Pharmacokinetic insights in individual drug response

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Defining the optimal dose of atrasentan by evaluating the exposure-response relationships of albuminuria and body weight

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Abstract

Aims: This study aimed to identify the optimal dose of the endothelin-1 receptor antagonist atrasentan with maximal albuminuria reduction and minimal signs of sodium retention, as manifested by increase in body weight.

Methods: Data from the RADAR-JAPAN studies were used, evaluating the effect of 0.75 or 1.25 mg/day of atrasentan in 161 patients with type 2 diabetes and kidney disease. Individual pharmacokinetic parameters were estimated using a population pharmacokinetic approach. Subsequently, changes in the urinary albumin-to-creatinine ratio (UACR) and body weight from baseline after two weeks' exposure were modelled as a function of the pharmacokinetic parameters.

Results: Concomitant administration of clopidogrel was identified as a covariate that influenced the apparent clearance of aleglitazar. Patients using clopidogrel had a mean predicted area under the plasma concentration-time curve ($AUC_{0\text{-}24}$) of 174.7 ng·h/mL (SD: ±112.9 ng·h/mL) versus 142.2 ng·h/mL (SD: ±92.6 ng·h/mL) in patients without clopidogrel. The effect of aleglitazar compared to placebo on HbA1c, haemoglobin, serum creatinine and adiponectin was modified by concomitant clopidogrel use (P for interaction 0.007, 0.002, <0.001 and <0.001, respectively).

Conclusions: The individual response curves for UACR and body weight crossed at approximately the mean trough concentration of 0.75 mg atrasentan, indicating that atrasentan 0.75 mg/day is the optimal dose for kidney protection with maximal efficacy (albuminuria reduction) and safety (minimal sodium retention).

Introduction

Defining the dose of a drug with optimal efficacy and safety is important for a drug's development programme and its use in clinical practice. This is especially important for drugs with a narrow therapeutic window, or drugs for which the efficacy and safety exposure-response curves overlap.

Endothelin Receptor Antagonists (ERAs) are an example of a class of drugs with a narrow therapeutic window. The class is tested for cardiovascular protection, including reducing the progression of kidney disease.[1-4] Albuminuria lowering is believed to be an efficacy biomarker that reflects the drug's efficacy to delay progression of kidney disease, whereas the sodium retention during endothelin receptor antagonism is a biomarker for unwanted side effects. The optimal dose of an ERA for kidney protection is a balance between maximal albuminuria lowering and minimal sodium retention.

Atrasentan is an ERA that has been shown to decrease albuminuria at relatively low doses of 0.75 and 1.25 mg/day in the dose-finding phase 2 RADAR trial.[5] However, even at these low doses, atrasentan also caused sodium retention as manifested by increases in body weight. The aim of the current study is to employ exposure-response analyses to identify the optimal atrasentan dose with maximal albuminuria reduction and minimal sodium retention.

Materials & Methods

Clinical trial design and patient population

Data from 161 participants in the RADAR (NCT01356849) and JAPAN (NCT01424319) trials were used. The RADAR and JAPAN trials assessed the effect of atrasentan on albuminuria reduction. The design and primary results of both trials were previously published.[5] To be eligible, participants were required to have a urinary albumin-to-creatinine ratio (UACR) between 300 to 3500 mg/g and an estimated glomerular filtration rate (eGFR) between 30 to 75 mL/min/1.73m^2. As per protocol, all participants received the maximum tolerated labeled daily dose of a renin-angiotensin-aldosterone-system (RAAS) inhibitor. Patients were randomly allocated to 12-weeks of treatment with atrasentan at doses of 0.75 or 1.25 mg/day, or a placebo using a double-blind design. The primary endpoint of the trial was the change in UACR over time.

Three consecutive first-void urine specimens were collected at baseline and every 2-weeks thereafter to determine urinary albumin and creatinine concentrations. Blood samples were sparsely collected to determine plasma atrasentan exposure. In line with previous reports of this trial, changes in body weight were used as proxy for sodium retention. Analyses focused on

changes in sodium retention after 2 weeks of atrasentan therapy in order to maximise detection of atrasentan on sodium retention.

Pharmacokinetic and pharmacodynamic analyses

The population pharmacokinetic model was previously published.[6] The original data file and model results were combined to generate a simulation dataset (data transformations and visualisations were performed in R version 3.4.2 [R Foundation for Statistical Computing, Vienna, Austria]). For each individual, the simulation dataset contained dosing information, demographics and post-hoc Bayesian pharmacokinetic parameter estimates (e.g. individual absorption rate, clearances and volumes of distribution). For simulation purposes, all available pharmacokinetic observations were set at missing. In order to obtain additional individual pharmacokinetic parameters (e.g. area-under-the-plasma-concentration-time-curve [AUC]), atrasentan exposure was simulated at day 14 after first dosing in time steps of 0.1 hour. Simulations were run in NONMEM 7.3 (ICON Development Solutions, Ellicott City, MD, USA), using the individual post-hoc Bayesian parameter estimates and the original model structure.

