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ORIGINAL RESEARCH

Introducing candesartan 32 mg plus hydrochlorothiazide 25 mg in previously untreated patients with severe essential hypertension

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Purpose: To investigate the efficacy of candesartan 32 mg and hydrochlorothiazide (HCTZ) 25 mg combination in patients with severe essential hypertension.

Patients and methods: In this prospective, open-label, single-group study, 106 previously untreated patients with a baseline systolic blood pressure (SBP) of 150–200 mmHg, and a diastolic blood pressure (DBP) of 110 to 120 mmHg, started with candesartan 16 mg during the first week. HCTZ 12.5 mg was added at week 2 and from fourth week onwards candesartan 32 mg plus HCTZ 25 mg was given over 6 weeks. The primary efficacy endpoint was mean reduction in SBP and DBP after 9 weeks. Response was defined as a decrease in SBP to <140 mmHg and/or by ≥20 mmHg and in DBP to <90 mmHg and/or by ≥10 mmHg. A second response criterion defined blood pressure reduction below 140/90 mmHg.

Results: Blood pressure was lowered from 180.0 ± 11.7/114.7 ± 3.1 mmHg by SBP 44.4 ± 16.8 and DBP 32.0 ± 11.3 mmHg ($P < 0.0001$). Response was 92.4% and 64.8% achieved <140/90 mmHg. Each titration step produced a statistically significant and clinically relevant decrease in SBP and DBP, but a level below 140/90 mmHg was achieved by >50% of the patients only after the third titration step. Adverse reactions were reported by 3.8% of the patients. The disorders were in line with the known safety profile of the study drugs.

Conclusion: A stepped treatment approach with candesartan/HCTZ combinations is effective and safe to achieve a swift blood pressure reduction in newly diagnosed, severe hypertension. The target of <140/90 mmHg was reached by >50% of the patients only after taking the full dose of candesartan 32 mg and HCTZ 25 mg.

Keywords: primary therapy of newly diagnosed hypertension, fixed combination, decrease in blood pressure, response rates, candesartan

Introduction

Arterial hypertension currently affects more than 25% of the adult population globally and its prevalence is expected to increase further.[1] Untreated arterial hypertension is associated with an increased risk for major cardiovascular events and damage of other organs over time and thus contributes significantly to overall morbidity and mortality.[2–4] Although scientific and clinical knowledge about currently marketed antihypertensive drugs is sound, individualized therapy continues to be discussed.[5] Depending on the severity of the hypertension and the associated risk factors, there are different classes and combinations of drugs to choose from.

Most hypertensive patients require more than 1 anti-hypertensive drug. Severe hypertension usually requires 2 or more agents for sufficient treatment response.

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Antihypertensive drug combinations are generally favored for tolerability reasons, because doses of the constituent combined agents are usually lower than in monotherapy.

This study focused on starting an antihypertensive treatment in patients with previously untreated, severe essential hypertension. It is known from daily clinical experience that the start and maintenance of a successful antihypertensive drug treatment is impaired by factors like low compliance – especially if more than 1 drug is used – and by the possibly negative subjective perception of a rapidly induced decrease of blood pressure (BP) as well as the potential side effects of each class of antihypertensives.

To overcome these potential reasons for treatment failure, the Joint National Committee 7 guidelines suggest considering a fixed combination, but with stepwise dose titration from initiation.[6] Accordingly, we prospectively studied a 3-step titration of a combination of the angiotensin receptor blocker (ARB) candesartan cilexetil and hydrochlorothiazide (HCTZ) in patients with severe essential hypertension, in order to understand and characterize its effects.

To capture the efficacy of this therapy, we defined treatment response as a decrease in systolic blood pressure (SBP) to <140 mmHg and/or by at least 20 mmHg, a decrease in diastolic blood pressure (DBP) to <90 mmHg and/or by at least 10 mmHg and, with reference to the WHO-ISH (World Health Organization-International Society of Hypertension) guidelines on managing hypertension, as achieving BP values below 140/90 mmHg.[7] In addition, we put special emphasis on adverse events (AEs) and changes in laboratory parameters over time, so as to capture safety information.

