Sakubitril/valsartan u kliničkoj praksi: pogled nefrologa

Sacubitril/valsartan in Clinical Practice: A Nephrologist Point of View

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SAŽETAK: U travnju 2019. godine u Zagrebu je održan Simpozij „Kontroverze u hipertenziji, kardiovaskularnoj protekciji i nefrologiji". Na dinamičan i zanimljiv način razni supspecijalisti predstavili su strategiju liječenja bolesnika s brojnim komorbiditetima, njezinu kompleksnost te rizik od nuspojava nekritičnih primjena lijekova. Objavljene su smjernice, ali usprkos ili upravo zahvaljujući njima, došlo se do spoznaje da je individualan pristup bolesniku i dalje ključan pri odluci o načinu liječenja. Svrha je ovoga članka prikazati kontroverzu primjene sakubitril/valsartana u bolesnika s kroničnom bubrežnom bolesti.

SUMMARY: In April 2019, the symposium "Controversies in hypertension, cardiovascular protection and nephrology" was held in Zagreb. In dynamic and interesting ways, various subspecialists presented strategies of treating patients with numerous comorbidities, the complexity of the treatment strategy, and the risk of side effects. Guidelines were published, but despite them or even because of them, we have realized that an individual approach to the patient remains crucial to the decision on the treatment. The goal of this article is to describe the controversy over the application of sacubitril/valsartan in patients with chronic kidney disease.

KLJUČNE RIJEČI: sakubitril/valsartan, kronična bubrežna bolest, nuspojave liječenja.

KEYWORDS: sacubitril/valsartan, chronic kidney disease, dialysis, side effects.

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Dobro je poznato da lijekovi koji blokiraju reninsko-angiotenzinsko-aldosteronski sustav (RAAS) poboljšavaju prognozu bolesnika s arterijskom hipertenzijom, zatajivanjem srca, dijabetesom i kroničnom bubrežnom bolesti (CKD). Međutim, kombiniranje lijekova iz ove skupine povećava rizik od hiperkalemije, hipotenzije i akutnog zatajenja bubrega.[1] Starenjem populacije, povećanjem komorbiditeta te istodobnim brzim napretkom farmakoterapije, napose pojavom fiksnih kombinacija, pred kliničare se stavlja sve veći izazov u pronalaženju ravnoteže između pozitivnog učinka i saniranja posljedica liječenja. Suvremeni pristup uklanja tabu s primjene inhibitora angiotenzin-konvertirajućeg enzima (ACEi) i sartana u bolesnika s CKD-om i renovaskularnom hipertenzijom (RVH). Implantacija stenta u renalne arterije (RA) uz istodobnu primjenu ACEi ili sartana pokazala je dobrobit na smanjenje krutosti krvnih žila u ovakvih bolesnika, a time i bolju regulaciju arterijskoga tlaka (AT).[2] Velika istraživanja upućuju na ograničenja endovaskularne intervencije na RA u sprječavanju napredovanja bubrežne bolesti, a upitan je i stupanj koristi od intervencije nakon istraživanja CORAL.[3]

It is well known that drugs that block the renin-angiotensin-aldosterone system (RAAS) improve the prognosis of patients with hypertension, heart failure, diabetes, and chronic kidney disease (CKD). However, the combination of drugs from this group increases the risk of hyperkalemia, hypotension, and acute renal failure.[1] With an increasing elderly population and a rising number of comorbidities, with simultaneous rapid pharmacotherapy progress especially after polypill formation, clinicians are finding it increasingly challenging to strike a balance between positive effects and remedying the consequences of their own treatment. The modern approach eliminates the taboo of using angiotensin convertase inhibitors (ACEi) and sartans in patients with CKD and renovascular hypertension (RVH). Renal artery stenting with simultaneous administration of ACEi or sartans showed benefit for reducing blood vessel stiffness in these patients and thus improved blood pressure control.[2] Large studies have shown the limitations of endovascular intervention on RAAS in preventing progression of renal disease, and the benefit of intervention has also been in question as a result of the CORAL study.[3]

