Stručni rad | Professional article

Psorijaza, kardiovaskularni rizik i antihipertenzivni lijekovi

Psoriasis, Cardiovascular Risk, and Antihypertensive Drugs

Saida Rezaković[1]*, Mima Georgieva[2], Lidija Počanić[3]

[1] Poliklinika "Eskulap", Zagreb, Hrvatska
Policlinic "Eskulap" Zagreb, Croatia

[2] Opća bolnica Zabok, Zabok, Hrvatska
Zabok General Hospital, Zabok, Croatia

[3] Klinička bolnica Dubrava, Zagreb, Hrvatska
Dubrava Clinical Hospital, Zagreb, Croatia

RECEIVED:
November 11, 2014
UPDATED:
December 1, 2014
ACCEPTED:
December 6, 2014

SAŽETAK: Psorijaza je kronična upalna bolest koja pogađa 1-2% odrasle opće populacije. Bolest nije ograničena samo na kožu, već je povezana s nizom komorbiditeta, koji značajno utječu na kvalitetu života i predstavljaju povišeni rizik od različitih medicinskih poremećaja. Posljednjih godina, brojne publikacije su pokazale povišenu učestalost srčanožilnih bolesti i metaboličkog sindroma u bolesnika s psorijazom. Iako etiopatogenetska povezanost između ovih stanja još uvijek nije razjašnjena, čini se da dijele zajedničke patofiziološke puteve u vidu sličnih upalnih komponenti. S obzirom na povišenu prevalenciju kardiovaskularnih komorbiditeta u bolesnika, psorijazi bi trebalo pristupiti kao multisistemskoj bolesti. Stoga je potreban multidisciplinarni pristup u cilju najučinkovitijeg liječenja bolesnika sa psorijazom.

Kardiološki lijekovi često su povezani s nastankom ili pogoršanjem psorijaze, među kojima su beta-blokatori najčešći uzročni lijekovi. Potrebno je prepoznati ovu povezanost, s obzirom na to da je to kožna nuspojava koja značajno utječe na kvalitetu života, predstavlja veliko psihološko opterećenje i stigmatizaciju za bolesnika te ima značajan utjecaj na daljnju terapijsku suradljivost.

ABSTRACT: Psoriasis is a chronic inflammatory disease affecting 1-2% of the adult general population. Disease is not limited only to the skin but is associated with a number of comorbidities, which significantly affect quality of life and present a higher risk of various medical disorders. Over recent years, numerous publications have shown increased frequency of cardiovascular disease and metabolic syndrome in patients with psoriasis. Although the etiopathogenetic relationship between these conditions is still not entirely clear, it seems that they share common pathophysiological elements in terms of similar inflammatory components. Considering the increased prevalence of cardiovascular comorbidities in patients, psoriasis should be approached as a multisystem disease. Therefore, a multidisciplinary approach is needed in order to most effectively manage patientswith psoriasis . In addition, cardiac drugs have been frequently reported to induce or exacerbate psoriasis, among which beta-blockers are found to be the most common triggering drug. It is thus important to acknowledge this relationship, as this is cutaneous drug adverse reaction which significantly affects quality of life and is a great psychological burden and stigma for the patient, as well as having a great impact on further treatment compliance.

KLJUČNE RIJEČI: kardiovaskularni rizik, metabolički sindrom, komorbiditeti, beta-blokatori, psorijaza uzrokovana lijekovima.

KEYWORDS: cardiovascular risk, metabolic syndrome, comorbidities, beta-blockers, drug induced psoriasis.

CITATION: Cardiol Croat. 2014;9(11-12):563-568. | **DOI:** http://dx.doi.org/10.15836/ccar.2014.563

***ADDRESS FOR CORRESPONDENCE:** Havidićeva 9/11, HR-10000 Zagreb, Croatia. / Phone: +385-91-655-3701 / E-mail: saida.rezakovic@gmail.com

ORCID: Saida Rezaković, http://orcid.org/0000-0002-5065-637X • Mima Georgieva, http://orcid.org/0000-0002-2084-1822 • Lidija Počanić, http://orcid.org/0000-0002-9322-1309

UVOD

Psorijaza je definirana kao kronična, recidivirajuća, upalna bolest kože. Ipak, ona nije ograničena samo na kožu, s obzirom na to da postoji široki raspon komorbiditetnih stanja povezanih sa pso-

INTRODUCTION

Psoriasis is defined as a chronic, relapsing, inflammatory skin disease. However, it is not limited only to the skin, considering there is a wide range of comorbid conditions associated with

rijazom, uključujući srčanožilne bolesti (SŽB), pretilost, dijabetes, arterijsku hipertenziju (AH), dislipidemiju i metabolički sindrom, koji su u bolesnika sa psorijazom učestaliji nego u osoba bez te bolesti. Cilj ovog rada je prikazati najznačajnije kardiovaskularne i metaboličke poremećaje kod ove grupe bolesnika, kao i prikazati ulogu kardioloških lijekova, posebice beta-blokatora u razvoju i pogoršanju psorijaze.

