Immunotherapeutic Lessons for the Allergist from a Rheumatology Perspective

Keith M Hull, MD, PhD
Medical Officer
Division of Pulmonary, Allergy, and Rheumatology Products,
Center for Drug Evaluation and Research
US Food and Drug Administration
Disclaimers

- In this presentation I am relaying personal views and opinion. This presentation is not intended to convey official US FDA policy, and no official support or endorsement by the US FDA is provided or should be inferred.

- The materials presented are available in the public domain.

- I do not have any financial interest or conflict of interest with any pharmaceutical company.
# Biologic TNF Inhibitors

<table>
<thead>
<tr>
<th>Drug (Trade Name)</th>
<th>Infliximab (Remicade)</th>
<th>Etanercept (Enbrel)</th>
<th>Adalimumab (Humira)</th>
<th>Golimumab (Simponi)</th>
<th>Certolizumab (Cimzia)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year Approved</strong></td>
<td>1998</td>
<td>1998</td>
<td>2002</td>
<td>200</td>
<td>2009</td>
</tr>
<tr>
<td><strong>Class</strong></td>
<td>IgG1</td>
<td>TNFR2</td>
<td>IgG1</td>
<td>IgG1</td>
<td>IgG1 / Fab</td>
</tr>
<tr>
<td></td>
<td>Chimeric</td>
<td>Fc-Fusion</td>
<td>Human</td>
<td>Human</td>
<td>PEG</td>
</tr>
<tr>
<td><strong>Antigen Specificity</strong></td>
<td>TNF-α</td>
<td>TNF-α LT</td>
<td>TNF-α</td>
<td>TNF-α</td>
<td>TNF-α</td>
</tr>
</tbody>
</table>
Biologic TNF Inhibitors

**Treatment Successes**
- Rheumatoid Arthritis
- Plaque Psoriasis
- Psoriatic Arthritis
- Ankylosing Spondylitis
- Crohn’s Disease
- Ulcerative Colitis

**Treatment Failures**
- Vasculitis
- Congestive Heart Failure
- Sepsis
- COPD
- Asthma
Role of TNF-α in Asthma

- Increased levels of TNF-α have been reported in bronchial biopsies and induced sputum from subjects with severe asthma.

- Monocytes and macrophages of subjects with asthma have higher TNF-α production compared with cells from subjects without asthma.

- Inhilation of TNF-α in normal subjects increases airway hyperresponsiveness and causes influx of neutrophils.

- TNF-α levels increase the adhesion of eosinophils to respiratory epithelium and promotes neutrophil chemotaxis, adhesion, and transendothelial migration.
TNF Inhibitor Trials in Asthma
TNF Inhibitor Trials in Asthma

• Successful Trials
  – Howarth PH et al., *Thorax* 2005; 60: 1012
  – Berry MA et al., *N Engl J Med* 2006; 354: 697

• Unsuccessful Trials
  – Morjaria JB et al., *Thorax* 2008; 63: 584
  – Holgate ST et al., *Eur Respir J* 2011; 37: 1352
  – Wenzel SE et al., *Am J Respir Crit Care Med* 2009; 179: 549
Clinical Differences Between TNF Inhibitors
Clinical Data Suggesting Differences Between TNF Inhibitors

• Differences between etanercept and the mAb TNF inhibitors in granulomatous disease
  – Crohn’s Disease
  – Tuberculosis

• Switching between TNF antagonists

• Treatment of Psoriasis
Additional Mechanisms of Action of TNF Inhibitors
APOPTOSIS

TNF/ TNFR Physiology

Reverse Signaling

sTNF-α

mTNF-α

Death Domains

TNF-RI

Immunocompetent Cells

NF-κB

INFLAMMATION

Most Nucleated Cells

TNF-RII

APOPTOSIS
6 Potential Differences Between TNF Inhibitors

- Ability to neutralize TNF
- Binding affinities for sTNF and mTNF
- Pharmacokinetics
- Ability to induce apoptosis
- Ability to mediate CDC and ADCC
- Ability to mediate reverse signaling of mTNF
Binding Affinities of TNF Inhibitor

<table>
<thead>
<tr>
<th>Drug</th>
<th>$K_D$ (M)</th>
<th>sTNF</th>
<th>mTNF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td></td>
<td>3.04 x $10^{-11}$</td>
<td>4.83 x $10^{-10}$</td>
</tr>
<tr>
<td>Adalimumab</td>
<td></td>
<td>2.73 x $10^{-11}$</td>
<td>4.68 x $10^{-10}$</td>
</tr>
<tr>
<td>Etanercept</td>
<td></td>
<td>1.18 x $10^{-11}$</td>
<td>4.45 x $10^{-10}$</td>
</tr>
</tbody>
</table>

Kaymakcalan Z et al., Clin Immunol 2009; **131**: 308-316
## Comparison of TNF Inhibitor Functions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>$t_{1/2}$</th>
<th>Apoptosis</th>
<th>CDC</th>
<th>ADCC</th>
<th>Reverse Signaling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>TNF-α</td>
<td>8-10 d</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>TNF-α</td>
<td>10-20 d</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>TNF-α</td>
<td>14 d</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>?</td>
</tr>
<tr>
<td>Etanercept</td>
<td>TNF-α LT</td>
<td>4 d</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>+</td>
</tr>
</tbody>
</table>
Conclusions
Conclusions

• Clinical activity of TNF inhibitors may vary within the same clinical disease due to differences in their molecular construction

• Differences in the mechanism of action of the TNF inhibitors include
  – binding of lymphotoxin
  – apoptosis
  – CDC and ADCC
  – Reverse Signaling through mTNF
Conclusions

- Overall, the clinical data suggest that TNF inhibitors are ineffective in treating patients with asthma but a different class of TNF inhibitor could potentially be therapeutic