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Evaluation of physician global assessment in patients with b/tsDMARD therapy selection aligned with a molecular signature response classifier: an analysis from The Study to Accelerate Information of Molecular Signatures (AIMS) in Rheumatoid Arthritis

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BACKGROUND

Despite drug therapies that improve lives, tens of millions of patients annually are subjected to therapy using a "trial-and-error" approach because, until recently, it was not possible to use a patient's unique molecular profile to inform targeted therapy selection.

A blood-based molecular signature response classifier (MSRC) was shown to predict non-response to tumor necrosis factor-alpha inhibitor (TNFi) therapies in patients with rheumatoid arthritis (RA). This MSRC integrates disease associated gene expression and clinical features (anti-CCP, sex, BMI, PtGA)[1].

A recent study demonstrated that patient response to treatment, as defined by ACR50 at 6 months, informed by an MSRC result was more than 3 times better when an MSRC informed therapy selection (predicted non-responders prescribed an alternative mechanism of action vs predicted non-responders prescribed a TNFi; PNR-altMOA=34.8% vs PNR-TNFi=10.3%, p-value=0.05)[1] (see Figure 1). Furthermore, when patients with no prediction of non-response were prescribed a TNFi for treatment (NP-TNFi), their outcomes (CDAI improvement ≥MID) were improved by 5 times compared to the cohort receiving TNFi therapy despite a signal of non-response from an MSRC (NP-TNFi=45.8% vs PNR-TNFi=10.3%, p-value = 0.005)[1].

Figure 1

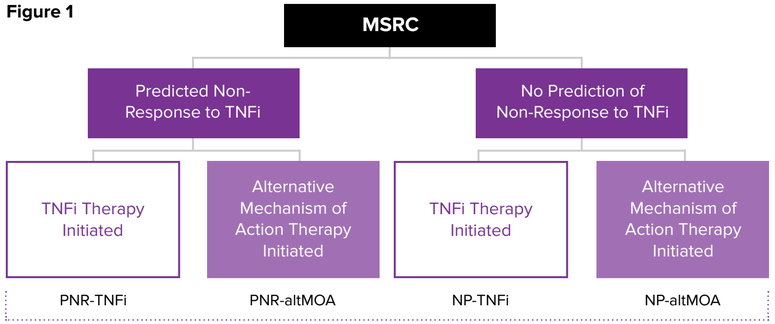

Figure 1: For this analysis, patients are categorized by molecular signature response classifier result and b/tsDMARD selection. Potential treatment selections are either tumor necrosis factor-alpha inhibitor (TNFi) therapy or an alternative mechanism of action (altMOA). PNR-TNFi: patients with a molecular signature of non-response to TNFi who were treated nonetheless with TNFi therapy; PNR-altMOA: patients with a molecular signature of non-response who received a non-TNFi b/tsDMARD; NP-TNFi: patients without a molecular signature of non-response detected who were treated with a TNFi according to usual care; NP-altMOA: patients without a molecular signature of non-response detected who were treated with a non-TNFi b/tsDMARD according to usual care

OBJECTIVES

The objective of the Study to Accelerate Information of Molecular Signatures (AIMS) in RA was to build a clinical/molecular database of longitudinal data from RA patients managed in real-world settings with a focus on utilization of an MSRC test. The objective of this analysis was to evaluate physician global assessment (PGA) scores (0-100 visual analog scale) at 3 and 6 months and swollen joint counts at 3 months in RA patients with moderate to severe disease activity at baseline who received MSRC testing prior to a treatment decision.

METHODS

This analysis reports on data from patients enrolled in AIMS between Sep 2020 and Oct 2021 who initiated a new b/tsDMARD, or continued existing therapy, following MSRC testing. Patients were ≥18 years of age with a clinical diagnosis of RA. Each had a PGA score measured at 3 or 6 months (n = 560). The cohort is composed of 560 subjects from 49 unique sites: 511 subjects paid in-person visits; 16 subjects paid remote visits; 33 subjects were missed to follow-up at 3 months; and 281 subjects paid an in-person visit at 6 months.

The cohort was divided into patients whose targeted therapy selection was Aligned (PNR-altMOA, NP-TNFi or no prediction of non-response prescribed a drug with an alternative mechanism of action, NP-altMOA) and Not Aligned (PNR-TNFi) with MSRC results. Improvement from baseline of PGA was evaluated at 3 and 6 months, and swollen joints was evaluated at 3 months.