PSORIJAZA, KARDIOVASKULARNE BOLESTI I METABOLIČKI SINDROM

Mnogobrojne epidemiološke studije su pokazale povezanost psorijaze s komorbiditetima koji povisuju rizik od SŽB, uključujući AH, dijabetes, dislipidemiju i pretilost[1-13]. Koncept nazvan "psorijatični marš" je predložen kako bi opisao ove povezanosti. Ova stanja nastaju kao posljedica ubrzane aterogeneze i endotelne disfunkcije[9,14-17]. Iako podliježeći patofiziološki mehanizmi nisu još uvijek do kraja razjašnjeni, čini se da bi povišeni rizik od SŽB mogao biti povezan sa zajedničkim patogenetskim mehanizmima kod psorijaze i ateroskleroze[7,8,14,18]. Kronična upala ima glavnu ulogu u obje ove bolesti, poglavito preko povišenih razina proupalnih citokina i imunoloških medijatora koji uzrokuju oksidacijski stres i stvaranje slobodnih radikala[2,11,14,19-27]. Nadalje, sustavna upala uzrokuje inzulinsku rezistenciju koja dovodi do smanjenog oslobađanja vazodilatacijskog čimbenika kao što je dušični oksid aktivirajući endotelnu staničnu disfunkciju te uz ubrzanu aterosklerozu posljedično uzrokuje komplikacije kao što su infarkt miokarda ili moždani udar[26,28,29]. Nadalje, povišena aktivnost renin-angiotenzin sustava u bolesnika sa psorijazom dodatno pridonosi razvoju AH[25,30]. Osim mogućih ranije spomenutih patofizioloških mehanizama, s obzirom na veliko psihološko opterećenje i značajno smanjenu kvalitetu života, oboljeli od psorijaze su skloni vođenju nezdravog stila života uključujući loše prehrambene navike, pušenje, tjelesnu neaktivnost i pretjeranu konzumaciju alkohola, koji mogu također djelomično objasniti povišenu prevalenciju SŽB i metaboličkog sindroma u tih bolesnika[2,21,22,31].

Metabolički sindrom (MS), koji se sastoji od nekoliko rizičnih čimbenika za SŽB kao što su AH, abdominalna debljina, intolerancija glukoze i dislipidemija, pokazuje visoku povezanost sa psorijazom[2,4,21-23,25,32-36]. Ova je povezanost čini se posebice naglašena nakon 40-te godine života[2]. Nasuprot jakoj korelaciji između težine kožnih lezija i kardiovaskularnog rizika, odnos između težine bolesti i MS-a nije toliko izražen[2,21,24,35]. Ipak, čini se da postoji povezanost s dužim trajanjem psorijaze i ranom pojavom bolesti[21,35].

S obzirom na brojne kardiovaskularne rizike prisutne kod psorijaze, epidemiološke studije pokazuju da ova grupa bolesnika ima povišenu prevalenciju koronarne bolesti srca, periferne vaskularne boelsti, dijabetesa tip II, AH, hiperlipidemije u usporedbi s općom populacijom, ukazujući na povišeni rizik od kardiovaskularnog morbiditeta kao i mortaliteta povezanog s kardiovaskularnim doagađajima[2,34,36-40]. Značajan broj dokaza pokazuje kako je psorijaza neovisni čimbenik rizika za infarkt miokarda i kardiovaskularni mortalitet, posebice u mlađoj životnoj dobi[5,29,37,38,41]. Također, težina kliničkih simptoma se dovodi u vezu s povišenim mortalitetom u bolesnika sa psorijazom, sugerirajući da bi pojava kardiovaskularnih komplikacija mogla biti ograničena na teške oblike

psoriasis, including cardiovascular disease, obesity, diabetes, arterial hypertension, dyslipidemia, and metabolic syndrome, which have been found at a higher prevalence in patients with psoriasis compared to the general population. The aim of this review is to present the most significant cardiovascular and metabolic disorders in this subset of patients, as well as to present the role of cardiac medications, especially beta-blockers, in development and aggravation of psoriasis.

PSORIASIS, CARDIOVASCULAR DISEASE AND METABOLIC SYNDROME

Multiple epidemiological studies have found psoriasis to be associated with comorbidities that increase the risk of cardiovascular disease, including hypertension, diabetes, dyslipidemia, and obesity[1-13]. The concept of the so-called "psoriatic march" has been suggested in order to describe these relationships. These conditions occur as a result of accelerated atherogenesis and endothelial dysfunction[9,14-17]. Although the underlying pathophysiological mechanism has still not been fully elucidated, it seems that increased cardiovascular disease risk may be linked to the common pathogenic mechanisms in psoriasis and atherosclerosis[7,8,14,18]. Chronic inflammation plays a major role in both of these conditions, mainly through increased levels of proinflammatory cytokines and immunological mediators that cause oxidative stress and free radical production[2,11,14,19-27]. Furthermore, systemic inflammation causes insulin resistance, which results in reduced release of vasodilating factors such as nitric oxide and triggers endothelial cell dysfunction, which along with the accelerated atherosclerosis subsequently lead to complications such as myocardial infarction or stroke[26,28,29]. In addition, elevated activity of the renin-angiotensin system in patients with psoriasis also contributes to the development of hypertension[25,30]. Other than the possible pathophysiological mechanisms mentioned above, due to the high psychological burden and substantial impairment of quality of life, patients with psoriasis tend to lead an unhealthy lifestyle including poor dietary habits, smoking, physical inactivity, and excessive alcohol consumption, which can also partly explain a higher prevalence of cardiovascular disease and metabolic syndrome in these patients[2,21,22,31].

