Clinician’s Corner

Brand vs. Generics: Easy to Blame, but Hard to Prove

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Since 2009, the U.S. market share for generics has risen from 63% to 84%. This significant transformation has been driven largely by the need to understand and contain rising healthcare costs for private and government payers. Despite the majority of patients taking generic medication, it is not unusual to hear patients and providers voice frustration with coverage issues or concern that a newly refilled medication is less effective than the original prescription.

“A lot of times, the doctor gives you a sample and it is the brand name. But when you go to get the medicine, it is too expensive. So you end up with the generic. You can really tell the difference... just how effective they are.”

(Sewell K et al 2011)

This quote, from a 2011 focus group study in rural Alabama highlights what many patients and providers perceive about prescription medication.

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Treating Sjögren’s – The Future!

The Sjögren’s Syndrome Foundation (SSF) highlighted the progress made in encouraging clinical trials during November’s SSF luncheon meeting during the American College of Rheumatology (ACR) annual conference. Topics included the SSF Clinical Trials Consortium and Targets for New Therapeutics – The Science; in addition, updates on Outcome Measures were mentioned, and the SSF hosted an international meeting on Classification Criteria.

The SSF Clinical Trials Consortium (CTC) held its first international meeting in 2014 and is now seeing many of its efforts come to fruition after working with companies and clinical research centers to increase interest in Sjögren’s. First established by the SSF with the late Elaine Alexander, MD, PhD as its chair, the CTC mission is to increase the availability and accessibility of therapies for treating Sjögren’s. Three major goals were developed...
The therapeutic decision has been made is not transparent to most patients. Historically, once the provider diagnoses their patient’s disease, reviews the guidelines and chooses a medication, their overt involvement in the medication use process was essentially done. Over the last ten to fifteen years, the complexity of insurance coverage, the number of medications available and the rise of medication therapy management services have made it crystal clear that several of the biggest barriers to achieving patients’ health goals are between provider’s visits. This article will review patient’s perceptions of generics, review the FDA’s process in determining therapeutic equivalence and consider other factors that should influence provider’s communication of these issues with their patients.

Two studies during this time span help to highlight how patients view this steady march of generics into their homes. In 2009, a nationally mailed survey of commercially insured adults identified several very interesting but conflicting findings. The patient’s average age was 53 years old with 66% female and most identified as Caucasian/white. The patients overwhelmingly found generics to be cost-effective, at least as safe from side-effects, and a better value. However, only 38% preferred to take generics for themselves. This discrepancy between the perceived efficacy, safety and value of generics and the patient’s personal preference for them also appeared to be influenced by the lack of professional guidance from their medical team. Over half of the patients noted that their provider seldom or never discussed brand-generic issues. One explanation for this finding could be that the complexity of the therapeutic decision-making captures the providers’ focus, and once the prescription is written, the baton is handed off to the pharmacy and patient to complete.

This theme was picked up in the 2011 article from Sewell. Their study of 30 African-American adults from two counties in rural Alabama found several important themes. These groups perceived differences between brand and generic medications from efficacy to side effects, even going as far as saying generics were “not the real thing.” The last two themes, (lack of) trust in the medical system and settling for generics because of cost, appeared to drive their earlier views of generics being inferior. On the topic of communication with providers, these patients were respectful of providers training and knowledge but felt that the relationship with the pharmaceutical companies significantly influenced their prescribing habits.

The original perception study was redone in 2012 with 172 women from an OB/GYN practice in the northeast. The average age was 29 years old, 84% were Caucasian, and 20% had not completed high school. The perception that generics were safe, effective and comparable to their brand counterparts was similar to the 2009 study. The patient’s personal preference for generics was still low at 45% but higher than in 2009. In spite of the significant increase of generics nationally during this timeframe, only 30% discussed the issue with their provider.

It is clear from the sources above that there are multiple social and economic factors that may affect patient’s views and usage of generics. Even with the increasing use of generics from 2009 to 2012, the communication between providers and their patients remained low. I believe this is the key to resolving the mistrust of the system and perception of differences in the medications. When providers include the patient in the complex prescribing decision-making process, the provider will be able to identify important patient concerns as well as communicate their own perceptions regarding the importance of brand, generic, route, dose, frequency and other important aspects.
APPROVED FOR DRY MOUTH RELIEF in Sjögren’s Patients

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IMPORTANT SAFETY INFORMATION

CONTRAINdications: Aquoral is contraindicated for any patient with a known history of hypersensitivity to any of its ingredients.

PRECAUTIONS: Read package insert carefully before using this spray. Avoid contact with eyes. Flush eyes with water if accidental introduction into eyes should occur.

INTERACTIONS: There are no known interactions with medicinal or other products. Please see full Prescribing Information provided.


Please see full Prescribing Information on next page.
of the specific medication needed to solve the patient’s medical problem.