Material and methods

Study design

This prospective, multicenter, open-label, single arm study comprised a 3-week titration phase starting with candesartan cilexetil 16 mg once daily monotherapy over 1 week and continuing from week 2 onwards with the combination of candesartan cilexetil 16 mg plus hydrochlorothiazide (HCTZ) 12.5 mg once daily for 2 weeks. From the beginning of the fourth study week onwards, candesartan cilexetil 32 mg plus HCTZ 25 mg once daily were given over a total of 6 weeks (Figure 1). The investigators were allowed to shorten the titration intervals if this fitted the needs of individual patients and if there was no particular risk for these patients.

Patients were recruited in 10 sites in Germany and 8 sites in the Ukraine. Before starting patient enrolment, the study was reviewed and approved by a central Independent Ethics Committee or an Institutional Review Board as well as by a National Regulatory Agency, according to country-specific requirements. The Ethics Committee of the national co-ordinating investigator in Germany emphasized that diagnostics were necessary if the patients did not respond to the study treatment and that these diagnostics must not be delayed due to the participation in the study. Moreover, basic diagnostics had to be performed and the results had to be available for monitoring. Patients with an imminent hypertensive crisis, ie, a blood pressure above 180/120 mmHg in combination with symptoms of organ damage, eg, deteriorating mental status, severe headache, epistaxis, blurred vision, arrhythmias or thoracic pain were to be excluded from the study. These requirements were implemented in the clinical conduct of the study.

This trial was performed in accordance with the Declaration of Helsinki and the International Conference on Harmonisation/Good Clinical Practice.

The study was listed on the Internet under clinicaltrials.gov with the identifier NCT01012479.

Patient selection

Adult male and female outpatients (age range 25–74 years) with a confirmed essential hypertension defined as SBP between 150 and 200 mmHg and DBP between 110 and 120 mmHg measured according to the recommendations of the American Heart Association 2005 were considered for the study if they had not received antihypertensive treatment before the start of the study.[8] Patients were not eligible if they

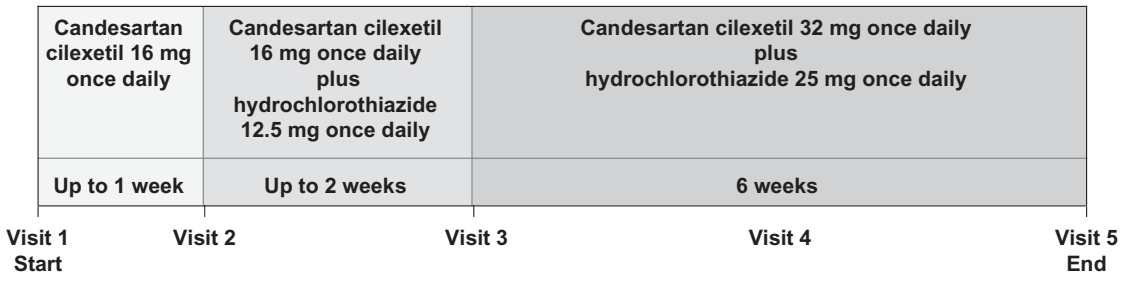

Figure 1 Study treatment.

had a known or suspected secondary hypertension, impaired renal or hepatic function, bilateral renal artery stenosis, solitary kidney or post-renal transplant status. A myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention, or cerebral accident within the previous 6 months also excluded patients from the study. Other exclusion criteria were suspected or diagnosed hypertrophic obstructive cardiomyopathy, angina pectoris, chronic heart failure, peripheral arterial occlusive disease, or hypertensive retinopathy, hemodynamically relevant stenosis of the aortic or mitral valve, clinically relevant and refractory hypo- or hyperkalemia, uncorrected volume or sodium depletion, or gout/relevant hyperuricemia.

