

THE USE OF A BLINDED TRUNCATED ULTRASOUND POWER DOPPLER JOINT COUNT VALIDATES EFFICACY DATA FROM AN EARLY PHASE OPEN LABEL DRUG STUDY TREATING RHEUMATOID ARTHRITIS THU0086

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Introduction

- Small open label pilot trials generate important information on tolerability, toxicity, pharmacokinetics, and antigenicity in the early phase investigation of new compounds in the treatment of rheumatoid arthritis (RA). However, because the standard disease activity measures (DAMs), such as the disease activity score in 28 joints (DAS28) have a major subjective component, the efficacy data acquired in such trials is generally felt to be much less reliable than that obtained in blinded trials.
- Incorporating more objective DAMs, and performing them in a blinded fashion, might enhance the validity of efficacy data in such an early clinical setting.
- One possible disease activity measure to fulfill this role would be an ultrasound power Doppler joint count (UPDJC) which has been shown to correlate with conventional clinical measures [1].

Methods

- The results of an open label trial in which Staph Protein A (PRTX-100, Protalex Inc.) was given to patients with active RA has been previously reported [2].
- PRTX-100 was infused once a week intravenously for four weeks, followed by five monthly infusions
- Standard disease activity measurements were obtained and in addition, an UPDJC was performed utilizing a truncated methodology [3] in which three sites at the dorsal wrist and three dorsal metacarpal sites were analyzed bilaterally for a total of twelve sites studied.
- UPDJCs were acquired in less than five minutes per study.
- There were a total of 117 UPDs performed on eleven patients.
- These UPDs were stored digitally and subsequently read twice in a blinded fashion after completion of the study by the investigator (CW). Each joint site was subjectively scored from 0 (normal) to 3 (severe) with a possible total score of 0 - 36.
- Intra-observer reliability was determined by two-way random intra-class correlations (ICC).
- Significant changes of UPDJCs and clinical DAMs from baseline to single time points were assessed by the paired T test and correlations were performed by the Spearman's coefficient (Rho).
- Effect size was determined by standardized mean difference (SMD).
- Clinical assessments and UPDJCs were obtained weekly for the first month, then monthly for five more months.

