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Klinička iskustva s losartanom i njegovim dodatnim pogodnostima pri liječenju arterijske hipertenzije

Clinical experiences with losartan and its additional benefits in the treatment of hypertension

Polona Knavs Vrhunec, Breda Barbič Žagar, Sandra Pišek
Krka, d. d., Novo mesto, Slovenia

SAŽETAK: *Losartan je selektivni antagonist angiotensin II podtip 1 (AT1) receptora. Omogućava specifičniju i potpuniju blokadu aktivnosti angiotenzina II nego što to čine ACE inhibitori. Losartan je već dokazan kao učinkovit lijek za snižavanje arterijskog tlaka koji se uzima jednom dnevno, a ima visoku podnošljivost i zaštitna svojstva u dijabetičnoj nefropatiji. Rezultati studije LIFE su pokazali pozitivne učinke blokatora angiotenzinskih receptora losartana kod visoko rizičnih pacijenata s arterijskom hipertenzijom. Za razliku od drugih antagonista angiotenzin II receptora, losartan također ima urikozurički učinak i pozitivan učinak na erektilnu funkciju muškaraca. Sigurnost i učinkovitost Krkinog losartana (Lorista®) je testirana u nekoliko kliničkih ispitivanja i popratnih studija. Krkin losartan se pokazao sigurnim i učinkovitim u monoterapiji, kao i u kombinaciji s hidroklorotiazidom.*

KLJUČNE RIJEČI: *arterijska hipertenzija, arterijski tlak, antagonist angiotenzin II receptora.*

ABSTRACT: *Losartan is a selective angiotensin II subtype 1 (AT1) receptor antagonist. It provides a more specific and complete blockade of the actions of angiotensin II than ACE inhibitors. Losartan has already been established as an effective once-daily blood-pressure-lowering drug with excellent tolerability, and protective properties in diabetic nephropathy. Results from LIFE study demonstrated the beneficial effects of angiotensin receptor blocker losartan at high risk hypertensive patients. Unlike other angiotensin II receptor antagonists, losartan has also uricosuric effect and positive effect on erectile function of men. Safety and efficacy of Krka's losartan (Lorista®) was tested in several clinical trials and follow up studies as well. Krka's losartan was proved to be safe and effective in monotherapy as well as in combination with hydrochlorothiazide.*

KEYWORDS: *hypertension, blood pressure, angiotensin II receptor antagonist.*

Renin-angiotenzinski sustav igra važnu ulogu u regulaciji kardiovaskularne homeostaze. Angiotenzin II uzrokuje vazokonstrikciju, smanjuje izlučivanje natrija i vode preko stimulacije sekrecije aldosterona i omogućava simpatičku aktivnost. Svi ovi učinci povisuju arterijski tlak (AT).

Učinkovitost losartana u snižavanju AT kod hipertenzivnih pacijenata je dokazana u nekoliko studija. U studiji LIFE analizirane su razlike između blokatora angiotenzin II receptora (losartan) i beta-blokatora (atenolol) u antihipertenzivnom liječenju pacijenata s artrijskom hipertenzijom i hipertrofijom lijeve klijetke (HLK). HLK je poznata kao snažan i neovisan prediktor dugoročnih neželjenih kliničkih ishoda kod pacijenata s hipertenzijom i koronarnom bolesti srca (KBS).

U studiju LIFE su uključeni muškarci i žene u dobi između 55 i 80 godina s prethodno neliječenom ili liječenom esencijalnom hipertenzijom, sa sistoličkim AT od 160 do 200 mmHg, dijastoličkim krvnim tlakom od 95 do 110 mmHg i s dokumentiranom HLK. Za konačnu analizu bili su dostupni podaci od 9.193 pacijenata. Pacijenti su praćeni barem 4 godine. Usporedno s antihipertenzivnom terapijom na bazi atenolola (s ili bez dodatka hidroklortiazida, HCTZ), pacijenti koji su nasumično odabrani za antihipertenzivnu terapiju losartanom (s ili bez dodatka HCTZ-a) su pokazali:

- 13% manje kardiovaskularnog pobola i smrtnosti,
- 25% manje moždanih udara,
- 25% manje novonastalog dijabetesa,

The renin-angiotensin system plays an important role in the regulation of cardiovascular homeostasis. Angiotensin II causes vasoconstriction, decreases sodium and water excretion via stimulation of the secretion of aldosterone and facilitates sympathetic activity. All of these effects increase blood pressure (BP).

