

GUSELKUMAB KAO USPEŠNA ČETVRTA LINIJA TERAPIJE

GUSELKUMAB AS A SUCCESSFUL FOURTH-LINE THERAPY

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Sažetak

Guselkumab je monoklonsko antitelo koje selektivno inhibira p19 subjedinicu interleukina-23, čime postiže kontrolu inflamatornih procesa u psorijazi i psorijaznom artritisu. Pokazao je značajnu efikasnost i dobar bezbednosni profil kod biološki naivnih, kao i kod prethodno lečenih pacijenata. Prikazujemo slučaj muškarca starosti 42 godine sa plak-psorijazom, uspešno lečenog guselkumabom nakon nezadovoljavajućeg terapijskog odgovora na primenu metotrek-sata, adalimumaba, ustekinumaba i sekukinumaba. Pri započinjanju lečenja guselkumabom psorijaza je bila izražena (Psoriasis Area and Severity Index 22, Body Surface Area 50%, Dermatology Life Quality Index 20/30), dok je nakon 14 meseci postignuto gotovo potpuno povlačenje promena (Psoriasis Area and Severity Index 1.9, Body Surface Area 3%, Dermatology Life Quality Index 7/30) bez neželjenih reakcija. Ovaj prikaz ističe izraženu kliničku efikasnost guselkumaba čak i kod pacijenata koji su prethodno lečeni višestrukim biološkim terapijama. U poređenju sa anti-tumorski faktor nekroze- α , anti-interleukin-12/23 i anti-interleukin-17 lekovima, guselkumab pokazuje selektivnije i trajnije delovanje uz jednostavniji režim doziranja. Njegova primena kao uspešne četvrte linije terapije potvrđuje značaj interleukin-23 inhibicije kao dragocenog terapijskog pristupa u refraktornoj psorijazi i psorijaznom artritisu.

Ključne reči: monoklonska antitela; psorijaza; psorijazni artritis; biološka terapija; ishod lečenja; interleukin-23

Abstract

Guselkumab is a monoclonal antibody that selectively inhibits the p19 subunit of interleukin-23, providing a targeted mechanism for controlling inflammatory pathways in psoriasis and psoriatic arthritis. It has demonstrated high efficacy and favorable safety profile in both biologic-naïve and biologic-experienced patients. We present a case of a 42-year-old male with plaque psoriasis successfully treated with guselkumab after inadequate responses to methotrexate, adalimumab, ustekinumab, and secukinumab. At guselkumab initiation, the disease was extensive (Psoriasis Area and Severity Index 22, Body Surface Area 50%, Dermatology Life Quality Index 20/30). After 14 months of therapy, the patient achieved near-complete skin clearance (Psoriasis Area and Severity Index 1.9, Body Surface Area 3%, Dermatology Life Quality Index 7/30) with no adverse events. This case highlights the robust clinical efficacy of guselkumab even in patients previously treated with multiple biologic agents. Compared to anti-tumor necrosis factor- α , anti-interleukin-12/23, and anti-interleukin-17 therapies, guselkumab demonstrates superior selectivity, durability of response, and convenient dosing. Its effectiveness as a fourth-line option reinforces interleukin-23 inhibition as a valuable therapeutic strategy in refractory psoriasis and psoriatic arthritis.

Keywords: Antibodies, Monoclonal; Psoriasis; Arthritis, Psoriatic; Biological Therapy; Treatment Outcome; Interleukin-23

Uvod

Guselkumab je monoklonsko antitelo imunoglobulina G1 λ klase koje selektivno vezuje i inhibira p19-podjedinicu interleukina-23 (IL-23), jednog od ključnih citokina uključenih u inflamatorni proces. Koristi se u lečenju umerene do teške plak-psorijaze i psorijaznog artritisa,

Introduction

Guselkumab is an immunoglobulin G1 λ monoclonal antibody that selectively targets and inhibits the p19 subunit of interleukin-23 (IL-23), a key cytokine in the inflammatory process. It is approved for the treatment of moderate to severe plaque psoriasis and psoriatic arthritis.

