Trial-and-Error Treatment Leads to Delayed Disease Control of Moderate-to-Severe Rheumatoid Arthritis

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1. BACKGROUND

Effective management of rheumatoid arthritis (RA) is necessary to maximize patient quality of life and avoid/delay short- and long-term complications of the disease. However, the choice of therapy for patients who have failed or are intolerant to conventional synthetic DMARDs is arguably based on population experience and not individualized to the patient. To assess the potential impact of precision medicine on outcomes, we examined time and treatments prior to low disease activity (LDA) for patients with moderate-severe RA after initiating biologic (b) or targeted synthetic (ts) DMARDs.

2. METHODS

Data: PIONEER-Rheumatology, an EMR and open text-extracted database specific to care given by the American Rheumatology Network. Study population: Adult (18+ years old) patients with RA who initiated b/tsDMARDs for the first time between 2014 and 2021 (index), with ≥90 days history, ≥365 days follow up, CDAI >10 at index (closest to but within -365 to +13 days), and with 1+ CDAI ≤10 indicating Low Disease Activity (LDA) occurring >14 days after index [FIGURES 1&2]. Analyses: Time to LDA from (1) first b/tsDMARD and from (2) initiation of last b/tsDMARD prior to the date LDA was achieved. Statistical comparisons: Pairwise Mann Whitney U test with Bonferroni adjustment (median time to LDA), Pearson's chi-square with proportions comparisons by Z-test with Bonferroni adjustment (categorical characteristics).

3. RESULTS

Study population characteristics (n=1713). [TABLE 1] Prior to achieving LDA, 81% (1390) received 1, 14% (241) received 2, and 5% (82) ≥3 b/tsDMARDs. The proportions of patients achieving LDA at time points from index (initial b/tsDMARD) and last b/tsDMARD are shown in FIGURE 1. For the subset achieving LDA with 1 b/tsDMARD (n=1390), median (IQR) months from index to disease control was 4.75 (2.30-10.78). [TABLE 2] For patients achieving LDA after 2 b/tsDMARDs (n=241), median (IQR) months from index to LDA was 14.53 (7.79-21.76) and from initiation of the last b/tsDMARD to LDA was 4.93 (2.07-9.90). For those achieving LDA after ≥3 b/tsDMARDs (n=82), median (IQR) months from index was 23.16 (15.12-31.91) and from initiation of the last b/tsDMARD to LDA was 5.59 (2.38-11.81). Comparisons between 1, 2, and ≥3 b/tsDMARDs groups revealed statistically significant differences in time from first b/tsDMARD to LDA (all p<0.001) and a lack of significant differences in time from last b/tsDMARD to LDA (all p>0.99) [TABLE 2, FIGURE 3] and evaluated characteristics [TABLE 1].

4. CONCLUSIONS

These results suggest selection of an ineffective therapy initially via trial-and-error prescribing may delay disease control by 3-fold for some patients [TABLE 2] with moderate-severe RA. As such, implementation of precision medicine to predict response/non-response to a b/tsDMARD meets an unmet need in standard practice.

