TELBLOK-H
Telmisartan/Hydrochlorothiazide combination

Hypertension is best managed by maintaining blood pressure below 140/90 mmHg.Individuals with persistent resting diastolic blood pressure (DBP) > 90 mmHg and or systolic blood pressure (SBP) > 140 mmHg are at increased risk of cardiovascular morbidity and mortality.It has been estimated that a 5-6 mmHg reduction in DBP and 10 mmHg reduction in systolic BP lowers the risk of stroke by approximately 33% and of coronary events by approximately 17%.

Blood pressure lowering effect may be enhanced when two classes of antihypertensive agents are coadministered.To achieve the recommended blood pressure targets, it is now acknowledged that many patients require a combination of antihypertensive agents.

The combination of an ARB and a low dose of thiazide diuretic increases the antihypertensive efficacy, but not at the expense of tolerability, compared with the individual components administered alone.

Hydrochlorothiazide belongs to thiazide group of diuretics.Thiazide diuretics inhibit the Na^+-Cl^- transport in distal convoluted tubule and therefore increase Na^+ and Cl^- excretion.

Thiazide diuretics are widely used for the treatment of hypertension, either alone or in combination with other antihypertensive drugs.Thiazide diuretics are inexpensive, as efficacious as other classes of antihypertensive agents, and well tolerated.Thiazides can be administered once daily and do not require dose titration. Moreover, thiazides have additive or synergistic effects when combined with other classes of antihypertensive agents.

Rationale of Telmisartan and Hydrochlorothiazide combination

- **Complementry mechanism of action**

  1.Reduction in peripheral resistence with ARB
  2.Reduction of fluid volume with Diuretics

- **ARBs counteract reactive increase in blood pressure related to diuretic induced renin secretion**

- **ARBs ameliorates diuretic induced potassium depletion**

- **Well tolerated; fewer metabolic disturbances**

- **No significant variation in pharmacokinetic parameters of telmisartan in presence of hydrochlorothiazide**

Combination of telmisartan with hydrochlorothiazide was found to be more effective than each agent alone in lowering blood pressure.Indeed , combining telmisartan with hydrochlorothiazide enhances the antihypertensive efficacy of telmisartan in patients not adequately controlled with telmisartan alone.

Study 1

Comparison of a Fixed-Dose Combination of 40 mg Telmisartan Plus 12.5 mg Hydrochlorothiazide With 40 mg Telmisartan in the Control of Mild to Moderate Hypertension. (19)

Objective: To investigate whether a fixed-dose combination of 40 mg of the angiotensin II antagonist telmisartan plus 12.5 mg of the diuretic hydrochlorothiazide (HCTZ) was superior to 40 mg telmisartan in patients with mild to moderate hypertension who failed to respond adequately to 40 mg telmisartan monotherapy.

Methods: Nonresponders (n = 327) were double blind and randomized to 40 mg telmisartan + 12.5 mg HCTZ (n = 160) or 40 mg telmisartan (n = 167).

Results: After 8 weeks of treatment, 40 mg telmisartan + 12.5 mg HCTZ lowered diastolic blood pressure (DBP) by an additional 3.5 mm Hg (P < .01) and systolic blood pressure (SBP) by 7.4 mm Hg (P < .01) compared with 40 mg telmisartan. Most of the additional effect of the combination was seen after 4 weeks of treatment. At week 8, blood pressure was normalized (SBP <140 mm Hg and DBP <90 mm Hg) in 51.6% of patients on 40 mg telmisartan + 12.5 mg HCTZ compared with 23.5% on 40 mg telmisartan (P < .05). The combination of 40 mg telmisartan + 12.5 mg HCTZ normalized DBP in 64.8% of patients, whereas 40 mg telmisartan normalized DBP in 40.1% (P < .05). SBP decreased by >=10 mm Hg from baseline in 63.5% of patients receiving the fixed-dose combination compared with 42.6% of those receiving 40 mg telmisartan (P < .05). Both treatments were well tolerated.

Conclusion: fixed-dose combination of 40 mg telmisartan + 12.5 mg HCTZ is clinically and statistically superior to 40 mg telmisartan in patients with mild to moderate hypertension failing to respond to 40 mg telmisartan alone.