Metabolic syndrome (MS), which is comprised of several cardiovascular disease risk factors such as hypertension, abdominal obesity, glucose intolerance, and dyslipidemia, shows high association with psoriasis[2,4,21-23,25,32-36]. This relationship seems to be particularly pronounced after the age of 40[2]. As opposed to a strong correlation between severity of skin lesions and cardiovascular risk, the relation between disease severity and MS is not so signficant[2,21,24,35]. However, there seems to be a strong relationship between greater duration of psoriasis and early onset of the disease[21,35].

Considering numerous cardiovascular risk factors which are present in psoriasis, epidemiological reports and studies show that this group of patients have increased prevalence of ischemic heart disease, peripheral vascular disease, cerebrovascular disease, type II diabetes, hypertension, and hyperlipidemia compared with the general population, indicating an increased risk of cardiovascular morbidity as well as mortality related to cardiovascular events[2,34,36-40]. A large amount of evidence shows that psoriasis is an independent risk factor for myocardial inf-

psorijaze[6,19,29,37,38,41,42]. Nadalje, duže trajanje bolesti je također povezano s povišenim kardiovaskularnim rizikom[5,15,40]. Stoga, rana supresija aktivnosti bolesti kao i godišnja procjena kardiovaskularnog rizika i redovito praćenje, preporučuju se za sve bolesnike sa psorijazom, a posebice za one s teškim kliničkim oblicima[7,8,15,24,36,40,43,44]. Neka istraživanja ukazuju na to da sustavna terapija psorijaze, korištenjem bioloških lijekova ili metotreksata, može utjecati na kardiovaskularne ishode, smanjujući dugoročni kardiovaskularni rizik[5,29,42,45-49]. Nadalje, edukacija bolesnika o zdravim životnim navikama, uključujući gubitak prekomjerne tjelesne težine, prihvaćanje zdravih prehrambenih navika, redovita tjelesna aktivnost i prestanak pušenja ključni su za smanjenje kardiovaskularnog rizika[50].

PSORIJAZA I ANTIHIPERTENZIVNI LIJEKOVI

Studije koje procjenjuju nuspojave povezane s antihipertenzivnim lijekovima ukazuju na to da su psorijaziformne erupcije jedne od najčešćih povezanih s ovom grupom lijekova. Beta-blokatori su kardiološki lijekovi koji su najčešće povezani s izazivanjem/pogoršanjem psorijaze, iako su kao uzročni lijekovi također opisani i blokatori kalcijevih kanala i inhibitori angiotenzin konvertirajućeg enzima[51-64]. Beta-blokatori su lijekovi koji su u širokoj upotrebi u liječenju angine pektoris, aritmija, srčanog zatajivanja te AH. Iako ovi lijekovi imaju dobar sigurnosni profil, beta-blokatori su uobičajeno prepoznati kao mogući uzročni čimbenici za psorijazu. Patofiziološki mehanizmi ove povezanosti još uvijek su nepoznati, iako bi moguće objašnjenje moglo biti u blokiranju epidermalnih beta(2) receptora, koje dovodi do smanjenja intraepidermalnog cAMP (3'-5'-ciklički adenozin monofosfat), važnog za staničnu diferencijaciju i inhibiciju proliferacije, posljedično dovodeći do ubrzane proliferacije keratinocita[51,62,63]. Uzimajući u obzir trajanje liječenja beta-blokatorima, pojava simptoma može značajno varirati, od nekoliko dana pa sve do 16 mjeseci nakon početka terapije beta-blokatorima[52,63]. Ovako dugo razdoblje latencije može uzrokovati poteškoće u identificiranju psorijaziformne erupcije kao moguće neželjene reakcije na lijek, s obzirom na to da se većina reakcija uzrokovana lijekovima javlja relativno brzo nakon izlaganja lijeku.

Iako klinička prezentacija uključuje široki spektar simptoma i gotovo sve kliničke tipove psorijaze, psorijaza uzrokovana ili pogoršana beta-blokatorima je klinički različita od kronične vulgarne psorijaze (najčešćeg oblika). Tipično, kožne promjene su manje crvene i ljuskave, a eritematoskvamozni plakovi nisu toliko debeli. Nadalje, ove kožne promjene rijetko zahvaćaju tipične lokalizacije kao što su koljena, laktovi i donji dio leđa, područja koja su uobičajeno zahvaćena kod psorijaze[56] **(slika 1)**. Također, rjeđi klinički tipovi kao i teži oblici psorijaze mogu često biti vidljivi, uključujući pustularnu psorijazu (prisutnost pustula na eritematoznom i ljuskavom plaku), palmoplantarnu psorijazu (eritematoskvamozne lezije lokalizirane na dlanovima i tabanima), eritrodermiju i generaliziranu psorijazu[63] **(slika 2)**. Treba naglasiti kako su sve te kliničke manifestacije neovisne o dozi lijeka.

