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Original scientific paper

The Treatment of Moderate and Severe Chronic Plaque Psoriasis With Biologics and Biosimilar Drugs

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ABSTRACT: Psoriasis is a chronic, immune-mediated inflammatory skin disease. The condition greatly affects people's quality of life to the extent that it could be life-ruining and stigmatizing. A better understanding of psoriasis pathophysiology allowed the development of targeted therapies, including biologics and biosimilars which are recommended as an option for moderate to severe plaque psoriasis. Our results have shown that administration of biologics (adalimumab and secukinumab) and adalimumab biosimilar led to a significant improvement in the PASI response after 16 weeks. Most patients who have been treated for more than a year have the same PASI response.

Keywords: psoriasis, PASI, biologics, adalimumab, secukinumab, biosimilars.

INTRODUCTION

Psoriasis is a chronic, immune-mediated inflammatory skin disease, consisting of red, scaly plaques occurring most commonly on the elbows, knees, scalp, and lower back, but any skin surface can be affected. Psoriasis affects between 1% and 5% of the population worldwide (Carrascosa et al., 2018).

The condition greatly affects people's quality of life to the extent that it could be life-ruining and stigmatising (Ayala-Fontánez al, 2016). Psoriasis is now considered a systemic disease associated with psychological, metabolic, arthritic, and cardiovascular comorbidities. Approximately 125 million people worldwide have psoriasis. Twelve studies reported the incidence of psoriasis in all ages, with the incidence of the disease varying from 31.4 per 100 000 person-years in Eastern Europe (Russia) to 521.1 per 100 000 person-years in Western Europe (Germany) (Parisi et al., 2020).

Plaque psoriasis is the most common variant of psoriasis. The most rapid advancements addressing plaque psoriasis have been in its pathogenesis, genetics, comorbidities, and biologic treatments. Plaque psoriasis is associated with several comorbidities including psoriatic arthritis, cardiometabolic diseases, and depression (Armstrong & Read, 2020).

In patients with psoriasis, assessing the severity of the disease is an important guideline in deciding whether to treat the patient with local therapy only or with phototherapy and systemic therapy. After the introduction of therapy, the assessment of the severity of the disease is necessary for monitoring the effectiveness of treatment.

Three instruments (scales) are most commonly used to assess the severity of the disease in patients with psoriasis: Psoriasis Area and Severity Index (PASI), Body Surface Area (BSA) and Dermatological Life Quality Index (DLQI) (Oji & Luger, 2015).

PASI is the most commonly used scale to assess skin involvement and clinical severity in patients with psoriasis. In this method, the surface of the affected skin with psoriatic lesions (Area) and the severity of psoriatic lesions (Severity) are evaluated to assess the condition of the disease. Within this score, the degree of redness (Erythema), the thickness of psoriatic plaque (Induration) and scaling (Scaling) are determined. These values are determined specifically for certain parts of the skin of the body: head, torso,

arms and legs and are finally added together. The PASI value ranges from 0, which indicates a disease-free state, to a maximum of 72. A PASI value above 10 indicates moderate to severe, and a PASI scores greater than 20 indicates severe psoriasis. Estimation of treatment effect was measured by PASI response relative to baseline PASI score. PASI-50 indicates a 50% reduction in the initial PASI score and indicates a mild improvement in skin lesions; PASI-75 indicates a 75% reduction in the PASI score which is interpreted as a marked improvement. PASI-90 means a 90% reduction in the initial PASI score and almost completely clean skin; PASI-100 signifies a 100% therapeutic response and complete withdrawal of skin lesions and completely clean skin (Silva et. al, 2013; Mattei et al., 2014; Oji & Luger, 2015).

Conventional treatments for moderate to severe psoriasis, including phototherapy with ultraviolet B (UVB), photochemotherapy with psoralens and ultraviolet A (PUVA), methotrexate, cyclosporine, and acitretin are limited by well-known and characteristic side effects, incomplete effectiveness in some patients, and demanding treatment schedules which result in decreased patient compliance (Bahner et al., 2009).

Fundamental research on the pathogenesis of psoriasis has substantially increased our understanding of skin immunology, which has helped to introduce innovative and highly effective therapies. (Grän et al., 2010). In the last two decades, a better understanding of psoriasis pathophysiology allowed the development of targeted therapies, including biologics, biosimilars and small molecules. Biologic drugs have revolutionized the treatment of psoriasis and other rheumatological diseases. Biologics and biosimilars are recommended as an option for moderate to severe plaque psoriasis as well as those with moderate to severe PsA (Gisondi et al., 2019; Kamata & Tada, 2020; Korman, 2020).

