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Biological Drug Use in Patients with Psoriasis: Our Clinical Experiences

Psöriazisli Hastalarda Biyolojik İlaç Kullanımı: Klinik Tecrübelerimiz

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ABSTRACT Objective: Biological drugs are used mainly in psoriasis in dermatology, but are increasingly used in the treatment of many other inflammatory dermatoses. They are preferred as a treatment option especially in patients with psoriasis who do not respond to conventional therapies. In this study, we aimed to evaluate the features and treatment outcomes of patients with psoriasis in our clinic using biological agents. **Material and Methods:** Between June 2014 and February 2018, 87 patients with psoriasis using biological drugs in the dermatology clinic were evaluated. The demographic data, laboratory data and clinical information of the patients were obtained retrospectively by screening patient files. **Results:** 82.8% (n=72) of patients with psoriasis used biological drugs for the first time, whereas 17.2% (n=15) used more than one biological drug. The drug with the highest duration of drug survival was adalimumab. The most preferred biologics in the treatment of obese patients with psoriasis were infliximab and ustekinumab, whereas adalimumab and ustekinumab were the most preferred biologics for patients with arthritis. In 20.7% (n=18) of the cases, the biological drug was combined with methotrexate and 70.1% (n=61) received isoniazid prophylaxis before treatment. **Conclusion:** Biological drugs have become a well-tolerated and effective treatment option in patients when conventional treatments are inadequate. Although the main goal of biological drugs was to achieve clinical remission, they did not show the same effect in every patient. Approximately one in five patients with psoriasis has switched to another biological drug due to treatment failure or side effects.

Keywords: Psoriasis; biological therapy

ÖZET Amaç: Biyolojik ilaçlar dermatolojide esas olarak psöriaziste kullanılmaktadır, ancak diğer birçok inflamatuar dermatozun tedavisinde giderek daha fazla kullanılmaktadır. Özellikle konvansiyonel tedavilere cevap vermeyen psöriazisli hastalarda tercih edilirler. Bu çalışmada kliniğimizde biyolojik ajan kullanan psöriazisli hastaların klinik özelliklerini ve tedavi sonuçlarını değerlendirmeyi amaçladık. **Gereç ve Yöntemler:** Haziran 2014 ile Şubat 2018 tarihleri arasında, dermatoloji kliniğinde biyolojik tedavi kullanan 87 psöriazis hastası değerlendirildi. Hastaların demografik verileri, laboratuvar verileri ve klinik bilgileri hasta dosyaları taranarak retrospektif olarak elde edildi. **Bulgular:** Psöriazisli hastaların %82,8'i (n=72) ilk kez biyolojik ilaç kullanırken, %17,2'si (n=15) birden fazla biyolojik ilaç kullanmıştı. İlaç sağkalım süresi en yüksek olan ilaç adalimumab idi. Obez psöriazisli hastaların tedavisinde en çok tercih edilen biyolojikler infliximab ve ustekinumab iken, artritli hastalarda en çok tercih edilen biyolojikler adalimumab ve ustekinumab idi. Olguların %20,7'sinde (n=18), biyolojik ilaç metotreksat ile kombine edildi ve %70,1'i (n=61) tedavi öncesi izoniazid profilaksisi aldı. **Sonuç:** Geleneksel tedavilerin yetersiz olduğu hastalarda biyolojik ilaçlar iyi tolere edilen ve etkili bir tedavi seçeneği haline gelmiştir. Biyolojik ilaçların temel amacı klinik remisyona ulaşmak olsa da, her hastada aynı etkiyi göstermemiştir. Psöriazisli beş hastadan yaklaşık birinde, tedavi başarısızlığı veya yan etkiler nedeniyle başka bir biyolojik ilaca geçilmiştir.

Anahtar Kelimeler: Psöriyazis; biyolojik tedavi

Biological agents are protein based and they are derived from living cells. Biological drugs developed in recent years have become a good treatment option for many inflammatory diseases that do not respond to conventional treatments. Although they are mainly used in psoriasis in the field of dermatology, they have been reported to be effective in the

treatment of many inflammatory dermatoses such as granulomatous diseases, neutrophilic diseases, hidradenitis suppurativa (HS) or pityriasis rubra pilaris.[1] In patients with psoriasis, biological treatments have been shown to reduce the severity of the illness, to prevent co-morbidities associated with psoriasis, to reduce the length of hospital stay and to improve quality of life.[2,3] In this study, we aimed to evaluate the characteristics and treatment outcomes of patients with psoriasis using biological agents in our clinic.

