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BRIEF REPORT

Evaluation of Serum Creatinine Changes With Integrase Inhibitor Use in Human Immunodeficiency Virus-1 Infected Adults

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This retrospective chart review evaluated changes in serum creatinine and creatinine clearance (CrCl) after initiation of an integrase inhibitor (INSTI)-based regimen as initial treatment in human immunodeficiency virus-infected adults. Serum creatinine and CrCl changes were similar to those seen in clinical trials for INSTIs. No renal-related serious adverse events or discontinuations occurred.

Keywords. creatinine clearance; human immunodeficiency virus; integrase inhibitor; renal.

Dolutegravir (DTG), raltegravir (RAL), and elvitegravir are integrase strand transfer inhibitors (INSTIs), and, combined with other antiretroviral agents (ARVs), are preferred for the treatment of human immunodeficiency virus (HIV)-1 positive treatment-naive and treatment-experienced patients [1]. Controlled clinical trials of RAL, DTG, and the fixed-dose combination tenofovir/emtricitabine/cobicistat/elvitegravir (EVG/c) have highlighted excellent viral load suppression and overall tolerability [2–6]. In the case of DTG and EVG/c, the potential for increases in serum creatinine ([SCr] 0.1–0.2 mg/dL) have been noted [3–6]. Cobicistat is the offending agent in the EVG/c formulation. Currently, EVG/c is not recommended for initiation in patients with creatinine clearance (CrCl) under 70 mL/min.

The rise in SCr with DTG and cobicistat use is due to decreased tubular secretion of creatinine [7, 8]. Cobicistat affects the efflux of creatinine by inhibiting the multidrug and toxin extrusion protein 1 (MATE1) [7], a renal creatinine transporter, whereas DTG blocks the uptake of creatinine from the blood by inhibiting the organic cation transporter 2 (OCT2) [8]. In clinical trials of DTG and EVG/c, elevations in SCr generally occurred within the first 4 weeks of therapy and plateaued thereafter; few cases of renal toxicity were noted [3–6].

Dolutegravir and EVG/c are often used concurrently with other potentially nephrotoxic agents; therefore, differentiating the cause and clinical significance of increases in SCr may be challenging. Tenofovir disoproxil fumarate (TDF) is a part of many antiretroviral regimens including the elvitegravir-based fixed-dose combination. Tenofovir disoproxil fumarate has been associated with elevated SCr and renal toxicity. Tenofovir-based renal insufficiency generally occurs early in therapy with significant increases in SCr should renal toxicity occur. A new formulation of tenofovir, tenofovir alafenamide, is expected to decrease the renal issues associated with TDF. Other agents that may be used concurrently in HIV-infected patients also may increase SCr, including angiotensin-converting enzyme inhibitors, sulfamethoxazole/trimethoprim, and prescription or over-the-counter nonsteroidal anti-inflammatory agents.

Overall, renal insufficiency in HIV-infected patients is a concerning comorbidity with multiple contributing factors. To verify the safety profile of INSTIs, it is important to describe the impact of INSTIs on renal function beyond the controlled clinical trial environment. The rate and clinical significance of increased SCr due to DTG and EVG/c outside of clinical trials is unknown because limited post-marketing data has been collected. The current study evaluated the clinical significance of short- and long-term changes in baseline SCr and CrCl associated with the use of an INSTI-based antiretroviral regimen among people living with HIV.

METHODS

In this single-center retrospective chart review, medical records of all HIV-positive adult patients attending the Ryan White Title III/IV clinics at the University of Toledo Medical Center (UTMC) were screened for prescriptions for an INSTI between June 2007 and February 2015. Included patients were ≥18 years of age, HIV-1 infected, initiated or switched to a first- or second-line ARV regimen containing DTG, RAL, or EVG/c and a nucleoside or nucleotide transcriptase inhibitor backbone (tenofovir/emtricitabine, abacavir/lamivudine, or zidovudine/lamivudine), and had ≥3 SCr draws within 60 weeks of INSTI initiation. Patients were excluded if they were pregnant, had HIV-associated nephropathy, or had a baseline estimated CrCl (eCrCl) <50 mL/min. Subjects with advanced hepatic disease or an acquired immune deficiency syndrome-defining

