Anti-albuminuric efficacy of a combination of angiotensin converting enzyme inhibitor & angiotensin receptor blocker in type 1 DM with nephropathy


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Background & objective: The efficacy of the combination of angiotensin receptor blockers (ARBs) and angiotensin converting enzyme (ACE) inhibitors in patients of type 1 diabetes mellitus (DM) with nephropathy is debatable. The antialbuminuric efficacy of dual blockade in patients of type 1 DM with micro- or macroabuminuria were evaluated.

Methods: In this open label observational study 30 patients (20 male 10 female) with type 1 DM were included who were initially treated with telmisartan 80 mg for eight weeks followed by addition of ramipril 10 mg for a further eight weeks. Albuminuria reduction was studied at the end of each phase.

Results: Therapy with telmisartan for 8 wk resulted in a 39 per cent ($P<0.01$) reduction in albumin excretion rate (AER). Combination therapy with telmisartan and ramipril produced a further reduction in AER of 33.4 per cent ($P<0.01$), amounting to a total AER reduction of 59 per cent ($P<0.001$). Dual blockade was more effective in the group of macroalbuminuric as compared to microalbuminuric subjects ($P<0.05$). Telmisartan produced a significant reduction in SBP ($P<0.05$). The addition of ramipril produced a further reduction in BP, the total reduction being 10.3 in SBP and 7.2 mmHg in DBP ($P<0.001$ for both). There was an increase in mean serum potassium of 0.39 mmol/l ($P<0.01$) from baseline at the end of the study period and two patients had hyperkalemia > 5.5 mmol/l with dual blockade.

Interpretation & conclusion: Dual blockade with ramipril enhanced the antialbuminuric efficacy of telmisartan and further reduced blood pressure. The effect of dual blockade was more pronounced in the macroalbuminuric subjects and it was well tolerated. However, careful monitoring of serum potassium is required.

Key words ACE inhibitors - ARBs - nephropathy - type 1 diabetes mellitus
both systemic and intraglomerular hypertension, hyperglycaemia and genetic predisposition².

Current recommendations by the American Diabetes Association (ADA) support the use of angiotensin converting enzyme (ACE) inhibitors in type 1 diabetes with micro- or macroalbuminuria, and consider angiotensin receptor blockers (ARBs) an alternative, if ACE inhibitors are not tolerated. This is in contrast to type 2 diabetes with microalbuminuria where ARBs and ACE inhibitors are considered equivalent, and in type 2 diabetes with proteinuria and or renal insufficiency, ARBs are the drug of choice¹. Several studies are available regarding the use of ARBs in type 2 diabetes²⁴⁻⁶. However, literature is scanty in type 1 DM pertaining to the use of ARBs. Only few studies, all from a single center, are available on the efficacy of ARBs use in type 1 DM with macroalbuminuria⁷⁻⁸.

ACE inhibitors and ARBs interrupt the renin angiotensin aldosterone system (RAAS) at different levels, and the combination of these classes of drugs may have an additive effect on albumin excretion and renoprotection. A recent meta-analysis of studies in diabetic nephropathy concluded that dual blockade was more efficacious for reduction of albuminuria in both type 1 and type 2 diabetes, but the meta-analysis included only three studies in type 1 DM patients⁹. However, dual blockade has come into disrepute after the recent Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) trial¹⁰ which has shown that dual blockade is more efficacious in BP reduction compared to single agent, but dual blockade was associated with more renal dysfunction with some requiring haemodialysis. Therefore, we planned to evaluate the efficacy of dual blockade with both ACE inhibitors and ARB at optimal doses in patients with type 1 DM and nephropathy.

### Material & Methods

**Screening and recruitment:** The present open label observational study (CTR no. NCT00738660) was performed in 58 consecutive patients with type 1 DM with nephropathy attending the Endocrinology Clinic of Postgraduate Institute of Medical Education & Research (PGIMER) Chandigarh, between January 2007 and January 2008, of which 30 completed the study (Fig. 1). Ethical approval for the study protocol was obtained from the institutional review board. The inclusion criteria were: age >14 yr; type 1 diabetes (DM diagnosed by ADA criteria with history of diabetic ketoacidosis), HbA1c <7.5 per cent and albuminuria defined by albumin excretion rate (AER) >20µg/min in two timed overnight urine samples. The exclusion criteria were: patients with serum creatinine of more than 3 mg/dl at baseline, hyperkalemia >5.5 mmol/l, active urinary sediment or urinary tract infection (UTI), uncontrolled hypertension or congestive cardiac failure, suspected or proven non-diabetic renal disease. Details of the study population are enumerated in the Table. There was an initial six week run-in period during which treatment was optimized as per protocol (Fig 1).

