VODIČ EVROPSKOG RESPIRATORNOG UDRUŽENJA U LEČENJU SARKOIDOZE: KLINIČKI PRISTUP I PREDLOZI

PREGLEDNI RAD

REVIEW ARTICLE

EUROPEAN RESPIRATORY SOCIETY PRACTICE GUIDELINES IN TREATMENT OF SARCOIDOSIS: CLINICAL APPROACH AND SUGGESTIONS

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SAŽETAK

Sarkoidoza može da zahvati bilo koji organ i time dovede do značajnog narušavanja kvaliteta života, čak i porasta mortaliteta. Neurosarkoidoza, sarkoidoza srca i fibroza pluća u sklopu sarkoidoze pluća su oblici sarkoidoze koji imaju najvišu stopu smrtnosti, ali i najmanju stopu odgovora na dosadašnju terapiju. Grupa eksperata iz oblasti sarkoidoze, uz podršku Evropskog respiratornog udruženja, kreirala je vodič za lečenje najčešćih oblika sarkoidoze, te dala predloge za dalja ispitivanja u cilju kreiranja novih terapijskih protokola. Dokazi su dobijeni pregledom dosadašnje literature. Cilj ovog rada je približavanje ovih smernica lekarima u svakodnevnoj kliničkoj praksi, kako bi se poboljšao kvalitet života kod obolelih i smanjio mortalitet od sarkoidoze.

Ključne reči: sarkoidoza, lečenje, Evropsko respiratorno udruženje, kortikosteroidi, imunomodulatori

ABSTRACT

Sarcoidosis can affect any organ and thus lead to a significant impairment of quality of life, even to an increase in mortality. Neurosarcoidosis, cardiac sarcoidosis, and pulmonary fibrosis in sarcoidosis are the forms of sarcoidosis with the highest mortality rate, and with the lowest response rate to the current therapy. A group of experts in the field of sarcoidosis, supported by the European Respiratory Society, created practice guidelines in the treatment of the most common forms of sarcoidosis, and provided suggestions for further research so as to create new therapeutic protocols. The evidence was obtained by reviewing literature. The aim of this paper is to bring these guidelines closer to doctors in daily clinical practice, in order to improve patients' quality of life and reduce mortality from sarcoidosis.

Keywords: sarcoidosis, treatment, European respiratory society, corticosteroids, immunomodulators

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UVOD

I pored dosadašnjih ispitivanja, sarkoidoza predstavlja bolest nepoznate etiologije i nepredvidivog toka [1]. Iako je najčešći oblik sarkoidoze akutna plućna sarkoidoza, kod koje može da dođe do spontane regresije, hronična plućna sarkoidoza i ekstrapulmonalna sarkoidoza (posebno neurosarkoidoza i sarkoidoza srca) dovode do značajnog narušavanja kvaliteta života, kao i porasta mortaliteta [2]. Kortikosteroidi i dalje predstavljaju prvu liniju terapije u lečenju simptomatske forme bolesti, a u njihovoj primeni postoje dva problema: 1) određene forme bolesti ne reaguju na primenu kortikosteroida, i 2) dugotrajna upotreba kortikosteroida dovodi do razvoja značajnih neželjenih efekata [3]. Uzimajući u obzir sve ove faktore, Evropsko respiratorno udruženje (ERS), globalno udruženje zdravstvenih radnika koje ima za cilj edukaciju i unapređenje znanja iz oblasti respiratorne medicine, donelo je nove smernice u lečenju sarkoidoze [4]. Cilj ovog rada je pregled novih smernica ERS-a, te namera da se one učine dostupnim što većem broju lekara.

METODOLOŠKI PRISTUP

Smernice je kreirala grupa eksperata na čelu sa R.Baughman i D.Valeyre. Njeni članovi su specijalisti i istraživači sa višegodišnjim iskustvom u lečenju sarkoidoze, kao i pacijenti oboleli od sarkoidoze. Metodologija je zasnovana na GRADE strukturi, koja se bazira na rangiranju postojećih preporuka, njihovoj proceni, razvoju novih preporuka i njihovoj evaluaciji u kliničkoj praksi [5]. Grupa eksperata je razvila ukupno osam PICO (patients, interventions, comparison, outcomes) pitanja iz kojih je kreirala 12 preporuka za 7 PICO pitanja (Tabela 1). PICO pitanja su formirali eksperati i tiču se prepreka prisutnih u lečenju sarkoidoze, dok su odgovori dobijeni pregledom medicinski relevantne literature, te su bazirani na medicini zasnovanoj na dokazima. Pored preporuka, grupa eksperata je dala i informacije o primeni alternativnih tretmana, u slučajevima kada nije postojalo dovoljno dokaza za samu preporuku. Oblasti kojima je dat značaj su sarkoidoza pluća, sarkoidoza kože, sarkoidoza srca, neurosarkoidoza, zamor u sarkoidozi i sarkoidozom posredovana neuropatija malih vlakana. Protokoli zasnovani na preporukama kreirani su za svaku od oblasti. Važno je napomenuti da su prethodne smernice kreirane 1999. godine u saradnji ERS-a, Američkog torakalnog udruženja (ATS) i Svetske organizacije za sarkoidozu i druge granulomatozne bolesti (WASOG), ali da je vremenom akcenat stavljen na dva ključna faktora: rizik od trajnog oštećenja funkcije organa ili smrti i narušavanje kvaliteta života [6,7]. Ova dva faktora su stavljena u prvu liniju prilikom odabira terapije, prevashodno uvođenja antiinflamatorne tera-

