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MEETING ABSTRACTS Open Access

Treatment of SLE: Bridging the Gap from Clinical Trials to Practice

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These abstracts originated from the "Treatment of SLE: Bridging the Gap from Clinical Trials to Practice" Symposium held during the Annual Congress of the American College of Rheumatology on 11 November 2012. The symposium and subsequent publication of this supplement were funded by an unrestricted educational grant from Human Genome Sciences.

INTRODUCTION

A1

Treatment of SLE: bridging the gap from clinical trials to the clinic – a meeting report

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Systemic lupus erythematosus (SLE) is a complicated disease that frustrates many clinicians with its wide variety of presentations, signs, and symptoms. SLE is defined as a chronic disease characterized by inflammation of various organs, primarily the skin and joints. The disease does not have a clear etiologic picture. Immunologic abnormalities, highlighted by the production of various antinuclear antibodies, are a prominent feature. Patients with SLE suffer a variety of symptoms, most commonly related to the skin, musculoskeletal, hematologic, and serologic organs. In the recent past, a diagnosis of SLE implied a decreased lifespan resulting from internal organ system involvement or the toxic effects of therapy; however, recent improvements in research and clinical trials have provided clinical data that have dramatically enhanced survival in SLE patients. Nonetheless, SLE mortality rates remain a major concern.

Many clinicians in the field of rheumatology have substantial knowledge and practice gaps related to the diagnosis and care of patients with lupus. Even SLE experts disagree on points of SLE management. To address some of the issues, this supplement will present insights from internationally known experts in the field of lupus research and patient care.

The four abstracts in this supplement summarize live presentations at an educational symposium titled "Treatment of SLE: Bridging the Gap from Clinical Trials to Practice". Conceptually intertwined with the pathogenesis of SLE, the newly evolving topic of targeted therapy is the focus of this educational activity. A review of the current scientific implications for the biologic basis of SLE pathogenesis and the therapeutic management of the disease will increase rheumatologists' medical understanding of the molecular and cellular basis of SLE pathogenesis that is crucial to improving outcomes in these patient populations.

An adapted version of each of the full presentations given at the symposium is attached to each abstract. These adaptations bridge knowledge gaps on the latest SLE clinical research, biologic agents, and targeted therapies, as expert faculty compile and critically appraise new evidence and interpret its implications for improving the clinical management of patients with SLE.

The presentations are designed to address issues for clinical immunologists and rheumatologists who provide care for patients with SLE but who do not necessarily practice in the field of lupus. To that end, the expert faculty members provide analyses of the grueling and complex matrix of basic science and clinical science and then offer insight into how to translate those advances from the bench to the bedside.

The presentations start, appropriately, with a historical overview of SLE from its first reference during the 1100s, through the neoclassic period of the 1800s when it began to be defined, and into the modern era that began with the laboratory discovery of SLE cells. Weaved into this overview are descriptions of the most important contributions from the leading practitioners and researchers.

The faculty are among the most respected in the field. Bevra Hahn, MD, Professor Emerita of Medicine at the David Geffen School of Medicine at UCLA, has been in the field for a long time. She is a prolific author who has many contributions to medicine, including being the lead author on the American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Dr Hahn's presentation 'Unmet Needs: Therapeutic Standards of Care' focuses on the evidence-based best practices for SLE and how to fit the American College of Rheumatology guidelines into clinical care.

Michelle Petri, MD, MPH, Professor of Medicine at the Johns Hopkins University School of Medicine, Baltimore, MD, has organized several outstanding educational initiatives in lupus. She is lead author of the most recent classification criteria for lupus. In her presentation 'Measuring Disease Activity and Severity in Clinical Trials and the Clinic: Same or Different?' Dr Petri discusses the revised clinical and immunologic criteria for the classification of SLE, necessitated by substantial advances in knowledge of immunologic interplay of SLE. The question of when to monitor patients with stable disease has perplexed many clinicians, and Dr Petri describes evidence showing when specific variables usually can be detected and offers clinical guidance based on the evidence. She also presents a convincing argument for limiting the use of high-dose prednisone therapy, which has shown significant evidence of increased morbidity and mortality. To help those relying on prednisone, she describes some options found to be effective in head-to-head trials.

Daniel Wallace, MD, is a clinical leader and a highly respected clinical trial investigator. His presentation 'Clinical Impact of Biologic Therapy in the Treatment of SLE' is a thoroughly researched and referenced review of clinical trial data on biologic therapies in SLE, providing insights into the subtleties of the responder indexes, their impact on potential new therapies, and their potential use in clinical practice. He finishes with an in-depth review of belimumab, the clinical trial evidence base (including American College of Rheumatology and European League

Against Rheumatology annual meetings and peer-reviewed literature), and his summary of its clinical implications for practice.
The goal of these presentations is to provide readers with a review the current evidence regarding SLE and translate it into implications for clinical practice. By providing the current best practices and addressing the identified knowledge and practice gaps, the supplement has the potential to substantially improve outcomes in this patient population.
Competing interests
LHC has received consulting fees from Amgen, BMS, Centocor, Genentech/Roche, Pfizer, Sanofi Aventis and Savient.

MEETING ABSTRACTS

A2
Historical overview
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Medical understanding systemic lupus erythematosus (SLE) has evolved dramatically since its first reference during the 1100s, through the neoclassic period of the 1800s when researchers began to refine the definition, and into the modern era with transformative laboratory investigations and discoveries altering the diagnosis and treatment. Weaved into this historic overview are descriptions of the most important contributions of the leading practitioners and researchers.
Competing interests
LHC has received consulting fees from Amgen, BMS, Centocor, Genentech/Roche, Pfizer, Sanofi Aventis and Savient.

