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Losartan
In Diabetic Nephropathy

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Contents

Abstract

▲ Losartan is an orally active, selective, nonpeptide, angiotensin II AT_1 receptor antagonist.

▲ Losartan 50 or 100 mg/day was significantly more effective than placebo in reducing the incidence of a doubling of serum creatinine, end-stage renal disease (ESRD) or death (43.5% vs 47.1%, p = 0.02) in a pivotal, well designed trial (Reduction of Endpoints in Non insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan [RENAAL] study) in 1513 patients with type 2 diabetes mellitus and proteinuria.

▲ Losartan also significantly reduced the incidence of doubling of serum creatinine level (p = 0.006), ESRD (p = 0.002), ESRD or death (p = 0.01) and doubling of serum creatinine and ESRD (p = 0.01) compared with placebo in the RENAAL trial. There were similar incidences of overall mortality and morbidity and mortality from cardiovascular causes between treatment groups.

▲ In addition, data from several nonblind and double-blind studies indicates that losartan effectively reduces the mean albumin excretion rate. Two double-blind studies show that losartan has similar effects to enalapril on kidney function.

▲ Data from 4058 patients (3300 with essential hypertension) who have received losartan (10–150 mg/day) in clinical trials indicate it is well tolerated. In the RENAAL study 17.2% and 21.7% of losartan and placebo recipients discontinued treatment because of adverse events, but causality was not determined.

Features and Properties of Losartan (Cozaar®[1])		
New Indication		
For use in delaying the progression of renal disease in patients with type 2 diabetes mellitus with proteinuria		
Mechanism of action		
An orally active, nonpeptide, selective angiotensin subtype 1 receptor antagonist		
Pharmacokinetic profile (after a single 50mg dose)		
	E3174	**Losartan**
Peak plasma concentration (C_{max})	0.25 μg/L	0.29 μg/L
Time to achieve C_{max}	4.1h	1h
Volume of distribution	12L	34L
Terminal elimination half-life	6.4h	2.1h
Renal clearance	1.6 L/h	4.3 L/h
Adverse events		
Most frequent (causality not determined)		Upper respiratory tract infection, dizziness, cough

1 Use of tradenames is for product identification purposes only and does not imply endorsement.

By 2010, approximately 221 million people worldwide are expected to have diabetes mellitus.[1] Around 20–30% of patients with the disease develop diabetic nephropathy, a progressive microvascular complication of diabetes that can lead to severe renal disease and eventual renal failure.[2] In the US, for example, diabetes is the most common cause of end-stage renal disease (ESRD) accounting for approximately 40% of new cases of ESRD.[2] The incidence of diabetic nephropathy has increased alarmingly in the last 30 years, mainly as a consequence of the worldwide increase in patients with the more common type 2 form of diabetes; these patients now constitute more than 50% of patients with diabetes who start dialysis treatment.[2,3]

Hypertension, poor glycaemic control and hyperlipidaemia are among the risk factors for the development of diabetic nephropathy and there is a particularly strong relationship between hypertension and ESRD.[2] Several large clinical trials have shown that blockade of the renin-angiotensin system with ACE inhibitors provides a renoprotective effect in patients with type 1 diabetes and diabetic nephropathy.[4-6] In addition, recent studies have shown similar beneficial effects with angiotensin II receptor antagonists in patients with type 2 disease.[7-9] The renoprotective effects of both these groups are independent of their antihypertensive effects.

Losartan (Cozaar®) is an angiotensin II subtype 1 (AT_1) receptor antagonist which was recently approved by the US FDA for use in delaying the progression of renal disease in patients with type 2 diabetes with proteinuria.[10] The purpose of this review is to discuss the use of losartan in this indication. Losartan is approved worldwide for use in hypertension and reviews in this indication are available elsewhere.[11,12]

1. Pharmacodynamic Profile

The pharmacodynamic properties of losartan have been previously reviewed[11,12] and a brief overview of the data is provided below together with any recent relevant data.

