Objective, design and basic characteristics of HEMERA clinical study

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SAŽETAK: *Arterijska hipertenzija predstavlja jedan od glavnih čimbenika rizika kardiovaskularnih bolesti. Najnovija klinička istraživanja i smjernice upozoravaju nas da je u većine pacijenata potrebno više vrsta medikamenata za postizanje ciljnih vrijednosti arterijskog tlaka (AT). U većini kliničkih istraživanja, kombinacija dvaju ili više lijekova predstavljala je najčešće korišteni režim liječenja za učinkovito sniženje AT i postizanje unaprijed određenih ciljnih vrijednosti. Ciljevi kliničkog istraživanja HEMERA su određivanje udjela pacijenata koji su postigli ciljne vrijednosti AT primjenom antihipertenzivnog liječenja prema skupinama, usporedba učinka antihipertenzivnog liječenja prema skupinama liječenja (terapija na bazi ramiprila i losartana u kombinaciji s hidroklorotiazidom (HCTZ) i amlodipinom) i procjena sigurnosti četiri različite skupine ispitanika: ramipril ili losartan kao monoterapija, ramipril ili losartan s HCTZ ili amlodipinom te kombinacija liječenja s tri lijeka: ramipril ili losartan s HCTZ i amlodipinom. Ovo kliničko istraživanje je međunarodno i provodit će se u tri države (Hrvatska, Rusija i Ukrajina) kao multicentrična, otvorena, prospektivna, komparativna kontrolirana studija s paralelnim skupinama. Uključivanje ispitanika u Hrvatskoj i Rusiji je još u tijeku, a u Ukrajini je već završeno.*

KLJUČNE RIJEČI: *arterijska hipertenzija, ramipril, losartan, hidroklorotiazid, amlodipin.*

SUMMARY: *Hypertension is one of the main risk factors for cardiovascular diseases. Latest studies and guidelines warn us that in many patients more than one drug is necessary to achieve the target blood pressure (BP). In most clinical studies, a combination of two or more drugs has been the most widely used treatment regimen to reduce BP effectively and reach the predetermined goal. The objectives of HEMERA clinical study are determination of the percentage of patients reaching target BP in each version of antihypertensive treatment performed, comparison of both versions (ramipril-based and losartan-based therapy in combination with hydrochlorothiazide (HCTZ) and amlodipine) of antihypertensive treatment and evaluation of safety of the four different treatment arms: ramipril or losartan as monotherapy, ramipril or losartan with HCTZ or amlodipine and combination treatment with 3 drugs: ramipril or losartan with HCTZ and amlodipine. The clinical study is going to be an international study carried out in 3 countries (Croatia, Russia and Ukraine) as a multicenter, open-label, prospective, comparative, parallel-group, controlled study. The recruitment in 2 countries (Croatia and Russia) is still in process, while the study was already conducted in Ukraine.*

KEYWORDS: *hypertension, ramipril, losartan, hydrochlorothiazide, amlodipine.*

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Pozadina

Kardiovaskularne bolesti (KVB) predstavljaju glavni uzrok smrti diljem Europe i odgovorne su za više od 4,3 milijuna umrlih svake godine[1]. Veliki broj istraživanja je pokazao da su kardiovaskularni morbiditet i mortalitet povezani s vrijednostima i sistoličkog arterijskog tlaka (SAT) i dijastoličkog arterijskog tlaka (DAT)[2,3]. Iako postoji pet različitih skupina lijekova za kontrolu arterijske hipertenzije (AH), i dalje mnogo ljudi ne postiže svoje ciljne vrijednosti arterijskog tlaka (AT). Stoga bi, sukladno Europskim smjernicama ESH-ESC iz 2007. godine, radi kontrole AH ove bolesnike trebalo liječiti kombinacijom dvaju ili više lijekova iz različitih skupina antihipertenziva[4].

