Short Report

Rationale for and study design of the sulodexide trials in Type 2 diabetic, hypertensive patients with microalbuminuria or overt nephropathy

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Abstract

Background Patients with Type 2 diabetes and albuminuria are at high risk to progress to end-stage renal disease (ESRD). Although angiotensin receptor blockers confer renoprotection, many diabetic patients still develop overt nephropathy and reach ESRD. Glycosaminoglycans belong to the same family as heparin and heparinoids. Pilot studies with sulodexide, a glycosaminoglycan, have shown that sulodexide can reduce urinary albumin excretion rates in diabetic patients. No hard renal end-point data are available.

Methods Two multicentre, double-masked, randomized placebo controlled trials were designed to study the renoprotective potential of sulodexide. The Sulodexide Microalbuminuria Trial examined the efficacy of sulodexide given over 26 weeks in 1000 patients with Type 2 diabetes, hypertension and microalbuminuria. The Sulodexide Overt Nephropathy Trial examined the efficacy of sulodexide in 2240 patients with Type 2 diabetes, hypertension and proteinuria ≥ 900 mg/24 h.

Results The primary outcome of The Sulodexide Microalbuminuria Trial was (i) conversion to normoalbuminuria and at least a 25% decrease in the urinary albumin creatinine ratio (UACR), or (ii) at least a 50% reduction in UACR. The primary outcome of The Sulodexide Overt Nephropathy Trial was time to a composite end point of doubling of serum creatinine or ESRD.

Conclusions The sulodexide nephropathy programme will document whether therapy with sulodexide confers renal protection in Type 2 diabetes and nephropathy.

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Keywords albuminuria, diabetes, glycosaminoglycans, proteinuria, sulodexide

Abbreviations ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ESRD, end-stage renal disease; GAG, glycosaminoglycan; RAAS, renin–angiotensin–aldosteron system; SeDBP, seated diastolic blood pressure; SeSBP, seated systolic blood pressure; SUN, sulodexide nephropathy; UACR, urinary albumin creatinine ratio

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Background

Epidemiology

The number of people with Type 2 diabetes mellitus is expected to double, reaching 380 million persons worldwide

by 2025 [1]. Diabetes is associated with increased renal and cardiovascular morbidity and mortality.

Approximately 40% of all diabetic patients will develop diabetic nephropathy, which is the most important cause of end-stage renal disease (ESRD) in the USA, Europe and Japan [2,3]. It is anticipated that the prevalence of ESRD will further increase as a result of the growth in the population of patients with Type 2 diabetes, earlier onset of diabetes and the longer life expectancy of diabetic patients. Prevention of nephropathy and delay of ESRD are key management goals in patients with diabetes.

Prevention and intervention for diabetic nephropathy

Patients with diabetes can have normoalbuminuria, micro-albuminuria, overt nephropathy or ESRD. Changes between these stages are currently considered a hallmark of progression (or regression) of disease.

Several trials have recently shown that inhibition of the renin–angiotensin–aldosterone system (RAAS) using either angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) is of value beyond blood pressure reduction in both Type 1 and Type 2 diabetic patients with microalbuminuria and overt nephropathy [4–9].

The Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) and the Irbesartan in Micro-albuminuria (IRMA-2) trial have assessed the value of early intervention [7,8]. These trials showed that treatment with trandolopril or irbesartan reduced the onset of microalbuminuria and overt nephropathy. However, despite RAAS intervention, 6% of the patients developed microalbuminuria in a median follow-up time of 3.6 years in the BENEDICT trial [7] and 5% developed overt nephropathy in 2 years in the IRMA-2 trial [8].

The Captopril in Diabetic Nephropathy trial, The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) and the Irbesartan in Diabetic Nephropathy trial (IDNT) reported a 48%, 16% and 20% relative risk reduction, respectively, in patients with overt nephropathy progressing to ESRD. Despite this important therapeutic gain, the residual risk on optimal treatment is still devastatingly high. Of the patients assigned to the active treatment group, 22% (Captopril trial, mean follow-up 3.0 years), 44% (RENAAL mean follow-up 3.6 years), and 33% (IDNT, mean follow-up 2.6 years) of patients reached the primary composite end point (Table 1).

