ANAFILAKTIČKI ŠOK IZAZVAN SUBKUTANOM IMUNOTERAPIJOM ALERGENOM *AMBROSIA ELATIOR* – PRIKAZ SLUČAJA

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CASE REPORT

ANAPHYLACTIC SHOCK CAUSED BY SUBCUTANEOUS IMMUNOTHERAPY WITH THE ALLERGEN *AMBROSIA ELATIOR* – CASE REPORT

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SAŽETAK

Uvod: Senzibilizacija na polen ambrozije može dovesti do simptoma alergijskog rinitisa, konjuktivitisa i alergijske astme. Alergenska imunoterapija (AIT) je imunomodulatorna terapijska procedura koja pored kratkoročnog kurativnog (smanjenje simptoma bolesti) ima i dugoročni preventivni efekat (sprečavanje progresije alergijskog rinitisa u alergijsku astmu i/ili sprečavanje razvoja teže forme bolesti). Dva glavna modaliteta primene alergenske imunoterapije koja se koriste u kliničkoj praksi su subkutana imunoterapija alergenom (engl. *subcutaneous allergen immunotherapy – SCIT)* i sublingvalna imunoterapija alergenom (engl. *sublingual allergen immunotherapy – SLIT*). Oba modaliteta imaju podjednaku efikasnost u smanjenju simptoma bolesti, ali je primena *SCIT*-a povezana sa većim rizikom od ispoljavanja lokalnih i sistemskih neželjenih reakcija.

Prikaz slučaja: U ovom radu prikazan je pacijent koji je razvio kliničku sliku anafilaktičkog šoka u toku indukcione faze *SCIT*-a ekstraktom polena *Ambrosia-e elatior*. Opisan je klinički tok kao i brzo i efikasno terapijsko zbrinjavanje ovog životno ugrožavajućeg stanja.

Zaključak: Kada se primenjuje pravilno doziranje, u medicinskoj ustanovi i pod lekarskim nadzorom, *SCIT* ambrozijom je veoma bezbedna i dobro tolerisana opcija lečenja alergijskog rinitisa. Lokalne reakcije na mestu subkutane primene javljaju se češće u odnosu na sistemske neželjene reakcije. Anafilaktički šok je najteži oblik sistemske alergijske reakcije koji zahvata više organskih sistema i može se završiti smrtnim ishodom, najčešće zbog opstrukcije disajnih puteva i kardiovaskularnog kolapsa. Neophodna je edukacija medicinskog osoblja kao i pacijenata o pravilnom lečenju ovog teškog stanja. Na osnovu procene faktora rizika kod svakog pacijenta, teške reakcije na *SCIT* se mogu predvideti i izbeći odgovarajućim merama predostrožnosti, kao i profilaktičkim merama. Očekuje se da buduće inovacije u alergenskoj imunoterapiji dodatno poboljšaju efikasnost i bezbednost ovakvog vida lečenja alergijskih bolesti.

Ključne reči: alergenska imunoterapija, *SCIT*, anafilaktički šok, ambrozija

ABSTRACT

Introduction: Sensitization to ragweed pollen can lead to symptoms of allergic rhinitis, conjunctivitis, and allergic asthma. Allergen immunotherapy (AIT) is an immunomodulatory therapeutic procedure that, in addition to short-term curative effect (reduction of disease symptoms), also has a long-term preventive effect (preventing the progression of allergic rhinitis into allergic asthma and/or preventing the development of a more severe form of the disease). The two main AIT administration modalities used in clinical practice are subcutaneous allergen immunotherapy (SCIT) and sublingual allergen immunotherapy (SLIT). Both modalities are equally effective in reducing disease symptoms, but the use of SCIT is associated with a higher risk of local and systemic adverse reactions.

Case report: A patient who developed a clinical picture of anaphylactic shock during the induction phase of SCIT with *Ambrosia elatior* pollen extract is presented in this article. The clinical course is described as well as the quick and effective therapeutic management of this life-threatening condition.

Conclusion: When properly dosed, in a medical facility and under medical supervision, SCIT with *Ambrosia elatior* is a very safe and well-tolerated treatment option for allergic rhinitis. Local reactions at the site of subcutaneous administration occur more often than systemic adverse reactions. Anaphylactic shock is the most severe form of a systemic allergic reaction that affects multiple organ systems and can end in death, usually due to airway obstruction and cardiovascular collapse. It is necessary to educate the medical staff as well as the patients regarding the proper treatment of this difficult condition. Based on the assessment of risk factors in each patient, severe reactions to SCIT can be predicted and avoided with appropriate precautions and prophylactic measures. Future innovations in AIT are expected to further improve the efficacy and safety of this form of treatment for allergic diseases.

Keywords: allergen immunotherapy, SCIT, anaphylactic shock, ambrosia

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UVOD

Alergija na polen ambrozije je poslednjih godina postala važan zdravstveni problem. Ambrozija (rod *Ambrosia* iz porodice *Asteraceae*) je biljka koja je izvorno poreklom iz Severne Amerike. U svetu su dve vrste najrasprostranjenije, obična (ili kratka) ambrozija (*A. artemisiifolia* ili *A. elatior*) i velika ambrozija (*A. trifida*), koje su i klinički najrelevantnije zbog visokog potencijala da izazovu simptome alergijskog rinitisa i alergijske astme [1].

Ambrosia elatior je najinvazivnija korovska jednogodišnja biljka, u smislu zahvatanja velikih područja [2]. Danas je široko rasprostranjena na području cele Republike Srbije kao i u okruženju. Polen *Ambrosia*-e *elatior* je dobro poznat po svom velikom potencijalu da izazove reakcije preosetljivosti tipa I u periodu cvetanja, koji vrhunac dostiže u avgustu i septembru, a uočen je sve duži period polinacije [2]. Jedna stabljika ambrozije proizvede do 45 grama polena godišnje, a jedan gram polena sadrži oko 30 miliona polenovih zrna. Dovoljno je od 8 do 10 polenovih zrna ambrozije po kubnom metru da bi se ispoljile alergijske manifestacije. Oko 50% polenskih alergija izazvano je polenom ambrozije. U Evropi postoji prosečna prevalencija senzibilizacije na alergene polena ambrozije od 14%; sa rasponom od najveće vrednosti zabeležene u Mađarskoj od 54% do 3,5% u Italiji. Pretpostavlja se da će klimatske promene i sve veće zagađenje vazduha u narednim godinama povećati alergenski potencijal polena [2].

Senzibilizacija na polen ambrozije može dovesti do tegoba u vidu alergijskog rinitisa, alergijskog konjuktivitisa i alergijske astme. Brojne studije ukazuju na to da velika izloženost polenu ili povećana koncentracija polena u određenom vremenskom periodu rezultira visokom stopom senzibilizacije i pojavom simptoma. U Evropi, najmanje jedan od petoro ljudi pati od respiratorne alergije na ambroziju. Smatra se da će do 2050. godine koncentracija ambrozije biti povećana do četiri puta. Istrajnost u iskorenjivanju ambrozije jedini je način da se smanji veliki broj respiratornih alergija [2].

