Characterizing Non-Response to Methotrexate Monotherapy Among Rheumatoid Arthritis Patients in a Large Real-World Longitudinal Cohort

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Background

- Methotrexate (MTX) monotherapy is the first choice among disease-modifying drugs (DMARDs) for most moderate-to-severe rheumatoid arthritis (RA) patients, consistent with treatment guidelines[1]
- However, response to, and tolerability of, MTX varies among patients[2]
- Understanding the proportion of patients with MTX non-response in a real-world setting and identifying its predictors could enable earlier access to alternative or additional medications and improve management of disease progression

Objectives

- The objectives of this study were, using data from a large, geographically representative US cohort of RA patients, to describe the pattern of non-response among patients initiating MTX monotherapy and to identify predictors of non-response to MTX

Methods

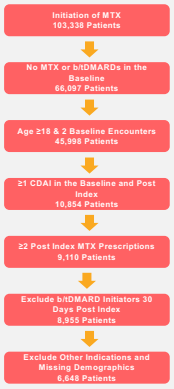
Data Source

- The OM1 RA Registry (OM1, Inc; Boston, MA) follows more than 210,000 RA patients in the US managed by rheumatologists longitudinally with deep clinical data, including laboratory, patient-reported and disease activity information, and linked administrative claims starting from 2013

Inclusion and Exclusion Criteria

- In this retrospective observational study, patients aged ≥ 18 years initiating MTX between 01 January 2014 and 01 August 2020 without previous bDMARD/tsDMARD utilization were identified.
- The first MTX date was the index date, with ≥1 Clinical Disease Activity Index (CDAI) measurement and ≥2 all-cause healthcare encounters required in the preceding 12 months (baseline)
- Patients initiating a bDMARD/tsDMARD within 30 days of the index date or with a history of other conditions where the same bDMARD/tsDMARDs are indicated were excluded

Figure 1. Study Cohort Attrition



Methods Cont'd.

Study Outcome

- MTX non-response was defined as failing to attain remission or low disease activity (i.e., CDAI >10) within 4 to 8 months and/or the initiation of a bDMARD/tsDMARD within 8 months following the index date (with or without continuing MTX; non-response could include patients discontinuing MTX due to tolerability)

Statistical Analyses

- Baseline characteristics were summarized with descriptive statistics.
- Multivariate logistic regression with age, gender, region, race, payor, year of index, the most recent CDAI and body mass index (BMI) measurements from the baseline, and Charlson comorbidity index (CCI) was used to investigate risk factors of non-response
- Odds ratios (OR) and 95% confidence intervals (CI) were reported.
- Statistical significance was set at P <0.01
- All analyses were performed using the Instant Health Data (IHD) software (Panalgo LLC, Boston MA, USA)

Results

- Among 6,648 eligible RA patients, 3,748 (56.4%) were classified as non-responders
- Among non-responders, 20.8% had evidence of the initiation of a bDMARD/tsDMARD in the post-index and 49.5% had CDAI >10

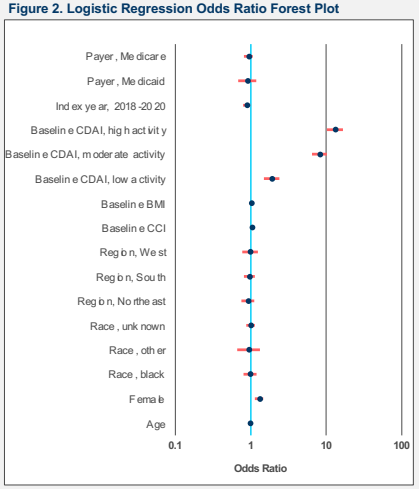
Table 1. Baseline Characteristics Overall and by Responder Status

Statistic	Overall	Responders	Non-responders
Age	61.6 (13.3)	63.9 (13.0)	59.8 (13.3)
Female	5,059 (76.1%)	2,096 (72.3%)	2,963 (79.1%)
Region			
Midwest	905 (13.6%)	366 (12.6%)	539 (14.4%)
Northeast	1,115 (16.7%)	520 (17.9%)	595 (15.9%)
South	4,063 (61.1%)	1,759 (60.7%)	2,304 (61.5%)
West	565 (8.5%)	255 (8.8%)	310 (8.3%)
Race			
Black	597 (9.0%)	243 (8.4%)	354 (9.5%)
White	4,305 (64.8%)	1,935 (66.7%)	2,370 (63.2%)
Other	166 (2.5%)	73 (2.5%)	93 (2.5%)
Unknown	1,580 (23.8%)	649 (22.4%)	931 (24.8%)
Payor			
Commercial	3,768 (56.7%)	1,516 (52.3%)	2,252 (60.1%)
Medicare	2,590 (39.0%)	1,273 (43.9%)	1,317 (35.1%)
Medicaid	290 (4.4%)	111 (3.8%)	179 (4.8%)
CDAI	15.6 (10.4)	11.3 (9.5)	18.9 (9.8)
CCI	1.4 (1.1)	1.4 (1.1)	1.4 (1.1)
BMI	30.4 (7.1)	29.7 (6.8)	30.9 (7.3)

Results Cont'd.

- Baseline characteristics are summarized in **Table 1** for the overall cohort and stratified by MTX responder status
- ORs resulting from the multivariate logistic regression for non-response are reported in **Figure 2**
- Being female (OR =1.3 [95% CI, 1.1-1.5]), increasing baseline CDAI (OR: Low activity=1.9 [1.5-2.4], moderate activity=8.1 [6.5-10.2], high activity=13.0 [10.2-16.6]) and higher BMI (OR=1.01 [1.00-1.02]) were significantly associated with non-response
- Being older was found protective of non-response (OR=0.98 [0.98-0.99])
- The C-statistic was 0.74.
- An alternative logistic regression model with the same set of covariates except the baseline CDAI had a C-statistic of 0.61.

Figure 2. Logistic Regression Odds Ratio Forest Plot



Results Cont'd.

- The significant covariates in the model without CDAI were the same as in the previous model. Being from the Northeast (OR =0.8 [95% CI, 0.7-0.9]) and having an index date in 2018 through 2020 (OR =0.9 [95% CI, 0.8-0.9]) were found protective of non-response
- CDAI measurements from the baseline, post-index and the change in CDAI from the baseline through post-index are assessed in **Table 2**
- The responders had lower baseline CDAI measurements and a greater decrease in their CDAI measurements from the baseline through post-index

Table 2. Baseline, Post-Index CDAI and Change in CDAI

Statistic	Responders	Non-responders
Baseline CDAI		
Mean (SD)	11.3 (9.5)	18.9 (9.8)
Median (IQR)	8 (4-17)	18 (13.5-24)
Post Index CDAI		
Mean (SD)	4.45 (2.59)	18.1 (8.3)
Median (IQR)	4.50 (2.50-6.50)	17.5 (13.5-22)
Change in CDAI		
Mean (SD)	6.81 (9.29)	0.89 (10.2)
Median (IQR)	3.50 (0-12)	0 (-4.50-6)

Conclusion

- We found that over half of patients qualified as MTX non-responders at approximately 6 months
- Significant predictors of non-response were younger age, female gender, higher CDAI score and BMI
- CDAI had a great impact in model predictive power
- Maximizing improvement as quickly as possible and deploying more tailored escalation of care may be aided by identifying RA patients at higher risk of early MTX treatment failure

References

1. Smolen JS, et al. *Annals of the Rheumatic Diseases* 2020;79:685-699.
2. Verstappen SM, et al. *Int J Clin Rheumtol.* 2012;7(5):559–567.

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