spondylitis. Cochrane Database Syst Rev. 2008;(1)

89. Dougados M, Dijkmans B, Khan M, Maksymowych W, van der Linden S, Brandt J. Conventional treatments for ankylosing spondylitis. Ann Rheum Dis. 2002;61 3(3):40-50.

90. Kollnberger, S., Bird, L., Cell-surface expression and immune receptor recognition of HLA-B27 homodimers. Arthritis and rheumatism, 2002; 46(11), 2972–2982.

91. Zochling J, van der Heijde D, Dougados M, Braun J. Current evidence for the management of ankylosing spondylitis: a systematic literature review for the ASAS/EULAR management recommendations in ankylosing spondylitis. Ann Rheum Dis. 2006;65(4):423-432.

92. Chen J, Liu C. Is sulfasalazine effective in ankylosing spondylitis? A systematic review of randomized controlled trials. J Rheumatol. 2006;33(4):722-731.,

93. Chen J, Veras MM, Liu C, Lin J. Methotrexate for ankylosing spondylitis. Cochrane Database Syst Rev. 2013;(2):CD004524.

94. Haibel H, Brandt HC, Song IH, et al. No efficacy of subcutaneous methotrexate in active ankylosing spondylitis: a 16-week open-label trial. Ann Rheum Dis. 2007;66(3):419-421.

95. Braun J, Brandt J, Listing J, et al. Long-term efficacy and safety of infliximab in the treatment of ankylosing spondylitis: an open, observational, extension study of a three-month, randomized, placebo-controlled trial. Arthritis Rheum. 2003;48(8):2224-2233.

96. Sieper J, Baraliakos X, Listing J, et al. Persistent reduction of spinal inflammation as assessed by magnetic resonance imaging in patients with ankylosing spondylitis after 2 yrs of treatment with the anti-tumour necrosis factor agent infliximab. Rheumatology (Oxford). 2005;44(12):1525-1530.

97. Callhoff J, Sieper J, Weiß A, Zink A, Listing J. Efficacy of TNFα blockers in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis: a meta-analysis. Ann Rheum Dis. 2015;74(6):1241-1248.

98. Moll JM, Wright V. Psoriatic arthritis. Semin Arthritis Rheum. 1973;3(1):55-78.

99. Onen M. and Yuvruk E. Atlantoaxial subluxation in a patient with psoriatic arthritis: a case report. Journal of Turkish Spinal Surgery,2020. 31(4):254-256.

100. Gezer I. And Levendoğlu F. Psöriasis Hastalarında Psöriatik Artrit Görülme Sıklığı ve Psöriatik Artritin Klinik. Genel Tıp Derg, 2016;26(2):58-61.

101. Köseoğlu H, Yücel AE. Psöriyatik Artrit. Türkiye Klinikleri İmmünolojiRomatoloji Dergisi, 2004: 44-53.

102. Chandran V, Schentag CT, Brockbank JE, et al. Familial aggregation of psoriatic arthritis. Ann Rheum Dis. 2009;68(5):664-667.

103. Szodoray P, Alex P, Chappell-Woodward CM, et al. Circulating cytokines in Norwegian patients with psoriatic arthritis determined by a multiplex cytokine array system. Rheumatology, 2007;46(3):417-425.

104. Casciano F, Pigatto PD, Secchiero P, Gambari R, Reali E. T Cell Hierarchy in the Pathogenesis of Psoriasis and Associated Cardiovascular Comorbidities. Front Immunol. 2018;9:1390.

105. Veale DJ, Fearon U. The pathogenesis of psoriatic arthritis. Lancet. 2018;391(10136):2273-2284.

106. Pitzalis C. Skin and joint disease in psoriatic arthritis: what is the link?. Br J Rheumatol. 1998;37(5):480-483.

107. Moll JM, Wright V. Familial occurrence of psoriatic arthritis. Ann Rheum Dis. 1973;32(3):181-201.

108. Erdem HR. Psoriatik artritin klinik özellikleri. Turkish Journal Rheumatology 2000;15(1):31-8.

109. Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006;54(8):2665-2673.

110. Gordon KB, Ruderman EM. The treatment of psoriasis and psoriatic arthritis: an interdisciplinary approach. J Am Acad Dermatol. 2006;54(3-2):85-91.

111. Mease PJ. Psoriatic arthritis: update on pathophysiology, assessment and management. 2011;70(1):77-84.

112. Mease PJ. Psoriatic arthritis assessment and treatment update. Curr Opin Rheumatol. 2009;21(4):348-355.

113. Gül U, Gönül M, Kiliç A, Erdem R, Cakmak SK, Gündüz H. Treatment of psoriatic arthritis with etanercept, methotrexate, and cyclosporin A. Clin Ther. 2006;28(2):251-254.