Study 2

Telmisartan/Hydrochlorothiazide in Comparison with Losartan/Hydrochlorothiazide in Managing Patients with Mild-to-Moderate Hypertension(20)

Objective: To evaluate the antihypertensive efficacies of fixed-dose combinations of angiotensin II receptor blockers with hydrochlorothiazide (HCTZ) 12.5 mg

Methods: a multicenter, randomized, prospective, open-label, blinded-endpoint study was performed in 805 patients with mild-to-moderate hypertension randomized to once-daily treatment with telmisartan 40 mg plus HCTZ (T40/H12.5), losartan 50 mg plus HCTZ (L50/H12.5), or telmisartan 80 mg plus HCTZ (T80/H12.5), with the primary objective of comparing T40/H12.5 with L50/H12.5 and evaluating the additional response of T80/H12.5. Efficacy was assessed by ambulatory blood pressure monitoring (ABPM), clinic seated cuff sphygmomanometry and calculated responder rates after 6 weeks' active treatment. The primary endpoint was reduction from baseline in the last 6-h mean (relative to dosing) diastolic blood pressure (DBP) measured using 24-h ABPM. **Results:**Compared with the L50/H12.5 group, the mean reductions in the last 6-h mean DBP for the T40/H12.5 and T80/H12.5 groups were significantly greater: -2.0 mmHg (p=0.0031) and -2.8 mmHg (p=0.0003), respectively.

Conclusion: T40/H12.5 provided clinically and statistically significantly superior blood pressure reductions compared with L50/H12.5 during the last 6 h of the 24-h dosing interval.

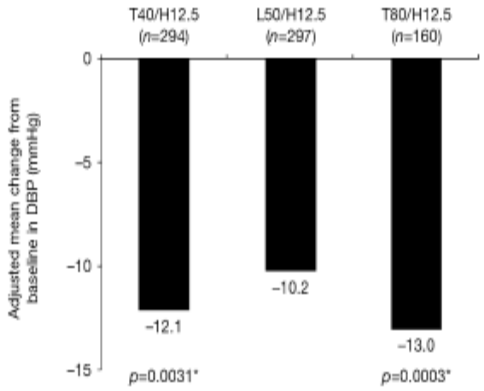

Fig. 1. *Adjusted mean reductions from baseline in the last 6-h (relative to dosing) mean DBP with T40/H12.5, L50/H12.5 and T80/H12.5. *Compared with L50/H12.5.*

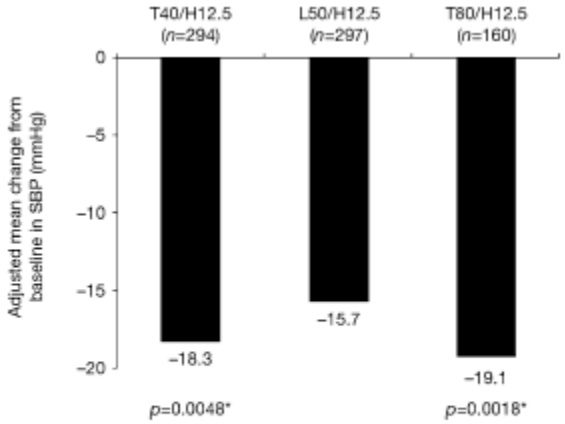

Fig. 2. *Adjusted mean reductions from baseline in the last 6-h (relative to dosing) mean SBP with T40/H12.5, L50/H12.5 and T80/H12.5. *Compared with L50/H12.5.*

Study 3

Efficacy and tolerability of a fixed-dose combination of telmisartan plus hydrochlorothiazide in patients uncontrolled with telmisartan monotherapy(21)

Objective: The antihypertensive effects of a telmisartan 80 mg˜hydrochlorothiazide (HCTZ) 12.5 mg fixed-dose combination and telmisartan 80 mg monotherapy were compared in patients with a history of mild-to-moderate essential hypertension and inadequate BP control (DBP >90 mm Hg) following 8 weeks of telmisartan monotherapy.

Methods: At the end of 8 weeks, 491 patients (62.9% men; mean age 55.3 years) whose DBP was >90 mm Hg were double-blind randomized to once-daily telmisartan 80 mg˜HCTZ 12.5 mg (*n* = 246) or telmisartan 80 mg (*n* = 245). Trough (24 h post-dose) clinic BP was measured after 4 and 8 weeks of double-blind therapy.

Results: At the end of double-blind treatment, patients receiving telmisartan 80 mg˜HCTZ 12.5 mg had significant additional decrements in clinic SBP˜DBP over telmisartan 80 mg of -5.7˜3.1 mm Hg ($P < 0.01$). The proportion of patients with normalised BP (SBP <140 mm Hg *and* DBP <90 mm Hg) was significantly greater in the telmisartan 80 mg˜HCTZ 12.5 mg group than the telmisartan 80 mg group (41.5% *vs* 26.1%; $P < 0.05$). Both treatments were well tolerated.

