How Will Epidemiology Drive the Treatment of Rheumatic Disorders in 2007 and Beyond?

Epidemiologists study the factors that affect the health and illness of populations. Their contribution goes beyond, well beyond, "number crunching" and serves as the foundation and logic for interventions made in the interest of public health and preventive medicine. Epidemiology is highly regarded in evidence-based medicine for identifying risk factors for disease and determining which factors are associated with disease outcomes.

The development of new interventions follows a predictable path: the risk factor is first identified from an epidemiological study; a pharmaceutical company develops and tests a product to address the treatment need; the treatment is validated through numerous independent studies, and a license is obtained for the distribution of the product.

Though the process appears simple, problems occur when the findings from large population, randomized clinical trials (RCTs) are generalized to the individual patient. The individual patient may differ from the RCT inclusion/exclusion criteria, the motivation of the study subject to participate, and the demographics of the trial participants. Multiple trials may produce outcomes that may not directly answer the question "is drug A more effective than drug B." Assuming drug A is more effective than B, should all patients then be treated with drug A? Drug A may cost more than drug B, or have inconvenient side effects, or an inconvenient mode of administration. Despite the RCT that demonstrated the statistical superiority of A over B, some patients given B can respond quite well on the inferior drug.

In the ideal world, we would like to identify patients that have an adequate response to drug B, despite the superior performance of A, and save the added expensive of using the new drug/treatment protocol.

The epidemiologist can identify the factors influencing treatment outcome, which might include demographics such as age, gender, comorbidity, ethnicity, education, compliance, and lifestyle.

As an example, anti-tumor necrosis factor-α (TNF-α) therapies, though important treatment for rheumatoid arthritis (RA), are expensive and have the potential of serious toxicity. Some patients don't improve despite therapy. Therefore, it would be beneficial to be able to predict the patients who will respond, so that the use of these drugs can be targeted. In a study based on the observational British Society for Rheumatology Biologics Registry, which examined clinical factors present at the start of anti-TNF-α therapy, smoking was identified as a factor that favored better outcomes for RA patients with etanercept vs infliximab after 6 months of treatment [Hyrich KL et al. *Rheum* 2007]. Age, disease duration, rheumatoid factor, and the previous number of DMARDs did not predict response to either drug.

Disease specific factors such as disease duration, previous treatments, disease activity, and severity are also used by the epidemiologist to predict treatment outcome. For

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instance, a good, moderate, or poor response to DMARD therapy can predict response to other DMARDs and methotrexate [Hyrich KL et al. *Rheum* 2006] and the rate of serious infection is higher (unadjusted incidence rate ratio of 4.28) in RA patients treated with anti-TNF agents vs RA patients treated with DMARDs [Dixon WG et al. *Arthritis Rheum* 2006].

Genetic variation can also predict patients most likely to benefit from treatment. Specific genetic polymorphisms have been shown to be predictors of response to treatment of early RA. The presence of 2 HLA-DRB1 alleles encoding the shared epitope (SE) (compared with 1 or 0 copies) was associated with response to treatment with standard-dose etanercept (odds ratio [OR] 4.3, 95% CI 1.8-10.3). Among Caucasian patients, 2 extended haplotypes that included the HLA-DRB1 alleles *0404 and *0101 (both of which encode the SE) and 6 single-nucleotide polymorphisms in the LTA-TNF region were associated with response to treatment. The ORs for the association of these haplotypes with achievement of an ACR50 response at 12 months were 2.5 (95% CI 0.8-7.3) and 4.9 (95% CI 1.5-16.1) for the haplotypes containing,*0404 and *0101 respectively. These findings are useful for identifying patients who are most likely to benefit from treatment with methotrexate or etanercept [Criswell LA et al. *Arthritis Rheum* 2004].

Epidemiology has identified an increased risk of cardiovascular disease mortality associated with inflammatory disease, and a possible reason. Hypertension, smoking, diabetes, and ESR (erythrocyte sedimentation rate) were all found to be significant risk factors for cardiovascular death ($p<0.01$ for each). However, multivariable Cox regression analyses, controlled for cardiovascular risk factors and comorbidities, revealed that the risk of cardiovascular death was significantly higher among RA patients with at least 3 ESR values ≥60 mm/hour (hazard ratio 2.03). These results indicate that markers of systemic inflammation confer a statistically significant additional risk for cardiovascular death among patients with RA, even after controlling for traditional cardiovascular risk factors and comorbidities [Maridt-Kremers H et al. *Arthritis Rheum* 2005]. Knowing a patient has RA increases the need to manage cardiovascular risk.

The juxtaposition of economic and clinical evaluations raises new issues in the design of clinical trials. Current pivotal phase 3 trials do not provide pharmacoeconomic guidelines at the time of regulatory and formulary decision making. Efficacy trials answer the question "does the drug work under optimal circumstances," and not questions about the effectiveness of a drug, ie the more relevant question for economic analysis being, "does the drug work in usual care?"

So called "effectiveness trials" more closely reflect routine clinical practice. They use a more flexible dosage regimen, and a "usual care" instead of a placebo comparator. Patients randomized are more representative of actual practice and outcomes include quality of life and utility measures. They are more suited to provide the data needed to estimate the real benefit of the treatment in actual care. When costs are applied and compared with these benefits, one can estimate the efficiency of allocating resources to this new drug. Increasing the use of effectiveness trials in phase 3 would decrease the need for economic modeling [Bombardier C and Maetzel A. *Ann Rheum Dis* 1999].

Epidemiologists contribute significantly to the identification of health risks and the development of new interventions by identifying risk factors for disease and outcome, identifying risk factors for treatment efficacy, and developing new models for addressing individualized therapy protocols.

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