A3
Unmet needs: therapeutic standards of care
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Many unmet needs exist for practitioners caring for patients with systemic lupus erythematosus (SLE). The top need is for a blockbuster drug with glucocorticoid efficacy but fewer side effects. They also need better markers to identify responders without waiting 3 to 6 months to see clinical improvement. Current therapeutic goals are to induce and maintain responses while minimizing side effects. Therapy selection varies depending on disease severity and response to previous therapies. Therapies for SLE target different areas in the immunologic process, primarily T-cell and B-cell lymphocytes for mycophenolate mofetil (MMF), azathioprine, and anti-B-lymphocyte stimulator, and a wider array of cells for glucocorticoids. The American College of Rheumatology recently published treatment guidelines for the use of adjunctive therapies in patients with lupus nephritis that recommend hydroxychloroquine as background therapy in all of these patients, and it established target levels for blood pressure, and low-density lipoprotein to reduce complications. Data were inadequate to make recommendations regarding glucocorticoid doses for induction of improvement (thus 0.5 to 1 mg/kg/day is the recommendation) or for tapering or discontinuing prednisone. Renal biopsy is recommended for all patients with active lupus nephritis, previously untreated, to provide data for classification of glomerular disease and thus enable selection of appropriate therapy. Recommendations for induction therapy include either MMF or cyclophosphamide (CYC). MMF has the advantage of being equally effective in all races and being formulated for oral administration. CYC is less effective in African Americans and Latinos but is equivalent in Caucasians and Asians. Low-dose CYC is an option for Caucasians. Teratogenicity is a concern with MMF, CYC, and methotrexate, but hydroxychloroquine, glucocorticoids, and azathioprine can be used during pregnancy, if necessary. New evidence suggests that improvements in proteinuria and C3/C4 blood levels may predict response as early as 8 weeks. Clinical trials with belimumab for lupus nephritis are not yet available although it did not appear to worsen renal disease in patients without active lupus nephritis. Belimumab is approved by the US Food and Drug Administration for use in antinuclear antibodies and/or anti-DNA-positive SLE patients with active disease that persists despite standard treatments. Investigators continue to research other targeted therapies for high response rates, less toxicity, and less need for chronic glucocorticoid treatment.

A4
Measuring disease activity and severity in clinical trials and the clinic: same or different?
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Standardized criteria to classify systemic lupus erythematosus (SLE) disease activity provide a well-defined methodology to accurately assess SLE. These criteria were recently revised to reflect new knowledge of SLE, both clinical and immunologic. Although developed to classify SLE, these criteria can help with the diagnosis in clinical practice. Research has also provided additional evidence of elevated morbidity and mortality associated with high-dose prednisone therapy, defined as greater than 6 mg/day. At these doses, significant increases in organ damage and cardiovascular events occur. Use of NSAIDs is also known to raise cardiovascular risk. Better options include intermittent intramuscular triamcinolone and hydroxychloroquine. The question of how often to monitor patients with stable SLE is confounded by the many variables showing clinical activity and their average frequency of occurrence. Nevertheless, the evidence suggests that 3 months is the ideal time for follow-up testing. Although there is no confirmed technical standard for measuring SLE disease activity, two primary instruments are available in the clinic: the Physicians Global Assessment and the SELENA-SLEDAI instrument. Each has varying degrees of ability to detect changes in disease activity as well as clinical usefulness. In clinical trials, outcomes are measured by the SLE Responder Index, an instrument that defines response based on criteria from SELENA-SLEDAI, Physicians Global Assessment, and British Isles Lupus Assessment Group index. In clinical practice, responses are primarily based on improvements in disease activity, especially reduced flares. Improvements in serology also matter, as patients with high anti-DNA or low complement are twice as likely to flare during the next year. Quality-of-life criteria are important to patients. Overall, the goal is to accurately measure clinical improvement in the patient's SLE disease activity.

A5
Clinical impact of biologic therapy in the treatment of SLE
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Biologic therapies have generated substantial research interest for treating autoimmune diseases, resulting in several US Food and Drug Administration approvals. However, clinical trial results in systemic lupus erythematosus (SLE) populations have failed to meet efficacy expectations, primarily owing to methodological flaws in design, especially outcome measures. To address these issues, the US Food and Drug Administration published a guidance document for clinical trial design in SLE that included specific efficacy endpoints for measuring disease severity. Belimumab was the first biologic approved for SLE based on positive responses measured with the SLE Responder Index, which required a decrease in inflammation, no new organ domains being involved, and improvement in physician global assessment. Trials of other biologics have used other versions of SLE Responder Index responder indices. In addition to belimumab, a score of other biologic

agents are being investigated, primarily those targeting T cells, B cells, complement, and tolerogen-targeting agents. Their development stages and clinical trial results vary. Belimumab has generated the greatest amount of clinical trials, as investigators try to further define its role in clinical practice. Results have been shared in many forums, including annual meetings of the American College of Rheumatology and European League Against Rheumatism, along with publications in the medical literature. These findings indicate that belimumab is effective in patients with more active disease who are able to wait up to 3 months for improvement. Additionally, it can be considered for patients with active disease despite therapy with NSAIDs, antimalarials, immunosuppressives, or corticosteroids, especially if the benefits of treatment outweigh its risks or if the patient is intolerant to steroids or immunosuppressives.

Competing interests

DJW has received consulting fees from Novo Nordisk, GSK, Pfizer, Lilly and UCB and been on advisory committees or review panels for UCB.

Cite abstracts in this supplement using the relevant abstract number, e.g.: Wallace DJ: Clinical impact of biologic therapy in the treatment of SLE. *Arthritis Research & Therapy* 2013, **15(Suppl 2):**A5