Mepolizumab (Nucala®, GlaxoSmithKline plc.) for the Treatment of Severe Asthma with Eosinophilia

February 12, 2016

CTAF Overview

- Core program of the Institute for Clinical and Economic Review (ICER)
- Goal: Help patients, clinicians, insurers, and policymakers understand and apply evidence to improve the quality and value of health care
- Deliberation and voting by CTAF Panel – independent clinicians, methodologists, and public representatives
- Supported by grants from the Blue Shield of California Foundation, the California HealthCare Foundation, and the Laura and John Arnold Foundation

Agenda

- Public Meeting Convened, Topic Overview | 12:40 pm
- Presentation of the Evidence and Economic Modeling, Q&A | 12:45 – 1:30 pm (Dr. Jeff Tice, Melanie Whittington, and Dr. Dan Ollendorf)
- Public Comments | 1:30 – 2:00 pm
- CTAF Deliberation and Votes | 2:00 – 2:30 pm
- Policy Roundtable Discussion | 2:30 – 3:20 pm
- Reflections from CTAF Panel | 3:20 – 3:30 pm
- Summary, Closing Remarks | 3:30 pm
  - Download meeting materials: http://tinyurl.com/ctaf-mepo

Evidence Review

Jeffrey A. Tice, MD
Division of General Internal Medicine
University of California, San Francisco
Disclosures:
I have no conflicts of interest

Key review team members:
Dan Ollendorf, PhD
Jed Weissberg, MD
Shanshan Liu, MS, MPH
Elizabeth Russo, MD

Mepolizumab
- Humanized monoclonal antibody to IL-5
  - Binds to IL-5, decreasing IL-5 signaling, leading to decreased eosinophils in blood and tissue
- FDA-approved November 2015
  - Mepolizumab 100 mg SC every 4 weeks in MD office
  - Requires reconstitution by office staff
  - Indication: Patients ≥ 12 years old with severe eosinophilic asthma
    - Blood eosinophils ≥ 150 cell/µL at initiation or eosinophils ≥ 300 cell/µL in prior year

Topic in Context
- Asthma: 22 million Americans
- Severe asthma
  - Daily symptoms limiting normal activities; 2+ exacerbations requiring oral corticosteroids (OCS) in past year
  - 5-10% of asthma but 50% of costs
  - Standard treatment: inhaled corticosteroids (ICS) plus long acting beta agonist (LABA)
  - Additional therapies: leukotriene inhibitors, theophylline, and omalizumab
  - OCS used for asthma exacerbations and chronically for severe asthma not controlled without OCS
  - Chronic OCS associated with many long-term complications: infections, diabetes, osteoporosis, myopathy, obesity, glaucoma, depression, delirium, hypertension, adrenal suppression, cataracts, etc.

Methods
- Systematic review following PRISMA guidelines
- Target population (FDA indication):
  - Adults and children ages 12 years and older with severe, uncontrolled asthma and evidence of eosinophilic inflammation
- Intervention
  - Mepolizumab 100 mg SC (primary)
  - Mepolizumab 75 mg IV (similar pharmacodynamics)
- Comparator:
  - Standard treatment for severe asthma (OCS added to daily ICS and other controller therapy alone)
Double-blind RCTs
- MENSA trial (100 mg SC or 75 mg IV vs. placebo):
  - 576 patients age 12+ years and at least 2 asthma exacerbations in past year
  - 24 week F/U
- SiRIUS trial (100 mg SC vs. placebo):
  - 135 patients age 12+ years requiring 5-35 mg of prednisone daily for at least 6 months
  - 36 week F/U
- DREAM trial (75 or 250 or 750 mg IV q 4 weeks):
  - 616 patients age 12+ years and at least 2 asthma exacerbations in past year
  - 52 week F/U