Procedures

Study specific procedures were performed only after patients had been informed about the nature, purpose, risk, and benefits of the study and after they had agreed to participate in the study by signing the informed consent form. At visit 1, the inclusion and exclusion criteria were checked and the demographic data, medical history, and concomitant medications were recorded. A physical examination and blood sampling for safety laboratory analyses were performed. BP and pulse rate were measured and an automated sphygmomanometer and a diary were dispensed together with the first package of the study medication. The patients were instructed on how and when to take the study medication and to document at least 2 BP measurements per day in the diary and to return the unused medication and the completed diary at visit 2. Between visits 1 and 2, the investigator called the patients daily from day 1 to day 3 for safety reasons. In case of poor treatment response, the investigator was allowed to re-schedule visit 2 to an earlier date. If the laboratory results from the visit 1 sample revealed incompatibility with the study selection criteria, the patients were immediately withdrawn from further participation. At visit 2, the patients' eligibility for the study was re-checked. The BP and pulse rate as well as AEs or changes in the concomitant medication were recorded. The same procedures were completed at visits 3 and 4. In addition, serum creatinine and potassium were determined at visit 3. The physical examination and the laboratory tests as from visit 1 were repeated and the diary and the unused tablets were collected. AEs or changes in the concomitant medication were recorded.

Efficacy parameters

BP was measured after 15 minutes recovery from any previous exertion and after sitting for at least 5 minutes. The automated sphygmomanometer Omron 705 IT (Omron Healthcare, Inc., Bannockburn, IL) was used at all times. This device is graded 'A' for both systolic and diastolic BP measurements according to the British Hypertension Society criteria and it meets the Association for the Advancement of Medical Instrumentation SP10 standard.[9] At visit 1, SBP and DBP were measured 3 times each on both arms. The arm giving the highest median DBP was used for all future measurements. At all further visits, BP was measured 3 times in that arm. All measured values were documented. For the efficacy evaluation, the median of the 3 values was always used. The BP measurement after the last dosing was performed at trough level, ie, approximately 24 hours after the last intake of the study medication.

Safety parameters

AEs, that is, any untoward medical occurrence not necessarily having a causal relationship with the study treatment, were recorded based on the patients' spontaneous reporting or their answers to a neutral question from the investigator such as 'have you felt any untoward or unusual symptoms other than those related to your illness?'.

Laboratory tests comprised variables of hematology and clinical chemistry and were done locally. Samples were taken at visits 1, 3, and 5 (Figure 1). The estimated glomerular filtration rate (eGFR) was calculated from the serum creatinine using the Cockcroft-Gault equation.[10]

The physical examination focused on the respiratory, cardiovascular, and neurological systems.

Statistical methods

In this exploratory study, the mean reductions in SBP and DBP were defined as primary efficacy criteria. Response rates and pulse rate were secondary outcomes. Response to treatment was defined as a decrease in SBP to <140 mmHg and/or by at least 20 mmHg and a decrease in DBP to <90 mmHg and/or by at least 10 mmHg, as well as reaching a BP below 140/90 mmHg. This is consistent with current treatment guidelines.[11]

The data were analyzed using descriptive statistical methods. Data from all centers participating in the study were pooled to obtain adequate numbers for analysis. Missing values at visit 5 were replaced by the last measurement obtained during treatment (last observation carried forward, LOCF).

Continuous variables were analyzed descriptively using standard summary statistics. For categorical variables, frequencies of patients were presented.

The Safety Set included all patients who received at least 1 dose of study medication. The Full Analysis Set comprised all patients who received at least 1 dose of study medication, had baseline values, and recorded at least 1 post-baseline efficacy measurement.

Results

Baseline characteristics

All 106 patients who received at least 1 dose of study medication were included in the Safety Set. One patient had no post-baseline efficacy measurements, so that the Full Analysis Set consisted of 105 patients of which 101 patients completed the study according to the protocol. The reason for withdrawal of 4 patients from the study was incompatibility with the selection criteria detected only after the patients were already randomized.

The baseline results of the 105 patients in the Full Analysis Set are summarized in Table 1: 5/106 (4.7%) patients in the Safety Set entered the study, with an eGFR below 60 mL/min. Their age ranged between 61 and 72 years and none of them had renal disease listed as a concomitant illness.

Efficacy

Primary efficacy criterion

After treatment with the study medication over 9 weeks, the mean SBP of 180.0 ± 11.7 mmHg at study start decreased by 44.4 ± 16.8 mmHg (LOCF). During the same time, the initial DBP of 114.7 ± 3.1 mmHg was lowered by 32.0 ± 11.3 mmHg (LOCF) (Figure 2). Both changes were found to be statistically significant ($P < 0.0001$). At the last study visit, the average BP values were 135.6 ± 15.3 mmHg for the SBP and 82.7 ± 10.4 mmHg for the DBP.