INTRODUCTION

Despite the previous research, the cause of sarcoidosis remains unknown, and its course is unpredictable [1]. Although the most common type of sarcoidosis is acute pulmonary sarcoidosis, where spontaneous regression may occur, chronic pulmonary sarcoidosis and extrapulmonary sarcoidosis (especially neurosarcoidosis and cardiac sarcoidosis) significantly impair quality of life and lead to an increase in mortality [2]. Corticosteroids remain first-line therapy for treating symptomatic disease, but there are two problems about their use: 1) certain types of the disease are not corticosteroid-responsive, (2) long-term use of corticosteroids leads to the development of significant side effects [3]. Taking all these factors into consideration, European Respiratory Society (ERS), a global association of healthcare professionals which aims to educate and improve knowledge in the field of respiratory medicine, has adopted new guidelines in the treatment of sarcoidosis [4]. The aim of this paper is to review new ERS guidelines and bring them closer to as many doctors as possible.

METHODOLOGY

Guidelines were created by a group of experts led by R. Baughman and D. Valeyre. Its members are specialists and researchers with extensive experience in the treatment of sarcoidosis, as well as patients suffering from sarcoidosis. Methodology is based on the GRADE approach which involves ranging the current guidelines, evaluating them, developing new guidelines, and evaluating them in practice [5]. The group of experts developed eight PICO (patients, interventions, comparison, outcomes) questions out of which they made 12 recommendations for seven PICO questions (Table 1). The PICO questions were developed by experts, and they pertain to the obstacles to the treatment of sarcoidosis, whereas the answers were obtained by reviewing relevant medical literature and are thus based on evidence-based medicine. In addition to the recommendations, the group of experts provided information on using alternative treatments in cases where there was not enough evidence for making recommendations. The areas of focus were pulmonary sarcoidosis, cutaneous sarcoidosis, cardiac sarcoidosis, neurosarcoidosis, sarcoidosis-associated fatigue, and sarcoidosis-associated small-fiber neuropathy. Protocols based on recommendations were created for each area. It is important to mention that the previous guidelines were created in 1999 by ERS, the American Thoracic Society (ATS), and the World Association of Sarcoidosis and other Granulomatous Disorders (WASOG) and that over time the emphasis has been put on two key

Tabela 1. PICO pitanja.

Kod pacijenata sa plućnom sarkoidozom, da li uvođenje kortikosteroida ima benefite u odnosu na odsustvo terapije?	Kod pacijenata sa klinički manifestnom bolesti, uz visok rizik za porast mortaliteta i/ili pogoršavanje kvaliteta života, savetuje se primena kortikosteroida. (snažna preporuka)
Kod pacijenata sa plućnom sarkoidozom, da li je potrebno dodavati druge imunomodulatore uz kortikosteroide?	Kod pacijenata na terapiji kortikosteroidima, kod kojih se održava aktivnost bolesti, sa visokim rizikom za porast mortaliteta i/ili pogoršavanje kvaliteta života, ili postoji rizik od značajnih neželjenih efekata primene kortikosteroida, savetuje se uvođenje metotreksata u terapiju. (uslovna preporuka) Kod pacijenata na kombinovanoj terapiji kortikosteroidima sa drugom imunomodulatornom terapijom, kod kojih se održava aktivnost bolesti, sa visokim rizikom za porast mortaliteta i/ili pogoršavanje kvaliteta života, savetuje se uvođenje infliksimaba u terapiju. (uslovna preporuka)
Kod pacijenata sa kožnom sarkoidozom, da li uvođenje kortikosteroida ima benefite u odnosu na odsustvo terapije?	Kod pacijenata kod kojih se održavaju kožne promene uprkos lokalnoj terapiji, savetuje se oralna terapija kortikosteroidima. (uslovna preporuka)
Kod pacijenata sa kožnom sarkoidozom, da li je potrebno dodavati druge imunomodulatore ukoliko se kontrola bolesti ne postigne primenom kortikosteroida?	Kod pacijenata na kombinovanoj terapiji kortikosteroidima sa drugom imunomodulatornom terapijom, kod kojih se održava aktivnost bolesti uprkos primeni terapije, savetuje se uvođenje infliksimaba u terapiju. (uslovna preporuka)
Kod pacijenata sa klinički manifestnom sarkoidozom srca, da li je potrebno uvoditi imunomodulatornu terapiju?	Kod pacijenata sa srčanom sarkoidozom, kod kojih dolazi do razvoja poremećaja ritma ili smanjenja funkcije, savetuje se uvođenje kortikosteroida (sa ili bez druge imunomodulatorne terapije). (snažna preporuka)
Kod pacijenata sa neurosarkoidozom, da li uvođenje kortikosteroida (sa ili bez druge imunomodulatorne terapije) ima benefite u odnosu na odsustvo terapije?	Kod pacijenata sa manifestnom neurosarkoidozom, savetuje se uvođenje kortikosteroida. (snažna preporuka) Kod pacijenata sa manifestnom neurosarkoidozom, koji su već na terapiji kortikosteroidima, savetuje se uvođenje metotreksata. (uslovna preporuka) Kod pacijenata sa manifestnom neurosarkoidozom, koji su već na kombinovanoj terapiji kortikosteroidima i drugim imunomodulatorima (metotreksat, azatioprin, mikofenolat mofetil), savetuje se uvođenje infliksimaba. (uslovna preporuka)
Kod zamora u sarkoidozi, da li je potrebno uvoditi imunomodulatornu, stimulatornu ili fizikalnu terapiju?	Kod prisustva zamora u sarkoidozi, savetuje se fizikalna i pulmološka rehabilitacija u trajanju od 6 do 12 meseci. (uslovna preporuka) Ukoliko se ne postigne smanjenje zamora, uprkos primeni fizikalne i pulmološke rehabilitacije, savetuje se primena metilfenidata ili armodafinila u trajanju od 8 nedelja kako bi se izbegao razvoj tolerancije. (uslovna preporuka)
Kod pacijenata sa SFN, da li je potrebno uvoditi imunomodulatornu terapiju?	Nemoguće je dati preporuke, s obzirom na nedostatak dokaza.