U bolesnika koji koriste beta-blokatore, a prezentiraju se s naglom pojavom psorijaze ili naglim pogoršanjem već postojeće psorijaze, ovi lijekovi bi se uvijek trebali uzeti u obzir kao mogući okidači, posebice u slučajevima kada se istovremeno

arction and cardiovascular mortality, particularly at a younger age[5,29,37,38,41]. In addition, the severity of clinical symptoms is associated with increased mortality in patients with psoriasis, suggesting that occurrence of cardiovascular complications may be restricted to the severe form of psoriasis[6,19,29,37,38,41,42]. Longer duration of the disease is also associated with higher cardiovascular risk[5,15,40]. Therefore, early suppression of disease activity as well as annual evaluation of cardiovascular risk and regular follow-up are recommended for all patients with psoriasis, particularly those with severe clinical forms[7,8,15,24,36,40,43,44]. Some research suggests that systemic treatment of psoriasis using biologic drugs or methotrexate may affect cardiovascular outcomes, reducing long-term cardiovascular risk[5,29,42,45-49]. Furthermore, educating patients on healthy lifestyle habits including weight loss, healthy diet, regular physical activity, and smoking cessation are vital to reduce cardiovascular risk factors[50].

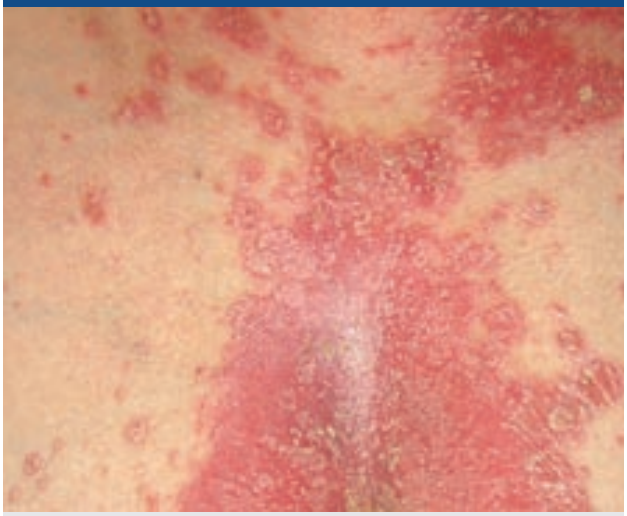
PSORIASIS AND ANTIHYPERTENSIVE DRUGS

Studies evaluating adverse drug reactions associated with antihypertensive drugs indicate that psoriasiform eruptions are among the most common reactions associated with this group of agents. Beta-blockers are cardiac drugs most frequently associated with the induction/exacerbation of psoriasis, although calcium-channel blockers and angiotensin-converting-enzyme inhibitors (ACE inhibitors) have been described as triggering drugs as well[51-64]. Beta blockers are drugs that have been widely used in the management of angina pectoris, arrhythmia, heart failure, and hypertension. Although these agents have a good safety profile, beta-blockers are commonly identified as possible triggering factors for psoriasis. The underlying pathophysiological mechanism of this association is still unknown, although a possible explanation could be blockage of epidermal beta(2) receptors, leading to a decrease in intraepidermal cAMP (3'-5'-cyclic adenosine monophosphate), which is important for cellular differentiation and inhibition of proliferation, consequently causing accelerated proliferation of keratinocytes[51,62,63]. Depending on the duration of beta-blocker therapy, onset of symptoms can vary greatly, from several days to up to 16 months after initiation of beta-blocker therapy[52,63]. This long latency period can cause difficulties in identifying psoriasiform eruption as a possible drug adverse event, since the majority of drug induced reactions tend to occur soon after drug exposure.

Although clinical presentation includes a broad spectrum of symptoms and almost all clinical types of psoriasis, psoriasis provoked or aggravated by beta-blockers tends to be clinically different from chronic psoriasis vulgaris (the most common type): skin lesions are less red and scaly and erythematosquamous plaques are not so thick. Moreover, these skin lesions rarely affect typical localizations, such as knees, elbows, and low back, which are typically affected in psoriasis[56] **(Figure 1)**. Rare clinical types and more severe forms of psoriasis are more frequently seen, including pustular psoriasis (presence of pustules on erythematous and scaly plaque), palmoplantar psoriasis (erythematosquamous lesions localized on the palms of hands and soles of feet), erythroderma, or generalized psoriasis[63] **(Figure 2)**. It should be noted that all of these clinical manifestations are dose independent.

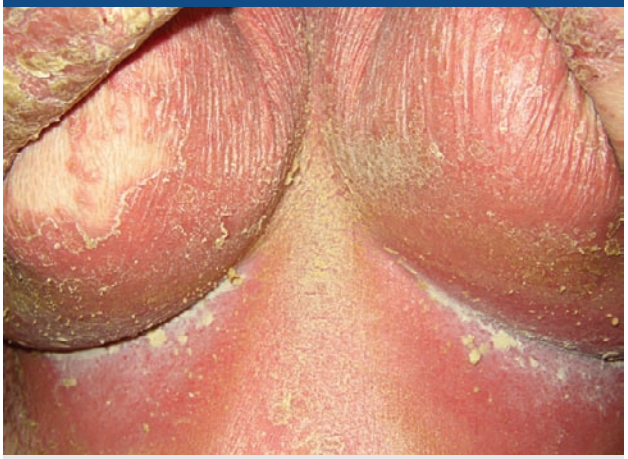
In patients using beta-blocker therapy presenting with sudden onset of psoriasis or aggravation of preexisting psoriasis,

FIGURE 1.



Less common distribution of skin lesions typically found in beta blocker-induced psoriasis.

FIGURE 2.