At the end of the run in period all patients with target glycaemic control (HbA1c <7.5%) underwent screening for microalbuminuria in two successive overnight urine samples of nine hours duration. Microalbuminuria was defined as an AER between 20-199 µg/min and macroalbuminuria defined as an AER >200 µg/min¹¹. Those found to have an AER ≥20 µg/min in both urine samples were included in the study, if only one sample was positive for microalbuminuria, the test was repeated on a subsequent day and patient was included only if two samples showed an AER>20µg/ min. Since the range of urine albumin assay was 10-150 mg/l, those samples with dipstick positive proteinuria were analysed for protein content using Technicon R500 autoanalyser (Bayer Diagnostics, Germany). The urine albumin content was estimated in the same aliquot after appropriate dilution, the degree of dilution was guided by the protein content of urine.

### Table. Clinical and biochemical profile of study population

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n=30)</th>
<th>8th week Telmisartan (n=30)</th>
<th>16th week Dual blockade (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical SBP (mmHg)</strong></td>
<td>123.63 ± 9.2</td>
<td>119.63 ± 10.83</td>
<td>113.3 ± 9.41***</td>
</tr>
<tr>
<td><strong>Clinic DBP (mmHg)</strong></td>
<td>75.87 ± 7.39</td>
<td>74.5 ± 8.15</td>
<td>68.57 ± 6.79***</td>
</tr>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td>6.42 ± 0.57</td>
<td>-</td>
<td>6.03 ± 0.67*</td>
</tr>
<tr>
<td><strong>Creatinine (mg/dl)</strong></td>
<td>0.82 ± 0.36</td>
<td>0.884 ± 0.33</td>
<td>0.881 ± 0.79**</td>
</tr>
<tr>
<td><strong>GFR (ml/min)</strong></td>
<td>123.67 ± 41.41</td>
<td>110.62 ± 3.6</td>
<td>115.12 ± 41.48</td>
</tr>
<tr>
<td><strong>Potassium (mmol/l)</strong></td>
<td>4.38 ± 0.45</td>
<td>4.5 ± 0.508</td>
<td>4.77 ± 0.591**</td>
</tr>
<tr>
<td><strong>LDL cholesterol (mg/dl)</strong></td>
<td>103.83 ± 31.54</td>
<td>87.15 ± 32.31</td>
<td>83.46 ± 29.01**</td>
</tr>
</tbody>
</table>

Values represented as mean (SD)

SBP, systolic blood pressure, DBP, diastolic blood pressure, GFR, glomerular filtration rate

*P <0.05, **P<0.01, ***P<0.001 compared to baseline
samples. Albuminuria was estimated by immunoturbidimetry Hemocue albumin system (Angelholm AD, Sweden), inter- and intra-assay coefficients of variation were less than 5 per cent. During subsequent evaluations at the end of 8 weeks and at the end of 16 weeks the mean albumin excretion rate from two successive overnight urine samples was taken as the mean. Urine creatinine concentration was measured in all the timed samples by Jaffes method\(^\text{12}\) using Technicon R500 autoanalyser. Serum creatinine and lipid profile were measured by Roche autoanalyser and HbA1c was measured by colorimetric method\(^\text{13}\), glomerular filtration rate (GFR) was estimated using the modified diet in renal disease (MDRD) formula\(^\text{14}\).

Clinical protocol: All patients recruited into the study underwent a detailed physical examination including for other diabetic complications. At baseline and at each visit, blood pressure was measured with an appropriate sized cuff in right arm with the patient seated and after 15 min of rest. Three readings were taken 5 min apart and the mean of these readings was taken as the clinic BP.

The study consisted of two phases. In the first phase, telmisartan was started at a dose of 40 mg per day and after 2 wk up-titrated to 80 mg per day to be taken between 0800-1000 h which was continued for 6 more weeks, and at the end of 8 wk urinary albumin was done. Immediately following the completion of the first phase assessments, ramipril was added at a dose of 5 mg per day and after 2 wk up-titrated to 10 mg per day to be taken between 1200-1400 h and was continued for 6 more weeks. At the end of the second phase at 16 weeks urine albumin was measured again.

