The Fabrazyme®, Angiotensin Receptor Blocker And ACE Inhibitor Treatment For Fabry Nephropathy (for the FAACET investigators)

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OBJECTIVES

Patients with Fabry nephropathy lose kidney function despite treatment with enzyme replacement therapy (ERT). The FAACET study (NCT00446862) examined control of urine protein/creatinine ratio (UPCR) with antiproteinuric therapy in patients receiving agalsidase beta (1 mg/kg every 2 weeks). Ten international study sites participated. The current analysis focuses on the reasons why individual patients did not achieve the titration goal for UPCR of <=0.5 g/g during the initial titration and subsequent treatment phase of the FAACET study.

METHODS

Adults with confirmed Fabry disease, trated with agalsidase beta at 1 mg/kg every two weeks were included if baseline estimated GFR (eGFR) was < 60 ml/min/1.73 m^2 and UPCR .0.5 g/day, or baseline eGFR <125 ml/min/1.73 m^2 and UPCR >1 g/day. Renin-Angiotension System (RAS) blockade was achieved with Angiotensin Converting Enzyme (ACE) inhibitor or Angiotension Receptor Blocker (ARB) therapy. Subjects who were already receiving RAS blockade at enrollment were included based on historical data obtained before ACE inhibitor or ARB therapy was started; treatment was continued without any wash out period. ACE inhibitor or ARB therapy was titrated during 3 monthly visits to a UPCR goal of ≤ 0.5 g/day, and the patients were then followed at a study visit every 3 months for the next 18 months at which vital signs, serum electrolytes and serum creatinine, UPCR, concomitant medications and adverse events were recorded. The primary objective of the FAACET Study was reduction of the first morning UPCR to < 0.5 gram/gram. The primary outcome measure was the regression slope of estimated GFR with time in years.

RESULTS

Twenty four patients (9 females/15 males) completed the protocol with 18 months follow-up during the treatment arm following the initial 3 month titration period. Average age was 44 ± 9 (SD) yrears, with 1.8 ± 0.2 years follow up. Thirteen subjects achieved and maintained the target UPCR of ≤0.5 g/day during the active treatment period. Their initial baseline eGFR was 70 ± 8 ml/min/1.73 m^2, and their initial baseline UPCR was 0.5 ± 0.1 g/g. Eleven subjects did not achieve and/or maintained the target UPCR of ≤0.5 g/day during the active treatment period. Their initial baseline eGFR was 74 ± 8 ml/min/1.73 m^2, and their initial baseline UPCR was 0.8 ± 0.3 g/g.

eGFR Slopes in Groups Stratified by Achieved UPCR (mean values ± SEM)*

Averaged UPCR Strata	Number	Gender	Averaged eGFR Slope	Averaged UPCR Strata
≤0.5 g/g	13	6 F/7 M	– 1.0 ± 0.3	0.3 ± 0.3
>0.5 g/g	11	3 F/8 M	– 5.3 ± 1.1	1.1 ± 0.2

*UPCR (g/g ± SEM; eGFR slope (ml/min/1.73 m^2 ± SEM)

Those who did not maintain average UPCR ≤0.5 g/g throughout the active treatment period were more likely to be male, had higher baseline UPCR, and had not received previous RAS blockade. Obstacles to achieving averaged target UPCR included dietary salt excess, hypotension, and occasional hyperkalemia. Hypotension was often associated with the use of longer acting RAS blockade agents, and other concomitant medications like diuretics and beta-blockers.

CONCLUSIONS

The eGFR slope was associated with achieved UPCR in adult patients with Fabry nephropathy treated with Fabrazyme at 1 mg/kg intravenously every two weeks and antiproteinuric therapy with RAS blockade. The majority of patients could be titrated to UPCR ≤0.5 g/day, and had eGFR slopes not different from zero over the subsequent 18 month treatment period. Effective antiproteinuric therapy is an important adjunct to ERT in treating patients with Fabry nephropathy, and those who respond to RAS blockade have stable eGFR and minimal adverse events during the follow up period.

REFERENCES:

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