Inhibitor angiotenzin-konvertirajućeg enzima (ACE) ramipril i blokator angiotenzin II receptora (ARB) losartan predstavljaju odlično istražene i dokazane antihipertenzivne lijekove bilo kao monoterapija ili u kombinaciji s hidroklorotiazidom i amlodipinom[5-11]. Međutim, prema našim saznanjima nedostaje kliničkih istraživanja kojima se uspoređuje učinkovitost i sigurnost različitih kombinacija režima liječenja ovim lijekovima.

Predstavljamo plan provedbe i temeljne značajke kliničkog istraživanja HEMERA koja će se baviti već navede-

Background

Cardiovascular diseases (CVD) are the main cause of death in Europe: accounting for over 4.3 million deaths each year[1]. A large number of trials have demonstrated that cardiovascular morbidity and mortality bear a relationship with both systolic blood pressure (SBP) and diastolic blood pressure (DBP)[2,3]. Although there are five different groups of drug to control hypertension, there are still many people who don't achieve their target blood pressure (BP). Therefore according to ESH-ESC European guidelines for the management of arterial hypertension published in 2007, these patients should be treated with a combination of two or more drugs from different antihypertensive groups[4].

Angiotensin-converting enzyme (ACE) inhibitor ramipril and angiotensin II receptor blocker (ARB) losartan are both extensively studied and well-proven antihypertensive drugs: either as monotherapy or in combination with hydrochlorothiazide or amlodipine[5-11]. However, to our knowledge there is lack of clinical studies comparing efficacy and safety of different combination treatment regimens of these medicines.

Herein, we present the design and the baseline characteristics of HEMERA clinical study to address the above

nim konceptima: procjenom sigurnosti i kliničkom učinkovitosti dva režima liječenja terapijom na bazi ramiprila i losartana u kombinaciji s hidroklorotiazidom i amlodipinom.

Plan istraživanja

Istraživanje HEMERA predstavlja međunarodnu, multicentričnu, otvorenu ("open-label"), komparativnu, kontroliranu studiju s paralelnim skupinama koju sponzorira Krka d.d., Novo mesto, Slovenija. U studiju su uključene tri zemlje: u Hrvatskoj će studija biti provođena u 12 kliničkih centara, u Rusiji u 11, dok je u Ukrajini, gdje je studija već završena, bilo uključeno 10 centara.

concepts: evaluation of safety and clinical efficacy of the two treatment regimens of ramipril-based and losartan-based therapy in combination with hydrochlorothiazide and amlodipine.

Study design

HEMERA is an international multicenter, open-label, prospective, comparative, parallel-group, controlled study, sponsored by Krka, d.d., Novo mesto, Slovenia. There are 3 different countries included in the study: in Croatia the study will be conducted in 12 clinical centers, in Russia in 11, while in Ukraine, where the study has already been finished, there were 10 centers included.

Table 1. *Principal investigator centers in Croatia.*

Institution	Department	City
Clinical Hospital Centre Rijeka	Cardiovascular Diseases	Sušak, Rijeka
Clinical Hospital Centre Rijeka	Nephrology & Dialysis	Sušak, Rijeka
Health Centre Zagreb — Centar	Outpatient Cardiology	Medveščak, Zagreb
Clinical Hospital Dubrava	Cardiovascular Diseases	Zagreb
Clinical Hospital Dubrava	Nephrology	Zagreb
Clinical Hospital Sestre milosrdnice	Cardiovascular Diseases	Zagreb
Clinical Hospital Sestre milosrdnice	Nephrology & Dialysis	Zagreb
Clinical Hospital Centre Slit	Internal Medicine	Split
General Hospital Zadar	Nephrology	Zadar
Clinical Hospital Centre Osijek	Cardiovascular Diseases & Intensive Care	Osijek
Clinical Hospital Centre Osijek	Nephrology	Osijek
Institute for Cardiovascular Diseases Prevention and Rehabilitation	Outpatient Cardiology	Zagreb

Trajanje cijele studije iznosit će 12 ili 13 tjedana (potreban je jedan tjedan za razdoblje ispiranja i 12 tjedana liječenja) za svakog pojedinog bolesnika. Ako bolesnik barem 12 tjedana prije randomizacije nije bio podvrgnut antihipertenzivnom liječenju, tada neće biti razdoblja ispiranja. Nakon završetka studije bolesnici će moći nastaviti terapiju prema svom osobnom, najprikladnijem načinu liječenja.

