

CHANGES IN PLASMA BIOMARKER PANEL OF CARDIOVASCULAR RISK WITH BIOLOGIC AGENTS IN RHEUMATOID ARTHRITIS

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Introduction

Two large registries recently reported a beneficial effect of anti-TNF biologics on cardiovascular (CV) risk in RA.

Yet, the mechanism of CV risk reduction with anti-TNFs remains unclear.

It is also unknown if this effect is specific to the anti-TNF class of biologics. CRP reduction with statins predicts CV risk in the general population, but this may reflect improvements in other candidate CV risk biomarkers.

Objectives

- To investigate the effects of biologics on a CV panel of plasma cytokines, matrix metalloproteinases (MMPs), VEGF, high sensitivity (hs) CRP and cardiac troponin-I (cTnI) panel.
- To compare the effects of anti-TNF biologics (infliximab, adalimumab, and etanercept) and T-cell costimulatory modulation (abatacept) on the CV risk plasma panel.

Methods

We examined the above plasma biomarker panel at baseline and at 3-month follow-up obtained from an observational cohort of 60 RA patients. Biomarker assays were performed using a fluorescence based, highly sensitive Erenna Immunoassay system (Singulex, Inc).

Clinical assessments included DAS28-ESR. Change in each biomarker was assessed as the ratio of the post-drug to the pre-drug value using the Wilcoxon signed rank test for the overall cohort, as well as the anti-TNF and abatacept groups separately.

References:

- Kremer J. *Ann Rheum Dis* 2005, 64 suppl 4; iv 37-41.
- Greenberg J. *Ann Rheum Dis* 2011, 70 (4): 576-82.
- Dixon W. *Arthritis Rheum* 2007, 56 (9): 2905-12.
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Results

The study cohort (n=60) included 33 anti-TNF drug starts (11 adalimumab, 18 etanercept, 4 infliximab) and 27 abatacept drug starts. 76% were female, mean (SD) age of 52 (13) years (Table 1). Baseline biomarkers levels by treatment groups are presented in Table 2.

Across all biologic drugs, significant reductions were observed for DAS28-ESR and hsCRP as expected. Other significant reductions were observed for VEGF, IL-17F, IL-6, proMMP-9, and total MMP-9 (Table 3). Although the effect size varied between the anti-TNF and abatacept groups, the only significant difference in drug effects was for TNF ($p < 0.001$) and sTNF RII ($p = 0.0065$) levels.

Table 2. Baseline Biomarkers Levels by Treatment Group

Biomarker	Abatacept	Etanercept	Adalimumab	Infliximab
VEGF pg/ml	113 (247)	225 (768)	42.1 (23.6)	70.3 (30.3)
IL-17A pg/ml	0.859 (0.831)	1.7 (3.56)	1.03 (0.93)	2.21 (1.77)
IL-17F pg/ml	404 (872)	467 (749)	262 (290)	1019 (1366)
IL-17 A/F pg/ml	24.9 (116)	14 (51.5)	9.45 (27.6)	17.5 (20.1)
IL-1 beta pg/ml	3.23 (10.2)	0.968 (1.45)	4.24 (12.1)	8.78 (11.4)
IL-1 RA pg/ml	548 (471)	487 (267)	575 (227)	434 (264)
IL-6 pg/ml	10.9 (14.6)	10.3 (12.8)	32.4 (69.1)	58.7 (81.6)
IL-6 R alpha ng/ml	50.9 (12.6)	54.1 (13.2)	50.6 (12.9)	50.5 (15.1)
Total MMP9 ng/ml	891 (1068)	1444 (1659)	1340 (1049)	489 (153)
Pro MMP9 ng/ml	215 (332)	352 (495)	354 (337)	24.5 (4)
MMP2 ng/ml	71 (12.8)	69.5 (25.5)	69 (14.2)	65.1 (17.2)
TIMP2 pg/ml	152 (33.8)	144 (42.1)	141 (29.5)	124 (15.5)
MMP2/TIMP2 ng/ml	62.8 (10.6)	62.7 (22)	60.1 (11.2)	60.1 (11.1)
TNF alpha pg/ml	51.8 (179)	10.4 (11.4)	6.1 (1.99)	7.85 (5.54)
sTNF RII ng/ml	26 (73.1)	350 (1296)	12.8 (19.8)	77.9 (144)
sTNF RI pg/ml	1959 (1310)	1950 (807)	1947 (548)	1934 (494)
cTnI pg/ml	1.98 (1.6)	1.9 (1.48)	4.56 (10.6)	1.7 (0.7)

For all biomarkers, provided mean value and SD in brackets

Conclusions

Biologic therapies reduced plasma hsCRP as expected, as well as plasma MMP9, VEGF and IL-17F levels. MMP9 and VEGF have been reported as CV risk biomarkers in the general population.

Our results indicate:

- MMP9 and VEGF are responsive to RA immunomodulatory biologics.

- IL-17F is another pro-inflammatory biomarker that is responsive to immunomodulatory therapy and should be further explored as a biomarker of cardiovascular risk.

Table 1. Treatment groups demographics and baseline characteristics

	Abatacept	Etanercept	Adalimumab	Infliximab
Number of Subjects, N	27	18	11	4
Female (%)	23 (85)	15 (83)	11 (100)	3 (75)
Age, years, mean (SD)	49.5 (13)	54.5 (12)	54 (13)	52 (6)
DAS28, mean (SD)	5.64 (1.34)	5.7 (1.7)	5.57 (1.28)	5.66 (1.89)

Table 3. Ratio of week 12 to Baseline Biomarker Values

Biomarker	N	Median Ratio	P-value
DAS28	60	0.92	<0.001
CRP	60	0.81	0.013
VEGF	59	0.77	0.0029
IL-17A	59	1.06	0.564
IL-17F	60	0.76	<0.001
IL-17A/F	59	0.91	0.262
IL-1 beta	51	1.01	0.811
IL-1 RA	60	0.9	0.184
IL-6	60	0.84	0.0498
IL-6 R alpha	60	0.99	0.863
Total MMP9	60	0.77	0.0162
Pro MMP9	60	0.7	0.0198
MMP2	60	1.01	0.491
TIMP2	60	1.0	0.892
MMP2/TIMP2	60	1.0	0.496
TNF-alpha	60	1.04	0.087
sTNF RII	60	1.01	0.716
sTNF RI	60	1.02	0.212
cTnI	57	1.07	0.193