- Losartan is an orally active, selective nonpeptide AT_1 receptor antagonist. The active parent, losartan, is converted into an active metabolite E3174 (see section 2), which is 10–40 times more potent at blocking the AT_1 receptor than the parent compound.[13]
- In brief, losartan dose-dependently inhibits the pressor response to exogenous angiotensin II by up to 95%, increases plasma renin and angiotensin levels, has inconsistent effects on aldosterone levels and has no effect on plasma bradykinin or C-reactive protein levels.[12,14] The drug also has no effect on insulin sensitivity or haematological or haemorheological parameters, but it does have a uricosuric effect and improves baroreceptor function.[12]
- Losartan decreases left ventricular mass index in patients with hypertension, decreases systemic vascular resistance, pulmonary capillary wedge pressure, left ventricular end-diastolic and end-systolic volume in patients with heart failure and increases cardiac index in this latter group of patients. Losartan has no negative effects on QT dispersion.[12] Losartan preserves renal function and decreases proteinuria (see section 3).
- Taken together, data from two small double-blind, placebo-controlled crossover studies indicate that losartan 50 mg/day for 4 weeks improves conduit vessel and forearm endothelial function in patients with type 2 diabetes.[15,16] In one study ($n = 9$), losartan decreased acetylcholine (10–40 μg/min), induced forearm vascular resistance ($p < 0.05$) and increased forearm blood ratio (flow in infused to noninfused arm) [$p < 0.01$].[15] In a further study ($n = 12$), losartan improved nitrous oxide-mediated dilation in the conduit vessels of patients with type 2 disease.[16]
- In a randomised, double-blind, placebo-controlled crossover study in 16 volunteers, losartan 50 mg/day for 7 days significantly reduced hypoglycaemia-induced increases in plasma adrenaline (epinephrine) [6480 vs 8970 pmol/L, $p < 0.001$]

and adrenocorticotropin (21 vs 26 pmol/L, $p < 0.01$) levels compared with placebo.[17]

- The renoprotective effect of losartan in patients with type 2 diabetes may be mediated by a reduction in renal transforming growth factor-β (TGF-β) production.[18,19] In a randomised study in 21 patients with co-existing hypertension and elevated albumin excretion rate (10–200 μg/min), losartan 50 mg/day for 8 weeks reduced urinary TGF-β excretion by 23.2% versus 0% for placebo ($p = 0.04$).[19] In a further study, plasma TGF-β levels were reduced compared with baseline ($p < 0.01$) in seven patients with elevated plasma TGF-β levels (mean 9 μg/L) who received losartan 50–100 mg/day for 8 weeks.[18]

2. Pharmacokinetic Profile

An overview of previously published pharmacokinetic data[12] on losartan and its pharmacologically active carboxylic acid metabolite E3174 is given below supplemented with available data in renal impairment.

- After absorption, the oral bioavailability of losartan is approximately 33%. The peak plasma concentration (C_{max}) of the parent compound and active metabolite after a single 50mg dose is 0.29 and 0.25 μg/L. Time to achieve C_{max} is 1 and 4.1 hours, respectively. Values for plasma protein binding and volume of distribution are 98.7% and 99.8% and 34 and 12L, respectively, for the parent compound and active metabolite. The absorption of losartan is not affected by food, and multiple-dose administration does not alter the pharmacokinetic properties of losartan or E3174.[12]

Losartan undergoes significant first pass metabolism with approximately 14% of the dose converted into the active metabolite, E3174. The terminal elimination half-life ($t_{1/2}$) and renal clearance for losartan and E3174 are 2.1 and 6.4 hours and 4.3 and 1.6 L/h, respectively. Approximately 35% of an oral dose of losartan is excreted in the urine with the remainder excreted in the faeces.[12]

