Office of Minority Health Progress Update

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February 29, 2016

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)

- December, 2015 FDA-Johns Hopkins/CERSI Workshop: "Clinical Trials: Assessing Safety and Efficacy for a Diverse Population"

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

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Abstract

Systemic lupus erythematosus (SLE) is a complex autoimmune disease affecting between 1.4 and 2.0 million Americans. It manifests itself mostly in women, particularly in African Americans and Hispanics. Patients with SLE have higher levels of the B cell-activating factor, BAFF and the proliferation-inducing ligand, APRIL. In 2011, BAFF was the therapeutic target of the first drug approved by the FDA for SLE. Although this was a milestone in the treatment of this disease, it was only effective in a subset of patients, with decreased efficacy in African American women. This study investigated the levels of BAFF, APRIL, and their receptors, TACI, BCMA and BAFF-R, in peripheral blood mononuclear cells (PBMCs) of African and European American women with or without systemic lupus erythematosus (SLE). The mRNA expression levels of APRIL, BLyS and their receptors were detected by quantitative real time real-time PCR (QRT-PCR). Our findings showed that there were a significant increase in mRNA expression levels of BAFF ($p<0.05$), BCMA ($p<0.05$) and TACI ($p<0.05$) in patients with lupus. Interestingly, mRNA expression level of BAFF was significantly higher in African Americans compared to European Americans ($p<0.05$). However, the mRNA expression level of APRIL was significantly higher in European Americans ($p<0.05$). Furthermore, BAFF levels were examined in relation to SLEDAI score and age of patient. These results revealed that African American women with a SLEDAI score of six or less (≤ 6) had a higher level of expression of BAFF than European Americans ($p<0.05$). Lupus women less than 50 years of age also had higher mRNA expression levels of BAFF than those older than 50 ($p<0.05$). These results will be correlated with protein levels. In conclusion, BAFF expression may be influenced by ethnicity, SLEDAI score and age, factors that may play a role in the therapeutic response of the drug for this target.

Background

Lupus is a chronic autoimmune disease that can damage any part of the body. The disease has many forms, but the most common is systemic lupus erythematosus (SLE) [1]. SLE is the type of lupus that can effect the entire body system and has been associated with inflammation of the joints, skin, organs, and in severe cases can be life threatening [1]. Studies have shown that ninety percent of patients diagnosed with lupus are women [1], where women of childbearing age are most likely to be diagnosed with the disease. Certain ethnic groups are also at a higher risk of developing the disease. Studies have shown that African American women are three times more likely to be diagnosed with lupus compared to European American women [1] and if the disease is diagnosed at an early age, it tends to be more severe in African American women than any other ethnicity [1]. Two type II transmembrane proteins have been associated with systemic lupus erythematosus, BAFF (B-cell activating factor) and APRIL (a proliferation inducing ligand) [2]. BAFF (TALL-1, THANK, BLyS, and zTNF4, TNFSF 13B), a member of the TNF family, is a fundamental survival factor for mature B cells [3]. APRIL is a second molecule related to BAFF. And also plays a role in influencing the survival of mature plasma B cells. BAFF and APRIL pathogenic pathways are present in many human autoimmune diseases, such as SLE [3]. Elevated expression levels of BAFF and APRIL levels have been documented in patients with SLE [2]. Both BAFF and APRIL bind to two receptors called BCMA (B cell maturation antigen, TNFRSF 17) and TACI (transmembrane activator and CAML interactor, TNFRSF 13B) [4]. BCMA was identified as a translocation event in a human T cell lymphoma, yet its expression is mostly limited to mature B cells [4]. TACI is found on some T and B cells [4]. A third BAFF receptor, called BAFF-R (TNFRSF 13C) selectively binds BAFF and not APRIL [4]. In 2011, BAFF was the therapeutic target of the first drug approved by the FDA for SLE in fifty years. Although this was a milestone in the treatment of this disease, it was only effective in a subset of patients, with decreased efficacy in African American women. This study investigated the levels of BAFF, APRIL, and their receptors, TACI, BCMA and BAFF-R, in peripheral blood mononuclear cells (PBMCs) of African and European American women with or without systemic lupus erythematosus (SLE).

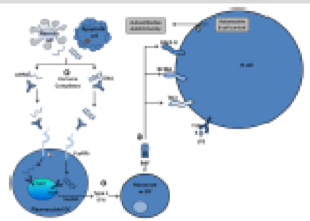

Figure 1: Schematic illustrating the role of BAFF, APRIL and their receptors in SLE

Methodology

- **Samples.** RNA samples were obtained from females of African and European American descent with or without SLE (40 SLE samples and 24 healthy/non-lupus samples).
- **RNA Quantification.** RNA concentration was determined for each sample.
- **RNA Integrity.** RNA integrity was determined using Experion RNA Assay according to the manufacturers (BIORAD) procedure. RNA samples with RIN > 8 were used for this study.
- **cDNA Synthesis.** cDNA was synthesized using 50ng of RNA. Reverse transcription was performed using a Qiagen RT^2 First Strand Kit following manufacturers protocol. cDNA was diluted to a final concentration of 20ng/uL.
- **QRT-PCR.** QRT-PCR was performed using multiplexing method. Using the BIORAD CFX96 Real-Time PCR system each sample was evaluated in triplicates using 100ng of cDNA. Primers utilized are listed below:

Primer Assay	Primer 1 (5'-3')	Primer 2 (5'-3')	5'- 3' Dye Quencher
18s rRNA	[illegible]	[illegible]	[illegible]
BAFF	[illegible]	[illegible]	[illegible]
APRIL	[illegible]	[illegible]	[illegible]
TACI	[illegible]	[illegible]	[illegible]
BCMA	[illegible]	[illegible]	[illegible]
BAFF-R	[illegible]	[illegible]	[illegible]

- **mRNA expression level.** Quantification of the relative amount of target gene was calculated using ΔΔCT method (Target gene = $2^{-\Delta\Delta CT}$).
- **Statistical analysis.** Data were expressed as mean ±SEM. Student's t-test was used to determine the statistical significance between lupus and non-lupus samples. And two-way ANOVA with tukey correction was used to perform statistical analysis between disease state (lupus and non-lupus) and ethnicity (African American and European American). $p<0.05$ was considered to be statistically significant. GraphPad Prism was used for all analyses.

