Postizanje kontrole arterijskog tlaka telmisartanom i kombinacijom fiksne doze telmisartana i hidroklorotiazida

Achieving Blood Pressure Control with Telmisartan and Fixed Dose Combination of Telmisartan and Hydrochlorothiazide

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SAŽETAK: Arterijska je hipertenzija glavni uzrok kardiovaskularnih bolesti kao što su infarkt miokarda, ishemijski moždani udar, zatajivanje srca, bubrežna insuficijencija i drugi klinički događaji. Stoga je, uz primjerene promjene životnih, navika potrebno učinkovito liječenje antihipertenzivima kako bi se bolesnicima ne samo ublažili simptoma nego i pružila kardiovaskularna zaštita. Studija TANDEM provedena je kako bi se procijenile učinkovitost i sigurnost monoterapije telmisartanom (Tolura®) i kombinacije fiksne doze telmisartana i hidroklorotiazida (Tolucombi®) u odraslih bolesnika s arterijskom hipertenzijom. U ovoj neintervencijskoj postautorizacijskoj studiji učinkovitosti i sigurnosti sudjelovala su ukupno 1234 pacijenata. Pacijenti su liječeni monoterapijom telmisartanom ili kombinacijom fiksne doze telmisartana i hidroklorotiazida jednom na dan tijekom četiri mjeseca. Studija je pokazala da Tolura® i Tolucombi® znatno smanjuju sistolički i dijastolički arterijski tlak ($p < 0,0001$) te da ih hipertenzivni bolesnici dobro podnose.

SUMMARY: Arterial hypertension represents the main cause of cardiovascular disorders, such as myocardial infarction, ischemic stroke, heart failure, renal insufficiency, and other clinical events. Therefore, an effective antihypertensive pharmacotherapy is clearly needed, in addition to proper lifestyle changes, in order to provide not only symptomatic relief but also cardiovascular protection. The TANDEM study was undertaken to evaluate the efficacy and safety of telmisartan monotherapy (Tolura®) and the fixed-dose combination of telmisartan/hydrochlorothiazide (Tolucombi®) in adult hypertensive patients. A total of 1,234 patients were enrolled in this non-interventional post-authorization efficacy and safety study. Patients were treated with telmisartan monotherapy or the fixed-dose combination of telmisartan/hydrochlorothiazide once daily for four months. The study demonstrated that Tolura® and Tolucombi® reduce systolic and diastolic blood pressure significantly ($p<0.0001$) and that they are well tolerated by hypertensive patients.

KLJUČNE RIJEČI: arterijska hipertenzija, arterijski tlak, učinkovitost, sigurnost, telmisartan.

KEYWORDS: hypertension, blood pressure, efficacy, safety, telmisartan.

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Uvod

Arterijska hipertenzija (AH) globalni je zdravstveni problem koji zahvaća oko milijarde ljudi diljem svijeta. Povezana je s povećanim kardiovaskularnim i renalnim pobolom[1] te je također vodeći rizični čimbenik za smrtnost u svijetu, uzrokujući gotovo 7,5 milijuna smrti godišnje (13 % svih smrtnih ishoda)[2]. Ukupno kardiovaskularne bolesti (KVB) zahvaćaju oko 128 milijuna osoba godišnje, a očekuje se da će se taj broj povećavati zbog starenja populacije te rastućeg udjela populacija s kardiovaskularnim čimbenicima rizika[3].

Introduction

Hypertension is a global health problem affecting about one billion individuals worldwide. It is associated with increased cardiovascular and renal morbidity[1] and also represents the leading risk factor for death in the world, causing an estimated 7.5 million deaths a year (13% of all deaths)[2]. Moreover, the total burden of cardiovascular disease (CVD) affects about 128 million people annually, with these figures expected to rise because of aging and a greater number of the population having cardiovascular risk factors[3].

Telmisartan je učnkovit i dugodjelojući antagonist angiotenzin II receptora tipa 1 koji je indiciran za liječenje esencijalne hipertenzije i za kardiovaskularnu prevenciju[4]. Djelotvornost telmisartana u kontroli vrijednosti arterijskoga tlaka (AT) dobro je potkrijepljena. Njegov se učinak pojavljuje tri sata nakon prve doze (s najvišim smanjenjem vrijednosti AT-a nakon četiri do osam tjedana od početka liječenja) i traje bez prekida 24 sata nakon uzimanja lijeka. Telmisartan učinkovito smanjuje i sistolički arterijski tlak (SAT) i dijastolički arterijski tlak (DAT). U većini studija u kojima je telmisartan uspoređivan s drugim lijekovima (uz dodatak hidroklorotiazida, HCTZ, ili bez njega), pokazao je sličnu ili čak veću djelotvornost, uz bolji profil podnošljivosti[5]. Na osnovi tih podataka telmisartan je važna opcija u liječenju hipertenzije[4].