Tabela 1. Prikaz terapijskih modaliteta, trajanja terapije i rezultata
Table 1. Preview of therapy, duration and results

Biološki lek/ Biologic therapy	Trajanje terapije/ Duration of therapy	Inicijalni/ Initial PASI, BSA	Po obustavi leka/ After discontinuation PASI, BSA
Adalimumab	17 meseci/months	PASI 14.4	PASI 0.9, BSA 0.5%
Ustekinumab	13 meseci/months	PASI 0.9, BSA 0.5%	PASI 13.4, BSA 13%
Secukinumab	24 meseci/months	PASI 15.8, BSA 15%	PASI 7.2, BSA 5%
Guselkumab	14 meseci/months - trenutno/ongoing	PASI 22, BSA 50%	PASI 1.9, BSA 3%

naročito kod pacijenata sa nezadovoljavajućim odgovorom na drugu sistemsku terapiju [1].

Guselkumab je pokazao efikasnost i kod biološki naivnih pacijenata, kao i kod onih koji su prethodno lečeni drugim biološkim agensima [2].

Predstavljamo slučaj u kome je guselkumab uspešno primenjen kao terapija četvrte linije u lečenju psorijaze, uz prikaz kliničke slike, protokola evaluacije (PASI skor, DLQI, EARP) i terapijskog pristupa (**Tabela 1**).

Prikaz slučaja

Muškaracu starom 42 godine dijagnostikovana je psorijaza 2000. godine. Inicijalna sistemska terapija obuhvatala je metotreksat u dozi od 15 mg nedeljno tokom dve godine. Zbog pogoršanja bolesti (PASI 14,4) tokom terapije metotreksatom, uveden je adalimumab u kombinaciji sa niskom dozom metotreksata (5 mg nedeljno) u cilju prevencije formiranja antitela protiv leka (ADA) [3,4].

Odgovor na terapiju adalimumabom bio je zadovoljavajući (PASI 0,9, BSA 0,5%, DLQI 1/30, EARP 0/10), ali zbog ograničene dostupnosti leka, nakon 17 meseci terapije pacijentu je prepiisan ustekinumab. Godinu dana kasnije, tokom lečenja ustekinumabom (PASI 13,4, BSA 13%, DLQI 8/30, EARP 0/10), pacijent je prijavio da šest meseci unazad ima izraženu mučninu dani-ma nakon primene leka (**Slike 1 a, b i c**). Nakon detaljne gastroenterološke evaluacije, uzrok mučnine nije utvrđen. S obzirom na prisutne simptome i nedostatak terapijske efikasnosti, nakon 13 meseci terapije (PASI 15,4, BSA 15%, DLQI 12/30, EARP 0/10), odlučeno je da se ustekinumab zameni trećim biološkim lekom, sekukinumabom.

Terapija sekukinumabom trajala je dve godine, uz dodatak metotreksata u dozi od 15 mg nedeljno tokom poslednje godine. Zbog nezadovoljavajućeg efekta, terapija sekukinu-

riatic arthritis, particularly in patients who have responded inadequately to previous systemic therapy [1].

Guselkumab has demonstrated clinical effectiveness in both biologic-naïve patients and those previously treated with other biologics [2].

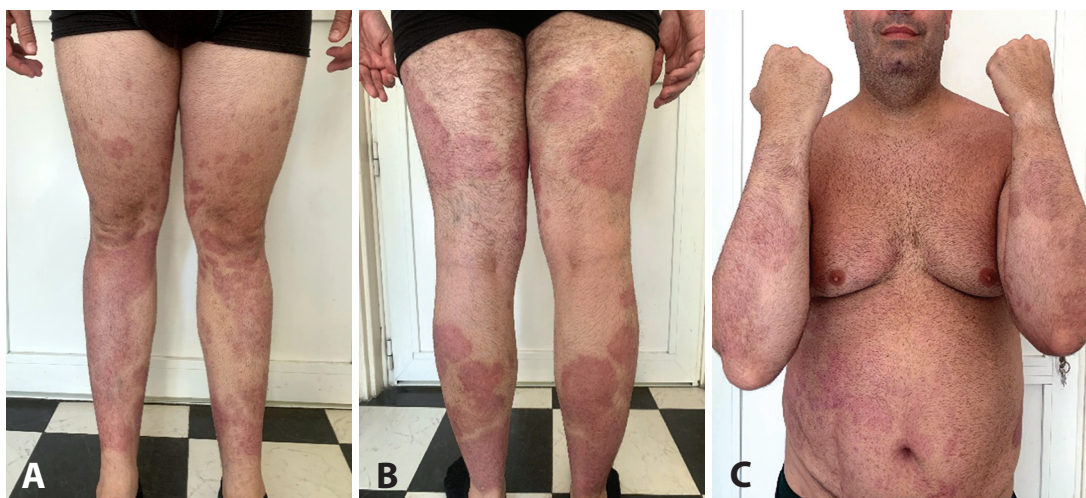
Here, we present a case in which guselkumab was successfully used as a fourth-line therapy in psoriasis management. We describe the clinical course, assessment protocol (PASI, DLQI, EARP) and therapeutic approach (**Table 1**).

