Office of Minority Health Progress Update

Jonca Bull, MD
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2016- The Year of Clinical Trial Diversity
Priority One: Improve the Completeness and Quality of Demographic Subgroup Data (Quality)

1.1 Reviewing and developing a work-plan for updating and/or finalizing, relevant guidance on demographic subgroup data

- Update of 2005 Industry Guidance on the Collection of Race and Ethnicity Data
Priority One: Improve the Completeness and Quality of Demographic Subgroup Data (Quality)- cont

1.3 Strengthen FDA Reviewer training by adding education/training around demographic inclusion and health disparities (prevalence, severity, disease course)

1.4 Enhancing FDA’s systems for collecting, analyzing and communicating diverse clinical information to optimize safe and effective use of medical products in diverse populations over the total product life cycle
   – Medwatch forms have been revised to include data fields to collect race and ethnicity data
Priority One: Improve the Completeness and Quality of Demographic Subgroup Data (Quality) - cont

1.5. Conducting research on specific areas of public health concern related to demographic subgroups

- OMH plans to develop research projects leading to better understanding of medical product clinical outcomes in racial/ethnic demographic subgroups

1. “Racial And Sex Difference In Prosthetic Aortic Valve Selection And Risk Factors For Patient Outcome—An Observational Study Of Medicare Beneficiaries”

2. “An Epigenome-Wide Association Study (EWAS) of Peripheral Blood Mononuclear Cells from African American and European American Women With and Without Lupus”

3. “Molecular Characterization of Racial Disparities and Outcome in Multiple Myeloma”
Expression levels of BAFF, APRIL, and their receptors in Peripheral Blood Mononuclear Cells of European and African-American Women with Systemic Lupus Erythematosus

Maya Barnes¹, Stancy Joseph², Edward Treadwell³, Beverly Word², and Beverly Lyn-Cook²

¹Arkansas State University, Jonesboro, AR, ²FDA National Center for Toxological Research, Jefferson, AR and the ³East Carolina Brody School of Medicine, Greenville, NC.

Abstract
Systemic lupus erythematosus (SLE) is a chronic, autoimmune disease affecting between 1.4 and 2.3 million Americans. It affects both men and women, particularly in African Americans and Hispanics. Patients with SLE have higher levels of the B-lymphocyte activating factors BAFF and APRIL and the proliferation-inducing ligand, APRIL. BAFF is the therapeutic target of the first drug approved by the FDA for SLE. Although this was a milestone in the treatment of this chronic disease, BAFF is still challenging. This study investigated the levels of BAFF, APRIL, and their receptors, BAFF-R, APRIL-R, and TACI in patients with SLE. Importantly, clinical expression of BAFF is significantly higher in African-American compared to European-American patients (p=0.08). However, the BAFF-R expression levels were significantly higher in European-American patients (p=0.08). Furthermore, SLE disease severity was positively correlated with BAFF levels. These results indicate that African-American patients with SLE have higher levels of BAFF, which may be influenced by ethnicity, SLE disease severity, and other factors that may play a role in the therapeutic response of the drug for SLE.

Methodology
- Samples: RNA samples were obtained from African and European-American decent with and without SLE (9 SLE samples and 9 healthy/non-lupus samples).
- RNA Quantification: RNA concentration was determined for each sample.
- RNA Integrity: RNA integrity was determined using the Bioanalyzer 2100 instrument according to the manufacturer’s instructions (Agilent). RNA samples with an RIN > 6 were used for this study.
- qRTPCR: qRTPCR was performed using a 96-well plate. Following primer and probe sets specific for each gene, expression levels were calculated using the ΔΔCT method.

Results
- qRTPCR analysis demonstrated that BAFF and APRIL expression levels were higher in African-American patients with SLE compared to European-American patients (p=0.08).
- SLE severity was positively correlated with BAFF levels, indicating that BAFF expression may be influenced by ethnicity, SLE disease severity, and other factors that may play a role in the therapeutic response of the drug for SLE.

Conclusions
- BAFF expression is significantly higher in African-American patients with SLE compared to European-American patients with SLE. This finding suggests that BAFF may play a role in the development and progression of SLE in African-American patients.
- SLE severity is positively correlated with BAFF levels, indicating that BAFF may be a potential therapeutic target for the treatment of SLE.
- Future studies are needed to further investigate the role of BAFF and APRIL in SLE and their potential as therapeutic targets.

Reference
Race Differences Reported for PK, Safety, and Efficacy for Approved NMEs

<table>
<thead>
<tr>
<th>NME labeling (n=167)</th>
<th>NMEs with difference reported</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PK</strong></td>
<td>19</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>6 (All in Asians – afatinib, pertuzumab, ado-trastuzumab emtansine, alvimopan, mirabegron, simeprevir)</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>3 (All in Blacks/ African Americans – azilsartan medoxomil, belimumab, croxetelin)</td>
</tr>
<tr>
<td><strong>Dose change</strong></td>
<td>1 (in Asians – eltrombopag olamine)</td>
</tr>
<tr>
<td><strong>Post-marketing studies</strong></td>
<td>4 (simeprevir, belimumab, telaprevir, ioflupane I123)</td>
</tr>
<tr>
<td><strong>PGx</strong></td>
<td>11 (germline differences in CYP2D6, CYP2C19, G6PD, IL28B)</td>
</tr>
</tbody>
</table>
## Labeling Recommendations

