Therapeutic Drug Monitoring of the Biosimilar SB2 (RENFLEXIS™, Infliximab-abda) using LabCorp Infliximab Assays for Drug Level and Anti-Drug Antibodies

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I. Introduction

Therapeutic drug monitoring (TDM) of infliximab (IFX) concentration and anti-infliximab antibody (ADA) titer informs physician clinical decision-making in the management of inflammatory bowel disease (IBD). A TDM-based approach may improve clinical efficacy and longevity of anti-TNFa agents. The LabCorp IFX TDM test (drug and ADA levels) has been validated and published in peer-reviewed literature [1, 2] and is widely used by clinicians to help maximize treatment response [3].

Recently approved by the FDA for treatment of IBD, Renflexis™ (SB2, infliximab-abda) is a biosimilar of the originator anti-TNFa inhibitor (infliximab). The aim of this study was to validate the LabCorp IFX TDM test for the quantification of serum SB2 concentrations and ADA.

II. Assay Validation

Drug Assay Method:
The IFX drug assay reaction utilizes a capture reagent that consists of TNFa bound to human anti-human TNFa antibody immobilized onto a Mesoscale Discovery (MSD) 96-well plate. The signal antibody is a monoclonal anti-infliximab conjugated with an electrochemiluminescent reagent (SULFO-TAG) reporter molecule.

Using the same design, the SB2 drug assay was developed and validated. It was calibrated using SB2 standards which were prepared by spiking a donor serum pool with SB2 drug.

ADA Assay Method:
The IFX ADA assay utilizes both biotinlated and SULFO-TAG-conjugated drug. Antibody reactions form a sandwich between biotin- and SULFO-TAG-conjugated drug molecules. Analysis is done on a MSD 96-well streptavidin plate using electrochemiluminescent signal. The SB2 ADA assay method was developed and validated using the same experimental principles with both biotin-conjugated and SULFO-TAG reporter are conjugated to SB2 drug instead of originator IFX.

III. Results

Both SB2 drug level and ADA showed excellent agreement to IFX drug level and ADA, respectively (Table 1). Across the entire measuring range, SB2 assay accuracy (±12% bias) and precision (≤10% CV) were equivalent to that of the IFX assay (±5% bias and <10% CV, respectively). Most importantly, spike and recovery of Renflexis using the IFX drug assay was equivalent to the recovery of originator IFX using the IFX drug assay. Using the same donor serum pool, two sets of spike & recovery samples were prepared: SB2 at 0.25, 0.5, 1.0, 2.0, 4.0, 8.0 & 16.0 µg/mL, target and originator IFX at the same dilution concentrations. Targets were read using the originator IFX and SB2 drug assays, respectively.

Percent recovery of SB2 ranged from 87% to 114%; IFX recovery was 83% to 110%. Therefore, average spike and recovery was 99% for both SB2 and IFX assays. Furthermore, linearity of serial dilutions of SB2 was also assessed using the originator IFX assay, demonstrating excellent recovery and linearity (Table 1, right).

Both the SB2 drug assay and IFX drug assay were used to analyze 51 serum samples of IBD patients treated with originator IFX (Figure 1). The calculated linear regression between the two methods was y = 1.11x - 0.13, r = 0.99.

At the same time, the SB2-specific anti-drug antibody assay performed essentially identically to the originator IFX ADA assay in terms of precision (≤10% CV), accuracy (±5% bias), linearity, drug tolerance and sensitivity (Table 2). Furthermore, SB2-ADA positive serum samples from IBD patients were tested using both SB2 ADA and originator IFX ADA assays; antibody titer values were compared to yield a linear regression of y = 1.10x - 0.87, r = 0.99. (Figure 2).

Additionally, confirmatory testing using three known IFX ADA positive patient samples was performed for both the originator IFX assay and the SB2-specific anti-drug antibody assay. Confirmatory testing involved the addition of the corresponding drug (either originator infliximab or Renflexis drug) to each sample. In true ADA-positive samples, the excess drug competes with drug antibodies and suppresses the resulting signal of the assays demonstrated appropriate signal suppression in the presence of excess drug; both assays exhibited recoveries of <10% for each sample (Table 2).

Finally, twenty-five drug-naive human serum samples were tested using the SB2-specific anti-drug antibody assay to confirm the lack of false positive ADA. All patient samples tested as less than the LLOQ of 22 ng/mL (Table 2).

IV. Conclusion

This study demonstrates complete cross-reactivity of Renflexis (SB2, infliximab-abda) vs. originator infliximab using the LabCorp IFX TDM assay. Analytical performance of all tested parameters demonstrated equivalency. Healthcare providers can confidently use the LabCorp IFX TDM test to monitor Renflexis (SB2, infliximab-abda) serum drug levels and ADA titers in their patients.

V. References

2. KY Chun & JM Yang, The Relationship Between Serum Infliximab and Adalimumab Concentrations and Their Corresponding Anti-Drug Levels: Analysis of over 50,000 Patient Results Using Lab Developed Chemiluminescent Immunoassays. Poster P1207 25th UEG Week Oct 28- Nov 1, 2017 Barcelona Spain

Table 1: Drug Assay Analytical Performance

<table>
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<tr>
<th>Sample</th>
<th>Theoretical Dose (µg/mL)</th>
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<th>IFX Drug Assay</th>
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Table 2: Anti-Drug Antibody Assay Performance

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Figure 1: Drug Assay Method Comparison

Figure 2: Anti-Drug Antibody Assay Method Comparison