Severe form of beta blocker-induced psoriasis – erythroderma.

no opaža neadekvatan terapijski odgovor na konvencionalne metode liječenja psorijaze. U ovim slučajevima, terapija beta-blokatorima treba biti prekinuta, barem kratkotrajno, s obzirom na to da regresija promjena koja nakon toga nastupa ima ne samo terapijsku već i dijagnostičku važnost, sugerirajući da se psorijaziformna erupcija razvila zbog korištenja terapije beta-blokatorima[56]. Bolesnike treba savjetovati da izbjegavaju pretjerano izlaganje suncu, alkohol, pušenje, traumu i stres, s obzirom na to da ti čimbenici mogu pogoršati klinički tijek. U smislu prepoznavanja ove nuspojave kao i uzročnog lijeka, dijagnosticiranje može biti pravi izazov, pogotovo kod grupe bolesnika s pozitivnom osobnom ili obiteljskom anamnezom psorijaze, u kojih se progresija kožnih promjena može uočiti i nakon prekida lijeka[51,53,63]. Ipak, kod većine slučajeva prekid terapije beta-blokatorima će pridonijeti kliničkom poboljšanju te se opaža brzo povlačenje kožnih promjena u roku od nekoliko dana do tjedana nakon prekida uzročnog lijeka[51,63,64].

ZAKLJUČCI

Bolesnici sa psorijazom imaju brojne komorbiditete uključujući metabolički sindrom i SŽB, koji značajno smanjuju očekivano trajanje života i značajno pridonose morbiditetu i mortalitetu. Brojne studije ukazuju na to kako bi bolesnici sa psorijazom, posebice s umjereno do jako izraženim oblikom bolesti, trebali biti monitorirani za kardiovaskularni rizik u cilju prevencije ili usporenja progresije SŽB i poboljšanja zdravstvenih ishoda.

Zaključno, u cilju što boljeg zbrinjavanja svih potreba kod ovih bolesnika, njihovi komorbiditeti trebaju biti prepoznati i bolesnici trebaju biti podvrgnuti rutinskom probiru za kardiovaskularne rizike te prikladno liječeni. Nadalje, trebamo biti svjesni da antihipertenzivni lijekovi, posebice beta-blokatori mogu uzrokovati ili pogoršati psorijazu. Uzimajući u obzir da beta-blokatori mogu biti neophodni za dobru kardiovaskular-

these medications should always be taken into consideration as possible triggers, particularly in cases when there is simultaneously inadequate therapeutic response to conventional therapy for psoriasis. In these cases, beta-blocker therapy should be discontinued, at least for a short period of time, since the consequent regression of skin lesions will have not only therapeutic but a diagnostic value as well, suggesting that psoriasiform eruption had developed due to beta blocker therapy[56]. Patients should be advised to avoid excessive sun exposure, alcohol, smoking, trauma, and stress, as these factors can worsen the clinical course of psoriasis. In terms of identifying this adverse reaction and offending drug, diagnosis can be truly challenging, especially for the subset of patients with a positive personal or family history of psoriasis, in whom progression of skin lesions can be observed even after cessation of the drug[51,53,63]. However, for the majority of cases, discontinuation of beta blocker therapy will contribute to clinical improvement, and rapid resolution of the skin lesions can be observed within a few days to weeks after stopping the offending drug[51,63,64].

CONCLUSION

Patients with psoriasis exhibit numerous comorbidities, including metabolic syndrome and cardiovascular disease, which substantially reduce patient life expectancy and significantly contribute to morbidity and mortality. Numerous studies suggest that patients with psoriasis, particularly those with moderate to severe psoriasis, should be monitored for cardiovascular risks in order to prevent or to slow cardiovascular disease progression and improve health outcomes.

In conclusion, to fully address the medical needs of patients with psoriasis, their comorbidities must be acknowledged and recognized, and patients need to be routinely screened for cardiovascular risks and managed appropriately. Furthermore, clinicians must be aware that antihyprtensive medications, particularly beta-blocker agents, might induce or aggravate psoriasis. Considering these medications may be necessary for managing the patient's cardiovascular function, it is difficult to

nu funkciju bolesnika, teško je dati opće algoritme u liječenju, u smislu prestanka terapije. Stoga, odluka o ukidanju beta-blokatora i promjene drugim lijekom, mora biti utemeljena na individualnom omjeru koristi i rizika.

give general algorithms of management in terms of cessation of therapy. Therefore, the decision on the withdrawal of beta-blocker therapy and converting to an alternative antihypertensive agent must be based upon an individual benefit-risk ratio.

