PTPN22 and HLA SE are not Associated with Discontinuation of TNFα Inhibitors or Methotrexate in a Large Rheumatoid Arthritis cohort

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Background

One-third of RA patients are still not achieving the ACR50 despite the use of therapies such as MTX and TNFα inhibitors.

Multiple replication studies have demonstrated the PTPN22 single nucleotide polymorphism to be a predictor of RA risk and likely of RA severity. The HLA-DRB1 "shared epitope" alleles (HLA SE) are established severity markers.

Study Aims

It is not known if HLA SE and PTPN22 predict drug response. We aim to determine whether these genes are associated with the discontinuation of TNFα inhibitors and MTX.

Methods--Genomics

–HLA-DRB1 alleles were assessed by low resolution genotyping and PTPN22 missense SNP(rs2476601) by Sequenom genotyping.

–Genotypes were classified as single or double HLA SE alleles and as PTPN22 TC or TT alleles.

Methods—Patient data collection

–Patients enrolled in prospective registry collecting genetic, demographic and functional status data.
–All diagnosed by a primary rheumatologist according to ACR criteria.
–At enrollment and one year we determined medication use through patient self-report and assessed the multi-dimensional health assessment questionnaire (MDHAQ).

Results—Cohort demographics

	Total cohort (N=933)**	Total with at least 1 HLA SE allele (N=455)	Total PTPN22 positive (N=183)
Age (mean, SD)	57.3 14.1	58.1 13.7*	55.5 15.1
Sex (% female)	768(82.3)	450(80.9)	151(82.5)
Disease duration (mean, SD)	14.4 12.5	14.4 12.3	16.6 12.8*
Rheumatoid factor (N, % positive)	567(62.6)	319(58.8)*	131(72.4)*
Anti-CCP (N, % positive)	594(65.4)	345(62.8)*	135(75.4)*
Nodular (N, % positive)	331(36.3)	192(35.4)	70(40.0)*

*Significant difference with total and complementary group **142(35.6%) had discontinued TNFα inhibitors

Results—Discontinuation models

Discontinuation Association with HLA SE and PTPN22 at Baseline

	HLA SE	PTPN22
TNFα inh discontinuation (N,%)	107(34.1)	113(34.8)
Univariate model	OR 0.7 (95% CI0.4-1.1)	OR 1.0 (95% CI 0.6-1.7)
MTX discontinuation (N,%)	193(36.2)	199(36.5)
Univariate model	OR 1.1 (95% CI 0.7-1.6)	OR 1.2 (95% CI 0.8-1.8)

–No models were significant, even with discontinuations at one year included.
–Additional adjustments for anti-CCP positivity, sex, disease duration and MDHAQ did not affect significance or odds ratios.

Conclusion

In our large cohort disease susceptibility and severity markers have no predictive value in determining discontinuation of TNFα inhibitors and MTX.

These results indicate that a mechanism beyond increased disease severity may underlie inadequate drug response.