RESULTS

The PNR-altMOA cohort had significant improvement in PGA scores at 3 & 6 months compared to the PNR-TNFi cohort (3m: PNR-altMOA=18.4, n=163 vs PNR-TNFi =7.2, n=140, p-value=0.01; 6m: PNR-altMOA=13.1, n=80 vs PNR-TNFi=-1.11, n=90, p-value=0.013).

The patient cohort NP-TNFi showed a trend of greater improvement in PGA scores at 3 & 6 months compared to PNR-TNFi (3m: NP-TNFi=11.5, n=134 vs PNR-TNFi=7.2, n=140, p-value=0.791; 6m: NP-TNFi=13.3, n=76 vs PNR-TNFi =-1.11, n=90, p-value=0.075) (Figure 2). Moreover, predicted non-responders prescribed an altMOA showed a trend of improvement in swollen joints at 3 months compared to predicted non-responders prescribed a TNFi (PNR-altMOA= 3.15, n=163 vs PNR-TNFi=1.7, n=140, p-value=0.08). The patient cohort NP-TNFi showed significantly more improvement in swollen joints at 3 months (NP-TNFi= 3.71, n=134 vs PNR-TNFi=1.7, n=140, p-value=<0.001). Characteristics of the cohorts are reported in Table 1.

Figure 2: Patient cohorts based on MSRC result and treatment choice

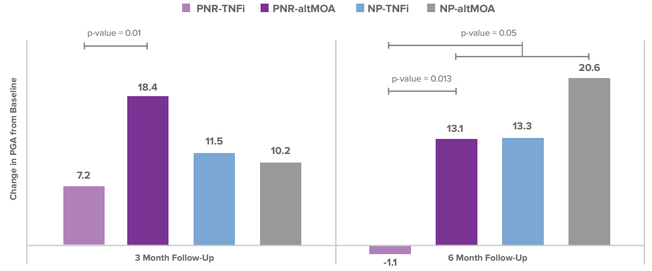

Figure 2: Change in physician global assessment (PGA) from baseline. Providers used MSRC results to inform b/tsDMARD selection resulting in four patient subsets based on MSRC results and treatment choice. PNR-TNFi: patients with a molecular signature of non-response to TNFi who were treated nonetheless with TNFi therapy. This treatment selection is not aligned with the recommendations of the MSRC test results. Three treatment paths align with recommendations of MSRC results: PNR-altMOA: patients with a molecular signature of non-response who received a non-TNFi b/tsDMARD, NP-TNFi: patients without a molecular signature of non-response detected who were treated with a TNFi according to usual care, NP-altMOA: patients without a molecular signature of non-response detected who were treated with a non-TNFi b/tsDMARD according to usual care. Statistically significant values observed at 3 months between cohort PNR-TNFi vs PNR-altMOA, p-value=0.01, at 6 months between cohort PNR-TNFi vs PNR-altMOA, p-value = 0.013, and between cohort PNR-TNFi vs all other cohorts (PNR-altMOA, NP-TNFi, NP-altMOA), p-value = 0.05