LITERATURE

1. Mallbris L, Akre O, Granath F, et al. Increased risk for cardiovascular mortality in psoriasis in patients but not in outpatients. Eur J Epidemiol. 2004;19:225–30. **DOI:** http://dx.doi.org/10.1023/B:EJEP.0000020447.59150.f9
2. Baeta IG, Bittencourt FV, Gontijo B, Goulart EM. Comorbidities and cardiovascular risk factors in patients with psoriasis. An Bras Dermatol. 2014;89(5):735–44. **DOI:** http://dx.doi.org/10.1590/abd1806-4841.20142874
3. Li WQ, Han JL, Manson JE, et al. Psoriasis and risk of nonfatal cardiovascular disease in U.S. women: a cohort study. Br J Dermatol. 2012;166(4):811–8. **DOI:** http://dx.doi.org/10.1111/j.1365-2133.2011.10774.x
4. Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis. J Am Acad Dermatol. 2006;55:829–35. **DOI:** http://dx.doi.org/10.1016/j.jaad.2006.08.040
5. Armstrong EJ, Harskamp CT, Armstrong AW. Psoriasis and major adverse cardiovascular events: a systematic review and meta-analysis of observational studies. J Am Heart Assoc. 2013;2(2):e000062. **DOI:** http://dx.doi.org/10.1161/JAHA.113.000062
6. Yeung H, Takeshita J, Mehta NN, et al. Psoriasis severity and the prevalence of major medical comorbidity: a population-based study. JAMA Dermatol. 2013;149(10):1173–9. **DOI:** http://dx.doi.org/10.1001/jamadermatol.2013.5015
7. Torres T, Bettencourt N. Psoriasis: the visible killer. Rev Port Cardiol. 2014;33(2):95–9. **DOI:** http://dx.doi.org/10.1016/j.repc.2013.06.017
8. Torres T, Sales R, Vasconcelos C, Selores M. Psoriasis and cardiovascular disease. Acta Med Port. 2013;26(5):601–7. **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed/24192101?dopt=Abstract
9. Yiu KH, Yeung CK, Zhao CT, et al. Prevalence and extent of subclinical atherosclerosis in patients with psoriasis. J Intern Med. 2013;273(3):273–82. **DOI:** http://dx.doi.org/10.1111/joim.12002
10. Imbalzano E, Casale M, D'Angelo M, et al. Cardiovascular risk and psoriasis: a role in clinical cardiology? Angiology. 2015 Mar 25; [Epub ahead of print] **DOI:** http://dx.doi.org/10.1177/0003319714527339
11. Osto E, Piaserico S, Maddalozzo A, et al. Impaired coronary f low reserve in young patients affected by severe psoriasis. Atherosclerosis. 2012;221(1):113–7. **DOI:** http://dx.doi.org/10.1016/j.atherosclerosis.2011.12.015
12. Ahlehoff O, Gislason GH, J¨rgensen CH, et al. Psoriasis and risk of atrial fibrillation and ischaemic stroke: a Danish Nationwide Cohort Study. Eur Heart J. 2012;33(16):2054–64. **DOI:** http://dx.doi.org/10.1093/eurheartj/ehr285
13. Toussirot E, Aubin F, Dumoulin G. Relationships between Adipose Tissue and Psoriasis, with or without Arthritis. Front Immunol. 2014 Aug;5:368. **DOI:** http://dx.doi.org/10.3389/fimmu.2014.00368
14. Pirro M, Stingeni L, Vaudo G, et al. Systemic inflammation and imbalance between endothelial injury and repair in patienst with psoriasis are associated with preclinical atherosclerosis. Eur J Prev Cardiol. 2014; pii: 2047487314538858. **DOI:** http://dx.doi.org/10.1177/2047487314538858
15. Shaharyar S, Warraich H, McEvoy JW, et al. Subclinical cardiovascular disease in plaque psoriasis: association or causal link? Atherosclerosis. 2014;232(1):72–8.
16. Dinc M, Aydin E, Balta S, Demirkol S, Karaman M. Subclinical inf lammation and cardiovascular risk in psoriasis. J Intern Med. 2014;276(2):195. **DOI:** http://dx.doi.org/10.1111/joim.12185
17. Balta I, Balta S, Demirkol S, et al. Aortic arterial stiffness is a moderate predictor of cardiovascular disease in patients with psoriasis vulgaris. Angiology. 2014;65(1):74–8. **DOI:** http://dx.doi.org/10.1177/0003319713485805
18. Miller IM, Ellervik C, Yazdanyar S, Jemec GB. Meta-analysis of psoriasis, cardiovascular disease, and associated risk factors. J Am Acad Dermatol. 2013;69(6):1014–24. **DOI:** http://dx.doi.org/10.1016/j.jaad.2013.06.053