FIGURE 1: Study Diagram

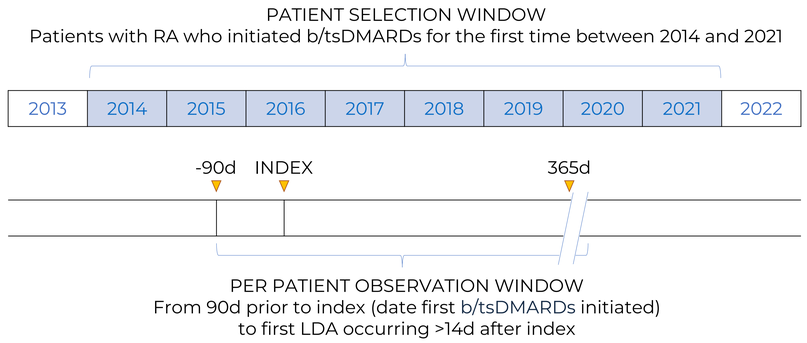

FIGURE 2: Patient Disposition

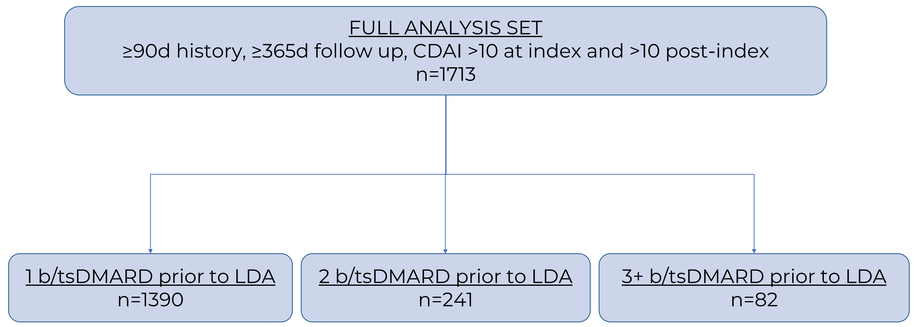

FIGURE 3: Proportion achieving LDA at time points by no. b/tDMARDs

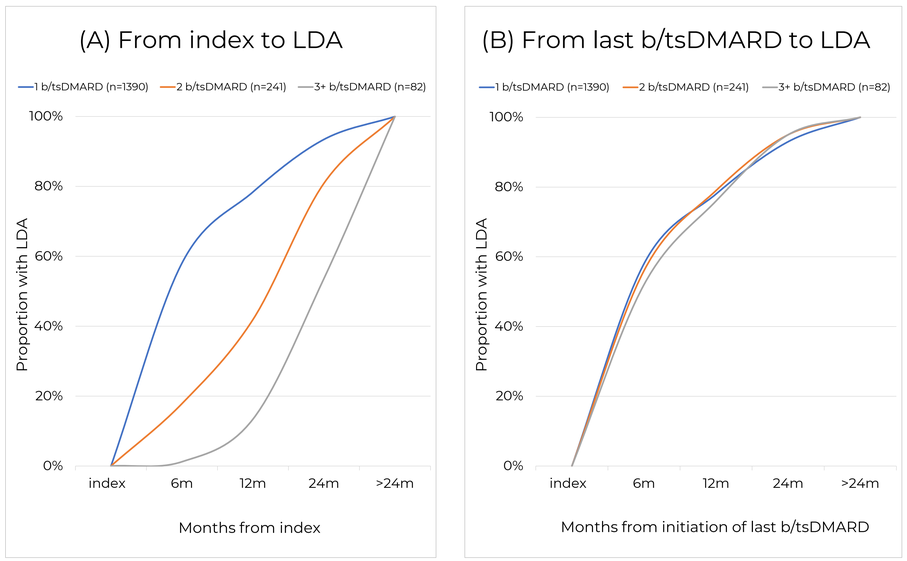

TABLE 1: Study Population Characteristic

No. (%) patients unless indicated	All Patients (n=1713)	1 b/tsDMARD prior to LDA (n=1390)	2 b/tsDMARD prior to LDA (n=241)	3+ b/tsDMARD prior to LDA (n=82)
Female	1269 (74.1%)	1020 (73.4%)	181 (75.1%)	68 (82.9%)
Age At Index - median (IQR)	59 (50,69)	60 (50,69)	58 (49,67)	52 (43,64)
<40	191 (11%)	149 (11%)	27 (11%)	15 (18%)
40-64	916 (53%)	730 (53%)	136 (56%)	50 (61%)
≥65	606 (35%)	511 (37%)	78 (32%)	17 (21%)
Race				
American Indian or Alaska Native	11 (0.6%)	10 (0.7%)	1 (0.4%)	
Asian	15 (0.9%)	11 (0.8%)	2 (0.8%)	2 (2.4%)
Black	89 (5.2%)	78 (5.6%)	8 (3.3%)	3 (3.7%)
Native Hawaiian Pacific Islander	1 (0.1%)	1 (0.1%)		
Other	93 (5.4%)	69 (5.0%)	17 (7.1%)	7 (8.5%)
White	998 (58.3%)	821 (59.1%)	132 (54.8%)	45 (54.9%)
Unspecified	506 (29.5%)	400 (28.8%)	81 (33.6%)	25 (30.5%)
CDAI				
Moderate (>10 and ≤22)	996 (58.1%)	844 (60.7%)	120 (49.8%)	32 (39.0%)
Severe (>22)	717 (41.9%)	546 (39.3%)	121 (50.2%)	50 (61.0%)
History - median (IQR) months	15 (7,43)	16 (7,44)	13 (6,43)	10 (6,31)
Follow-up - median (IQR) months	37 (25,54)	37 (25,54)	37 (26,56)	41 (31,53)
Prior csDMARD (any)	1565 (91.4%)	1268 (91.2%)	223 (92.5%)	74 (90.2%)
Methotrexate	1332 (77.8%)	1086 (78.1%)	183 (75.9%)	63 (76.8%)
Hydroxychloroquine	560 (32.7%)	434 (31.2%)	96 (39.8%)	30 (36.6%)
Leflunomide	235 (13.7%)	186 (13.4%)	38 (15.8%)	11 (13.4%)
Azathioprine	29 (1.7%)	24 (1.7%)	4 (1.7%)	1 (1.2%)
Sulfasalazine	165 (9.6%)	134 (9.6%)	23 (9.5%)	8 (9.8%)
Mycophenolate	5 (0.3%)	5 (0.4%)		
Cyclosporine	5 (0.3%)	5 (0.4%)		
Index b/tsDMARD Target				
B-cell	62 (3.6%)	59 (4.2%)	2 (0.8%)	1 (1.2%)
IL1	1 (0.1%)	1 (0.1%)		
IL6	79 (4.6%)	64 (4.6%)	13 (5.4%)	2 (2.4%)
JAK	180 (10.5%)	142 (10.2%)	34 (14.1%)	4 (4.9%)
T-cell	189 (11.0%)	157 (11.3%)	26 (10.8%)	6 (7.3%)
TNF	1202 (70.2%)	967 (69.6%)	166 (68.9%)	69 (84.1%)

Comparisons between 1, 2, and ≥3 b/tsDMARDs groups revealed lack of significant differences (p>0.05) for evaluated characteristics. Though differences in proportions are apparent for disease severity categories, significance was not reached (p=0.161).

TABLE 2: Median (IQR) months to LDA

Reference point	All Patients (n=1713)	1 b/tsDMARD prior to LDA (n=1390)	2 b/tsDMARD prior to LDA (n=241)	3+ b/tsDMARD prior to LDA (n=82)
From index*	6.08 (2.76,13.97)	4.75 (2.30,10.78)	14.53 (7.79,21.76)	23.16 (15.12,31.91)
From initiation of last b/tsDMARD before LDA	4.83 (2.27,10.75)	4.75 (2.30,10.78)	4.93 (2.07,9.90)	5.59 (2.38,11.81)

*Median time to LDA significantly different (p<0.001) between groups.

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