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U praksi i dalje postoje dvojbe, napose kad je riječ o bolesnicima s rezistentnom hipertenzijom i RVH koja nije prepoznata navrijeme, a koji su razvili veći stupanj bubrežnog zatajenja, uz pridruženu šećernu bolest i perifernu arterijsku bolest i/ili koronarnu bolest srca. Takav profil bolesnika zahtijeva višekratnu dijagnostičku i intervencijsku primjenu kontrastnih sredstava, što pridonosi progresiji razvoja CKD-a. Bolesnici s RVH na kroničnom programu hemodijalize (HD) često imaju hipertenziju koja je refraktarna na dostupnu medikamentnu terapiju, što je važno u trenutku odluke o metodi liječenja referiranjem na istraživanja koja daju prednost medikamentnoj terapiji u odnosu prema endovaskularnoj intervenciji, uz obrazloženje da se zbog citokinske oluje koja je izazvala reverzibilne promjene u bubregu neće intervencijom oporaviti bubrežna funkcija, dok je više puta dokazan pozitivan učinak na smanjenje vrijednosti AT-a stentiranjem RA u takvih bolesnika.[4]

Opetovane hospitalizacije česte su u bolesnika s RVH zbog razvoja plućnog edema, a kod pridružene šećerne bolesti i razvoja septičkih stanja zbog hemodinamske nestabilnosti provodimo postupke akutne HD. Uglavnom je riječ o starijim bolesnicima sa šećernom bolesti te koronarnom bolesti srca, koji u terapiji imaju metformin, ACEi, spironolakton i supstituciju kalijem uz diuretik Henleove petlje.

Pri nekritičnoj primjeni metformina, spironolaktona i supstitucije kalijem, siguran je razvoj hiperkalemije i laktacidoze. Indicirana je akutna kontinuirana hemodijafiltracija, vezana za postavljanje privremenoga centralnoga venskog pristupa, čime bolesnike izlažemo rizicima koje takvi postupci nose u hitnoći, ali i stenozi i fibrozi potencijalnoga budućega pristupnog mjesta. Kako je riječ o hitnom postupku, određeni broj ovakvih bolesnika nema poznate markere hepatitisa i anti-HIV, što ih izlaže riziku od infekcije. Pod nekritičnom primjenom metformina misli se ovdje na nerazumijevanje da glomerularna filtracija ne korelira uvijek s visinom serumskog kreatinina, nego je važno u svakog bolesnika individualno procijeniti i voditi brigu o prilagodbi doze lijeka ili potpunom ukidanju, ovisno o bubrežnoj funkciji.

Nove smjernice za liječenje arterijske hipertenzije ističu korist od primjene fiksnih kombinacija kao lijekova prvog izbora i antagonista mineralokortikoidnih steroidnih receptora (MRA) u bolesnika s rezistentnom hipertenzijom.[5] Međutim, MRA imaju nizak sigurnosni profil, osobito u bolesnika s CKD-om zbog visoke učestalosti hiperkalemije. Nedavno je razvijena nova generacija nesteroidnih MRA koji pokazuju veću selektivnost za receptore, čime se smanjuje učestalost neželjenih nuspojava, pa time spomenute lijekove čini prikladnima za primjenu u bolesnika s CKD-om. Nakon istraživanja EPHESUS te dokaza o manjem broju nuspojava, eplerenon je sve češće u kliničkoj primjeni i u bolesnika s većim stupnjem CKD-a jer takvi bolesnici nerijetko imaju kronično srčano zatajivanje (CHF).[6] Ispitivanja su pokazala bolji profil sigurnosti s održanom učinkovitošću lijeka u usporedbi sa steroidnim MRA.

Gotovo da nema bolesnika na kroničnom programu HD-a koji zbog suvremenoga shvaćanja kardioprotekcije i smanjenja kardiovaskularnog (KV) rizika i ukupne smrtnosti nema u terapiji blokator RAAS-a. Kako postoje istraživanja koja ističu pozitivan učinak MRA i u bolesnika na HD-u, počeli smo ga uključivati u terapiju. Oprez je nužan, ali postoji i zona komfora jer se serumski kalij na HD-u može pratiti češće nego u

In practice there are still dilemmas, particularly when it comes to patients with resistant hypertension and RVH who have developed a higher stage of renal failure with associated diabetes mellitus and peripheral arterial disease and/or coronary artery disease. Such a patient profile requires multiple diagnostic and interventional application of contrast media, which contributes to the progression of CKD development. Patients with RVH on hemodialysis often have hypertension that is refractory to available medical therapy, which is important when deciding on the treatment method by referring to studies that favor the therapeutic treatment of endovascular interventions, with the explanation that due to irreversible changes in the kidney caused by the cytokine storm has no intervention will restore the renal function, while a positive effect of renal stenting has been demonstrated on the reduction of blood pressure in these patients[4].

Re-hospitalization is common in patients with RVH due to the development of pulmonary edema, and if there is associated diabetes and sepsis, acute HD procedures are performed due to hemodynamic instability of these patients. These are generally older patients with diabetes mellitus and coronary disease who receive metformin, ACEi, spironolactone, and potassium substitution with loop diuretic in their therapy.