Post-hoc analysis of the RENAAL as well as the IDNT trial revealed that the albuminuria-reducing effect of losartan and irbesartan explains a substantial part of its renoprotective effect independent of the effect on blood pressure [10,11]. The degree of initial reduction of albuminuria was the most important predictor for renal events in the long term.

Since reduction of albuminuria is correlated linearly with renoprotection and residual albumin excretion determines the renal risk in the long term, additional albuminuria-lowering therapies should be considered.

Effects of glycosaminoglycans in diabetic nephropathy

Preclinical and pilot clinical studies in patients with diabetes have reported that glycosaminoglycans (GAGs) possess the ability to diminish albumin excretion [12,13]. The most widely investigated GAG in diabetic subjects is sulodexide [14–18]. Sulodexide does not have anticoagulant properties when given orally. It bears strong chemical similarities with heparin and low molecular weight heparin. Sulodexide is composed of 80% fast-moving heparan sulphate and 20% dermatan sulphate [19].

Several mechanisms have been described that explain the remodelling effects of sulodexide. Sulodexide given to diabetic rats down-regulates TGF-β expression, restores negatively charged heparan sulphate in the glomerular basement membrane and inhibits heparanase-1 in renal epithelial cells [20,21].

In a pilot study, which included patients with Type 1 or Type 2 diabetes, 4 months of treatment with sulodexide 200 mg/day lowered albumin excretion by 60–70% compared with placebo [22]. The reduction in albumin excretion remained

Table 1 Risk reduction and residual risk on optimal treatment

Study	Primary (composite) end point	Median follow-up time	Risk reduction vs. placebo	Residual risk on optimal treatment (% of patients with primary end point extrapolated to 5 years)
BENEDICT	Time to onset of microalbuminuria	3.6 years	6%†	8%
IRMA-2	Time to onset of diabetic nephropathy	2.0 years	70%	13%
Captopril CSG	Time to doubling of serum creatinine	3.0 years	48%	36%
RENAAL	Time to doubling serum creatinine, ESRD*, death	3.4 years	16%	64%
IDNT	Time to doubling serum creatinine ESRD*, death	2.6 years	20%	63%

*End-stage renal disease (ESRD) is defined as the need for dialysis or renal transplantation.
†Risk reduction vs. verapamil.
CSG, Collaborative Study Group.