Ultrasound Power Doppler JC

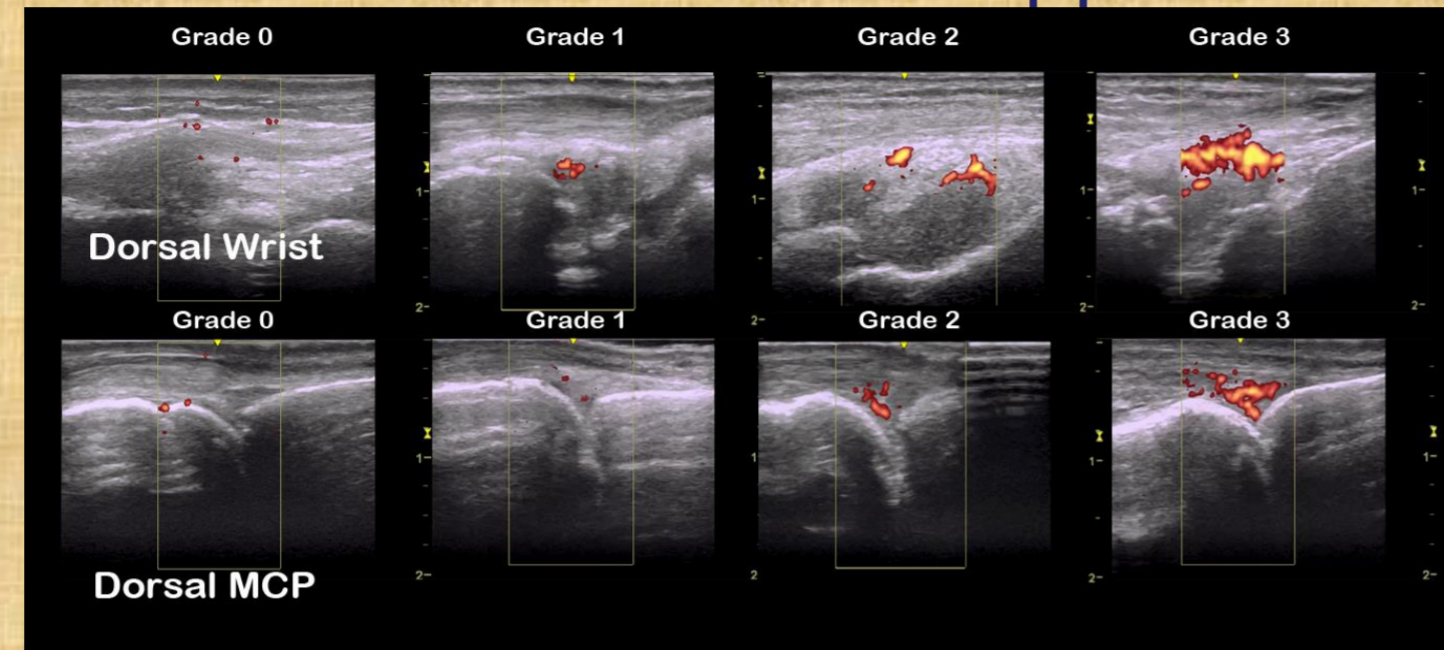


Figure 1. Examples of subjective grading of 0 (normal) to 3 (severe) is shown for the dorsal wrist site and the dorsal MCP site.

Results

- Intra-observer UPDJC score reproducibility was high (ICC = 0.886).
- Significant reductions ($p < 0.05$) in UPDJCs and the DAS28 were found at week 4 and on all subsequent visits (Table 1).
- Correlations between UPDJCs and DAMs total scores were moderate to strong. However, the total differences (mean change) from baseline vs total visits did not correlate, except for CRP vs UPDJCs ($n = 67$ $p = 0.471$, $p < 0.001$). But, some individual time points such as baseline vs month six showed several significant changes in mean differences (Table 2).
- SMDs for both UPDJCs and DAMs were high, but higher for the DAS28 (1.00-2.16) than for the UPD (0.83-1.10).

Timepoint	N	UPDJC	SD	Prob ¹	DAS28ESR		DAS28CRP		Prob ¹
					SD	Prob ¹	SD	Prob ¹	
Screen	11	8.2	3.3	NS					
Baseline	11	8.9	3.6	NS	5.92	1.08	5.2	1.05	
Week 1	11	8.5	3.0	NS					
Week 2	10	8.4	3.4	NS					
Week 3	10	6.9	3.8	NS	4.82	1.44	*		
Week 4	10	7.1	3.1	*	4.54	1.48	**	3.91	1.68
Month 2	10	7.2	3.2	*	3.76	1.41	***	3.34	1.56
Month 3	9	6.3	2.5	*	4.05	1.73	*	3.54	1.82
Month 4	9	7.1	3.6	*	3.54	1.47	***	2.83	1.51
Month 5	9	7.0	3.8	*	3.97	1.59	**	3.18	1.73
Month 6	11	7.2	3.7	*	4.08	1.67	**	3.10	1.76