The simulated pharmacokinetic profiles per individual were used to obtain the following individual pharmacokinetic parameters on day 14; maximum plasma atrasentan concentration (C_{max}), trough concentration (C_{trough}, [on day 15]) and average steady state concentration (C_{ss}). The individual AUC for day 14 (AUC_{d14}) was calculated by the amount administered/individual clearance. Subsequently, regression analyses were performed to assess the association between the change from baseline in log-transformed UACR and body weight after two weeks with C_{trough}, C_{max}, C_{ss}, and AUC_{d14}.

Results

Baseline characteristics of patients assigned to atrasentan 0.75 and 1.25 mg doses were reported previously.[5] The mean C_{trough} (2.5^{th} to 97.5^{th} Percentile [P]) of atrasentan at week 2 was 1.7 ng/mL (0.4 to 4.7) and 3.4 ng/mL (1.0 to 10.0) for the 0.75 and 1.25 mg dose, respectively. After 2 weeks treatment with either 0.75 or 1.25 mg of atrasentan, UACR decreased by 34.0% ($P<0.01$) and 40.1% ($P<0.01$), respectively, compared to baseline, with a large variation among individuals [2.5^{th} to 97.5^{th} P: -68.4 to 70.5 and -76.2 to 12.3]. The mean increase in body weight [2.5^{th} to 97.5^{th} P] with 0.75 and 1.25 mg of atrasentan was 0.9 kg [-1.0 to 3.0] and 1.1 kg [-1.0 to 4.0], respectively. The individually predicted values for C_{trough}, C_{ss} and C_{max} and AUC_{d14} correlated significantly to both individual UACR and body weight responses (Table 1). Figure 1 shows that the exposure-response curves for albuminuria and body weight crossed at a mean C_{trough} corresponding to approximately 0.75 mg of atrasentan per day. At the mean C_{trough} of the 1.25 mg dose, a slightly larger albuminuria response

was observed, at the expense of a larger increase in body weight probably because of a larger degree of sodium retention. Results were similar when C_{ss}, C_{max} and AUC_{d14} were modelled (Figure S1).

Table 1. Associations between pharmacokinetic parameters and albuminuria and body weight response at 2 weeks

	Mean (95%CI) % change in UACR per 2-fold increase in atrasentan concentration	P-value	Mean (95%CI) change in body weight in kg per 2-fold increase in atrasentan concentration	P-value
Ctrough	-9.8 (-15.7 to -3.5)	0.003	0.31 (0.10 to 0.52)	0.004
Css	-10.2 (-16.3 to -3.6)	0.003	0.30 (0.08 to 0.52)	0.008
Cmax	-10.3 (-16.6 to -3.5)	0.004	0.28 (0.05 to 0.51)	0.019
24-hr AUC_{d14}	-9.9 (-16.1 to -3.3)	0.004	0.30 (0.08 to 0.52)	0.008

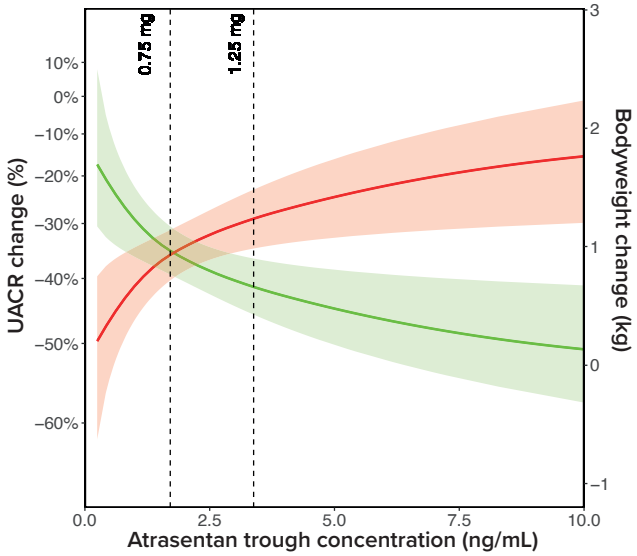

Figure 1. Predicted atrasentan trough concentrations versus predicted albuminuria (green) and predicted body weight response (red). The mean predicted response (solid line) is shown for the 95% prediction intervals (shaded areas). The dotted lines represent the mean atrasentan trough concentrations for 0.75 and 1.25 mg doses.

