SANAMED
2024; 19(1): 45–49
ISSN-1452-662X

DOI: 10.5937/sanamed0-48793
UDK: 616.517-085; 606:616.517
ID: 142813449
Original article

SWITCHING BIOLOGICS IN PSORIASIS: CHALLENGES AND EXPERIENCE FROM A SMALL TERTIARY HEALTH-CARE CENTER

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Primljen/Received 18. 01. 2024. god. Prihvaćen/Accepted 17. 03. 2024. god. Pubublished online first 18. 03. 2024. god.

Abstract: **Objective**: Psoriasis, a chronic inflammatory skin disease, significantly impacts patients' quality of life. Over the last decade, therapeutic goals have aimed to complete skin clearance and restore normal patient activities, minimizing the disease's impact on social, family, and work activities. Biologics have emerged as a promising solution to achieve better disease control without organ-specific side effects, helping meet these therapeutic goals. However, it was soon noticed that approximately 30% of patients do not sufficiently react to the therapy in the long term, and the need for switching biologics emerges.

Findings: We present our experience with biologic switching over a specific period. Seventeen patients required a switch in biologic agents, with three undergoing a second switch. The cohort predominantly consisted of males (14 out of 17), with an average BMI of 29.81. The primary reasons for switching were secondary failure (loss of initial treatment efficacy), followed by primary failure. Adverse reactions were the least common cause, highlighting the satisfactory safety profile of biologics. One patient underwent dose escalation of secukinumab due to efficacy failure but ultimately ended up switching the biologic.

Conclusion: Biologic agents approved for the treatment of psoriasis showed a favorable safety profile without compromising efficacy. The increasing demand for higher efficacy in psoriasis treatment aims to alleviate the disease's multifaceted impact on patients. It is anticipated that biologic switching, primarily due to inadequate therapeutic response and less frequently due to adverse reactions, will become more prevalent in clinical practice. Literature and our clinical experience suggest that constitutional factors influence treatment success. As new agents and targets emerge, the established standards for biologic switching may require ongoing revision.

Keywords: psoriasis, biologics, switch, primary failure, secondary failure, inefficacy.

INTRODUCTION

Psoriasis is a chronic inflammatory disease affecting approximately 1 to 3% of the general population and significantly impacting patients' quality of life (1, 2). It is estimated that more than 30% of patients develop psoriatic arthritis. Furthermore, studies have confirmed a strong correlation between psoriasis and metabolic syndrome, posing a high risk for cardiovascular events (3, 4, 5). Physical and emotional discomforts related to psoriatic skin changes are common causes of sick leave and work absenteeism, highlighting the multisystemic nature of the disease.

Despite the availability of various treatment modalities for psoriasis, systemic agents often present organ-specific toxicity. The introduction of biologics for moderate to severe clinical forms of psoriasis brought new hope for patients and healthcare providers, initially observed for their lack of organ-specific side effects. However, approximately 30% of patients do not respond adequately to long-term therapy, necessitating a switch in biologics.

The need to alter biological treatment primarily arises due to four reasons: (I) inefficacy due to primary failure (not achieving a ≥ 50% Psoriasis Area and Severity Index [PASI] score improvement at 24 weeks of treatment); (II) inefficacy due to secondary failure (losing the efficacy that was present after commenc-

ing treatment, also known as biologic fatigue); (III) adverse events; and (IV) other factors such as lack of compliance and unhealthy lifestyle habits (6-9).

AIM

The increasing trend in biologic switching is due to the arrival of new agents with higher efficacy and potency, as well as patients' growing demands for complete skin clearance. The aim of our study is to assess the reasons for switching biologics and to analyze our previous experiences with these treatments. To our knowledge, there are few reports on this topic; therefore, we believe our study, even with a smaller sample, could contribute to a better understanding and potentially serve as a foundation for further research.

PATIENTS AND METHODS

As of 2019, three biologic agents have been available in Montenegro, a small Mediterranean country with a population of approximately 619,000, for the treatment of psoriasis. Adalimumab was first introduced in 2019, followed by secukinumab in 2020, and guselkumab at the end of 2021.

This retrospective study was conducted to evaluate patient characteristics necessitating biologic agent switching, as well as the frequency and reasons for treatment alteration. All patients undergoing biologic treatment in Montenegro must receive approval from three dermatologists at the Clinic of Dermatovenereology, Clinical Center of Montenegro. This center is the only site in the country authorized to approve biologic treatment. We collected data on patients who switched treatments, including age, gender, smoking habits, body mass index, initial PASI score, and number of biologic alterations. Clinical efficacy was assessed using the PASI (Psoriasis Area and Severity Index) score. This report is in alignment with the Statement of Human Rights stated by the Helsinki Declaration.