¹: P = <0.05*, P = <0.005**, P = <0.0005***

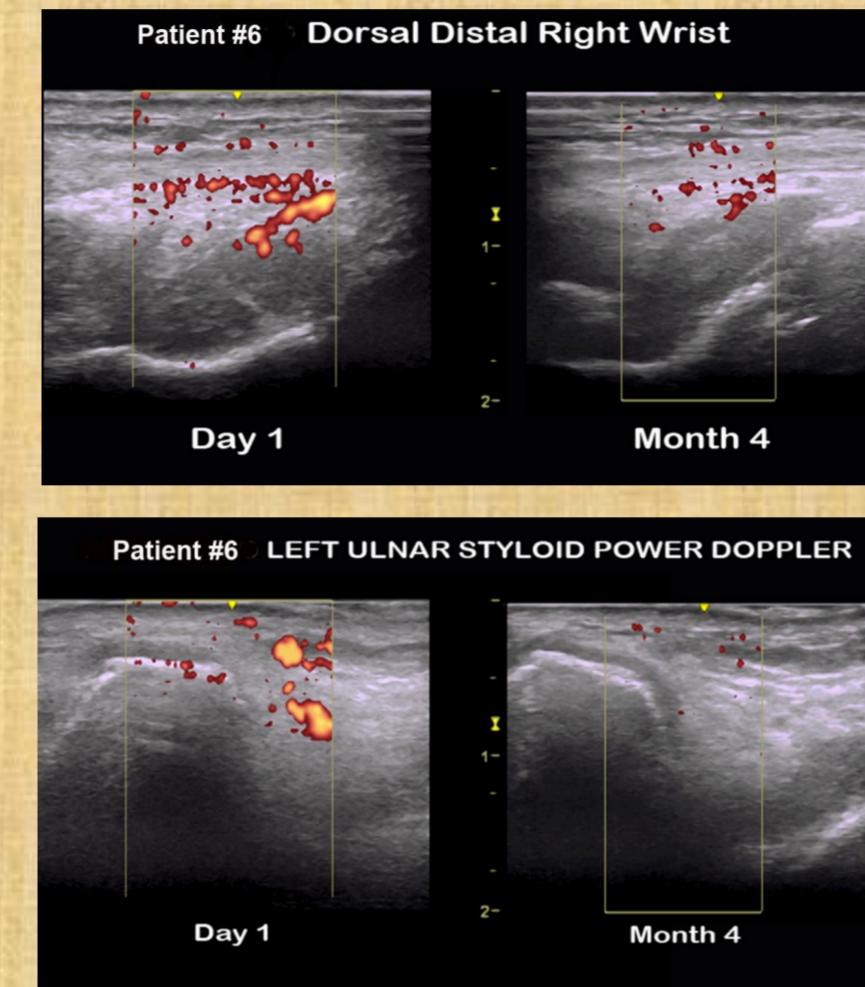


Figure 2 and 3 shows examples of the power doppler signal for patient #6 in the PRTX105 study at the distal right wrist and left ulnar styloid comparing day 1 with month 4. All parameters and locations are the same, and yet, marked differences in signal intensity are easily identified. In this case the wrist goes from grade 3 to grade one, and the styloid goes from grade 2 to normal.

