

PRIMENA JAK INHIBITORA U TERAPIJI ALOPECIJE AREATE

USE OF JAK INHIBITORS IN THE TREATMENT OF ALOPECIA AREATA

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Sažetak

Alopecija areata predstavlja hronično, imunoposredovano autoimuno oboljenje koje pogađa folikule dlake, nokte i povremeno pigmentni epitel mrežnjače. Najčešće zahvata folikule dlake u anagenoj fazi i dovodi do potpunog ili delimičnog gubitka kose, bez trajnog oštećenja folikula dlake i bez stvaranja ožiljka. Patogeneza bolesti je složena i obuhvata genetske faktore, imunofaktore, faktore iz spoljašnje sredine, oksidativni stres, alergiju, mikrobiom, kao i druge faktore koji dovode do autoimunih poremećaja u normalnom ciklusu kose. Današnja terapija alopecije areate obuhvata topikalne ili sistemske kortikosteroide, minoksidil, metotreksat i azatioprin koji pokazuju ograničenu efikasnost, naročito u težim slučajevima alopecije. Istraživanjem patogeneze alopecije areate, naučnici su došli do novih terapijskih modaliteta u lečenju poput inhibitora Janus kinaze. Inhibitori Janus kinaze predstavljaju male molekule koji mogu blokirati jednu ili više tirozin kinaza u JAK-STAT (engl. Janus kinase/signal transducer and activator of transcription pathway) signalnom putu, uključujući JAK1, JAK2, JAK3 i tirozin kinazu 2. Na taj način blokiraju različite citokinske i inflamatorne puteve i dovode do imunosupresije. Trenutni podaci ukazuju na to da su oralni inhibitori Janus kinaze (baricitinib, ritlecitinib, deuruxolitinib, brepocitinib) obećavajuća nova klasa lekova. Inhibitori Janus kinaze mogu izazvati značajan ponovni rast dlake, sa blagim do umerenim neželjenim dejstvima, i zbog toga im se danas daje prednost u odnosu na kortikosteroide.

Ključne reči: alopecija areata; inhibitori Janus kinaze; dermoskopija; ishod lečenja; neželjene reakcije na lekove

Abstract

Alopecia areata (AA) is a chronic, immune-mediated autoimmune disease that affects hair follicles, nails, and occasionally the retinal pigment epithelium. The disease most commonly involves hair follicles in the anagen phase and leads to complete or partial hair loss without permanent damage to the hair follicles and without scar formation. The pathogenesis of alopecia areata is complex and includes genetic factors, immune factors, environmental influences, oxidative stress, allergy, microbiome, as well as other factors that lead to autoimmune disorders in the normal hair cycle. Current alopecia areata therapy includes topical or systemic corticosteroids, minoxidil, methotrexate, and azathioprine, which show limited efficacy, especially in more severe forms of alopecia. Advances in understanding the pathogenesis of alopecia areata have led to the development of new treatments, such as Janus kinase inhibitors. Janus kinase inhibitors are small molecules capable of blocking one or more tyrosine kinases within the JAK-STAT (Janus kinase/signal transducer and activator of transcription pathway) signaling pathway, including JAK1, JAK2, JAK3 and tyrosine kinase 2. This way, they block various cytokine and inflammatory signaling pathways and induce immunosuppression. Current data indicates that oral Janus kinase inhibitors (baricitinib, ritlecitinib, deuruxolitinib, brepocitinib) constitute a promising new drug class. Janus kinase inhibitors can induce substantial hair regrowth with mild-to-moderate adverse effects and are therefore increasingly favored over corticosteroids.

Key words: Alopecia Areata; Janus Kinase Inhibitors; Dermoscopy; Treatment Outcome; Drug-Related Side Effects and Adverse Reactions

Uvod

Alopecija areata (AA) predstavlja hronično, imunološki posredovano autoimuno

Introduction

Alopecia areata (AA) is a chronic, immune-mediated autoimmune disease that af-

oboljenje koje pogađa folikule dlake, nokte i povremeno pigmentni epitel mrežnjače. Najčešće zahvata folikule dlake u anagenoj fazi i dovodi do potpunog ili delimičnog gubitka kose, bez trajnog oštećenja folikula dlake i bez stvaranja ožiljka [1].

Prevalencija AA u opštoj populaciji iznosi 0,1–0,2% i može se javiti kod svih osoba bez obzira na etničku pripadnost, pol ili starost [1,2].

Patogeneza bolesti je složena i obuhvata genetske faktore, imunološke faktore, faktore iz spoljašnje sredine, oksidativni stres, alergiju, mikrobiom, kao i druge faktore koji dovode do autoimunih poremećaja u normalnom ciklusu kose. Folikul dlake se smatra „imuno-privilegovanim mestom“ jer je u folikulu dlake smanjena ekspresija molekula glavnog kompleksa imunohistokompatibilnosti (MHC) klase I u anagenim folikulima dlake, što može izolovati autoantigene od prezentacije CD8 + T-ćelijama. Pored toga, sekrecija lokalnih imunosupresivnih molekula u folikulu dlake, kao što su transformišući faktor rasta b1 (engl. Transforming growth factor-TGF- β 1), interleukin-10 (IL-10), α -melanocit-stimulišući hormon (α -MSH), indolamin-2,3-dioksigenaza (IDO) i vazoaktivni crevni peptid (VIP) mogla bi doprineti formiranju lokalne imunoinhibitorne sredine i očuvanju folikula kao „imuno-privilegovanog mesta“ [1,3].