114. Partsch G, Steiner G, Leeb BF, Dunky A, Bröll H, Smolen JS. Highly increased levels of tumor necrosis factor-alpha and other proinflammatory cytokines in psoriatic arthritis synovial fluid. J Rheumatol. 1997;24(3):518-523.

115. Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. Lancet. 2000;356(9227):385-390.

116. Gossec L, Smolen JS, Ramiro S, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. Ann Rheum Dis. 2016;75(3):499-510.

117. Coates LC, Kavanaugh A, Mease PJ, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 Treatment Recommendations for Psoriatic Arthritis. Arthritis Rheumatol. 2016;68(5):1060-1071.

118. Sarzi-Puttini P, Atzeni F. New biological treatments for psoriatic arthritis. Isr Med Assoc J. 2014;16(10):643-645.

119. Gossec L, Coates LC, de Wit M, et al. Management of psoriatic arthritis in 2016: a comparison of EULAR and GRAPPA recommendations. Nat Rev Rheumatol. 2016;12(12):743-750.

120. Yasui K. Immunity against Mycobacterium tuberculosis and the risk of biologic anti-TNF-α reagents. Pediatr Rheumatol Online J. 2014;12:45. Published 2014 Oct 2.

121. T.C. Sağlık Bakanlığı. Tüberküloz Tanı ve Tedavi Rehberi. Ankara, Sağlık Bakanlığı Yayını No: 862, 2011, ISBN: 978-975-590-411-5.

122. Duarte A. Patient Fact Sheet: TNF inhibitors. American College of Rheumatology Communications and Marketing Commitee [serial online] 2019; https://www.rheumatology.org/Portals/0/Files/TNF-Inhibitors-Fact-Sheet.pdf

123. Van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum. 1984;27(4):361-368.

124. Acosta Felquer ML, FitzGerald O. Peripheral joint involvement in psoriatic arthritis patients. Clin Exp Rheumatol. 2015;33(5 Suppl 93):S26-S30.

125. Law ST, Taylor PC. Role of biological agents in treatment of rheumatoid arthritis. Pharmacol Res. 2019;150:104497.

126. He C, Xue C, Zhu G, Kang P. Efficacy and safety of interleukin-17 inhibitors in the treatment of chronic rheumatic diseases: A combined and updated meta-analysis [published online ahead of print, 2021 Mar 25]. J Clin Pharm Ther.

127. Wu Q, Zhao Y, Xu D, Zhang Z, Li Z. Efficacy of methotrexate and etanercept biosimilar rhTNFR:Fc in Chinese patients with active rheumatoid arthritis: A controlled, randomized and multicenter study. Sci Rep. 2020;10(1):14270.

128. Infliximab (including biosimilars of infliximab): Drug information. UpToDate, Inc. [serial online] 2021; accessed April 2021, https://www-uptodate-com.lproxy.yeditepe.edu.tr/contents/infliximab-including-biosimilars-of-infliximab-drug-information

129. M Castillejo Becerra C, Ding Y, Kenol B, Hendershot A, Meara AS. Ocular side effects of antirheumatic medications: a qualitative review. BMJ Open Ophthalmol. 2020;5(1):e000331.

130. Checkley LA, Kristofek L, Kile S, Bolgar W. Incidence and Management of Infusion Reactions to Infliximab in an Alternate Care Setting. Dig Dis Sci. 2019;64(3):855-862.

131. Remicade: Kısa Ürün Bilgisi. [serial online] 2021; accessed April 2021, https://www.msd.com.tr/static/pdf/REMICADE_100mg_Konsantre_IV_Infuzyon_Cozeltisi_Hazirlamak_Icin_Liyofilize_Toz_Iceren_Flakon_KUB.pdf

132. Fouda GE, Bavbek S. Rituximab Hypersensitivity: From Clinical Presentation to Management. Front Pharmacol. 2020;11:572863

133. Rituximab (intravenous) including biosimilars of rituximab: Drug information. UpToDate, Inc. [serial online] 2021; accessed April 2021, https://www-uptodate-com.lproxy.yeditepe.edu.tr/contents/rituximab-intravenous-including-biosimilars-of-rituximab-drug-information

134. Haroon N, Inman RD. Infectious complications of biological therapy. Curr Opin Rheumatol. 2009;21(4):397-403.

135. Reynolds A, Koenig AS, Bananis E, Singh A. When is switching warranted among biologic therapies in rheumatoid arthritis?. Expert Rev Pharmacoecon Outcomes Res. 2012;12(3):319-333.

136. Strand V, Miller P, Williams SA, Saunders K, Grant S, Kremer J. Discontinuation of Biologic Therapy in Rheumatoid Arthritis: Analysis from the Corrona RA Registry. Rheumatol Ther. 2017;4(2):489-502.