Annual Exacerbation Rates

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Baseline</th>
<th>End</th>
<th>Rate Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>MENSA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 SC</td>
<td>194</td>
<td>3.8</td>
<td>0.8</td>
<td>0.5 (0.4-0.6)</td>
</tr>
<tr>
<td>75 IV</td>
<td>191</td>
<td>3.5</td>
<td>0.9</td>
<td>0.5 (0.4-0.7)</td>
</tr>
<tr>
<td>Placebo</td>
<td>191</td>
<td>3.6</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>SIRIUS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 SC</td>
<td>69</td>
<td>3.3</td>
<td>1.4</td>
<td>0.7 (0.5-1.0)</td>
</tr>
<tr>
<td>Placebo</td>
<td>66</td>
<td>2.9</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>DREAM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75 IV</td>
<td>153</td>
<td>3.7</td>
<td>1.2</td>
<td>0.5 (0.4-0.7)</td>
</tr>
<tr>
<td>Placebo</td>
<td>155</td>
<td>3.7</td>
<td>2.4</td>
<td></td>
</tr>
</tbody>
</table>

Oral Corticosteroid Use (mg/day)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Baseline</th>
<th>End</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIRIUS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 SC</td>
<td>69</td>
<td>10.0</td>
<td>3.1</td>
<td>6.9</td>
</tr>
<tr>
<td>Placebo</td>
<td>66</td>
<td>12.5</td>
<td>10.0</td>
<td>2.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Baseline</th>
<th>End</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIRIUS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 SC</td>
<td>69</td>
<td>12.4</td>
<td>8.6</td>
<td>3.8</td>
</tr>
<tr>
<td>Placebo</td>
<td>66</td>
<td>13.2</td>
<td>10.5</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Median dose reduction: 50% versus 0%, P=0.007

Quality of Life
- Statistically significant modest improvements
  - Asthma Control Questionnaire
  - St. George's Respiratory Questionnaire
Adverse Events
- Injection site reactions 8% versus 3%
- No difference in SAEs
- No difference in hypersensitivity reactions
- Opportunistic infections
  - Patients with parasitic infections excluded
  - Nominally more herpes zoster infections
    - 2/263 versus 0/257

Effectiveness: Controversies and Uncertainties
- Relatively small number of patients treated with SC
  - MENSA: 194 participants
  - SIRIUS: 69 participants
- Short duration of follow-up
  - MENSA: 32 weeks
  - SIRIUS: 24 weeks
- Key subgroups too small to evaluate
  - African descent: n = 39
  - Ages 12 to 17 years: n = 27

Effectiveness: Summary
- Moderate certainty of comparable or better net benefit for mepolizumab as add-on maintenance treatment compared with standard of care
- Other benefits or disadvantages:
  - Potential reduction in long-term harms associated with chronic OCS use
  - Injection that requires office visit every four weeks creates travel burden and may decrease long-term adherence
    - Conversely, monitoring and opportunity for patient education may offer additional benefits
  - New mechanism of action to treat severe asthma

Public Comments Received
- Mepolizumab 75 mg IV data should be included as it has equivalent pharmacodynamics
- Unpublished, ongoing open label continuation studies of the published trials provide data on the durability of the benefits
- Potential long term benefits through effects on airway remodeling may lead to greater benefits with mepolizumab treatment
- The large placebo effect on exacerbation rates suggests that optimization of standard therapy alone may greatly improve outcomes
Research Question
What are the outcomes, costs, and cost-effectiveness of mepolizumab plus standard of care (SoC) compared with SoC alone?

Methods
- Population: adults with severe, uncontrolled asthma and evidence of eosinophilic inflammation

<table>
<thead>
<tr>
<th>Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>50</td>
</tr>
<tr>
<td>Female</td>
<td>57%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>90%</td>
</tr>
<tr>
<td>Mean FEV, % of predicted</td>
<td>61%</td>
</tr>
<tr>
<td>Mean reversibility</td>
<td>28</td>
</tr>
<tr>
<td>Mean blood eosinophil</td>
<td>445</td>
</tr>
</tbody>
</table>

- Payer perspective: direct medical care and drug costs
- Time Horizon: lifetime
Model Structure