U osnovi nastanka AA je imunološki proces koji je posredovan T-limfocitima sa dominantnim Th1/Interferon- γ (IFN- γ) odgovorom koji dovodi do stimulacije CD8+NKG2D+ efektivnih T-ćelija. T-ćelije infiltriraju određene folikule kose. IL-15 je takođe u većoj meri prisutan u obolelim folikulima kose, aktivirajući CD8+NKG2D+ citotoksične T-ćelije koje proizvode IFN- γ , što dovodi do nastanka pozitivne povratne sprege koja podstiče dodatnu produkciju IL-15. Posledično dolazi do prelaza folikula kose iz distrofične anagene u katagenu fazu, što za rezultat ima nastanak AA [4]. Međutim, epitelne matične ćelije koje se nalaze u folikulu dlake nisu uglavnom napadnute, tako da AA može biti reverzibilan proces čak i u većini teških slučajeva. Ponovno uspostavljanje „imunoprivilegovanosti folikula“ dlake je verovatno preduslov za spontanu ili dugoročnu remisiju. Stoga, ubrzavanje i podsticanje procesa ponovnog uspostavljanja „imunološke privilegovanosti folikula“ dlake bi mogla biti obećavajuća strategija lečenja [5].

ffects hair follicles, nails, and occasionally the retinal pigment epithelium. The disease most commonly involves hair follicles in the anagen phase and leads to complete or partial hair loss without permanent damage to the hair follicles and without scar formation [1].

The prevalence of AA in the general population is estimated at 0.1-0.2% and it can occur in individuals regardless of ethnicity, sex or age [1,2].

The pathogenesis of AA is complex and includes genetic factors, immune factors, environmental influences, oxidative stress, allergy, microbiome, as well as other factors that lead to autoimmune disorders in the normal hair cycle. The hair follicle is regarded as an “immune-privileged site” because anagen hair follicles show reduction in expression of major histocompatibility complex (MHC) class I molecules, which can isolate autoantigens from presentation by CD8 + T cells. In addition, secretion of local immunosuppressive molecules within the hair follicle, such as transforming growth factor b1 (TGF-b1), interleukin-10 (IL-10), α -melanocyte-stimulating hormone (α -MSH), indoleamine-2,3-dioxygenase (IDO) and vasoactive intestinal peptide (VIP) may contribute to the formation of a local immunoinhibitory environment and preserve the follicle as an “immune-privileged site” [1,3].

The development of AA is an immune process that is mediated by T lymphocytes with a dominant Th1/Interferon- γ (IFN- γ) response that leads to the stimulation of CD8+NKG2D+ effector T cells. T cells infiltrate specific hair follicles. IL-15 is also more abundant in diseased hair follicles, activating CD8+NKG2D+ cytotoxic T-cells that produce IFN- γ , resulting in a positive feedback loop that promotes additional IL-15 production. As a result, the transition of hair follicles from dystrophic anagen to catagen phase occurs, which results in the formation of AA [4]. However, the epithelial stem cells found in the hair follicle are not generally attacked, so AA can be a reversible process even in most severe cases. Re-establishment of the “follicular immune privilege” of the hair is probably a prerequisite for spontaneous or long-term remission. Therefore, accelerating and stimulating the process of re-establishing the “immunological privilege of the hair follicle” could be a promising treatment strategy [5].

Klinička slika karakteristična je po pojavi malog, izolovanog, glatkog, neožilnog, okruglog ili ovalnog „pečata“ bez kose na koži glave ili bilo kom području gde raste dlaka. Najčešća mesta gubitka kose su teme i brada [2,4]. Vremenom kod mnogih osoba dolazi do spontanog rasta kose u roku od jedne godine, ali bolest može i da napreduje do alopecije totalis (AT), odnosno potpunog gubitka kose na skalpu ili do alopecije universalis (AU) koja predstavlja gubitak dlaka na celom telu [2]. Većina pacijenata doživljava nepredvidive epizode recidiva i remisije [1]. Postoji i redak difuzni oblik alopecije areata koja se manifestuje celokupnim stanjivanjem kose i primarno ovaj oblik alopecije zahvata temeni deo glave [4].

Za procenu verovatnoće ponovnog rasta kose na osnovu nalaza trihoskopije može se koristiti alopecia areata prediktivni skor (AAPS), dok se za procenu težine alopecije areata koristi SALT skor (Severity of Alopecia Tool) [4,6].

Pri pregledu kože glave dermoskopom mogu se uočiti određeni znakovi koji su značajni za dijagnozu i procenu aktivnosti bolesti. Neki od znakova koji se dermoskopski mogu uočiti su žute tačke, kratke velus dlake, dlake u obliku uzvičnika i crne tačke. Žute tačke predstavljaju ispunjen infundibulum dlake keratinskim materijalom i sebumom i one ukazuju na verovatnoću opstanka folikula dlake. Kratke velus dlake su tanke i nepigmentisane dlake, koje ukazuju na ponovni rast dlaka u AA. Nasuprot njima, uočene dlake u obliku uzvičnika i crne tačke ukazuju na aktivni oblik AA [7].