Case report

A 42-year-old male was diagnosed with psoriasis in 2000. His initial systemic treatment consisted of methotrexate, 15 mg per week for two years. Due to worsening (PASI 14.4) on methotrexate, adalimumab was initiated with low-dose methotrexate (5 mg/week) to reduce the risk of anti-drug antibody (ADA) formation [3,4].

The patient responded well to adalimumab (PASI 0.9, BSA 0.5%, DLQI 1/30, EARP 0/10). However, after seventeen months the therapy was discontinued due to limited availability of adalimumab, and ustekinumab was introduced. One year later, during ustekinumab therapy (PASI 13.4, BSA 13%, DLQI 8/30, EARP 0/10), the patient reported severe nausea occurring after each drug administration over the previous six months (**Figure 1 a-c**). Gastrointestinal evaluations did not identify a cause. Given the worsening psoriasis (PASI 15.4, BSA 15%, DLQI 12/30, EARP 0/10) after 13 months of treatment and persistent nausea, ustekinumab was discontinued and secukinumab was initiated.

Secukinumab treatment lasted for two years; methotrexate (15 mg/week) was added



Slika 1. Klinička slika tokom terapije ustekinumabom: A, B i C – Na trupu i ekstremitetima eritematozni plakovi, prekriveni skavomom

Figure 1. Clinical presentation during ustekinumab therapy: A, B and C – Erythematous plaques and scale on trunk and extremities

mabom i metotreksatom je prekinuta (PASI 7,2, BSA 5%, DLQI 13/30, EARP 0/10).

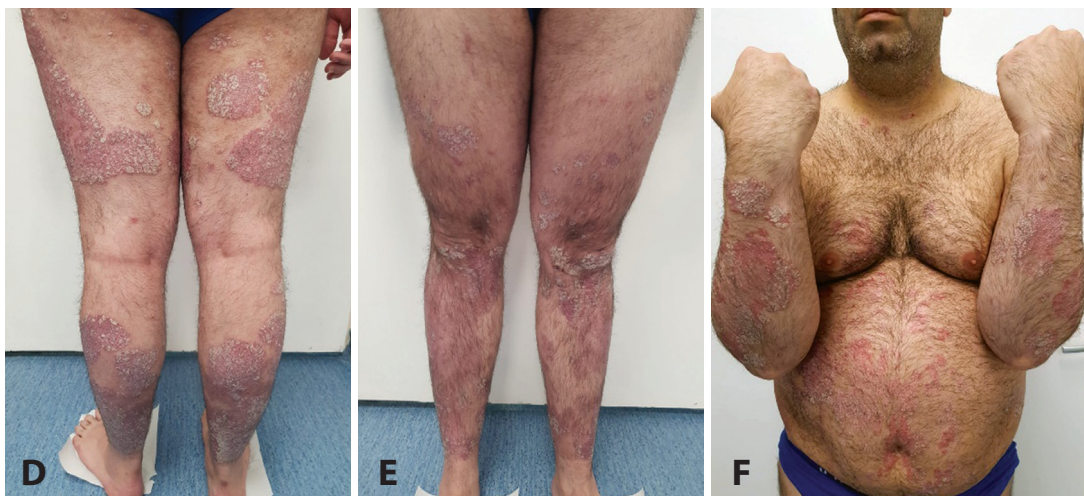
Tokom narednih 14 meseci, zbog izostanka odgovora na sistemsku terapiju, pacijentu je ordinirana samo lokalna kortikosteroidna terapija.

Metotreksat u dozi od 25 mg nedeljno ponovno je ordiniran šest meseci pre započinjanja četvrte biološke terapije. Guselkumab je uveden sa inicijalnim vrednostima PASI 22, BSA 50%, DLQI 20/30, EARP 0/10 (**Slike 2 d, e i f**). Pacijent

during the final year. Due to insufficient efficacy, both secukinumab and methotrexate were stopped (PASI 7.2, BSA 5%, DLQI 13/30, EARP 0/10).

