

The mitochondrial translocator protein (TSPO) single nucleotide polymorphism *rs6971* may influence pain and fatigue in rheumatoid arthritis (RA); Results of a preliminary study

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Background: The burden of pain and fatigue in patients with rheumatoid arthritis, despite apparent amelioration of joint inflammation, is well known. Translocator protein (TSPO) is a mitochondrial transporter, highly expressed in macrophages and microglia. The exact biological functions of TSPO remain under investigation. However, TSPO has long been demonstrated to have a critical role in the synthesis of neurosteroid. Neurosteroids are known to have facilitatory effects on GABA-A receptors in the brain, thus affecting mood, cognition and pain. Microglial upregulation of TSPO has been demonstrated in the thalamus of patients with chronic pain. Affinity of TSPO for its ligands is determined by a Single Nucleotide Polymorphism (SNP) *rs6971*. Homozygotes have low affinity, heterozygotes have moderate affinity, and wild types have high affinity binding for TSPO ligands. *rs6971* has been demonstrated to have a functional impact on neurosteroid synthesis. A recent study of patients with fibromyalgia demonstrated high affinity binders experienced significantly worse pain, and more fibromyalgia symptoms compared to moderate and low affinity binders. We sought to investigate the impact of TSPO binding affinity on tender joint and fatigue scores in anti-TNF inhibitor therapy (TNFi) responders with RA.

Methods: 45 patients with ACR criteria confirmed RA (age range 34-84 years, 20 male, 25 female) deemed as adequately responding to TNFi as per NICE criteria at 3 months, underwent genotyping for *rs6971*, using fluorescent probes on DNA extracted from whole blood. Those with fibromyalgia, depression and anxiety were excluded. Patients were grouped according to TSPO binding affinity, and change in FACIT-F score and tender joint count pre- and 3 months post-TNFi initiation were compared, using student T test.

Results: In keeping with healthy volunteer studies of *rs6971* frequency, 56% patients were high, 27% moderate and 18% low affinity binders. Age and gender did not differ significantly between high affinity and moderate/low affinity binders, nor did the proportion of patients with diagnosed osteoarthritis. Average increase in FACIT-F in high affinity binders was significantly lower than seen in moderate/low affinity binders (12.0% compared to 37.6%, $p = 0.04$). Average decrease in tender joint count in high affinity binders was significantly lower than in moderate/low affinity binders (32.9% compared to 59.8%, $p = 0.02$). Interestingly, average decrease in swollen joint count

was significantly higher in high affinity binders compared to moderate/low affinity binders (54% compared to 25%, $p = 0.02$).

Conclusion: Although this study is limited by cohort size, this is the first data indicating that rs6971 may influence pain and fatigue in RA. Larger studies, utilizing more sophisticated measures of pain and fatigue, over a longer time period would further clarify these findings. By further investigating the biological function of TSPO, we may be able to better understand the pathogenesis of chronic pain and fatigue in patients with RA.

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