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ORIGINAL RESEARCH

META-INSTI: metabolic adverse events following integrase strand transfer inhibitor administration in spontaneous adverse event reports

Milena M Murray[1,2], Lara Fakhouri[1], Spencer E Harpe[1]

[1]Midwestern University College of Pharmacy, Downers Grove, IL, USA; [2]Northwestern Medicine, Glen Ellyn, IL, USA

Abstract

Background: Metabolic effects of integrase strand transfer inhibitors (INSTIs) have been reported. The FDA Adverse Event Reporting System (FAERS) is a publicly available database that captures spontaneously reported adverse events. The objective of this study was to evaluate the relationship between INSTIs and metabolic adverse events using the FAERS database.

Methods: FAERS data were queried from quarter 4 of 2007 through quarter 4 of 2019 and limited to adults. The Standardized MedDRA Query for 'hyperglycaemia/new-onset diabetes mellitus' (H/DM) was used to identify metabolic adverse events of interest. Weight gain was analysed as a separate event. Reporting odds ratios (RORs) and 95% CIs were calculated for the INSTI class and individual agents.

Results: Over 10.1 million FAERS reports were identified. Any INSTI was mentioned as a primary and/or secondary suspect agent in 18,400 (0.18%) reports (bictegravir: 1414 [0.01%]; dolutegravir: 7840 [0.08%]; elvitegravir: 4034 [0.04%]; raltegravir: 5551 [0.05%]). RORs (95% CI) for H/DM and weight gain for any INSTI were 1.20 (1.15–1.27) and 2.16 (1.96–2.38). For individual agents, RORs (95% CI) for H/DM and weight gain were as follows: bictegravir, 1.23 (1.10–1.37) and 6.82 (5.50–8.41); dolutegravir, 1.28 (1.19–1.39) and 1.86 (1.58–2.18); elvitegravir, 0.76 (0.56–1.02) and 1.63 (1.37–1.92); and raltegravir, 1.00 (0.90–1.11) and 3.29 (2.77–3.91). H/DM was noted in 159 bictegravir and 712 dolutegravir reports.

Conclusion: Overall, H/DM was associated with bictegravir and dolutegravir and weight gain with all INSTIs. Clinicians should know the potential relationship between INSTIs and metabolic effects and institute appropriate monitoring.

This paper was previously presented: META-INSTI: Metabolic Adverse Events Following Integrase Strand Transfer Inhibitor Administration in Spontaneous Adverse Event Reports. Platform Presentation. ID Week. Virtual 2020.

Keywords: HIV, hyperglycaemia, INSTI, metabolic, weight gain.

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Introduction

Integrase strand transfer inhibitors (INSTIs) are the mainstay of therapy in the treatment of HIV. National guidelines recommend them as first-line therapy for most people with HIV (PWH).[1] These agents are generally well tolerated; however, metabolic adverse events, such as weight gain and hyperglycaemia, have been reported with this drug class.[1,2] These effects may cause concern or require increased monitoring. Weight gain is of concern, especially in PWH, who may already be overweight or obese.

Several studies have found metabolic adverse events following the use of INSTIs. Weight gain and hyperglycaemia were common amongst individuals taking antiretroviral therapy (ART) but were more common with INSTIs.[2] A review comparing weight gain amongst INSTIs *versus* non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) reported that

INSTIs, specifically dolutegravir and bictegravir, were associated with significantly more weight gain when compared with NNRTIs and PIs.[3] Additionally, case reports have noted significant increases in blood glucose with several INSTIs.[4–6]

The FDA Adverse Event Reporting System (FAERS) is a publicly available database that captures spontaneously reported adverse events. Analysis of these data allows for determining whether rare or unknown events represent a cause for concern. These adverse events represent 'real-world' post-marketing pharmacovigilance data. The objective of this study was to evaluate the relationship between INSTIs and metabolic adverse events using the FAERS database.

Methods

FAERS data were queried from quarter 4 of 2007 through quarter 4 of 2019 and limited to adults. The Standardized MedDRA Query for "hyperglycaemia/new-onset diabetes mellitus" (20000041; H/DM) was used to identify metabolic adverse events of interest. Weight gain was defined as increased weight or increased BMI and was analysed as a separate event. Reporting odds ratios (RORs) and 95% CIs were calculated for the INSTI class and individual agents. The Midwestern University Institutional Review Board approved this study in May 2020.

