ACR70 Response and Its Dependence on Deep Tissue Efficacy

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The aim was to examine the demographic, clinical, and serum markers of tissue remodelling as predictors linked to ACR20, ACR50 and ACR70 responses to tocilizumab.

Background

Over the past decade, drugs developed for rheumatoid arthritis (RA) have been approved based on an ACR20 response rate of 60%.

There is an increasing need for new RA drugs to achieve an ACR100 response in a significant portion of patients. Achieving ACR100 can profoundly improve patients' quality of life by reducing pain, enhancing physical function, and decreasing fatigue.

The key question remains: which patients are likely to achieve ACR100?

An important aspect of RA pathogenesis involves the destruction and remodelling of bone, cartilage, and synovial tissue. Serum biomarkers that measure collagen and other extracellular matrix fragments can be used to assess disease activity at the tissue level. Examples include C1M (type I collagen destruction), C4M (type IV collagen destruction), and Osteocalcin (bone formation) [1].

Methods

A post-hoc analysis of the two active treatment arms (n=388) of the LITHE study was conducted [2]. LITHE was a double-blinded phase 3 RCT testing the efficacy of tocilizumab (4 and 8 mg/kg) on a background of MTX versus placebo in a DMARD-IR population. A logistic regression model was used to identify predictors (alpha=0.05) of ACR20, ACR50, and ACR70 response at week 16 of the study. Patients had a mean age of 52 years and were primarily normal weight white women (71.4%, 82.1%). Predictors included baseline demographics (age, sex, race, BMI) and clinical scores (DAS-ESR, steroid use (Y/N), number of previous DMARDs, disease duration). Additionally, baseline and 4-week percentage change in serum biomarkers (C1M, C2M, C3M, C4M, C6M, CRP, CRPM, CTX-I, ICTP, MMP3, Osteocalcin, PINP, VICM) were analysed. Fourteen patients were excluded due to missing data

Refs.

1. Bay-Jensen AC, Platt A, Byrjalsen I, Vergnoud P, Christiansen C, a. Karsdal MAM. Effect of tocilizumab combined with methotrexate on circulating biomarkers of synovium, cartilage, and bone in the LITHE study. Semin Arthritis Rheum. 2014;43:470–8. **2. Fleischmann RM**, Halland AM, Brzosko M, Burgos-Vargas R, Mela C, Vernon E, et al. Tocilizumab inhibits structural joint damage and improves physical function in patients with rheumatoid arthritis and inadequate responses to methotrexate: LITHE study 2-year results. Journal of Rheumatology. 2013;

Results

Odd ratios (95%-CI) for SD difference (baseline) or 10% 4-wk change in the biomarkers

		ACR20	ACR50	ACR70
Demographic and clinical data	Age			
	Sex			
	Race	2.13 [1.26 - 3.62]		
	BMI	0.94 [0.91 - 0.99]		
	Steroid use (Y/N)			
	No. of prev. DMARDs			
	DAS-ESR at BL	0.75 [0.59 – 0.96]		
Bone and cartilage destruction	C1M_BL			
	C1M_pct_04			
	ICTP_BL		0.64 [0.48 – 0.86]	1.90 [1.22 – 2.94]
	ICTP_pct_04	0.01 [0.00- 0.09]	0.0044 [0.0002 – 0.08]	129 [2.97 – 6230]
	OC_BL			
	OC_pct_04			0.92 [0.86 – 0.99]
	CTXI_BL			
	CTXI_pct_04			
	C2M_BL			
	C2M_pct_04			
Connective tissue destruction	C3M_BL			
	C3M_pct_04			
	C4M_BL			
	C4M_pct_04	0.90 [0.83 - 0.98]	0.83 [0.75 – 0.92]	1.15 [1.00 – 1.32]
	C6M_BL			
	C6M_pct_04			
	MMP3_BL			
	MMP3_pct_04			
Inflammation	VICM_BL			
	VICM_pct_04			
	CRP_BL			
	CRP_pct_04			

BL, Baseline; _pct_04, percentage change from baseline to 4 weeks

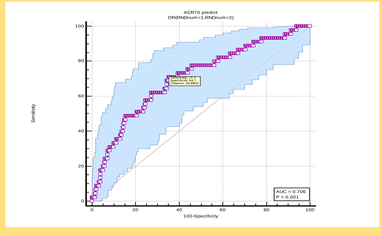
The ACR20, ACR50, and ACR70 response rates at week 16 were 52.6%, 27.1%, and 12.1% when combining the two active treatment arms.

Positive predictors for ACR20 included race, DAS-ESR, BMI, and 4-week change in C4M and ICTP.

Positive predictors for ACR50 were baseline ICTP and 4-week change in ICTP and C4M.

Positive predictors for ACR70 were baseline ICTP and 4-week change in ICTP, Osteocalcin, and C4M.

The AUC of the ACR70 predictive model was 0.71 with a sensitivity of 71.1 and specificity of 64.7 Patients scoring above the median in the model had a 3.5 times higher likelihood of achieving an ACR70 response.



Conclusion

While predictors of moderate response (ACR20) included clinical, demographic, and biomarker factors, predictors of **significant response (ACR70) were exclusively biomarkers of extracellular matrix fragmentation.**

To achieve remission (ACR70 or ACR100) may require therapeutic interventions that specifically target and address tissue remodelling processes