Since 2004, 11 biologics for psoriasis treatment have been approved by Food and Drug Administration (FDA) and the European Medicines Agency (EMA). These include etanercept, infliximab, adalimumab, ustekinumab, secukinumab, ixekizumab, guselkumab, tildrakizumab, risankizumab, and certolizumab pegol. According to the mechanism of action, biologics can be divided into several groups: antagonists of tumour necrosis factor-alpha (TNF-α), interleukin (IL) antagonists: (anti-IL-17A, anti-p40-IL12/23, anti-p19-IL 23, anti -p19/p40-IL 23) (Ivanić et al., 2021) (Table 1). All these biological medicines are given at defined intervals by subcutaneous injection or intravenous infusion.

Table 1. Mechanism of action, biological structure and biosimilars approved biological drugs for psoriasis

Biologics and mechanism of action	Biological structure
Anti-TNF-α	
Etanercept	Soluble TNFR2 coupled to the Fc portion of IgG1
Infliximab	Human/mouse chimeric IgG1mAb
Adalimumab	Human IgG1mAb
Certolizumab pegol	Humanized (from mouse) mAb, PEGYlated Fab fragment
Anti-IL-17A	
Secukinumab	Human IgG1 kmAb
Ixekizumab	Humanized IgG4 mAb
Brodalumab	Human IgG2 mAb
Anti-p40-IL12/23	
Ustekinumab	Human (IgG1)
Anti-p19-IL 23	
Guselkumab	Human IgG1 mAb
Tidrakizumab	Human IgG1λ mAb
Anti-p19/p40-IL 23	
Risankizumab	Humanized IgG1 aAb

TNF-α (tumor necrosis factor alfa); IgG (immuoglobulin G); IL (interleukin); mAb (monoclonal antibodies), p (portion); R (receptor)

Biosimilars are biotherapeutic products that are highly similar in terms of quality, efficacy and safety to an already licensed reference biotherapeutic product. Last nine years tumour necrosis factor (TNF)-alpha biosimilar agents have been approved for the treatment of psoriasis and other autoinflammatory conditions. Adalimumab, for convenience and efficacy reasons, is the most suitable for the treatment of psoriasis of the anti-TNFα agents with available biosimilars. Since 1913. the US FDA and /or the European Medicines Agency have approved eight biosimilars of adalimumab for the treatment of psoriasis. Given that these agents showed pharmacokinetic, efficacy, safety, and immunogenicity profiles comparable to those of the originator, adalimumab biosimilars were licensed for all indications approved for reference adalimumab based on extrapolation. (Puig et al., 2019; Reynolds et al., 2019; Zhou et al., 2021).

MATERIALS AND METHODS

Our research presents a retrospective cross-sectional study of the treatment effects on patients with moderate to severe plaque psoriasis with biologics and biosimilar drugs. These patients are currently being treated at the Clinic for Skin and Venereal Diseases of the University Clinical Center of the Republic of Srpska in Banja Luka.

The treatment of psoriasis with biological drugs in our Clinic started in June 2020. University Clinical Centre of the Republic of Srpska is the first institution in Bosnia and Herzegovina with biologics for psoriasis treatment. Biological drugs that we treat our patients with psoriasis are adalimumab (brand name Humira), adalimumab biosimilar (brand name Amgevita) and secukinumab (brand name Cosentix). Since these drugs are extremely expensive, patients are included in the therapy successively, depending on the approval by the Health Insurance Fund of the Republic of Srpska.

Adalimumab and adalimumab biosimilar are administered subcutaneously at a dose of 80 mg during the first week, 40 mg a week later, and then 40 mg every two weeks. Secukinumab is used in a subcutaneous dose of 300 mg once a week during the first 4 weeks, and then the treatment continues at 300 mg once a month.

Until this time this type of therapy is used by a total of 23 adult patients of both genders. PASI score was used to assess disease severity. Patients who had a PASI score ≥10–19 before treatment were rated as moderate psoriasis, and with a PASI score ≥ 20 as severe psoriasis. Out of the total number of respondents, 13 patients have been treated for more than a year, so we have results for them even after one year of treatment.

