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Case Report

Association of Long-term Administration of the Survivin mRNA-Targeted Antisense Oligonucleotide LY2181308 With Reversible Kidney Injury in a Patient With Metastatic Melanoma

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A 57-year-old man with metastatic melanoma was treated with the survivin inhibitor and antisense oligonucleotide LY2181308 as part of a First-in-Human Dose trial. After 18 months of treatment, he developed kidney injury and the treatment was discontinued. At 9 months and before the development of kidney injury, LY2181308 concentrations were 8- to 10-fold higher relative to median predicted values, but within the targeted exposure considered to be safe. However, at 17 months, 28 days after stopping LY2181308 therapy, LY2181308 concentration exceeded the predicted range by 38-fold. His decreased kidney function was slow to improve after stopping treatment. A kidney biopsy showed signs of acute tubular injury with regeneration. Complete recovery of kidney function occurred 6 months after treatment was stopped. The relationship between high exposures and slow LY2181308 clearance with the gradual improvement in kidney function after stopping the antisense treatment suggests that the oligonucleotide was related to the kidney injury. Based on this case report, kidney function should be monitored frequently in patients receiving long-term treatment with antisense oligonucleotides that specifically target survivin, particularly when they receive concomitant angiotensin-converting enzyme inhibitors or nonsteroidal anti-inflammatory drugs.
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INDEX WORDS: Antisense oligonucleotide; survivin; kidney injury.

Survivin, a 16.5-kDa protein, is an inhibitor of apoptosis expressed in a wide range of human cancers. When overexpressed, it is associated with poorer prognosis.[1,2] The protein is an ideal target for therapeutic intervention because with the exception of activated T cells, gastrointestinal crypt cells, renal tubular cells,[3] and regenerating liver, survivin is not expressed in normal adult tissue.[4] LY2181308 is a second-generation antisense oligonucleotide that binds to the translation initiation codon of the survivin transcript, inducing RNase H–dependent degradation of the messenger RNA/antisense complex. The First-in-Human Dose (FHD) Study showed that these oligonucleotides were well tolerated, accumulated in tumor tissue, and induced significant downregulation of tumor survivin messenger RNA and protein expression.[5]

LY2181308 is formulated with a phosphate buffer and diluted in normal saline solution before infusion. After intravenous loading doses given daily for 3 days, it is administered using weekly maintenance intravenous infusions. LY2181308 has a multiphasic pharmacokinetic plasma disposition with rapid 90% tissue distribution, including the kidney. It is eliminated in urine together with its metabolites (smaller nucleotide chains derived from digestion by endogenous exo- and endonucleases).[6]

We report on a patient who received an unusually long treatment with a second-generation antisense oligonucleotide and developed reversible kidney injury.

CASE REPORT

A 57-year-old man with metastatic melanoma participating in an FHD Study with LY2181308 developed decreased kidney function over weeks. Three years previously (March 2005), an ocular melanoma had been diagnosed. This was treated initially using radiotherapy followed 8 months later by ocular enucleation. When he developed lung and liver metastases, he received a 3-month course of treatment with dacarbazine and interferon. After relapse 2 months later, he entered the FHD Study (April 2006).[5,7] Before treatment in the study, he had a blood pressure of 141/89 mm Hg. After 5 months of LY2181308 administration, diastolic blood pressure readings were >100 mm Hg. He was started on 2.5 mg of ramipril and, 3 months later, 25 mg of atenolol. He had intermittent thrombocytopenia (lowest platelet count, $60 \times 10^9/\mu L$) associated with fluctuating lactate dehydrogenase levels (140-342 U/L).

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A year after starting treatment, the patient reported increasing fatigue. Computed tomography showed no new lesions and unchanged metastases. His baseline serum creatinine level, which varied from 1-1.4 mg/dL (88-124 μmol/L; corresponding to an estimated glomerular filtration rate [eGFR] of 60-80 mL/min/1.73 m^2 [1.0-1.3 mL/s/1.73 m^2])[8] increased to 1.8 mg/dL (159 μmol/L; eGFR, 41 mL/min/1.73 m^2 [0.68 mL/s/1.73 m^2]). During a 2-week period, it deteriorated to 2.0 mg/dL (177 μmol/L; eGFR, 37 mL/min/1.73 m^2 [0.62 mL/s/1.73 m^2]) despite stopping ramipril therapy. LY2181308 therapy then was discontinued and a nephrology opinion was requested. None of the other 40 FHD participants had developed hypertension or kidney injury. However, this participant had received the largest cumulative dose of LY2181308 in the FHD Study, consisting of 74 intravenous 750-mg doses over 18 months.

During the nephrology review, the patient reported a short course of ibuprofen therapy 4 months previously. On examination, body mass index was 29 kg/m^2, blood pressure was 122/72 mm Hg, and there were no other significant abnormal clinical findings. A leukocyte esterase urine dipstick test was weakly positive for leukocytes with no demonstrable proteinuria or hematuria. There was polyclonal hypergammaglobulinemia, but no paraproteinemia. No blood film was requested. Staging computed tomography and ultrasonography showed that the kidneys were both 11 cm in bipolar length with a normal appearance. Magnetic resonance angiography showed that the vasculature was normal.

