Improvement in Clinical Disease Activity Index (CDAI) When Treatment Selection Is Informed by the Tumor Necrosis Factor-α Inhibitor Molecular Signature Response Classifier: Analysis from the Study to Accelerate Information of Molecular Signatures (AIMS) in Rheumatoid Arthritis

Vibeke Strand, Lixia Zhang, Alix Arnaud, Erin Connolly-Strong, Sam Asgarian, & Johanna B. Withers.

INTRODUCTION

Background

- Without timely therapeutic intervention, chronic inflammation causes progressive joint damage leading to deformities, disability, and increased mortality in patients with rheumatoid arthritis (RA)
- Biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARD) have become integral to the treat-to-target paradigm designed to gain low disease activity or remission
- 27 - 38% of patients with RA who inadequately respond to methotrexate achieve ACR50 responses at 6 months on tumor necrosis factor-α inhibitor (TNFi) therapies
- Near equivalent efficacy and safety profiles between b/tsDMARD, a lack of clinically validated biomarkers for patient stratification, and an inability to prioritize b/tsDMARD selection by clinical guidelines have led to a preponderance of trial-and-error treatment selection

PrismRA® Test Description

- A blood-based molecular signature response classifier analytically and clinically validated to identify patients with RA who are likely to be inadequate responders to TNFi therapies

Methods

- AIMS is a clinical database of real-world longitudinal data from patients with RA across a network of 72 private and academic rheumatology practices in the US
- This study reports an interim analysis of data collected from patients who received PrismRA testing between September 2020 and November 2021
- The primary and secondary endpoints of the clinical outcomes analysis were changes from baseline in absolute CDAI scores at 24 weeks (n=274) and 12 weeks (n=470), respectively

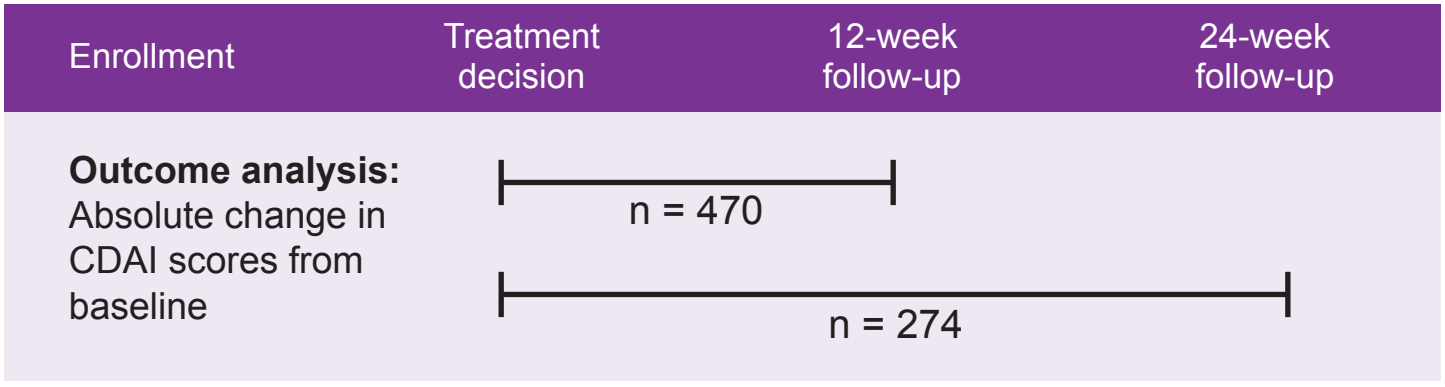
PATIENT COHORT DEMOGRAPHICS & STUDY DESIGN

Inclusion criteria:

- Age ≥18 years with a clinical diagnosis of RA
- b/tsDMARD-naïve or TNFi-exposed at time of PrismRA testing
- Moderate or high disease activity at baseline (CDAI >10)
- Data to calculate CDAI were available at baseline and at least one follow-up visit
- Changes in doses of concomitant medications permitted

Exclusion criteria:

