

In Quest of the Holy Grail: Efficacy versus Effectiveness in Rheumatoid Arthritis



In this issue of *The Journal*, Papadopoulos, *et al* report the results of an observational study of Greek patients with rheumatoid arthritis (RA) treated with disease modifying antirheumatic drugs (DMARD)¹. Some of their findings were similar to those reported by others: poor continuation rates after 5 years, with less than half of the patients continuing the original drug, and best overall results for methotrexate (MTX), with drug survival rates ranging from 17% for D-penicillamine to 55% for MTX. Other findings were more unusual. Practice patterns were somewhat different from those reported in other countries, with a more frequent use of D-penicillamine and cyclosporine and infrequent use of sulfasalazine. In addition, there was surprisingly low toxicity from cyclosporine, which showed the best survival rate after MTX. Elsewhere in this issue, Pope, *et al* describe practice patterns of Canadian rheumatologists when prescribing DMARD². This study shows broad use of DMARD by rheumatologists, as expected, with increasing preference for the use of combination therapy and higher drug dosages, suggesting a more aggressive treatment of the disease.

Why are these studies important? What do they add to more traditional research on therapeutics, namely clinical trials? The current paradigm in medical practice is “evidence based medicine,” which can be defined as the conscientious, explicit, and judicious use of current best evidence from health care research in making decisions about the care of individual patients.

Randomized clinical trials are considered the best evidence of efficacy, and are the guiding force in evidence based medicine because of their experimental design that reduces bias and confounding. But are clinical trials enough for health care decision-making? What can observational studies and surveys provide to attain our ultimate goal of improvement in health outcomes? A great deal, I would argue.

Very unfortunately, the potential benefits of new thera-

pies as reported in trials are too frequently reduced once they are implemented in clinical practice in the community. Efficacy can be defined as the extent to which a specific intervention produces a beneficial effect under ideal conditions; the determination of efficacy is based on the results of randomized clinical trials³. Effectiveness is the extent to which a specific intervention produces a beneficial effect when deployed in the field (e.g., in the community).

Efficacy is largely based on the pharmacological effects of a therapy, but effectiveness takes into account many other aspects, as diverse as individual patient characteristics, health system features, or societal influences. These effects are not easily evaluated in clinical trial settings.

A useful model of community effectiveness that has been applied to preventive interventions such as immunization can also be operationalized to evaluate therapeutic effectiveness in the treatment of chronic diseases in the community at large. In this model:

$$\text{community effectiveness} = \text{efficacy} \times \text{access} \times \text{diagnosis} \times \text{recommendation} \times \text{adherence}$$

It is not sufficient for a therapy to be efficacious to be effective in the community — i.e., in the population of patients with the disease of interest at large. In addition to its pharmacological and physiological effects, to be effective, an intervention has to be accessible to those who can benefit from it; these individuals have to be identified appropriately, and their caregivers have to recommend and prescribe the therapy; finally, patients must adhere to treatment at the recommended dosing for therapeutic coverage to fully achieve the benefits of therapy. Poor adherence can result from a number of factors such as lack of compliance, withdrawals due to adverse events, or financial reasons.

How does this apply to RA? The prognosis of RA remains poor and for the most part unpredictable. Despite a clear shift in the past decade towards more aggressive and

See DMARD in early RA, page 261, and Prescribing trends in DMARD for RA, page 255

better drug therapies, the cure for RA remains elusive. There appears to be a trend towards better functional outcomes, and perhaps improved quality of life, but “hard,” objective outcomes such as mortality have remained unchanged for the past 40 years⁴. Therapies that once seemed promising, such as plasmapheresis, levamisole, and auranofin, did not survive initial “hype” to live up to expectations. Even MTX, possibly the best of traditional DMARD, is at best a mediocre drug: few patients achieve true remission, those who respond experience flares if the drug is discontinued, and overall, only about half of patients continue MTX 5 years after starting treatment. In addition, joint damage progresses during treatment, even in patients who appear to benefit clinically and symptomatically. Clinical trials can establish that a drug *will not* be effective if it is not efficacious, but cannot prove that an efficacious drug will, in fact, be effective.

So, what is in store for the future? The “biologics era” brings new hope, but it is still early to fully evaluate the impact of these new agents on the longterm outcome of RA. Despite initial, well deserved enthusiasm, these drugs cannot be seen as a cure yet. Most patients only have partial responses to treatment, with few remissions, and a sizable percentage does not respond at all.