For the next 14 months, due to poor response of systemic therapy, only topical corticosteroids were prescribed.

The patient was later restarted on methotrexate (25 mg/week) for six months, before initiating a fourth biologic therapy. Guselku-



Slika 2. Klinička prezentacija na početku terapije guselkumabom: D, E i F – Na trupu i ekstremitetima infiltrirani, eritematozni plakovi prekriveni skvavomom

Figure 2. Clinical presentation at initiation of guselkumab therapy: D, E and F – Infiltrated, erythematous plaques and scale on extremities and trunk



Slika 3. Klinička slika tokom terapije guselkumabom: G – Rezidualne hiperpigmentovane makule na donjim ekstremitetima; H – Rezistentne eritematozne papule i plakovi na potko- lenicama; I – Potpuno povlačenje promena na koži

Figure 3. Clinical presentation during guselkumab therapy: G – Residual hyperpigmented macules and patches on lower extremities; H – Resistant erythematous plaques and papules on lower legs; I – complete skin clearance

jent je na terapiji guselkumabom 14 meseci, sa značajnim kliničkim poboljšanjem (PASI 1,9, BSA 3%, DLQI 7/30, EARP 0/10) (**Slike 3 g, h i i**).

Diskusija

Guselkumab je u brojnim studijama pokazao bolju kliničku efikasnost u poređenju sa adalimumabom, antitelom usmerenim protiv faktora nekroze tumora alfa (anti-TNF- α), kao i dugotrajniji efekat u terapiji plak-psorijaze [5, 6]. Treba istaći da guselkumab ima povoljniji bezbednosni profil, sa manjom učestalošću ozbiljnih neželjenih efekata i manjim brojem kontraindikacija u odnosu na adalimumab [7].

Ustekinumab, monoklonsko antitelo koje inhibira interleukin-12 (IL-12) i interleukin-23 (IL-23) putem njihove zajedničke p40-podjedinice, pokazalo je efikasnost u terapiji plak-psorijaze. Iako oba leka, ustekinumab i guselkumab, deluju na IL-23 put, guselkumab specifično inhibira p19-podjedinicu IL-23 omogućavajući selektivniju blokadu citokina. Klinički dokazi pokazuju da guselkumab pruža dugotrajniju efikasnost i bolju stabilnost odgovora u lečenju plak-psorijaze u odnosu na ustekinumab, što se može pripisati njegovom selektivnijem mehanizmu dejstva [8,9]. Važno je istaći da guselkumab pokazuje i superiornu

mab treatment was introduced with baseline disease severity of PASI 22, BSA 50%, DLQI 20/30, EARP 0/10 (**Figure 2 d-f**). He continues therapy with maintained response and without adverse events (PASI 1.9, BSA 3%, DLQI 7/30, EARP 0/10) (**Figure 3 g-i**).

Discussion

Guselkumab has shown superior clinical efficacy compared to adalimumab (anti-TNF- α) in several trials, with more durable responses in plaque psoriasis [5,6]. Safety data indicate a lower incidence of serious adverse events and fewer contraindications relative to adalimumab [7].

Ustekinumab, a monoclonal antibody targeting interleukin-12 (IL-12) and interleukin-23 (IL-23) via their shared p40 subunit, has demonstrated efficacy in the treatment of plaque psoriasis. Although both ustekinumab and guselkumab target the IL-23 pathway, guselkumab selectively inhibits the p19 subunit of IL-23, resulting in more targeted cytokine blockade. Clinical evidence indicates that guselkumab provides superior long-term efficacy and greater durability of response in plaque psoriasis compared with ustekinumab, likely due to its more specific mechanism of action [8,9]. Moreover, guselkumab has

efikasnost u lečenju psorijatičnog artritisa u odnosu na ustekinumab. Kliničke studije i indirektne komparativne analize ukazuju da guselkumab postiže značajno bolje rezultate u ublažavanju kožnih i zglobnih simptoma, sa višim ACR20/50 stopama odgovora i većim procentom pacijenata koji dostižu PASI90 [10].