U istraživanju HEMERA usporedit će se ACE inhibitor ramipril i ARB losartan i njihove kombinacije s hidroklorotiazidom i blokatorom kalcijevih kanala amlodipinom.

Općenito, svaki bolesnik će obaviti četiri do pet posjeta (**Slika 1**):

• tjedan -1: 1. posjet (početak studije, period ispiranja za one bolesnike koji su već liječeni od AH),

• tjedan 0: 2. posjet (randomizacija i početak liječenja antihipertenzivnim lijekom)

• tjedan 4: 3. posjet (zadržavanje prethodnog liječenja ako je dostatno ili dodavanje drugog antihipertenzivnog lijeka)

• tjedan 8: 4. posjet (zadržavanje prethodnog liječenja ako je dostatno ili dodavanje trećeg antihipertenzivnog lijeka)

The duration of the entire study will be 12 or 13 weeks (1 week of a washout period if needed and 12 weeks of treatment) in each individual patient. If the patient did not receive antihypertensive treatment at least 12 weeks before randomization there will not be any washout period. After conclusion of the study the patients will be able to continue the therapy with their personal, most suitable treatment.

The HEMERA study will compare an ACE inhibitor ramipril versus ARB losartan and their combinations with hydrochlorothiazide and calcium channel blocker amlodipine.

Generally, each patient will undergo four to five visits (**Figure 1**):

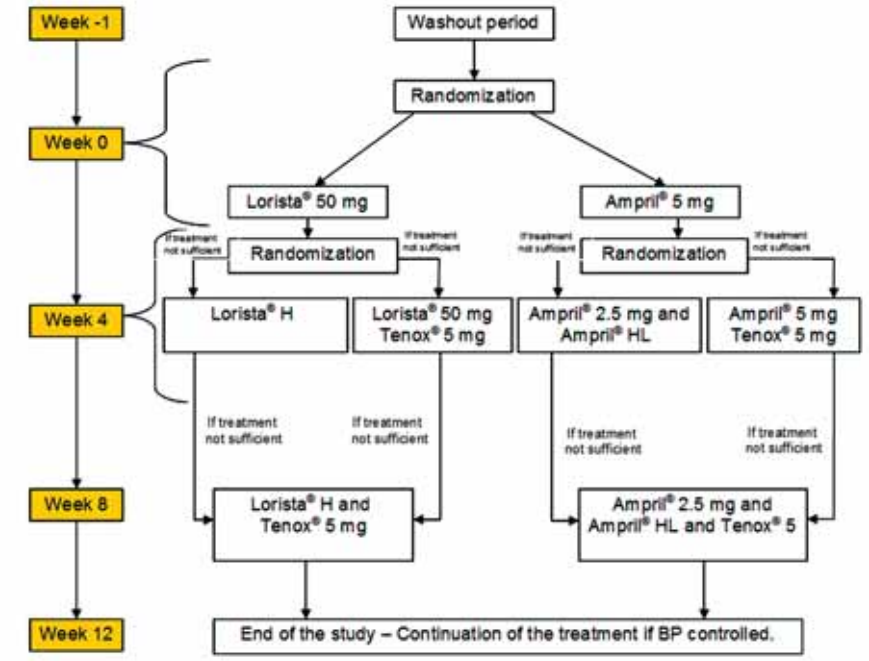
• week -1: 1st visit (beginning of the study (washout period for those patients who are already treated for arterial hypertension),

• week 0: 2nd visit (randomization and initiating of the treatment with antihypertensive medicine)

• week 4: 3rd visit (maintaining previous treatment if sufficient or adding a second antihypertensive medicine)

• week 8: 4th visit (maintaining previous treatment if sufficient or adding a third antihypertensive medicine)

Figure 1. *The time and events schedule gives the schematic layout of HEMERA clinical study.*



Lorista® = losartan

Lorista® H = 50 mg of losartan and 12.5 mg of HCTZ

Ampril® = ramipril

Ampril® HL = 2.5 mg of ramipril and 12.5 mg of HCTZ

Tenox® = amlodipine

• tjedan 12: 5. posjet (završetak studije, konačno mjerenje postignutog AT-a, nastavak aktualnog liječenja ako je postignuta kontrola AT-a).