The effect of treatment of study patients was analyzed according to age, sex, duration of psoriasis and association with psoriatic arthritis (PsA). We evaluated the effects of biological and biologically similar drugs using PASI responses (PASI-50, PASI-75, PASI-90 and PASI-100).

Statistical analysis was performed using the SPSS 20 software package. The results were described descriptively, by mean values ($\bar{X}$), standard deviations (SD) for continuous variables, and percentages (%) for categorical variables. Differences between the mean values of the variables were analyzed using the independent samples t-test, while the differences between the frequencies of individual groups of patients were tested using the Chi-squared test. P values <0.05 are considered statistically significant.

RESULTS

Out of the total number of subjects in the study, only one patient due to psoriatic arthritis had previously been on biological therapy. Other patients are receiving biologics for the first time. Slightly more than half of the subjects (52.2%) receive biologics adalimumab (brand name Humira), 30.4% biosimilar adalimumab (brand name Amgevita), and the least secukinumab (brand Cosentix) (17.4%).

Almost two thirds (73.9%) of the respondents are male, while 26.1% are female. The result of the $\chi 2$ test shows that there is a statistically significant difference between the number of male and female patients ($\chi 2$ (2) = 5.261, p = 0.022).

At the start of biological therapy, the youngest patient was 19, and the oldest was 72 old. The mean age of patients was 40.87 ± 13.29 years, and 52.2% of patients were younger than 40 years. The results of the independent t-test indicate that there are no statistically significant differences in mean age between male and female patients (t (21) = -0.272, p = 0.788).

47.8% of patients with psoriasis are between 10 and 20 years old, 39.1% less than 10, and 13% of patients over 20. The results of the independent t-test indicate that there is no statistically significant difference in the duration of disease between male and female patients (t (21) = 0.196, p = 0.847). The results also show that in patients older than 40, the disease has lasted 22.6 years on average, which is 10.38 years longer than in patients younger than 40. This difference is statistically significant (p = 0.011).

Moderate plaque psoriasis is present in 52.2% of subjects, and severe psoriasis in 47.8%. The difference in the severity of the disease was not statistically significant (χ (1 = 0.15, p = 0.901).

In 31.1% of patients, psoriasis was associated with psoriatic arthritis, and 60.9% did not have affected joints. The difference is not statistically significant (p = 0.27).

Until now 39.1% of patients have been on biological therapy for more than one year, while in 60.9% of subjects the treatment lasts less than 12 months (Table 2).

Table 2. Demographic and clinical characteristics of the study group

Variables	Biologics			Total N%	P
	Adalimumab N%	Adalimumab biosimilar N%	Secukinumab N%		
Number of patients	12 (52.2)	7 (30.4)	4 (17.4)	23 (100.0)	
Age (years), $\bar{X}$ ± SD	45.50±13.43	31.86±11.77	42.75±8.77	40.87±13.29	0.788**
Age 18-39 years	5 (21.7)	6 (26.1)	1 (4.3)	12 (52.2)	
Age ≥ 40 years	7 (30.4)	1 (4.3)	3 (13.0)	11 (47.8)	
Gender					
Male	7 (30.4)	6 (26.1)	4 (17.4)	17 (73.9)	0.022*
Female	5 (21.7)	1 (4.3)	-	6 (26.1)	
Duration of psoriasis (years)					
< 10 years	6 (26.1)	3 (13.0)	-	9 (39.1)	
10-20 years	6 (26.1)	4 (17.4)	1 (4.3)	11 (47.8)	
>20 years	-	-	3 (13.0)	3 (13.0)	
Clinical type of psoriasis					
Moderate (PASI ≥10-19)	7 (30.4)	4 (17.4)	1 (4.3)	12 (52.2)	0.901*
Severe (PASI ≥ 20)	5 (21.7)	3 (13.0)	3 (13.0)	11 (47.8)	
Association with psoriatic arthritis					
Yes	5 (21.7)	3 (13.0)	1 (4.3)	9 (39.1)	0.279*
No	7 (30.4)	4 (17.4)	3 (13.0)	14 (60.9)	

*N (%) – number (percentage), $\bar{X}$ – mean, SD – standard deviation, PASI - Psoriasis Area and Severity Index, * Chi-squared test; ** independent t-test*

Until now 39.1% of patients have been on biological therapy for more than one year, while in 60.9% of subjects the treatment lasts less than 12 months.

