Adalimumab Treatment Significantly Reduces Hospitalization Risk for TNF-Antagonist–Naïve Patients With Crohn’s Disease

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Background

• Adalimumab, a fully human monoclonal antibody that targets tumor necrosis factor (TNF), is approved for the treatment of adults with moderate to severe Crohn’s disease (CD)

• In CD, adalimumab is effective for the induction and maintenance of remission in patients with moderate to severe disease who have had an inadequate response to conventional therapy or who have lost response or are unable to tolerate infliximab\textsuperscript{1–3}

• The Crohn’s Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (CHARM) was a Phase III trial of adults with CD of more than 4 months’ duration and a CD Activity Index (CDAI) score between 220 and 450\textsuperscript{1}

• In CHARM, approximately one-half of patients enrolled were naïve to TNF-antagonist therapy

\textsuperscript{2}Hanauer SB, et al. Gastroenterology. 2006;130:323–33.
Study Aim

• This *post-hoc* analysis of CHARM evaluated the risk of all-cause and CD-related hospitalizations for TNF-antagonist–naïve patients treated with adalimumab or placebo
Study Sample

• This analysis included all randomized TNF-antagonist–naïve patients in the CHARM trial (49.8%, n=388)

• Patients received induction dosing (adalimumab 80 mg at baseline and 40 mg at Week 2) and were randomized at Week 4 to the following groups:
  – Adalimumab 40 mg every other week (eow)
  – Adalimumab 40 mg weekly
  – Placebo
Study Design (CHARM)

Open-Label

Week 0
N=854

Week 2:
40-mg adalimumab

Week 4
N=778

Week 4:
Stratification by CR-70 response status

Randomized

Week 26

Week 40 mg eow

40 mg weekly

Placebo

Flare/nonresponse

40-mg adalimumab eow/weekly open-label at/after Week 12

Week 56
Study Measures

- All-cause hospitalization
  - Any hospitalization regardless of reason
- CD-related hospitalization
  - Hospitalization caused by adverse outcomes related to CD, complications of CD, or treatment for CD
- Hospitalization events were identified and confirmed by review of serious adverse event reports
Statistical Methods for Hospitalization Analyses

• Patients with hospitalization were followed from Week 4 until the first hospitalization event

• Patients without hospitalization were followed from Week 4 until:
  – Switch to open-label adalimumab at or after Week 12
  – 70 days after early termination, if they discontinued CHARM
  – First dose in open-label extension, if they completed CHARM
• Descriptive analysis
  – The Kaplan-Meier method was used to estimate the risk of all-cause and CD-related hospitalizations for the combined adalimumab groups vs. placebo
  – The log-rank test was used to compare differences in hospitalization rates between the combined adalimumab groups and placebo
Statistical Methods for Hospitalization Analyses, cont.

• Multivariate analysis
  – The Cox proportional-hazards model was used to estimate the effect of adalimumab (treatment groups combined) on hospitalization risk after controlling for baseline variables, such as
    ▪ Age
    ▪ Sex
    ▪ Race
    ▪ Duration of CD
    ▪ Smoking status
    ▪ Presence or history of stenosis
    ▪ Presence of fistula
    ▪ Steroid use at baseline
    ▪ CDAI score at Week 4
## Baseline Demographics and Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Adalimumab EOW+Weekly</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients, n (%)</td>
<td>257 (66.2)</td>
<td>131 (33.8)</td>
<td>388 (100)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>106 (41.3)</td>
<td>54 (41.2)</td>
<td>160 (41.2)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>234 (91.1)</td>
<td>121 (92.4)</td>
<td>355 (91.5)</td>
</tr>
<tr>
<td>Black</td>
<td>12 (4.7)</td>
<td>4 (3.1)</td>
<td>16 (4.1)</td>
</tr>
<tr>
<td>Asian</td>
<td>9 (3.5)</td>
<td>2 (1.5)</td>
<td>11 (2.8)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (0.8)</td>
<td>1 (0.6)</td>
<td>6 (1.6)</td>
</tr>
<tr>
<td>Age (yrs), mean±SD</td>
<td>37±11.6</td>
<td>36±11.5</td>
<td>37±11.5</td>
</tr>
<tr>
<td>Body weight (kg), mean±SD</td>
<td>70.5±17.2</td>
<td>71.5±19.4</td>
<td>70.8±17.9</td>
</tr>
<tr>
<td>Disease duration (yrs)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>7.1</td>
<td>5.8</td>
<td>6.7</td>
</tr>
<tr>
<td>Minimum, maximum</td>
<td>0.2, 40.3</td>
<td>0.1, 40.3</td>
<td>0.1, 40.3</td>
</tr>
</tbody>
</table>