Iako AA nije životno ugrožavajuća bolest, to je hronično stanje koje karakterišu česti relapsi gubitka kose i progresija stanja što može dovesti i do razvoja psiholoških poremećaja poput depresije, anksioznosti i suicidalnosti. Zbog toga se lečenje AA zasniva ne samo na pružanju medikamentnog tretmana nego i na pružanju adekvatne psihološke podrške i pomoći obolelim osobama [1,2].

Današnja terapija AA obuhvata topikalne ili sistemske kortikosteroide, minoksidil, metotreksat i azatioprin koji pokazuju ograničenu efikasnost, naročito u težim slučajevima alopecije. Sam terapijski pristup zavisi od velikog broja faktora kao što su starost, obim i težina bolesti kao i očekivanja pacijenta [2,8].

Istraživanjem patogeneze AA, naučnici su došli do novih lekova u lečenju AA poput inhibitora Janus kinaze (JAK) [2].

The clinical presentation of AA is characterized by the appearance of a small, solitary, smooth, non-scarring, round or oval patch of hair loss on the scalp or any other hair-bearing area. The most common sites of hair loss are the scalp and the beard area [2,4]. Over time, spontaneous hair growth occurs in many people within one year, but the disease can also progress to alopecia totalis (AT), defined as complete scalp hair loss, or alopecia universalis (AU), which is the loss of hair over the entire body [2]. Most patients experience unpredictable episodes of relapse and remission [1]. A rare diffuse form of alopecia areata also exists, manifesting as generalized hair thinning that primarily affects the crown of the head [4].

For estimating the likelihood of hair regrowth based on trichoscopic findings, the Alopecia Areata Predictive Score (AAPS) can be used, whereas disease severity is assessed with the Severity of Alopecia Tool (SALT) score [4,6].

When examining the scalp with a dermoscope, certain signs can be observed that are significant for the diagnosis and assessment of disease activity. Some of the signs that can be observed dermoscopically are yellow dots, short vellus hairs, exclamation point hairs and black dots. The yellow dots represent a hair infundibulum filled with keratin material and sebum, and they indicate the likelihood of hair follicle survival. Short vellus hairs are thin and unpigmented hairs, indicative of hair regrowth in AA. In contrast, the observed exclamation point hairs and black dots indicate the active form of AA [7].

Although AA is not a life-threatening disease, it is a chronic condition characterized by frequent relapses of hair loss and disease progression, which may lead to the development of psychological disorders such as depression, anxiety and suicidal tendencies. Therefore, the treatment of AA is based not only on medical treatment, but also on providing adequate psychological support and assistance to affected individuals [1,2].

Current AA therapy includes topical or systemic corticosteroids, minoxidil, methotrexate, and azathioprine, which show limited efficacy, especially in more severe forms of alopecia. The therapeutic approach depends on a large number of factors such as age, extent and severity of the disease as well as the patient's expectations [2,8].

JAK inhibitori

Inhibitori Janus kinaze (JAK) predstavljaju male molekule koji mogu blokirati jednu ili više tirozin kinaza u JAK-STAT (engl. Janus kinase/signal transducer and activator of transcription pathway) signalnom putu, uključujući JAK1, JAK2, JAK3 i tirozin kinazu 2 (TYK2). Na taj način blokiraju različite citokinske i inflamatorne puteve i dovode do imunosupresije [9].

Mnogi od inflamatornih odgovora uključenih u patogenezu AA dele uobičajenu signalnu transdukciju putem JAK-STAT puta, u kojem proinflamatorni citokini poput IFN- γ i IL-15 aktiviraju JAK. Blokada ovog puta putem JAK inhibitora se nalazi u osnovi nove terapije AA [10].

Nedavna studija je pokazala da JAK inhibitori mogu blokirati T-limfocitima posredovan imunoodgovor u folikulima dlake, podstaći rast matičnih ćelija folikula dlake i inicirati angiogenezu, pri čemu oba procesa nastaju tokom faze rasta dlake. JAK inhibitori mogu ubrzati prelazak folikula dlake iz telogene faze u anagenu fazu [9].

Danas postoje dve generacije JAK inhibitora. Prvu generaciju čine mali molekuli koji deluju kao neselektivni inhibitori JAK, u koje spadaju baricitinib i tofacitinib. U lekove druge generacije ubrajaju se filogotinib i upadacitinib koji su selektivni inhibitori JAK [11].

Baricitinib selektivno inhibira JAK 1 i 2. Pokazao je 100 puta veću selektivnost za JAK1 i JAK2 u odnosu na JAK3. Niži afinitet za JAK3 bi potencijalno mogao da smanji imunosupresivne efekte koji se očekuju kao posledica inhibicije JAK3. Baricitinib ima oralnu bioraspoloživost od približno 80%. Poluživot mu je 12 sati. Približno 75% leka se eliminiše putem urina, a 20% putem fecesa. Od eliminisanog leka, 69% je nepromenjeno u urinu, a 15% u fecesu [12].

Baricitinib je odobren za lečenje umerenog do teškog reumatoidnog artritisa i umerenog do teškog atopijskog dermatitisa. Od 2022. godine, baricitinib je odobren za tešku alopeciju areata [12].