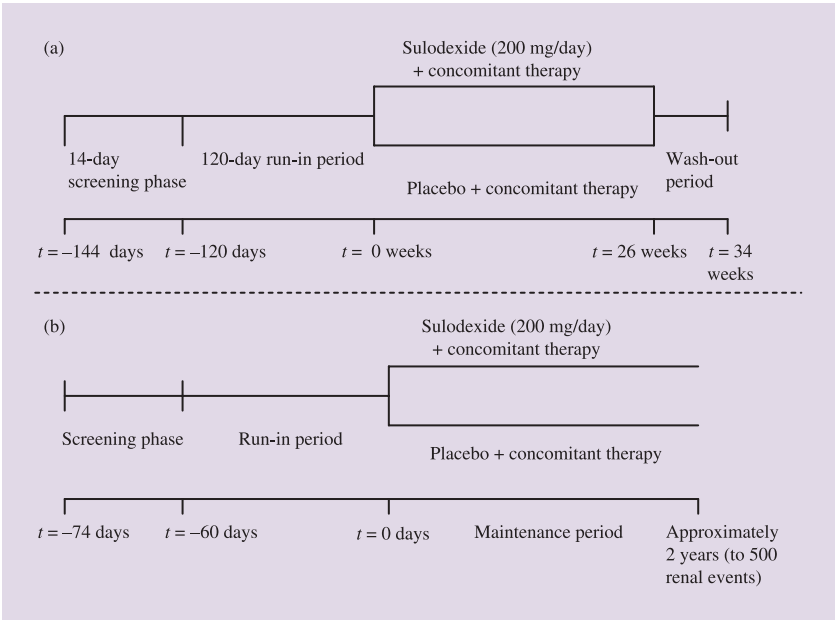

FIGURE 1 (a) Overview of the design of the The Sulodexide Microalbuminuria Trial (SUN-Micro Trial) and (b) overview of the design of The Sulodexide Overt Nephropathy Trial (SUN-Overt trial).

significant in a subgroup of diabetic patients receiving ACEIs. Although this study was of an exploratory nature, the results are in accordance with previous small pilot trials.

Because the studies performed with sulodexide were of short duration, it is unknown whether sulodexide's beneficial effect in lowering albuminuria will be associated with preservation of renal function. The Collaborative Study Group (CSG) has developed a sulodexide nephropathy programme consisting of two phase III trials with sulodexide in patients with Type 2 diabetes and nephropathy. These trials address the continuum of diabetic nephropathy and answer the question whether sulodexide adds benefit in early and/or late stages of diabetic nephropathy on top of current best practice, which is use of RAAS inhibitors and intensive diabetes, blood pressure and cholesterol management.

The Sulodexide Microalbuminuria Trial

The Sulodexide Microalbuminuria Trial (SUN-Micro Trial) is designed to assess the effects of sulodexide in 1000 patients with Type 2 diabetes and persistent microalbuminuria. The SUN-Micro Trial is a multicentre, international, randomized, double-masked, placebo-controlled trial to test the hypothesis that 26 weeks of therapy with sulodexide will increase the number of patients experiencing regression to normoalbuminuria and at least a 25% decrease in the urinary albumin creatinine ratio (UACR), or a 50% or greater decrease in the UACR. Patients will be randomized to 200 mg sulodexide or placebo while on therapy with Food and Drug Administration (FDA)-defined maximum doses of ACEI or ARB therapy. This background therapy including ACEI/ARB is representative of the use of these agents in the target population. Enrollment of 1000 patients is anticipated in approximately 200 centres worldwide.

Patient population

Eligible subjects should be aged 18 years or older, have Type 2 diabetes and a serum creatinine ≤ 133 μmol/l. Persistent microalbuminuria is defined as a UACR of 4.0–22.6 mg/mmol in men and 5.1–22.6 mg/mmol in women, based on the geometric mean of three first morning urine samples [27].

Study design

The study consists of screening, run-in, qualifying, randomization, maintenance and wash-out periods. A study scheme is provided in Fig. 1(a).

Patients who are not receiving a maximum approved dose of an ACEI or ARB begin treatment with 300 mg/day irbesartan for a minimum 120-day run-in period. Patients who meet the study inclusion criteria who have taken a maximum approved dose of an ACEI or ARB for at least 120 days and have adequate blood pressure control proceed directly to randomization. The target blood pressure is a seated systolic blood pressure (SeSBP) ≤ 130 mmHg and a seated diastolic blood pressure (SeDBP) ≤ 80 mmHg. However, it is likely that target blood pressure will be unattainable in some patients, hence the blood pressure must be controlled to at least SeSBP ≤ 150 mmHg and SeDBP ≤ 90 mmHg in order to proceed to randomization.