MATERIAL AND METHODS

The study has been approved by the local ethics committee. Between June 2014 and February 2018, 87 patients with psoriasis using biological drugs were evaluated. Demographic data, laboratory data and clinical data of the patients were obtained retrospectively by screening patient files. Following data were recorded: the biological agent used, the duration of the disease, previous treatments, response to treatment, duration of drug survival, previous use of biological drugs, reason for withdrawal of a previous biological drug and presence of psoriatic arthritis and obesity, other accompanying diseases, having received isoniazid prophylaxis in the past and whether the treatment is combined with methotrexate. Psoriasis area severity index (PASI) score was calculated before treatment and every three months in patients receiving biological treatment. At the end of the third month for biological agents, 75% improvement in PASI score was accepted as treatment success and 50%-75% improvement as partial response. In both cases, the biological drug was continued. When partial response was obtained, methotrexate was added to the biological treatment. In the third month, the improvement in PASI score below 50% and the decrease in PASI score below 50% during maintenance therapy was accepted as treatment failure.[4] In the event of treatment failure, the drug was replaced with another biological drug after the purification period. A biological drug therapy was started in patients in whom the body surface area is affected by 10% and over, who do not respond to conventional systemic treatments, in whom these treatments are contraindicated, or patients with severe psoriasis such as erythrodermic, pustular psoriasis. In addition to topical treatments, all cases used a variety of treatments including systemic methotrexate, acitretin and cyclosporine.

SPSS v.17.0 package program was used for statistical evaluation of obtained data in study (SPSS Inc, Chicago, Illinois, USA). Continuous data were summarized as mean±standard deviation, while categorical data were summarized as number and percentage.

RESULTS

87 (90.6%) cases treated with biological drugs for psoriasis were included in the study. Demographic and clinical characteristics of patients with psoriasis are given in Table 1. Diabetes (9.1%), hypertension (8.0%) and coronary artery disease (4.6%) were the most common accompanying diseases. Of the patients with psoriasis, 62.1% (n=54) cases received narrowband UVB treatment. Before the administration of biological drugs, 97.7% (n=85) of the cases received methotrexate, 39.1% (n=34) received acitretin and 20.7% (n=18) received cyclosporine treatment. 79 (90.8%) patients had plaque psoriasis while in 8 (9.2%) patients biological drugs were initiated due to erythrodermic and pustular psoriasis. While 82.8% (n=72) of the cases used a biological drug for the first time, 10.4% (n=9) of the remaining cases previously used infliximab, 3.5% (n=3) previously used adalimumab and 3.5% (n=3) previously used infliximab and adalimumab. The proportion of patients using more than one biological drug was 17.2% (n=15). In 33.3% of patients who used more than one medication, the drug was stopped because of side effect and in 66.7% (n=10) the drug was discontinued due to treatment failure. In addition, 33.3% (n=5) of patients using more than one biological drug were obese. In one patient using adalimumab, biological therapy was interrupted due to interstitial lung disease. In 4 patients using infliximab, the biological treatment was stopped because of myocardial infarction, cerebrovascular event, interstitial lung disease and infusion reaction. In other patients who used more than one biological drug, the medica-

TABLE 1: Demographic and clinical characteristics of patients with psoriasis.

Gender % (n)	
Male	51.7 (45)
Female	48.3 (42)
Average age of patients (year)	42.9±13.7 (min-max:16-84)
Mean disease duration (year)	14.9±10.9 (min-max:3-58)
Psoriatic arthritis % (n)	12.6 (11)
Obesity % (n)	9.2 (8)
Isoniazid prophylaxis % (n)	70.1 (61)
Combination of biological drug with methotrexate % (n)	20.7 (18)
PASI score	
Before treatment	21.8±4.9 (min-max:12.8-28.0)
Third months	2.7±1.0 (min-max:1.1-4.8)

PASI: Psoriasis area severity index.

tion was interrupted because the patients did not respond to treatment. None of the cases under treatment with biological drugs developed malignancy or serious infection. Table 2 shows the characteristics of the biological agents used in patients with psoriasis. In 11 (61.1%) cases with psoriatic arthritis, methotrexate was combined with biologics from the beginning of the treatment, while in 7 (38.9%) cases with no psoriatic arthritis it was combined with biologics in partial response to treatment. In 95.8% (n=69) of the patients using biological drugs for the first time, the biological drug achieved success per se and in 4.2% of the patients it achieved treatment success combined with methotrexate.