**Therapeutic equivalence**

Beginning in the late 1970’s, and due to increasing pressure at the state level to curtail costs, the FDA began a process to determine the biologic and therapeutic equivalence of prescription medications. According to the FDA, a generic drug is bioequivalent to its brand name reference drug only if it meets the four criteria in Table 2. For a drug product to be approved as a generic, its maximum concentration (Cmax) and “Area Under the Curve” (AUC) must fall within an 80%-125% range of the reference product (brand medication) with an inclusive 90% confidence interval. In practice, the mean of the study data lies in the center of the 90% confidence interval. Therefore, the mean of the data is very close to a test/reference ratio of 1 (or 100% equal). This also means that a small number of individual medication lots can vary significantly, up to 20% and still be considered equivalent. The importance lies in identifying and communicating when the patient variables or medication variables are important enough to check the “Dispense As Written” (DAW) box on the prescription or spend the extra time to go through the prior authorization process with the insurance company.

### Table 2

**U.S. FDA Orange Book Definitions, 34th edition**

<table>
<thead>
<tr>
<th>Pharmaceutical Equivalents</th>
<th>Drug products with: same active ingredient, same dosage form, same route of administration, identical strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic Equivalents</td>
<td>Drug products with: same pharmaceutical equivalence, expected to have same clinical effect and safety profile</td>
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The Orange Book is the compendium that contains the list of the test (generic) and reference (brand) medications. When there are no known or suspected bioequivalence problems, these medications receive a rating of AA (conventional dosage form), AN (solutions), AO (oil injectable), AP (aqueous injectable), and AT (topical). When there are actual or potential bioequivalence problems between two or more medications, the issue has to be resolved with “adequate” in vivo (tested in whole living organisms) or in vitro testing (tested in a laboratory environment). These medications receive an AB rating. Generic and brand medications that do not pass the bioequivalence standard are given a B rating.

An example of the hidden complexity of this system is levothyroxine sodium. First, it is considered a narrow therapeutic index (NTI) medication. These medications are defined in the federal register as having less than a 2-fold difference in median lethal and effective dose. This means the traditional margin for error is much smaller than normal. The safe and effective use of these medications requires careful titration and patient monitoring. The second reason is that there are multiple reference-listed brands for levothyroxine sodium. Unithroid, Synthroid, Levoxyl and Levothroid have all completed studies to establish their therapeutic equivalence to other reference-listed brands and generics. Therefore, while Synthroid and levothyroxine sodium are AB2 rated AND Levoxyl and levothyroxine sodium are AB3 rated, Synthroid and Levoxyl are not AB rated and therefore are not therapeutically interchangeable.

Unlike medications with a broader difference between effective and lethal doses, drugs that have an NTI are of special concern to the FDA and providers due to their small margin of error. Examples of NTI medica-
tion include: levothyroxine, warfarin, lithium, phenytoin, and digoxin. Switching between brand and generic or different generic products is particularly concerning with these medications and may require increased vigilance to recommended monitoring. To address this issue, the FDA passed a ruling that NTI medications should require a tighter range (90% to 105%). The hope was that by tightening the range, this would lead to less variability and address what providers and patients were finding when refills were processed and clinical markers were found or perceived to be different.

Layered on top of the therapeutic equivalent system are the pharmaceutical alternatives NOT addressed in the Orange Book or by the FDA. These medications have the same active ingredients but may dissolve, absorb, or function in a specific patient’s body very differently than the original medication prescribed. Examples of these include:

- Tetracycline hydrochloride 250mg vs. Tetracycline phosphate complex 250mg
  - OR
- Quinidine sulfate 200mg caps vs. quinidine sulfate 200mg tabs
  - OR
- Verapamil hydrochloride 120mg extended-release vs. verapamil hydrochloride 120mg sustained-release

Depending on what the difference was and how the prescription was written, the patient could receive a medication that performs very differently compared to what they used in the past. Vigilant pharmacists and patients catch many of these differences before they leave the pharmacy, but some are very subtle. By definition, any of the above changes at the pharmacy would need to be relayed back to the provider and a new prescription written. The final piece of evidence on this issue from the Orange Book preface is both self-explanatory and insightful towards the solution to several of the concerns raised:

“The FDA evaluation of therapeutic equivalence in no way relieves practitioners of their professional responsibilities in prescribing and dispensing such products with due care and with appropriate information to individual patients.”

Regardless of the perception or reality of differences between brand and generic medications, it is important to note that the system is not currently set up to compare one generic to another. Yet, it is possible for a pharmacy to receive shipment from a different manufacturer and, with a sticker notification on the bottle, send the new generic medication to the patient.

