Comparative effectiveness of three TNF inhibitors for rheumatoid arthritis:

Quasi experiment with no large risk on confounding

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Initiation of DREAM

- A registry of the use of TNF blocking agents in daily clinical practice was started on request of Dutch Health Care Institute (ZINL)

- Objective: to determine the cost-effectiveness of these expensive ‘new’ drugs in daily clinical practice
Comparative effectiveness (1)

- Three different TNF alpha inhibitors on the market/ in the pipeline
- Which one to prefer?
- RCT was not granted

Comparative effectiveness (2)

- Difference in availability of TNFi
- \( \rightarrow \) Quasi experiment
- Comparable to instrumental variable analysis
The DREAM study

- Inclusion of every RA patient that started with one of the TNF inhibitors since February 2003
- Collaboration between 11 hospitals in the Netherlands
- Regularly visits to assess medication use, effects and adverse events
- Clinical outcomes, patient reported outcomes; resource utilization

707 with at least 1 year FU and fully accessible data (August 2007)

<table>
<thead>
<tr>
<th></th>
<th>Adalimumab N=267</th>
<th>Etanercept N=289</th>
<th>Infliximab N=151</th>
<th>p-value</th>
<th>Missing values (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% rheumatoid factor +</td>
<td>81.0</td>
<td>71.1</td>
<td>77.7</td>
<td>0.022</td>
<td>1</td>
</tr>
<tr>
<td>% female</td>
<td>70.0</td>
<td>68.9</td>
<td>70.2</td>
<td>0.939</td>
<td>0</td>
</tr>
<tr>
<td>% with ≥ one erosion</td>
<td>71.7</td>
<td>65.3</td>
<td>72.7</td>
<td>0.157</td>
<td>1</td>
</tr>
<tr>
<td>Age</td>
<td>55.1 (12.6)</td>
<td>54.6 (14.2)</td>
<td>57.8 (13.4)</td>
<td>0.05</td>
<td>0</td>
</tr>
<tr>
<td>Disease duration (years) *</td>
<td>7.7 (2.7-13.6)</td>
<td>6 (2.1-13.4)</td>
<td>7.7 (2.7-14.1)</td>
<td>0.356</td>
<td>1</td>
</tr>
<tr>
<td>N previous DMARDs *</td>
<td>3 (2-4)</td>
<td>3 (2-4.75)</td>
<td>3 (2-5)</td>
<td>0.385</td>
<td>0</td>
</tr>
<tr>
<td>HAQ</td>
<td>1.3 (0.7)</td>
<td>1.4 (0.7)</td>
<td>1.4(0.7)</td>
<td>0.176</td>
<td>10</td>
</tr>
<tr>
<td>DAS28</td>
<td>5.3 (1.3)</td>
<td>5.5 (1.2)</td>
<td>5.2 (1.3)</td>
<td>0.059</td>
<td>4</td>
</tr>
</tbody>
</table>
Controlling for confounding

- Statistically significant differences, rheumatoid factor, age and DAS28 (outcome measures).
- Are the differences relevant?
  - Magnitude of the difference
  - Association with the outcome
- Fitting propensity score failed because none of the factors predicted choice of treatment (is in line with results on previous slide)
- Linear mixed model for repeated measures, baseline DAS28 included by using random effect for patient and rheumatoid factor was included as a co-varianteffect

Effectiveness: disease activity

A: DAS 28 over time

Mean difference over time 0.5, p-value <0.0001
Corrected for RF+: 0.53, p-value <0.0001
Conclusion concerning comparison

- One TNFi was less effective compared to the other two TNFis
- Effect was relatively large (0.6 = clinically relevant)
- Results were plausible (dose finding studies show the same results)
- Consistent with results from other observational studies
- In this case very little differences in baseline prognostic factors due to:
  - Availability issues
  - No expected difference in performance of the drugs
Conclusion

• In the absence of head-to-head comparisons, a comparison using observational data is first best alternative if

  • Outcome is accurately measured (objective vs subjective)
  • Loss of follow-up is minimalized
  • Effect is large, consistent and biological plausible
  • Potential biases are corrected for sufficiently
  • Dose response relation