At each office visit patients were enquired regarding specific side effect of drugs. Patients were withdrawn from study if they developed any severe adverse events including estimated GFR decreased by $\geq 50$ per cent and/or serum potassium $>5.5$ mmol/l. (Fig. 2).

Statistical analysis: Sample size calculated by Epi Info version 8 was 30 to achieve a power of 80 per cent for detecting a difference of 30 per cent in AER with an $\alpha$ of 0.05. Statistical analysis was carried out using statistical...
program for the Social Sciences (Release 10.01, PC Windows; SPSS Inc., Chicago IL). Comparison of variables for significance was done by Wilcoxon’s signed rank test (for data with skewed distribution) and paired samples “t test” (for data approximating normal distributions). Normality of distribution was assessed using skewness. Univariate correlations were done by the Spearman’s method. Comparison between groups was done with the Mann-Whitney U test.

**Results**

**Baseline characteristics of study population:** Thirty patients (10 females) completed the study. The mean age of patients was 26.1 ± 9.69 yr and mean duration of diabetes was 12.4 ± 8.1 yr. The mean body mass index was 19.73 ± 2.28 kg/m² and the HbA1c at baseline was 6.4 ± 0.6 per cent. The mean SBP and DBP were 123.6 ± 9.2 and 75.9 ± 7.4 mmHg, respectively (Table). Twenty patients were hypertensive by the ADA criteria. Ten patients had macroalbuminuria and 20 had microalbuminuria. Two patients had eGFR less than 60 ml/min at baseline. Twenty three of these patients had never received ACE inhibitors/ARBs prior to the study. Eighteen (60%) patients had neuropathy, 16 (53.3%) had retinopathy which was seen more in macroalbuminurics. None had macrovascular complications.

**Effect on urine albumin excretion:** AER declined by 39 per cent at 8 wk (from baseline value of 441.37 ± 137.83 to 269.85 ± 44.9 µg/min; P<0.01) with telmisartan. Dual blockade with ramipril and telmisartan produced a further reduction in AER of 33.4 per cent (from 269.85 ± 44.9 at 8 wk to 167.59 ± 44.9 µg/min at 16 wk; P<0.01), with a total AER reduction of 59 per cent from baseline value (P<0.001) at the end of the study. For the macroalbuminuric subjects the degree of reduction in AER was 39.8 per cent (from baseline value of 1168.28 ± 308.54 to 702.65 ± 183.65 µg/min; P<0.05) with telmisartan, further reduction with dual blockade was 40.3 per cent (from 702.65 ±183.65 at 8 wk to 419.27 ± 92.52 µg/min at 16 wk; P<0.05) and a total reduction of 64.1 per cent (P<0.01). For the microalbuminuric subjects the degree of reduction in AER was 31 per cent (from baseline value of 77.92 ± 10.39 to 53.54 ± 12.49 µg/min; P<0.05) with telmisartan, further reduction with dual blockade was 22 per cent (from 53.54 ± 12.49 at 8 wk to 41.75 ± 11.87 µg/min at 16 wk; P=0.19) and a total reduction of 46.2 per cent (P<0.05). Dual blockade was more effective in the group of macroalbuminuric as compared to microalbuminuric subjects (64.1 vs 46.2% reduction; P<0.05 (Fig. 3).

There was a significant reduction in SBP by 10.3 mm Hg (P<0.001) which was accounted by 4 mmHg fall with telmisartan (P<0.05) and further 6.3 mmHg reduction by ramipril (P<0.001). DBP also showed a significant reduction of 7.2 mmHg from baseline (P<0.01) in which dual blockade resulted in a fall of 5.9 mm Hg (P<0.001), while telmisartan alone led to non significant fall of 1.3 mm Hg. All the patients tolerated therapy well except two hypertensive patients who complained of postural giddiness at the initiation of therapy and later tolerated well. No episode of hypotension was recorded.

