Brief Communication

A retrospective study evaluating efficacy and safety of linagliptin in treatment of NODAT (in renal transplant recipients) in a real world setting

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ABSTRACT

New-onset diabetes after transplantation (NODAT) is frequently encountered after kidney transplant. In the present study, we retrospectively evaluated the safety and efficacy of linagliptin monotherapy in 21 renal transplant recipients in a real world setting. We found linagliptin monotherapy is effective for glycemic control in NODAT, even on glucocorticoids and standard dose of tacrolimus. There was no alteration of tacrolimus drug levels or estimated glomerular filtration rate (eGFR) and minimal side effects, including weight gain and hypoglycemia. Well-designed, powered randomized controlled of antiglycemic agents in NODAT are needed.

Key words: Linagliptin, new-onset diabetes after transplantation, renal transplant

Introduction

New-onset diabetes after transplantation (NODAT) is a frequent complication encountered in solid organ transplant recipients like kidney. NODAT has negative impact on renal allograft survival, cardiovascular risk, and patient survival. Safe and adequate glycemic control may alter the outcome. In the present study we retrospectively evaluated the safety and efficacy of linagliptin monotherapy in renal transplant recipients in a real world setting.

Materials and Methods

Renal allograft recipients with stable renal function and without any past history of diabetes were evaluated for NODAT by routine 2 h oral glucose tolerance test using the definition established by the 2003 International Guidelines.[1] Consecutive NODAT patients were prescribed linagliptin monotherapy (5 mg/day, single dose). Fasting, postprandial plasma glucose (FPG, PPG) and glycosylated hemoglobin (HbA1c) were evaluated at baseline, after 12 weeks, and after 24 weeks of therapy. Safety and tolerability of linagliptin was assessed and any adverse event (AE) recorded during course of therapy was assessed. Hypoglycemia and other treatment related events were noted, including effect on tacrolimus and levels and changes in renal function. Our patients were on stable dose of prednisolone (5 mg/day) and standard dose of tacrolimus (target levels 3-7 ng/mL).

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Results

In our retrospective study, 21 NODAT patients (with 12 males and nine females) received linagliptin monotherapy and were followed-up for 24 weeks. Mean age of the patients was 57.1 years (standard deviation (SD): 6.4) and mean body mass index was 22.3 kg/m^2 (SD: 1.8). Majority (18/21) of patients had NODAT of less than 12 weeks duration, three patients had NODAT for 3-6 months.

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Baseline mean FPG (mg/dL) was 148.57 ± 262.68, PPG (mg/dL) was 209.57 ± 47.44 and HbA1c (%) was 8.2 ± 0.78. With 12 weeks of linagliptin therapy, mean decrease in FPG and PPG was 25.21 and 40.07 mg/dL, respectively. After 24 weeks, FPG and PPG decreased by 26.2 and 58.12 mg/dL, respectively. Similarly HbA1c decreased by 0.36 and 0.6% after 12 and 24 weeks of therapy, respectively. After 24 weeks of linagliptin therapy, there was significant decrease in mean FPG (mg/dl): 121.6 ± 20.78 ($P < 0.05$), mean PPG (mg/dl): 151.45 ± 28.65, and mean HbA1c (%) was 7.6% ± 0.67 ($P < 0.005$. 15 (71.43%); patients achieved HbA1c <7%, including four patients with HbA1c <6.5%.

Two patients required rescue insulin therapy with HbA1c >9%. Weight gain was minimal with linagliptin (mean: 0.88 kg, SD: 0.22). There was a single minor hypoglycemic episode with linagliptin and one case of headache with sinusitis, but no patient discontinued linagliptin because of side effects. There was no significant change in tacrolimus level and tacrolimus dose remained unchanged over the study period. No change in estimated glomerular filtration rate (eGFR) occurred with linagliptin. eGFR was 62.9 ± 0.4 mL/min at entry and 66.5 ± 5.6 mL/min at week 24.

Discussion

Sulanc *et al.*, previously reported high rate (>50%) of NODAT in post kidney transplant patients, using the definition established by the 2003 International Guidelines.[2] Early pharmacologic intervention, soon after transplantation, is necessary for NODAT as it frequently occurs within the first 3 months posttransplant.[2] NODAT is a difficult problem, an ideal agent should stimulate beta-cell function, improve insulin resistance, be easily administered, and well-tolerated without hypoglycemia.

No randomized controlled trial has been conducted to assess the efficacy and safety of antiglycemic agents for the treatment of NODAT. Cardiometabolic and antineoplastic benefits of metformin in such high risk patients, needs consideration though concerns exist regarding gastrointestinal tolerability and lactic acidosis in the context of renal insufficiency (RI) or renal allograft insufficiency.[3]

Incretin class of agents including glucagon-like peptide-1 (GLP-1) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors stimulate beta-cell function, slow gastric emptying, and decrease insulin resistance. GLP-1 agonists cannot be used with a low GFR and may cause nausea. DPP-4 inhibitors can be used with low GFR, infrequently cause nausea, and have a low hypoglycemia potential. Within this class, linagliptin has primarily nonrenal route of elimination, with only 5% of the dose being excreted via the kidneys.[4] Thus, linagliptin needs no dose adjustment in patients with impaired renal function.[5] This contrasts with other DPP-4 inhibitors that are predominantly cleared by renal excretion and requires dose adjustment with creatinine clearance.[6] In type 2 diabetes patients with severe RI (eGFR <30 mL/min/1.73 m^2), linagliptin (5 mg/day) provided clinically meaningful improvements in glycemic control with very low risk of severe hypoglycemia, stable body weight, and no cases of drug-related renal failure.[7] In our study in NODAT (post renal transplant) there was significant improvement in glycemic control with minimal weight gain and only single minor hypoglycemic episode with linagliptin. No significant change in tacrolimus level or eGFR occurred with linagliptin. A previous 3-month study of 15 patients in NODAT (postrenal transplant) with sitagliptin at 100 mg/day (eGFR adjusted) improved HbA1c from baseline of 7.2 ± 0.1% to 6.7% ± 0.2%.[8] Their immunosuppression regimen was free of glucocorticoids and used low dose tacrolimus (target levels 2- 4 ng/mL) or sirolimus (target levels 4-6 ng/mL).[8] Our patients were on glucocorticoids and standard dose of tacrolimus (target levels 3-7 ng/mL) reflecting real world settings, but there was significant improvement in HbA1c. These results suggest that further robust studies should be pursued with DPP-4 inhibitors in patients with NODAT.

Conclusions

Linagliptin monotherapy is effective for glycemic control in NODAT (after renal transplant) on glucocorticoids and standard dose of tacrolimus. There was no alteration of tacrolimus drug levels or eGFR and minimal side effects. But well-designed, randomized controlled trials are required relating to the use of antiglycemic agents in NODAT. Such trials should be suitably designed and powered to ascertain any significant efficacy and/or safety difference with rival agents.

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