**Conclusion**

The federal government has been in the business of standardizing medications that are therapeutically equivalent for the last 40 years. This process does a great job for the majority of patients and medications. However, individual patients (organ function, complexity of disease) or specific medications (NTI) may be outliers in the normal distribution of biologic and therapeutic equivalency. These outliers may be perceived, or actually found to be, different enough to affect health outcomes. By improving the communication between provider and patient during the final therapeutic decision-making process regarding the most important parts of their therapy (dose, route, administration, adherence, monitoring, etc), the provider can empower their patient to advocate for consistent medication therapy. In the event that the exact medication product is required, dispense as written or prior authorization are important tools for providers to use, when appropriate. An educated patient who is an active participant in their healthcare can help providers and pharmacists correctly manage the complexity inherent in our medication use system.

The author wishes to note special thanks to Albany College of Pharmacy and Health Sciences senior students Ashleigh Tallman and Charmi Shah for their research and initial draft work.

**References**

to accomplish this mission: 1) support and promote objectives that facilitate the design of clinical trials; 2) increase industry partnerships with the SSF; and 3) engage in dialogue with government agencies that oversee therapy approval. (i.e. FDA, EMA).

While many barriers exist in getting new therapies to market in Sjögren’s, tremendous progress has been made or is underway. Several factors are contributing to the increased interest and subsequent plans for clinical trials in Sjögren’s, including the development of biomarkers; novel diagnostics that are coming onto the market to speed up and increase precision of diagnosis as well as the number of those diagnosed; internationally-accepted classification criteria becoming finalized over the next year; and internationally-accepted outcome measures finally being in place. The SSF made the development of biomarkers and novel diagnostics a top priority for its research grants over the last few years, and it is partnering with companies that are interested in or already developing biomarkers or marketing diagnostics that have been approved. It also has hosted and participated in international meetings to gain international agreement on criteria and outcome measures.

(Editor’s Note: Please see the update on Outcome Measures in this newsletter. An update on Classification Criteria will be provided in a future issue of the Quarterly.)

Interest in Sjögren’s is increasing substantially – especially compared to just one year ago. The Foundation now has more than half a dozen Corporate Members with whom it’s working closely on programs and initiatives that will increase attention for Sjögren’s. The SSF is increasing industry partnerships by letting companies know that the SSF can be a key player in assisting them from the earliest stages of initial interest and discussions about Sjögren’s all the way through identification of potential therapies, design of and subsequent recruitment for clinical trials, navigation of government agency processes, and post-approval marketing. The SSF currently is connecting Corporate Members to key opinion leaders and specialty centers in Sjögren’s, spearheading patient surveys and convening patient focus groups.

Finally, the SSF is initiating a dialogue with government agencies that oversee therapy approval and learning what it can do to assist with the development of guidelines for new drug/product approval, speed approval of new Sjögren’s therapies, and, subsequently, ensure corporate interest in drug development. For the November 2014 SSF luncheon meeting at the ACR, an FDA Regulatory Update was provided by Nikolay Nikolov, MD, Clinical Team Leader, Division of Pulmonary, Allergy and Rheumatology Products (DPARP), Center for Drug Evaluation and Research (CDER), Food and Drug Administration. Dr. Nikolov discussed aspects that are critical in the development of therapies in Sjögren’s, including clearly defining the population for a specific therapy and endpoints that reflect the proposed benefits of that therapy, efficacy and safety considerations, and trial design. The CTC Steering Committee deemed development of a Guidance Document for drug approval in Sjögren’s as its top priority and will be engaging in dialogue related to this priority in 2015.

The CTC regularly reviews therapeutics that are promising, under consideration, or already in clinical trials for Sjögren’s so that it can work with companies to ensure their success. In addition, the SSF maintains a list of clinical centers around the world that have the infrastructure, expertise, interest and patient populations
to conduct clinical trials in Sjögren’s. Currently, that list includes nearly 80 physicians and dentists at about 50 U.S. medical centers and many more worldwide.

We must recognize that the international community as a whole needs to work together and be involved in key initiatives in Sjögren’s and especially in encouraging new therapies. The SSF has started with a very small Steering Committee as top priorities are determined and will expand to include many members who are leaders in the Sjögren’s community as it moves forward. Led by myself, members of the Steering Committee include Hendrika Bootsma (Netherlands); Simon Bowman (UK); Steven Carsons (US); Denise Faustman (US); Xavier Mariette (France); Stanley Pillemer (US); Kathy Sivils (US); Claudio Vitali (Italy); Frederick Vivino (US); and Daniel Wallace (US).

All of us working in Sjögren’s and connected with the SSF are looking forward to the next decade in Sjögren’s and the start of major changes in the treatment of this disease!

Targets for New Therapeutics – The Science

by Denise Faustman, MD, PhD

While Sjögren’s patients face potential complications in any body organ or system, we are all aware that the clinical picture can differ greatly from one patient to another and present different spectrums of the disease. Currently, our ability to treat the many symptoms is negligible, and, in fact, no systemic therapies currently are available and FDA-approved for Sjögren’s. The complexity presented by the variation in patient symptoms in addition to previously lacking key elements needed for the successful conduction of clinical trials in Sjögren’s has meant that developing systemic treatments for Sjögren’s has faced numerous obstacles. However, future prospects for treating Sjögren’s are rapidly changing.