U studiji sprovedenoj u 2022. godini King i saradnici uključili su pacijente sa teškim oblikom alopecije areata (50–94% gubitka kose) ili veoma teškim oblikom AA (95–100% gubitka kose), sa trenutnom epizodom AA koja traje > 6 meseci, a < 8 godina, bez spontanog poboljšanja u poslednjih 6 meseci ili koja traje > 8 godina, ali sa epizodama ponovnog rasta u prethodnih 8 godina [13].

Advances in understanding of pathogenesis of AA have led to the development of new treatments of AA, such as Janus kinase (JAK) inhibitors [2].

JAK inhibitors

Janus kinase (JAK) inhibitors are small molecules capable of blocking one or more tyrosine kinases within the JAK-STAT (Janus kinase/signal transducer and activator of transcription pathway) signalling pathway, including JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2). This way, they block various cytokine and inflammatory signalling pathways and induce immunosuppression [9].

Many of the inflammatory responses involved in the pathogenesis of AA share a common signal transduction through the JAK-STAT pathway, in which pro-inflammatory cytokines such as IFN- γ and IL-15 activate JAK. Blockade of this pathway by JAK inhibitors underlies a novel therapeutic approach for AA [10].

A recent study demonstrated that JAK inhibitors can block the T-lymphocyte-mediated immune response in hair follicles, promote hair follicle stem cell growth, and initiate angiogenesis, both processes occurring during the hair growth phase. JAK inhibitors can accelerate the transition of hair follicles from the telogen phase to the anagen phase [9].

Currently, two generations of JAK inhibitors are recognized. The first generation comprises small molecules that act as non-selective JAK inhibitors, including baricitinib and tofacitinib. Second-generation drugs include filogotinib and upadacitinib, which are selective JAK inhibitors [11].

Baricitinib selectively inhibits JAK1 and JAK2 and demonstrates 100-fold greater selectivity for JAK1 and JAK2 over JAK3. Its lower affinity for JAK3 may potentially reduce the immunosuppressive effects expected as a consequence of JAK3 inhibition. Baricitinib has an oral bioavailability of approximately 80% and a half-life of 12 hours. Approximately 75% of the drug is eliminated via urine and 20% through faeces. Of the eliminated fraction, 69% is unchanged in urine, and 15% in faeces [12].

Baricitinib is approved for the treatment of moderate to severe rheumatoid arthritis and moderate to severe atopic dermatitis. As of 2022, baricitinib is approved for severe alopecia areata [12].

Tabela 1. Procenat pacijenata sa postignutim SALT skorom na različitim dozama baricitiniba**Table 1.** Percentage of patients with achieved SALT score at different doses of baricitinib

Baricitinib/Baricitinib	SALT 30 12. nedelja/weeks	SALT 50 ≤16 nedelja/weeks
4 mg	33,3%	38,1%
2 mg	29,6%	31,8%
1 mg	17,9%	18,2%
Placebo/Placebo	10,7%	4,5%

U 12. nedelji lečenja baricitinibom (faza 2) u dozi od 4 mg, 2 mg, 1 mg i placebo, 33,3%, 29,6%, 17,9% i 10,7% pacijenata je postiglo SALT30. Od pacijenata koji su završili 16 nedelja terapije ili su ranije prekinuli terapiju (87 pacijenata), SALT50 odgovor je postigao 38,1%, 31,8%, 18,2% i 4,5% pacijenata lečenih baricitinibom u dozi od 4 mg, 2 mg, 1 mg i placebo (**Tabela 1**) [12,13].

U 36. nedelji lečenja, značajno veći udeo pacijenata je postigao SALT ≤ 20 u grupi koja je primala baricitinib od 4 mg i 2 mg u poređenju sa placebo. SALT 10 rezultat je postignut kod većeg broja pacijenata u grupi koja je primala baricitinib 4 mg (40,7%, $P = 0,008$) i baricitinib 2 mg (25,9%, $P = 0,046$) u poređenju sa placebo (0%) [12,13].

U fazi 3 ovog istraživanja, formirane su dve randomizovane, placebo kontrolisane studije (BRAVE-AA1 i BRAVE-AA2) sa rezultima na skali za procenu težine alopecije (SALT) od 50 ili više (opseg, od 0 – bez gubitka kose glave do 100 – potpuni gubitak kose glave). Pacijenti su nasumično raspoređeni u odnosu 3 : 2 : 2 da primaju baricitinib jednom dnevno u dozi od 4 mg, 2 mg ili placebo. Procenat pacijenata sa SALT rezultatom od 20 ili manje u 36. nedelji je bio 38,8% za dozu od 4 mg baricitiniba, 22,8% za dozu od 2 mg i 6,2% sa placebo u prvoj studiji, a u drugoj studiji 35,9%, 19,4% i 3,3%. Razlika između upotrebe 4 mg i 2 mg baricitiniba u odnosu na placebo

In a 2022 study, King et al. included patients with severe AA (50-94% hair loss) or very severe AA (95-100% hair loss), with a current episode of AA lasting > 6 months and < 8 years without spontaneous improvement in the previous 6 months or disease duration > 8 years, but with episodes of regrowth in the previous 8 years [12,13].