Exacerbation is defined as one of three subcategories:
1. Asthma related event that requires an oral steroid burst of at least three days (but not ED visit or hospitalization)
2. Asthma related event that requires ED visit (but not a hospitalization)
3. Asthma related event that requires a hospitalization

Key Assumptions
- Treatment effect observed during the trials is consistent throughout the model time horizon
- Excess risk of death from exacerbation assumed only for hospitalized cases
- Oral corticosteroid use above 5mg/day is potentially harmful to the patient
- Exacerbation utility is the same across treatment strategies
- Non-exacerbation utilities are different across treatment strategies based on SGRQ mapping

Results: Base Case

Mepolizumab + SoC vs. SoC Alone

<table>
<thead>
<tr>
<th></th>
<th>QALYs</th>
<th>Treatment Costs</th>
<th>Non-Treatment Costs</th>
<th>ICER ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mepolizumab + SoC</td>
<td>15.12</td>
<td>$706,111</td>
<td>$15,465</td>
<td></td>
</tr>
<tr>
<td>SoC alone</td>
<td>13.59</td>
<td>$98,083</td>
<td>$33,552</td>
<td></td>
</tr>
<tr>
<td>Incremental</td>
<td>1.53</td>
<td>$608,028</td>
<td>-$18,087</td>
<td>$385,546/QALY</td>
</tr>
</tbody>
</table>

Treatment costs include the cost of mepolizumab and SoC. Non-treatment costs include the cost of exacerbations and chronic OCS use.

Results: One-way Sensitivity Analysis

† This value is a function of three inputs: (1) Annual cost of chronic oral corticosteroid use, (2) Annual cost of adverse events due to chronic oral corticosteroid use, (3) Treatment-specific percent using chronic oral corticosteroids >5mg per day.
Results: Scenario Analysis

Cost of Mepolizumab

<table>
<thead>
<tr>
<th>ICER</th>
<th>Price per Vial (discount from base-case)</th>
<th>Price per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>$50,000/QALY</td>
<td>$266 (89.4%)</td>
<td>$3,458</td>
</tr>
<tr>
<td>$100,000/QALY</td>
<td>$599 (76.0%)</td>
<td>$7,787</td>
</tr>
<tr>
<td>$150,000/QALY</td>
<td>$932 (62.7%)</td>
<td>$12,116</td>
</tr>
<tr>
<td>$385,546/QALY</td>
<td>$2,500</td>
<td>$32,500</td>
</tr>
</tbody>
</table>

Key Model Limitations

- Limited long-term follow-up data
- Clinical outcomes and benefits observed in trial may not be constant through time
- Lack of absenteeism data to account for productivity differences from a societal perspective
- Responder scenario and comparison with omalizumab not conducted
- Wholesale acquisition cost of drugs may not represent true transaction cost of drugs

Conclusions

- Adding mepolizumab to SoC for adult patients with severe eosinophilic asthma appears to confer clinical benefits in terms of reduced rates of exacerbation and improved quality of life
- However, the estimated cost-effectiveness of mepolizumab exceeds commonly-cited thresholds
- Achieving levels of value more closely aligned with patient benefit would require discounts of two-thirds to three-quarters from current list price of mepolizumab
Public Comments Received

- Omalizumab (Xolair) was not modeled as a comparator
- Thresholds of $50,000 to $150,000/QALY are too low when assessing primarily employed populations
- More clarity needed on how trial data was extrapolated to assume lifetime clinical effects
- Payer perspective does not account for substantial out-of-pocket costs incurred by patients on multiple medications

Disclosures:

I have no conflicts of interest.