Many needed variables are coming together to set the stage for a burgeoning interest in and development of potential new therapies. As mentioned in the summary on the SSF Clinical Trials Consortium and presented in this issue, we finally have established outcome measures. We also are close to validating classification criteria that are embraced by the international community. These initiatives will substantially increase corporate interest in developing new therapies and already are doing so. In addition, our experience with immunological therapies in other diseases and knowledge of the many options that exist for intervening in the cascade of immunological events that take place in the development of Sjögren’s is escalating. In fact, more therapies for Sjögren’s than at any previous time are in the planning or preliminary stages of development while others already are in clinical trials for Sjögren’s. In Sjögren’s, opportunities are available for objective measurements (such as dry mouth and dry eye) that don’t exist for closely-related diseases, a fact that contributes to the increasing interest in clinical trials in Sjögren’s.

We will start by taking a brief look at just a few of the potential therapies under investigation or being considered for use in Sjögren’s.

**B Cell Inhibitors or Modulators**

**Rituximab**

This chimeric monoclonal antibody depletes all B cells (but not plasma cells) and specifically targets the receptor CD20, the role of which is unclear. It requires antibody-dependent cell-mediated cytoxicity (ADCC). Like other therapies either used off-label or considered promising for Sjögren’s, rituximab was developed originally for B cell lymphoma. It subsequently was approved for use with methotrexate in severe rheumatoid arthritis (RA).

Results from Phase III trials using rituximab in Sjögren’s are expected in late 2015. Carubbi et al in late 2014 remarked on the growing evidence for efficacy of rituximab in Sjögren’s, although the use of rituximab was questioned by the 2014 publication by Devauchelle-Pensac et al following a randomized trial showing lack of effectiveness at week 24 in alleviating symptoms and disease activity. (SSF Medical and Scientific Advisory Board leaders commented on this latter study in Faustman DL et al in Ann Int Med, Sep 2014).

**Epratuzumab**

Epratuzumab has a slightly different B cell target: CD22, in the Ig superfamily. Rather than depleting B cells, it modulates and inhibits B cell proliferation, and binding results in rapid internalization of cell surface CD22. In contrast with rituximab, epratuzumab is a humanized IgG1-kappa monoclonal antibody. Phase 3 trials currently are wrapping up in lupus, and, if deemed successful, trials may be conducted in Sjögren’s. Initial open-label trials in Europe showed promise.

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BAFF/BLyS Targets

Belimumab

This human monoclonal antibody inhibits B-cell activating factor (BAFF), which is also known as B-lymphocyte stimulator (BLYS). Belimumab was the first FDA-approved therapy (March 2011) for systemic lupus erythematosus (SLE). While Phase II trials in RA failed, belimumab appears promising for Sjögren’s after Phase II open-label trials were carried out in Paris, France and Pisa, Italy. Dryness, fatigue, musculoskeletal joint pain, global disease activity and reduction of B cell biomarkers were primary endpoints. In addition to a reduction in signs and symptoms of Sjögren’s, lymphocytic infiltration was decreased in some cases. Interestingly, another study carried out in Pisa and published in 2014 showed efficacy for sequential therapy with belimumab followed by rituximab in treating B cell lymphoproliferation in Sjögren’s. Patients had been followed for 3½ years by the time of publication and highlighted the need for future longer-term studies of the therapies given both sequentially and concomitantly.

VAY736

VAY736 targets BAFF-R. Clinical trials for this fully human HuCAL-based antibody in Sjögren’s are just now getting underway in Germany, the U.S., France and the Netherlands. Patients with relapsing remitting multiple sclerosis and pemphigus vulgaris also are being recruited for studies of VAY736.

T Cell Regulation and Cytokine Targets

Abatacept

Initially developed for RA, this Fc fusion protein with extracellular domain of CTLA-4 binds to CD80/CD86 (B7-1, B7-2) and prevents T cell signaling. It also inhibits TNF (tumor necrosis factor) alpha, interferon-gamma & interferon-2. Randomized, placebo double-blinded clinical trials are recruiting patients at the University Medical Centre Groningen, the Netherlands (PI Hendrika Bootsma), and an open-label Phase II study is underway at the Cleveland Clinic Foundation (PI Qingping Yao) for patients with inflammatory arthritis associated with Sjögren’s.

Baminercept

Baminercept is a lymphotxin-β receptor IgG1 fusion protein that leads to reduced activation of T cells, dendritic cells and possibly the vascular endothelium. Phase II trials have completed enrollment and currently are underway at nine centers in the U.S. Sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH), the trials are led by Principle Investigators (PIs) E. William St. Clair, MD, at Duke and Judith James, MD at the Oklahoma Medical Research Foundation. While the therapy did not meet endpoints in rheumatoid arthritis (RA), it remains a potential candidate for Sjögren’s.

