Biologic drug and anti-drug antibody monitoring: TNF inhibitors infliximab, adalimumab and certolizumab pegol in 128,537 patient samples

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Introduction

Serum assays to measure biologic drugs, especially TNF inhibitors, and their anti-drug antibodies (ADAb) are utilized to manage suboptimal response and to proactively titrate doses and dosing intervals. Sensitive, drug-tolerant and high-resolution anti-drug antibody assays are an increasingly important tool necessary for detection and management of immunogenicity, especially when low-intermediate in titer and potentially reversible.[1]

Aims and methods

Serum samples from 72,819, 53,131 and 2,587 patients were analyzed for infliximab (IFX), adalimumab (ADL), and certolizumab pegol (CTZ) drug (in µg/mL) and corresponding anti-drug antibodies (in ng/mL) as measured by drug-specific lab developed chemiluminescent immunoassays. Drug assays measure the free ADAb-unbound fraction of drug when serum ADAb are present. All ADAb assays detect total antibodies (including IgM & IgG subtypes), and their drug tolerance has been validated. Drug-specificity of ADAbs is verified by a confirmatory test step. An extensive blinded method comparison of our IFX and Anti-IFX assays has been published.[2]

Results

Drug and ADAb results are summarized in Table 1. Immungenicity rates were 31%, 29% and 68% for IFX, ADL and CTZ, respectively.

ADAb-free samples were used to evaluate distribution of drug levels. Even in the absence of immunogenicity, many patients are subtherapeutic, 25%, 45% and 40%, for IFX, ADL and CTZ, respectively, when using proposed therapeutic targets of 5 µg/mL for IFX, 7.5 for ADL, and 20 for CTZ.[3]

	IFX	ADL	CTZ
Therapeutic Target Drug Concentration (µg/mL)[3]	5.0	7.5	20.0
Range of Drug Concentrations in ADAb-Negative Samples	n=50,325 0.4 to 593 µg/mL	n=37,653 0.6 to 74 µg/mL	n=837 1.0 to 138 µg/mL
Distribution of Drug Concentrations in Anti-Drug Ab-negative samples	25%: <5.0 µg/mL 27%: 5-10 µg/mL 27%: 11-20 µg/mL 21%: >20 µg/mL	45%: <7.5 µg/mL 37%:7.5-12 µg/mL 14%: 13-20 µg/mL 4%: >20 µg/mL	40%: <20 µg/mL 32%: 20-39 µg/mL 28%: >40 µg/mL
Immunogenicity	n=22,494 31%	n=15,478 29%	n=1,750 68%
Range of ADAb Titers	22 to 582,749 ng/mL	25 to 863,115 ng/mL	40 to 236,148 ng/mL
Anti-Drug Ab Titer Designation Cut-points (ng/mL)	Low: <200 High: >1,000	Low: <100 High: >800	Low: <1,000 High: >5,000
Inverse Relationship Between Drug and Anti-Drug Ab Levels?	yes	yes	yes
Interpretive Comments for Anti-Drug Ab	Anti-drug antibody levels should be interpreted in the context of the concomitant free drug concentration at trough. Low titer anti-drug antibodies may be transient while high titers are likely to be more consequential.		
	Some immunogenicity is reversible. Elimination of intermediate titer and some high titer anti-drug antibodies has been achieved with dose escalation and/or methotrexate or thiopurine.		Non-neutralizing anti-pegol antibodies cannot be ruled out.

Table 1. Analysis of IFX, ADL, CTZ and respective anti-drug antibodies.

Results (continued)

Therapeutic levels were observed in 27% for IFX, 37% for ADL and 32% for CTZ. Higher drug concentrations in the remaining samples may represent non-trough collected samples.

A wide range of immunogenicity titers was observed. Analyses of the inverse relationship between ADAb and drug led to determination of cut-points for low/high titer designations where in the setting of high ADAb, almost invariably, concomitant free drug is very low or nil. As a good rule, anti-drug antibodies should be interpreted in the context of the concomitant free drug trough concentration.

Conclusion

Here, we report concentrations of TNF-inhibitors used to treat IBD and their anti-drug antibodies in >128,000 patient samples. Though clinical histories and blood collection timing are not known, we observed that many patients may have insufficient drug levels. Immunogenicity to TNF inhibitors was frequent where a wide numeric range of ADAb was observed. Numeric ADAb antibody results should be interpreted with the help of titer designations by the laboratory because low to intermediate titers may be transient or reversible whereas high titers with nil or very low drug indicate refractory immunogenicity. High resolution ADAb assays have enabled the early detection and successful reversal of intermediate titers of Anti-IFX and Anti-ADL with dose escalation +/- co-immunommodulator.[1] Thus, biologic TDM aims to optimize drug efficacy and longevity by informing and expediting adjustments to medication.

References

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