Pacijenti i metode

Neintervencijska klinička studija TANDEM uključivala je ukupno 1234 pacijenta s arterijskom hipertenzijom. Cilj je studije bio odrediti sigurnost i djelotvornost telmisartana i kombinacije fiksne doze (KFD) telmisartana i HCTZ-a u liječenju AH-a u svakodnevnoj ambulantnoj kliničkoj praksi. Hipertenzivni pacijenti s područja cijele Slovenije uključeni su u studiju od rujna 2014. do lipnja 2015. godine. Pacijenti su u ovu neintervencijsku kliničku studiju uključivani na temelju indikacija u sažetku opisa svojstva lijeka.[6]

Pri početnoj je evaluaciji (prvi posjet) svaki pacijent dobio detaljan opis ciljeva i postupaka studije te je zamoljen da se potpiše informirani pristanak za sudjelovanje u studiji prije no što je ikakav postupak proveden. Protokol ove otvorene, prospektivne studije IV. faze u trajanju od 16 tjedana aktivnog liječenja predan je Središnjemu etičkom povjerenstvu Republike Slovenije koji ga je i odobrio.[6]

Tijekom razdoblja od 16 tjedana uključeni su pacijenti sudjelovali u trima posjetima liječniku: prvi posjet bio nakon uključenja u studiju, drugi nakon jednog mjeseca liječenja, a treći nakon četiri mjeseca liječenja. Pri prvom bi posjetu liječnik propisao telmisartan ili KFD telmisartan/HCTZ te odredio dozu na temelju početne vrijednosti AT-a. Terapija se sastojala od telmisartana ili KFD telmisartan/HCTZ tableta u dozama do 80 mg telmisartana i do 25 mg HCTZ. Ako su vrijednosti AT-a nakon četiri tjedna liječenja i dalje bile više od 140/90 mmHg, liječnik bi ili povećao dozu ili promijenio liječenje u KFD.[6]

Sigurnosni profil liječenja procjenjivao se na temelju anamneze i kliničkoga pregleda. Pacijente se pitalo da navedu bilo koje kliničke znakove ili simptome koje su doživjeli od prošlog posjeta, a klinički su pregledi služili za otkrivanje mogućih patoloških znakova ili nuspojava. Sve su opažene nuspojave stratificirane s obzirom na vrijeme kad su se pojavile te s obzirom učestalost, težinu, terapijske mjere i ishode.[6]

Rezultati

Od 1234 uključena pacijenata, otprilike su polovica bile žene (55.5%). Srednja je životna dob bila 64,9 ± 11,4 godine. Statistička je analiza uključivala 1228 pacijenata (6 pacijenata došlo je samo na prvi posjet).[6]

Telmisartan is a potent, long-lasting antagonist of the angiotensin II type-1 receptors and is indicated for the treatment of essential hypertension and cardiovascular prevention[4]. The efficacy of telmisartan in controlling blood pressure (BP) has been well documented. Its effect arises three hours after the first dose (with maximum BP reduction attained four to eight weeks after the beginning of the therapy) and persists constantly over 24 hours after dosing. Telmisartan effectively reduces both systolic blood pressure (SBP) and diastolic blood pressure (DBP). In most of the studies in which telmisartan was compared with other medication (with or without addition to hydrochlorothiazide; HCTZ), it showed similar or even higher efficacy, with a better tolerability profile[5]. Based on these data, telmisartan represents an important treatment option for hypertension[4].

Patients and Methods

A total number of 1,234 patients with arterial hypertension were included in the non-interventional clinical study TANDEM. The study was designed to determine the safety and efficacy of telmisartan and the fixed-dose combination (FDC) telmisartan/HCTZ in the treatment of arterial hypertension in a real-life outpatient setting. Hypertensive patients were selected throughout Slovenia and enrolled in the study from September 2014 to June 2015. Patients were included in this non-interventional clinical study according to indications in the summary of product characteristics.[6]

At the initial evaluation (visit 1), each patient received a detailed explanation of the objectives and procedures of this study and was asked to sign an informed consent to participate before any procedure was performed. The protocol of this open, prospective phase IV, 16-week active treatment study was submitted to and approved by the Republic of Slovenia National Medical Ethics Committee.[6]