Table 1 Baseline characteristics

Parameter	Full analysis set: N = 105	
Sex: male	n (%)	60 (57.1)
Most frequent concomitant diseases		
Metabolic and nutritional disorders	n (%)	64 (61.0)
Most frequent concomitant drugs		
Blood glucose-lowering drugs	n (%)	10 (9.5)
Age [years]	Mean ± SD	52.5 ± 10.1
Body mass index [kg/m^2]	Mean ± SD	30.4 ± 4.8
Systolic blood pressure [mmHg]	Mean ± SD	180.0 ± 11.7
	Median (minimum–maximum)	179 (152–208)
Diastolic blood pressure [mmHg]	Mean ± SD	114.7 ± 3.1
	Median (minimum–maximum)	114 (108–128)

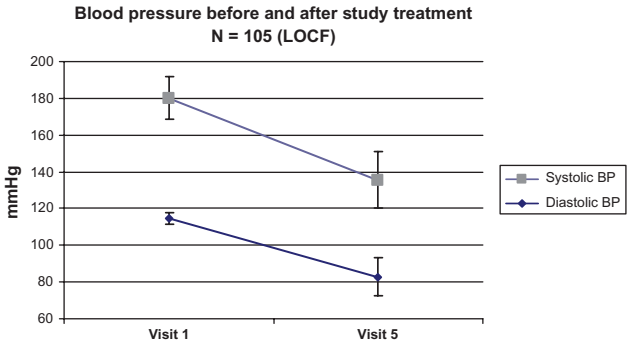

Figure 2 Blood pressure before and after study treatment (N = 105, LOCF).
Abbreviation: BP, blood pressure.

Secondary efficacy endpoints

Response to treatment at study end

At the end of the study, response in terms of a decrease of the SBP to <140 mmHg and/or by at least 20 mmHg and a decrease of the DBP to <90 mmHg and/or by at least 10 mmHg diastolic was found in 97/105 (92.4%) patients; 68/105 (64.8%) patients achieved a BP of <140/90 mmHg.

Response to treatment by titration step

In addition to the above described results from the end of the study, the effect of each individual titration step during the study was investigated.

Looking at the effect of the first titration step only, we found that no more than 33.3% of the patients reached a decrease in SBP to <140 mmHg and/or by at least 20 mmHg and a decrease in DBP to <90 mmHg and/or by at least 10 mmHg (combined response). At the same time, only 2.9% of the patients had a BP below 140/90 mmHg.

At the end of the second titration step, the proportion of patients showing the combined response went up to 77.1%. When searching for BP values of <140/90 mmHg, however, we found that 22.9% of the patients had this type of response.

The last titration step, ie, the maximizing of both the candesartan cilexetil dose and the HCTZ dose to the final amount of 32 mg and 25 mg, produced an increase in the rate of combined response from 77.1% to 92.4%. Looking at the treatment target of a BP below 140/90 mmHg, titration step 3 improved the proportion of responders from 22.9% to 64.8% (Figure 3).

Changes in pulse rate

Between the first and the individual last visit of each patient, the mean pulse rate decreased by 3.0 ± 14.5 beats