Ultrasound Grey Scale

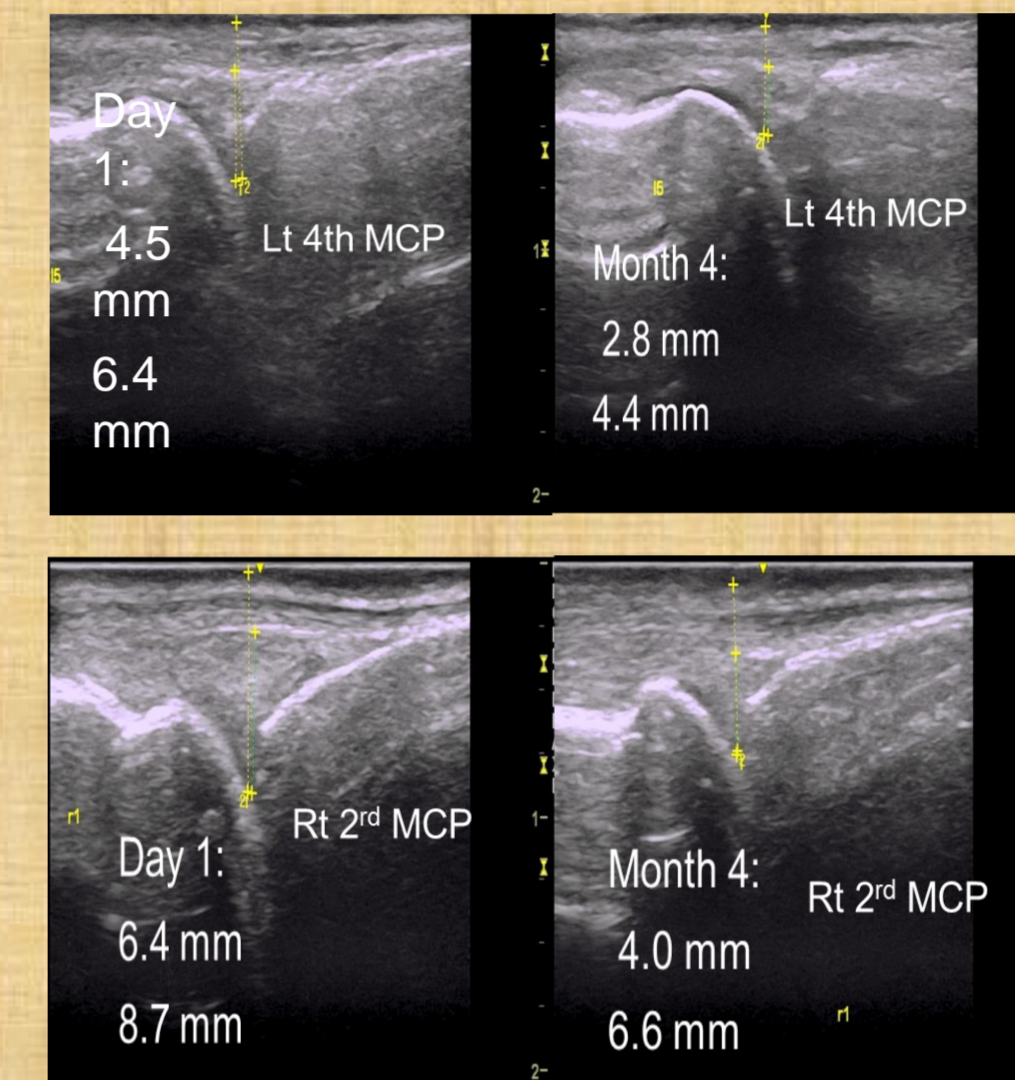


Figure 4 and 5 are grey scale ultrasound images which compares two of patient #6's MCP joints at Day 1 vs Month 4 of the PRTX105 trial. There is marked reduction of the distance from the base of the joint to the joint capsule surface (upper number) and the base of the joint to the surface of the digit (lower number).

Discussion

- UPDJCs have been demonstrated to be a useful tool for measuring RA disease activity, but the lack of a standardized examination method has limited its clinical use. Several studies have now shown that truncated joint counts (limited numbers) are sensitive-to-change and can monitor short term responses to RA therapies [3,4].
- UPDJCs and DAMs decreased in parallel and correlations were moderate to strong, but mean changes did not correlate, except for baseline vs month six. Such finding in previous studies has suggested that UPDJCs and DAMs capture different aspects of disease activity that present different kinetics of response over time [5].

Conclusions

- The use of a truncated UPDJC in this small open label trial was feasible, reproducibly read, and significantly correlated with conventional disease activity measures.
- The inclusion of UPD in this open label pilot trial adds validation to the efficacy data.

References

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Table 2. Correlations of Scores Between UPDJC and Disease Activity Measures

Disease Act Measure	Correlation of whole numbers			Correlation of changes from baseline to Month 6			
	N	UPD vs	Prob ¹	Disease Act Measure	N	UPD vs	Prob ¹
DAS28CRP	71	$\rho = .780$	***	DAS28CRP	11	$\rho = .639$	*
DAS28ESR	98	$\rho = .745$	***	DAS28ESR	11	$\rho = .542$	*
ESR	97	$\rho = .440$	***	ESR	11	$\rho = .043$	NS
CRP	63	$\rho = .540$	***	CRP	11	$\rho = .588$	*
Jt Pain	111	$\rho = .446$	***	Jt Pain	11	$\rho = .152$	NS
Jt Swelling	113	$\rho = .468$	***	Jt Swelling	11	$\rho = .509$	*
Pt Global	113	$\rho = .313$	***	Pt Global	11	$\rho = .422$	NS
Dr Global	113	$\rho = .634$	***	Dr Global	11	$\rho = .342$	NS
CDAI	113	$\rho = .502$	***	CDAI	11	$\rho = .365$	NS
Vectra ³	33	$\rho = .525$	***	Vectra ³	11	$\rho = .093$	NS

¹: P = <0.05*, P = <0.005**, P = <0.0005*** ²: Spearman's Rank Correlation Coefficient ³: 12 Bio marker test, Crescendo Co.