Primarni ishod studije HEMERA je postizanje ciljnih vrijednosti AT: SAT niži od 140 mmHg i DAT niži od 90 mmHg (za dijabetičare i visokorizične bolesnike: ciljna vrijednost SAT niži od 130 mmHg i DAT niži od 80 mmHg).

Razlika srednjeg SAT i DAT pri kraju liječenja (nakon 12. tjedna) će se u usporedbi s početnim vrijednostima (u tjednu 0) mjeriti kod bolesnika iz oba režima liječenja te također kod bolesnika iz sve četiri ispitne skupine.

Uvjeti izbora bolesnika

U studiju će biti uključeni bolesnici iznad 18 godina s blagom do umjerenom AH. To će biti:

— novootkriveni, prethodno neliječeni hipertenzivni bolesnici,

— hipertenzivni bolesnici čija bolest je već neuspješno liječena bilo monoterapijom ili kombinacijom antihipertenzivnih lijekova (fiksne doze ili kombinacije nefiksnih doza),

— hipertenzivni bolesnici čija bolest je već liječena antihipertenzivnim lijekovima, međutim terapija je povučena bez obzira na uzrok, jedan mjesec ili više prije ulaska u studiju,

— hipertenzivni bolesnici čija bolest je već dostatno liječena antihipertenzivnim lijekovima, međutim, terapija je povučena zbog neželjenih nuspojava,

Broj bolesnika koji će sudjelovati u ovoj studiji (u sve tri zemlje) je određen kako bi se osigurala ispitna osjetljivost, npr. mogućnost da se studijom otkriju razlike među terapijama. Izračunata sveobuhvatna veličina uzorka bolesnika koji će doseći kraj studije će biti otprilike 350. Zbog

• week 12: 5th visit (end of the study, final measurement of achieved BP, continuation of the current treatment if BP is controlled)

The primary endpoint of HEMERA study is the achievement of BP target goal: SBP lower than 140 mmHg and DBP lower than 90 mmHg (for diabetic patients and high-risk patients: the target goal means SBP lower than 130 mmHg and DBP lower than 80 mmHg).

The difference of mean SBP and DBP at the end of treatment (after week 12) compared to the baseline values (at week 0) will be measured in patients of both treatment regimens, and also in patients of all four treatment arms.

Patient eligibility criteria

In the study the patients above 18 years with mild to moderate arterial hypertension (AH) will be included. These will be:

— newly discovered, previously untreated hypertensive patients,

— hypertensive patients whose disease has already been unsuccessfully treated either with monotherapy or combination of antihypertensive medicines (fixed dose or non-fixed dose combinations),

— hypertensive patients whose disease has already been treated with antihypertensive medicines, however the therapy was withdrawn regardless of the cause, one month or more before entering the study,

— hypertensive patients whose disease has already been sufficiently treated with antihypertensive medicines; however, the therapy was withdrawn due to undesirable adverse reactions.

The number of patients to participate in this trial (in all 3 countries) has been determined to assure the assay sensitivity e.g. the ability of a trial to detect differences between treatments. The calculated overall sample size of patients reaching the endpoint will be approximately 350.

procijenjenih 10% bolesnika koji će otpasti tijekom studije očekujemo da broj bolesnika upisanih u fazi ispiranja bude oko 386.

Sve ozbiljne nuspojave će biti prijavljene Projektnom uredu (Krka d.d., Novo mesto, Slovenija). One koje se procjene ozbiljne, povezane s lijekovima korištenim u studiji i neočekivane će biti prijavljene sponzoru studije u svrhu prijave regulatornim službama.