19. Takeshita J, Mohler ER, Krishnamoorthy P, et al. Endothelial cell-, platelet-, and monocyte/macrophage-derived microparticles are elevated in psoriasis beyond cardiometabolic risk factors. J Am Heart Assoc. 2014;3(1):e000507. **DOI:** http://dx.doi.org/10.1161/JAHA.113.000507
20. Späh F. Inf lammation in atherosclerosis and psoriasis: common pathogenic mechanisms and the potential for an integrated treatment approach. Br J Dermatol. 2008;159:10–7. **DOI:** http://dx.doi.org/10.1111/j.1365-2133.2008.08780.x
21. Sommer DM, Jenisch S, Suchan M, Christophers E, Weichenthal M. Increased prevalence of metabolic syndrome in patients with moderate to severe psoriasis. Arch Dermatol Res. 2006;298(7):321–8. **DOI:** http://dx.doi.org/10.1007/s00403-006-0703-z
22. Albareda M, Ravella A, Castellu M, Saborit S, Peramiquel L, Vila L. Metabolic syndrome and its components in patients with psoriasis. Springerplus. 2014;3:612. **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed/25392783?dopt=Abstract
23. Padhi T. Garima. Metabolic syndrome and skin: psoriasis and beyond. Indian J Dermatol. 2013;58(4):299–305. **DOI:** http://dx.doi.org/10.4103/0019-5154.113950
24. Kimball AB, Gladman D, Gelfand JM, et al. National psoriasis foundation clinical consensus on psoriasis comorbidities and recommendations for screening. J Am Acad Dermatol. 2008;58:1031–42. **DOI:** http://dx.doi.org/10.1016/j.jaad.2008.01.006
25. Armstrong AW, Harskamp CT, Armstrong EJ. The association between psoriasis and hypertension: a systematic review and meta-analysis of observational studies. J Hypertens. 2013;31(3):433–42. **DOI:** http://dx.doi.org/10.1097/HJH.0b013e32835bcce1
26. Malibris L, Akre O, Granath F, et al. Increased risk for cardiovascular mortality in psoriasis inpatients but not in outpatients. Eur J Epidemiol. 2004;19:225–30. **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed/15117115?dopt=Abstract
27. Kim JA, Montagnani M, Koh KK, Quon MJ. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. Circulation. 2006;113:1888–904. **DOI:** http://dx.doi.org/10.1161/CIRCULATIONAHA.105.563213
28. Boehncke WH, Boehncke S, Tobin AM, Kirby B. The "psoriatic march": a concept of how severe psoriasis may drive cardiovascular comorbidity. Exp Dermatol. 2011;20:303–7. **DOI:** http://dx.doi.org/10.1111/j.1600-0625.2011.01261.x
29. Ahlehoff O, Gislason GH, Charlot M, J¨rgensen CH, Lindhardsen J, Olesen JB, et al. Psoriasis is associated with clinically significant cardiovascular risk: a Danish nationwide cohort study. J Intern Med. 2011;270:147–57. **DOI:** http://dx.doi.org/10.1111/j.1365-2796.2010.02310.x
30. Ena P, Madeddu P, Glorioso N, Cerimele D, Rappelli A. High prevalence of cardiovascular diseases and enhanced activity of the renin-angiotensin system in psoriatic patients. Acta Cardiol. 1985;40(2):199–205. **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed/3887825?dopt=Abstract
31. Christophers E. Comorbidities in psoriasis. J Eur Acad Dermatol Venereol. 2006;20:52–5. **DOI:** http://dx.doi.org/10.1111/j.1468-3083.2006.01773.x
32. Kim GW, Park HJ, Kim HS, Kim SH, Ko HC, Kim BS, et al. Analysis of cardiovascular risk factors and metabolic syndrome in korean patients with psoriasis. Ann Dermatol. 2012;24(1):11–5. **DOI:** http://dx.doi.org/10.5021/ad.2012.24.1.11
33. Mallbris L, Ritchlin CT, StÂhle M. Metabolic disorders in patients with psoriasis and psoriatic arthritis. Curr Rheumatol Rep. 2006;8:355–63. **DOI:** http://dx.doi.org/10.1007/s11926-006-0065-8
34. Dregan A, Charlton J, Chowienczyk P, Gulliford MC. Chronic inf lammatory disorders and risk of type 2 diabetes mellitus, coronary heart disease, and stroke: a population-based cohort study. Circulation. 2014;130(10):837–44. **DOI:** http://dx.doi.org/10.1161/CIRCULATIONAHA.114.009990