<table>
<thead>
<tr>
<th>Recommendation in FDA approved labeling</th>
<th>Example drug</th>
<th>Racial/ethnic information in the labeling</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indicated for a specific racial population</td>
<td>Isosorbide dinitrate/hydralazine</td>
<td>Indicated for self-identified blacks</td>
<td>Based on retrospective analyses, an effect on survival was reported in blacks, with little evidence to suggest an effect in the whites</td>
</tr>
<tr>
<td>Contraindicated in case of G6PD deficiency which is present in a higher frequency in specific racial populations</td>
<td>Rasburicase</td>
<td>Contraindicated in G6PD deficiency. Screen patients at a higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) prior to starting therapy</td>
<td>Recommendations to screen patients at a higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) prior to starting therapy because of the increased risk of hemolysis in patients with G6PD deficiency</td>
</tr>
<tr>
<td>Warnings and precautions directed at a specific racial population</td>
<td>Carbamazepine</td>
<td>Boxed warning for HLA-B*1502 in Asian patients</td>
<td>Incidence of adverse event and prevalence of genetic factor are higher in Asian populations</td>
</tr>
<tr>
<td>Recommendations for considering alternative therapy for a specific racial population</td>
<td>ACE inhibitors or Angiotensin II antagonists, e.g., candesartan and losartan</td>
<td>A general statement for African-Americans/blacks in the labeling of a number of drugs belonging to this class because of the smaller effect size observed</td>
<td>Pathophysiologically, hypertension is driven less by the renin-angiotensin-aldosterone system in African-Americans/blacks</td>
</tr>
<tr>
<td>Different dosing recommendation for a specific racial population</td>
<td>Rosuvastatin</td>
<td>Lower initial starting dose in Asians</td>
<td>Based on clinical observation of ~2-fold higher exposure in Asians compared to Caucasians</td>
</tr>
</tbody>
</table>

泾: glucose-6-phosphate dehydrogenase; HLA-B: human leukocyte antigen B; ACE: angiotensin-converting enzyme; CYP3A5: Cytochrome P450 3A5.
Priority Two: Participation- identifying barriers to subgroup enrollment in clinical trials and employing strategies to encourage greater participation

2.1 Seeking further clarity about barriers to subgroup participation rates

- April, 2015 Institute of Medicine Roundtable : “Strategies for Ensuring Diversity, Inclusion, and Meaningful Participation in Clinical Trials”
- University of Maryland project with School of Public Health/Center for Health Equity

2.2 Implementing Efforts to Enhance Appropriate Use of Enrollment Criteria in Clinical Trial Protocols

- September, 2015 OHOP-OMH Mini Symposium: “Racial/Ethnic Representation in Oncology Clinical Trials In the Era of Precision Medicine”
Priority Two: Participation- identifying barriers to subgroup enrollment in clinical trials and employing strategies to encourage greater participation

2.3 Collaborating with NIH, Industry and other interested stakeholders to broaden diverse participation in clinical research

– NIH Inclusion Governance Group

– September, 2015 OMH-NLM webinar: “Get to Know Clinical Trials.gov!”

– Work with community groups- sit on planning/steering committees for meetings and conferences (ex: AWARE for All-educating patients about clinical research)
Priority Two: Participation- identifying barriers to subgroup enrollment in clinical trials and employing strategies to encourage greater participation

2.4: Using FDA’s communication channels to encourage clinical trial participation by demographic subgroups

— Developing 6 PSA’s to raise awareness about clinical trial diversity, with plans to translate into other languages
— Written (or contributed) articles for FDA Voice Blog, Patient and Provider Network newsletter, external blogs (ex: APHA), and consumer updates
— Clinical trials and minorities webpage, brochure/infographic translated in Spanish
Concluding thoughts

- Inclusion of US racial/ethnic demographic subgroups in clinical trials in adequate numbers are important to look for differences that impact the safety and efficacy profile of the medical products in US demographic subgroups.

- Medical product development is increasingly carried out EX US
  - Study populations less representative of the US demographic subgroups
  - Limitations in characterizing drug safety and efficacy in US populations
  - Limit access to clinical trials in the US

- Big data may play a role in helping to close the gap

- Continued initiatives are needed to increase the enrollment of underrepresented demographic subgroups in FDA clinical trials.
2016: The Year of Diversity in Clinical Trials

Posted on January 27, 2016 by FDA Voice

By: Robert M. Califf, M.D.

Controlled clinical trials provide a critical base of evidence for evaluating whether a medical product is effective before the product is approved for marketing. One challenge that remains for FDA is ensuring that research participants are representative of the patients who will use the medical product.

Moving from the result of a clinical trial to applying it in practice is complex. But it's generally agreed that the composition of the population enrolled in a trial should help FDA reviewers, clinicians, or policy makers to have confidence that the trial results will apply to future practice.

Furthermore, a wide range of people should have the opportunity to participate in trials, both for access to new therapies and to have the chance to contribute to better treatment of everyone, an important altruistic goal for many Americans.
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Questions?

Research Can Improve People’s Health

Research helps doctors and scientists better understand, prevent, and treat diseases.

Research also helps scientists find out if medicines work and are safe for people to use.

How YOU can become a research volunteer:

Ask your doctor or nurse. They might know if there is a research study that is right for you.

Become a Research Volunteer

Research needs you
It’s YOUR decision

Some other words that describe research are:
• study
• clinical trial
• protocol

Research has led to important discoveries that make our lives better.

Some examples are:
• new medicines to treat cancer, diabetes, heart disease, HIV/AIDS, and other diseases & conditions
• vaccines
• ways to stop smoking
• faster medical imaging machines

For more information about participating in research studies please visit or call:

clinicaltrials.gov
www.nih.gov/health/clinicaltrials
OMH@fda.hhs.gov
1-888-INFO-FDA
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