SFN- neuropatija malih vlakana

pije u cilju prevencije ovih neželjenih događaja. Grupa eksperata se prilikom kreiranja smernica oslanjala na davanje preporuka za antiinflamatornu terapiju (Tabela 2), s obzirom na to da terapija komplikacije same sarkoidoze (transplantacija pluća, hidrocefalus, ugradnja pejsmejkera zbog poremećaja ritma) zbrinjava bez posebnih ograničenja u odnosu na iste komplikacije druge etiologije [8,9].

factors: the rik of permanent organ damage or death and quality of life impairment [6,7]. These two factors were considered first when selecting the therapy, especially anti-inflammatory therapy which is supposed to prevent these adverse events. When creating the guidelines, the group of experts relied on providing recommendations for anti-inflammatory therapy (Table 2), given that the therapy treats the complications of sarcoidosis itself (lung transplantation, hydrocephalus,

Table 1. PICO questions

In patients with pulmonary sarcoidosis, does the introduction of corticosteroids have beneficial effects compared to the absence of therapy?	In patients with clinically manifest disease, and with a high risk of an increase in mortality and/or deterioration of quality of life, the use of corticosteroids is advised. (Strong recommendation)
In patients with pulmonary sarcoidosis, is it necessary to add other immunomodulators when corticosteroids are used?	In patients on corticosteroid therapy, where the activity of the disease is maintained and where there is a high risk of increased mortality and/or deterioration of the quality of life, or a risk of significant side effects of corticosteroid administration, it is advised that methotrexate is introduced into therapy. (Conditional recommendation) In patients on combined therapy with corticosteroids and other immunomodulatory therapy, where the activity of the disease is maintained and there is a high risk of increased mortality and/or deterioration of the quality of life, it is advised that the infliximab is introduced into therapy. (Conditional recommendation)
In patients with cutaneous sarcoidosis, does the introduction of corticosteroids have beneficial effects compared to the absence of therapy?	In patients in whom skin changes persist despite local therapy, oral corticosteroid therapy is advised. (Conditional recommendation)
In patients with cutaneous sarcoidosis, is it necessary to add other immunomodulators if disease control is has not been achieved with the use of corticosteroids?	In patients on combined therapy with corticosteroids and other immunomodulatory therapy, where the activity of the disease is maintained despite therapy, it is advised that infliximab is introduced into therapy. (Conditional recommendation)
In patients with clinically manifest cardiac sarcoidosis, is it necessary to introduce immunomodulatory therapy?	In patients with cardiac sarcoidosis, who develop rhythm disturbances or a decrease in function, it is advised that corticosteroids are introduced (with or without other immunomodulatory therapy). (Strong recommendation)
In patients with neurosarcoidosis, does the introduction of corticosteroids (with or without other immunomodulatory therapy) have beneficial effects compared to the absence of therapy?	In patients with manifest neurosarcoidosis, the introduction of corticosteroids is advised. (strong recommendation) In patients with manifest neurosarcoidosis, who are already on corticosteroid therapy, the introduction of methotrexate is advised. (conditional recommendation) In patients with manifest neurosarcoidosis, who are already on combined therapy with corticosteroids and other immunomodulators (methotrexate, azathioprine, mycophenolate mofetil), the introduction of infliximab is advised. (Conditional recommendation)
In sarcoidosis-associated fatigue, is it necessary to introduce immunomodulatory, stimulatory, or physical therapy?	In sarcoidosis-associated fatigue, physical and pulmonary rehabilitation is advised for 6 to 12 months. (Conditional recommendation) If a reduction in fatigue has not been achieved, despite physical and pulmonary rehabilitation, it is advised to use methylphenidate or armodafinil for 8 weeks so as to avoid the development of tolerance. (Conditional recommendation)
In patients with SFN, is it necessary to introduce immunomodulatory therapy?	It is impossible to make recommendations, as there is a lack of evidence.

SFN- small fiber neuropathy

FORME BOLESTI

Sarkoidoza pluća

Najčešća forma bolesti je sarkoidoza pluća. Budući da je već dokazano da razvoj plućne fibroze ili plućne hipertenzije predstavlja glavne faktore za mortalitet u ovoj formi bolesti, za osnov lečenja uzeto je održavanje ravnoteže između kontrole aktivnosti bolesti sa jedne strane, i neželjenih efekata terapije sa druge strane

insertion of a pacemaker due to rhythm disorders) with no special restrictions when compared to the same complications of a different etiology [8,9].