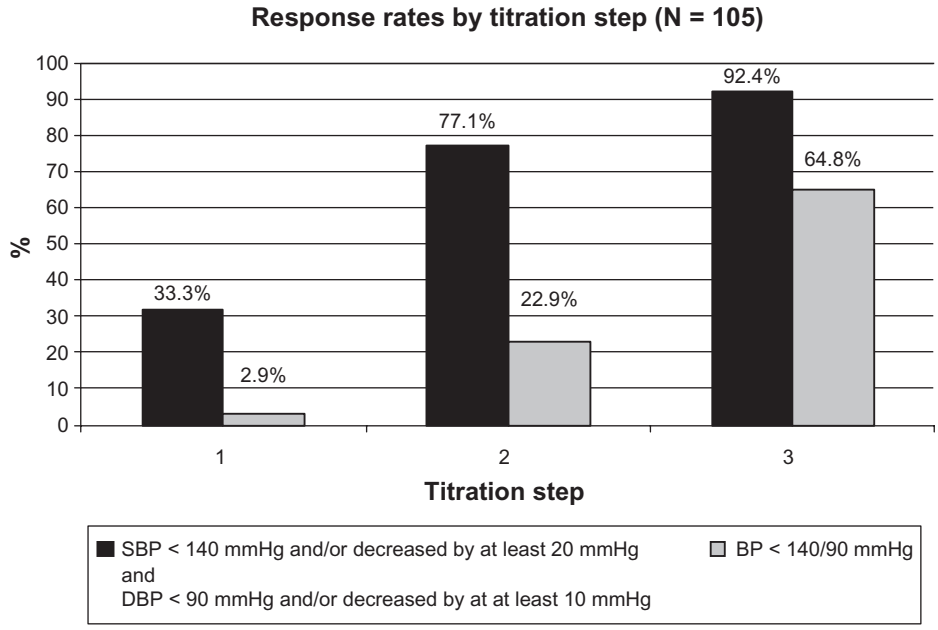

Figure 3 Treatment response rates by titration step (N = 105).
Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

per minute (bpm). The change in the pulse rate over time ranged from –44.0 to 62.0 bpm with a median of –4.0 bpm.

Changes in blood pressure by titration step

Looking at the changes in BP by titration step we found that the decreases achieved during each individual titration step from baseline were of statistical significance. Figure 4 shows the magnitude of the decreases by titration step.

For SBP, the largest decrease, ie, 17.3 ± 16.4 mmHg, was found during the second titration step. DBP showed a different pattern in that the most pronounced decrease, ie, 14.3 ± 9.8 mmHg, emerged already during the first

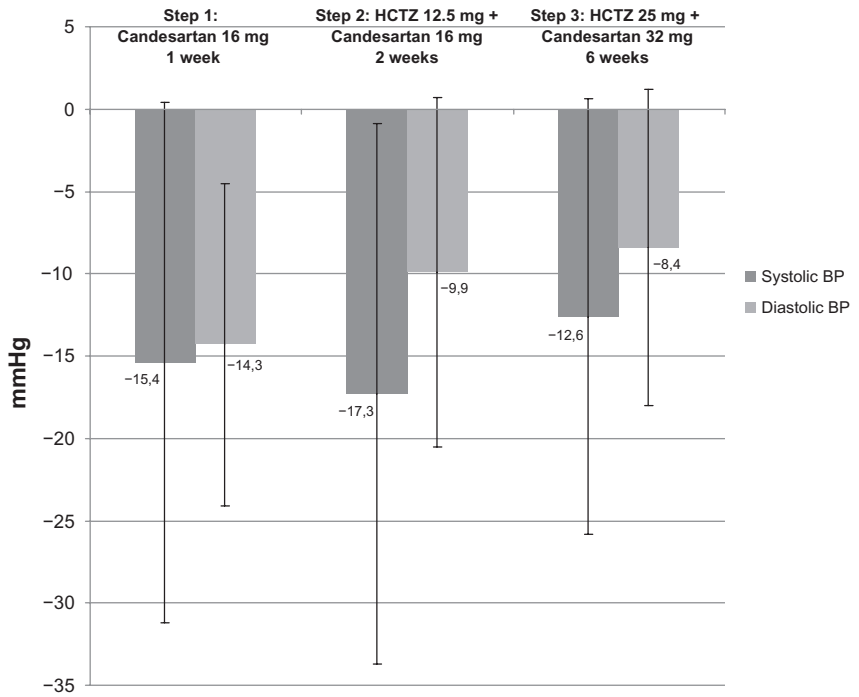

Figure 4 Decrease in blood pressure by titration step: mean ± SD (N = 105).
Abbreviations: BP, blood pressure; HCTZ, hydrochlorothiazide.

titration step. The smallest decreases for both the SBP and the DBP occurred during titration step 3, ie, 12.6 ± 13.2 mmHg for the SBP and 8.4 ± 9.6 mmHg for the DBP.

Safety

In total, 38 AEs were reported in 30/106 (28.3%) patients. Thereof, a causal relation with the study medication was assessed for 5 events reported from 4/106 (3.8%) patients. These 5 events included: increase in alanine aminotransferase (ALAT) to >8 × the upper limit normal (ULN), and in aspartate aminotransferase (ASAT) to >10 × ULN, both in the same patient, and at the last study visit 1 patient had vertigo, 1 had palpitations and 1 had hyperglycemia. These disorders are consistent with the known safety profile of the study medication. None of the causally related AEs were severe and/or serious, or led to withdrawal from the study. All patients recovered from these events.