At week 12 of treatment with baricitinib (phase 2) at doses of 4 mg, 2 mg, 1 mg and placebo, 33.3%, 29.6%, 17.9% and 10.7% of patients, respectively, achieved SALT30. Among patients who completed 16 weeks of therapy or discontinued earlier (87 patients), SALT50 response was achieved by 38.1%, 31.8%, 18.2%, and 4.5% of patients treated with baricitinib 4 mg, 2 mg, 1 mg, and placebo, respectively (**Table 1**) [13].

At week 36 of treatment, a significantly greater proportion of patients achieved SALT ≤ 20 in the baricitinib 4 mg and 2 mg groups compared with placebo. The SALT 10 score was achieved in more patients in the baricitinib 4 mg (40.7%, $P = 0.008$) and baricitinib 2 mg (25.9%, $P = 0.046$) groups compared with placebo (0%) [12,13].

In phase 3 of this program, two randomized, placebo-controlled trials (BRAVE-AA1 and BRAVE-AA2) were conducted in patients with a Severity of Alopecia Tool (SALT) score ≥ 50 (range 0 = no scalp hair loss to 100 = complete scalp hair loss). Patients were randomized

Tabela 2. Procenat pacijenata sa postignutim SALT ≤ 20 u 36. nedelji, BRAVE-AA1 i BRAVE-AA2 studije**Table 2.** Percentage of patients achieving SALT ≤ 20 at week 36, BRAVE-AA1 and BRAVE-AA2 studies

Baricitinib/Baricitinib	BRAVE- AA1	BRAVE-AA2
4 mg	38,8%	35,9%
2 mg	22,8%	19,4%
Placebo/Placebo	6,2%	3,3%
Statistička značajnost/Statistical significance	$p < 0,001$	$p < 0,001$

bila je u obe studije statistički značajna ($p < 0,001$) (**Tabela 2**) [13].

U studiji koju su sprovedi Džang (Zhang) i saradnici bio je uključen 61 pacijent sa ume-
renim do teškim oblikom alopecije areate. Is-
pitanici su bili podeljeni u tri grupe. Prva grupa
pacijenata lečena je sistemskim kortikosteroi-
dima (SC), druga grupa lečena je tofacitini-
bom, a treća kombinovanom terapijom [14].

Težina alopecije zabeležena je korišće-
njem SALT skora. SALT50, SALT90 i SALT100
su definisani kao 50, 90 i 100% ponovnog
rasta dlake [14].

U grupi koja je primala SC, 66,7% (12/18)
pacijenata je postiglo SALT50. Prosečno tra-
janje lečenja je bilo 6,2 meseca. 61,1% (11/18)
pacijenata je postiglo SALT90 (prosečna
dužina lečenja je 5,3 meseca), a 50% pacije-
nata je postiglo SALT100 (prosečno trajanje
lečenja je 5,1 mesec) (**Tabela 3**) [14].

U grupi koja je primala tofacitinib, 60%
(12/20) pacijenata je postiglo SALT50 za
prosečno trajanje terapije u dužini od 12,5
meseci. 50% (10/20) pacijenata je postiglo
SALT90 (za 13,2 meseca lečenja), a 30% pac-
ijenata je postiglo SALT100 (za 14,4 meseca
lečenja) (**Tabela 4**) [14].

U kombinovanoj grupi, 78,3% (18/23) paci-
jenata postiglo je SALT50. Prosečno trajanje
terapije bilo je 10,4 meseca. 56,5% pacijenata

in a 3:2:2 ratio to receive once-daily baricitinib
4 mg, 2 mg, or placebo. The proportion of pa-
tients achieving SALT ≤ 20 at week 36 was
38.8% with baricitinib 4 mg, 22.8% with 2 mg,
and 6.2% with placebo in BRAVE-AA1, and
35.9%, 19.4%, and 3.3%, respectively, in BRAVE-
AA2. The differences between both baricitinib
doses and placebo were statistically significant
in both trials ($p < 0.001$) (**Table 2**) [13].

In a study conducted by Zhang et al., 61
patients with moderate-to-severe alopecia
areata were included. The participants were
divided into three groups. The first group was
treated with systemic corticosteroids (SC), the
second with tofacitinib, and the third with
combination therapy [14].

Disease severity was recorded using the
SALT score. SALT50, SALT90, and SALT100
were defined as 50%, 90%, and 100% hair
regrowth, respectively [14].

In the SC group, 66.7% (12/18) of patients
achieved SALT50, with a mean treatment du-
ration of 6.2 months. SALT90 was achieved
by 61.1% (11/18) of patients (mean duration
5.3 months), and 50% achieved SALT100
(mean duration 5.1 months) (**Table 3**) [14].