Table 1. Demographics and baseline characteristics

Variable	PNR-TNFi	PNR-altMOA	UC-TNFi	UC-altMOA	P-value (PNR-TNFi vs UC-TNFi)	P-value (PNR-TNFi vs PNR-altMOA)
N	159	176	145	80		
Age (year), mean (SD)	53.5 (13.8)	57.6 (12.9)	55.9 (14.4)	59.7 (13.2)	0.135	0.005
Female, n (%)	n=142 (0.89)	n=159 (9)	n=96 (66)	n=58 (72)	<0.001	0.858
Duration of disease (years), median (IQR; n)	2.7 (Q1=0.5, Q3=8,IQR=7.5,n=157)	5 (Q1=1.925,Q3=0.05,IQR=8.1,n=174)	1.6 (Q1=0.4,Q3=5.1, IQR=4.8,n=142)	5.9 (Q1=2.125,Q3=6.275, IQR=14.1,n=80)	0.034	0.002
Race, n (%)					0.346	0.896
White	n=128 (81)	n=142 (81)	n=124 (86)	n=64 (8)		
Other	n=18 (11)	n=18 (1)	n=8 (6)	n=8 (1)		
Black or African American	n=11 (7)	n=11 (6)	n=9 (6)	n=5 (6)		
Asian	n=1 (1)	n=3 (2)	n=3 (2)	n=1 (1)		
Am. Indian or Alaskan Native	n=1 (1)	n=2 (1)	n=1 (1)	n=2 (3)		
TNFi-naïve, n (%)	n=128 (81)	n=148 (84)	n=120 (83)	n=71 (89)	0.672	0.473
RF positive, n (%)	n=33 (32)	n=58 (48)	n=36 (47)	n=20 (45)	0.039	0.011
CDAI Category-High, n (%)	n=114 (72)	n=141 (8)	n=82 (57)	n=37 (46)	0.004	0.073
CDAI Category-Moderate, n (%)	n=45 (28)	n=35 (2)	n=63 (43)	n=43 (54)	0.007	0.069
HAQ at baseline mean (SD)	0.8 (0.6)	0.8 (0.05)	0.5 (0.4)	0.6 (0.5)	<0.001	0.758
Tender joints at baseline, mean (SD)	14.8 (9.4)	16.8 (9.5)	11.8 (8.5)	10.9 (8.9)	0.004	0.057
Swollen joints at baseline, mean (SD)	8.4 (7)	9.9 (6.6)	7.8 (7.1)	6.4 (6.4)	0.447	0.042
Methotrexate, n (%)	n=81 (51)	n=91 (52)	n=92 (63)	n=30 (38)	0.036	0.907
Prednisone, n (%)	n=35 (22)	n=50 (28)	n=52 (36)	n=27 (34)	0.007	0.217
Hydroxychloroquine, n (%)	n=18 (11)	n=13 (7)	n=15 (1)	n=11 (14)	0.859	0.26
JAK, n (%)	n=0 (0)	n=86 (49)	n=0 (0)	n=45 (56)		
Tofacitinib	n=0 (0)	n=31 (18)	n=0 (0)	n=12 (15)		
Upadacitinib	n=0 (0)	n=48 (27)	n=0 (0)	n=23 (29)		
Baricitinib	n=0 (0)	n=7 (4)	n=0 (0)	n=10 (12)		
T-Cell, n (%): Abatacept	n=0 (0)	n=58 (33)	n=0 (0)	n=19 (24)		
TNFi, n (%)	n=159 (1)	n=0 (0)	n=145 (1)	n=0 (0)		
Certolizumab	n=18 (11)	n=0 (0)	n=28 (19)	n=0 (0)		
Adalimumab	n=57 (36)	n=0 (0)	n=56 (39)	n=0 (0)		
Etanercept	n=23 (14)	n=0 (0)	n=24 (17)	n=0 (0)		
Golimumab	n=40 (25)	n=0 (0)	n=28 (19)	n=0 (0)		
Infliximab	n=21 (13)	n=0 (0)	n=9 (6)	n=0 (0)		
IL-6, n (%)	n=0 (0)	n=23 (13)	n=0 (0)	n=12 (15)		
Tocilizumab	n=0 (0)	n=18 (1)	n=0 (0)	n=10 (12)		
Sarilumab	n=0 (0)	n=5 (3)	n=0 (0)	n=2 (3)		
B-Cell, n (%): Tocilizumab	n=0 (0)	n=7 (4)	n=0 (0)	n=4 (5)		
IL-17a, n (%): Secukinumab	n=0 (0)	n=2 (1)	n=0 (0)	n=0 (0)		

CONCLUSIONS

The incorporation of MSRC testing into the b/tsDMARD selection process can improve patient outcomes and can help identify which patients may experience less benefit from TNFi therapies.

Support and disclosures: Johanna Withers, Lixia Zhang, and Sam Asgarian are all shareholders of Scipher Medicine

References: 1. Vibeke Strand, Stanley B. Cohen, Jeffrey R. Curtis, Lixia Zhang, Alan J. Kivitz, Robert W. Levin, Angela Mathis, Erin Connolly-Strong & Johanna B. Withers (2021): Clinical utility of therapy selection informed by predicted nonresponse to tumor necrosis factor-α inhibitors: an analysis from the Study to Accelerate Information of Molecular Signatures (AIMS) in rheumatoid arthritis, Expert Review of Molecular Diagnostics, DOI: 10.1080/14737159.2022.2020648.