Conclusion: Telmisartan 80 mg˜HCTZ 12.5 mg fixed-dose combination confers significant additional BP reductions compared with continuation of telmisartan monotherapy in non-responders.

Telmisartan with hydrochlorothiazide **(Telblok-H)** is indicated in

- Moderate to severe hypertension
- Patients not controlled with monotherapy

Dosage : Telblok-H tablet contains telmisartan 40mg with hydrochlorothiazide 12.5 mg for once daily administration.

Clinical trials with telmisartan :

The Telmisartan versus Ramipril in renal ENdothelium DYsfunction (**TRENDY**) trial examined endothelial function of the renal vasculature as a therapeutic

target in patients with hypertension and type 2 diabetes, but without albuminuria. The rationale was that blockade of the renin-angiotensin system (RAS) is cardio- and renoprotective at later stages of the disease, but the impact of blockade of the RAS at earlier stages of disease is unknown. The results of TRENDY indicate that the endothelial function, as assessed by basal nitric oxide activity, can be improved after RAS blockade. These data complement the results of the Diabetics Exposed to Telmisartan And enalaprIL (DETAIL) trial, which demonstrated that telmisartan and enalapril similarly decelerate the progression of overt diabetic nephropathy.(22)

AMADEO

The Efficacy of Telmisartan Compared With Losartan in Reducing Proteinuria in Hypertensive Type 2 Diabetic Patients With Overt Nephropathy (AMADEO) study results showed that telmisartan reduced creatinine and BP levels after one year of treatment compared with losartan.

Researchers enrolled 860 patients with hypertension (BP >130 mm Hg/ 80 mm Hg) and overt nephropathy defined as proteinuria (spot urine $\geq$700 mg/g creatinine), serum creatinine $\leq$3 mg/dL in women and $\leq$3.2 mg/dL in men. After a run-in period, they randomly assigned 419 patients to 40 mg of telmisartan and 441 patients to 50 mg of losartan for two weeks, and then titrated the doses to 80 mg of telmisartan and 100 mg of losartan, for 50 weeks.

The average age of the patients in both arms was 60. Serum creatinine was 1.54 in the telmisartan group and 1.55 in the losartan group.

The primary endpoint was change from baseline in morning spot urinary protein creatinine; the telmisartan group was superior to losartan (0.71; 95% CI, 0.66-0.77 vs. 0.80; 95% CI, 0.74-0.87). No significant BP reductions were noted between the two medications.

"Telmisartan provides greater reduction in proteinuria over losartan,"

-The Ongoing Telmisartan Clinical trial Programme include over 54000 patients.

The PROTECTION programme

(Programme of research to show Telmisartan End-organ protection)

The objective is to assess the benefits of the drug in patients at high risk of renal,cardiac and vascular damage.It involves more than 6500 patients in more than 30 countries.This programme comprises 10 trials comparing telmisartan with ARBs, ACE inhibitors and CCBs in patients at risk of target organ damage or with renal disease. 5 studies will evaluate the effects of telmisartan on early morning bloodpressure BP control.3 of them will examine the effects of a fixed dose combination of telmisartan and hydrochlorothiazide in patients with mild to moderate hypertension, and in hard to treat,at risk populations such as patients with diabetes,obesity and elderly with isolated systolic hypertension.

PRoFESS (Prevention Regimen For Effectively avoiding Second Strokes)

The world's largest secondary stroke prevention trial

- 15,000 patients with recent ischaemic stroke
  - 32 countries, 600 study centres
- Two primary analyses:
  - Telmisartan added to standard antiplatelet therapy versus standard antiplatelet therapy alone
  - ER-DP + ASA compared with Clopidogrel
- Treatment period up to 4 years
- Primary outcome is time to recurrent stroke (target is 2,280 strokes)

ONTARGET/TRANSCEND

(ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial / Telmisartan Randomized Assessment study in ACE-I Intolerant subjects with cardiovascular disease)

Largest ARB cardiovascular protection trial ever undertaken

- 31000 patients (aged ≥55 years) over 5.5 years
- Compares telmisartan, ramipril and the combination
- Parallel TRANSCEND trial(5000 patients) compares telmisartan with placebo in ACE-inhibitor intolerant patients
- Patients at high risk of cardiovascular events, with history of
  - coronary artery disease
  - peripheral vascular disease
  - stroke or recent ischaemic attack

- diabetes mellitus type 1 or 2 with target-organ damage

► Primary endpoint is a composite of cardiovascular death, stroke, acute myocardial infarction and hospitalization for congestive heart failure

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