The efficacy of losartan in reducing BP in hypertensive patients was demonstrated in several studies. The LIFE study analysed the differences between an angiotensin II receptor blocker (losartan) and a beta-blocker (atenolol) in antihypertensive treatment with patients with hypertension and left ventricular hypertrophy (LVH). LVH is known to be a strong and independent predictor of long-term adverse clinical outcomes in patients with hypertension and coronary heart disease (CHD).

In LIFE study, men and women between 55 and 80 years of age with previously untreated or treated essential hypertension, with systolic BP of 160 to 200 mmHg, diastolic BP of 95 to 110 mmHg, with documented LVH were included. Data of 9193 patients were available for final analyses. Patients were monitored for at least 4 years. Compared with atenolol-based antihypertensive therapy (with or without concomitant hydrochlorothiazide, HCTZ), patients who were randomized to losartan-based antihypertensive therapy (with or without concomitant HCTZ) displayed:

- 13% less cardiovascular morbidity and mortality,
- 25% less stroke,
- 25% less new-onset diabetes,

• 39% manje ukupne smrtnosti među pacijentima s dijagnosticiranim dijabetesom[1].

Također, učinkovitost losartana u smanjenju proteinurije kod dijabetičkih i nedijabetičkih bolesnika je dokazana u nekoliko kliničkih studija. Studija *The Reduction of Endpoints in NIDDM (Non-Insulin-Dependent Diabetes Mellitus) with the Angiotensin II Antagonist Losartan (RENAAL)* je pokazala da losartan smanjuje rizik od razvoja primarnog zajedničkog ishoda, tj. udvostručenja vrijednosti serumskog kreatinina, završnog stupnja bubrežne bolesti (ESRD) ili svih uzroka smrti za 16,1% (p = 0,02). To je bila dvostruko slijepa, randomizirana, placebo-kontrolirana studija u kojoj je ukupno 1.513 pacijenata oba spola u dobi između 31 i 70 godina s dijabetesom tipa 2 i proteinurijom praćeno tijekom prosječno 3,4 godine. Također, losartan je umanjio rizik samog ESRD-a (smanjenje rizika 28,6%, p = 0,002) te kombiniranog krajnjeg ishoda ESRD-a ili smrti (smanjenje rizika 19,9%, p = 0,01). Losartan je kod usporedbe s placebom povezan sa 34,3% smanjenjem proteinurije (p = 0,001) te je također reducirao stupanj smanjenja bubrežne funkcije za 18,5% (p = 0,01)[2,3].

Dokazano je da losartan također ima pozitivne učinke kod muškaraca s arterijskom hipertenzijom i seksualnom disfunkcijom. Erektilna funkcija i seksualno zadovoljstvo popravili su se nakon 12 tjedana korištenja terapije losartanom. Pacijenti uključeni u studiju su na početku imali vrijednosti AT između 140/90 i 179/109 mmHg (sistolički/dijastolički) ili su bili liječeni antihipertenzivima. Podaci o seksualnoj funkciji su prikupljeni putem samopopunjavanja upitnika na početku i nakon 12 tjedana terapije. U grupi sa seksualnom disfunkcijom, seksualno zadovoljstvo se povećalo s početnih 7,3% na 58,1% nakon 12 tjedana (p < 0,001). Erektilna disfunkcija se smanjila sa 75,3% na 11,8% nakon 12 tjedana, a kvaliteta života nakon terapije se poboljšala kod 73,7%, ostala je nepromijenjena kod 25,5%, a smanjila se kod 0,8% pacijenata[4].

Još jedan pozitivni učinak liječenja losartanom je njegov učinak na sniženje vrijednosti mokraćne kiseline u serumu. Placebom kontrolirana studija je pokazala sigurnost i učinkovitost losartana u snižavanju vrijednosti mokraćne kiseline u serumu kod 63 pacijenta s hipertenzijom i hiperurikemije inducirane tijazidima. Serumske razine mokraćne kiseline su u usporedbi s placebom znatno snižene nakon tri tjedna terapije losartanom. Losartan u dozi od 50 mg dnevno, s ili bez HCTZ-a, je znatno povisio izlučivanje mokraćne kiseline urinom[5].

