Changes in Diverse Disease Activity Measures Are Highly Correlated Following the Initiation of Most Treatment Modalities in the Management of Longstanding Rheumatoid Arthritis

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Abstract

Background/Purpose: Treating rheumatoid arthritis (RA) patients to target (T2T) has been shown to result in better outcomes in patients with relatively recent onset RA. The implementation of this method requires performing disease activity measures (DAMs) with the disease activity score in 28 joints (DAS28) being the most commonly used. The use of clinically based DAMs in patients with longstanding RA is problematic as structural damage, and other comorbidities can lead to elevated scores because of the impact on composite elements not related to inflammation i.e. patient global and tender joint count. Including additional DAMs, such as a power Doppler joint count (UPD) and multibiomarker disease activity (MBDA) could possibly lead to better assessment of this patient population. The purpose of this abstract is to determine the changes in these three diverse DAMs and the relationships of these changes following the initiation of specific treatment modalities in patient with longstanding RA.

Methods: Patients at a community based rheumatology clinic undergo DAM assessments on a routine basis as part of the implementation of a T2T strategy. These assessments include the DAS28CRP, a UPD, and the MBDA. The UPD includes scoring at six dorsal wrist and six dorsal MCP sites. Patients underwent assessments prior to change in therapy, and then generally about six months later. Patients who were on biologics and found to be under inadequate control, had their biologic discontinued and the new therapy added later, depending on the half-life of the discontinued medication. The average duration of RA in patients at this clinic is > 10 years. The average DAS28CRP 4.18 +/- 1.32, average MBDA 41.4 +/- 14, and the average UPD 7.8 +/- 4.3.

Results:

	N	Δ DAS28C RP AVG	SD	Prob	Δ MBDA AVG	SD	Prob	Δ UPD AVG	SD	Prob	DAS28CRP Vs MBDA	UPD Vs MBDA	DAS28CRP Vs UPD
MTX/Leflunomide	10	-1.63	0.83	0.00002	-12.4	8.0	0.00025	-3.2	2.8	0.003	r = 0.510*	r = 0.325	r = 0.425
Anti-TNFs	16	-0.94	1.24	0.0029	-11.5	11.8	0.007	-3.0	3.8	0.003	r = 0.454*	r = 0.488*	r = 0.573*
Tocilizumab	12	-1.44	1.13	0.0004	+6.3	11.4	0.044	-4.5	3.3	0.001	r = -0.252	r = -0.148	r = 0.277
Abatacept	10	-0.88	2.04	0.08	-2.5	10.8	0.24	-5	6.6	0.02	r =0.341	r =-0.736*	r = 0.619*
Tofacitinib	11	-1.27	1.03	0.001	-11.3	13	0.035	-2.2	2.6	0.01	r =0.209	r =-0.707*	r = 0.565*

Conclusion: Changes in diverse DAMs have moderate to high correlations following the initiation of specific therapy with most treatment modalities utilized in the management of longstanding RA. Tocilizumab did not have a positive correlation between DAS and the MBDA, which has been previously reported, and is presumed to be secondary to its mode of action which leads to significant elevation of IL-6 in the serum. Tofacitinib, a Jak-1 inhibitor, did not have a significant correlation between DAS and the MBNA, which has also been reported recently for another Jak-1 inhibitor in development, but had significant correlation with UPD and the MBNA in this study. This data suggest the validity of adding more diverse DAMs, such as UPD, and MBDA to clinical measures, such as the DAS28CRP, as endpoints in the implementation of a T2T strategy in the management of longstanding RA.

Introduction

- Treating rheumatoid arthritis patients to target (T2T) has been shown to result in better outcomes in patients with new onset or relatively recent onset rheumatoid arthritis (RA) [1] in regimented and well defined settings. Implementing this strategy in a rheumatology clinic is problematic with a preponderance of RA patients with longstanding disease who have other chronic diseases and joint deformities, severe osteoarthritis (OA), and other comorbidities which can lead to confounding results when using traditional clinically oriented disease activity measures (DAMs).
- The most frequently used DAM, the disease activity score in 28 joints (DAS28), is composed of four composite measurements, two of which, the tender joint count, and patient global assessment, are subjective. Also, one of two phase reactants (PR) are incorporated into the index. But these phase reactants are often normal, even in the presence of very active disease. As a result of these types of problems, a patient with minimal or no inflammation can manifest a DAS28 of moderate to high-moderate disease activity or a stoical patient with a normal PR may manifest an erroneously low score leading to false clinical decision making.
- The ultrasound power Doppler joint count (UPDJC) and multiple biomarker disease activity (MBDA, Vectra-DA) blood test are two options that may provide additional insights in the assessment of patients with long standing RA as they assess distinctive but differing inflammatory constructs compared to the DAS28..

Methods

- Patients at a community based rheumatology clinic undergo DAM assessments on a routine basis as part of the implementation of a T2T strategy [2]. These assessments include the DAS28CRP, a UPDJC (figure 2), and the MBDA. Patients underwent assessments prior to change in therapy, and then generally about four months later. Patients who were on biologics and found to be under inadequate control, had their biologic discontinued and the new therapy added later, depending on the half-life of the discontinued medication. The differences between the values of the three DAMs at these time points were determined . Pearson Correlation coefficients of these changes between DAMs were also calculated.
- DAMs obtained on patients who were considered stable on their medications for six or more months were defined as steady state assessments and correlations between the three DAMs were ascertained.