RESULTS

From the initiation of biologic treatments in 2019 until March 2022, we observed 17 patients who required alteration of their treatment. Tables 1 and 2 present the demographic and clinical characteristics of these patients, including the first-line biologic used before switching and the reasons for treatment alteration.

It is noteworthy that three patients underwent biologic switching twice. Each of these patients transitioned from adalimumab to secukinumab, and subsequently from secukinumab to guselkumab. All three patients switched both times due to secondary failure.

One patient required dose escalation of secukinumab due to primary failure but ultimately switched to a different biologic.

Table 1. *Characteristics of the Patients Observed in the Study*

Parameter	**Results**
Gender	Nº of patients (percent of patients)
Male	14 (82.3%)
Female	3 (17.7%)
Age	
Mean	51.58 years old (y.o.)
Range	28 y.o.-75 y.o.
BMI	
Mean	29.81
Range	22.2-40.7
Initial PASI	
Mean	26.17
Range	10-60
Smoking habit	Nº of patients (percent of patients)
Yes	10 (59%)
No	7 (41%)

Table 2. *Reasons for switching the biologics divided according to different agents*

Reasons for Switching	Adalimumab	Secukinumab	Guselkumab
Number of patients	9	8	0
Inefficacy due to primary failure	1	2	/
Inefficacy due to secondary failure	6	9	/
Infection/ inflammation	2	0	/

We did not observe any biologic switching due to serious or unforeseen adverse reactions. However, one patient, who was administered an anti-TNF agent, experienced reactivation of latent tuberculosis infection (LTBI). Additionally, there was one case where a patient experienced joint swelling after each dose of adalimumab. Upon reporting this to the dermatologist, we recommended an evaluation for potential underlying internal diseases. Consequently, she discontinued the treatment and opted not to switch to another biologic while undergoing further examination.

DISCUSSION

In recent years, switching biologics has become an important issue for discussion as new targets have been discovered and new biologics with higher efficacy introduced. The most common reasons for switching biologics relate to primary and secondary inefficacy (10, 11). In this regard, our study confirms such

findings, as the most common reasons in our patients were due to lack of efficacy. Regarding adverse reactions, they were not frequently observed. This underscores the favorable safety profile of the biologics (7, 8). We did not observe any other reasons for switching, such as lack of compliance.

The global prevalence of latent tuberculosis infection (LTBI) was estimated at 23.6% in 2019 (12). Although the exact reactivation rate is uncertain, around 5% are believed to experience reactivation (13, 14). Medications that interfere with patients' immune systems, particularly anti-TNF-alpha agents, pose a higher risk for reactivating LTBI and developing active tuberculosis. This is due to the necessity of TNF in forming granulomas to contain M. tuberculosis (15, 16). Our findings indicate no LTBI reactivation associated with anti-IL-17 and -23 agents (8).

Regarding gender prevalence, according to our observation, switching biologics was more prevalent in males. This is in accordance with the study conducted by Honda H et al., but the actual reason for such gender disparity is not known. According to the same study, the mean initial PASI of our cohort aligns with their results (7).

A smoking habit does not significantly influence the outcome of therapy in our cohort. The average body mass index in our patients was 29.81. A recent study by Pirro F et al. reported that obesity adversely affects the clinical response of biologics in psoriatic patients, with anti-interleukin agents being more affected by body mass index compared to anti-tumor-necrosis agents (17). A meta-analysis by Wu MY et al. stated that treatment with anti-TNF-alpha inhibitors appears to be associated with an increase in body weight and BMI, whereas treatment with anti-IL-12/23 and anti-IL-17 biologics does not. This association should be considered before initiating biologics in overweight patients (18).

An important discussion point is the timing of commencing a new biologic agent. According to guidelines published by Tsai YC et al. a washout period is recommended when switching is due to side effects, but not necessary for lack of efficacy (8). In our clinical practice, we temporarily ceased biologic administration until resolving infections and observed the washout period prior to starting new biologic treatment.

The same guidelines affirm that switching to the same class of biologics can still be effective, with firm evidence shown in biologics targeting IL-17. However, when switching is due to side effects, it is advisable to switch to a biologic targeting a different molecule. In our cases, we always transitioned to an agent with a different target molecule, due solely to the availability of just one agent from the same class (8).

Regarding dose escalation, a research study by Honda H et al. showed that some patients needed a subsequent biologic switch mainly due to inefficacy after dose escalation. The study emphasized the presence of refractory cases needing a biologic switch ultimately (7). In our experience, we did not attempt dose escalation, except in one case which resulted in efficacy failure and ultimately led to a biologic switch. Based on available data, if inefficacy occurs (both primary and secondary), dose escalation often does not bring PASI improvement. Thus, in our previous clinical practice, we preferred to immediately change the biologic agent rather than trying dose escalation.