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Table 1. Baseline Characteristics and Absolute and Percent Changes From Baseline in Serum Creatinine and Creatinine Clearance

Characteristic	RAL	DTG	EVG/c
N	29	24	62
Age, yr mean (SD)	45 (11)	48 (15)	40 (11)
Gender (%M)	66	83	56
Race (%White)	80	79	53
CD4 < 200 cell/μL,%	31	13	5
HIV RNA ≤ 50 cp/mL,%	66	46	60
ART-experienced, %	70	46	77
Tenofovir in regimen, %	93	71	100
Viral load undetectable[a], %	90	96	87
Baseline SCr, mg/dL (median; IQR)	0.96 (0.85–1.09)	0.95 (0.87–1.06)	0.90 (0.75–1.0)
Change in SCr, mg/dL (median; IQR)	0.05 (–0.02 to 0.19)	0.12 (0.07–0.18)	0.10 (0.02–0.20)
%Change in SCr, mg/dL (median; IQR)	4.5 (–2.4 to 16.7)	14.5 (7.67–19.38)	12.0 (2.17–23.56)
Baseline CrCl, mL/min (median; IQR)	85 (78–105)	78 (68–105)	94 (80–116)
Change in CrCl, mL/min (median; IQR)	–3 (–12 to 2)	–10 (–16 to –6)	–9 (–18 to –1)
%Change in CrCl, mL/min (median; IQR)	–3 (–14 to 3)	–13 (–16 to –7)	–10 (–19 to –2)
Time to first draw, mo (median; IQR)	2 (1–3)	2 (1–4.5)	2 (1–4)
Time to last draw, mo (median; IQR)	13 (11–14)	10 (8–11)	12 (11–14)

Abbreviations: ART, antiretroviral therapy; CrCl, creatinine clearance; DTG, dolutegravir; EVG/c, elvitegravir/cobicistat/tenofovir/emtricitabine; HIV, human immunodeficiency virus; IQR, interquartile range; RAL, raltegravir; RNA, ribonucleic acid; SCr, serum creatinine; SD, standard deviation.

[a] Viral loads were considered undetectable if below the level of detection for the commercial assay used (example: <400, 75, 50, 40 copies/mL).

condition were also excluded because these conditions could negatively impact renal function. The primary outcome was absolute change in SCr from baseline to 60 weeks after initiation of an INSTI-based regimen. Secondary outcomes include the percentage change in creatinine from baseline, the absolute and percentage change in CrCl from baseline, and documentation of renal adverse effects and discontinuation rates due to renal insufficiency.

Demographic data, baseline and end-of-study CD4 count and viral load, antiretroviral and concurrent medication history, SCr, eCrCl, and comorbidities were collected from the medical records. All SCr were recorded from baseline through 60 weeks for each patient. Creatinine clearance was estimated using the Cockcroft-Gault equation (using ideal body weight or actual body weight if less than ideal). Baseline SCr was determined by the highest value within the preceding 14 weeks before initiation of INSTI. The changes in SCr and eCrCl were determined by the change from baseline to the last draw within the 24- to 60-week window after initiation of INSTI. The incidence of a significant SCr rise was defined as >50% or 0.5 mg/dL increase in SCr over baseline. This research was conducted with the approval of the UTMC institutional review board.