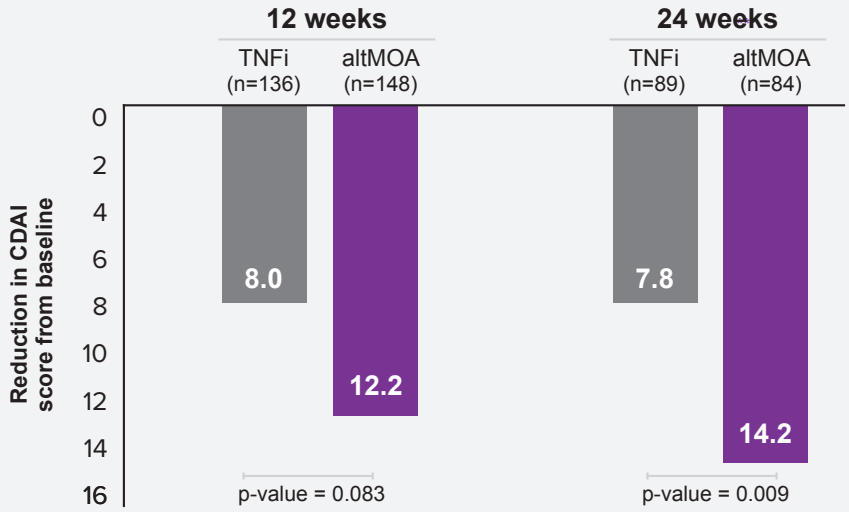
- Treated w/ a b/tsDMARD other than TNFi at time of PrismRA testing
- b/tsDMARD changed between initial treatment and first follow-up visit



RESULTS

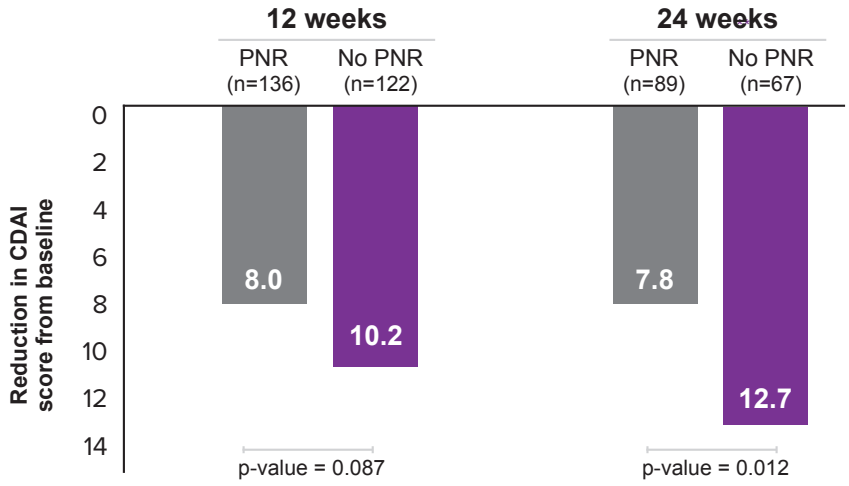
Absolute Change in CDAI for Predicted Non-Responders (PNR)

Patients with a molecular signature of inadequate response treated with an altMOA experienced a **1.8-fold greater improvement** in CDAI scores than patients treated with a TNFi at 24 weeks



Absolute Change in CDAI for Patients on TNFi Therapy

Patients without a molecular signature of inadequate response treated with a TNFi experienced a **1.6-fold greater improvement** in CDAI scores than patients with a molecular signature at 24 weeks



- In patients with baseline high disease activity (HDA), 38.9% of patients achieved lower than moderate disease activity in response to TNFi compared to 55.7% with altMOA therapy (43.2% relative improvement)
- A greater proportion of predicted non-responders experienced worsening CDAI scores when treated with a TNFi compared with an altMOA therapy (baseline HDA: 27.8% in PNR-TNFi vs. 17.1% in PNR-altMOA)

CONCLUSION

- A trial-and-error approach to treatment selection in RA has thus far been a necessity given the paucity of evidence supporting pairing of individual patient disease biology to specific b/tsDMARD options
- Treatment selection informed by PrismRA for patients with RA results in a near 2-fold greater improvement in CDAI scores for patients with a molecular signature of TNFi inadequate response treated with non-TNFi b/tsDMARD
- Data adds to the growing evidence supporting the clinical utility of PrismRA and shows that integration into RA management results in improved clinical outcomes
- Most of the improvements in CDAI scores were evident by the 12-week follow-up visit, indicating that when PrismRA is used to inform treatment selection, outcomes improve in a timely manner