Prvi korak u lečenju alergijskih respiratornih bolesti podrazumeva primenu konvencionalne terapije (antihistaminici, lokalna i sistemska primena glikokortikoida, stabilizatori mastocita, antagonisti leukotrijenskih receptora). Alergenska imunoterapija (AIT) je jedini modalitet lečenja koji može da menja tok bolesti i modifikuje imunski odgovor preusmeravanjem sa patološkog *T helper 2* (*TH2*) ka *T helper 1* (*TH1*). Ovakav vid lečenja primenjuje se unazad više od 100 godina. Dva glavna modaliteta alergenske imunoterapije koja se koriste u kliničkoj praksi su subkutana imunoterapija alergenom (engl. *subcutaneous allergen immunotherapy – SCIT*) i sublingvalna imunoterapija alergenom (engl. *sublingual allergen immunotherapy – SLIT*). Iako

INTRODUCTION

Allergy to ragweed pollen has become a significant health problem in recent years. Ambrosia (genus *Ambrosia* of the *Asteraceae* family) is a plant originally from North America. Worldwide, two species are the most widespread, common (or short) ragweed (*A. artemisiifolia* or *A. elatior*) and giant ragweed (*A. trifida*), which are also the most clinically relevant due to their high potential to cause symptoms of allergic rhinitis and allergic asthma [1].

Ambrosia elatior is the most invasive annual weed, in terms of covering large areas [2]. At present, it is widespread throughout the Republic of Serbia as well as in the surrounding region. *Ambrosia elatior* pollen is well known for its high potential to cause type I hypersensitivity reactions during the flowering season, which peaks in August and September, and an increasingly long pollination period has been observed [2]. One stalk of ragweed produces up to 45 grams of pollen per year, and one gram of pollen contains about 30 million pollen grains. Between 8 and 10 ragweed pollen grains per cubic meter is sufficient to provoke allergic manifestations. About 50% of pollen allergies are caused by ragweed pollen. In Europe, there is an average prevalence of sensitization to ragweed pollen allergens of 14%; with a range between the highest value recorded in Hungary of 54% to 3.5% in Italy. It is believed that climate change and increasing air pollution will also increase the allergenic potential of pollen in the coming years [2].

Sensitization to ragweed pollen can lead to complaints in the form of allergic rhinitis, allergic conjunctivitis, and allergic asthma. Numerous studies indicate that high exposure to pollen or an increased concentration of pollen over a period of time results in a high rate of sensitization and the onset of symptoms. In Europe, at least one in five people suffer from a respiratory allergy to ragweed. It is believed that by 2050, the concentration of ragweed will increase up to four times. Persistent eradication of ragweed is the only way to reduce a large number of respiratory allergies [2].

The first step in the treatment of allergic respiratory diseases involves the use of conventional therapy (antihistamines, local and systemic application of glucocorticoids, mast cell stabilizers, leukotriene receptor antagonists). Allergen immunotherapy (AIT) is the only treatment modality that can alter the course of the disease and modify the immune response by redirecting it from pathological T helper 2 (TH2) to T helper 1 (TH1). This type of treatment has been in use for more than 100 years. The two main modalities of allergen immunotherapy applied in clinical practice are subcutaneous allergen immunotherapy (SCIT) and sublingual allergen immunotherapy (SLIT). Although

je utvrđeno da su oba pristupa efikasna u smanjenju simptoma bolesti, *SCIT* je povezan sa povećanim rizikom od nastanka sistemskih neželjenih efekata [3].

Anafilaktički šok je najteži oblik alergijske reakcije koji zahvata više organskih sistema i ukoliko se ne primeni hitna i neodložna medicinska pomoć, može se završiti smrtnim ishodom, najčešće zbog opstrukcije disajnih puteva i kardiovaskularnog kolapsa. Nastaje usled reakcije specifičnog alergena sa IgE antitelima na površini mastocita i bazofila, nakon čega dolazi do njihove aktivacije i oslobađanja medijatora, u prvom redu histamina, i nastanka kožnih, respiratornih, kardiovaskularnih, gastrointestinalnih i neuroloških simptoma. Tri najčešća pokretača anafilakse su hrana, venomi insekata i lekovi. Simptomi se uglavnom javljaju unutar jednog sata od izlaganja specifičnom alergenu [4,5].

PRIKAZ SLUČAJA

Pacijent starosti 40 godina prvi put je pregledan u alergološkoj ambulanti Klinike za alergologiju i imunologiju Univerzitetskog kliničkog centra Srbije (UKCS), juna 2021. godine. Anamnestički podaci ukazivali su na to da godinama unazad pacijent u proleće i kasno leto ima tegobe u vidu kijanja u seriji, nazalne opstrukcije, učestale bistre sekrecije iz nosa, uz prisustvo svraba nosa i grla. Povremeno se javljao i osećaj kratkog daha uz neproduktivni kašalj. U ličnoj anamnezi negirao je postojanje drugih hroničnih oboljenja kao i uzimanje redovne terapije. U detinjstvu je lečen zbog čestih bronhitisa. Poslednjih 5 godina povremeno je imao blaže epizode otežanog disanja koje je uspešno kupirao primenom kratkodelujućeg beta2 agonista (engl. *short-acting beta2 agonist – SABA*). Avgusta 2021. godine imao je epizodu težeg oblika bronhospazma zbog čega je lečen intravenskom primenom kortikosteroida. U sklopu dijagnostike su urađene *PRICK* kožne probe na panel inhalacionih alergena kojima je dokazana polisenzibilizacija na grinje, kućnu prašinu i sva tri tipa polena (drveće, trava, korov). Kod pacijenta je urađen nespecifični bronhoprovokacioni test sa metaholinom, koji je bio negativan (detektovan pad *FEV1* za 6,2 %). Određivan je nivo specifičnih IgE antitela (*radioallergosorbent test – RAST*) na panel inhalacionih alergena: *Ambrosia elatior* – klasa 3, poleni trava – klasa 4, raž – klasa 4; ostali alergeni nisu dali značajniju pozitivnost.

Objektivnim pregledom nije utvrđeno postojanje bronhoopstrukcije. U redovnu terapiju uveden je antihistaminik (levocetirizin), intranazalni kortikosteroid (mometazon furoat), antagonist leukotrijenskih receptora (montelukast), kao i, po potrebi, inhalaciona fiksna kombinacija kortikosteroida i dugodelujućeg beta2 agonista (budesonid/formoterol), imajući u vidu prethodne epizode bronhospazma i mogućnost da

both approaches have been found to be effective in reducing symptoms of disease, SCIT is associated with an increased risk of systemic side effects [3].