TYPES OF SARCOIDOSIS

Pulmonary sarcoidosis

Pulmonary sarcoidosis is the most common type of sarcoidosis. Since it has been proven that the develop-

Tabela 2. Imunomodulatorni lekovi u sarkoidozi

Lek	Doza	Neželjeni efekti	Parametri za praćenje	Napomena
Prednizon	20 mg dnevno, potom 5-10 mg dnevno, pa na drugi dan	Dijabetes, arterijska hipertenzija, osteoporoza, gojaznost, glaukom, promena raspoloženja	Osteodenzitometrija, krvni pritisak, glikemija	Kumulativna toksičnost
Metotreksat	10-15 mg nedeljno	Mučnina, leukopenija, hepatotoksičnost	Kompletna krvna slika, hepatogram i azotne materije u serumu	Izbegavati u bubrežnoj insuficijenciji
Leflunomid	10-20 mg dnevno	Mučnina, leukopenija, hepatotoksičnost	Kompletna krvna slika, hepatogram i azotne materije u serumu	Izbegavati u bubrežnoj insuficijenciji
Azatioprin	50-250 mg dnevno	Mučnina, leukopenija, infekcije, maligni potencijal	Kompletna krvna slika	
Mikofenolat mofetil	500-1500 mg dva puta dnevno	Dijareja, leukopenija, infekcije, maligni potencijal	Kompletna krvna slika	Manjak iskustva u primeni u sarkoidozi
Infliksimab ili biosimilari*	3-5 mg/kg inicijalno, drugi ciklus za 2 nedelje, potom na 4-6 nedelja	Infekcije, alergijske reakcije	Pre uvođenja isključiti prethodnu tuberkulozu, gljivičnu infekciju, srčanu insuficijenciju, malignitet, bolest demijelinizacije	Životno ugrožavajuće alergijske reakcije
Adalimumab*	40mg na 1-2 nedelje	Infekcije	Pre uvođenja isključiti prethodnu tuberkulozu, gljivičnu infekciju, srčanu insuficijenciju, malignitet, bolest demijelinizacije	Manje toksičan u odnosu na infliksimab
Rituksimab*	500-1000 mg na 1-6 meseci	Infekcije	Isključiti raniji virusni hepatitis, pratiti vrednosti IgG u toku terapije	Moguć nastanak IgG deficijencije
Depo preparat kortikotropina*	40-80 jedinica dva puta nedeljno	Dijabetes, arterijska hipertenzija, anksioznost	Kompletna krvna slika, glikemija	Neželjeni efekti najčešći na dan primene
Hidroksihlorokin	200-400 mg dnevno	Gubitak vida	Pregled očnog dna	Slab uticaj na srčanu sarkoidozu i neurosarkoidozu

* lekovi rezervisani za pacijente kod kojih nije postignuta kontrola bolesti drugim agensim

[10,11]. Pored porasta mortaliteta, nemali broj pacijenata ima značajno narušen kvalitet života usled prisustva tegoba vezanih za simptome respiratornog sistema, koje takođe treba uzeti u obzir prilikom odabira vrste i trajanja terapije. U proceni bolesti koriste se ispitivanja disajne funkcije (spirometrija, difuzijski kapacitet pluća za CO), radiografija (RTG) i kompjuterizovana tomografija (CT) grudnog koša. Ultrasonografija srca se primenjuje ukoliko postoji sumnja na razvoj plućne hipertenzije, usled oštećenja plućnog parenhima [12].

Iakoje određeni broj obolelih od sarkoidoze pluća asimptomatski, dosadašnje studije su pokazale da uvođenje oralnih kortikosteroida dovodi do poboljšanja/stabilizacije disajne funkcije, kao i unapređenja disajne funkcije [13]. Parenteralna primena kortikosteroida nije pokazala značajnije benefite u odnosu na oralnu primenu [14]. Takođe, inhalatorna primena kortikosteroida nije dovela do značajnih benefita [15]. Studije su pokazale najpotentniji efekat kortikosteroidne terapije u ranim fazama bolesti, dok bi samo trajanje terapije trebalo da bude između 3 i 6 meseci. Trajanje terapije kraće od 3 meseca povezano je sa recidiviranjem bo-

ment of pulmonary fibrosis or pulmonary hypertension are the strongest predictors for mortality in this type of the disease, the treatment is based on maintaining a balance between controlling the disease on one hand and side effects of the therapy on the other [10,11]. Apart from an increase in mortality, quite a few patients have significantly impaired quality of life due to the presence of problems related to respiratory symptoms, which should also be taken into consideration when choosing the type and length of therapy. In disease assessment, pulmonary function tests (spirometry, diffusing capacity of the lungs for carbon monoxide), radiography (X-ray) and computed tomography (CT) of the chest are used. Echocardiography is applied if the development of pulmonary hypertension is suspected due to damage to the lung parenchyma [12].