137. Gabriel SE, Michaud K. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. Arthritis Res Ther. 2009;11(3):229.

138. Rolnick SJ, Pawloski PA, Hedblom BD, Asche SE, Bruzek RJ. Patient characteristics associated with medication adherence. Clin Med Res. 2013;11(2):54-65.

139. Jiang N, Yang P, Liu S, et al. Satisfaction of Patients and Physicians with Treatments for Rheumatoid Arthritis: A Population-Based Survey in China. Patient Prefer Adherence. 2020;14:1037-1047. Published 2020 Jun 23.

140. Larsson I. Patients' conceptions of their own influence on good treatment response to biological therapy in chronic inflammatory arthritis. Patient Prefer Adherence. 2017;11:1057-1067.

141. Orvain C, Boulch M, Bousso P, Allanore Y, Avouac J. Is there a place for CAR-T cells in the treatment of chronic autoimmune rheumatic diseases? [published online ahead of print, 2021 May 27]. Arthritis Rheumatol. 2021;10.1002/art.41812.

142. Vander Cruyssen B, Durez P, Westhovens R, De Keyser F. Seven-year follow-up of infliximab therapy in rheumatoid arthritis patients with severe long-standing refractory disease: attrition rate and evolution of disease activity. Arthritis Res Ther. 2010;12(3):R77.

143. Li HB, Wu LJ, Jiang N, et al. Treatment satisfaction with rheumatoid arthritis in patients with different disease severity and financial burden: A subgroup analysis of a nationwide survey in China. Chin Med J (Engl). 2020;133(8):892-898.

144. Patient education: Side effects from medicines (The Basics). UpToDate, Inc. [serial online] 2021

145. Clarke JB. Mechanisms of adverse drug reactions to biologics. Handb Exp Pharmacol. 2010;(196):453-474.

7. APPENDICES

7.1. Ethical Approval

Ethical approval of the study was accepted by; Yeditepe University Clinical Researches Ethical comittee (Report date: 30 December 2019, Number: 1142).

T.C. YEDİTEPE ÜNİVERSİTESİ

Sayı : 37068608-6100-15- 1798 **31/12/2019**
Konu: Klinik Araştırmalar
Etik kurul Başvurusu hk.

İlgili Makama (Selin Sarıkaya)

Yeditepe Üniversitesi Sağlık Bilimleri Fakültesi Eczacılık Fakültesi Dr. Öğr. Üyesi Beril Kadıoğlu Yaman'ın sorumlu araştırmacı olduğu **"Romatoloji Hastalıklarında Kullanılan Biyolojik İlaçların Güvenliğinin 'Biyolojik İlaçlarda Güvenlik Anketi' İle Değerlendirilmesi''** isimli araştırma projesine ait Klinik Araştırmalar Etik Kurulu (KAEK) Başvuru Dosyası **(1782)** kayıt Numaralı KAEK Başvuru Dosyası, Yeditepe Üniversitesi Klinik Araştırmalar Etik Kurulu tarafından **30.12.2019** tarihli toplantıda incelenmiştir.

Kurul tarafından yapılan inceleme sonucu, yukarıdaki isimi belirtilen çalışmanın yapılmasının etik ve bilimsel açıdan uygun olduğuna karar verilmiştir (**KAEK Karar No: 1142**).

Prof. Dr. Turgay ÇELİK
Yeditepe Üniversitesi
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7.2. Questionnaire 'Safety Survey of Biological Drugs'

BİYOLOJİK İLAÇ GÜVENLİK ANKETİ

Hastanın;

Cinsiyeti:	Yaşı:
Eğitim durumu:	
Tanı:	
Tedavi süresi:	

1. Romatolojik hastalığınız için kullandığınız ilaçlar nelerdir?
   1..... 5.....
   2..... 6.....
   3..... 7.....
   4..... 8.....
2. Romatolojik hastalığınız için kulllandığınız biyolojik ilaç(lar) nelerdir?
   Lütfen işaretleyiniz, başka bir biyolojik ilaç kullanıyor iseniz diğer bölümüne yazınız,
   Bu ilaçlardan birini kullanmıyorsanız lütfen ankete devam etmeyiniz.
   ☐ Humira ☐ Orencia ☐ Simponi ☐ Remicade ☐ Mabthera
   ☐ Amgevita ☐ Enbrel ☐ Cimzia ☐ Remsima ☐ Redditux
   ☐ Kineret ☐ Verxant ☐ Actemra ☐ Stelara ☐ Benlysta
   ☐ İlaris ☐ Copellor ☐ Prolia ☐ *diğer;*.....
3. Son 6 ay içinde ilaçlarınız dışında kullandığınız başka ilaç var mıdır? Var ise nelerdir?

	İlacın adı	Dozu	Kullanım süresi
1.	*Örn. Asprin*	*500mg tablet günde 1*	*24 ay*
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			
10.			