RESULTS

Two hundred seventy-four subjects were screened for inclusion (RAL, 114 subjects; EVG/c, 107 subjects; and DTG, 53 subjects) with 158 subjects being excluded due to the following: lack of or loss to follow up; missing data; noncompliance; started regimen before initiating care at UTMC (ie, no baseline values); on excluded ARVs. One hundred sixteen patients met the inclusion criteria (29 RAL, 24 DTG, and 62 EVG/c). Subjects tended to be white and male with a mean age between 40 and 48 years (see Table 1). Over 70% of RAL and EVG/c subjects were antiretroviral therapy (ART)-experienced. Baseline virologic suppression was seen in over 60% of RAL and EVG/c users versus only 46% of DTG users. Absolute and percentage changes in SCr and CrCl from baseline to last draw within 60 weeks of INSTI initiation are found in Table 1. The fixed-dose combination tenofovir/emtricitabine/cobicistat/elvitegravir and DTG were initiated in 5 and 7 subjects, respectively, with baseline CrCl <70 mL/min. Two of those subjects from each group had final CrCl levels that declined to <50 mL/min. Serum creatinine increases of ≥50% or 0.5 mg/dL after initiation of the INSTI-containing regimen were noted in 1 RAL user, 2 DTG users, and 3 EVG/c users. No patients required INSTI discontinued due to renal complications.

DISCUSSION

Dolutegravir and cobicistat are known to decrease tubular section of creatinine without affecting glomerular filtration. In clinical trials, they were shown to have an increase in SCr of 0.1–0.2 mg/dL that occurred early in treatment and remained stable throughout therapy. In our experiences, SCr and CrCl changes were similar to those seen in clinical trials for RAL, DTG, and EVG/c in patients with a baseline eCrCl >50 mL/min. An additional concern was the impact of increasing SCr in subjects with baseline eCrCl <70 mL/min. The elvitegravir-fixed dose combination was studied and approved for use only in subjects

with eCrCl >70 mL/min. To our knowledge, this restriction is primarily in place to minimize the risk of the eCrCl falling below 50 mL/min, a point at which the fixed-dose combination would need to be separated into its individual components to account for the renal dosing adjustments for tenofovir. In the EVG/c group, 4 subjects initiated therapy at eCrCl between 60 and 70 mL/min and 1 subject started at eCrCl of <60 mL/min. Two of these individuals had their eCrCl fall below 50 mL/min at the time of the last draw. For DTG, 5 subjects started therapy with an eCrCl between 60 and 70 mL/min and 2 subjects started at eCrCl <60 mL/min. Again, 2 subjects had their eCrCl fall below 50 mL/min at the time of the last draw. Based on clinical considerations at that time, regimens were not adjusted or changed for any of the 4 subjects with eCrCl <50 mL/min.

Individuals with increases in SCr of ≥50% and/or 0.5 mg/dL from baseline were identified. One, two, and three subjects from RAL, DTG, and EVG/c groups, respectively, met these criteria. One subject's (RAL) SCr was unusually low at baseline and returned towards the "normal" range for the patient over the study period. Upon follow up in these 6 patients, 4 of the 6 had their SCr return towards and remain within 0.3 mg/dL from baseline. The final patient's SCr increased by 0.53 mg/dL (55%) on EVG/c but remained relatively stable thereafter.

Overall, the study population was relatively healthy with a majority of patients having CD4 counts >200 cells/μL and undetectable viral loads at baseline. This would be expected because more patients are initiating ARVs at higher CD4 counts. In addition, subjects in this study could have been previously virologically suppressed, but they switched ART for simplification or avoidance of adverse effects. Patients with multiclass resistance or deep salvage therapies that might include combinations of protease inhibitors or nonnucleoside reverse-transcriptase inhibitors and INSTIs were not included in this analysis.

Limitations to this study include the single-center, retrospective chart review design and a relatively small sample size. Adherence was assessed by self-reports and achievement of virologic suppression. Unlike controlled clinical trials, and as expected in clinical practice, timing of follow-up and laboratory draws were inconsistent among patients, so the number of SCr measurements were not uniform throughout all groups. The requirement for, at minimum, a baseline SCr and 2 additional SCr levels (with at least 1 at ≥6 months after INSTI initiation) should provide a reasonable estimate of change in SCr and CrCl.

CONCLUSIONS

Serum creatinine and eCrCl changes in this standard clinical setting were similar to those seen in clinical trials for RAL, DTG, and the fixed-dose cobicistat-elvitegravir formulation. In this cohort, after initiation of the INSTI regimen, few patients had increases in SCr from baseline of >50% or 0.5 mg/dL and no discontinuations due to renal insufficiency were documented.

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Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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