Validation of the baseline ADAMTS5 mRNA levels as a prediction biomarker for the efficacy of infliximab ; a multicenter clinical trial

Kensei Tsuzaka[1,2], Masayoshi Nagata[2], Koichi Amano[3], Toshihide Mimura[4], Shin-ichiro Kagami[5], Yusuke Miwa[6], Keigo Ikeda[7], Takeshi Mitsuka[8], Hideo Kanai[9], Iwao Sekigawa[10]

[1]Iruma Heart Hospital, Saitama, JAPAN, [2]Tokyo Kenko Clinic, Tokyo, JAPAN, [3]Saitama Medical Center, Saitama Medical University, Saitama, JAPAN, [4]Saitama Medical University, Saitama, JAPAN, [5]Asahi General Hospital, Chiba, JAPAN, [6]Showa University School of Medicine, Tokyo, JAPAN, [7]Juntendo University Urayasu Hospital, Chiba, JAPAN, [8]Mitsuka Rheumatism Clinic, Chiba, JAPAN, [9]Kanai Medical Clinic, Chiba, JAPAN

PURPOSE

A disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS5) has been reported to play a key role in aggrecan degradation in cartilage. Lower level of the baseline blood ADAMTS5 mRNA level has been also reported to predict the better response to infliximab (IFX) in RA patients using a single-center study. In this study, we performed a prospective, multicenter, and observational study to derive and validate the baseline blood ADAMTS5 mRNA that would be predictive of the efficacy of IFX in RA patients.

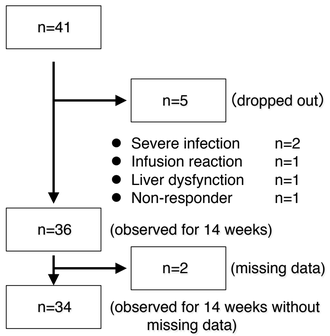
METHODS

1) Patients: 41 active (DAS28_ESR>3.2) RA patients who fulfilled 2010 ACR/EULAR classification criteria for RA were recruited from 9 hospitals in Japan and were received 3mg/kg of IFX at 0w, 2w, 6w, and 14 weeks.
2) Patient assessment
   IFX-treated patients were assessed before IFX treatment and after 14 weeks for DAS28_ESR, DAS28_CRP, SDAI, CDAI, Boolean, and HAQ, and were categorized according to the EULAR response criteria and EULAR remission criteria.
3) Quantification of ADAMTS5 mRNA
   Peripheral whole blood samples were collected at baseline and ADAMTS5 mRNA was quantified using real-time PCR (BiologicMate®).

PATIENT BACKGROUND

number of patients	41
Male: Female	29:12
Age (y/o)	54.1 ± 12.3
Disease duration (years)	4.5 ± 7.1
Dose of MTX at 0w (mg/week)	10.6 ± 2.8
Dose of predonisolone (mg/day)	1.8 ± 2.7
number of bio-naïve patients	38 (92.7%)
DAS28_ESR(0w)	5.07 ± 1.07
DAS28_CRP(0w)	4.23 ± 1.03
SDAI(0w)	23.5 ± 1.03
HAQ(0w)	1.10 ± 0.82
ADAMTS5 mRNA (Index)(0w)	4.09 ± 3.15

RESULTS



EFFECTIVENESS OF IFX

	after 14weeks
EULAR Response, %(no)	
Good	44.1%（15/34）
Moderate	41.2%（14/34）
None	14.7%（5/34）
DAS_ESR remission	29.4%（10/34）
DAS_CRP remission	41.1%（14/34）
SDAI remission	23.5%（8/34）
CDAI remission	23.5%（8/34）
Boolean remission	23.5%（8/34）

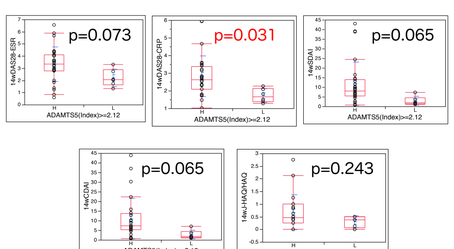
Cut-off value of ADAMTS5 mRNA for predicting SDAI remission by IFX

	Cut-Off value	AUC(%)
IFX	2.1×10^{-4}	0.677 for SDAI remission at 14 wks

No difference in the patient background between ADAMTS5 High (>2.1) and Low (≤ 2.1) groups

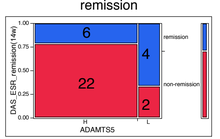
	ADAMTS5 High (n=28)	ADAMTS5 Low (n=6)	*p*-value
Age (y/o)	52.5 ± 11.8	57.2 ± 11.9	0.384
Disease duration (years)	4.2 ± 5.5	6.9 ± 12.8	0.417
Dose of MTX at 0w (mg/week)	10.6 ± 2.6	9.7 ± 2.9	0.422
Steroid usage （%）	39.3%	16.7%	0.269
Bio-naïve patients (%)	89.3%	100%	0.243
DAS28_ESR（0w）	5.15 ± 1.09	4.30 ± 0.84	0.081
DAS28_CRP (0w)	4.37 ± 1.06	3.55 ± 0.81	0.084
SDAI（0w）	24.4 ± 12.2	19.9 ± 10.4	0.404
HAQ (0w)	0.97 ± 0.77	0.76 ± 0.39	0.549

RA activity has been improved in the ADAMTS5 Low (≤ 2.1) group



Prediction of the remission after 14 weeks treatment by IFX using Low (≤ 2.1) ADAMTS5

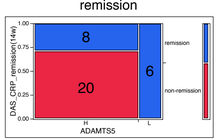
Prediction of DAS_ESR remission



p=0.027

Sensitivity = 40.0%
Specificity= 91.7%
PPV = 66.7%
NPV = 78.6%
Accuracy = 76.5%

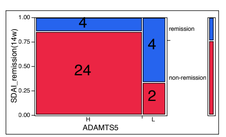
Prediction of DAS_CRP remission



p=0.001

Sensitivity = 42.9%
Specificity= 100.0%
PPV= 100.0%
NPV= 71.4%
Accuracy= 76.4%

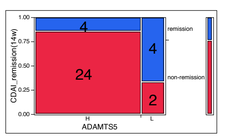
Prediction of SDAI remission



p=0.006

Sensitivity = 50.0%
Specificity= 92.3%
PPV= 66.7%
NPV= 85.7%
Accuracy= 76.5%

Prediction of CDAI remission



p=0.006

Sensitivity = 50.0%
Specificity= 92.3%
PPV= 66.7%
NPV= 85.7%
Accuracy= 76.5%

CONCLUSION

The baseline blood ADAMTS5 mRNA level was validated as a biomarker for the prediction of the response to IFX in RA patients using the multicenter clinical trial.