Although a certain number of patients with pulmonary sarcoidosis are asymptomatic, previous studies have shown that the introduction of oral corticosteroids improves/stabilizes pulmonary functions and enhances them [13]. Parenteral administration of corticosteroids has not shown significant beneficial effects in compari-

Table 2. Immunomodulatory drugs in sarcoidosis

Drug	Dosage	Side effects	Parameters to monitor	Note
Prednisone	20mg per day, then 5-10 mg per day, then every second day	Diabetes, arterial hypertension, osteoporosis, obesity, glaucoma, mood swings	Osteodensitometry, blood pressure, glycemia	Cumulative toxicity
Methotrexate	10-15 mg per week	Nausea, leukopenia, hepatotoxicity	Complete blood count, kidney, and liver functions	Avoid in renal failure
Leflunomide	10-20 mg per day	Nausea, leukopenia, hepatotoxicity	Complete blood count, kidney, and liver functions	Avoid in renal failure
Azathioprine	50-250 mg per day	Nausea, leukopenia, infections, malignant potential	Complete blood count	
Mycophenolate mofetil	500-1500 mg twice a day	Diarrhea, leukopenia, infections, malignant potential	Complete blood count	A lack of experience concerning its application in sarcoidosis
Infliximab or biosimilars*	3-5 mg/kg initially, the second cycle in 2 weeks, then every 4-6 weeks	Infections, allergic reactions	Prior to introduction, rule out previous tuberculosis, fungal infection, heart failure, malignancy, demyelinating disease	Life-threatening allergic reactions
Adalimumab*	40mg every 1-2 weeks	Infections	Prior to introduction, rule out previous tuberculosis, fungal infection, heart failure, malignancy, demyelinating disease	Less toxic compared to infliximab
Rituximab*	500-1000 mg every 1-6 months	Infections	Rule out previous viral hepatitis, monitor IgG values during therapy	Moguć nastanak IgG deficijencije
Depot corticosteroids *	40-80 units twice a week	Diabetes, arterial hypertension, anxiety	Complete blood count, glycemia	Side effects most common on the day of application
Hydroxychloroquine	200-400 mg per day	Loss of eyesight	Fundoscopic exam	Weak effect on cardiac sarcoidosis and neurosarcoidosis

*drugs intended for patients in whom disease control has not been achieved with other agents

lesti, dok terapija duža od 6 meseci dovodi do porasta rizika od neželjenih efekata kortikosteroidne terapije [13]. Inicijalno se savetuje primena 20mg prednizona, uz korekciju doze u zavisnosti od simptoma, biomarkera, radiografije grudnog koša, disajne funkcije i neželjenih reakcija kortikosteroidne terapije.

Ukoliko se ne postigne kontrola bolesti ili ukoliko dođe do značajnih neželjenih efekata kortikosteroidne terapije, savetuje se uvođenje metotreksata u terapiju, kako bi se održala disajna funkcija i kvalitet života. Potrebno je napomenuti da metotreksat nije pokazao značajnije poboljšanje disajne funkcije u monoterapiji, ali, u kombinaciji sa kortikosteroidnom terapijom, omogućava smanjenje doze kortikosteroida i time smanjuje rizik od nastanka komplikacija terapije [16,17]. Kada je reč o drugim imunomodulatorima, jedino se infliksimab pokazao korisnim, i to u lečenju hronične plućne sarkoidoze koja nije reagovala na primenu kortikosteroida i/ili metotreksata [18]. Drugi

son with oral administration [14]. Besides, inhaled corticosteroids have not shown significant beneficial effects [15]. Studies have proven the most potent effect of corticosteroid therapy in the early stages of the disease, with the length of therapy between 3 and 6 months. Therapies lasting for less than three months are associated with disease recurrence, whereas therapies exceeding six months lead to an increased risk of side effects of corticosteroids [13]. Initially, the administration of 20mg of prednisone is recommended, with dose correction depending on symptoms, biomarkers, X-ray, pulmonary function tests, and side effects of corticosteroid therapy.

If disease control has not been achieved or if significant side effects of corticosteroid therapy have occurred, it is recommended that methotrexate should be introduced to maintain pulmonary function and quality of life. It should be noted that methotrexate monotherapy has not provided a significant improvement in pulmonary function, but combined with corti-

imunomodulatori (azatioprin, leflunomid, mikofenolat mofetil, hidroksihlorokin) su takođe pokazali benefite, ali su neophodne veće studije sa jasnijim komparacijama, kako bi zauzeli značajnije mesto u terapiji [19]. Potencijalno mesto u lečenju mogu da imaju i oralni antifibrotici nintedanib i pirfenidon, kao i inhibitori faktora nekroze tumora (TNF) i njihovi biosimilari, ali je njihova primena i dalje u domenu teorije [20]. Ukoliko bi se dokazala efikasnost oralnih antifibrotika, njihova primena bi najpre bila u domenu četvrtog stadijuma sarkoidoze pluća, odnosno plućne fibroze u sklopu sarkoidoze, s obzirom na to da ta forma poseduje sve karakteristike progresivne plućne fibroze: pogoršanje kliničke slike i disajne funkcije u jedinici vremena, karakteristične promene opisane na kompjuterizovanoj tomografiji visoke rezolucije, i značajan porast mortaliteta [21]. Oralni antifibrotik nintedanib se već primenjuje u lečenju plućne fibroze u sklopu sistemskih bolesti vezivnog tkiva, te je moguće očekivati i efekat u lečenju četvrtog stadijuma sarkoidoze pluća [22].

