Viewpoint

Biomarkers for systemic lupus erythematosus: has the right time finally arrived?

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The concept of 'biomarkers' is a concept that is, at once, old and boring yet new and exciting. The notion that pathogenesis, risk, and prognosis can be apprehended by examining discrete aspects of the underlying disease process is not new. The identification of such markers is predicated on (1) understanding the disease process; (2) identifying aspects of pathogenesis that can be reliably and relatively easily determined; and (3) ascertaining that there is a close relationship between the marker and the outcome or characteristic of interest. In systemic lupus erythematosus (SLE), we have been using clinical indicators such as anti-double-stranded DNA antibodies and complement levels to monitor disease activity for just as long as we have been arguing about their sensitivity and specificity. The arguments arise from the heterogeneity of SLE patients with regard to clinical presentation, course, and response to therapy. Genetic factors and environmental contributors to risk and disease manifestations make the picture even more complex. Translate that to the modern era and you have 'Biomarkers in systemic lupus erythematosus I' [1].

Gabor Illei and colleagues have done a remarkable review of the literature in SLE in an attempt to identify markers, to assess their likely utility in SLE, and to propose a schema through which to test and apply them. The review of the literature was done by traditional methods: searching by key words and search engines, scouring the reference lists and doing deeper-level searches, and reading the more mechanistically inclined papers on SLE and immunology and imputing the utility of aspects of pathogenesis to the clinic. This comprehensive overview identifies possible, promising, and unlikely biomarkers in SLE, suggests schemata for validation, and makes the critical distinctions between biomarkers and clinical or surrogate endpoints. The latter distinction is of critical importance, and has important implications for the applications for which markers of various sorts might be useful.

A biomarker, according to Illei and colleagues, is 'a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention'. Clinical endpoints, however, are 'characteristics or variables that reflect how a patient feels, functions or survives'; and surrogate endpoints are 'biomarkers that are intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.'

Clinical and surrogate endpoints are primarily applicable to outcomes in clinical studies and can contribute to the basis for clinical decision-making, whereas biomarkers have a much farther reach. Biomarkers, in general, can be used for risk determination; for diagnosis; for subsetting patients according to prognosis; for predicting and assessing disease activity and status, as well as response to therapy; and in assessing outcomes. Biomarkers are also, by virtue of their short-term availability as predictors of longer-term events, useful for 'proof-of-concept studies' in the development or use of new or novel therapeutic interventions.

So, although Illei and colleagues have elegantly surveyed the field and imposed order and expectations where these were not previously articulated, why does this merit a Viewpoint in *Arthritis Research & Therapy*? Several reasons come to mind.

First is that the approach of the comprehensive overview of an entire literature with respect to a single question is

SLE = systemic lupus erythematosus.

now in transition. New tools in informatics are making it possible to fuel the search for biomarkers for SLE (for example) rapidly and with nuance. Rather than looking for articles using the same key words, or for bibliographic citations in a work of interest, the entire database of medical literature can be probed for the co-occurrence of terms of interest in an iterative and indirect fashion. By such strategies, it is now possible to make links that might not be intutitively obvious, links for which data is published but the implication has never been articulated, and novel links connecting fields that historically have not communicated [2]. Potentially informative biomarkers in SLE have been identified by using the traditional methods by Illei and colleagues, but current efforts are seeking to reproduce and refine this with the more powerful techniques of informatics and indirect inference (D Blair and PE Lipsky, personal communication). This approach has been used previously to good effect in several clinical areas: identifying a relationship between magnesium and migraine headaches that was previously unknown, and in examining the role of fish oils in Raynaud's phenomenon [3,4]. These inferred associations were then tested empirically with good success.

The second reason to focus on biomarkers in SLE at this time is practical. The lack of validated biomarkers for SLE disease activity and response to treatment have been identified as barriers to drug discovery, development and testing by clinical and basic researchers, industry, the US Food and Drug Administration, and patient advocates. Three meetings have been convened in 2003–2004 to develop a strategy for identifying and validating such markers, and the effort represents an unprecedented collaboration between academics, industry, patient advocates, and regulatory agencies. The steering and scientific advisory committees of the SLE Biomarker Working Group will be structuring the collaborative group, seeking and administering funding, and initiating the validation of the first five identified likely biomarkers for SLE.

Although the study of Illei and colleagues is the first systematic global overview of the literature seeking likely candidate biomarkers for validation in the near future, this will not be the last word on the topic.

Competing interests

None declared.

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