Anaphylactic shock is the most severe form of allergic reaction that affects multiple organ systems and if urgent and immediate medical assistance is not provided, it can end in death, most often due to airway obstruction and cardiovascular collapse. It is caused by the reaction of a specific allergen with IgE antibodies on the surface of mast cells and basophils, after which their activation and the release of mediators, primarily histamine, occurs, as well as the appearance of skin, respiratory, cardiovascular, gastrointestinal and neurological symptoms. The three most common triggers of anaphylaxis are food, insect venom, and medication. Symptoms generally appear within one hour of exposure to a specific allergen [4,5].

CASE REPORT

A 40-year-old patient was examined for the first time at the allergology unit of the Clinic of Allergology and Immunology of the University Clinical Center of Serbia (UCCS), in June 2021. The anamnestic data indicated that for a number of years the patient had been experiencing complaints in spring and late summer in the form of continuous sneezing, nasal obstruction, frequent discharge of a clear secretion from the nose, accompanied by an itchy nose and throat. Occasionally, there was also a sensation of shortness of breath with a non-productive cough. In his personal history, he denied the existence of other chronic diseases as well as taking any regular therapy. In childhood, he was treated for frequent bronchitis. For the previous five years, he occasionally had mild episodes of difficulty breathing, which he successfully managed with the use of a short-acting beta2 agonist (SABA). In August 2021, he had an episode of severe bronchospasm, for which he was treated with intravenous corticosteroids. As part of the diagnosis, prick skin tests were performed for a panel of inhalation allergens, which proved polysensitization to dust mites, house dust and all three types of pollen (trees, grass, weeds). A non-specific bronchoprovocation test with methacholine was performed on the patient, which was negative (a 6.2% drop in FEV1 was detected). The level of specific IgE antibodies (radioallergosorbent test - RAST) for a panel of inhalation allergens was determined: *Ambrosia elatior* – class 3, grass pollen – class 4, rye – class 4; other allergens did not show significant positivity.

Objective examination did not establish the presence of broncho-obstruction. An antihistamine (levocetirizine), intranasal corticosteroid (mometasone furoate), leukotriene receptor antagonist (montelukast)

pacijent u određenom periodu sezone polinacije ima indukovanu bronhijalnu hiperreaktivnost.

Novembra 2021. godine započeta je AIT (*SCIT*) sa ekstraktima polena *A. elatior* i mešavinom polena trava.

Januara 2022. godine pacijent je u ambulanti Klinike za alergologiju i imunologiju UKCS-a primio redovnu indukcionu dozu *SCIT*-a, koju je dobijao u nedeljnim intervalima (II rastvor – 1.000 proteinskih jedinica (*PNU*), 0,3 ml *SC*, sa ekstraktima *A. elatior* i mešavinom polena trava). Nakon 10 minuta od subkutane aplikacije ekstrakata, kod pacijenta se razvija gigantska urtika nadlaktice, na mestu dobijanja ekstrakta *A. elatior*, uz difuzni eritem kože sa hiperemijom konjuktiva, te subjektivnim osećajem otežanog disanja i gutanja. Nije bilo lokalne reakcije na mestu davanja ekstrakta mešavine polena trava (nadlaktica druge ruke). Objektivnim pregledom auskultacijski se konstatuje sviranje (engl. *wheezing*), a inspekcijski se uočava blaži otok uvule kao i pad arterijskog pritiska na 85/60 mmHg.

Na osnovu kompletne kliničke slike, postavlja se dijagnoza teške sistemske reakcije – anafilaktičkog šoka, i odmah se pristupa primeni hitnih terapijskih mera. Prvi terapijski postupak je bilo davanje epinefrina intramuskularno (*m. deltoideus*) u dozi od 0,5 ml u nerazblaženom obliku (koncentracija epinefrina u ampuli je 1:1,000). Nakon ove primarne terapijske mere, intravenski se ordiniraju kortikosteroidi (metilprednizolon u dozi od 2 mg/kg telesne težine), kristaloidni rastvori (0,9% NaCl, 1,000 ml iv u brzoj infuziji), i vrši se intramuskularna primena hloropiramina u dozi od 20 mg, daje se inhibitor protonske pumpe (pantoprazol 40 mg iv), i vrši intravenska primena infuzije aminofilina (500 mg u 250 ml 0,9% NaCl).

Primenjena terapija imala je povoljan efekat uz brzo (unutar nekoliko minuta) povlačenje kliničkog nalaza. Izmereni kontrolni *TA* iznosio je 115/70 mmHg, auskultacijski je detektovan normalan disajni šum, inspekcijski se pokazalo povlačenje eritema kože, hiperemije konjuktiva i edema uvule.

Naredna 24 časa, pacijent je bio opserviran u hospitalnim uslovima uz nastavak intravenske primene kortikosteroida (metilprednizolon, ukupno još 2 mg po kilogramu telesne težine, podeljeno na tri doze, u roku od 24 sata), rehidrataciju izotoničnim fiziološkim rastvorom i *per os* primenu antihistaminika (četvorostruka doza levocetirizina). Odložene sistemske reakcije se nisu javljale, kao ni potreba za naknadnim ordiniranjem epinefrina.

U daljem toku, obustavljena je subkutana primena alergenske imunoterapije. Pacijent nije bio motivisan za prevođenje na *SLIT*. Nastavljeno je lečenje konvencionalnom terapijom, odnosno antihistaminicima, intranazalnim kortikosteroidima, inhalacionim kortikosteroidima i po potrebi inhalacionom kombinacijom kortikosteroida i dugodelujućeg beta2 agonista (budesonid/formoterol). Ovo je uvedeno u redovnu terapiju, uzimajući u obzir prethodne epizode bronhospazma i mogućnost da pacijent ima indukovanu bronhijalnu hiperreaktivnost u određenom periodu sezone polinacije.

and, when necessary, an inhalation of a fixed combination of corticosteroids and a long-acting beta2 agonist (budesonide/formoterol) were introduced into regular therapy, taking into account previous episodes of bronchospasm and the possibility of the patient having induced bronchial hyperreactivity during a certain period of the pollination season.

In November 2021, the patient was started on AIT (SCIT) with *A. elatior* pollen extracts and a grass pollen mixture.

In January 2022, the patient received a regular induction dose of SCIT at weekly intervals, at the outpatient unit of the Clinic of Allergology and Immunology of the UCCS (solution II - 1,000 protein units (PNU), 0.3 ml SC, with extracts of *A. elatior* and a mixture of grass pollen). After 10 minutes of subcutaneous application of the extract, the patient developed giant urticaria on the upper arm, at the site where the *A. elatior* extract was administered, with diffuse erythema of the skin and with hyperemia of the conjunctiva, as well as subjective feeling of difficulty breathing and swallowing. There was no local reaction at the site of grass pollen mixture extract administration (other upper arm). Objective examination revealed the following: wheezing was detected with auscultation, while slight swelling of the uvula was observed on inspection. A drop in arterial pressure (85/60 mmHg) was also detected.