BCG Vaccine

This vaccine already has a 95-year safety profile due to its use worldwide for TB and at very high dose for bladder cancer. BCG induces TNF, a cytokine that promotes Treg generation and death of autoreactive T cells. Ongoing Phase III trials are taking place in Multiple Sclerosis (MS) in Italy, Phase II type 1 diabetes in Boston, Massachusetts and Phase II prevention trials in Denmark, Australia, and Turkey. Phase I trials in Sjögren’s are in the planning stages at the NIH. In multiple sclerosis, the use of BCG shows outstanding efficacy and safety in new onset disease and with seven years of follow-up is showing better outcomes than currently licensed drugs on the market.

Tocilizumab

Tocilizumab is an IL-6 inhibitor that is FDA-approved for polyarticular juvenile idiopathic arthritis. Phase II trials are currently underway by PI Jacques-Eric Gottenberg in Strasbourg, France for Sjögren’s.

Genetics and Epigenetics

The fields of genetics and epigenetics are entering an explosive new era. While we can only touch briefly on these areas here, these fields will open up a wide array of potential biomarkers and therapeutic targets. As reported in late 2013 and discussed in the summer 2014 issue of the Sjögren’s Quarterly by Kathy Sivils, PhD, Oklahoma Medical Research Foundation (OMRF), the first definitive genes associated with Sjögren’s have been identified. Lead author on the genetics article, a member of Dr. Sivils’ lab at OMRF and a current SSF research grantee, Christopher Lessard, PhD is studying long non-coding RNAs (lncRNAs) in Sjögren’s. Gene expression can vary based on complex mechanisms involving both proteins (such as transcription factors) and thousands of non-coding regulatory RNAs. A substantial number of dysregulated lncRNAs have been identified in Sjögren’s by the OMRF group and could open novel lines of investigation for diagnosis and treatment.

Other genomics-related studies were highly visible at the latest ACR annual meeting, including an abstract from the SSF Outstanding Abstract Honorable Mention awardee, Jessica Tarn, from Newcastle University, U.K. Tarn reported on “Whole Blood microRNA Signature for Primary Sjögren’s Syndrome-Related Lymphoma.”

A greater focus on biomarkers associated with specific complications and symptoms eventually will enable physicians to assess patients for risks so personalized

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Patients with dry mouth?

Their teeth need BasicBites™ - the soft chew with the vital and supportive benefits of saliva

Now there is a delicious breakthrough oral care innovation that can help dry mouth sufferers keep their teeth in the normal pH zone while supporting healthy tooth structure.

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monitoring and treatment plans can be followed. As noted by Konsta OD et al, several epigenetic mechanisms are defective in Sjögren’s and involve microRNA expression, DNA demethylation, and abnormal chromatin positioning associated with autoantibody production. Interestingly, epigenetic modifications may be reversible as evident in minor salivary glands after use of rituximab in Sjögren’s patients.5

The Future

Sjögren’s is poised to benefit from the new era of drug development that we are entering for many diseases with the increasing possibility of tailoring therapies to a specific patient’s needs. Therapies of the future most likely will be highly individualized by targeting specific signs and symptoms of Sjögren’s. In addition to learning more about what gene expression can tell us about risk, serum levels of other markers are being identified. For example, an ACR abstract by former SSF Outstanding Abstract Awardee Gaetane Nocturne et al demonstrated an association between the chemokine CXCL13 and the development of lymphoma in Sjögren’s.10 Serum levels of CXCL13 also were associated with B cell markers and high disease activity. Another 2014 ACR abstract by Rosaria Irace et al showed that serum levels of the chemokine CXCL4 were associated with microvascular impairment in Sjögren’s.11 And, 2014 SSF Outstanding Abstract awardee Maria Lauvsnes of Stavanger University Hospital in Norway reported on the association between anti-NR2 antibodies and hippocampal atrophy in Sjögren’s as well as lupus.12

In addition to new biologics currently under investigation, a combination or sequential use of different therapies may be found most efficacious. As mentioned earlier, a study published in 2014 by Salvatore De Vita et al using belimumab followed by rituximab demonstrated initial success and projected potential long-term benefits.3 We look forward to a better future in which more studies will expand our knowledge of the science exponentially and lead to more precise biomarkers and potential targets for therapeutics. That future is not far away.

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Outcome Measures Validated for Sjögren’s

Clinical trial design for Sjögren’s has made a major leap forward with the final validation of the EULAR-endorsed outcome measures known as the EULAR SS Disease Activity Index (ESSDAI) and EULAR SS Patient-Reported Index (ESSPRI). The validation study,1 published in March 2014, concludes a nearly decade-long effort by researchers to develop outcome measures that could be embraced consensually by the international community at large. The ESSDAI includes the 12 following domains: constitutional, lymphadenopathy, glandular, articular, cutaneous, pulmonary, renal, muscular, peripheral nervous system, central nervous system, haematological, and biological. The ESSPRI includes dryness, pain and fatigue that were considered by patients as the most important areas for needed improvement.3

More recently, two large prospective cohorts involving 790 patients were used to define the relevant thresholds of ESSDAI and ESSPRI to help both clinicians and the conduction of clinical trials.4 This large

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The 2014 Outstanding Abstract Award went to Maria Lauvsnes, MD from Stavanger University Hospital, Stavanger, Norway. Dr. Lauvsnes was awarded for her research entitled Hippocampal Atrophy Is Associated with Anti-NR2 Antibodies in Patients with Systemic Lupus Erythematosus and Primary Sjögren’s Syndrome. She shared the below summary of her work with us.