Pharmacokinetic profiling was performed at 1, 9, and 17 months of treatment with LY2181308 when serum creatinine level was 1.2 mg/dL (106 μmol/L; eGFR, 66 mL/min/1.73 m^2 [1.1 mL/s/1.73 m^2]), 1.3 mg/dL (115 μmol/L; eGFR, 59 mL/min/1.73 m^2 [0.98 mL/s/1.73 m^2]), and 1.9 mg/dL (168.0 μmol/L; eGFR, 40 mL/min/1.73 m^2 [0.67 mL/s/1.73 m^2]), respectively. Ramipril was coprescribed at 9 months, but not at months 1 and 17. Plasma total exposure to LY2181308 increased from 1.6- to 3-fold between months 1 and 9 (Fig 1A). This increase was within the 95th percentile of the model predictions developed from data obtained from the first month of pharmacokinetic sampling. Pharmacokinetic analysis 28 days after stopping LY2181308 therapy showed a 38-fold higher plasma concentration than the median predicted concentration and a 7.8-fold higher than expected plasma total exposure (Fig 1B).

Because serum creatinine level did not improve after a period of observation, a kidney biopsy was performed approximately 4 months after stopping LY2181308 therapy. The biopsy specimen contained 24 glomeruli, of which 3 were globally sclerosed. There was no evidence of processing artifact. The most striking change on light microscopy was evidence of acute tubular injury involving primarily the proximal tubules, with focal shedding of epithelial cells, nuclear debris in the tubular lumina, and florid regenerative nuclear changes (Fig 2A and B). Electron microscopy showed mitochondrial swelling of the tubular epithelial cells and lysosomal inclusions (Fig 2C). No apoptotic bodies were seen. Glomerular changes were subtle, with focal mild mesangial hypercellularity associated with thickened capillary walls (Fig 2D) and focal duplication of glomerular basement membrane (Fig 2E). There was no endotheliosis or capillary thrombosis. Electron microscopy confirmed glomerular focal basement membrane duplication with cellular interposition (Fig 2F). There were no electron-dense deposits. Immunofluorescence microscopy showed weak linear membrane staining for IgG (+) and trace mesangial staining for IgM (+/−). IgA, C3, C1q, and κ and λ light chains were negative. Interlobular arteries and arterioles showed no significant abnormality.

The patient was monitored continually, and 6 months after LY2181308 therapy was stopped, serum creatinine level had returned to 1.1 mg/dL (97 μmol/L; eGFR, 74 mL/min/1.73 m^2 [1.23 mL/s/1.73 m^2]). Eighteen months after stopping LY2181308 therapy, his tumor has not progressed and kidney function has remained stable.

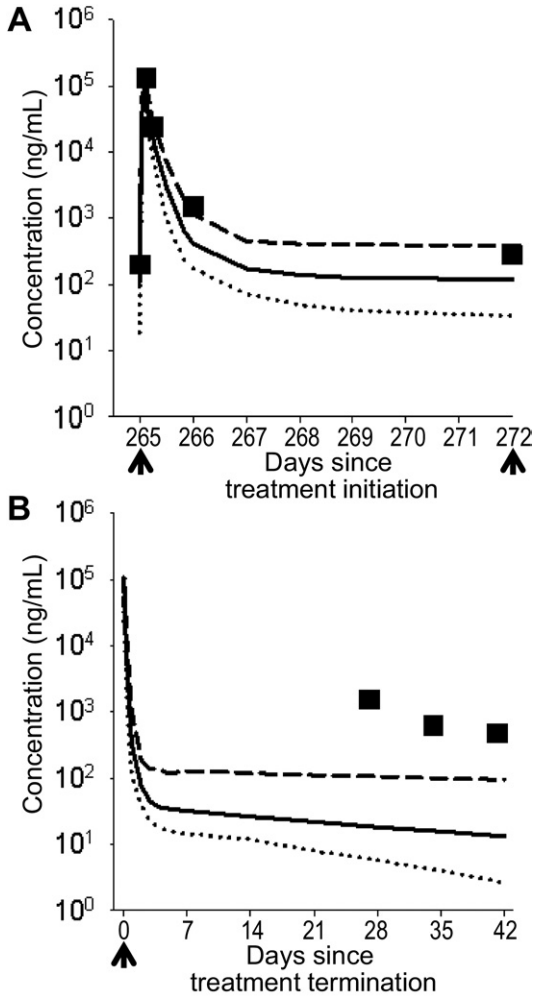

Figure 1. Pharmacokinetic (PK) profile of LY2181308 plasma concentration versus time after LY2181308 dosing. (A) At 9 months (day 265) after treatment initiation, serum creatinine was 1.3 mg/dL, and LY2181308 concentration was within the predicted pharmacokinetic exposure (solid squares). (B) After 17 months (525 days), serum creatinine was 1.9 mg/dL, and LY2181308 therapy was terminated (time 0 in graph); 28 days thereafter, plasma concentration was 38-fold higher than the median predicted exposure and exceeded the predicted 95th percentile. Each arrow represents an intravenous infusion of 750 mg of LY2181308; solid squares indicate observed PK concentration; solid, dotted, and dashed lines indicate median, 5th and 95th percentiles of predicted exposure.

DISCUSSION

Because antisense oligonucleotides accumulate in the liver and kidney[6] and survivin can be expressed in normal adult tubular cells,[3] the findings in this patient with metastatic melanoma are relevant for the future development of LY2181308 and other survivin inhibitors.

The small-molecule survivin inhibitor YM155 also has been associated with kidney toxicity and hence