Učinkovitost i sigurnost Lorista® u liječenju blage do umjerene arterijske hipertenzije dokazana je u popratnoj studiji u koju su bila uključena 1.356 pacijenta. U studiju su uključeni pacijenti oba spola s blagom do umjerenom arterijskom hipertenzijom kod koje je terapija ACE inhibitorima dovela do nuspojava te pacijenti s zatajenjem bubrega. Srednje snižavanje vrijednosti sistoličkog AT kod svih pacijenata je bilo od 158,6 mmHg ±18,3 na 136,6 mmHg ±10,1 (na kraju studije), a srednje sniženje dijastoličkog AT je bilo od 93,3 mmHg ±10,2 na 82,9 mmHg ±6,5. Na kraju studije je 75,4% pacijenata postiglo vrijednost AT od 140/90 mmHg ili manje te nije izvijestilo o nuspojavama[6].

U sažetku se može zaključiti da je losartan važan antihipertenziv. Dugotrajni podaci su pokazali da losartan sa svojim mehanizmom djelovanja, dobrom učinkovitosti povoljnom podnošljivošću i dodatnim pozitivnim učincima ima istaknuto mjesto u liječenju pacijenata s esencijalnom hipertenzijom.

• 39% less total mortality among patients with established diabetes[1].

In addition, efficacy of losartan in reducing proteinuria in diabetic and non-diabetic patients has been proved in several clinical studies as well. *The Reduction of Endpoints in NIDDM (Non-Insulin-Dependent Diabetes Mellitus) with the Angiotensin II Antagonist Losartan (RENAAL)* study showed that losartan reduced the risk of developing the primary composite endpoint of doubling of serum creatinine, end-stage renal disease (ESRD), or all-cause death by 16.1% (P = 0.02). This was a double-blind, randomized, placebo-controlled study in which a total of 1513 male and female patients aged between 31 and 70 years with type 2 diabetes and proteinuria were monitored over a mean of 3.4 years. In addition, losartan reduced the risk for ESRD alone (risk reduction 28.6%, P = 0.002) and the combined endpoint of ESRD or death (risk reduction 19.9%, P = 0.01). Losartan was associated with a 34.3% decrease in proteinuria (P = 0.001) when compared to placebo and also reduced the rate of decline in renal function by 18.5% (P = 0.01)[2,3].

Losartan has also proved to have beneficial effect in hypertensive men with sexual dysfunction. Erectile function and sexual satisfaction were namely improved after 12 weeks of losartan therapy. Patients included in the study had baseline BP between 140/90 and 179/109 mmHg (systolic/diastolic) or were currently receiving antihypertensive therapy. Data on sexual functioning were collected using a self-administered questionnaire at baseline and after 12 weeks of therapy. In the group with sexual dysfunction, sexual satisfaction increased from baseline 7.3% to 58.1% after 12 weeks (p < 0.001). Erectile dysfunction declined from 75.3% to 11.8% after 12 weeks, and quality of life improved in 73.7%, remained unchanged in 25.5%, and decreased in 0.8% of patients after therapy[4].

Another beneficial characteristic of losartan treatment is its effect on reduction of serum uric acid. A placebo-controlled study demonstrated the safety and efficacy of losartan in reducing serum uric acid at 63 patients with hypertension and thiazide-induced hyperuricemia. Serum uric acid levels were significantly lowered with losartan therapy as compared to placebo after three weeks of treatment. Losartan 50 milligrams daily, with or without HCTZ, significantly increased urinary uric acid excretion[5].

Efficacy and safety of Lorista® in the treatment of mild to moderate arterial hypertension, was proven in the follow-up study which included 1356 patients. Male and female patients with mild to moderate arterial hypertension in whom ACE inhibitor therapy induced adverse drug reactions, and patients with renal failure were included in the study. The mean reduction in systolic BP value in all patients was from 158.6 mm Hg ±18.3 to 136.6 mm Hg ±10.1 (at the end of the follow-up), and the mean reduction in diastolic BP was from 93.3 mm Hg ±10.2 to 82.9 mm Hg ±6.5. At the end of the follow-up as many as 75.4% of the patients achieved a BP value of 140/90 mm Hg or less and reported no adverse drug reactions[6].

In summary, it can be concluded that losartan is an important antihypertensive agent. Long term data outlined that losartan with its mechanism of action, good efficacy, favourable tolerability profile and with additional beneficial effects takes a prominent position in the management of patients with essential hypertension.

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E-mail: breda.zagar@krka.biz

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