Hyperkalemia and lactic acidosis often developed in non-critical use of metformin, spironolactone, and potassium substitution and represent life-threatening conditions for the patient. Acute continuous hemodialysis is indicated, along with the introduction of a temporary central venous approach, which exposes the patients to the risks that such procedures bring when applied in an emergency, as well as to fibrosis and stenosis of the potential future access point. Since this is an emergency procedure, in a number of these patients markers of hepatitis and anti-HIV are not known, which exposes them to the risk of infection. Under non-critical metformin therapy, there is a misunderstanding that glomerular filtration does not always correlate with serum creatinine, but it is important to individually evaluate and to perform dose adjustment or complete withdrawal depending on the renal function in each patient.

New guidelines for the treatment of arterial hypertension emphasize the benefit of the use of fixed combinations as first choice drugs and antagonists of mineralocorticoid steroid receptors (MRAs) in patients with resistant hypertension.[5] However, MRAs has a low safety profile, especially in patients with CKD, because of the high incidence of hyperkalemia. Recently, a new generation of nonsteroidal MRAs has been developed that show greater selectivity for receptors, reducing the incidence of unwanted side effects, thus making these drugs suitable for use in patients with CKD. Following the EPHESUS study and evidence of reduced number of side-effects, eplerenone is more common in clinical use in patients with a higher degree of CKD because patients often have chronic heart failure (CHF).[6] Studies have shown a better safety profile with sustained drug efficacy compared with steroid MRAs.

There are almost no patients in hemodialysis due to the modern understanding of cardioprotection and reduction of cardiovascular risk (KV) and overall mortality without RAAS blocker therapy. As there are studies that emphasize the positive effect of MRAs in hemodialysis patients, we started to include it in therapy. Caution is required, but there is also a safety zone because serum potassium in hemodialysis can be monitored more frequently than in the preterminal stage of

preterminalnoj fazi CKD-a. Aldosteron je mineralokortikoidni hormon s dobro poznatim učinkom na bubrežne tubule, što dovodi do zadržavanja vode i reapsorpcije kalija. Ostali učinci tog hormona uključuju indukciju proinflamatorne aktivnosti koja uzrokuje fibrozno oštećenje ciljnih organa, srca i bubrega. Blokiranje receptora aldosterona važna je farmakološka strategiju za izbjegavanje ozbiljnih kliničkih stanja koja potječu od CHF-a i CKD-a.[7]

Bolesnici na HD-u imaju brojne čimbenike rizika za razvoj kardiovaskulanih incidenata, a uzmemo li u obzir da je uglavnom riječ o bolesnicima starije životne dobi, koronarografija nije rutinski primjenjiva dijagnostička metoda za koronarnu bolest u asimptomatskih bolesnika. Biomarker koji nam je dostupan u rutinskoj primjeni, ali nedovoljno određivan u nefroloških bolesnika jest moždani natriuretski peptid (BNP).

Bolesnici s kardiorenalnim sindromom veliki su terapijski izazov za kardiologe i nefrologe. U ispitivanju PARADIGM-HF sakubitril/valsartan primijenjen je zajedno s drugim medikamentima za liječenje zatajivanja srca, umjesto ACEi ili drugog blokatora receptora angiotenzina II (ARB).[8] Bolesnici koji su imali sistolički AT niži od 100 mmHg, teško oštećenje bubrežne funkcije (eGFR manje od 30 mL/min/1,73 m^2) bili su isključeni pri probira i stoga nisu bili prospektivno ispitivani. Kardiovaskularne koristi od sakubitril/valsartana u bolesnika sa zatajivanjem srca pripisuju se povećanju količine peptida, kao što su natriuretski peptidi, koje s pomoću LBQ657 neprilizin razgrađuje, i istodobnoj inhibiciji učinaka angiotenzina II koju provodi valsartan. Djelovanje natriuretskih peptida rezultira vazodilatacijom, natriurezom i diurezom, povećanjem glomerularne filtracije i protoka krvi kroz bubrege, inhibicijom otpuštanja renina i aldosterona, smanjenjem simpatičke aktivnosti te antihipertrofičnim i antifibrotičkim učincima. Valsartan inhibira štetne kardiovaskularne i renalne učinke angiotenzina II tako što selektivno blokira AT1 receptor te također inhibira otpuštanje aldosterona ovisno o angiotenzinu II. To sprječava održanu aktivaciju RAAS-a. U ispitivanju PARADIGM-HF sakubitril/valsartan smanjio je vrijednost NT-proBNP-a u plazmi i povećao vrijednost BNP-a u plazmi i cGMP-a u urinu u usporedbi s enalaprilom. Odavno je poznato da povišena razina BNP-a povećava rizik od razvoja preterminalnog u terminalni stadij CKD-a te da je razina BNP-a prediktor prognoze u preddijaliznih bolesnika s CKD-om.[9]