Eligible patients are randomized to placebo or 200 mg sulodexide in a 1 : 1 ratio. Patients are seen 8, 16, 22 and 26 weeks after randomization for assessment of blood pressure, UACR and adverse events. At the end of the 26-week maintenance period, the study drug will be discontinued and patients will proceed to an 8-week wash-out period to determine urinary albumin excretion after stopping sulodexide. It is of critical importance to ensure stability of ACEI or ARB therapy,

Table 2 Primary and secondary outcome parameters; (a) The Sulodexide Microalbuminuria Trial (SUN-Micro Trial) and (b) The Sulodexide Overt Nephropathy Trial (SUN-Overt Trial)

(a)

The Sulodexide Microalbuminuria Trial
1 The primary end-point parameters consist of
(i) conversion from microalbuminuria to normoalbuminuria and at least a 25% reduction in UACR level relative to baseline, or
(ii) at least a 50% reduction in UACR relative to baseline at the end of 26 weeks treatment
2 The secondary end points consist of
(i) percentage of patients achieving normoalbuminuria or 50% reduction in UACR at weeks 8, 16 and 26 on therapy and at 4 and 8 weeks off therapy
(ii) observed UACR and change from baseline at weeks 8, 16 and 26 on therapy and after 4 and 8 weeks off therapy
(iii) percentage of patients progressing to overt nephropathy (UACR ≥ 22.6 mg/mmol) at weeks 4, 8 and 16 on therapy and 4 and 8 weeks off therapy
(iv) percentage change from baseline on additional end points including serum creatinine, MDRD estimated glomerular filtration rate and serum albumin

(b)

The Sulodexide Overt Nephropathy Trial
1 The primary outcome is time to a composite end point of
(i) doubling of the serum creatinine from baseline
(ii) ESRD as defined by renal transplantation, need for dialysis or serum creatinine ≥ 530 μmol/l
2 The secondary end-point parameters consist of
(i) incidence rate of the composite primary end point of a doubling of the serum creatinine from baseline or ESRD
(ii) time from randomization until the occurrence of a doubling of the serum creatinine from baseline or ESRD
(iii) incidence rate of a doubling of serum creatinine from baseline or ESRD
(iv) change from baseline in UPCR and UACR
(v) time to all-cause mortality
3 The tertiary end-point parameters consist of
(i) time from randomization until the first occurrence of the cardiovascular composite end point of cardiovascular death, non-fatal myocardial infarction, congestive heart failure requiring hospitalization, stroke, and coronary and peripheral vascular procedures
(ii) time from randomization to the first occurrence of individual components of the cardiovascular composite end point

ESDR, end-stage renal disease; MDRD, modification of diet in renal disease; UACR, urinary albumin creatinine; UPCR, urinary protein creatinine ratio.

glycaemic control and lipid-lowering therapies during the course of the study. The blood pressure achieved during the run-in period must remain constant throughout the course of the maintenance and wash-out periods.

Statistical consideration

It is estimated that 25% of the patients assigned to 200 mg/day sulodexide will achieve the primary composite end point at the end of the maintenance period, whereas a success rate of 15% in the placebo group is estimated. To achieve 90% power at the 0.0125 significance level, at least 1000 patients will be required after adjusting for a drop-out rate of 5%.

Efficacy assessment

End-point parameters

The primary and secondary end-point parameters are presented in Table 2.

Efficacy analysis

The efficacy analysis is primarily based on the intent-to-treat population, which is defined as all randomized patients. The per-protocol population is defined as all patients in the intent-to-treat population who complete the 26-week treatment with no major protocol violations.

The Sulodexide Overt Nephropathy Trial

The Sulodexide Overt Nephropathy Trial (SUN-Overt trial) investigates the effects of sulodexide in 2240 hypertensive patients with Type 2 diabetes and overt nephropathy (protein excretion ≥ 900 mg/24 h). It is a multicentre, international, randomized, double-masked, placebo-controlled trial to test the hypothesis whether therapy with sulodexide will significantly increase the time to the first occurrence of the composite end point of a doubling of the serum creatinine from baseline or ESRD defined as serum creatinine ≥ 530 μmol/L, need for dialysis or renal transplantation. Patients will be randomized

to 200 mg/day sulodexide or placebo on top of background 100 mg/day losartan or 300 mg/day irbesartan. On the basis of the RENAAL and IDNT trials, 100 mg/day losartan and 300 mg/day irbesartan are the only studied ARBs approved for renoprotection in patients with Type 2 diabetes and hypertension. This study is designed to achieve consistent RAAS inhibition with limited background therapy. Enrollment of 2240 patients will take place in approximately 270 centres worldwide.

