FORWARD
The National Databank for Rheumatic Diseases

Individuals with RA and the AA genotype at MICA rs1131896 are 6× more likely to experience a clinically important improvement in disease activity with a TNF inhibitor.

MHC Class I Polypeptide-Related Sequence A Variant Predicts Real-World Response to Anti-TNF Therapy

Kristin Wipfler[1], Joshua Baker[2], and Kaleb Michaud[1,3]

1 FORWARD, The National Databank for Rheumatic Diseases, Omaha, NE 2 University of Pennsylvania, Philadelphia, PA 3 University of Nebraska Medical Center, Omaha, NE

BACKGROUND

- MHC class I polypeptide-related sequence A (MICA) is a protein involved in the activation of NK and T cells
- Variants within the MICA gene have been linked to susceptibility to numerous rheumatic diseases, and one variant (rs1051792) has been associated with therapeutic response to TNF inhibitors in patients with RA[a]
- Objective: to examine the relationships between MICA variants and TNF inhibitor response in individuals with RA in a real-world setting

METHODS

- Data were provided by adults with RA who provided biosamples and initiated a TNF inhibitor during observation in FORWARD
- Genotyping was performed with the Illumina Global Screening Array platform, and non-silent common MICA variants were included in this analysis
- Change in disease activity following TNF inhibitor initiation was measured by PAS-II MCID
- Logistic regression models for achieving MCID were generated for each of the four variants by number of minor alleles present (0, 1, or 2; 0 referent)

RESULTS

- A total of 197 participants met inclusion criteria, 70 of whom (36%) reached the MCID for improved PAS-II following TNF inhibitor initiation
- Of the four variants examined, rs1131896 was significantly associated with improved disease activity following initiation of a TNF inhibitor
  - Individuals who were homozygous for the minor allele had 6× the odds of achieving the MCID for improved PAS-II
  - Heterozygous individuals did not have a significant association between their genotype and improved PAS-II scores

CONCLUSION

- Individuals with RA who are homozygous for the minor allele at MICA rs1131896 are significantly more likely to experience clinically important improvements in disease activity following use of a TNF inhibitor
- While other MICA variants have been associated with rheumatic diseases and drug response, this is the first study to link rs1131896 with TNF outcomes
- This variant may serve as a useful predictor of TNF inhibitor response as part of ongoing efforts to improve precision medicine for RA

Table 1. Baseline characteristics of FORWARD Biobank TNFi initiators.

Characteristic	TNFi Initiators (n=197)
Age, years, mean (SD)	58.9 (12.4)
RA duration, years, mean (SD)	14.7 (12.9)
Female, %	92.9
White, %	93.4
Hx smoking, %	37.1
BMI, kg/m^2, mean (SD)	29.0 (7.0)
RDCI, 0-9, mean (SD)	2.0 (1.6)
Glucocorticoid use, %	39.1
Baseline PAS-II, mean (SD)	3.6 (1.9)

Table 2. Genotype distributions of the four variants investigated.

Variant	Genotype	Genotype n (%)	Reached MCID n (%)
rs1063632	GG	163 (83.2)	59 (36.2)
	GA	32 (16.3)	10 (31.2)
	AA	1 (0.5)	1 (100.0)
rs1051794	GG	104 (52.8)	43 (41.4)
	GA	74 (37.6)	22 (29.7)
	AA	19 (9.6)	5 (26.2)
rs1131896	GG	107 (56.9)	33 (30.8)
	GA	67 (35.6)	24 (35.8)
	AA	14 (7.5)	9 (64.3)
rs9266825	CC	112 (57.7)	45 (40.2)
	CA	70 (36.1)	21 (30.0)
	AA	12 (6.2)	3 (25.0)

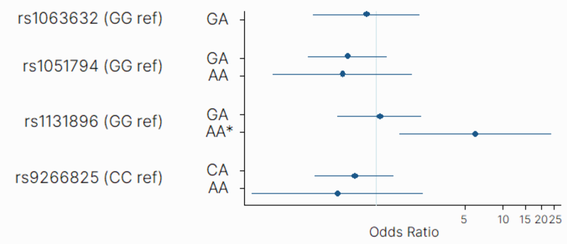

Figure 1. Odds ratios and 95% confidence intervals for each genotype as a predictor of achieving PAS-II MCID following TNFi initiation. Adjusted for baseline PAS-II, age, sex, white race, smoking history, calendar year, RA duration, BMI glucocorticoid use, and Rheumatic Disease Comorbidity Index (RDCI). For each variant, the association with reaching the MCID was assessed for both the heterozygous genotype and minor allele homozygotes, with major allele homozygotes as the reference. For rs1063632, the minor allele homozygote group was omitted from the model due to inadequate sample size. Genotypes marked with an asterisk (^) are statistically significant (p<0.05).

References

a Iwaszko, M. et al. Association of MICA-129Met/Val polymorphism with clinical outcome of anti-TNF therapy and MICA serum levels in patients with rheumatoid arthritis. *Pharmacogenomics J* 20, 760–769 (2020).

Disclosures

KW and KM have no disclosures to declare. JB is a consultant for Bristol-Myers Squibb, Pfizer, and RediTrex.