In the tofacitinib group, 60% (12/20) of pa-
tients achieved SALT50 after a mean treatment
duration of 12.5 months. SALT90 was achieved
by 50% (10/20) of patients (13.2 months of

Tabela 3. Odgovor kod primene kortikosteroida: procenat pacijenata sa postignutim SALT skorom i prosečna dužina trajanja terapije

Table 3. Corticosteroid response: percentage of patients with achieved SALT score and average duration of therapy

SALT skor/score	Broj pacijenata Number of patients	Procenat pacijenata % Percentage of patients %	Prosečno trajanje terapije (meseci) Average duration of therapy (months)
SALT 50	12/18	66,7%	6,2
SALT 90	11/18	61,1%	5,3
SALT 100	9/18	50%	5,1

Tabela 4. Odgovor kod primene tofacitiniba: procenat pacijenata sa postignutim SALT skorom i prosečna dužina trajanja terapije

Table 4. Tofacitinib response: percentage of patients with achieved SALT score and average duration of therapy

SALT skor/score	Broj pacijenata Number of patients	Procenat % Percentage%	Prosečno trajanje terapije (meseci) Average duration of therapy (months)
SALT 50	12/20	60%	12,5
SALT 90	10/20	50%	13,2
SALT 100	6/20	30%	14,4

je postiglo SALT90 (za 8 meseci lečenja), a 26,1% pacijenata je postiglo SALT100 (za 6,4 meseca lečenja) (**Tabela 5**) [14].

U prospektivnoj studiji sprovedenoj 2021. godine, ispitanici su imali umereni do teški oblik AA. Svi učesnici su pre uključenja u studiju bili lečeni ciklosporinom. Kod 18 ispitanika koji nisu postigli SALT50 na primenjeni ciklosporin, terapija je promenjena u sublingvalno primenjeni tofacitinib 5 mg dva puta dnevno tokom 12 nedelja. Kod 37,5% ovih pacijenata nakon primene sublingvalnog tofacitiniba došlo je do poboljšanja kliničke slike dok je 12,5% ispitanika postiglo SALT 50 [10].

Otvorena uporedna studija za procenu efikasnosti JAK inhibitora kod 75 pacijenata sa AA (> 30% gubitka kose), AU i AT otkrila je značajno poboljšanje kliničke slike sa prosečnom promenom SALT rezultata od $93,8 \pm 3,25$ i $95,2 \pm 2,69$ u grupama sa tofacitinibom i ruxolitinibom. Stoga se smatra da nema potrebe za kombinovanjem JAK inhibitora sa sistemskim steroidima [11].

U prospektivnoj studiji sprovedenoj 2024. godine 706 pacijenata je randomizovano u grupe koje su primale deuruksolitinib 8 mg dva puta dnevno ($n = 351$), deuruksolitinib 12 mg dva puta dnevno ($n = 215$) ili placebo ($n = 140$). Lečenje je završilo 316/351 (90%), 197/215 (91,6%) i 129/140 (92,1%) pacijenata u grupama sa 8 mg dva puta dnevno, 12 mg dva puta dnevno i placebo. Obe doze deuruksolitiniba dovele su do značajno većeg udela pacijenata koji su postigli SALT rezultat ≤ 20 nakon 24 nedelje u odnosu na placebo. Značajno veći procenat pacijenata koji su primali deuruksolitinib postigao je SALT rezultat ≤ 20 nakon 8, 12, 16 i 20 nedelja u odnosu na placebo. Udeo pacijenata koji su postigli SALT rezultat ≤ 10 nakon 24 nedelje takođe je bio značajno veći u grupama sa 8 mg dva puta

treatment), and 30% achieved SALT100 (14.4 months of treatment) (**Table 4**) [14].

In the combined-therapy group, 78.3% (18/23) of patients achieved SALT50, with a mean treatment duration of 10.4 months. SALT90 was achieved by 56.5% of patients (8.0 months of treatment), and 26.1% achieved SALT100 (6.4 months of treatment) (**Table 5**) [14].

In a prospective study conducted in 2021, participants had moderate-to-severe AA. All subjects had previously been treated with cyclosporine before inclusion. Among 18 participants who did not achieve SALT50 with cyclosporine, therapy was switched to sublingual tofacitinib 5 mg twice daily for 12 weeks. Clinical improvement was observed in 37.5% of these patients after sublingual tofacitinib, while 12.5% achieved SALT50 [10].

An open comparative study evaluating the efficacy of JAK inhibitors in 75 patients with AA (> 30% hair loss), AU, and AT revealed significant clinical improvement, with mean SALT score changes of 93.8 ± 3.25 and 95.2 ± 2.69 in the tofacitinib and ruxolitinib groups, respectively. Therefore, it is considered that there is no need to combine JAK inhibitors with systemic steroids [11].

In a prospective study conducted in 2024, 706 patients were randomized to receive deuruxolitinib 8 mg twice daily ($n = 351$), deuruxolitinib 12 mg twice daily ($n = 215$), or placebo ($n = 140$). Treatment was completed by 316/351 (90.0%), 197/215 (91.6%), and 129/140 (92.1%) patients in the 8 mg, 12 mg, and placebo groups, respectively. Both doses of deuruxolitinib resulted in a significantly greater proportion of patients achieving a SALT score ≤ 20 after 24 weeks compared with placebo. A significantly higher percentage of patients receiving deuruxolitinib achieved SALT ≤ 20 at weeks 8, 12, 16, and 20 compared with placebo. The proportion of patients achieving

Tabela 5. Procenat pacijenata sa postignutim SALT skorom i dužina trajanja terapije

Table 5. Percentage of patients with achieved SALT score and duration of therapy

Grupa/Group	SALT 50		SALT 90		SALT 100	
	%	meseci/months	%	meseci/months	%	meseci/months
Sistemski kortikosteroidi Systemic corticosteroids	66,7	6,2	61,1	5,3	50	5,1
Tofacitinib/Tofacitinib	60	12,5	50	13,2	30	14,4
Kombinovana terapija Combined therapy	78,3	10,4	56,5	8,0	26,1	6,4

dnevno (20,8%) i 12 mg dva puta dnevno (34,5%) u odnosu na placebo (0%) [15].

