GENETIC POLYMORPHISM IN DIHYDROFOLATE REDUCTASE IMPACTS METHOTREXATE POLYGLUTAMATION IN ADULT RHEUMATOID ARTHRITIS

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OBJECTIVE AND METHODS

- To examine the influences of variant in the dihydrofolate reductase gene (DHFR: rs1382539 G/A) on MTX accumulation
- Two US based cohorts of consented adult RA patients were analyzed

RESULTS

- Cohort 1: N= 187 patients (mean age 55 years under median 15 mg/week MTX) evaluated at a single visit for MTXPG levels (>3 months).
  - Linear mixed effect models revealed that carriers of the rs1382539 A/A genotype (n=4 patients [10%]) demonstrated the following relative to carriers of the GG or GA genotype
    - 0.8 nmol/L per mg lower MTX polyglutamation rate (median 26 nmol/mg; p<0.05)
    - 16% lower long-chain MTXPG3-5 (median 36% [IQR 18-55] vs 41 nmol/L [IQR: 28-60]; p<0.05)
    - 0.8 nmol/mg; p=0.01) than carriers of the GG or GA genotype.
    - While the rs1382539 variant was not significantly associated with clinical efficacy (p>0.05), lower RBC MTXPG3 levels and percent long-chain MTXPG3-5 levels associated with higher DAS28 in that cohort (p<0.05).
- Cohort 2: N= 38 patients (mean age 55 years) enrolled in a dose escalation study (starting 7.5 mg/week) for 6 months (206 study visits).
  - Lower RBC MTXPG3 levels (estimate=-11±5 nmol/L; p=0.03)
  - Lower percent long-chain MTXPG3-5 (estimate=-15±1%; p=0.02)
  - Lower polyglutamate rate (estimate=-0.9±0.4 nmol/mg; p=0.01)
  - While the rs1382539 variant was not significantly associated with clinical efficacy (p>0.05), lower RBC MTXPG3 level and percent long-chain MTXPG3-5 levels associated with higher DAS28 in that cohort (p<0.05).

CONCLUSION

Our data indicate that the rs1382539 G/A variant in DHFR impacts MTX polyglutamation in adult RA, which can indirectly contribute to clinical efficacy in some patients.