One serious adverse event (SAE) was observed: a patient was hospitalized due to chest pain and diagnostic cardiac catheterization was performed. As result, the chest pain was specified as of non-cardiac origin. This SAE was assessed as not causally related and as recovered.

An increase in gamma glutamyltransferase to >3 × ULN found at study visit 1 caused 1 patient to be withdrawn immediately from the study. This laboratory result retrospectively proved to be noneligibility of this patient for the study, rather than an untoward medical occurrence during the trial. There were no further AEs leading to withdrawal from the study.

The statistical analysis of the laboratory results did not provide any unexpected safety findings on the combination of candesartan cilexetil and HCTZ. A summary of the results is provided in Table 2.

As expected, the average results for hemoglobin, hematocrit, and red blood cell count decreased very slightly over time.

The mean ASAT and ALAT increases over time were accompanied by a median representing a mild decrease so that a clear trend did not become obvious.

The mean serum creatinine was found to increase very mildly over time which translated to a slight decrease of the eGFR. Figure 5, a scatter plot, shows that 1 patient contributed a strong decrease in the eGFR: the result fell over time from 204.4 mL/minute to 116.8 mL/minute which was still above the normal range (50–100 mL/minute.). The study data did not provide any further explanation or follow-up eGFR results for this patient. It is assumed that the high difference was caused by technical laboratory issues rather than by changes in the kidney function of this patient. The results of all other patients were close to the line of no change.

To explore further the effect of the study treatment on renal function, the change in the eGFR between visit 1 and visit 3 was analyzed. As the largest decrease in BP occurred during this interval, we expected to find a decrease of the eGFR as a sign of the reduced glomerular pressure. The actual results, ie, a mean increase by 0.4 ± 13.0 mL/minute together with a median increase of –0.4 mL/minute, indicated no change. Hence, we could find no signs of blood pressure reduction translating into a general negative impact on the kidney function.

Discussion

In patients with newly diagnosed, severe essential hypertension, the start of an antihypertensive treatment is clearly indicated to prevent organ damage. The selection

Table 2 Laboratory results: baseline and change from baseline at the end of the study (last observation carried forward for potassium, creatinine and eGFR)

Parameter	Baseline		Absolute change at end of study	
	Mean ± SD (median)	n	Mean ± SD (median)	n
Hemoglobin [mmol/L]	9.0 ± 1.0 (8.8)	106	–0.2 ± 0.7 (–0.2)	104
Hematocrit [%]	42.7 ± 5.4 (42.0)	106	–1.5 ± 5.1 (–1.0)	104
Red blood cell count [/pL]	4.8 ± 0.6 (4.8)	105	–0.2 ± 0.5 (–0.1)	103
ASAT [U/L]	28.1 ± 11.7 (26.0)	106	3.6 ± 51.1 (–1.0)	104
ALAT [U/L]	35.3 ± 17.3 (33.5)	106	1.3 ± 42.1 (–1.0)	103
GGT [U/L]	42.3 ± 28.8 (35.0)	101	0.1 ± 16.4 (0.2)	97
Sodium [mmol/L]	140.7 ± 3.8 (141.0)	106	–0.7 ± 3.7 (–1.0)	104
Potassium [mmol/L]	4.6 ± 0.7 (4.4)	106	–0.1 ± 0.8 (–0.0)	104
Serum creatinine [µmol/L]	85.4 ± 18.2 (83.6)	106	1.4 ± 11.8 (0.4)	104
eGFR [mL/minute]	110.5 ± 33.4 (106.7)	106	–1.6 ± 15.7 (–0.3)	104
eGFR [mL/minute] Starting eGFR < 60 mL/minute	55.6 ± 2.1 (55.7)	5	3.6 ± 10.9 (3.4)	5
eGFR [mL/minute] Starting eGFR ≥ 60 mL/minute	113.2 ± 31.9 (108.6)	101	–1.9 ± 15.9 (–0.6)	99

Abbreviations: ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; GGT, gamma glutamyltransferase.