Based on the overall clinical presentation, a diagnosis of severe systemic reaction - anaphylactic shock was established and immediate therapeutic measures were applied. The first therapeutic procedure was the administration of epinephrine intramuscularly (*m. deltoideus*) at a dose of 0.5 ml in undiluted form (the concentration of epinephrine in the vial is 1:1,000). After this primary therapeutic measure, intravenous corticosteroids (methylprednisolone at a dose of 2 mg/kg body weight), crystalloid solutions (0.9% NaCl, 1,000 ml iv in rapid infusion) were administered, intramuscular administration of chloropyramine at a dose of 20 mg was performed, a proton pump inhibitor (pantoprazole 40 mg iv) was given, and an intravenous infusion of aminophylline (500 mg in 250 ml 0.9% NaCl) was administered.

The applied therapy had a beneficial effect with a rapid (within a few minutes) withdrawal of the clinical findings. Repeated measurement of blood pressure detected a BP of 115/70 mmHg, normal breathing sounds were detected by auscultation, while inspection showed that the skin erythema, conjunctival hyperemia, and uvular edema had receded.

During the following 24 hours, the patient was under observation in hospital with a continuation of intravenous corticosteroid therapy (methylpredniso-

kosteroidima u kombinaciji sa dugodelujućim beta2 agonistima (engl. *long-acting beta2 agonist – LABA*), kao i antagonistima leukotrijenskih receptora.

DISKUSIJA

Reakcije preosetljivosti tipa I (rani tip) na polen ambrozije mogu se manifestovati kao simptomi alergijskog rinitisa, rinokonjunktivitisa i alergijske astme.

Alergijski rinitis je najčešća atopijska manifestacija, globalni zdravstveni problem koji pogađa 10% do 40% populacije. Alergijski rinitis klinički karakterišu paroksizmalne epizode kijanja, rinoreje, nazalnog svraba i nazalne opstrukcije. Alergijski rinitis je glavni faktor rizika za razvoj alergijske astme [2].

Alergijska astma je hronična inflamatorna bolest donjih disajnih puteva uzrokovana IgE antitelima, posredovanom senzibilizacijom na inhalacione alergene. Glavna karakteristika bolesti je inflamacija i bronhijalna hiperreaktivnost sa reverzibilnom opstrukcijom disajnih puteva. Klinički se prezentuje ponavljanim epizodama sviranja i stezanja u grudima, suvim kašljem i kratkim dahom.

Dijagnostikovanje alergijskog rinitisa, kao i alergijske astme, koji su izazvani polenom ambrozije, obuhvata detaljnu anamnezu (simptomatologija ima sezonski karakter), *in vivo* (kožni *PRICK* testovi, nazalni test provokacije alergenom i nespecifični bronhoprovokacioni test), kao i *in vitro* dijagnostiku (određivanje koncentracije specifičnih IgE antitela u serumu) [1].

Standardni protokoli lečenja alergijskog rinitisa i astme podrazumevaju lokalnu i sistemsku primenu glikokortikoida (intranazalna, inhalaciona, *per os* i parenteralna primena), intranazalnu i sistemsku primenu antihistaminika, primenu antagonista leukotrijenskih receptora, antiholinergika, teofilinskih preparata, bioloških lekova i alergenske imunoterapije.

Pacijent prikazan u ovom radu je imao tipične simptome sezonskog alergijskog rinitisa. U sezoni polena ambrozije je imao nekoliko epizoda bronhospazma, koje su zahtevale kratkotrajnu parenteralnu primenu glikokortikoida. Nespecifični bronhoprovokacioni test sa metaholinom, koji je urađen izvan sezone polena, bio je negativan uz uredan spirometrijski nalaz. Imajući u vidu kliničku sliku, zaključeno je da pacijent može imati simptomatsku bronhijalnu hiperreaktivnost (intermitentnu astmu) u sezoni polena korova. Iz tog razloga je, izvan sezone polenacije korova, lečen prema prvom koraku *GINA* protokola za lečenje astme, kombinovanom inhalacionom terapijom po potrebi (budesonid 160 mcg/formoterol 9 mcg).

Alergenska imunoterapija može se sprovoditi kao *SCIT* ili *SLIT*. Oba načina primene su bezbedna,

lone, a total of 2 mg per kilogram of body weight, divided into three doses, within 24 hours), rehydration with isotonic saline, and *per os* administration of antihistamines (quadruple dose of levocetirizine). Delayed systemic reactions did not occur nor did the need for subsequent administration of epinephrine arise.

Subsequently, the subcutaneous application of allergen immunotherapy was discontinued. The patient was not willing to transfer to SLIT. Treatment continued with conventional therapy, i.e. antihistamines, intranasal corticosteroids, inhalation of corticosteroids in combination with long-acting beta2 agonists (LABA), as well as leukotriene receptor antagonists.

DISCUSSION

Type I (immediate reaction) hypersensitivity reactions to ragweed pollen can manifest as symptoms of allergic rhinitis, rhinoconjunctivitis, and allergic asthma.

Allergic rhinitis is the most common atopic manifestation, a global health problem affecting 10% to 40% of the population. Allergic rhinitis is clinically characterized by paroxysmal episodes of sneezing, rhinorrhea, nasal itching, and nasal obstruction. Allergic rhinitis is the main risk factor for the development of allergic asthma [2].

Allergic asthma is a chronic inflammatory disease of the lower respiratory tract caused by IgE antibodies, through mediated sensitization to inhaled allergens. The main characteristic of the disease is inflammation and bronchial hyperreactivity with reversible airway obstruction. Clinically, it presents with repeated episodes of wheezing and tightness in the chest, dry cough, and shortness of breath.

Diagnosing allergic rhinitis and allergic asthma caused by ragweed pollen includes detailed anamnesis (symptomatology is seasonal), in vivo (skin prick tests, nasal allergen provocation test, and non-specific bronchoprovocation test), as well as in vitro diagnostics (determining the concentration of specific IgE antibodies in the serum) [1].

Standard protocols for the treatment of allergic rhinitis and asthma include local and systemic administration of glucocorticoids (intranasal, inhalation, oral, and parenteral administration), intranasal and systemic administration of antihistamines, administration of leukotriene receptor antagonists, anticholinergics, theophylline preparations, biologic medications, and allergen immunotherapy.