Strand V, Zhang L, Arnaud A, Connolly-Strong E, Asgarian S, Withers JB. Improvement in clinical disease activity index when treatment selection is informed by the tumor necrosis factor-α inhibitor molecular signature response classifier: analysis from the study to accelerate information of molecular signatures in rheumatoid arthritis. *Expert Opin Biol Ther.* 2022;22(6):801-807. doi:10.1080/14712598.2022.2066972.

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Patient Outcomes Improve When a Molecular Signature Test Guides Treatment Decision-Making in Rheumatoid Arthritis

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INTRODUCTION

Background

- Rheumatoid arthritis (RA) is a chronic autoimmune disease that can lead to irreversible joint damage with subsequent disability
- Tumor necrosis factor-α inhibitors (TNFi) are most frequently prescribed to RA patients who fail first-line therapy, but only 27% to 38% of TNFi-prescribed patients will reach treat-to-target goals (ACR50 at 6 months)
- Although there are numerous alternative mechanism of action (altMOA) biologic or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARD) to TNFi, they all share similar efficacy and safety profiles

PrismRA® Test Description

- A precision medicine molecular signature response classifier validated to predict treatment outcomes in RA patients based on disease biology
- PrismRA analyzes individualized clinical and molecular data to stratify patients by their probability of inadequately responding to TNFi therapy

Methods

- Comparative cohort study that evaluated RA patient outcomes between a PrismRA-tested arm (n=489) and an external control arm (n=761)
- The external control arm was constructed from real-world data derived from a large de-identified US-based EHR database
- Propensity score (PS) analyses were implemented to balance measured baseline characteristics between patients in the PrismRA-tested and the external control arm

Inclusion Criteria

- Clinical diagnosis of RA
- ≥18 years of age
- Either b/tsDMARD-naïve, b/tsDMARD-experienced and initating a new b/tsDMARD, or TNFi-exposed
- Moderate or high RA baseline disease activity (CDAI>10)
- Medication dose adjustments permitted

Primary Endpoints

- The proportion of RA patients achieving CDAI low disease activity or remission (CDAI-LDA/REM), remission alone (CDAI-REM), and minimally important differences in changes in CDAI (CDAI-MID)* at 6 months from baseline

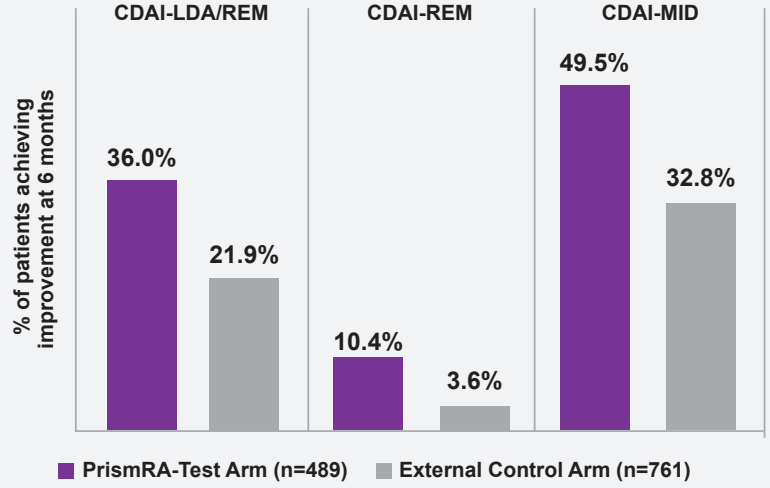
Clinical Validity

- Clinical validity was assessed in patients who received a TNFi therapy after PrismRA testing (n = 369)
- ACR50 criteria at 6 months were used to define response to treatment
- All other inclusion criteria were the same as reported above in the Inclusion Criteria section

*CDAI-MID: minimally important difference defined as a reduction from baseline CDAI scores of >6 for moderate and >12 for high disease activity