Conclusions

- BAFF expression is significantly higher in lupus samples compared to non-lupus samples, African American women with lupus vs. European American with lupus, and in lupus samples from patients younger than 50.
- There was a significant increase of APRIL expression in European American women with lupus as compared to African American women with lupus. There was no significant change in APRIL expression between lupus and non-lupus samples.
- TACI levels were increased in lupus samples, and in African American women with lupus as opposed to the levels in European American women with lupus samples.
- BCMA expressed higher levels in lupus patients vs. non-lupus patients and was also increased in African American women with lupus vs. European American women with lupus.
- There was no significant difference in BAFF-R levels between lupus and non-lupus samples, or between African American women with lupus and European American women with lupus.
- Ethnicity, age, and disease state may play a significant role in the therapeutic response of the drug for treatment of SLE.

Reference

1. Lupus Foundation of America Inc. (2015). *Statistics on Lupus.* Retrieved July 1, 2015, from LUPUS Foundation on America: http://www.lupus.org/about/statistics-on-lupus
2. Davidson, A. (2012). The Rationale for BAFF Inhibition in Systemic Lupus Erythematosus. *Current Rheumatology Reports, 14*(4), 295–302. doi:10.1007/s11926-012-0258-2
3. Vincent, F., Saulep-Easton, D., Figgett, W., Fairfax, K., & Mackay, F. (2013). The BAFF/APRIL system: Emerging functions beyond B cell biology and autoimmunity. *Cytokine & Growth Factor Reviews*, 24(3), 203-215. doi:10.1016/j.cytogfr.2013.04.003
4. Vincent, F., Morand, E., Schneider, P., & Mackay, F. (2014). The BAFF/APRIL system in SLE pathogenesis. *Nature Reviews Rheumatology Nat Rev Rheumatol*, 10, 365-373. doi:10.1038/nrrheum.2014.33

Results

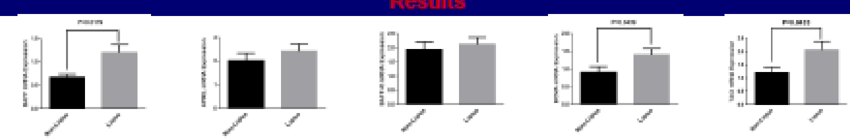

Figure 2. mRNA expression in lupus and non-lupus(healthy) women

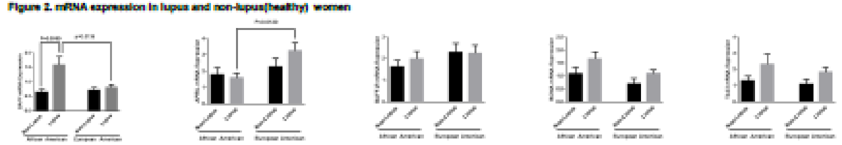

Figure 3. mRNA expression in lupus and non-lupus (healthy) women of African and European American descent

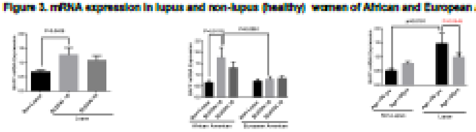

Figure 4. mRNA expression of BAFF in lupus and non-lupus women based on SLEDAI score, ethnicity and age

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

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

Ramamoorthy A, et al., CPT, 2015

Labeling Recommendations

Recommendation in FDA approved labeling	Example drug	Racial/ethnic information in the labeling	Rationale
Indicated for a specific racial population	Isosorbide dinitrate/ hydralazine	Indicated for self-identified blacks	Based on retrospective analyses, an effect on survival was reported in blacks, with little evidence to suggest an effect in the whites
Contraindicated in case of G6PD deficiency which is present in a higher frequency in specific racial populations	Rasburicase	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	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
Warnings and precautions directed at a specific racial population	Carbamazepine	Boxed warning for *HLA-B*1502* in Asian patients	Incidence of adverse event and prevalence of genetic factor are higher in Asian populations
Recommendations for considering alternative therapy for a specific racial population	ACE inhibitors or Angiotensin II antagonists, e.g., candesartan and losartan	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	Pathophysiologically, hypertension is driven less by the renin-angiotensin-aldosterone system in African-Americans/blacks
Different dosing recommendation for a specific racial population	Rosuvastatin	Lower initial starting dose in Asians	Based on clinical observation of ~2-fold higher exposure in Asians compared to Caucasians
	Tacrolimus	Higher dose in African-American transplant patients	Based on clinical observation; metabolized by CYP3A5 and African-American/black populations have low prevalence of reduced function variants compared to Caucasians

G6PD: glucose-6-phosphate dehydrogenase; HLA-B: human leukocyte antigen B; ACE: angiotensin-converting enzyme; CYP3A5: Cytochrome P450 3A5.

Ramamoorthy A, et al., CPT, 2015

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.

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

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.

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

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