The patient presented in this paper had typical symptoms of seasonal allergic rhinitis. During the ragweed pollen season, he had several episodes of bronchospasm, which required short-term parenteral administration of glucocorticoids. A non-specific bron-

efikasna i mogu dovesti do indukcije tolerancije na senzibilisani alergen, koja se održava više godina nakon prestanka lečenja. I urođeni i adaptivni imunski odgovori koji doprinose alergijskoj inflamaciji su potisnuti *AIT*-om. Urođeni imunski odgovor je modulisan smanjenjem broja mastocita, bazofila, eozinofila i cirkulišućih urođenih limfoidnih ćelija grupe 2. Indukcija blokirajućih antitela specifičnih za alergene, imunosupresivnih citokina i regulatornih T i B ćelijskih fenotipova, ključni su pro-tolerogeni adaptivnog imunskog odgovora [6]. Inhibicija oslobađanja medijatora iz mastocita i bazofila delimično je zavisna od IL10, koji direktno inhibira IgE zavisnu aktivaciju mastocita i proizvodnju njihovih citokina. Rezultat toga je značajno smanjenje nakupljanja inflamatornih ćelija, kao što su eozinofilni i neutrofilni granulociti, u šoknim tkivima (sluznica nosa i bronhija) [7].

SCIT dovodi do smanjenja proizvodnje imunoglobulina E (IgE) specifičnog za alergen i povećanja proizvodnje imunoglobulina G (IgG) specifičnog za alergen (IgG4). Indukovana IgG antitela se takmiče sa IgE antitelima za epitope na antigenima, čime ispoljavaju efekat blokiranja. Nakon izlaganja alergenu, antigen prezentujuće ćelije su u stanju da usmere imunski odgovor ka TH1, a time i prema imunotoleranciji, i verovatno su ključne za efekat *SCIT*-a [7]. Kao nosači aeroalergena kod *SCIT*-a služe aluminijum ili tirozin, i na taj način se odlaže oslobađanje alergena [7]. U okviru *SCIT*-a se mogu se primenjivati nemodifikovani ekstrakti sa nativnim alergenima kao i hemijski modifikovani ekstrakti alergena (alergoidi) [8].

Tokom sprovođenja *SCIT*-a postoje dve faze, indukcija i održavanje. U toku faze indukcije postepeno povećanje doze alergena, odnosno njegove koncentracije, vrši se na nedeljnom nivou, a nakon postizanja doze održavanja terapija se daje u intervalima od 4 do 6 nedelja tokom 3 do 5 godina [7]. Doza održavanja je ona doza kojom se klinički postiže tolerogeni efekat [3].

Naš pacijent je sistemsku neželjenu reakciju razvio u fazi indukcije, nakon dobijanja II rastvora (1.000 proteinskih jedinica - *PNU*) u dozi od 0,3 ml.

Uvođenje alergenske imunoterapije u lečenju alergijske astme generalno se vrši sa većim oprezom i ne može se koristiti kao zamena za konvencionalnu antiastmatičnu terapiju. AIT se preporučuje kod astme koja je dobro kontrolisana, kao dodatna (engl. *add on*) terapija farmakološkoj. Kod takvih pacijenata ovakav vid terapije može značajno da smanji bronhijalnu hiperreaktivnost, simptome bronhijalne opstrukcije kao i potrebu za korišćenjem drugih terapijskih opcija, pre svega kortikosteroida [8].

SCIT, kao terapijska opcija lečenja alergijskog rinitisa ima i preventivni uticaj na razvoj alergijske astme.

choprovocation test with methacholine, which was performed outside the pollen season, was negative with normal spirometry findings. Bearing in mind the clinical presentation of the patient, the conclusion was that the patient may have symptomatic bronchial hyperreactivity (intermittent asthma) in the weed pollen season. This is why, outside the weed pollination season, he was treated according to the first step of the GINA protocol for the treatment of asthma, with combined inhalation therapy as needed (budesonide 160 mcg/formoterol 9 mcg).

Allergen immunotherapy can be administered as SCIT or SLIT. Both methods of administration are safe, effective and can induce tolerance to the sensitized allergen, which is then maintained for many years after treatment is discontinued. Both innate and adaptive immune responses contributing to allergic inflammation are suppressed by AIT. The innate immune response is modulated by reducing the number of mast cells, basophils, eosinophils, and circulating group 2 innate lymphoid cells. Induction of allergen-specific blocking antibodies, immunosuppressive cytokines and regulatory T and B cell phenotypes are key pro-tolerogens of the adaptive immune response [6]. Inhibition of mediator release from mast cells and basophils is partially dependent on IL10, which directly inhibits IgE-dependent activation of mast cells and their cytokine production. The result is a significant reduction in the accumulation of inflammatory cells, such as eosinophilic and neutrophilic granulocytes, in the nasal mucosa and bronchial tissue [7].

SCIT leads to a decrease in the production of allergen-specific immunoglobulin E (IgE) and an increase in the production of allergen-specific immunoglobulin G (IgG4). Induced IgG antibodies compete with IgE antibodies for epitopes on antigens, thereby exerting a blocking effect. After allergen exposure, antigen-presenting cells can direct the immune response towards TH1, and thus towards immunotolerance, and are probably key in achieving the effect of SCIT [7]. Aluminum or tyrosine are used as carriers of aeroallergens in SCIT, and in this way the release of allergens is delayed [7]. Within SCIT, unmodified extracts with native allergens as well as chemically modified allergen extracts (allergoids) can be applied [8].

During the implementation of SCIT there are two phases, induction and maintenance. During the induction phase, the allergen dose, i.e. its concentration, is gradually increased on a weekly basis, and after reaching the maintenance dose, the therapy is given at intervals of 4 to 6 weeks for a period of 3 to 5 years [7]. The maintenance dose is the dose that clinically achieves a tolerogenic effect [3].

Dodatna prednost primene *SCIT*-a u odnosu na drugu konvencionalnu terapiju odnosi se i na mogućnost modifikacije toka bolesti kao i na prevenciju razvoja astme i novih senzibilizacija [9].

Primer prave indikacije za alergensku imunoterapiju sa ekstraktima ambrozije bio bi pacijent sa alergijskim rinitisom (AR) izazvanim senzibilizacijom na ambroziju, poželjno bi bilo monosenzibilisan, čiji simptomi nisu dobro kontrolisani uobičajenom farmakoterapijom [8]. Većina pacijenata sa AR-om je polisenzibilisana, ali postoje dokazi da je primena alergenske imunoterapije i kod ovih pacijenata efikasna, i da polisenzibilizacija nije kontraindikacija za AIT. Dokazi iz randomizovanih kliničkih studija sugerišu da je efekat terapije veći kod pacijenata kod kojih su simptomi izraženiji [8].

Naš pacijent je bio polisenzibilisan (poleni trava i korova) i kod njega je uvedena *SCIT* istovremeno sa alergenima *Ambrosia*-e *elatior* i mešavinom polena trava.

Faktore rizika treba pratiti kod svih pacijenata pre započinjanja *SCIT*-a (razmotriti prekid terapije beta blokatorima, sprovoditi redovne spirometrijske kontrole astme, izbegavati injekcije imunoterapije kod pacijenata sa aktuelnom kliničkom slikom respiratorne infekcije ili teškim pogoršanjem alergijskog rinitisa ili astme, izbegavati neadekvatno doziranje, lošu tehniku primene, izbegavati naporno vežbanje ili konzumiranje alkohola) [10].