Analysis of the PASI response after 16 weeks of biological and biosimilar treatment showed that most patients (60.9%) had a PASI-100 response, 17.4% PASI-90, and also 17.4% PASI-70. Only one patient (4.3%) had no improvement in biosimilar adalimumab therapy. The result of the $\chi 2$ test shows that there is a statistically significant difference ($p = 0.001$).

In 39.1% of patients on biologic therapy for more than a year, we assessed the PASI response after 12 months and found that half of the patients (50.1%) still had a PASI-100 response (completely clean skin), 21.5% PASI-90 (almost clean skin), and 7.1% PASI-70 (significant improvement in skin changes). Two patients experienced worsening psoriasis and their current biologic was replaced by another (Table 3).

Table 3. PASI response after 16 weeks and 12 months

Variables	Biologics			Total N%	P
	Adalimumab N%	Adalimumab biosimilar N%	Secukinumab N%		
PASI response after 16 week					
PASI-50	-	-	-	-	0.001*
PASI-70	2 (8.8)	1 (4.3)	1 (4.3)	4 (17.4)	
PASI -90	3 (13.1)	-	1 (4.3)	4 (17.4)	
PASI-100	7 (30.5)	5 (21.7)	2 (8.7)	14 (60.9)	
No improvement	-	1 (4.3)	-	1 (4.3)	
PASI response after 12 months	7 (30.4)	3 (13.0)	4 (17.4)	14 (39.1)	
PASI-50	-	-	-	-	0.143*
PASI-70	-	-	1 (7.1)	1 (7.1)	
PASI -90	3 (21.5)	-	-	3 (21.5)	
PASI -100	3 (21.5%)	2 (14.3%)	2 (14.3)	7 (50.1)	
Exacerbation	1 (7.1)	-	1 (7.1)	2 (14.2)	
Biological therapy replacement	-	1 (7.1)	1 (7.1)	2 (14.2)	

*N (%) – number (percentage); PASI - Psoriasis Area and Severity Index; * Chi-squared test;*

Due to the positive QuantiFERON test during treatment, biological therapy was temporarily excluded (for two months) in two patients, while in one female patient treated with adalimumab, therapy was completely excluded due to suspected demyelinating disease.

DISCUSSION

The results of our study are that all patients except one receive biological therapy for the first time and that two-thirds of the respondents are men. The number of patients with moderate to severe psoriasis and also those who have or do not have psoriatic arthritis at the same time is equal. By assessing the PASI response after 16 weeks, we found that most patients have a PASI-100 response and a PASI-90 which means clear or almost clear skin. We also found that one-half of patients who have received biologic therapy for more than one year, after 12 months maintain a PASI 100/90 response. Only two patients in the study who experienced worsening psoriasis biologics were replaced.

The efficacy of adalimumab in the treatment of psoriasis has been reported in numerous studies. Mijušković and the authors of their study state that adalimumab in psoriasis, leads to a PASI-75 response in 71% of patients after 16 weeks of therapy. According to another study, a PASI-75 response was achieved in 79%, and PASI-90 in 51.9% of patients. In the latter study, the efficiency was compared to methotrexate

in increasing doses (7.5 to 25 mg), which achieved PASI-75 in 35.5%, and PASI-90 in 13.6% of patients after 16 weeks of therapy. After therapy discontinuation, a rebound phenomenon was not reported, but continuous use is more efficient, taking into account the efficiency decrease after discontinuation and the reintroduction of adalimumab into therapy (Mijušković et. al, 2016).

In their research, authors state that at week 16, 71% of adalimumab and 7% of placebo-treated patients achieved greater than or equal to 75% improvement in the PASI score. During weeks 33 to 52, the percentage of patients rerandomized to placebo who lost adequate response (defined as < 50% improvement in the PASI response relative to baseline and at least a 6-point increase in PASI score from week 33) was 28% compared with 5% of patients treated continuously with adalimumab. Authors concluded that adalimumab is efficacious and well-tolerated in the treatment of chronic plaque psoriasis (Menter et. al, 2008).

The phase III randomized controlled evaluation of adalimumab every other week dosing in moderate to severe psoriasis trial (REVEAL) reported that the primary efficacy endpoint was the percentage of patients achieving at least 75% improvement in the PASI score at week 16. Post hoc subgroup analyses were conducted to determine relationships between adalimumab efficacy and/or safety and age group, sex, race, baseline weight intervals, baseline body mass index, disease duration, baseline severity, prior treatments, and comorbidities. that treatment of moderate to severe psoriasis with adalimumab led to consistent 75% or greater improvement in PASI score response rates across the majority of patient subgroups, with no significant differences in serious adverse events (Menter et. al, 2010). The conclusion of phase III clinical trial REVEAL in a 52-week trial of adalimumab therapy for moderate to severe chronic plaque psoriasis is that adalimumab efficacy was well maintained over more than 3 years of continuous therapy for patients with sustained initial PASI- 75 responses. Maintenance was best at the PASI-100 level (Gordon et al., 2012).