The study presented in the abstract was part of my PhD work. As cognitive impairment is common in primary SS, one of the aims of my PhD work has been to explore whether anti-NR2 antibodies could play a role in the development of cognitive impairment in primary SS. Anti-NR2 antibodies are autoantibodies directed against the NR2 receptors, a glutamate receptor subtype that is very important for memory and learning and which are especially abundant in the hippocampus. Murine systemic lupus erythematosus (SLE) studies have demonstrated that these antibodies can cause cognitive dysfunction and hippocampal atrophy when they gain access to mouse brains, and they have been linked to cognitive dysfunction and depression in SLE patients.

In a study published last year, we found that anti-NR2 antibodies were associated with poorer performance in several memory tests in primary SS patients, and we found these antibodies in a higher proportion of the depressed primary SS patients than the non-depressed primary SS patients. In the same study, we demonstrated that the hippocampus was smaller in primary SS patients compared to healthy control subjects. Though demonstrated in murine models, hippocampal atrophy has not been linked to anti-NR2 antibodies in humans previously.

In the current study, we wanted to explore whether hippocampal size differed between SLE and primary SS patients with anti-NR2 antibodies compared to patients without. We analyzed MRI images with computer-based methods and found that the patients with anti-NR2 antibodies had atrophy in some parts of the hippocampus compared to the patients without these antibodies. There were no difference in hippocampal size between SLE and primary SS patients, and we did not find any association between hippocampal size and disease duration, anti-phospholipid antibodies or current use of corticosteroids.

To read the abstract in its entirety please visit this link: http://acrabstracts.org/advanced-search/ and search for abstract #1169 or on the SSF website at http://www.sjogrens.org/home/research-programs/outstanding-abstract.
study allowed us to define disease activity levels with the ESSDAI, ranging from low (less than 5 points on the ESSDAI scale), moderate (between 5 and 13 points) and high (14 points and higher). Those with moderate disease activity were deemed as the most likely group for inclusion in clinical trials, as ethical considerations might prevent using a placebo in severe disease activity patients. Minimal Clinically Important Improvement (MCII) was defined as a decrease of at least 3 points for the ESSDAI. For ESSPRI, patients rated each of their main symptoms (dryness, fatigue, and pain) on a 0-10 scale, and they also answered a question to determine whether their health status had significantly improved using a 5-point Likert scale. Based on these answers, MCII for the ESSPRI was defined as a decrease of at least 1 point or 15%.

While objective measures have been available for the dry mouth and dry eye that occur in Sjögren’s, no activity index previously has gone through the rigorous validation and obtained the broad acceptance for measuring all systemic manifestations for this multi-system and complex disease until the development of the ESSDAI and ESSPRI. These latest outcome measures were tested against other indexes currently in use, including the Physician Global Assessment (PGA), Profile of Fatigue and Discomfort (PROFAD), Sicca Symptoms Inventory (SSI), SS Disease Activity Index (SSDAI) and Sjögren’s Systemic Clinical Activity Index (SCAI). ESSDAI was found to provide greater sensitivity to change compared with ESSPRI. ESSDAI and ESSPRI were poorly correlated with each other, demonstrating that they assessed two different components of the disease.

No single score is perfect for all therapies and for all patients with Sjögren’s. However, a new system has been desperately needed to improve the design of clinical trials, and the ESSDAI and ESSPRI are now established as rigorously validated and are hopefully consistent activity indexes for measuring how well therapies are working for Sjögren’s patients. Until recently, ESSDAI and ESSPRI have most frequently been designated as secondary outcome measures, while primary endpoints have focused on dryness, and, to a lesser extent, fatigue, quality of life measures, and serology. For therapies of the future, a critical issue will be to determine which Sjögren’s patients are most likely to benefit from a specific treatment and ensure selection of these patients for a clinical trial testing this specific treatment. These factors will greatly influence the designation of a primary endpoint. The ESSDAI could be used in patient selection by requiring a minimum ESSDAI score for inclusion in clinical trials testing biologically active therapies, whereas therapies focusing on symptom relief might use the ESSPRI as the main endpoint. Regardless, having validated global scores through ESSDAI and ESSPRI that together include systemic, dryness and patient measures add critical tools needed for the design of clinical trials in Sjögren’s.

References
Transitions...

