TNF-inhibitors Slow Radiographic Progression in Ankylosing Spondylitis

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Relentless Radiographic Progression

Link between spinal inflammation and new bone formation in AS...?
Continuous NSAID use retards radiographic progression

TNFi Rx → ↓MRI-defined inflammation (STIR)

Do TNF-inhibitors affect radiographic progression?

- Long duration of FU required
- Unethical to do placebo controlled trials for long periods
- Comparison with historic cohorts not ideal
- Stage of disease and duration of AS might be significant
- Confounders like smoking have to be adjusted
- Baseline damage is a strong predictor and should be corrected for in analysis
- Large numbers are needed to show a significant effect after correcting for other relevant factors

Study Centers
**Methods**

- Patients followed prospectively across all 5 centers
- Standardized protocol with X-rays done every 2 years
- Patients with AS (Mod. New York criteria)
  - At least two sets of spinal radiographs for mSASSS
  - Not having advanced bamboo spine at baseline
- Clinical evaluation and laboratory assessment: at least once a year
- Disease activity at baseline
  - BASDAI
  - ESR
  - CRP
- Variables studied
  - Baseline mSASSS
  - Baseline age
  - Age of onset of axial symptoms
  - Duration of disease

**mSASSS Scoring**

- 3 Readers
- Blinded to treatment
- Status score
  - ICC: 0.966 (95% C.I. 0.947 – 0.978)
  - p < 1 x 10^-35
  - Cronbach's α: 0.982
- Change score
  - ICC: 0.528 (95% C.I. 0.264 – 0.720)
  - p = 0.0002
  - Cronbach's α: 0.697.

**Cohort**

- N: 334 Patients
- Mean Age: 40.7 ± 13.8 years
- Mean disease duration: 16.4 ± 12.8 years
- Mean age of onset: 24.2 ± 9.9 years

- Males: 77%
- HLA-B27: 83.4%

**Males Tend to Progress Faster**

- Mean baseline CRP: 1.48 ± 1.96 mg/L
- Mean ESR: 17.7 ± 19.5 mm/hour
- Mean baseline mSASSS score: 9.6 ± 14.5
- Progressors: 102
  - Increase in 2 mSASSS units in 2 years

**No Effect of HLA-B27 on Progression**

- 30.5% Progressors
- 69.5% Non-Progressors

- Negative
- Positive
Effect of Smoking on Progression

- Smoking: Yes vs. No
- Smoking Pack Years: 0-10 vs. >10

Effect of Baseline mSASSS on Progression

- mSASSS = 0
- mSASSS = 1-10
- mSASSS > 10

Effect of Baseline Inflammation on Radiographic Progression

- ESR < 20
- ESR = 20-40
- ESR > 40

TNF-inhibitor Naïve and Treated Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>TNF-inhibitor Naïve (N=133)</th>
<th>TNF-inhibitor Treated (N=201)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>42.50±14.6</td>
<td>39.43±13.2</td>
</tr>
<tr>
<td>Male (%)</td>
<td>67.7</td>
<td>82.6*</td>
</tr>
<tr>
<td>HLA-B27 (%)</td>
<td>84.96</td>
<td>82.41</td>
</tr>
<tr>
<td>Disease Duration (yrs)</td>
<td>16.38±14.4</td>
<td>16.47±11.8</td>
</tr>
<tr>
<td>Baseline mSASSS</td>
<td>8.20±13.8</td>
<td>10.60±14.9</td>
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<tr>
<td>Smoking (pack-yrs)</td>
<td>3.34±8.3</td>
<td>3.87±8.0</td>
</tr>
<tr>
<td>ESR (baseline)</td>
<td>17.02±17.3</td>
<td>18.11±20.9</td>
</tr>
<tr>
<td>CRP (baseline)</td>
<td>1.69±1.9</td>
<td>1.33±2.0</td>
</tr>
<tr>
<td>BASDAI (baseline)</td>
<td>3.61±2.4</td>
<td>4.64±2.5*</td>
</tr>
</tbody>
</table>

* p<0.002

Multivariate Analysis: Predicting Progressors

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pre-Matching</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline mSASSS</td>
<td></td>
<td>1.061</td>
<td>1.040-1.083</td>
<td>1 x 10^-17</td>
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<tr>
<td>Baseline ESR</td>
<td></td>
<td>1.025</td>
<td>1.010-1.039</td>
<td>0.001</td>
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<tr>
<td>Smoking (Pack Years)</td>
<td></td>
<td>1.051</td>
<td>1.014-1.091</td>
<td>0.007</td>
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<tr>
<td>TNF-inhibitor use (Yes/No)</td>
<td></td>
<td>0.498</td>
<td>0.274-0.905</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Early use of TNF-inhibitor use reduces rate of radiographic progression

OR: 0.36; CI:0.15-0.91; p=0.03

Mean Rate of mSASSS

- N=39
- N=42
- N=120

Delay in Starting TNF-Inhibitor (Years)
Longer Use of TNF-Inhibitors Decreases Radiographic Progression

Best results when TNF-inhibitors started within 10 years of disease onset

Conclusions

- First study to show disease modifying effect of TNF-inhibitors in AS
- Early use of TNFi is most effective
- Sustained treatment reduces progression
- Smoking and baseline inflammation are risks
- Baseline damage is the strongest predictor of future radiographic progression in AS.

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