

Analysis of the Popliteal Lymph Node as a Biomarker to Monitor Arthritic Flare in Male versus Female Tumor Necrosis Factor-Transgenic Mice with Inflammatory Arthritis

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Background: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammation in peripheral synovial joint tissue and is suggested to be more severe in women. The popliteal lymph node (PLN) has been found to be a biomarker of arthritic flare in the human TNF- α transgenic (TNF-Tg) mouse model of inflammatory arthritis. The PLN as a biomarker has not been assessed in male versus female TNF-Tg mice. The goal verify that anti-TNF therapy is equally effective in reducing the severity of arthritis in male and female TNF-Tg mice using PLN volume as a marker of arthritic flare.

Methods: Male and female TNF-Tg mice aged 3 months were subdivided into two groups and treated with either placebo or anti-TNF therapy for six weeks. Biweekly, power-Doppler (PD) ultrasound imaging was taken of right and left PLNs in each subgroup (n=6 per subgroup). 3D reconstructions were created using Amira image analysis software to determine total volume, PD volume, and normalized PD volume within the PLN. Two-way ANOVA was used to compare groups with a p<0.05 being significant. Mice were sacrificed at the end of treatment and knee tissue was collected for histologic analysis (n=6 per subgroup).

Results: There was a decrease in the PLN volumes in the anti-TNF treated groups compared to the placebo-treated groups for both sexes (p<0.05). The average PD volumes and normalized PD ratios were also lower in the anti-TNF treated mice but did not reach statistical significance in either sex. Additionally, in the anti-TNF treated groups, there was no difference in PLN volumes between males and females at the end of therapy. The PLN volume as a biomarker was validated by knee histology, which demonstrated increased inflammatory cell infiltrate in the joint tissue of placebo-treated mice compared to anti-TNF treated mice, but this has not yet been quantified.

Conclusions: Anti-TNF therapy was equally effective in decreasing arthritic severity in males and female TNF-Tg mice compared to placebo-treated mice of both sexes, as determined by PLN volume. Furthermore, increased PLN size positively correlates to joint inflammation and serves as an appropriate biomarker for arthritic flare.