Comparison of assays used for therapeutic drug monitoring of anti-TNFα inhibitors in inflammatory bowel disease

Stefania Cheli[1], Diego Savino[1], Dario Cattaneo[1], Emilio Clementi[2,3]

1 Unit of Clinical Pharmacology, ASST Fatebenefratelli Sacco, University Hospital, Milano, Italy;
2 Clinical Pharmacology Unit, Department of Biomedical and Clinical Sciences, L. Sacco University Hospital, Università degli Studi di Milano, Milan, Italy;
3 Scientific Institute IRCCS Eugenio Medea, Bosisio Parini, Italy

INTRODUCTION

Anti-tumor necrosis factor alpha (anti-TNFα) inhibitors are used extensively for the management of moderate to severe inflammatory bowel disease (IBD) in both adult and paediatric patients. TDM has become key component of managing anti-TNFα therapy in order to achieve the target serum concentrations for efficacy due to the variability in the pharmacokinetics of these drugs.

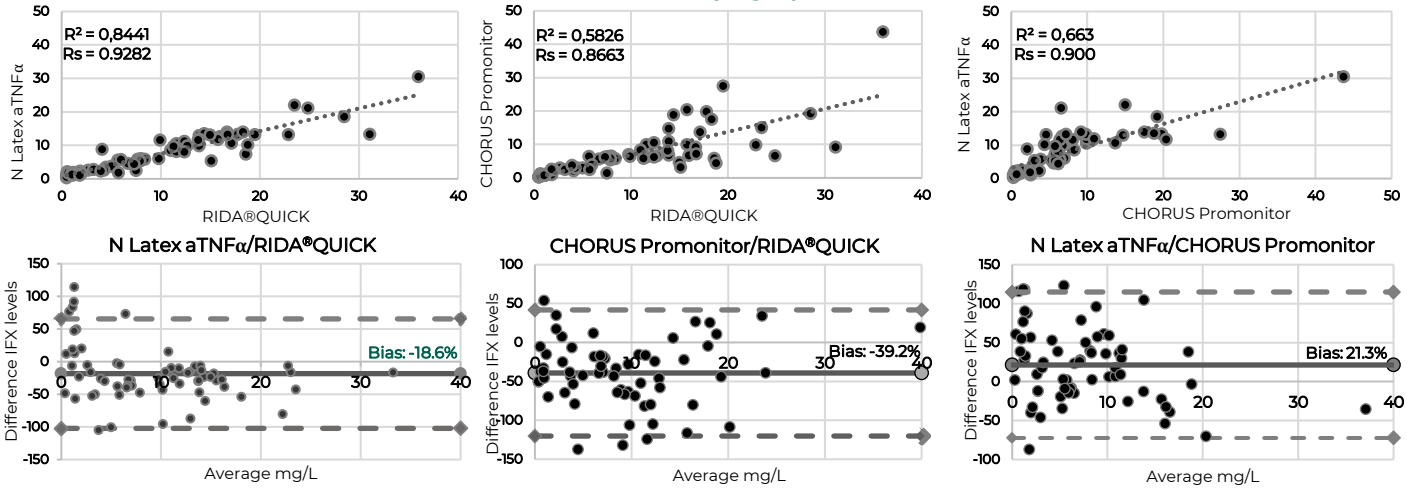
MATERIALS AND METHODS

Trough serum concentrations were measured with three different commercial kits: RIDA®QUICK (lateral flow techniques by r-biopharm AG), N Latex aTNFα (nephelometric assay by Siemens Healthcare GmbH) and CHORUS Promonitor (monotest immunoassay by DIESSE Diagnostica Senese) according to the manufacturers' instructions. Anti-drug antibodies (ADAs) detection were performed in samples with undetectable drug levels (<1 mg/L) using ELISA methods commercialized by the same manufacturers: RIDASCREEN® anti-IFX/ADM Antibodies (ELISA microplates by r-biopharm) and CHORUS Promonitor Anti-IFX/ADM (monotest immunoassay by DIESSE Diagnostica Senese); Siemens does not currently hold the kits.

RESULTS

120 IBD patients were collected, 65 treated with Infliximab (IFX) and 58 with Adalimumab (ADM). Linear regression (R^2 and Rs Spearman Correlation) and Bland-Altman plots of trough level for each assay pair are shown in these graphs.

IFX TDM (mg/L)



The concordance between methods was better for patient classification within the subtherapeutic range (TL < 3mg/L). The disagreement for elevated concentrations (TL ≥ 7 mg/L) could be due, in part, to the higher upper quantification limit of CHORUS Promonitor test than the other two kits, which implies that an extra dilution or extrapolation out of the calibration range was required in RIDA®QUICK and N Latex aTNFα assays, respectively.

Trough Levels (TL, mg/L)	N° of patients (%)			Differences (%)		
	RIDA®QUICK	N Latex aTNFα	CHORUS Promonitor	N Latex aTNFα vs RIDA®QUICK	CHORUS Promonitor vs RIDA®QUICK	N Latex aTNFα vs CHORUS Promonitor
IFX TL < 3	23	30.8	33.8	7.8	10.8	-3
IFX TL: 3-7	15.5	20	35.4	4.5	19.9	-15.4
IFX TL ≥ 7	61.5	49.2	30.8	-12.3	-30.7	18.4

ADM TDM

Concerning ADM trough level, the greatest concordance was found between RIDA®QUICK and N Latex aTNFα assays (R^2 = 0,916), however the correlations with CHORUS are also good (R^2 = 0,757 vs RIDA®QUICK and R^2= 0,806 vs N Latex aTNFα). Moreover, the Bland-Altman analysis shows a good agreement between the three techniques with low biases and less than 10% of the values outside the 95% limits of agreement. Additionally, the levels categorization based on the therapeutic ADM ranges revealed few differences between the three assays.

ADAs

Anti-IFX Antibodies		RIDASCREEN® (ng/ml)		
		Positive	Negative	Total
CHORUS Promonitor (AU/ml)	Positive	25	0	25
	Negative	1*	6	7
	Total	26	6	32
Analysis		Cohen's k: 0.904 agreement: 96.87 %		

Anti-ADM Antibodies		RIDASCREEN® (ng/ml)		
		Positive	Negative	Total
CHORUS Promonitor (AU/ml)	Positive	13	0	13
	Negative	2*	8	10
	Total	15	8	23
Analysis		Cohen's k: 0.819 agreement: 91.30 %		

*These discrepancies were due to samples measured close to the lower detection limits of the two methods. For CHORUS Promonitor, in one anti-ADM test, the correct result was obtained after sample pre-dilution.

CONCLUSIONS

In this study, we found a good mathematical correlation of IFX and ADM trough levels measured with all the three tested kits, demonstrating that they are all suitable for clinical use. A statistically significant correlation is not sufficient to prove that these tests are interchangeable, especially during the longitudinal follow-up of individual patient.

DIESSE

Sistema Socio Sanitario Regione Lombardia
ASST Fatebenefratelli Sacco