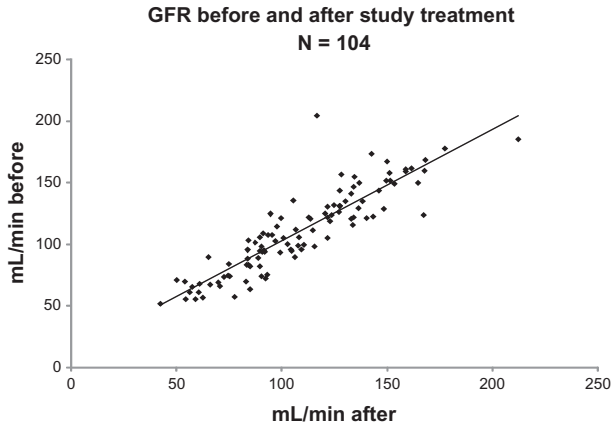

Figure 5 Glomerular filtration rate before and after study treatment (N = 104).

of antihypertensive therapy is key for an effective and safe reduction of blood pressure within a short period, and the patient's long-term compliance and prognosis will depend on the success of this regimen.

The approach of using fixed dose combinations either as a first-line treatment or earlier in patients with comorbidities, which require rapid blood pressure reduction, is endorsed by current guidelines.[6,12,13]

ARB plus diuretic combinations have established their additive effects with an enhanced tolerability in numerous clinical trials and are nowadays well proven options in clinical practice. Combination with an ARB permits low dose treatment with diuretics, which limits their metabolic side effects.

This prospective, single-group, multicenter study in patients with severe, previously untreated, essential hypertension investigated the efficacy and safety of the combination of candesartan cilexetil and HCTZ when up titrated in line with the guidelines. When initiating antihypertensive medication, what is needed ideally is rapid BP decrease without causing adverse effects either secondary to the decreasing BP or due to the compounds of the medication. We found that each of the 3-dose steps used in this study made a key contribution to treatment success: the first titration step translated into the highest decrease in the DBP. The second titration step provided the most pronounced effect on the SBP. However, only the third titration step ensured a response rate in terms of a blood pressure of $<$140/90 mmHg in 65% of the patients, compared with only 23% of the patients at the end of the second titration step. We concluded that this method of upward titration is quick and effective in managing BP.

Rapid BP reduction was shown to have a prognostic effect in high risk, hypertensive patients. In a large scale clinical trial comparing 2 antihypertensive regimens, significantly less strokes occurred during the first 3 months in the treatment arm with quicker BP reduction, compared with the other regimen achieving slower BP reduction.[14,15] The BP reductions and safety profile are consistent with previous data on this combination.[16–21] Equally, the safety results are compatible with the known safety profile of this medication.

According to the literature on changes over time in serum creatinine and eGFR, a slight rise in serum creatinine concentrations during treatment with ARBs, translating into a decrease in the eGFR, is an indicator of the intended reduced glomerular pressure.[22] A mild decrease of the eGFR was found throughout our study population, originating from the mild serum creatinine elevations observed. However, a medically important risk arising from this effect on the eGFR did not become obvious.

Elevations of liver enzymes are described as a very rare adverse reaction to candesartan cilexetil. For the single incidences of increased liver enzymes during this study, the available data did not allow a sound judgement to be made on the impact of the trial medication.

Conclusion

The present study showed that the combination of candesartan cilexetil and HCTZ is an effective and safe primary treatment for newly diagnosed hypertension with systolic blood pressures between 150 and 200 mmHg and diastolic blood pressures between 120 and 110 mmHg.

A titrated start with 16 mg candesartan cilexetil over 1 week followed by 16 mg candesartan cilexetil plus 12.5 mg HCTZ led to a significant decrease in blood pressure, but only the last titration step guaranteed that the target blood pressure below 140/90 mmHg was achieved.

Disclosure

This study was funded and coordinated by Takeda Pharma GmbH, Aachen, Germany, with study management support from ClinResearch GmbH. The sponsor was involved in the study design and the analysis of data. Professor Baumgart received fees from Takeda Pharma for data interpretation and the final manuscript. Dr Naudts received fees from Takeda Pharma for his role as co-ordinating investigator.

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