35. Nisa N, Qazi MA. Prevalence of metabolic syndrome in patients with psoriasis. Indian J Dermatol Venereol Leprol. 2010;76(6):662–5. **DOI:** http://dx.doi.org/10.4103/0378-6323.72462
36. Zhu TY, Li EK, Tam LS. Cardiovascular risk in patients with psoriatic arthritis. Int J Rheumatol. 2012;2012:714321. **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed/22645614?dopt=Abstract
37. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. JAMA. 2006;296:1735–41. **DOI:** http://dx.doi.org/10.1001/jama.296.14.1735
38. Gelfand JM, Dommasch ED, Shin DB, et al. The risk of stroke in patients with psoriasis. J Invest Dermatol. 2009;129(10):2411–8. **DOI:** http://dx.doi.org/10.1038/jid.2009.112
39. Khalid U, Ahlehoff O, Gislason GH, et al. Psoriasis and risk of heart failure: a nationwide cohort study. Eur J Heart Fail. 2014;16(7):743–8. **DOI:** http://dx.doi.org/10.1002/ejhf.113
40. Elsheikh RG. Amin Tel-S, El-Ashmawy AA, Abdalla SI. Evaluation of subclinical atherosclerosis in Egyptian psoriatic patients. J Saudi Heart Assoc. 2014;26(2):63–71. **DOI:** http://dx.doi.org/10.1016/j.jsha.2013.12.001
41. Wakkee M, Thio HB, Prens EP, Sijbrands EJ, Neumann HA. Unfavorable cardiovascular risk profiles in untreated and treated psoriasis patients. Atherosclerosis. 2007;190:1–9. **DOI:** http://dx.doi.org/10.1016/j.atherosclerosis.2006.07.011
42. Ryan C, Leonardi CL, Krueger JG, et al. Association between biologic therapies for chronic plaque psoriasis and cardiovascular events: a meta-analysis of randomized controlled trials. JAMA. 2011;306:864–71. **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed/21862748?dopt=Abstract
43. Ryan C, Kirby B. Dermatol Clin. Psoriasis is a systemic disease with multiple cardiovascular and metabolic comorbidities. 2015;33(1):41-55.
44. Khraishi M, Aslanov R, Rampakakis E, Pollock C, Sampalis JS. Prevalence of cardiovascular risk factors in patients with psoriatic arthritis. Clin Rheumatol. 2014;33(10):1495–500. **DOI:** http://dx.doi.org/10.1007/s10067-014-2743-7
45. Micha R, Imamura F, Wyler von Ballmoos M, et al. Systematic review and meta-analysis of methotrexate use and risk of cardiovascular disease. Am J Cardiol. 2011;108:1362–70. **DOI:** http://dx.doi.org/10.1016/j.amjcard.2011.06.054
46. Prodanovich S, Ma F, Taylor JR, Pezon C, Fasihi T, Kirsner RS. Methotrexate reduces incidence of vascular diseases in veterans with psoriasis or rheumatoid arthritis. J Am Acad Dermatol. 2005;52:262–7. **DOI:** http://dx.doi.org/10.1016/j.jaad.2004.06.017
47. Dominguez H, Storgaard H, Rask-Madsen C, et al. Metabolic and vascular effects of tumor necrosis factor-alpha blockade with etanercept in obese patients with type 2 diabetes. J Vasc Res. 2005;42:517–25. **DOI:** http://dx.doi.org/10.1159/000088261
48. Churton S, Brown L, Shin TM, Korman NJ. Does treatment of psoriasis reduce the risk of cardiovascular disease? Drugs. 2014;74(2):169–82. **DOI:** http://dx.doi.org/10.1007/s40265-013-0173-5
49. Ahlehoff O, Skov L, Gislason G, et al. Cardiovascular disease event rates in patients with severe psoriasis treated with systemic anti-inf lammatory drugs: a Danish real-world cohort study. J Intern Med. 2013;273(2):197–204. **DOI:** http://dx.doi.org/10.1111/j.1365-2796.2012.02593.x
50. Jensen P, Zachariae C, Christensen R, et al. Effect of weight loss on the cardiovascular risk profile of obese patients with psoriasis. Acta Derm Venereol. 2014;94(6):691–4. **DOI:** http://dx.doi.org/10.2340/00015555-1824
51. Tsankov N, Kazandjieva J, Drenovska K. Drugs in exacerbation and provocation of psoriasis. Clin Dermatol. 1998;16:333–51. **DOI:** http://dx.doi.org/10.1016/S0738-081X(98)00005-4
52. Abel EA, DiCicco LM, Orenberg EK, Fraki JE, Farber EM. Drugs in exacerbation of psoriasis. J Am Acad Dermatol. 1986;15:1007–22. **DOI:** http://dx.doi.org/10.1016/S0190-9622(86)70265-X
53. Kim GK, Del Rosso JQ. Drug-provoked psoriasis: is it drug induced or drug aggravated?: understanding pathophysiology and clinical relevance. J Clin Aesthet Dermatol. 2010;3(1):32–8. **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed/20725536?dopt=Abstract
54. Cohen AD, Bonneh DY, Reuveni H, Vardy DA, Naggan L, Halevy S. Drug exposure and psoriasis vulgaris: case control and case crossover studies. Acta Derm Venereol. 2005;85:299–303. **DOI:** http://dx.doi.org/10.1080/00015550510032823
55. Dika E, Varotti C, Bardazzi F, Maibach HI. Drug-induced psoriasis: an evidence-based overview and the introduction of psoriatic drug eruption probability score. Cutan Ocul Toxicol. 2006;25:1–11. **DOI:** http://dx.doi.org/10.1080/15569520500536568
56. Heng MC, Heng MK. Beta-adrenoceptor antagonist-induced psoriasiform eruption. Clinical and pathogenetic aspects. Int J Dermatol. 1988;27:619–27. **DOI:** http://dx.doi.org/10.1111/j.1365-4362.1988.tb02419.x
57. Steinkraus V, Steinfath M, Mensing H. Beta-adrenergic blocking drugs and psoriasis. J Am Acad Dermatol. 1992;27:266–7. **DOI:** http://dx.doi.org/10.1016/S0190-9622(08)80738-4
58. Halevy S, Livni E. Beta-adrenergic blocking drugs and psoriasis: the role of an immunologic mechanism. J Am Acad Dermatol. 1993;29:504–5. **DOI:** http://dx.doi.org/10.1016/S0190-9622(08)82012-9
59. Halevy S, Livni E. Psoriasis and psoriasiform eruptions associated with propranolol–the role of an immunologic mechanism. Arch Dermatol Res. 1991;283:472–3. **DOI:** http://dx.doi.org/10.1007/BF00371785
60. Basavaraj KH, Ashok NM, Rashmi R, Praveen TK. The role of drugs in the induction and/or exacerbation of psoriasis. Int J Dermatol. 2010;49:1351–61. **DOI:** http://dx.doi.org/10.1111/j.1365-4632.2010.04570.x
61. Fry L, Baker BS. Triggering psoriasis: the role of infections and medications. Clin Dermatol. 2007;25:606–15. **DOI:** http://dx.doi.org/10.1016/j.clindermatol.2007.08.015
62. Assem ESK, Banks RA. Practolol induced drug eruptions. Proc R Soc Med. 1973;66:179–81. **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed/4145974?dopt=Abstract
63. Tsankov N, Irena A, Kasandjieva J. Drug-induced psoriasis: recognition and management. Am J Clin Dermatol. 2000;1:159–65. **DOI:** http://dx.doi.org/10.2165/00128071-200001030-00003
64. Waqar S, Sarkar PK. Exacerbation of psoriasis with beta-blocker therapy. CMAJ. 2009;181(1-2):60. **DOI:** http://dx.doi.org/10.1503/cmaj.081433