Key review team members:

Rick Chapman, PhD, MS

Budget Impact: Methods

- Estimated # of patients age 12 and older with severe asthma with poorly controlled disease (defined as 2+ exacerbations in prior year) and eosinophilic inflammation (150+ cells/μl at treatment initiation):
  - ~320,000
- Assumed uptake: 10% by year 5
- Year 5 treated estimate: 32,035
Annual Budget Impact Threshold: Methods
- Based on calculations involving:
  - Target for overall health care cost growth (GDP+1%)
  - Number of new drug approvals annually
  - Contribution of drug spending to overall health care spending
- Serves as “policy trigger” for discussion of managing cost of new interventions
- 2015-2016 threshold is $904 million for drugs

Budget Impact: Results at 5 Years

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Eligible Population (thousands)</th>
<th>Number Treated (thousands)</th>
<th>Weighted BI per Patient ($)</th>
<th>Average BI per year (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mepolizumab</td>
<td>320</td>
<td>32.0</td>
<td>$93,043</td>
<td>$596.1</td>
</tr>
</tbody>
</table>

Public Comments Received
- No comments received on budget impact analysis

SUPPLEMENTAL SLIDES
Model-wide Inputs

<table>
<thead>
<tr>
<th>Model-wide Inputs</th>
<th>Value</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma-related mortality per 100 person years</td>
<td>0.4</td>
<td>de Vries et al., 2010</td>
</tr>
<tr>
<td>Additional risk of death given asthma hospitalization</td>
<td>2.48%</td>
<td>Watson et al., 2007</td>
</tr>
<tr>
<td>Additional risk of death given ED visit</td>
<td>0%</td>
<td>Assumed</td>
</tr>
<tr>
<td>Additional risk of death given oral corticosteroid burst</td>
<td>0%</td>
<td>Assumed</td>
</tr>
<tr>
<td>Disability for hospitalization</td>
<td>-0.2</td>
<td>Lloyd et al., 2007</td>
</tr>
<tr>
<td>Disability for ED visit</td>
<td>-0.15</td>
<td>Lloyd et al., 2007</td>
</tr>
<tr>
<td>Disability for oral corticosteroid burst</td>
<td>-0.10</td>
<td>Lloyd et al., 2007</td>
</tr>
<tr>
<td>Disability for chronic oral corticosteroid use</td>
<td>-0.023</td>
<td>NICE omalizumab manufacturer’s base-case, 2013</td>
</tr>
<tr>
<td>Cost for asthma-related hospital stay</td>
<td>$9,960</td>
<td>Cangelosi et al., 2015</td>
</tr>
<tr>
<td>Cost for asthma-related ED visit</td>
<td>$684</td>
<td>Cangelosi et al., 2015</td>
</tr>
<tr>
<td>Cost for oral corticosteroid burst exacerbation</td>
<td>$156</td>
<td>Cangelosi et al., 2015 &amp; Redbook®</td>
</tr>
<tr>
<td>Annual cost for Standard of Care</td>
<td>$5,738</td>
<td>Cangelosi et al., 2015 &amp; Redbook®</td>
</tr>
<tr>
<td>Annual cost of chronic oral corticosteroid use</td>
<td>$73</td>
<td>Redbook®</td>
</tr>
<tr>
<td>Annual cost of adverse events due to chronic oral corticosteroid use</td>
<td>$784</td>
<td>Shah et al., 2013</td>
</tr>
</tbody>
</table>