- Losartan is converted to E3174 by cytochrome P450 3A4 which is inhibited by grapefruit juice. In healthy volunteers (n = 9), grapefruit juice significantly increased time to drug appearance in the serum, mean residence time, and $t_{1/2}$ and significantly reduced the area under the plasma concentration-time curve (AUC) of E3174 ($p < 0.05$ in each case).[20]
- In patients with renal impairment or renal failure without diabetes, no clinically significant changes in the pharmacokinetic profile of losartan are observed because the proportion of drug eliminated renally is small. In a nonblind study in 18 patients with renal insufficiency who received losartan 100 mg/day for 7 days, the renal clearance of the drug was 3 and 0.14 L/h in patients with a creatinine clearance of ≥4.5 and 0.6–1.7 L/h, respectively ($p < 0.05$).[21] Corresponding values for E3174 were 0.96 and 0.08 L/h, respectively ($p < 0.05$). The steady-state AUCs were not significantly changed for either losartan or E3174. The $t_{1/2}$ of losartan showed little variation (2.1–3.2h).[21] In a further study in six patients with ESRD (creatinine clearance <0.6 L/h) undergoing haemodialysis, the pharmacokinetics of losartan and E3174 were not affected to a clinically significant level.[22]

3. Therapeutic Trials

The ability of losartan to delay the progression of diabetic nephropathy among patients with type 2 diabetes and proteinuria has been studied in one large pivotal clinical trial (the Reduction of Endpoints in Non insulin dependent diabetes with the Angiotensin II Antagonist Losartan [RENAAL Study][9]) on which the application to the US FDA for this indication was largely based. In addition, many preliminary studies[23-31] have investigated the effect of losartan on kidney function in patients with type 2 diabetes.

The RENAAL Study

Study Design

- The RENAAL study was a double-blind, placebo-controlled, multicentre study in 1513 patients randomised to receive either losartan 50mg once daily or placebo. The dosage of losartan was increased to 100mg once daily after 4 weeks in

patients whose trough systolic blood pressure (BP) was ≥140mm Hg and diastolic BP was ≥90mm Hg.[9]

- Patients were aged between 31 to 70 years with a diagnosis of type 2 diabetes and nephropathy (defined as the presence on two occasions of a ratio of urinary albumin [mg/L] to urinary creatinine [g/L], obtained from a first morning sample, of ≥300 [or a rate of urinary protein excretion of ≥0.5 g/day] and a serum creatinine value of between 115–265 μmol/L, with a lower limit of 133 μmol/L for male patients >60kg).[9] Patients with hypertension continued to take standard antihypertensive therapy (diuretics, calcium channel antagonists, α- or β-blockers etc.) throughout the study except those taking ACE inhibitors or angiotensin II receptor antagonists; these medications were replaced by other standard treatments. At baseline, there were no significant differences between treatment groups in patient demographics (sex, race, medical history) or laboratory parameters.
- The study was designed to be completed 3.5 years after the last patient underwent randomisation, resulting in a mean follow-up time of 4.5 years. However, the study was discontinued early as new evidence became available indicating that ACE inhibitors, which were excluded from the study, may be effective in reducing the incidence of cardiovascular events in patients with renal impairment, including those with diabetes.[9] The study had a mean follow-up of 3.4 years.
- Exclusion criteria included a diagnosis of type 1 diabetes or nondiabetic renal disease including renal artery stenosis, previous myocardial infarction or coronary artery bypass grafting in the previous month, previous cerebrovascular accident or percutaneous transluminal coronary angioplasty within the previous 6 months, previous transient ischaemic attack within the last year, chronic use of NSAIDs or aspirin >325 mg/day, or a history of heart failure before enrolment.[9,32]
- The primary efficacy measure was the incidence of a composite endpoint of the doubling of serum creatinine level (defined as the first serum creatinine level that was twice the baseline value, as confirmed by a second serum creatinine level taken at least 4 weeks after the initial doubling), the presence of ESRD (defined by the need for long-term dialysis or renal transplantation) or death. A composite endpoint of myocardial infraction, stroke, first hospitalisation for heart failure or unstable angina, coronary or peripheral revascularisation, or death from cardiovascular causes was a secondary endpoint. These were assessed according to an intention-to-treat approach. Other secondary endpoints included the progression of renal disease and changes in the level of proteinuria, both assessed by an on-treatment analysis.[9] Analyses of the components of both the primary and secondary composite endpoints were also prespecified.