*Disease duration was calculated as the time between the date of CD diagnosis and the date of induction in the study.
Kaplan-Meier Curve, Time to All-Cause Hospitalization*

3-Month Hospitalization Rates:
- Placebo: 10.4%
- EOW+Weekly: 3.6%

6-Month Hospitalization Rates:
- Placebo: 15.4%
- EOW+Weekly: 8.9%

12-Month Hospitalization Rates:
- Placebo: 20.3%
- EOW+Weekly: 12.7%

*Log-rank test demonstrated significant differences (p=0.02) in hospitalizations between placebo and adalimumab (eow+weekly combined).
Kaplan-Meier Curve, Time to CD-Related Hospitalization*

- **3-Month Hospitalization Rates:**
  - Placebo: 7.9%
  - EOW+Weekly: 1.7%

- **6-Month Hospitalization Rates:**
  - Placebo: 11.3%
  - EOW+Weekly: 5.2%

- **12-Month Hospitalization Rates:**
  - Placebo: 13.7%
  - EOW+Weekly: 6.8%

*Log-rank test demonstrated significant differences (p=0.01) in hospitalizations between placebo and adalimumab (eow+weekly combined).
## Multivariate Cox Proportional-Hazards Model

### All-Cause Hospitalization

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adalimumab (eow+weekly)</td>
<td>0.437</td>
<td>0.229–0.836</td>
<td>0.0124</td>
</tr>
<tr>
<td>Placebo</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Disease duration</td>
<td>1.045</td>
<td>1.007–1.086</td>
<td>0.0214</td>
</tr>
<tr>
<td>Age</td>
<td>0.994</td>
<td>0.994–0.964</td>
<td>0.7271</td>
</tr>
</tbody>
</table>
# Multivariate Cox Proportional-Hazards Model

## CD-Related Hospitalization

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adalimumab (eow+weekly)</td>
<td>0.335</td>
<td>0.146–0.769</td>
<td>0.0098</td>
</tr>
<tr>
<td>Placebo</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Disease duration</td>
<td>1.048</td>
<td>0.997–1.102</td>
<td>0.0673</td>
</tr>
<tr>
<td>Age</td>
<td>0.982</td>
<td>0.943–1.023</td>
<td>0.3911</td>
</tr>
</tbody>
</table>
# Hospitalization Risk by Duration of CD, cont.

## All-Cause Hospitalization

<table>
<thead>
<tr>
<th>Disease Duration</th>
<th>Sample Size</th>
<th>12-Mos. Hospitalization Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 years</td>
<td>64</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Adalimumab</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>4.7%*</td>
<td>16.1%</td>
</tr>
<tr>
<td>≥3 years</td>
<td>193</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>15.5%†</td>
<td>22.3%</td>
</tr>
</tbody>
</table>

*<p <0.05 vs. placebo; †p=0.06 vs. placebo.*

## CD-Related Hospitalization

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<tr>
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<td>31</td>
</tr>
<tr>
<td></td>
<td>Adalimumab</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>3.2%*</td>
<td>11.8%</td>
</tr>
<tr>
<td>≥3 years</td>
<td>193</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>7.9%*</td>
<td>14.8%</td>
</tr>
</tbody>
</table>
Conclusions

• For anti-TNF-naïve patients with CD, adalimumab significantly decreased risks of both all-cause and CD-related hospitalizations vs. placebo

• Adalimumab may provide significant benefit to patients with CD who have not been previously treated with TNF-antagonist therapy and, thus, may be associated with substantial costs savings