Treatment-Specific Model Inputs

<table>
<thead>
<tr>
<th>Treatment-Specific Model Inputs</th>
<th>Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>SoC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual exacerbation rate per person year</td>
<td>1.74</td>
<td>Ortega et al., 2014</td>
</tr>
<tr>
<td>Proportion of hospitalizations</td>
<td>6.75%</td>
<td>Ortega et al., 2014</td>
</tr>
<tr>
<td>Proportion of ED visits</td>
<td>5.75%</td>
<td>Ortega et al., 2014</td>
</tr>
<tr>
<td>Proportion of oral corticosteroid bursts</td>
<td>88.51%</td>
<td>Ortega et al., 2014</td>
</tr>
<tr>
<td>Discontinuation rate over entire time horizon</td>
<td>6%</td>
<td>Ortega et al., 2014</td>
</tr>
<tr>
<td>Utility value for non-exacerbation health state</td>
<td>0.77</td>
<td>Ortega et al., 2014</td>
</tr>
<tr>
<td>Percent using chronic oral corticosteroids &gt;5mg per day</td>
<td>68%</td>
<td>Bel et al., 2014</td>
</tr>
<tr>
<td>Mepolizumab + SoC (limited to parameters that differ from SoC alone)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual exacerbation rate per person year</td>
<td>0.83</td>
<td>Ortega et al., 2014</td>
</tr>
<tr>
<td>Proportion of hospitalizations</td>
<td>3.61%</td>
<td>Ortega et al., 2014</td>
</tr>
<tr>
<td>Proportion of ED visits</td>
<td>6.02%</td>
<td>Ortega et al., 2014</td>
</tr>
<tr>
<td>Proportion of oral corticosteroid bursts</td>
<td>90.36%</td>
<td>Ortega et al., 2014</td>
</tr>
<tr>
<td>Annual cost for mepolizumab</td>
<td>$32,500</td>
<td>Redbook®</td>
</tr>
<tr>
<td>Discontinuation rate over entire time horizon</td>
<td>5%</td>
<td>Ortega et al., 2014</td>
</tr>
<tr>
<td>Utility value for non-exacerbation health state</td>
<td>0.828</td>
<td>Ortega et al., 2014</td>
</tr>
<tr>
<td>Difference in utility value for non-exacerbation health state (compared to SoC alone)</td>
<td>0.059</td>
<td>Ortega et al., 2014</td>
</tr>
<tr>
<td>Percent using chronic oral corticosteroids</td>
<td>46%</td>
<td>Bel et al., 2014</td>
</tr>
</tbody>
</table>

Public Comments

Mepolizumab (Nucala®, GlaxoSmithKline plc.) for the Treatment of Severe Asthma with Eosinophilia

Questions for Deliberation

February 12, 2016
Comparative Clinical Effectiveness Example Question

For patients with "condition X," is the evidence "adequate" to demonstrate that the net health benefits of "intervention A" is greater than that of "comparator B"?
- Yes
- No

Care Value Example Question

Given the available evidence, what is the care value of "intervention A" vs. "comparator B"?
- Low
- Intermediate
- High

Provisional Health System Value Example Question

Given the available evidence, what is the provisional health system value of "intervention A" vs. "comparator B"?
- Low
- Intermediate
- High

Mepolizumab: Clinical Effectiveness

Q1. For patients with severe asthma and with an eosinophilic phenotype, is the evidence adequate to demonstrate that the net health benefit of adding mepolizumab to standard of care is greater than that of standard of care alone?
- Yes
- No
Mepolizumab: Care Value

Q2. Given the available evidence for patients with severe asthma and with an eosinophilic phenotype, what is the care value of adding mepolizumab to standard of care vs. standard of care alone?

A. Low

B. Intermediate

C. High

Comparative Clinical Effectiveness

Incremental Cost per Outcomes Achieved

Additional Benefits

Contextual Considerations

Care Value

Mepolizumab: Provisional Health System Value

Q3. Given the available evidence for patients with severe asthma and with an eosinophilic phenotype, what is the provisional health system value of adding mepolizumab to standard of care vs. standard of care alone?

A. Low

B. Intermediate

C. High

Care Value

Potential Health System Budget Impact

Provisional Health System Value

Mechanisms to Maximize System Value

Achieved Health System Value

Policy Roundtable Participants

- Neal Kohatsu, MD, MPH, Medical Director, California Department of Health Care Services
- Michael Peters, MD, MAS, Assistant Professor, UCSF Division of Pulmonary and Critical Care Medicine and Pulmonologist, UCSF Severe Asthma Clinic
- Kristina Philpott, MD, Chair, Allergy and Immunology Department, Palo Alto Foundation Medical Group
- Tony Van Goor, MD, MMM, CPE, FACP, Senior Director, Medical Affairs, Medical Director for Policy and Technology Assessment, Blue Shield of California
- Tonya Winders, MBA, President and CEO, Allergy & Asthma Network

Reflections from CTAFF Panel
Summary and Closing Remarks

Meeting Adjourned