CLINICAL UTILITY RESULTS

The PrismRA-tested arm had significantly higher response rates to therapies than the external-control arm



Patients in the PrismRA-tested arm had **2.01 – 3.14x** improved odds of achieving CDAI-LDA/REM, CDAI-REM, and CDAI-MID in response to b/tsDMARD therapy at 6 months compared to external control arm

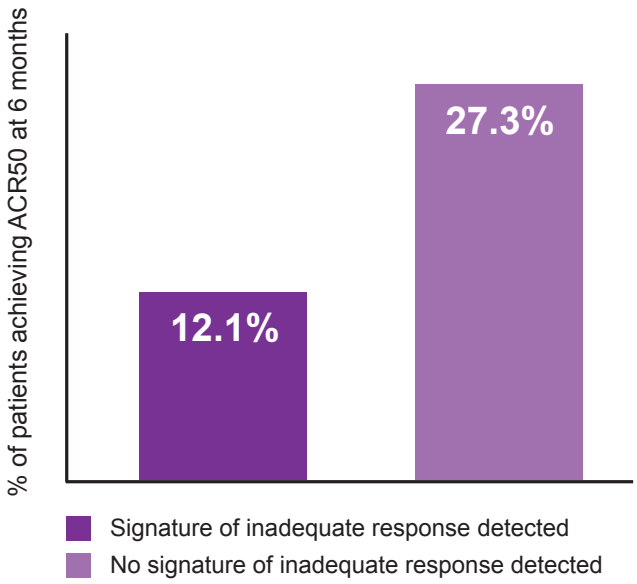
Primary Enpoint	Odds Ratio (95% CI; p-value)
% achieving CDAI-LDA/REM	**2.01** (1.55-2.60; p<0.0001)
% achieving CDAI-REM	**3.14** (1.94-5.08; p<0.0001)
% achieving CDAI-MID	**2.00** (1.58-2.55; p<0.0001)

CLINICAL VALIDITY RESULTS

Clinical validity of PrismRA was evaluated in TNFi-treated patients in the PrismRA-tested arm (n=369)

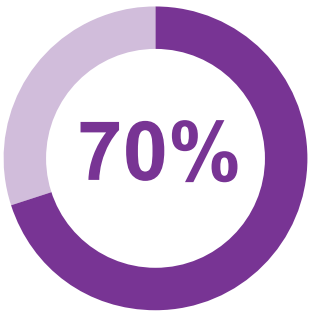
- Of patients with a signature of inadequate response, 88% did not achieve ACR50 on TNFi (PPV)
- 54% of patients who did not achieve ACR50 had a signature of inadequate response (sensitivity)
- 70% of patients who achieved ACR50 had no signature of inadequate response (specificity)

ACR50 response rates decline when treatment selection is not aligned with PrismRA results



CONCLUSION

- PrismRA identifies patients unlikely to respond to TNFi therapies so rheumatologists may more confidently direct such patients to alternative treatment options sooner
- Despite incomplete adherence (70% of providers prescribed a b/tsDMARD that aligned with test results), patient outcomes resulting from treatment selection guided by PrismRA test results were significantly superior to standard care practices
- Patients in the PrismRA-tested arm were as much as 3x more likely to reach remission than if treatment selection was not guided by PrismRA test results
- Because some patients with a signature of inadequate response were prescribed a therapy that did not align with test results, these results represent a conservative estimate of the benefit of PrismRA
- To date, PrismRA has been validated in more than 500 patients demonstrating that PrismRA is a robust and reliable assay that accurately detects a patient's signature of inadequate response across patient cohorts and different study designs
- Nearly 60% of tested patients had a signature of inadequate response and should not be prescribed a TNFi, thus broad adoption of PrismRA testing could shift RA treatment paradigms and significantly improve clinical outcomes



70% of patients tested with PrismRA were treated with a b/tsDMARD that was aligned with test results

3X

Patients were **3x as likely to achieve remission** on therapies aligned with PrismRA results

Curtis JR, Strand V, Golombek S, et al. Patient outcomes improve when a molecular signature test guides treatment decision-making in rheumatoid arthritis. *Expert Rev Mol Diagn.* 2022 Nov;22(10):973-982. doi: 10.1080/14737159.2022.2140586.

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