Nijedan od navedenih faktora rizika nije bio zabeležen kod našeg pacijenta.

Uzimajući u obzir faktore rizika od nastanka neželjenih reakcija, teške reakcije na *SCIT* se mogu predvideti i izbeći odgovarajućim merama predostrožnosti, kao i profilaktičkim merama. Moguća je premedikacija antihistaminicima kako bi se smanjila učestalost i težina potencijalnih sistemskih reakcija, ali ova mera ne eliminiše mogućnost javljanja sistemskih reakcija [8].

Kada se primenjuje na pravilan način, uz pravilno doziranje, u medicinskoj ustanovi i pod lekarskim nadzorom, *SCIT* je veoma bezbedna i dobro tolerisana opcija lečenja. U slučaju *SCIT*-a sa alergenskim ekstraktima koji sadrže adjuvanse na bazi aluminijuma, određeni neželjeni efekti, kao što su kontaktni dermatitis, reakcije tipa vaskulitisa ili granuloma, mogu se javiti usled reakcije na strano telo, iako je to veoma retko. Lokalne reakcije na mestu injekcije uključuju otok, svrab i crvenilo. Ove reakcije se pojavljuju relativno često, uglavnom prolaze spontano ili primenom H1-antihistaminika ili topikalnih kortikosteroida. U slučaju pojave intenzivnijih lokalnih reakcija (crvenilo i/ili otok preko 1 cm u prečniku) na mestu injekcije, neophodno je pažljivo isplanirati dalji nastavak alergenske imunoterapije (prekidanje terapije, korekcija doze i intervala davanja terapije) [8].

Our patient developed a systemic adverse reaction during the induction phase, after receiving solution II (1,000 protein units - PNU) at a dose of 0.3 ml.

The introduction of allergen immunotherapy in the treatment of allergic asthma is generally done with greater caution and cannot be used as a substitute for conventional antiasthmatic therapy. AIT is recommended in well-controlled asthma as an add-on to pharmacological therapy. In such patients, this type of therapy can significantly reduce bronchial hyperreactivity, symptoms of bronchial obstruction, as well as the need to use other therapeutic options, primarily corticosteroids [8].

SCIT, as a therapeutic option for the treatment of allergic rhinitis, also has a preventive effect on the development of allergic asthma. An additional advantage of using SCIT, as compared to other conventional therapy, is in connection with the possibility of modifying the course of the disease as well as preventing the development of asthma and new sensitizations [9].

An example of a true indication for allergen immunotherapy with ragweed extracts would be a patient with allergic rhinitis (AR) caused by sensitization to ragweed, preferably monosensitized, whose symptoms are not well controlled by conventional pharmacotherapy [8]. Most patients with AR are polysensitized, but there is evidence that allergen immunotherapy is also effective in these patients and that polysensitization is not a contraindication to AIT. Evidence from randomized clinical trials suggests that the effect of therapy is greater in patients with more severe symptoms [8].

Our patient was polysensitized (grass and weed pollen) and SCIT was introduced simultaneously with *Ambrosia elatior* allergens and a grass pollen mixture.

Risk factors should be monitored in all patients before starting SCIT (discontinuation of beta-blocker therapy should be considered, regular spirometry follow-ups of asthma should be performed, immunotherapy injections in patients with ongoing clinical presentation of respiratory infection or severe exacerbation of allergic rhinitis or asthma should be avoided, as well as inadequate dosing, poor application technique, strenuous exercise, and alcohol consumption) [10].

None of the abovementioned risk factors were noted in our patient.

Bearing in mind the risk factors for the occurrence of adverse reactions, severe reactions to SCIT can be predicted and avoided by using appropriate precautions and prophylactic measures. Premedication with antihistamines is possible to reduce the frequency and severity of potential systemic reactions, but this measure does not eliminate the possibility of systemic reactions [8].

Do pojave teške sistemske reakcije naš pacijent nije imao ispoljene značajnije lokalne reakcije (papula i/ili eritem > 3 mm) na mestima subkutanog aplikovanja oba alergena.

Rizik od teških alergijskih reakcija izazvanih *SCIT*-om je nizak, a i blage sistemske reakcije (urtikarija, laringealni ili bronhijalni spazam) poslednjih godina pokazuju tendenciju opadanja, zahvaljujući dobrom monitoringu tokom sprovođenja terapije. Međutim, kod malog broja pacijenata može doći do skoro fatalnih i fatalnih anafilaktičkih reakcija. Kliničari koji primenjuju alergensku imunoterapiju treba da prođu specijalizovanu obuku i da budu svesni faktora rizika i preventivnih mera kako bi izbegli teške alergijske reakcije izazvane *SCIT*-om [11]. Prepoznavanje pacijenata sa većim rizikom od sistemske reakcije (SR) predstavlja suštinski deo donošenja odluke da se započne *SCIT*. U tabeli 1 i 2 prikazane su apsolutne i relativne kontraindikacije za alergensku imunoterapiju [12]. Nekontrolisana astma je glavni faktor rizika za razvoj sistemske reakcije [13]. Nakon započinjanja alergenske imunoterapije važno je kontinuirano procenjivati rizik u odnosu na korist kod pacijenata koji se leče i oprezno povećavati dozu do postizanja doze održavanja [11]. Neželjene alergijske reakcije na *SCIT* se klasifikuju kao lokalne, sistemske i fatalne, rane ili kasne reakcije. Lokalne reakcije se javljaju kod 26% – 86% pacijenata koji primaju *SCIT* [3]. Sistemske reakcije mogu biti u rasponu težine od blagog rinitisa do fatalnog kardiopulmonalnog zastoja [14]. Stopa sistemskih reakcija različite težine je relativno niska i iznosi 0,1% – 0,2%. Većina odloženih sistemskih reakcija, koje se javljaju nakon 30 minuta, blage su do umerene po stepenu ozbiljnosti [3]. Obavezna je opservacija svih pacijenata u trajanju od najmanje 30 minuta nakon aplikacije alergenskog ekstrakta.

When administered correctly, at a proper dosage, in a medical facility, and under medical supervision, SCIT is a very safe and well-tolerated treatment option. In the case of SCIT with allergenic extracts containing aluminum-based adjuvants, certain side effects, such as contact dermatitis, vasculitis-type or granuloma-type reactions, may occur due to reaction to a foreign body, although this is very rare. Local reactions at the injection site include swelling, itching and redness. These reactions appear relatively often, they usually resolve spontaneously or with the use of H1-antihistamines or topical corticosteroids. In the event of more intense local reactions (redness and/or swelling over 1 cm in diameter) at the injection site, it is necessary to carefully plan further continuation of allergen immunotherapy (discontinuation of therapy, correction of the dose and interval of therapy administration) [8].