4. Son 6 ay içinde romatolojik hastalığınız için kullandığınız ilaçlardan bıraktığınız ilaç oldu mu?
   ☐ Evet ☐ Hayır (6.soruya geçiniz)
5. Hangi ilacı bıraktınız? Bırakma sebebiniz nedir?

	Bırakılan İlaç	Bırakma Sebebi
1.		
2.		
3.		
4.		
5.		
6.		
7.		

6. Son 6 ay içinde aşağıdaki enfeksiyonlardan birini geçirdiniz mi?

☐ Üst solunum yolu enfeksiyonu	☐ Alt solunum yolu enfeksiyonu
☐ Tüberküloz	☐ Hepatit
☐ Zona	☐ Deri enfeksiyonu
☐ Mantar enfeksiyonu	☐ İdrar yolu enfeksiyonu

☐ Diğer;.....

7. Son 6 ay içinde antibiyotik kullandınız mı? ☐ Evet ☐ Hayır

8. Son 6 ay içinde aşı oldunuz mu? ☐ Evet ☐ Hayır

2. Soruda işaretlediğiniz biyolojik ilaç: .....

Aşağıdaki soruları bu biyolojik ilacınıza göre cevaplayınız

9. Bu ilacı ne kadar süredir kullanıyorsunuz?.....
10. İlacı ne sıklıkla kullanıyorsunuz?.....
11. Her seferinde kaç uygulama yapıyorsunuz?.....
12. Bu ilaç size hangi durumlar için yarar sağladı?
    - ☐ Ağrılarımı azaltmakta
    - ☐ Eklemlerimdeki sertliği azaltmakta
    - ☐ Eklem kasılmalarımı azaltmakta
    - ☐ Özellikle sabahları oluşan eklem kasılmalarımı azaltmakta
    - ☐ Eklemlerimdeki şişliği azaltmakta
    - ☐ Hareket kabiliyetimi artırmakta
    - ☐ Kaslarımdaki güçsüzlüğü önlemekte
    - ☐ Diğer;.....
13. Sizce bu ilaç hastalığınızı ne kadar tedavi ediyor?
    - ☐ Tedavi etmiyor
    - ☐ Az tedavi ediyor
    - ☐ İyi tedavi ediyor
    - ☐ Bilmiyorum
14. Bu ilacı kullanmaktan rahatsızlık duyuyor musunuz?
    - ☐ Hayır, rahatsız etmiyor
    - ☐ Biraz rahatsız ediyor
    - ☐ Çok rahatsız ediyor
    - ☐ Bilmiyorum
15. İlacınıza ait aşağıdaki problemler sizi ne kadar rahatsız ediyor?

Lütfen puanlayınız;	*0 hiç*	*1 biraz*	*2 orta*	*3 çok*
☐ Dozları hatırlaması zor	0	1	2	3
☐ İlacın uygulaması zor	0	1	2	3
☐ İlacın uygulaması canımı yakıyor	0	1	2	3
☐ İlacın ücretini karşılaması zor	0	1	2	3
☐ İlacın yan etkileri çok	0	1	2	3
☐ İlacın uzun süreli sonuçlarında endişeleniyorum	0	1	2	3
☐ Bu ilaç başka problemlere sebep olmakta	0	1	2	3

16. İlaca bağlı olarak aşağıdaki yan etkileri görüyor musunuz?

Yan Etkiler	Evet	Hayır	Eklemek istediğiniz bir yorum var ise lütfen yazınız
Genel :			
Bulanık görme			
Kabızlık			
İshal			
İdrara çıkmada zorluk			
İdrara çok çıkma			
Tükürük, salya artışı			
Ağızda kuruluk			
Şiddetli baş ağrısı			
Mide bulantısı			
Kusma			
Kilo kaybı			
Kilo alma			
Cinsel rahatsızlıklar			
Kalp çarpıntısı			
Kas ve Hareket Kabiliyeti :			
Kaslarda yorgunluk hissetme			
Rahat oturup kalkamama			
Kas tutulması			
Kaslarda titreme			
Hareket etmekte zorluk			
Ruhsal Duygu Durum :			
Gergin ve sinirlilik			
Konsantrasyonda bozukluk			
Yorgun hissetme, çabuk yorulma			
Uyku problemleri			
Hafıza problemleri, unutkanlık			
Motivasyon bozukluğu, ilgisizlik			
İntihar düşüncesi			
Enjeksiyon bölgesinde :			
Kızarıklık, şişlik			
Yanma, ağrı hissi			
İlaç uygulama sonrası :			
Nefes darlığı			
Mide bulantısı			
Kusma			
Nabız düşmesi			
Nabız artması			
Enfeksiyon :			
Ateş			
Terleme, üşüme			
Boğaz ağrısı			
Öksürük			
Yorgun hissetme, kas ağrısı			
Alerjik reaksiyon :			
Dudakta, yüzde veya boğazda şişme			