Adalimumab is well established for the treatment of moderate-severe chronic plaque psoriasis in adults and has been recently more approved by European Union for use in pediatric patients with severe chronic plaque psoriasis. (Wu & Valdecantos, 2017).

ABP 501, United States: AMJEVITA™ (adalimumab-atto); European Union: AMGEVITA® (adalimumab) is the first approved biosimilar to adalimumab (Markus et al., 2019; Constantin et al., 2019). Biosimilars are cheaper than original drugs and are thus of interest to the public (Barszczewska & Piechota, 2021; Zagni et al., 2021)

The efficacy of secukinumab in the treatment of psoriasis has been reported in numerous studies. Thus, Mijušković and the authors state that secukinumab is a recombinant, highly affinitive, completely human monoclonal IgG1κ antibody that binds selectively and neutralizes IL-17A. After 12 weeks, the recorded PASI-75 response in clinical studies was 81.6% and 77.1% (for 300 mg) and 71.6% and 67% (for 150 mg). Anti-secukinumab antibodies were detected in a very small percentage (0.3 to 0.4%) causing no reduction in therapy efficiency or occurrence of adverse effects. The most common adverse effects are nasopharyngitis, headaches and upper respiratory tract infections. In a study that compared the efficacy of secukinumab and ustekinumab, after 52 weeks, 76% of patients who were given secukinumab and 61% of the patients who were given ustekinumab had PASI-90, while 46% of patients who were given secukinumab and 36% of patients who were given ustekinumab achieved PASI-100 (Mijušković Ž. et al., 2016).

The results of the CLEAR study among 676 randomized subjects, also reported that secukinumab demonstrated sustained superior efficacy in comparison with ustekinumab in clearing skin through week 52, greater improvement in quality of life, and a favourable and comparable safety profile (Blauvelt et al., 2017).

In SCULPTURE extension study has been shown that secukinumab has significant efficacy and a favourable safety profile in the treatment of moderate-to-severe psoriasis and psoriatic arthritis. This study

was demonstrated rapid onset of response (50% of patients achieve PASI-75 at week 4 and sustainability of results over 5 years. PASI 75/90/100 response in year 1 (88.9%, 68.5% and 43.8%) was held over the next 5 years (88.5%, 66.4% and 41%). In the conclusion of this study, it is stated that secukinumab 300 mg treatment delivered high and sustained levels of skin clearance and improved quality of life over 5 years in patients with moderate-to-severe psoriasis. Favourable safety established in the secukinumab phase 2/3 programme was maintained for 5 years (Bissonnette et. al, 2018).

In the review, Berg et al. examine the efficacy and safety of secukinumab for the treatment of psoriasis using the literature retrieved from the PubMed database. In clinical trials, treatment with secukinumab led to rapid and sustained improvement in PASI scores, with PASI-90 response rates up to 68.5% at 5 years. Long-term clinical trials and real-world data have established secukinumab as a safe and effective treatment for psoriasis (Berg et. al, 2021).

Drug survival of biologics represents their real-world effectiveness and safety. In a multinational, prospective, observational study by Seneschal J, et al. the authors concluded that only one in four patients achieved complete skin clearance after 6 months of treatment with biologics (Seneschal et al., 2020). Also, it is none that the drug survival for all biologics decreased by a certain percentage with time. (Lin, 2018). However, it is very important for every patient with moderate or severe psoriasis if they have clean or almost clean skin for several years. This gives them hope for future cure for their disease.

CONCLUSION

The advancement of biologic therapy has made it possible to set new standards of efficacy and safety in the treatment of moderate to severe psoriasis. The results of numerous studies show that the use of biological therapy in the treatment of moderate to severe psoriasis has excellent results which can greatly prevent the development of significant comorbidities and contribute to improving the quality of life of these patients. Our study is limited by its small sample size, but confirms these results. With the development of biosimilar drugs whose price is about 30-40% lower than generic drugs, we can expect greater availability of modern therapy to a wider population of patients.

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