Before the development of a severe systemic reaction, our patient had no significant local reactions (papules and/or erythema > 3 mm) at the sites of subcutaneous application of both allergens.

The risk of severe allergic reactions caused by SCIT is low, and even mild systemic reactions (urticaria, laryngeal or bronchial spasm) have shown a decreasing tendency in recent years, thanks to good monitoring during therapy. However, near-fatal and fatal anaphylactic reactions may occur in a small number of patients. Clinicians administering allergen immunotherapy should receive specialized training and be aware of risk factors and preventive measures to avoid severe allergic reactions caused by SCIT [11]. Identifying patients at higher risk of systemic reaction (SR) is an essential part of making the decision to initiate SCIT. Tables 1 and 2 show absolute and relative contraindications for allergen immunotherapy [12]. Uncontrolled asthma is a major risk factor for the development of a systemic reaction [13]. After starting aller-

Tabela 1. Apsolutne kontraindikacije za alergensku imunoterapiju

Table 1. Absolute contraindications for allergen immunotherapy

APSOLUTNE KONTRAINDIKACIJE ZA ALERGENSKU IMUNOTERAPIJU / *ABSOLUTE CONTRAINDICATIONS FOR ALLERGEN IMMUNOTHERAPY*
Nekontrolisana astma / *Uncontrolled asthma*
Aktivna autoimunska bolest / *Active autoimmune disease*
Aktivna maligna bolest / *Active malignancy*
Deca ispod 2 godine / *Children below two years of age*
Započinjanje tokom trudnoće / *Introduction of treatment in pregnancy*
SIDA / *AIDS*

Tabela 2. Relativne kontraindikacije za alergen specifičnu imunoterapiju

Table 2. Relative contraindications for allergen-specific immunotherapy

RELATIVNE KONTRAINDIKACIJE ZA ALERGEN SPECIFIČNU IMUNOTERAPIJU / *RELATIVE CONTRAINDICATIONS FOR ALLERGEN-SPECIFIC IMMUNOTHERAPY*
Autoimunska bolest u remisiji / *Autoimmune disease in remission*
Terapija beta blokatorima i ACE inhibitorima / *Treatment with beta blockers and ACE inhibitors*
Kardiovaskularne bolesti / *Cardiovascular disease*
Imunodeficijencije / *Immunodeficiency*
Psihijatrijske bolesti / *Psychiatric illnesses*
Trudnoća (nije kontraindikacija za nastavak terapije održavanja) / *Pregnancy (not a contraindication for continuing maintenance therapy)*

U prikazanom slučaju, pacijent je tešku sistemsku reakciju razvio nakon 10 minuta od dobijanja *SCIT*-a.

Kod pacijenata koji su razvili sistemsku reakciju je potrebno smanjiti dozu *SCIT*-a, odnosno nastaviti terapiju prethodnom dozom koja je dobro tolerisana. Kod pacijenata sa jednom teškom sistemskom reakcijom ili tri i više blažih sistemskih reakcija, potrebno je razmotriti potpuni prekid imunoterapije [11]. Prilagođavanje doze tokom sezone polena za visoko osetljive pacijente može smanjiti rizike od sistemskih reakcija [15].

Incidencija anafilakse je 21 na 100.000 ljudi godišnje, sa smrtnim ishodom u oko 0,65% slučajeva [4]. *PRICK* kožni testovi na alergene i *in vitro* testovi za određivanje serumskog specifičnog imunoglobulina E ne predviđaju pouzdano rizik od razvoja anafilakse [5]. Unutar dva sata od početka sistemske anafilakse od koristi može biti određivanje nivoa triptaze u serumu, što potvrđuje dijagnozu, a odraz je degranulacije mastocita [16].

Prvi farmakološki tretman anafilaktičkog šoka podrazumeva intramuskularnu primenu epinefrina. Sekundarne mere uključuju nadoknadu tečnosti, davanje H1 i H2 antagonista, primenu bronhodilatatora i kortikosteroidnih preparata [4].

Epinefrin je vazokonstriktor, smanjuje oslobađanje medijatora i edem sluzokože (preko a1-adrenergičkog receptora); ublažava bronhokonstrikciju (a1- i b2-adrenergički receptor), i ispoljava pozitivno inotropno i hronotropno dejstvo (b1-adrenergički receptor). Epinefrin bi trebalo primeniti intramuskularno u sredinu anterolateralne butine (lat. *vastus lateralis*), što dovodi do bolje apsorpcije od intramuskularne (IM) ili subkutane (engl. *subcutaneous – SC*) injekcije u deltoidni mišić. Ne postoje apsolutne kontraindikacije za primenu epinefrina [17].

Podaci ukazuju na to da se H1-antihistaminici češće koriste za lečenje pacijenata sa anafilaksom. Iako je histamin ključan u nastanku anafilakse, lečenje H1-antihistaminicima ne ublažava niti sprečava sve patofiziološke mehanizme anafilakse, uključujući i ozbiljnije komplikacije kao što su opstrukcija disajnih puteva, hipotenzija i šok. Pored toga, H1-antihistaminici ne deluju tako brzo kao epinefrin. Maksimalne koncentracije u plazmi se postižu u periodu između jednog i tri sata za H1-antihistaminike, u poređenju sa manje od 10 minuta za intramuskularnu primenu epinefrina. Ovo ukazuje na potrebu za dodatnom edukacijom lekara u zbrinjavanju anafilakse, kao i pacijenata u vezi sa odgovarajućim merama samopomoći kod anafilakse [18].

Prema podacima iz literature, dvofazna anafilaksa se javlja kod oko 20% odraslih sa simptomima koji se ponavljaju u roku od 1 h – 72 h (obično 8 h –10 h) nakon što je početna reakcija nestala. Ne postoje jasni prediktori razvoja druge faze anafilakse [17]. Pošto se po život opasne manifestacije mogu ponoviti tokom druge faze, neophodno je posmatranje pacijenata u

gen immunotherapy, it is important to continuously assess the risk versus benefit in patients being treated, and cautiously increase the dose until the maintenance dose is reached [11]. Adverse allergic reactions to SCIT are classified as local, systemic, and fatal, early or late reactions. Local reactions occur in 26% - 86% of patients receiving SCIT [3]. Systemic reactions can range in severity from mild rhinitis to fatal cardiopulmonary arrest [14]. The rate of systemic reactions of varying severity is relatively low and amounts to 0.1% - 0.2%. Most delayed systemic reactions occurring after 30 minutes are mild to moderate in severity [3]. All patients must be observed for at least 30 minutes after the application of the allergenic extract.

In the case presented in this article, the patient developed a severe systemic reaction 10 minutes upon receiving SCIT.

In patients who have developed a systemic reaction, it is necessary to reduce the dose of SCIT, i.e., continue therapy with the previous dose that was well tolerated. In patients with one severe systemic reaction or three or more milder systemic reactions, complete discontinuation of immunotherapy should be considered [11]. Dose adjustment during the pollen season for highly sensitive patients may reduce the risks of systemic reactions [15].