Frederick Vivino, MD, former Chair of the SSF Medical and Scientific Advisory Board, has been named Professor of Clinical Medicine at the Perelman School of Medicine, University of Pennsylvania in Philadelphia. Dr. Vivino also is Chief of the Division of Rheumatology for the Penn Presbyterian Medical Center and is Director of the Penn Sjögren’s Center at the university. Dr. Vivino chairs the SSF Clinical Practice Guidelines initiative and serves on the Steering Committee of the SSF Clinical Trials Consortium.

Julie Frantsve-Hawley, RDH, PhD has been named Executive Director of the American Association of Public Health Dentistry (AAPHD). Dr. Hawley formerly was Director of the Research Institute and Center for Evidence-based Dentistry at the American Dental Association (ADA). In her role at the ADA, she was and continues to be instrumental in working with the SSF on its Oral Clinical Practice Guidelines in Sjögren’s.

Vidya Sankar, DMD, MHS and Dr. Frantsve-Hawley recently joined the Board of Directors for the Friends of the National Institute for Dental and Craniofacial Research (FNIDCR). Dr. Sankar is an Associate Professor in the Department of Comprehensive Dentistry at the University of Texas Health Science Center, San Antonio Dental School and also serves on the SSF Board of Directors.

FNIDCR is a broad-based coalition of individuals, academic institutions, dental schools, patient advocate organizations, dental societies and corporations that understand the critical importance of dental, oral and craniofacial research to the health and well-being of people in the U.S. and globally. It focuses on support for the NIDCR and educates the public and key decision makers about the importance of investing in the NIDCR. The SSF has long been a member and leader in the FNIDCR, with SSF staff member Katherine Hammitt currently serving as FNIDCR Vice President.

The Sjögren’s International Collaborative Clinical Alliance (SICCA): A Data Registry and Biorepository for Public Use Access

The Sjögren’s International Collaborative Clinical Alliance (SICCA) registry is an NIH-funded international resource that was developed with the primary goal to provide data and biospecimens for the Sjögren’s syndrome (SS) scientific community that will advance the field of SS research, ultimately leading to effective management strategies and therapies.

The SICCA registry was initiated in 2003 by Drs. Troy Daniels and John Greenspan in five academically-based research groups located in Argentina, China, Denmark, Japan and the United States and directed from the University of California San Francisco. One group in the United Kingdom joined the effort in 2007, and three groups - two from the U.S. (Johns Hopkins University and University of Pennsylvania) and one from India joined in 2009. Each of the nine groups included rheumatologists, ophthalmologists, and oral medicine/pathology specialists with extensive track records in the diagnosis and management of SS. All groups enrolled participants using broad criteria to include individuals who have symptoms or signs indicating they may have or may develop SS as well as those with established disease. A standardized set of clinical and biological parameters and information from standardized questionnaires were collected at study entry and at two-year follow-up (the latter for a subset of participants).

As of September 30, 2012, when enrollment ended, 3,516 participants had enrolled in SICCA and undergone a standardized set of evaluations. Nearly a quarter (774) presented for a two-year follow-up visit. The cohort consists predominantly of women (91%) over the age of 50 (60%) with a high level of education (57% graduated from or attended a college/university).

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A large majority reported dry mouth (90%), dry eyes (86%), or both (80%). More than one third of participants had positive serologic test results (anti-SSA, rheumatoid factor, and/or antinuclear antibody titer ≥ 1:320), and hypergammaglobulinemia (IgG > 1445 mg/dL). More than half had salivary hypofunction defined by unstimulated whole salivary flow < 0.1 mL/min and focal lymphocytic sialadenitis on labial salivary gland biopsy (among whom 68% had a focus score ≥ 1 foci/4mm²). Bilateral parotid enlargement was seen in 12% at baseline. Nearly half the cohort (1574 participants) satisfied the provisional American College of Rheumatology classification criteria for SS.

To date, nearly 35 applications for dissemination of data and/or specimens have been received, the majority of which have been approved and fulfilled. Examples of project topics include "Autoantibody Landscape in Sjögren's Syndrome," "Epigenetic Profiling of Multiple Cell and Tissue Types in Sjögren's Syndrome," "IL-27 Suppression of TH17 Cell Functions In-vitro," and "Mass Spectrometry Tools in Pursuit of Salivary Biomarkers of Sjögren's Syndrome," to name a few.

SICCA is a unique public resource providing epidemiologic data and biospecimens to support rigorous research related to epidemiologic, pathogenesis, and genetic studies of SS. It is currently led by Drs. Caroline Shiboski and Lindsey Criswell. Details on how to submit a proposal to obtain SICCA biospecimens and/or data may be found at: http://sicca.ucsf.edu.

The SICCA biorepository and data registry is supported by NIH/NIDCR contract # HHSN-26820130057C.