Najnovija istraživanja ukazuju na to da su i ritlecitinib (inhibitor porodice JAK3 i tirozin-protein kinaze) i brepocitinib (inhibitor TYK2/JAK1) pokazali značajno smanjenje inflamatornih markera, uključujući Th1, aktivaciju Th1/NK/T-ćelija, ćelije povezane sa Th2, IL-23, Th22, Treg ćelije i JAK3, u uzorcima biopsije glave u 12. i 24. nedelji lečenja. Prema rezultatima ovog randomizovanog placebo kontrolisanog ispitivanja nakon 24 nedelje, SALT90 je postiglo 25% pacijenata u grupi koja je primala ritlecitinib i 34% pacijenata u grupi koja je primala brepocitinib, u poređenju sa 0% u placebo grupi, a oba leka su pacijenti dobro podnosili. S obzirom na mali broj neželjenih efekata, ova dva leka imaju potencijal da u budućnosti zamene postojeće lekove za lečenje AA [11,16].

Diskusija

Primena inhibitora Janus kinaze (JAK) predstavlja značajan napredak u terapiji AA. Razumevanje uloge JAK-STAT signalnog puta u patogenezi bolesti omogućilo je razvoj ciljane terapije JAK inhibitorima, koji deluju blokiranjem ključnih citokinskih signala uključenih u inflamatorni odgovor [1,11].

U poslednjih nekoliko godina, JAK inhibitori su pokazali značajnu efikasnost u terapiji umerene do teške alopecije areate, naročito kod pacijenata refraktornih na konvencionalnu terapiju [7,17]. Rezultati sistematskih pregleda i metaanaliza ukazuju da lekovi kao što su baricitinib, tofacitinib i ritlecitinib dovode do značajnog ponovnog rasta kose u poređenju sa placebom, uz prihvatljiv bezbednosni profil [2,9]. Ovi nalazi potvrđuju da inhibicija JAK signalizacije direktno utiče na ključne patogenetske mehanizme bolesti.

Baricitinib je trenutno jedan od najispitivanijih JAK inhibitora u terapiji alopecije areate, sa dokazima iz velikih randomizovanih studija, kao što su BRAVE-AA1 i BRAVE-AA2, koje pokazuju značajno poboljšanje AA u odnosu na placebo nakon 36 i 52 nedelje terapije [6,13]. Dugoročni rezultati ukazuju na održiv efekat, ali i potrebu za kontinuiranom terapijom kako bi se sprečio relaps bolesti [12]. Slični rezultati zabeleženi su i za deuruk-solitinib, koji je pokazao značajnu efikasnost u novijim randomizovanim studijama [15].

SALT ≤ 10 at week 24 was also significantly higher in the 8 mg twice-daily (20.8%) and 12 mg twice-daily (34.5%) groups compared with placebo (0%) [15].

Recent studies indicate that both ritlecitinib (a JAK3-family/tyrosine-protein-kinase inhibitor) and brepocitinib (a TYK2/JAK1 inhibitor) produced significant reductions in inflammatory markers – including Th1, Th1/NK/T-cell activation, Th2-associated cells, IL-23, Th22, Treg cells, and JAK3 – in scalp biopsy samples at weeks 12 and 24 of treatment. According to the results of this randomized placebo-controlled trial, after 24 weeks SALT90 was achieved by 25% of patients in the ritlecitinib group and 34% in the brepocitinib group, compared with 0% in the placebo group, and both drugs were well tolerated. Given the low incidence of adverse effects, these two agents have the potential to replace existing therapies for AA in the future [11,16].

Discussion

The use of Janus kinase (JAK) inhibitors represents a significant advancement in the treatment of AA. Understanding the role of the JAK-STAT signaling pathway in the disease pathogenesis has enabled the development of targeted therapy with JAK inhibitors, which act by blocking key cytokine signals involved in the inflammatory response [1,11].

In recent years, JAK inhibitors have demonstrated significant efficacy in the treatment of moderate-to-severe alopecia areata, particularly in patients refractory to conventional therapy [7,17]. Results from systematic reviews and meta-analyses indicate that drugs such as baricitinib, tofacitinib, and ritlecitinib lead to significant hair regrowth compared to placebo, with an acceptable safety profile [2,9]. These findings confirm that inhibition of JAK signaling directly affects key pathogenetic mechanisms of the disease.

Baricitinib is currently one of the most extensively studied JAK inhibitors in the treatment of alopecia areata, with evidence from large randomized trials such as BRAVE-AA1 and BRAVE-AA2 demonstrating significant improvement in AA compared to placebo after 36 and 52 weeks of treatment [6,13]. Long-term results suggest a sustained effect, but also indicate the need for continuous therapy to prevent disease relapse [12]. Similar results

Tofacitinib, takođe pokazuje visoku stopu odgovora kod pacijenata sa umerenom i teškom formom bolesti, uključujući i slučajeve sa dugotrajnim trajanjem alopecije [8,14]. Međutim, varijabilnost u odgovoru na terapiju ukazuje na heterogenost bolesti i potrebu za individualizovanim pristupom lečenju [18].