U poređenju sa sekukinumabom, monoklonskim antitelom čiji je target interleukin-17A (IL-17A), ključni efektorski citokin Th17 puta, guselkumab je pokazao superiorne rezultate u postizanju viših nivoa nezahvaćenosti kože psorijazom (PASI90 i PASI100) u kliničkim ispitivanjima, što se verovatno može objasniti njegovim dejstvom na IL-23/Th17 osu [11]. U terapiji psorijaznog artritisa, i sekukinumab i guselkumab pokazuju značajno poboljšanje zglobnih i entezitis simptoma, ipak, sekukinumab ima prednost kod pacijenata sa zahvatanjem aksijalnog skeleta, s obzirom na dokazanu efikasnost kod ankilozantnog spondilitisa i neradiografskog aksijalnog spondiloartritisa [12]. Treba naglasiti da guselkumab, koji se primenjuje na osam nedelja nakon inicijalne faze, u poređenju sa sekukinumabom, koji zahteva primenu na četiri nedelje, pruža veću pogodnost za pacijente, samim tim bolju kompilijansu, kao i niže troškove lečenja [13].

Guselkumab je pokazao visoku efikasnost i kod pacijenata koji su prethodno lečeni drugim biološkim agensima. Kliničke studije kao i podaci iz realne kliničke prakse pokazuju da pacijenti već lečeni drugim biološkim lekom postižu značajno poboljšanje u čistoći kože uz guselkumab, iako su stope odgovora nešto niže u poređenju sa biološki naivnim pacijentima. Selektivna inhibicija IL-23 p19-podjedinice verovatno omogućava guselkumabu da prevaziđe rezistenciju viđenu kod drugih terapijskih opcija [2,5].

Zaključak

Guselkumab se pokazao kao visokoefikasna terapijska opcija za lečenje umerene do teške plak-psorijaze i psorijaznog artritisa. Selektivnom inhibicijom IL-23 p19-podjedinice, guselkumab obezbeđuje precizniji i dugotrajniji terapijski efekat u poređenju sa drugim biološkim lekovima, poput ustekinumaba, adalimumaba i sekukinumaba. Prikazani slučaj potvrđuje potencijal guselkumaba kao uspešne četvrte linije terapije, uz postizanje značajnog kliničkog poboljšanja, povoljan bezbednosni profil i jednostavniji režim doziranja. Zahvaljujući efikasnosti i praktičnosti primene, guselkumab

shown superior efficacy psoriatic arthritis, with clinical trials and indirect comparative analyses demonstrating greater improvements in both joint and skin symptoms, including higher ACR20/50 response rates and superior PASI90 outcomes [10].

Compared to secukinumab, a monoclonal antibody directed against interleukin-17A (IL-17A) – a key effector cytokine in the Th17 pathway – guselkumab has achieved higher rates of skin clearance (PASI90 and PASI100) in clinical trials, likely attributable to its upstream modulation of the IL-23/Th17 axis [11]. In psoriatic arthritis, both agents demonstrate significant improvements in joint and enthesitis symptoms; however, secukinumab offers advantages in patients with axial involvement due to its established efficacy in ankylosing spondylitis and non-radiographic axial spondyloarthritis [12]. Additionally, guselkumab's maintenance dosing schedule – every eight weeks after induction – provides greater convenience and may improve treatment adherence compared with secukinumab, which requires administration every four weeks. Guselkumab has also been associated with lower overall treatment costs [13].

Guselkumab has demonstrated robust efficacy in biologic-experienced patients as well. Clinical trials and real-world evidence show that patients previously treated with other biologic agents achieve meaningful skin clearance, although response rates are generally somewhat lower than in biologic-naïve populations. The selective inhibition of the IL-23 p19 subunit may help guselkumab to overcome resistance observed with other biologic therapies [2,5].

Conclusion

Guselkumab has emerged as a highly effective option for the management of moderate to severe plaque psoriasis and psoriatic arthritis. Its targeted inhibition of IL-23 p19 subunit provides superior selectivity, strong clinical durability, and a favorable safety and dosing profile compared with other biologics such as ustekinumab, adalimumab, and secukinumab. This case demonstrates that guselkumab can be an excellent fourth-line therapy in refractory psoriasis, resulting in substantial and sustained improvement. Given its efficacy, safety, and convenient dosing

predstavlja vredan terapijski izbor kod pacijenata sa ekstenzivnom plak-psorijazom, naročito kod onih koji su već lečeni biološkom terapijom.

regimen, guselkumab represents a valuable therapeutic option, particularly for patients with extensive disease who have been treated with multiple biologic agents.

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