**Recruitment Underway for Clinical Trials**

**NIH Clinical Trial for Vasculitis**

Volunteers are needed for a study on vasculitis as an autoimmune/rheumatic symptom or disease conducted by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) at the National Institutes of Health (NIH). Goals include learning the signs, symptoms, imaging tests, genetic markers and blood tests that can help identify vasculitis and predict what will happen over time. All study-related costs and tests are provided at no cost.

Participation includes a visit to the NIH Clinical Center for screening along with follow-up visits as needed; donation of blood samples (either at NIH or via a patient’s physician); and completion of questionnaires. Both those with vasculitis and those who are healthy to serve as controls may be eligible for participation. More information on the "Studies of the Natural History, Pathogenesis, and Outcome of Idiopathic Systemic Vasculitis" can be found at https://clinicaltrials.gov, identifier NCT02257866, or by calling 301-451-1450.

**DREAM Clinical Trial for Dry Eye Patients**

The Dry Eye Assessment and Management (DREAM) Trial is recruiting patients for its randomized clinical trial to determine efficacy and safety of Omega 3 for dry eye disease. Trials will take place at twenty sites across the U.S. and are funded by the National Eye Institute (NEI) at the NIH. Penny Asbell, MD, MBA, FACS, Professor of Ophthalmology at the Mount Sinai School of Medicine in New York, is the Study Chair.

Essential Fatty Acids (EFA) have been shown to reduce inflammatory responses, but randomized controlled trials for dry eye disease that provide strong empirical data are lacking. This is the first NEI-funded dry eye trial in which a wealth of information on dry eye disease will be collected independently of commercial concerns. The trial also will develop evidence-based information on the effects of Omega 3 on dry eye disease. Final data collection is expected in 2016 with an estimated study completion date of April 2017. For more information on clinical trial sites for this study, visit https://clinicaltrials.gov, identifier NCT02128763 or contact Dr. Penny Asbell by email at penny.asbell@mssm.edu or phone by calling 212-241-7977.

**NIDCR FY2016 Research Concepts Approved**

Research concepts for the National Institute of Dental and Craniofacial Research (NIDCR), NIH for Fiscal Year 2016 have been approved. Those of particular interest to researchers in Sjögren’s include:

- Immune System Plasticity in the Pathogenesis and Treatment of Complex Dental, Oral, and Craniofacial Diseases
- Novel or Enhanced Dental Restorative Materials for Class V Lesions

Sjögren’s research also might fall under the concepts of Pharmacogenomics of Orofacial Pain Management and the NIDCR Institutional Research Training Programs. Concepts represent early planning stages for initiatives in which NIDCR seeks to support research in an understudied and significant area of science.
The Patient Education Sheet, Health Insurance Tips – Part 1, contains tips on obtaining healthcare reimbursement. Part 2 addresses how to appeal a decision if you are denied coverage. Always appeal a denial! Be persistent and do not give up when first denied.

Information and documentation that will help you appeal a denial

- Your policy and claim numbers, employer name if your policy is through an employer, and the full name of the insured
- The therapy or procedure for which you were denied and why the denial letter stated you were denied
- Medical records that back up your diagnosis and medical problem that relates to the therapy in question
- A cost-benefit analysis when relevant - For example, you can compare the cost savings of obtaining punctal plugs or cauterization compared to the higher cost of having to pay for more moisture drops and ointment over a long period of time.

Letter of Medical Necessity

- This letter is usually written by the physician explaining why a therapy or other treatment is medically necessary.
- If the Letter of Medical Necessity is not signed by your physician, have your physician provide a letter of support for your appeal and reason for recommending or prescribing your therapy.
  - A Sample Letter of Medical Necessity for dental treatment can be found on the SSF website under “Brochures and Resource Sheets.”

Quotes from your health insurance policy that are helpful to your case

- For example, if your policy states that coverage is provided for a closely-related disease and/or similar symptom, quote that back to the insurance company. If the company cites a reason for covering the related disease or symptoms, such as an inflammatory response, use that. Quoting such statements and providing documentation about similar occurrences in Sjögren’s increases your chance for the success of an appeal.
- Cite two or more articles from respected medical journals backing your claim of medical necessity.

Refer to the SSF website as an authoritative source of medical information on Sjögren’s.
A new product for dry mouth has been created containing technology developed at Stony Brook University School of Dental Medicine. Ortek Therapeutics has developed sugar free chocolate soft chews named “BasicBites.”

BasicBites contain saliva-mimicking AlkaGen Technology™. This super saliva technology consists of two main ingredients - arginine bicarbonate and calcium carbonate. Arginine is a common amino acid found in saliva and is naturally present in many foods. It was discovered that certain healthy bacteria found on tooth surfaces use arginine to generate sustained base or alkali production. This helps keep teeth in the existing normal pH range. Calcium, which is also found in saliva, is available to coat and support healthy tooth structure. The bicarbonate and carbonate ingredients provide additional buffering and support arginine and calcium.

For more information about BasicBites, visit www.basicbites.com.