

Future management of systemic lupus erythematosus



Daniel J Wallace
Cedars-Sinai Medical
Center/David Geffen School
of Medicine at UCLA,
8737 Beverly Blvd,
Suite 302, Los Angeles,
CA 90048, USA
Tel.: +1 310 652 0920;
Fax: +1 310 360 4812;
dwallace@ucla.edu

‘Existing families of lupus medications will be complemented with newer agents, along with ... combinations of corticosteroids, immune suppressives and biologics’.

The management of systemic lupus erythematosus (SLE) will take on a completely new look in the next 10 years, some of which has little to do with lupus medications. By the year 2017, we will know which gene or set of genes causes lupus and under what set of circumstances these susceptibility genes are activated. Since women with SLE have a 10% risk of their daughter and a 2% risk of their son developing the disease, as well as a 50% probability of their offspring being antinuclear-antibody positive (in addition to having an increased prevalence of other autoantibodies), we should be able to identify individuals at risk [1]. It might be possible to vaccinate or give peptide toleragens to at-risk populations, with the goal being disease prevention. Additionally, environmental factors, including certain occupational exposures and immunogenic chemicals that promote auto-immune reactions will be better elucidated, which could lead to the implementation of protective measures.

The future of lupus management also hinges on an improved, statistically validated definition for the various forms of lupus and its variants: SLE, chronic cutaneous lupus, undifferentiated connective tissue disease, overlap syndromes, mixed connective-tissue disease and drug-induced lupus. A national data bank complemented with an electronic medical record accrual system, which in selected centers will include updated, validated clinical indices, will permit lupologists to better understand the epidemiologic, demographic, clinical and laboratory characteristics of the disorder. Outcomes will be easier to predict and the implementation of measures to circumvent an undesirable prognosis will be more focused. An integrated health system allowing access to rheumatologic expertise will be in place. Hopefully, rheumatologists will be able to work with

primary care physicians to improve the outcome and quality-of-life of the lupus patient. Some of the interventions outside of prescribing lupus medications, which in controlled studies have been shown to improve morbidity, mortality and quality-of-life, include [2]:

- Screening for osteoporosis and treating those at risk;
- Identifying patients at risk for antiphospholipid mediated thromboembolic events and utilizing prophylactic initiatives (e.g., low-dose aspirin);
- Recommending physical measures and exercise regimens that diminish the risks of muscle atrophy and bone demineralization while utilizing optimal ergonomic workplace dynamics;
- Smoking cessation measures;
- Screening for and interdicting accelerated atherogenesis, hyperlipidemia, hyperglycemia (especially in those on corticosteroids) and hypertension. This can be accomplished with periodic electrocardiograms, chest x-rays, laboratory testing, cardiac imaging, carotid duplex scanning, assessments of baseline pulmonary pressures and promotion of a cardioprotective diet [3];
- Patient education about the disease;
- Use of biofeedback, relaxation measures and cognitive behavioral regimens to treat the dysautonomia of lupus (e.g., Raynaud's, lupus headache and cognitive dysfunction).

Existing lupus medications will be complemented with newer agents, along with a more intelligent use of combinations of corticosteroids, immune suppressives and biologics.

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In those with serious lupus, the goal would be similar to that employed by oncologists: aggressive induction of remission, followed by maintenance therapy of a tapering regimen whereby toxic agents are gradually decreased in dose or discontinued. Examples of this include:

- Safer nonsteroidals that are effective, cardioprotective and gastroprotective;
- Standardized, efficacious topical nonsteroidals;
- More efficient vehicles for delivering topical medications;
- ‘Designer’ antimalarials that inhibit toll-receptor activation [4];
- ‘Designer’ methotrexates that promote adenosine release [5];
- Use of pharmacogenomics to identify and better manage patients who might be resistant or susceptible to the effects of lupus drugs, such as corticosteroids, methotrexate or azathioprine [6].
- Agents that target B cells via antibodies to CD20 (rituximab), CD22 (epratuzumab) or their precursors (inhibiting B-cell activation factor [BAFF; BLyS], APRIL, TRAIL and transmembrane activator and calcium modulating ligand interactor-Ig) [11,12];
- Agents that target cytokines, such as anti-tumor necrosis factor (TNF), interleukin (IL)-1, -6, -10, -12, -15, -17, -18 or -23 [13,14];
- Inhibition of interferon or toll-receptor activation [15].