Sarkoidoza kože

Kutana zahvaćenost je prisutna u oko 30% obolelih od sarkoidoze i najčešće predstavlja prve znake bolesti [23]. Stepen zahvaćenosti i tipovi promena su značajno varijabilni i dovode pre svega do narušavanja kvaliteta života. Baš zbog varijabilnosti u distribuciji, lečenje se primarno fokusira na estetski značajne lezije, te je moguća i lokalna, odnosno topikalna, primena terapije [24]. Tendencija spontane remisije je mala, te je, ukoliko se lokalnom terapijom ne postigne remisija, neophodna sistemska primena imunomodulatora. Pregledom dostupne literature, dolazi se do zaključka da monoterapija kortikosteroidima često ne dovodi do zadovoljavajuće kontrole bolesti, te je često neophodno kombinovanje sa drugim imunomodulatorima. Topikalna terapija kortikosteroidima savetuje se u lečenju lokalizovanih, pojedinačnih lezija po tipu plakova i papula, ali se ipak često viđaju recidivi. U slučaju opsežnijih lezija, ili hroničnih lezija tipa lupus pernio, neophodno je kombinovanje oralnih kortikosteroida sa nekim od drugih imunomodulatora, od kojih se daje prednost hlorokinu, hidroksihlorokinu i metotreksatu [25]. Ukoliko primena kortikosteroida, samostalno ili u kombinaciji sa drugim imunomodulatorima, ne postigne kontrolu bolesti, savetuje se primena infliksimaba. Treba napomenuti da su prilikom primene infliksimaba pacijenti podložniji infekcijama, kao i da su prisutne ozbiljne alergijske reakcije prilikom primene leka [26,27]. Svakako dostupnost kožnih promena značajno olakšava razvoj novih terapijskih agenasa, te se mogu očekivati novi modaliteti.

costeroid therapy it allows for a reduction in the dose of corticosteroids and thus reduces the risk of treatment-related complications [16,17]. When it comes to other immunomodulators, only infliximab has been useful in treating chronic pulmonary sarcoidosis unresponsive to corticosteroids and/or methotrexate [18]. Other immunomodulators (azathioprine, leflunomide, mycophenolate mofetil, hydroxychloroquine) have also shown beneficial effects, but large-scale studies with clearer comparisons are needed so that they could take a more significant position in treating pulmonary sarcoidosis [19]. Orally administered antifibrotic drugs nintedanib and pirfenidone, as well as tumor necrosis factor (TNF) inhibitors and their biosimilars may be potentially useful, but their application remains theoretical [20]. If effectiveness of orally administered antifibrotics were proven, they would first be applied in stage IV pulmonary sarcoidosis, i.e., pulmonary fibrosis in sarcoidosis, considering that this type has all characteristics of progressive pulmonary fibrosis: deterioration of clinical presentation and pulmonary function per unit of time, distinctive changes observed in high-resolution CT, and a significant increase in mortality [21]. Orally administered antifibrotic nintedanib has already been applied in treating pulmonary fibrosis within connective tissue diseases, so it is possible to expect it to show beneficial effects in treating stage IV pulmonary sarcoidosis as well [22].

Cutaneous sarcoidosis

Cutaneous involvement is present in approximately 30% of patients with sarcoidosis and it is usually the first sign of the disease [23]. The degree of involvement and the types of changes vary significantly leading to impaired quality of life. Due to uneven distribution, the treatment is primarily focused on aesthetically significant lesions, so local, i.e., topical, application of therapy is also possible [24]. The tendency of spontaneous remission is low, so if remission is not achieved with local therapy, systemic administration of immunomodulators is needed. Reviewing the available literature, we have concluded that corticosteroid monotherapy often does not lead to satisfactory disease control, so it is necessary to combine it with other immunomodulators. Therapy with topical corticosteroids is advised in treating localized, individual lesions of the plaque or papule type, but recurrence is still very common. In case of extensive lesions or chronic lesions of the lupus pernio type, it is necessary to combine oral corticosteroids with another immunomodulator, chloroquine, hydroxychloroquine and methotrexate being prefered over others [25]. If disease control has not been achieved by applying corticosteroids, either as monothera-

Sarkoidoza srca

Manifestna sarkoidoza srca se javlja u malom broju obolelih od sarkoidoze, ali se pretpostavlja da je prisutna i u do 30% svih slučajeva [28]. Najčešće se klinički manifestuje kao različiti poremećaji ritma, od ektopičnih žarišta, do blokova u sprovođenju [29]. Dosadašnje studije su pokazale smanjenje mortaliteta ukoliko se pacijentima ordiniraju kortikosteroidi u manifestnoj fazi bolesti, pogotovo ako se radi o atrioventrikularnim blokovima usled sarkoidoze. Trenutno ne postoje jasni dokazi za benefite kombinovane terapije kortikosteroida sa imunomodulatorima (metotreksat, azatioprin, mikofenolat mofetil, leflunomid i ciklofosfamid) u odnosu na monoterapiju kortikosteroidima [30]. Takođe, doze kortikosteroida veće od 0.5mg/kg nisu pokazale benefite u odnosu na doze ispod 0.5mg/kg, ali su bile povezane sa većim brojem neželjenih efekata kortikosteroidne terapije. U sarkoidozi srca, inflamacija unutar miokarda dovodi do, sa jedne strane fizičke kompresije miocita granulomima, i do toksičnog efekta oslobođenih medijatora inflamacije sa druge strane. Direktna posledica je uvećanje srčanih šupljina, pre svega leve komore, što dovodi do porasta mortaliteta, te supresija inflamacije koju izazivaju kortikosteroidi direktno smanjuje ove neželjene događaje [31,32,33]. U slučaju refraktorne bolesti, moguća je primena anti-TNF antitela [34].