During the 16-week period, the enrolled patients participated in three visits: the first visit upon inclusion in the study, the second after one month of the treatment, and the third after four months of the treatment. At the first visit, a physician prescribed telmisartan or FDC telmisartan/HCTZ, and determined the dosage according to the baseline BP level. The treatment consisted of telmisartan or FDC telmisartan/HCTZ tablets administered in doses of up to 80 mg telmisartan and up to 25 mg HCTZ. If ambulatory BP levels after four weeks of the treatment were still above 140/90 mmHg, the doctor upgraded either the therapy to FDC, or the dosage.[6]

History and physical examinations were used to assess the safety profile. The patients were asked about any signs or symptoms they experienced since their last visit, and physical examinations were carried out to identify any possible pathological signs of adverse events. All noted adverse events were stratified according to the time of occurrence, frequency, severity, therapeutic measures, and outcome.[6]

Results

Of the 1,234 enrolled patients, approximately half of them were women (55.5%). The mean age was 64.9±11.4 years. The

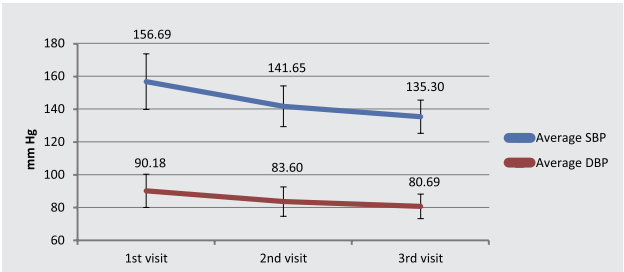

FIGURE 1. The average levels of systolic (SBP) and diastolic (DBP) blood pressure (mmHg) upon each visit. [6]

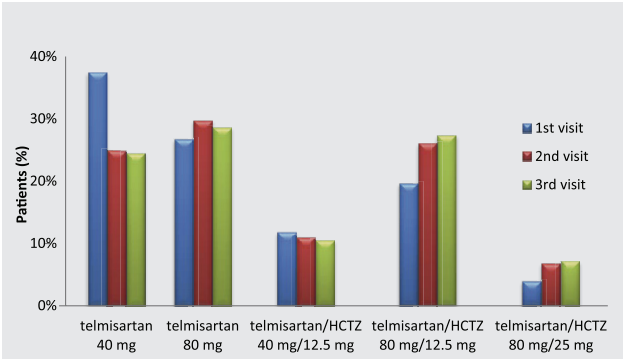

FIGURE 3. Percentage of patients who were treated exclusively with telmisartan and telmisartan/ hydrochlorothiazide (without combining these two medicines). [6]

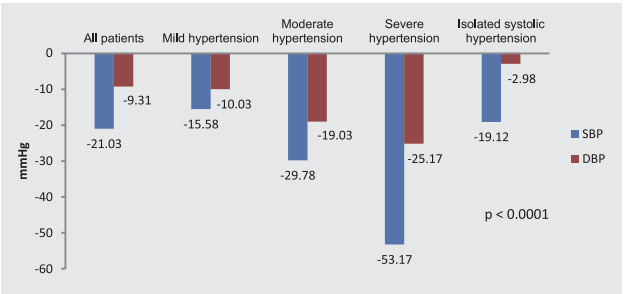

FIGURE 2. Average decreases in systolic (SBP) and diastolic (DBP) blood pressure between first and last visits in patients with different grades of hypertension and in patients with isolated systolic hypertension. [6]

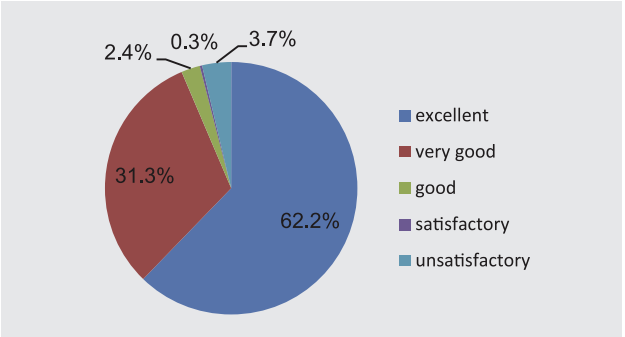

FIGURE 4. Clinical efficacy of treatment with telmisartan and its fixed-dose combination with hydrochlorothiazide. [6]