Pored toga, noviji selektivni inhibitori, kao što su ritlecitinib i brepocitinib, pokazuju obećavajuće rezultate kroz poboljšanje biomarkera bolesti i kliničkih ishoda, što ukazuje na potencijal za još precizniju ciljanu terapiju u budućnosti [16]. Razlike u selektivnosti prema JAK izoformama mogu imati značajan uticaj na efikasnost i bezbednost terapije, što je predmet aktuelnih istraživanja [11].

Iako su rezultati terapije JAK inhibitorima ohrabrujući, postoje određena ograničenja koja treba uzeti u obzir. Pre svega, dugoročna bezbednost ovih lekova još uvek nije u potpunosti razjašnjena, naročito u kontekstu povećanog rizika od infekcija, maligniteta i kardiovaskularnih događaja [2,17]. Takođe, visoka cena terapije i potreba za kontinuiranom primenom mogu predstavljati ograničavajuće faktore u svakodnevnoj kliničkoj praksi.

Takođe, relaps bolesti nakon prekida terapije predstavlja značajan izazov, što ukazuje da JAK inhibitori deluju pre svega supresivno, a ne kurativno [7]. Ovo naglašava potrebu za daljim istraživanjima koja bi se fokusirala na dugotrajnu remisiju i potencijalne kombinovane terapijske pristupe.

Zaključak

Jasno je da su inhibitori Janus kinaze budućnost terapije alopecie areate. Generalno, trenutni podaci ukazuju na to da su oralni inhibitori Janus kinaze (baricitinib, ritlecitinib, deuruxolitinib, brepocitinib) obećavajuća nova klasa lekova. Inhibitori Janus kinaze mogu izazvati značajan ponovni rast dlake, sa blagim do umerenim neželjenim dejstvima, i zbog toga im se danas daje prednost u odnosu na kortikosteroide.

Skraćenice

AA – Alopecija areata
JAK – Janus kinaza
JAK – STAT signalni put - engl. Janus kinase/signal transducer and activator of transcription pathway

have been reported for deuruxolitinib, which has shown significant efficacy in recent randomized studies [15].

Tofacitinib also shows a high response rate in patients with moderate-to-severe disease, including cases with long-standing alopecia [8, 14]. However, variability in treatment response indicates disease heterogeneity and the need for an individualized treatment approach [18].

In addition, newer selective inhibitors such as ritlecitinib and brepocitinib show promising results through improvements in disease biomarkers and clinical outcomes, suggesting the potential for even more precise targeted therapy in the future [16]. Differences in selectivity toward JAK isoforms may have a significant impact on both efficacy and safety, and this remains an area of ongoing research [11].

Although the results of JAK inhibitor therapy are encouraging, certain limitations must be considered. First, the long-term safety of these agents is still not fully clarified, particularly regarding an increased risk of infections, malignancies, and cardiovascular events [2,17]. In addition, the high cost of therapy and the need for continuous administration may represent limiting factors in everyday clinical practice.

Furthermore, disease relapse after treatment discontinuation represents a significant challenge, indicating that JAK inhibitors are primarily suppressive rather than curative agents [7]. This highlights the need for further research focused on long-term remission and potential combination therapeutic approaches.

Conclusion

It is evident that Janus kinase inhibitors represent the future of alopecia areata therapy. Overall, current data indicate that oral Janus kinase inhibitors (baricitinib, ritlecitinib, deuruxolitinib, brepocitinib) constitute a promising new drug class. Janus kinase inhibitors can induce substantial hair regrowth with mild-to-moderate adverse effects and are therefore increasingly favoured over corticosteroids.

Abbreviations

AA – Alopecia areata
JAK – Janus kinase
JAK – STAT signaling pathway - Janus kinase/signal transducer and activator of transcription pathway

MHC - glavni kompleks imunohistokompatibilnosti (engl. major histocompatibility complex)

TGF- β 1 – transformišući faktor rasta β 1

IL – Interleukin

α -MSH – α melanocit-stimulišući hormon

IDO – indolamin-2,3-dioksigenaza

VIP – vazoaktivni crevni peptid

IFN- γ – Interferon- γ

AT – Alopecija totalis

AU – Alopecija univerzalis

AAPS – Alopecia Areata Prediktivni Skor

SALT skor – engl. Severity of Alopecia Tool

TYK – Tirozin kinaza

SC – Sistemski kortikosteroidi

MHC – major histocompatibility complex

TGF- β 1 – Transforming growth factor

IL – Interleukin

α -MSH – α -melanocyte-stimulating hormone

IDO – indoleamine-2,3-dioxygenase

VIP – vasoactive intestinal peptide

IFN- γ – Interferon- γ

AT – Alopecia totalis

AU – Alopecia universalis

AAPS – Alopecia Areata Predictive Score

SALT score – Severity of Alopecia Tool

TYK – Tyrosine kinase

SC – Systemic corticosteroids

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