Study Results

- Losartan was significantly more effective than placebo in reducing the incidence of the primary composite endpoint of a doubling of serum creatinine, ESRD or death (43.5% vs 47.1%, p = 0.02: see figure 1). Compared with placebo, losartan also significantly reduced the incidence of doubling of serum creatinine level (p = 0.006), ESRD (p = 0.002), ESRD or death (p = 0.01) and doubling of serum creatinine and ESRD (p = 0.01) [see figure 1]. Risk reductions were 25%, 28%, 20% and 21%, respectively. There was no significant difference in mortality between the two treatment groups.[9]
- The beneficial effect of losartan on the primary composite endpoint, ESRD and ESRD or death was independent of its antihypertensive effect. Statistical analysis showed the small difference in trough BP between groups had no influence on outcome.[9]
- Incidences of morbidity and mortality from cardiovascular causes were similar between losartan and placebo (32.9% vs 35.2%); however, the occurrence of first hospitalisation with heart failure was significantly lower in losartan than in placebo recipients (11.9% vs 16.7%, p = 0.005).[9]
- An average reduction of 35% in the level of proteinuria (the urinary albumin to creatinine ratio) was seen in losartan recipients compared with a tendency to increase in recipients of placebo (value not reported) [p < 0.001]. In addition,

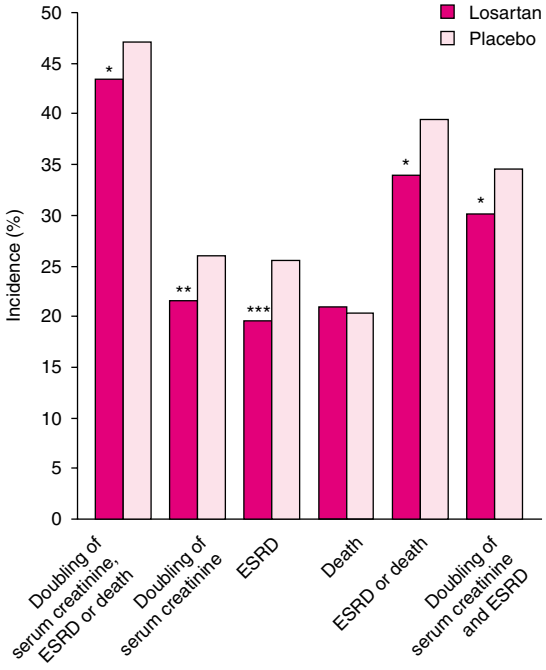

Fig. 1. Efficacy of losartan to delay the progression of diabetic nephropathy in patients with type 2 diabetes mellitus and proteinuria. Results of the Reduction of Endpoints in Non insulin dependent diabetes with the Angiotensin II Antagonist Losartan Study; a randomised, placebo-controlled, multicentre trial in which 1513 patients were randomised to receive losartan 50 to 100 mg/day (n = 751) or placebo (n = 762). Patients were followed-up for a mean of 3.4 years.[9] **ESRD** = end-stage renal disease; * $p \leq 0.02$, ** $p = 0.006$, *** $p = 0.002$ vs placebo.

losartan was significantly more effective than placebo in reducing the rate of decline in renal function as assessed by the reciprocal of the serum creatinine concentration (median slope –0.0056 vs –0.0069 L/mg/year, $p = 0.01$). Similarly, losartan recipients had a significantly lower decline in glomerular filtration rate versus placebo recipients (4.4 vs 5.2 ml/min/1.73m^2 of body-surface area/year, $p = 0.01$).[9]