The incidence of anaphylaxis is 21 per 100,000 people per year, with a fatal outcome in about 0.65% of cases [4]. Prick skin tests for allergens and in vitro tests for verifying serum specific IgE do not reliably predict the risk of developing anaphylaxis [5]. Within two hours of the onset of systemic anaphylaxis, determining serum tryptase levels can be useful, thus confirming the diagnosis and reflecting mast cell degranulation [16].

The first-line pharmacological treatment for anaphylactic shock involves the intramuscular administration of epinephrine. Secondary measures include fluid replacement, administration of H1 and H2 antagonists, use of bronchodilators and corticosteroid preparations [4].

Epinephrine is a vasoconstrictor, it reduces the release of mediators and mucosal edema (via the a1-adrenergic receptor); relieves bronchoconstriction (a1- and b2-adrenergic receptor), and exhibits a positive inotropic and chronotropic effect (b1-adrenergic receptor). Epinephrine should be administered intramuscularly in the middle of the anterolateral thigh (Lat. *vastus lateralis*), which leads to better absorption than intramuscular (IM) or subcutaneous (SC) injection into the deltoid muscle. There are no absolute contraindications for the use of epinephrine [17].

Data indicate that H1-antihistamines are more commonly used to treat patients with anaphylaxis. Although histamine is key in the development of anaphylaxis, treatment with H1-antihistamines does not

bolničkim uslovima 24 sata nakon očiglednog oporavka od anafilaktičke epizode [4]. Svi pacijenti sa rizikom od ponovne anafilakse treba da budu edukovani o odgovarajućoj upotrebi autoinjektora epinefrina [5].

Prikazani pacijent je ubrzo nakon dobijanja epinefrina (1:1.000) 0,5 ml intramuskularno, razvio dobar terapijski odgovor sa porastom arterijske tenzije i bronhodilatacijom. Uz ostale terapijske mere (intravenski glikokortikoidi, antihistaminici, infuzioni rastvori), koje su primenjivane tokom naredna 24 sata, došlo je do potpunog oporavka, bez razvoja odložene anafilakse.

Kod prikazanog pacijenta dalje lečenje alergijskog rinitisa i intermitentne alergijske astme nastavljeno je konvencionalnom terapijom, imajući u vidu da nije bio motivisan za prelazak na *SLIT*. Takođe, obustavljena je i *SCIT* sa mešavinom polena trava.

Alergenska imunoterapija je bezbedan vid lečenja alergijskog rinitisa sa malom incidencijom sistemskih reakcija. Individualni pristup, adekvatni odabir pacijenata, rana identifikacija faktora rizika, primena odgovarajućeg alergenskog ekstrakta i protokola minimiziraju sistemske reakcije. *SLIT* ima bolji bezbedonosni profil od *SCIT*-a i ova formulacija odobrena je za samoprimenu u Evropi i Severnoj Americi [3].

AIT trenutno prolazi kroz velika poboljšanja i inovacije, u smislu povećanja imunogenosti uz manju alergogenost, posebno sa novim adjuvansima, rekombinantnim ili modifikovanim alergenima, sintetičkim peptidima i novim putevima primene (epidermalni ili intralimfatički). Ovakav napredak je osnov veće efikasnosti i bezbednosti alergenske imunoterapije u budućnosti, sa većom zastupljenošću ovog modaliteta lečenja u svakodnevnoj kliničkoj praksi [8].

SPISAK SKRAĆENICA

AIT – alergenska imunoterapija
SCIT – subkutana imunoterapija (engl. *subcutaneous immunotherapy*)
SLIT – sublingvalna imunoterapija (engl. *sublingual immunotherapy*)
TH2 – T helper 2 limfociti
TH1 – T helper 1 limfociti
SABA – kratkodelujući beta2 agonist (engl. *short acting beta2 agonist*)
RAST – engl. *radioallergosorbent test*
LABA – dugodelujući beta2 agonist (engl. *long acting beta2 agonist*)
IPP – inhibitori protonske pumpe
AR – alergijski rinitis
IM – intramuskularni
SC – subkutani (engl. *subcutaneous*)
LR – lokalne reakcije
SR – sistemske reakcije
PNU – engl. *protein nitrogen units*

Sukob interesa: Nije prijavljen.

alleviate or prevent all pathophysiological mechanisms of anaphylaxis, including more serious complications such as airway obstruction, hypotension, and shock. In addition, H1-antihistamines do not act as quickly as epinephrine. Peak plasma concentrations are reached between one and three hours for H1-antihistamines, as compared to less than 10 minutes for intramuscular epinephrine. This indicates the need for additional training of physicians in the management of anaphylaxis, as well as the education of patients regarding appropriate self-help measures for anaphylaxis [18].

According to literature data, biphasic anaphylaxis occurs in about 20% of adults with symptoms that recur within 1 h – 72 h (usually 8 h – 10 h) after the initial reaction has disappeared. There are no clear predictors of the development of the second phase of anaphylaxis [17]. Since life-threatening manifestations may recur during the second phase, it is necessary to keep patients under observation in hospital for a period of 24 hours after apparent recovery from an anaphylactic episode [4]. All patients at risk of recurrent anaphylaxis should be educated on the appropriate use of epinephrine autoinjectors [5].

The patient presented in this article developed a good therapeutic response shortly after receiving 0.5 ml of epinephrine (1:1,000) intramuscularly, demonstrating an increase in arterial blood pressure and bronchodilation. With other therapeutic measures (intravenous glucocorticoids, antihistamines, infusion solutions), which were applied during the following 24 hours, there was a complete recovery, without the development of delayed anaphylaxis.

In the patient presented in this article, further treatment of allergic rhinitis and intermittent allergic asthma continued with conventional therapy as he was not willing to switch to SLIT. Also, SCIT with grass pollen mixture was discontinued.

Allergen immunotherapy is a safe form of treatm and North America [3].

AIT is currently undergoing major improvements and innovations, in terms of increased immunogenicity with less allergenicity, especially with new adjuvants, recombinant or modified allergens, synthetic peptides and new routes of administration (epidermal or intralymphatic). This progress is the basis for greater efficiency and safety of allergen immunotherapy in the future, with a greater prevalence of this treatment modality in daily clinical practice [8].

LIST OF ABBREVIATIONS AND ACRONYMS

AIT – allergen immunotherapy
SCIT – subcutaneous immunotherapy
SLIT – sublingual immunotherapy

TH2 – T helper 2 lymphocytes
TH1 – T helper 1 lymphocytes
SABA – short acting beta2 agonist
RAST – radioallergosorbent test
LABA – long acting beta2 agonist
PPI – proton pump inhibitors
AR – allergic rhinitis
IM – intramuscular
SC – subcutaneous
LR – local reactions
SR – systemic reactions
PNU – protein nitrogen units

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