Očekivanja studije HEMERA

Hipertenzija je još uvijek jedna od najvećih bolesti modernog doba[12]. Razlog za zabrinutost je činjenica da manje od jedne trećine hipertenzivnih bolesnika postigne vrijednost AT <140/90 mmHg[13]. To su bolesnici kojima je dijagnosticirana i liječena AH, a zbog nekog razloga je prihvaćena neadekvatna kontrola AT. Postoje radovi u kojima se navodi da je rješenje ovog problema korištenje kombinacije medikamenata[14]. Iako su do sada proučavane mnoge kombinacije, komparativni učinci različitih režima antihipertenzivnog liječenja i dalje nisu sigurni.

Kliničkom studijom HEMERA neće se samo predstaviti razlike između kombiniranih terapija liječenja, već će se također pokazati koristi korištenja različitih strategija liječenja u kombinaciji s profilom nuspojava. Korištenjem paralelnih ispitnih skupina u programu HEMERA će se pouzdano procijeniti komparativni učinci ACE inhibitora ramiprila i ARB losartana u monoterapiji i u kombinaciji s hidroklorotiazidom i blokatorom kalcijevih kanala amlodipinom.

On account of the estimated 10% drop-out during the trial we expect the number of patients enrolled in the washout phase to be around 386.

All serious adverse events will be reported to the Project office (Krka d.d, Novo mesto, Slovenia). Those judged to be serious, related to the study medicines, and unexpected will be reported to the study sponsor for being reported to the regulatory authorities.

HEMERA expectations

Hypertension is still one of the greatest disease burdens of the modern era[12]. It is quite concerning that less than one-third of hypertensive patients achieve a BP of <140/90 mmHg[13]. These are patients who have been diagnosed and treated for hypertension and for some reason inadequate BP control has been accepted. There are papers stating that a solution to this problem is the use of combination therapy[14]. Although many combinations have been studied so far, uncertainty still remains about the comparative effects of different antihypertensive treatment regimens.

HEMERA clinical study will not just present the differences between combination treatments, but will also show the benefits of using different treatment strategies in combination with the adverse effect profile. The use of parallel arms used in HEMERA program will reliably assess the comparative effects of ACE inhibitor ramipril and ARB losartan in monotherapy and in combination with the diuretic hydrochlorothiazide and calcium channel blocker amlodipine.

Dodatak

Kliničko istraživanje HEMERA "Vrednovanje kliničke djelotvornosti i neškodljivosti dvaju terapijskih režima: liječenje bolesnika s arterijskom hipertenzijom stupnja 1 (blaga) do stupnja 2 (umjerena) Amprilom® ili Loristom® u kombinaciji s HCTZ-om i Tenoxom®" (KCT 32/2009-HEMERA/HR) odobrena je Rješenjem Ministarstva zdravstva i socijalne skrbi Republike Hrvatske Ur. broj: 534-05-01-5/1-10/04.

Naziv studije HEMERA je odabran prema legendi o Hemeri. U grčkoj mitologiji Hemera (grčki: Ημερα "dan") je bila personifikacija dana i jedna od Protogena ili praiskonskih božanstava. Svake večeri je Hemerina majka Nyx svukla veo tame između sjajne atmosfere etera i nižih slojeva zraka donoseći čovjeku noć. Svakim jutrom je Hemera raspršila izmaglicu noći, te ponovno okupala zemlju sjajnim svjetlom nebesa.

Appendix

HEMERA clinical study (No. KCT 32/2009-HEMERA/HR) was approved by Ministry of Health and Social Welfare of the Republic of Croatia No. 534-05-01-5/1-10/04.

The name of the trial HEMERA was chosen because of Hemera's legend. In Greek mythology Hemera (Greek: Ημερα, "day") was the personification of day and one of the Protogenoi or primordial deities. Each evening Hemera's mother Nyx drew a veil of darkness between the shining atmosphere of the aither and the lower air of earth bringing night to man. With each morn Hemera dispersed night's mists, bathing the earth again in the shining light of heaven.

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