TABLE 2: The characteristics of the biological agents used in patients with psoriasis.

Biyological drugs	**Drug survival time (month)**
Adalimumab	33.3±24.6
Infliximab	27.5±21.6
Etanercept	23.6±16.1
Ustekinumab	13.2±9.3
Biological drugs according to frequency of use	**% (n)**
Adalimumab	31 (27)
Infliximab	29.9 (26)
Ustekinumab	25.3 (22)
Etanercept	13.8 (12)
Biologic drugs used in patients with psoriatic arthritis % (n)	
Adalimumab	36.4 (4)
Ustekinumab	27.3 (3)
Etanercept	27.3 (3)
Infliximab	9.1 (1)
Biological drugs used in obese patients	**% (n)**
Infliximab	62.5 (5)
Ustekinumab	37.5 (3)

DISCUSSION

Psoriasis is an immunologically mediated disease characterized with sharply marginated papules and plaques. Target mediators of biological drugs that play a role in the pathogenesis of the disease are TNF-α, IL-12, IL-17 and IL-23. Infliximab, adalimumab and etanercept inhibit the activity of TNF-a directly. Ustekinumab inhibits interleukin-mediated signaling pathways by inhibition of IL-12/23.[5] The preferred biologics in our clinic were adalimumab, infliximab, ustekinumab and etanercept, respectively. Infliximab and adalimumab have been the most commonly used drugs in patients who received biological drugs for the first time. Adalimumab was most frequently used in patients with psoriatic arthritis, whereas infliximab was most frequently used in patients with erythrodermic and pustular psoriasis.

Psoriasis is associated with metabolic disorders such as obesity, diabetes, dyslipidemia and fatty liver disease. It has been shown that patients with psoriasis may be more obese than the general population and that there is a relationship between pro-inflammatory cytokines and obesity in the pathogenesis of psoriasis.[6] In this study, the diseases most commonly associated with psoriasis were di-

abetes, hypertension and coronary artery disease. In our clinic, infliximab and ustekinumab treatments were preferred for obese psoriatic patients because dose adjustment according to weight was possible.

It is known that obesity increases the likelihood of being negatively affected by systemic therapies such as methotrexate and cyclosporine used in the treatment of psoriasis and reduces the effectiveness of biological drugs.[7,8] In this study, the rate of obesity in all patients was 9.2%, while this rate was 33.3% in patients using more than one biological drug. In a meta-analysis, obesity was associated with insufficient response to anti-TNF therapy in all immune-mediated inflammatory diseases. Anti-TNF treatment failure in obese patients was found to be 60% higher than normal weight individuals.[9]

The primary reason for discontinuation of biological drugs is either lack of efficacy at the beginning or loss of efficacy over time.[5] In a prospective multicenter study, it was reported that drug survival of ustekinumab was significantly better than TNF-α inhibitors.[10] In this study, adalimumab had the highest drug survival time whereas ustekinumab had the lowest drug survival time. This situation, which is contrary to literature, may be related to the late licensing of ustekinumab in our country compared to other biologicals. Compared with those who received biological treatment for the first time, a decrease in drug survival was reported in patients who used different biological drugs for the second and third time.[5] In this study, infliximab had the lowest rate of drug survival in patients who used biological drugs for the second or third time.

Infliximab is a TNF-α inhibitor administered by infusion. In a study conducted, infliximab was shown to cause a mild-to-moderate infusion reaction characterized by pruritus, flushing and dyspnea at a rate of 1.3%. Premedication with antihistamines or intravenous steroid treatments has not been reported to be protective.[11] In this study, the treatment in one patient was terminated because of infusion reaction. It is known that TNF-α inhibitors promote subclinical interstitial lung disease.[12] In this study, the treatment in two patients using adalimumab and infliximab was terminated because of interstitial AC disease. Studies have shown that psoriasis is an independent risk factor in diseases such as diabetes, atherosclerosis, myocardial infarction and stroke. On the other hand, TNF-α inhibitors have been shown to significantly reduce the risk of myocardial infarction in patients with psoriasis compared with topical treatment.[13] In this study, infliximab was discontinued in two patients because of cerebrovascular disease in one patient and myocardial infarction in another. We think that this situation, which is contrary to the literature, may be related to the fact that both patients are elderly and diabetic and infliximab is more frequently preferred in our clinic.