Many other innovative approaches are being investigated in animal models and in laboratories. Examples include inhibitors of adhesion molecules, T-cell vaccination, promotion of T-regulatory cells, agents that interfere with cell-surface receptor activation, mitogen-activated protein kinase, Fc receptors and even gene therapies.

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Although no drugs for lupus have been approved since 1966, the 2005 US FDA Guidance Document provides specific benchmarks to the pharmaceutical industry in order to assist them in navigating the approval status [101]. A candidate drug should be safe, improve clinical indices and response measures, halt the development of damage, better one’s quality of life and demonstrate organ specific ameliorative actions.

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Additionally, an accelerated approval process may be possible if specific, as yet to be agreed upon, surrogates or biomarkers (e.g., down-regulation of interferon signature expression and urinary cytokines) show benefits in a clinical trial. At present, over 20 biologic agents as well as stem cell therapies are either in clinical trials or have been given the go ahead for trials to begin in 2007. Some of these approaches involve:

- Therapies that target T-, B- and antigen-presenting-cell interactions, such as abatacept [7];
- Targeting the activation of complement, such as anti-C5a monoclonal antibodies [8];
- Inducing immune tolerance with peptides (edratide) or anti-DNA treatment (abetimus) [9,10];

What is on the imminent horizon that clinicians will have access to in the next 3 years? Rituximab, abatacept and anti-TNF agents are already available for off-label use. It is highly probable that belimumab (an anti-BLyS) and abetimus (LJP 394) will be approved in the next 2–3 years. Currently, 80% of lupus patients in the USA are treated by 20% of the rheumatologists. The future of its management predicts that more lupus patients will be treated at specialized lupus centers as the intricacies of the multiple new biologic therapies become more arcane and infusion requirements more complicated.

For those of us who trained 30 years ago, the first 20 years of our clinical practice utilized the same handful of reliable, inexpensive but modestly effective agents. In the last 10 years, a few additional agents, all used off-label, have improved the prognosis of our lupus patients (e.g., mycophenolate mofetil and leflunomide). Nevertheless, at least 50% of patients with serious lupus are still not with us 20 years later [16]. The next decade will see the introduction of perhaps as many as 20 new biologics that can potentially have a salutary effect upon SLE.

Executive summary

- In the next 10 years, we will close in on the environmental triggers and identify susceptibility genes for lupus, which will allow preventive measures and a possible vaccination for those at risk.
- The prognosis of lupus can be greatly improved by having patients treated at a lupus center which screens for risk factors (e.g., cardiac disease and antiphospholipid antibodies) and initiates a comprehensive integrated medical approach to treatment that includes lifestyle changes and proactive measures.
- The 2005 US FDA Guidance Document has spawned over 20 clinical trials with candidate antilupus therapies.
- The search for biomarkers that better assess outcomes in clinical trials is yielding a tremendous amount of useful information about the disease and hopefully will shorten the length of these trials.

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Website

101. Guidance for industry on developing drugs for treatments of systemic lupus erythematosus
www.fda.gov/ohrms/dockets/dockets/05d0106/05d0106.htm.

Affiliation

- Daniel J Wallace, MD, Clinical Professor of Medicine Cedars-Sinai Medical Center/David Geffen School of Medicine at UCLA, 8737 Beverly Blvd, Suite 302, Los Angeles, CA 90048, USA
Tel.: +1 310 652 0920;
Fax: +1 310 360 4812;
dwallace@ucla.edu