Povišena razina atrijskoga natriuretskog hormona (ANP) i BNP-a indikator su rizika od neželjenih srčanih događaja i istodobno su prediktor njihova ishoda u bolesnika na HD-u pa bi se stoga vrijednost NT-proBNP-a trebala češće određivati u bolesnika.[10,11]

Nameće se pitanje nije li upravo bolesnicima u preterminalnom stadiju CKD-a te onima na HD-u neopravdano uskraćen lijek koji bi trebali imati na vrhu ljestvice? Ako uzmemo u obzir da je kardiorenalni sindrom velik terapijski izazov jer se borimo za ravnotežu u interakciji srca i bubrega te svaki postotak povećanja ejekcijske frakcije lijeve klijetke znači ujedno i porast eGFR-a, jasna je potreba za timskim radom nefrologa i kardiologa. Nužno je, s obzirom na nuspojave kombinacije lijekova, indikaciju za primjenu sakubitril/valsartana proširiti u domenu nefrologa. Nadamo se da će budućnost pokazati da je izostavljanje ovog lijeka bolesnicima u preterminalnom stadiju CKD-a te onima na HD-u neopravdana u kliničkoj praksi. No, to će pokazati buduća istraživanja.

CKD. Aldosterone is a mineralocorticoid hormone with well-known effect on the kidney tubule leading to water retention and potassium reabsorption. Other effects of this hormone include induction of proinflammatory activity leading to fibrous damage to target organs, the heart, and kidneys. Blocking the aldosterone receptor is an important pharmacological strategy for avoiding serious clinical conditions caused by CHF and CKD.[7]

Hemodialysis patients have a number of risk factors for the development of cardiovascular incidents, and keeping in mind that these patients are mostly elderly, coronary angiography is not a routine diagnostic method for coronary heart disease in asymptomatic patients. Brain natriuretic peptide (BNP) is a biomarker available in routine use, but rarely determined in patients with CKD.

Patients with cardiorenal syndrome represent a major therapeutic challenge for cardiologists and nephrologists. In the PARADIGM-HF study, sacubitril/valsartan was administered in combination with other heart failure treatment instead of an ACE inhibitor or other angiotensin II receptor blocker (ARB).[8] Patients with systolic blood pressure below 100 mmHg, severe kidney damage (eGFR less than 30 mL/min/1.73 m^2) were excluded from screening and were therefore not prospectively investigated.

Cardiovascular uses of sacubitril/valsartan in patients with heart failure are attributed to the increase in the amount of unprivileged peptides, such as natriuretic peptides (NP), LBQ657, and simultaneous inhibition of angiotensin II effects by valsartan. NP action results in vasodilation, natriuresis and diuresis, increased glomerular filtration and blood flow through the kidneys, inhibition of renin and aldosterone release, decreased sympathetic activity, and antihypertrophic and antifibrotic effects. Valsartan inhibits the harmful cardiovascular and renal effects of angiotensin II by selectively blocking the AT1 receptor and also inhibits the release of aldosterone depending on angiotensin II. This prevents RAAS activation. In the PARADIGM-HF study, sacubitril/valsartan reduced plasma NT-proBNP and increased plasma BNP and cGMP in urine compared with enalapril. It has long been known that elevated BNP levels increase the risk of preterminal development in the terminal CKD stage and that BNP is a predictor of prognosis in prediabetes patients with CKD.[9]

The elevated levels of atrial natriuretic hormone (ANP) and BNP indicate the risk of unwanted cardiac events and are the predictor of their outcomes in hemodialysis patients, so NT-proBNP should therefore be more routinely prescribed in our patients.[10,11]

The question is whether patients in the preterminal stage of CKD and those in HD have been deprived of a drug for which they should have been at the top of the list? If we consider that cardiorenal syndrome is a great therapeutic challenge because we are struggling to balance the interaction of the heart and kidneys and every percentage of left ventricular ejection fraction increase is also an increase in eGFR, it is clear that cooperation between nephrologists and cardiologists is needed. Given the side-effects of drug combinations, it is necessary to extend the indication for the use of sacubitril/valsartan in the domain of the nephrologist. We hope that the future will show that leaving out this drug in the preterminal stage of CKD and for patients on dialysis is unjustified in clinical practice. But that will be shown by future research.

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