- In a cost analysis of data from the RENAAL study, (presented as an abstract), healthcare resource utilisation costs associated with ESRD were estimated by combining the number of days each patient experienced ESRD with the cost of ESRD over time.[33] Costing data for ESRD in patients with diabetes were obtained from the US Renal Data System. Total costs were taken as the cost associated with ESRD plus the cost of study therapy. Compared with placebo, losartan was estimated to significantly reduce the number of days with ESRD by 33.6% (actual values not reported) per patient over 3.5 years ($p = 0.004$) resulting in a decrease in cost associated with ESRD of $US5144 per patient ($p = 0.003$). After subtracting the cost of losartan therapy a net saving of $US3522 per patient over 3.5 years was obtained ($p = 0.04$) [year of costing not reported].[33]

Preliminary Studies

- In two randomised, double-blind studies the effects of losartan and enalapril on kidney function were similar. In a 12-week study in patients with hypertension with or without microalbuminuria, recipients of losartan 50 mg/day (n = 47) had similar reductions in the urinary albumin to creatinine ratio (0.33 vs 0.22 mg/mmol [geometric mean]) to recipients of enalapril 20 mg/day (n = 46).[26] In a 1-year multicentre study in 92 patients with early diabetic nephropathy, losartan (mean dose 86.3 mg/day) was as effective as enalapril (mean dose 16 mg/day) in reducing the rate of decline of the glomerular filtration rate (≈9% in both groups after 52 weeks of treatment).[24] Significant reductions in albumin excretion were noted in losartan (64.1 to 41.5 μg/min) and enalapril (73.9 to 33.5 μg/min) recipients ($p < 0.001$ for both groups) after 52 weeks of therapy.
- Losartan was significantly more effective than placebo in reducing the urinary mean albumin excretion rate in a 6-month randomised, double-blind, placebo-controlled study in patients with microalbuminuria (54.5 vs 78.5 μg/min, $p < 0.05$). BP did not change significantly in either group throughout the study.[23]
- In a nonblind, multicentre 8-week study, 90 patients with microalbuminuria were initially given losartan 50 mg/day. After 4 weeks, well controlled patients continued to receive losartan 50 mg/day. The remaining patients were randomised to receive either losartan 100 mg/day or losartan 50

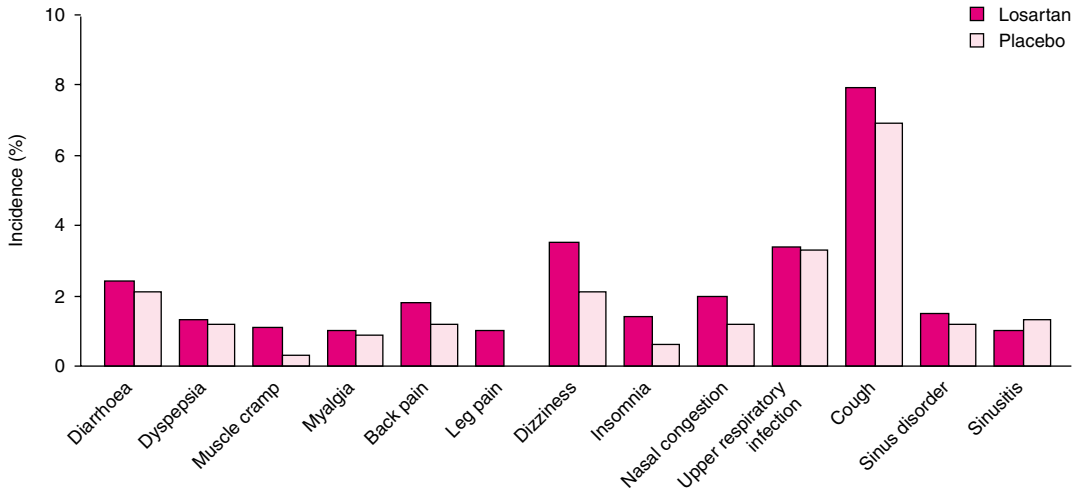

Fig. 2. Adverse events occurring in ≥1% of patients treated with losartan (10–150 mg/day) and more frequently in losartan (n = 1075) than in placebo (n = 334) recipients in four 6- to 12-week placebo-controlled trials. Causality was not determined.[10,13]

mg/day plus hydrochlorothiazide 12.5 mg/day. After 8 weeks of treatment, the albuminuria of losartan 100 mg/day recipients had reduced from 136.3 to 99.7 mg/24h (p = 0.002) compared with reductions of 107.7 to 64.2 mg/24h (p = 0.001) and 109.8 to 83.5 mg/24h (p = 0.006) in recipients of combination therapy and losartan 50 mg/day, respectively (no statistical comparisons between treatment groups were reported). Reductions in systolic and diastolic BP were similar in all treatment groups.[25]