Neurosarkoidoza

Klinička slika sarkoidoze je značajno varijabilna, imajući u vidu da se granulomi mogu javiti u bilo kom delu nervnog sistema [35]. Neurosarkoidoza je praktično uvek simptomatična, te je neophodno što pre započeti sa lečenjem [36]. U prvoj liniji se savetuje primena kortikosteroida, potom kombinacija sa, pre svega, metotreksatom, dok se infliksimab savetuje ukoliko se ne postigne kontrola bolesti. Ovi saveti su bazirani na više varijabli: kliničkom poboljšanju, progresiji bolesti, kvalitetu života, i neželjenim reakcijama na terapiju. Pregledom literature pokazano je da je učestalost recidiva značajno niža kod pacijenata na terapiji kortikosteroidima u odnosu na one bez terapije. Kombinovana primena kortikosteroida sa drugom terapijom (metotreksat, azatioprin, mikofenolat mofetil) je pokazala manji stepen recidiva u odnosu na monoterapiju kortikosteroidima. Studije su pokazale i da monoterapija kortikosteroidima ima bolji efekat u odnosu na monoterapiju drugim imunomodulatorima, te se može zaključiti da su kortikosteroidi ipak primarni terapijski agens za kontrolu bolesti [37]. Infliksimab je u retrospektivnim studijama pokazao efikasnost u poboljšanju radiografskog nalaza na magnetnoj rezonanci endokranijuma, kao i smanjenje tegoba, ali su i dalje potrebne prospy or in combination with other immunomodulators, the administration of infliximab is advised. It should be noted that when using infliximab patients are more prone to infections, as well as that there are serious allergic reactions when using the medication [26,27]. The accessibility of cutaneous changes significantly facilitates the development of new therapeutic agents, so new modalities can be expected.

Cardiac sarcoidosis

Clinically manifest cardiac involvement is found in a small number of patients with sarcoidosis, but it is supposed to be present in up to 30% of cases [28]. It is most often clinically manifested as various rhythm disorders, from ectopic foci to atrioventricular blocks [29]. Previous studies have shown a reduction in mortality if patients are prescribed corticosteroids in the manifest illness stage, especially in case of atrioventricular blocks due to sarcoidosis. Currently, there is no clear evidence of beneficial effects of corticosteroid therapy combined with immunomodulators (methotrexate, azathioprine, mycophenolate mofetil, leflunomide and cyclophosphamide) compared to corticosteroid monotherapy [30]. Besides, high doses of corticosteroids (>0.5mg/kg) have not shown greater beneficial effects than the doses < 0.5mg/kg, but they have been associated with a greater number of side effects of corticosteroid therapy. In cardiac sarcoidosis, myocardial inflammation results in granulomas compressing myocytes on one hand, and toxic effect of released inflammatory mediators on the other. The direct consequence is the enlargement of the heart chambers, especially the left ventricle, which leads to an increase in mortality, and suppression of inflammation by corticosteroids directly reduces these adverse events [31,32,33]. In case of refractory disease, it is possible to use anti-TNF antibodies [34].

Neurosarcoidosis

Clinical presentation of sarcoidosis varies significantly as granulomas may occur in any part of the nervous system [35]. Neurosarcoidosis is practically always symptomatic, so it is necessary to start the treatment as soon as possible [36]. The recommended first-line therapy includes the administration of corticosteroids, followed by a combination with methotrexate in the first place, whereas infliximab is recommended if disease control has not been achieved. These recommendations are based on several variables: clinical improvement, disease progression, quality of life, and adverse reactions to therapy. A review of literature has shown that the frequency of recurrence is significantly lower in patients on corticosteroid therapy than in those with no therapy. Recurrence rate is lower in patients whe-

pektivne studije koje bi to definitivno i potvrdile. Takođe, kombinovana primena infliksimaba i visokih doza kortikosteroida predstavljaju potencijalno značajnu kombinaciju, jer bi se njihovom kombinacijom mogao smanjiti neželjeni efekat visokih doza kortikosteroida [35,36]. Velika prepreka u ispitivanju terapije neurosarkoidoze predstavlja njena relativna retkost, te će biti potrebne multicentrične studije.

Neuropatija malih vlakana

Poseban entitet predstavlja neuropatija malih vlakana (SFN-small fiber neuropathy). SFN se retko javlja kao samostalni entitet, a u patofiziološkoj osnovi je gubitak tankih mijelinizovanih i nemijelinizovanih nervnih vlakana, što dovodi do poremećaja senzibiliteta, bolnih sindroma i poremećaja autonomnog nervnog sistema. S obzirom na različitu kliničku prezentaciju, koja može biti i posledica drugih bolesti, kao i odsustvo zlatnog standarda za dijagnostiku, smatra se da veliki broj slučajeva SFN-a biva nedijagnostikovan [38]. Upravo zbog ovih poteškoća u otkrivanju SFN-a, grupa preporuka ne može dati jasne smernice za lečenje. Monoklonalna TNF antitela se primenjuju u lečenju SFN-a u drugim etiologijama, sa relativno dobrim uspehom, te njihova primena u sarkoidozi zahteva dalja ispitivanja. Svakako je prethodno neophodno jasno definisati kriterijume za dijagnostikovanje SFN u sarkoidozi, kao i skrenuti pažnju kliničarima na ovaj entitet [39].