Patient population

Eligible subjects should be aged 18 years or older, with Type 2 diabetes, have a serum creatinine between 115 and 265 μmol/l in women and 133 and 265 μmol/l in men and a 24-h protein excretion rate ≥ 900 mg/24 h.

Study design

The study contains screening, run-in, qualifying, randomization, maintenance and termination phases. A study scheme is provided in Fig. 1(b).

During the screening phase, patients will be selected based on their serum creatinine and 24-h protein excretion. After screening, patients who have been on 100 mg/day losartan or 300 mg/day irbesartan for at least 60 days and have adequate and stable blood pressure control may bypass the run-in period. Patients not already on 100 mg/day losartan or 300 mg/day irbesartan, or using these ARBs but not meeting the blood pressure goals, proceed to a 60-day run-in period. The target blood pressure goal is a SeSBP ≤ 130 mmHg and a SeDBP ≤ 80 mmHg. However, it is likely that target blood pressure will be unattainable in some patients, hence the blood pressure must be controlled to SeSBP ≤ 160 mmHg and SeDBP ≤ 100 mmHg in order to proceed to randomization. Concomitant non-ACEI, non-ARB anti-hypertensive medication is allowed for blood pressure control. Patients are randomized to 200 mg/day sulodexide or placebo. After randomization, patients are seen at 1 month and every 3 months thereafter for assessment of blood pressure, renal function and adverse events. Patients with a doubling of serum creatinine from baseline, as confirmed by the Collaborative Study Group's central laboratory, will continue their randomized study medication and will be followed for all routine visits. Patients who undergo dialysis or renal transplantation must be withdrawn from study medication and will be followed for cardiovascular end points. An independent blinded end-point committee will review all potential renal and cardiovascular end points using predefined end-point criteria. The ARB dose will be constant throughout the whole study. The study will be terminated when 500 renal end points have occurred.

Statistical consideration

Based on a subset of patients in the IDNT trial who met the current entry criteria, it is assumed that 27.6% of the patients assigned to the placebo group will achieve the primary composite end point in 3 years. To ensure that a reduction of 20% can be detected, it is necessary to randomize 2016 patients to achieve 500 composite end points with 80% power at a significance level of 0.05. To account for 10% of patients lost to follow-up, a total number of 2240 patients is required (1120 per treatment group).

Efficacy assessment

End-point parameters

The primary, secondary and tertiary end-point parameters are presented in Table 2.

Efficacy analysis

The primary efficacy analysis will be based on the intent-to-treat population, which is defined as all randomized patients. An independent masked Endpoint Adjudication Committee will adjudicate all potential clinical end points occurring after randomization until study termination. The time to primary event will be compared between treatment groups. Secondary and tertiary efficacy analysis will also be compared.

Safety assessment will occur throughout the trial and include monitoring of adverse events and clinically important changes in laboratory parameters.

Conclusion

To slow the progression of diabetic nephropathy, current guidelines recommend intensive treatment of hypertension with ACEIs and ARBs, optimization of glucose control and protein restriction [23]. Despite these interventions, some patients with diabetes either do not respond to or tolerate therapy, and consequently progress.

Sulodexide potentially offers a new and unique mechanism for renoprotection.

Competing interests

HLH is a PhD fellow of the department of Clinical Pharmacology at the University Medical Centre Groningen and project coordinator of the sulodexide trials. MF has served as speaker for Novo Nordisk, Pfizer and Sanofi-Aventis. JV is a project coordinator for the Keryx 301 Microalbuminuria Study. AR is a project coodinator for the sulodexide trials and has been paid by Keryx. SS has conducted clinical trials for various pharmaceutical companies. JL has been reimbursed as an investigator in the Keryx sponsored study and as a speaker for the study. IK, DP, IF, TH and CA: none declared.

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