It is recommended for patients with psoriasis to be screened for latent tuberculosis infection before starting a biological therapy. The risk of developing active tuberculosis in patients treated with TNF-α inhibitors is significantly higher than in patients who do not use biological drugs.[14] In a study conducted in the USA where patients with psoriasis were evaluated before the biological drug treatment, the rate of latent tuberculosis was examined by the tuberculin test and found to be positive in about 4.5% of the cases.[15] In a study in Italy this rate was found to be 8.2%.[14] In this study, latent tuberculosis infection was diagnosed in the clinic for chest diseases by clinical evaluation, ppd / quantiferon test and chest x-ray. The prophylaxis was initiated 1 month before the start of the biological drug and continued for a total of 9 months. In this study, 70.1% of patients using biological drugs received isoniazid prophylaxis due to latent tuberculosis infection. In the general population of our country, tuberculin test positivity was reported at a high rate of 24-77%.[16] The rate of high latent tuberculosis infection in this study may be related to the endemicity of tuberculosis in our country.

In relation to abnormal granuloma formation, TNF- α blockers have been shown to exacerbate chronic tuberculosis infection. In a study in England, the incidence rate of tuberculosis was highest for adalimumab, followed by infliximab and etanercept. The interval between the use of TNF an-

tagonist and the diagnosis of tuberculosis was reported to be 18.5 months for adalimumab users, 13.4 months for etanercept users and 5.5 months for infliximab users.[17] In the follow-up visits performed every 6 months of patients who used biological drugs, no active tuberculosis infection was detected in this study. This may be related to the fact that the number of cases making up the study group is relatively small, and that patients who are at risk for Tbc have been receiving conservative treatment with 1x300 mg / day isoniazid for 9 months.

In a review of anti-drug antibodies against biological drugs in the treatment of psoriasis, anti-drug antibodies were associated with decreased drug concentrations and decreased response to treatment. While the use of methotrexate simultaneously with biological drugs is promising to prevent the formation of anti-drug antibodies in immune-mediated diseases such as rheumatoid arthritis and Crohn's disease, their use in psoriasis is rare.[18] It is known in literature that different biologics are combined with acitretin, methotrexate or cyclosporine.[19] In our clinic only methotrexate was combined with biological agents. There is no consensus that biological treatments should necessarily be combined with methotrexate. In 95.8% (n = 69) of the patients who had used biological drugs for the first time in our clinic, biological drugs alone provided treatment success. In a study, it was reported that TNF-α inhibitors had a synergistic effect with methotrexate, that this combination decreased immunogenicity, and that biologicals were positively effective on drug survival by increasing serum drug concentrations.[20] According to the European League Against Rheumatism Guideline, the combination of TNF-α inhibitors and methotrexate is recommended for the treatment of psoriatic arthritis.[21] In this study, methotrexate was used simultaneously with biological drugs in 20.7% of the cases. In our clinic, methotrexate was preferred in patients with psoriatic arthritis when switching to the biological drug and in patients with no psoriatic arthritis the drug was preferred in case of partial response to treatment.

In patients with psoriasis where conventional treatments are inadequate, biological drugs have become a well-tolerated and effective treatment option. Although remission is the ultimate treatment goal with biological drugs, each patient did not show the same efficiency. Approximately one in five patients with psoriasis has switched to another biological drug due to treatment failure or side effects. Having more information about diseases and biological drugs will be a guide for choosing the most appropriate biological drug.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Perihan Öztürk;* ***Design:*** *Hülya Nazik, Perihan Öztürk;* ***Control/Supervision:*** *Perihan Öztürk; Mehmet Kamil Mülayim, Hülya Nazik;* ***Data Collection and/or Processing:*** *Hülya Nazik;* ***Analysis and/or Interpretation:*** *Hülya Nazik;* ***Literature Review:*** *Hülya Nazik;* ***Writing the Article:*** *Hülya Nazik;* ***Critical Review:*** *Perihan Öztürk; Mehmet Kamil Mülayim;* ***References and Fundings:*** *Hülya Nazik;* ***Materials:*** *Hülya Nazik.*

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