CONCLUSION

Biologic agents approved for the treatment of psoriasis have shown a favorable safety profile without compromising efficacy. Furthermore, there is an increasing demand for higher efficacy to mitigate the various negative impacts of psoriasis. It is anticipated that the practice of switching biologics will become increasingly common in clinical settings, primarily due to inadequate therapeutic response, and less frequently due to infections and adverse reactions.

Studies have shown that after switching biologics, the subsequent agent is often administered at the scheduled time without a washout period. Our experience indicates that switching biologics often leads to better efficacy and more satisfactory clearance of skin lesions, aligning with recent studies on this topic. It is worth noting that correction of lifestyle habits helps achieve a better response to medications.

As presented in our results, there was no switch from guselkumab. Given its recent introduction into our clinical practice, it is likely the reason we did not observe any switches from this agent. Therefore, our report has a notable limitation regarding data on switching from guselkumab. Furthermore, the limitation of our report is the small sample size of observed patients, so reports on larger samples should be performed.

Conflict of Interests: The authors declare no conflicts of interest related to this article.

Funding: No

Note: Artificial intelligence was not used as a tool in this study.

Author contribution: All authors contributed equally to writing this article.

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Sažetak

ZAMENA BIOLOŠKIH LEKOVA KOD PSORIJAZE: IZAZOVI I ISKUSTVO IZ MALOG TERCIJARNOG ZDRAVSTVENOG CENTRA

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Uvod: Psorijaza je hronična inflamatorna bolest kože koja negativno utiče na kvalitet života pacijenata. U poslednjoj deceniji, terapijski ciljevi za pacijente obolele od psorijaze su visoko postavljeni, a to su postizanje čišćenja kože i omogućavanje pacijentu obavljanje svakodnevnih aktivnosti, tako da uticaj bolesti na društvene, porodične i radne aktivnosti bude minimalan ili nepostojeći. U smislu takve potrebe, biološki lekovi su se pokazali kao nada i obećanje za postizanje bolje kontrole bolesti. Međutim, ubrzo je uočeno da oko 30% pacijenata ne reaguje u dovoljnoj meri na terapiju dugoročno i javlja se potreba za zamenom bioloških lekova.

Rezultati: Ovde predstavljamo naše iskustvo za određeni vremenski period u vezi sa potrebom za zamenu bioloških lekova. Do sada je sedamnaest pacijenata bilo u potrebi za zamenom biološkog leka, a tri od njih su dva puta menjala lek. Od sedamnaest pacijenata, četrnaest su bili muškarci i tri žene. Prosečan BMI pacijenata bio je 29,81. Jedan pacijent je podvrgnut eskalaciji doze sekukinumaba zbog primarnog neuspeha, ali je ipak na kraju promenio biološki lek. Glavni razlozi za zamenu bioloških lekova bili su usled sekundarnog neuspeha (gubitak efikasnosti koji je bio prisutan nakon početka lečenja, biološki zamor) i nakon toga usled primarnog neuspeha. Srećom, zamena zbog neželjenih reakcija nije česta. Ovo dokazuje zadovoljavajući bezbednosni profil bioloških lekova.

Zaključak: Biološki agensi odobreni za lečenje psorijaze pokazali su povoljan bezbednosni profil, bez ugrožavanja efikasnosti. Potrebna je veća efikasnost lečenja psorijaze kako bi se smanjili svi negativni uticaji koje psorijaza ima na različite aspekte zdravlja i života pacijenata. Procenjuje se da će biološka promena biti sve češća u kliničkoj praksi. Javlja se uglavnom zbog neadekvatnog terapijskog odgovora, a ređe zbog neželjenih reakcija (kao što su infekcije). Podaci iz literature, kao i naše kliničko iskustvo sugerišu da konstitucionalni faktori mogu da utiču na uspeh lečenja. Sve u svemu, uspostavljeni su neki standardi i preporuke u zameni bioloških lekova, međutim kako se pojavljuju novi agensi i terapijske mete, potrebno je razmotriti potrebu za njihovom stalnom i kontinuiranom korekcijom.

***Ključne reči**:* psorijaza, biološki lekovi, zamena, primarni neuspeh, sekundarni neuspeh, neefikasnost.

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***How to cite this article**:* Bojic Djurovic M, Bojic M, Popovic A, Golubovic M, Raznatovic Djurovic M. Switching biologics in psoriasis: challenges and experience from a small tertiary health-care center. Sanamed. 2024; 19(1): 45-49. Doi: 10.5937/sanamed0-48793.