Results

After deduplication, the FAERS database contained over 10.1 million reports from quarter 4 of 2007 through quarter 4 of 2019, of which 732,591 (7.2%) reports were identified for this study. In addition, weight gain was noted in 109,566 (1.1%) reports. The most common reporters were consumers (49%) and physicians (23%) from the USA, United Kingdom and Japan. The mean (SD) age was 57 (17) years, and 63% of individuals experiencing adverse effects were women. An INSTI was mentioned as a primary and/or secondary suspect agent in 18,400 (0.18%) of reports for the adverse effects of interest. The number of reports were 1414 (0.01%) for bictegravir, 7840 (0.08%) for dolutegravir, 4034 (0.04%) for elvitegravir and 5551 (0.05%) for raltegravir.

The RORs (95% CI) for any INSTI related to H/DM and weight gain were 1.20 (1.15–1.27) and 2.16 (1.96–2.38). Specific INSTI agent RORs for H/DM and weight gain were as follows: bictegravir, 1.23 (1.10–1.37) and 6.82 (5.50–8.41); dolutegravir, 1.28 (1.19–1.39) and 1.86 (1.58–2.18); elvitegravir, 0.76 (0.56–1.02) and 1.63 (1.37–1.92); raltegravir, 1.00 (0.90–1.11) and 3.29 (2.77–3.91). H/DM was noted in 159 and 712 reports for bictegravir and dolutegravir, respectively.

Discussion

These results suggest that H/DM and weight gain were noted with several INSTIs analysed from the FAERS database. Current guidelines recommend monitoring for the development of glycaemic dysregulation that ART or HIV may cause.[1] INSTIs are reported to have a significant effect on weight; however, the role of the nucleoside reverse transcriptase inhibitor backbone in weight gain is still being studied.[2] Weight gain was initially credited to a 'return to health phenomenon'; however, data have indicated that INSTIs may be associated with weight gain.[7]

Several studies are available describing the impact of the INSTI class on weight. A pooled analysis of ART-naive PWH enrolled in eight clinical trials, including over 10,000 person-years follow-up, reported that the INSTI class was associated with more weight gain than PIs and NNRTIs.[8] A study compared weight gain after initiating an INSTI or PI-based HIV regimen in 1588 PWH for a median follow-up of 9.3 months.[9] PWH who began an INSTI had a 1.3-kg greater mean weight gain and a higher proportion with >5% weight gain than when initiating a PI-based regimen.[9] Increases in weight and BMI were seen in women switching to an INSTI (with or without tenofovir alafenamide) in a study of approximately 1500 women with HIV who did not have obesity.[10] In 156 PWH who switched to an INSTI-based regimen, the mean subcutaneous central adipose tissue area increased approximately three-fold (p=0.011), and the visceral adipose tissue area increased seven-fold (p<0.001).[11] A real-world retrospective study compared weight gain in PWH taking darunavir/cobicistat/emtricitabine/tenofovir alafenamide (n=452) to weight gain in PWH taking bictegravir/emtricitabine/tenofovir alafenamide (n=497) and reported that those in the latter group had significantly more weight gain at 9 months (mean weight difference 2.5 kg; p<0.01).[12]

The risk of diabetes in PWH can be four times greater than in the general population and manifests at an earlier age than in people without HIV.[1,13] The incidence of diabetes mellitus was studied in PWH taking INSTIs *versus* NNRTIs or PIs.[14] There were 265 incident cases of diabetes mellitus over 8 years in almost 20,000 PWH. New-onset diabetes mellitus occurred in 0.91% (31/3403) with an INSTI-based regimen, 1.37% (77/5601) with an NNRTI-based regimen and 1.50% (157/10,458) with a PI-based regimen.[14] Other risk factors for diabetes were age >37 years, Black race and BMI >30 kg/m^2. The ACTG A5260s study reported impaired glucose tolerance in 234 PWH.[15] The study aimed to correlate adipokines and metabolic and inflammatory markers over 96 weeks. The authors

reported a correlation between leptin changes and fasting glucose changes ($p<0.05$).[15]

Limitations of this analysis must be considered. The FAERS database is subject to bias, including the exclusion of healthy individuals and reporting bias. RORs offer an indication of potential signal strength. Interpretation of these results must be made considering these limiting factors. Additionally, the variance between bictegravir and dolutegravir may be due to the confounding issue of formulation availability. Dolutegravir is available as a separate agent and may be used with other agents, whereas bictegravir is only available as a fixed-dose, single-tablet regimen. Other study designs are required to determine the actual risk of H/DM with the INSTI class.

Conclusion

Overall, in this study of FAERS data, H/DM was associated with bictegravir and dolutegravir, and weight gain was associated with all INSTIs. Therefore, clinicians should be aware of the potential relationship with INSTIs and monitor PWH appropriately with regards to metabolic effects. Future clinical studies to evaluate these findings are warranted.

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Correspondence: Milena Murray, Midwestern University College of Pharmacy, Department of Pharmacy Practice, 555 31st St., Downers Grove, IL, 60515, USA. E-mail: mmurra@midwestern.edu

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