Od ukupnoga broja od 1228 pacijenata, u 98 (8 %) njih AH je bila nedavno dijagnosticirana te još nisu primali nikakve antihipertenzive (prethodno neliječeni pacijenti), dok je 1130 (92 %) pacijenata već bilo liječeno antihipertenzivima, prebačeno s drugoga antihipertenzivnog lijeka ili je trebalo dodatni antihipertenzivni lijek prije svega zbog nepostizanja ciljnih vrijednosti AT-a.[6]

Početna vrijednost SAT-a bila je 156,96 ± 16,92 mmHg (95 %-tni interval pouzdanosti 155,74 – 157,64 mmHg), a početna vrijednost DAT-a bila je 90,18 ± 10,14 (95 %-tni interval pouzdanosti 89,61 – 90,75 mmHg). Nakon 16 tjedana liječenja telmisartanom i njegovom KFD telmisartan/HCTZ, vrijednosti SAT-a i DAT-a znatno su se snizile (p < 0,0001). Prosječno apsolutno sniženje vrijednosti SAT-a između prvog i zadnjeg posjeta iznosilo je 21,03 ± 16,72 mmHg, a 9,31 ± 9,70 mmHg za DAT (**slika 1**).[6]

To je sniženje znatno koreliralo s početnim vrijednostima AT-a: veće sniženje AT-a opaženo je u bolesnika s višom početnom razinom AT-a. U pacijenata s početnim SAT-om ≥ 180 mmHg sniženje AT-a bilo je najveće (vrijednosti SAT-a snizile su se za 53,17 ± 20,69 mmHg, a DBP-a za 25,17 ± 8,74 mmHg), no sniženje AT-a između prvog i zadnjeg posjeta također je bilo značajno (p < 0,0001) i za sve druge razine AH-a. U pacijenata s izoliranom sistoličkom hipertenzijom AT se znatno snizio (p < 0,0001) između prvog i zadnjeg posjeta. SAT se snizio za 19,12 ± 15,34 mmHg, a DBP za 2,98 ± 7,81 mmHg (**slika 2**).[6]

Nakon četiri mjeseca liječenja telmisartan ili KFD telmisartan/HCTZ bio je jedini antihipertenziv u 55 % pacijenata.

statistical analysis included 1,228 patients (6 patients only came for the first visit).[6]

Of the total population of 1,228 patients, 98 (8%) had recently been diagnosed with hypertension and had not received any antihypertensive medicine (treatment-naïve patients), while 1,130 (92%) had already been treated with antihypertensives, switched from other antihypertensive medication, or needed an additional antihypertensive medicine primarily due to not achieving BP levels.[6]

The baseline SBP was 156.96±16.92 mmHg (95% confidence interval 155.74-157.64 mmHg) and DBP 90.18±10.14 (95% confidence interval 89.61-90.75 mmHg). After 16 weeks of treatment with telmisartan and its FDC telmisartan/HCTZ, SBP and DBP levels decreased significantly (p<0.0001). The average absolute decrease in SBP between first and last visits was 21.03±16.72 mmHg and 9.31±9.70 mmHg in DBP (**Figure 1**).[6]

The observed reductions were highly correlated with the baseline BP: higher BP reductions were observed with higher baseline BP levels. In patients with baseline SBP≥180 mmHg, reduction in BP was the highest (SBP decreased by 53.17±20.69 mmHg, and DBP by 25.17±8.74 mmHg), whereas reduction in BP between first and last visits was also significant (p<0.0001) in all other grades of hypertension. Among patients with isolated systolic hypertension, BP significantly decreased (p<0.0001) between the first and last visit. SBP decreased by 19.12±15.34 mmHg, and DBP by 2.98±7.81 mmHg (**Figure 2**).[6]

After four months of the treatment, telmisartan or FDC telmisartan/HCTZ was the only antihypertensive treatment in 55% of patients. Other patients were also concomitantly

Ostali su pacijenti usporedno liječeni i drugim antihipertenzivnim lijekovima. Na kraju studije 56 % pacijenata postiglo je ciljne vrijednosti AT-a uz 80 mg telmisartana ili 80 mg/12,5 mg KFD telmisartan/HCTZ-a (**slika 3**).[6]

Glede profila podnošljivosti, telmisartan i KFD telmisartan/HCTZ bili su vrlo podnošljivi u svim dozama. Analiza je pokazala da je incidencija nuspojava tijekom 16 tjedana liječenja bila niska jer je tijekom studije samo 2,7 % pacijenata doživjelo nuspojave povezane s liječenjem. Učestalost opaženih nuspojava bila je niska. Najčešće su nuspojave bile vrtoglavica, nadutost te hipotenzija. Samo je 1,2 % pacijenata prekinulo liječenje zbog nuspojava vezanih za liječenje.[6]