Therapy with telmisartan produced a significant fall in estimated GFR of 13 ml/min (10.5%; P<0.05) after initial 8 wk. Over the next 8 wk despite addition of ramipril, GFR remained stable with a net decrease of 8 ml/min (6.9%) at the end of the study. The mean creatinine rose significantly by 7.4 per cent at the end of the study. The mean creatinine rose significantly by 7.4 per cent (P<0.01) from 0.82 mg/dl at baseline to 0.88 mg/dl at the end of 16 weeks. Potassium rose significantly with dual blockade (8.7%, P<0.01), whereas it was non significant with telmisartan alone (2.7%). Two patients had a serum potassium >5.5 mmol/l towards the end of the study and were managed with potassium binding resin.

In univariate analysis the reduction in albuminuria with telmisartan correlated with reduction in clinic SBP but not DBP at the end of first phase (r= 0.664, P=0.013). However, no significant correlation either with systolic or with diastolic blood pressure was obtained with dual blockade at the end of the study.

**Discussion**

Our results showed significant reduction in urinary albumin excretion with dual blockade in optimal doses...
in patients with type 1 DM, however, the effect was more pronounced in macroalbuminuric subjects as compared to microalbuminuric subjects. It was accompanied by a significant reduction in both systolic as well as diastolic BP and correlated with reduction in SBP. Dual blockade therapy was well tolerated by majority of patients. Our results partly may also be attributed to good glycaemic control and concurrent statin therapy, which was lacking in previous studies7,8,15-17.

Angiotensin II and aldosterone are generated through multiple pathways and non ACE pathways contribute to 70 per cent of angiotensin II production. Hence, ACE inhibitors do not block RAAS completely9. ACE inhibitors but not ARBs prolong the half-life of bradykinin, a potent renoprotective vasodiator9 which may also contribute to additional reduction in intraglomerular hypertension. However, on prolonged treatment with ACE inhibitors alone ACE escape is seen resulting in increased levels of angiotensin II leading to decreased antialbuminuric and antihypertensive efficacy18,19. In a dual blockade strategy effects of ACE inhibitors and ARBs complement each other and ACE escape can be overcome.

There are limited data for dual blockade in type 1 DM with nephropathy9,15-17 which show that dual blockade in optimal doses results in an additional 36-46 per cent reduction in albuminuria above that seen with monotherapy with either agent alone. Dual blockade was also found to be more effective in patients with a higher albuminuria at baseline15,16. Our study also supported both these findings.

The daily doses of telmisartan and ramipril used in our study were optimal10,20. Literature suggests that dual blockade with submaximal doses of medications may be as effective as full doses with fewer side effects21, however recent studies have demonstrated that use of higher doses of these agents was superior to lower doses for reducing proteinuria11,22. Our study which used optimal doses of both medications showed a good short term antialbuminuric efficacy similar to previous studies2,17,19. However, long term studies are needed to confirm the concern that advantage of dual blockade disappears with their prolonged use21.

ACE inhibitors and ARBs have modest antihypertensive efficacy in diabetes and lead to mean reduction of 5.2 (2.1-8.4) mmHg in SBP and 5.3 (2.2-8.4) mmHg in DBP9. Our study showed reduction of 10.3 and 7.2 mmHg in systolic and diastolic blood pressure respectively, probably due to the younger age of our patients and shorter duration as the effects of treatment tend to wane with time.

Patients in our study tolerated the therapy well in contrast to the ONTARGET study10. This may be because the patients in our study were younger (26.1 yr) than in the ONTARGET study (66.4 yr) and had lesser co-morbidities. Despite being normotensive, our patients exhibited a good antialbuminuric response with dual blockade, which may be useful in long run in populations like ours.

Our study showed that reduction in albuminuria correlated significantly with a fall in SBP with telmisartan monotherapy similar to a study23 showing positive correlation between fall in BP and reduction in urine albumin excretion. This finding differs from some previous studies which showed reduction in albumin excretion to be independent of fall in BP7.

The net GFR reduction was 6.5 per cent in our study with a sharp fall during the first 8 wk followed by stabilization, this pattern of change in GFR has been well documented in previous studies6. Dual blockade with ramipril and telmisartan was associated with a significant increase in potassium, similar to previous studies where dual blockade was used4,7,17.

In conclusion, dual blockade with telmisartan and ramipril is particularly effective in patients with macroalbuminuria and had an additive effect on BP reduction. Dual blockade is safe and well tolerated, however, regular monitoring of serum potassium is required. Long term studies are required to substantiate these observations.

References