Zamor

Pod zamorom u sarkoidozi podrazumeva se zamor koji nije posledica zahvaćenosti bilo kog organa. On predstavlja jedan od najčešćih simptoma i odgovoran je za značajno smanjenje kvaliteta života, a može biti prisutan i kod potpune regresije bolesti [41,42]. Mehanizam nastanka zamora još uvek nije jasan, te je neophodno isključiti druge potencijalne uzroke. Takođe, s obzirom da je zamor čisto subjektivan simptom, javila se potreba za razvijanjem posebnih upitnika sa idejom da se kvantifikuje i tako olakša interpretacija i odluka o lečenju. Za razliku od prethodno prikazanih smernica, ovde grupa eksperata stavlja akcenat na pulmološku rehabilitaciju uz primenu metilfenidata ili armodafinila ukoliko se rehabilitacijom ne postigne poboljšanje simptoma. Medikamentozna terapija ima značajno ograničenje u vidu neželjenih efekata (insomnija, razvijanje zavisnosti, anksioznost), te su i studijski podaci o njenoj efikasnosti dosta ograničeni [42,43]. Glavno ograničenje u davanju snažnijih preporuka jeste odsustvo znanja o dugoročnoj efikasnosti terapije, kako medikamentozne, tako i fizikalne, te su pre svega potrebne dugoročne prospektivne studije.

re the use of corticosteroids is combined with another therapy (methotrexate, azathioprine, mycophenolate mofetil) in comparison with patients on corticosteroid monotherapy. Studies have also shown that corticosteroid therapy has a better effect than monotherapy with other immunomodulators, so it can be concluded that corticosteroids are primary therapeutic agents for disease control [37]. In retrospective studies, infliximab has proved to be effective in improving radiographic findings on MRI of the endocranium and in reducing symptoms, but prospective studies are needed to confirm this. Also, combined use of infliximab and high doses of corticosteroids is potentially significant, as this combination could reduce adverse effects of high doses of corticosteroids [35,36]. A major obstacle to testing the therapy for neurosarcoidosis is the fact that it is relatively rare, so multicenter studies will be needed.

Small fiber neuropathy

Small fiber neuropathy is an entity in itself. SFN rarely occurs as an individual entity and its pathophysiological basis involves the loss of thin myelinated and unmyelinated nerve fibers, which results in sensory disturbances, pain syndromes, and autonomic nervous system disorders. Considering different clinical presentation, which can be a consequence of other diseases as well, and the absence of a gold standard in diagnostics, it is believed that a large number of patients with SFN remain undiagnosed [38]. Due to these difficulties in detecting SFN, the group of recommendations cannot provide clear treatment guidelines. Anti-TNF monoclonal antibodies are relatively successfully used in treating SFN of other etiologies, and their use in sarcoidosis requires further studies. First of all, it is necessary to define diagnostic criteria for SFN in sarcoidosis, as well as draw physicians' attention to this entity [39].

Sarcoidosis-associated fatigue

Sarcoidosis-associated fatigue is fatigue which is not a result of any organ being affected with disease. It is one of the most common symptoms and it is responsible for a significant reduction in quality of life, and it can even be present in complete regression [41,42]. The mechanism of sarcoidosis-associated fatigue is not clear yet, so it is necessary to exclude other potential causes. Also, considering that fatigue is purely subjective symptom, there is a need to develop special questionnaires with the idea of quantifying it and thus facilitating interpretation and treatment decisions. Unlike the previously presented guidelines, the group of experts here emphasize pulmonary rehabilitation with the use of methylphenidate or armodafinil if rehabilitation does not improve symptoms. Pharmacotherapy

ZAKLJUČAK

Varijabilnost u kliničkoj slici sarkoidoze i dalje predstavlja izazov u kliničkoj praksi. Hronična plućna forma, fibroza pluća ili ekstrapulmonalne forme sarkoidoze (pre svega neurosarkoidoza i sarkoidoza srca) značajno narušavaju kvalitet života i povećavaju mortalitet obolelih. Grupa eksperata ERS-a sagledala je najčešće probleme u lečenju sarkoidoze u kliničkoj praksi i, oslanjajući se na dosadašnja istraživanja, definisala terapijske protokole za lečenje najčešćih oblika sarkoidoze, te predložila potencijalne pravce istraživanja novih terapijskih modaliteta.

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has significant limitations in the form of side effects (insomnia, development of addiction, anxiety), so study data on its effectiveness are also rather limited [42,43]. The main limitation in giving stronger recommendations is a lack of knowledge about the long-term effectiveness of both pharmacotherapy and physiotherapy, so long-term prospective studies are needed.

CONCLUSION

Variability in clinical presentation of sarcoidosis remains a challenge in clinical practice. Chronic pulmonary sarcoidosis, pulmonary fibrosis or extrapulmonary types of sarcoidosis (neurosarcoidosis and cardiac sarcoidosis in the first place) significantly impair quality of life and increase mortality. A group of ERS experts investigated the most common problems in treating sarcoidosis in clinical practice and, relying on previous research, they defined therapeutic protocols for treating the most common types of sarcoidosis and proposed potential research directions concerning new therapeutic modalities.

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