Klinička je učinkovitost liječenja bila vrlo dobra ili odlična u 93,5 % svih pacijenata. Vrijednosti AT-a u pacijenata bile su ili 139/89 mmHg ili niže (139/84 mmHg ili niže u dijabetičara) te nisu prijavili nikakve ili su prijavili samo blage nuspojave ili im je pak vrijednost AT-a bila 149/94 mmHg ili niža (149/89 mmHg ili niže u dijabetičara) te nisu prijavili nikakve nuspojave (**slika 4**).[6]

Studija je uključivala dvije podskupine pacijenata: oni koji su bili liječeni drugim antihipertenzivima, ali nisu postigli ciljne vrijednosti prije liječenja telmisartanom ili KFD telmisartan/HCTZ i pacijenti koji nisu bili prije toga liječeni. U objema je skupinama klinička djelotvornost lijeka bila odlična ili vrlo dobra u više od 93 % pacijenata nakon liječenja telmisartanom ili KFD telmisartan/HCTZ-om.[6]

Liječenje telmisartanom ili KFD telmisartan/HCTZ-om imalo je pozitivne učinke na sve stupnjeve hipertenzije te i u pacijenata s izoliranom sistoličkom hipertenzijom. Nakon četiri mjeseca liječenja telmisartanom ili KFD telmisartan/HCTZ-om AT je učinkovito smanjen, a gotovo dvije trećine pacijenata postigle su ciljne vrijednosti AT-a.[6]

Zaključak

Rezultati studije potvrdili su da telmisartani KFD telmisartan/HCTZ učinkovito smanjuju AT u pacijenata sa svim stupnjevima esencijalne hipertenzije u ambulantnim uvjetima. Većina pacijenata postigla je optimalne ciljne vrijednosti AT-a. Tijekom studije incidencija prijavljenih nuspojava bila je mala. Telmisartan (Tolura®) i KFD telmisartan/hidroklorotiazid (Tolucombi®) pokazali su se djelotvornom opcijom za učinkovitu kontrolu AT-a, što je ključni čimbenik koji utječe na kardiovaskularne ishode.[6]

treated with other antihypertensive medication. At the end of the study, 56% of patients achieved target BP with 80 mg of telmisartan or 80 mg/12.5 mg of FDC telmisartan/HCTZ (**Figure 3**).[6]

Concerning the tolerance profile, telmisartan and FDC telmisartan/HCTZ were very well tolerated at all doses. The analysis revealed that adverse event incidence during 16 weeks of treatment was low, as during the course of the study only 2.7% of patients experienced adverse events related to the treatment. The frequency of the observed adverse events was low. Among all the reported adverse events, dizziness, flatulence, and hypotension were most common. Only 1.2% of patients discontinued the treatment because of treatment-related adverse events.[6]

The clinical efficacy of the treatment was very good or excellent in 93.5% of all patients. Their BP was either 139/89 mmHg or lower (diabetic patients 139/84 mmHg or lower) and they reported no adverse effects or only mild ones; or their BP was 149/94 mmHg or lower (diabetic patients 149/89 mmHg or lower) and they reported no adverse effects (**Figure 4**).[6]

The study involved two subgroups of patients: those who had been treated with other antihypertensives but failed to achieve target levels before the treatment with telmisartan or FDC telmisartan/HCTZ, and those who had not been treated previously. Both subgroups showed excellent or very good clinical efficacy in more than 93% of patients after being treated with telmisartan or FDC telmisartan/HCTZ.[6]

The treatment with telmisartan or FDC telmisartan/HCTZ is beneficial in all grades of hypertension and also in patients with isolated systolic hypertension. After four months of treatment with telmisartan and FDC telmisartan/HCTZ, BP was effectively reduced, and almost two thirds of patients achieved target BP values.[6]

Conclusion

The results confirmed that telmisartan and FDC telmisartan/HCTZ effectively decrease BP in patients with all grades of essential hypertension in real-life settings. Most patients achieved optimal BP targets. During the course of the study, the reported adverse events incidence rate was low. Telmisartan (Tolura®) and FDC telmisartan/hydrochlorothiazide (Tolucombi®) seem to be a beneficial option for effective BP control, which is a key factor influencing cardiovascular outcomes.[6]

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