Discussion

This study showed a large individual variation in albuminuria and sodium retention (body weight) response after two weeks of treatment with a low dose of atrasentan. The observed variation in albuminuria and body weight response correlated to the variation in the estimated individual pharmacokinetic parameters of atrasentan. At the atrasentan C_{trough} equivalent to the administration of 0.75 mg atrasentan, a significant and clinically relevant reduction in albuminuria was observed with fewer signs of sodium retention in comparison to a C_{trough} equivalent to the administration of 1.25 mg atrasentan. Regulatory agencies have developed rigorous guidelines on how to use

dose-response data to support dose selection and drug registration.[7,8] Despite these rigorous guidelines, dose-finding studies to determine the optimal therapeutic dose are hampered by various factors. Firstly, dose-finding studies often include only a small number of patients per drug-dose arm. Combined with the consideration that the individual exposure and response to many drugs vary substantially among patients[9], the small sample size compromises accurate and precise determination of the optimal dose. Secondly, the patient population included in the dose-finding studies is not always representative of the population enrolled in confirmatory clinical trials and those who will eventually be treated in clinical practice; this is because the latter population is often more heterogeneous with varying degrees of renal or hepatic function, multiple comorbidities, and the use of many concomitant medications. Each of these factors can alter dose-exposure-response relationships.

A further problem in determining the optimal therapeutic dose is that its selection is based on an inadequate balance between efficacy and safety. Traditionally, dose finding is based on the drug's efficacy in modifying a single risk factor that the drug is targeting, for example, blood pressure for an antihypertensive drug. The safety is mainly established from a fixed set of parameters. However, many drugs have effects on other parameters (off-target effects), which may also be risk factors that contribute to clinical outcomes, either in a positive or negative way. The sodium retention effect of ERAs is one such off-target effect that contributes to clinical outcomes in a negative way. Therefore, dose selection should be based on the balance of drug effects on multiple parameters, both on those that contribute to protection and those that induce harm.

These problems in selecting the optimal therapeutic dose for an ERA are illustrated by the ERA avosentan. A phase III trial (ASCEND) with avosentan was terminated early due to an increased incidence of congestive heart failure probably caused by the sodium-retaining effects.[10] In hindsight, the increased sodium retention and congestive heart failure could have been expected, because the high doses of 25 mg and 50 mg used in the phase III trial were associated with significant sodium retention and peripheral edema in a prior dose finding trial.[11] Despite the high incidence of edema, the 25 mg and 50 mg dose were selected for the phase III outcome trial. This highlights the importance of careful dose selection when balancing maximal albuminuria reduction and minimal sodium retention.

Additionally, the high doses used in the ASCEND trial are not the only explanation for the increased edema and heart failure, but also the difference in populations studied in the phase III outcome trial and the dose-finding study. In the phase III trial, patients with overt diabetic nephropathy were enrolled; they had a mean eGFR of 33 ml/min/1.73m^2.[3] These patients are prone to sodium retention. However, in the dose-finding study, patients who

are less prone to sodium retention, with an estimated creatinine clearance of approximately 80 mL/min, were enrolled.[12] This finding also highlights the importance of strictly monitoring patients with diabetes and impaired kidney function for signs of sodium retention. For the development of the ERA atrasentan, the main inclusion and exclusion criteria for the phase II and III trials were kept similar, and the sodium-retaining effects of atrasentan were carefully analysed during the dose selection process. However, the sample size of the atrasentan phase II dose-finding study was small, thus limiting the accuracy and precision of the dose finding analyses.

In conclusion, the exposure-response analysis showed that 0.75 mg/day of atrasentan as an adjunct to RAAS inhibition is the optimal dose for renal protection with maximal albuminuria reduction while minimizing sodium retention.

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Conflicts of Interest

JK and JS report no conflicts of interest. H-HP has equity in Merck and Novo Nordisk and has received consulting and lecture fees from AstraZeneca, Abbott, Novartis, and Reata. DDZ is a consultant for and received honoraria (to employer) from AbbVie, Astellas, Bayer, Boehringer Ingelheim, Novo Nordisk, Fresenius, Janssen, and Mitsubishi Tanabe. HJLH is a consultant for from AbbVie, Astellas, AstraZeneca, Boehringer Ingelheim, Fresenius, Janssen, and Merck. He has a policy of all honoraria being paid to his employer. NM is employee of AbbVie and may own stock or stock options

Author contributions

JK and HJLH wrote the draft of this report. NM, JS and JK performed statistical analyses. All the authors contributed to interpretation and critical revision of the publication. HJLH takes full responsibility for this report.

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Supplementary Materials

Supplement Figure 1: Predicted Atrasentan steady state (A), maximum (B) concentration and area under the curve (C) versus predicted albuminuria (green) and predicted bodyweight response (red). The mean predicted response (solid line) is displayed with the 95% prediction intervals (shaded areas). The dotted lines represent the mean atrasentan trough concentrations for 0.75 mg and 1.25 mg dose. The mean (2.5th to 97.5th) steady state atrasentan 0.75 mg and 1.25 mg concentration was 1.9 ng/ml (0.5 to 5.2) and 3.3 ng/ml (1.2 to 11.3).The mean (2.5th to 97.5th) maximum atrasentan 0.75 mg and 1.25 mg was 2.3 (0.7 to 6.9) and 3.9 (1.7 to 14.8). The mean (2.5th to 97.5th) area under the curve for atrasentan 0.75 mg and 1.25 mg was 52.2 (15.9 to 173) and 83.4 (29.5 to 294).