- Data from further preliminary studies, published as abstracts, suggest that losartan reduces proteinuria,[30,31] may reduce albuminuria at least as effectively as lisinopril[28] and the combination of losartan with an ACE inhibitor may reduce microalbuminuria or proteinuria further than monotherapy with either agent in patients with type 2 diabetes and hypertension.[27,29]

4. Tolerability

Data on specific adverse events in patients with type 2 diabetes with proteinuria treated with losartan are very sparse. The following is a brief overview of tolerability data in 4058 patients (3300 with essential hypertension) who have received losartan in clinical trials. More than 1200 patients were treated for >6 months and over 800 were treated for more than 1 year.[10] Causality was not determined.

- In placebo-controlled trials, 2.3% and 3.7% of losartan and placebo recipients discontinued treatment because of adverse events. Corresponding figures in the RENAAL study (described in section 3) were 17.2% and 21.7% but the nature of these events was not described.[9] Figure 2 summarises adverse events occurring in≥1% of patients recieving losartan 10–150 mg/day (n = 1075) and which occurred more frequently than in placebo recipients (n = 334) in four 6- to 12-week trials. The most frequent adverse events in losartan recipients were upper respiratory tract infection (7.9% vs 6.9%), dizziness (3.5% vs 2.1%) and cough (3.4% vs 3.3%). The frequency of adverse events did not appear to be dose-related.[10,13]
- Asthenia/fatigue, oedema/swelling, abdominal pain, chest pain, nausea, headache and pharyngitis have also occurred in >1% of patients taking losartan but were no more frequent than in placebo recipients.[10]
- The incidence of dry cough with losartan was similar to that of placebo or hydrochlorothiazide in

a population that all had cough associated with ACE inhibitor therapy.[10]

- The following adverse events have been reported in post-marketing surveillance of losartan recipients: angioedema, vasculitis, anaphylactic reactions, hepatitis, dry cough, hyperkalaemia and hyponatraemia. Minor increases in blood urea, nitrogen or serum creatinine levels have been observed in <0.1% of patients with hypertension treated with losartan monotherapy.[10] In the RENAAL study, a small proportion of losartan and placebo recipients discontinued therapy because of increased serum levels of creatinine (1.2% and 1.5%) and potassium (0.5% and 1.1%).[9] Occasional elevations of liver enzymes and/or serum bilirubin levels have also been observed.[10]
- Decreases in haemoglobin and haematocrit levels of 0.11 grams percent and 0.09 volume percent have occurred frequently in patients treated with losartan monotherapy but were rarely of clinical importance. However, there have been reports of anaemia developing in losartan recipients undergoing renal dialysis.[10,34]

5. Dosage and Administration

- The usual starting dose in patients with type 2 diabetes and proteinuria is 50mg once daily. The dose may be increased to 100mg once daily based on BP response. A lower starting dose of 25mg once daily should be considered in patients with hepatic impairment.[13] Losartan may be administered with other antihypertensive agents as well as with insulin and other commonly used hypoglycaemic agents.[35] Like other angiotensin II receptor antagonists and ACE inhibitors the drug may cause fetal harm or death, especially during the second and third trimesters and should be discontinued as soon as possible in pregnant women.[13]

6. Losartan: Current Status

Losartan is approved in the US for the treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria (urinary albumin to creatinine ratio ≥300 mg/g) in patients with type 2 diabetes and a history of hypertension. Its use in this indication is supported by the results of the pivotal RENAAL study.

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