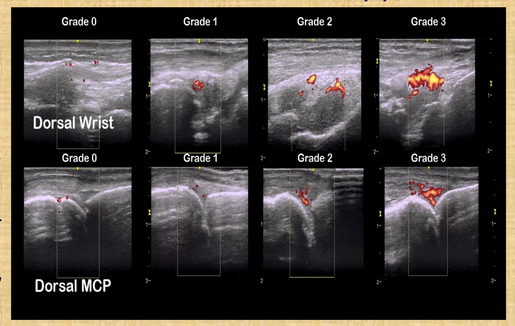
MBDA Blood Test

- Concentrations of 12 protein biomarkers (CRP, EGF, IL-6, Leptin, MMP-1, MMP-3, Resistin, SAA, TNF-R1, VCAM-1, VEGF-A, YKL-40) were measured in patient serum.
- MBDA scores were obtained from the Vectra DA test.
- Vectra DA is a validated measure of disease activity in patients with RA.

Patients with Long Standing RA

Figure 1. Patients with long standing RA and deformities from the clinic are shown.

Ultrasound Power Doppler JC



- Figure 2. UPDJC studies are shown. The method for preforming a truncated UPDJC was adopted [3] for the clinic.
- The UPDJC analyzes six synovial sites [2] for a total of twelve sites with each site assessed by a subjective scale of Grade 0 (normal) to Grade 3 (severe) leading to a possible score of 0-36.
- The vast majority of increased vascularity in joints in RA occurs in the dorsal wrist, and dorsal MCPs > PIPs, allowing for the truncated version of this Doppler JC.

Results

	N	N	Δ DAS28		Δ MBDA			Δ UPD		
Treatments	Patients	Timepts	AVG	SD	Prob[1]	AVG	SD	Prob[1]	AVG	SD	Prob[1]
MTX[2]/Leflunomide	11	11	-1.55	0.8	***	-11.4	8.2	***	-3.0	2.6	**
Anti-TNFs	15	18	-1.02	1.3	***	-13.3	11	***	-5.0	6.7	***
Tocilizumab	10	13	-1.34	0.8	***	(+)7.0	7.8	*	-4.5	4.0	***
Abatacept	13	16	-1.39	1.8	***	-3.9	11	NS	-3.3	6.2	*
Tofacitinib	23	26	-1.47	1	***	-8.6	11	***	-2.5	3.2	***
PRTX-100[3]	11	21	-1.79	1.3	***	-0.7	13	NS	-2.6	1.8	***

[1] P = <0.05*, P = <0.005**,P = <0.0005***, [2] Methotrexate, [3]Staph Protein A [4]

Table 1. Changes in Diverse Activity Measures Following Institution of Treatment

	DAS28 vs		UPD vs		DAS28 vs	
Treatments	MBDA	Prob[1]	MBDA	Prob[1]	UPD	Prob[1]
MTX[2]/Leflunomide	r = .588	*	r = .490	*	r = .480	*
Anti-TNFs	r = .488	*	r = .615	**	r = .329	NS
Tocilizumab	r = -.167	NS	r = -.154	NS	r = .248	NS
Abatacept	r = .775	***	r = .427	*	r = .427	*
Tofacitinib	r = .078	NS	r = .086	NS	r = .360	*
PRTX-100[3]	r = .323	*	r = .143	NS	r = .673	***

[1] P = <0.05*, P = <0.005**,P = <0.0005***, [2] Methotrexate, [3]Staph Protein A [4]

Table 2. Correlations of Changes Between Diverse Activity Measures Following Initiation of Treatment

	N	N	DAS28 vs		UPD vs		DAS28 vs	
Treatments	Patients	Timepts	MBDA	Prob[1]	MBDA	Prob[1]	UPD	Prob[1]
MTX/Leflunomide	113	172	r = .412	***	r = .501	***	r = .480	***
Anti-TNFs	99	144	r = .379	***	r = .382	***	r = .351	***
Tocilizumab	22	31	r = .582	***	r = .443	*	r = .775	***
Abatacept	32	48	r = .555	***	r = .511	***	r = .488	***
Tofacitinib	26	32	r = .022	NS	r = .085	NS	r = .492	**
PRTX-100[3]	10	21	r = .764	***	r = .499	*	r = .684	***
No Treatment	33	37	r = .372	*	r = .513	***	r = .182	NS

[1] P = <0.05*, P = <0.005**,P = <0.0005***, [2] Methotrexate, [3]Staph Protein A [4]

Table 3. Correlations Between Diverse Activity Measures At Steady State for Treatments

- All therapies studied showed significant reductions in at least two of the three diverse DAMs tested following institution of treatment.
- Tocilizumab demonstrated a significant increase in the MBDA.
- The majority of therapies studied demonstrated significant correlations in the changes between two DAMs in at least two out of the three measurements.
- Tocilizumab did not show significant correlations with any of the three measurements of changes following treatment and Tofacitinib did not show significant correlations with changes when the MBDA was involved in the correlations.
- All therapies showed significant correlations at steady state in the majority of correlations between DAMs with the exception of Tofacitinib, which did not have significant correlations when the MBDA was involved.

Discussion

- The increase in the MBDA with Tocilizumab was due to increases of IL-6 which occurred in all but one patient.
- Correlations between these diverse DAMs are not universal for every drug, and new therapies need to be investigated, as was done with PRTX-100.

Conclusion

- It is feasible to perform diverse disease activity measurements (DAMs), including non-clinically based DAMs such as the USPDJC and MBDA, within the time constraints of a twenty minute office visit.
- Several of the commonly employed therapies for RA are shown in this paper to lead to significant improvement in these DAMs and the DAS28, as well as showing significant correlations with these changes between the three DAMs for most therapies.
- This data suggests that the addition of non-clinical DAMs, such as the UPDJC and MBDA, would complement the value of more conventional clinical measures and facilitate the conduction of a T2T strategy in managing patients with longstanding RA.
- This data suggests the possibility and potential value of forming a composite DAM for RA in which these three DAMs are first equally weighted, and then combined together as a single score.

References

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