Let’s examine some of the available evidence in relation to antirheumatic drugs. As an illustration, the example below will use efficacy data from published clinical trials. Nowadays, efficacy in RA trials is frequently measured on the basis of American College of Rheumatology (ACR) criteria for improvement⁵. An ACR20 response is defined as a 20% improvement in the number of swollen and tender joints from baseline, with 20% improvement in at least 3 of the following 5 outcomes: patient and physician global assessments, pain, disability, and acute phase reactants. Using information from placebo controlled trials⁶⁻⁸ and ACR20 response criteria, we can estimate the absolute improvement or benefit obtained from a given intervention as follows:

$$\text{absolute benefit (efficacy)} = \text{improvement in drug group} - \text{improvement in placebo group}$$

Table 2. Potential community effectiveness of selected disease modifying antirheumatic drugs (DMARD)*. Values are percentages.

	Efficacy	Access	Diagnosis	Recommendation	Adherence	Community Effectiveness
DMARD						
Methotrexate	20	80	85	85	70	8
Leflunomide	26	80	85	85	70	11
Etanercept	48	80	85	85	70	19
Anakinra	16	80	85	85	70	6
Two scenarios to improve effectiveness						
New drug with enhanced efficacy	60	80	85	85	70	24
Etanercept, with modifications in other variables	48	90	90	90	80	28

* Community effectiveness is obtained by multiplying efficacy × access × diagnosis × recommendation × adherence.

Table 1 shows the efficacy estimates for various drugs, calculated on the basis of these clinical trials, using absolute benefit increases. This is just one variable in the effectiveness model presented above. The other variables are (A) access — in this context, access to the medical system and the ability to obtain or afford the required therapy; (B) diagnosis — which is not only the diagnosis of RA, but also the ability of the physician to recognize the need for a particular treatment in a given patient, at a time when this treatment may be beneficial; (C) medical recommendations — studies of practice patterns in a number of diseases have shown that even when evidence for efficacy is clear, diagnosis is correct, and the need recognized, recommendations for specific therapies are not adopted universally, and considerable numbers of patients remain untreated despite available evidence⁹. In RA, prompt treatment is vital, since patients with advanced disease and joint destruction do not respond to therapy as well as those with early disease; (D) finally, adherence is a major issue in rheumatic diseases. A number of studies have shown that compliance in RA is poor, ranging from 30 to 80%¹⁰⁻¹².

Table 2 shows the potential effectiveness of these therapies in the community of RA patients. Efficacy is based on the trial results from Table 1 and conservative estimates for the other variables in the model. Community effectiveness is calculated by multiplying the probabilities of the variables in the model. As can be seen, once these other factors are taken into account, the overall community effectiveness of

Table 1. Percentage of efficacy of selected disease modifying antirheumatic drugs (DMARD).

	ACR20 Drug	ACR20 Placebo	Efficacy (Absolute Benefit)	Ref
DMARD				
Methotrexate	46	26	20	Strand, <i>et al</i> ⁶
Leflunomide	52	26	26	Strand, <i>et al</i> ⁶
Etanercept	59	11	48	Moreland, <i>et al</i> ⁷
Anakinra	38	22	16	Cohen, <i>et al</i> ⁸

drugs that can be considered among the most effective for RA is limited, ranging between 8 and 19%. The two scenarios at the bottom of Table 2 show how change in one or more factors can influence overall effectiveness. In the first case, a new drug with an enhanced efficacy of 60% would result in an overall effectiveness of 24% if all other variables remained unchanged. In a trial with 20% of placebo responses, 80% of the patients would have to respond to the drug for an absolute benefit of 60%. On the other hand, using etanercept, but increasing the performance of the other components of the model, would result in an effectiveness rate of 28%.

Of course, this example is oversimplistic, based only on ACR20 efficacy data. A number of other important factors such as toxicity, joint damage, quality of life, etc., have not been considered. Further, we have assumed constant values for access, adherence, and the other variables, which we know vary among therapies, as can be seen in studies such as those of Papadopoulos and Pope^{1,2}. Nevertheless, this is a useful exercise to demonstrate how nonmedical aspects, medical practice patterns, and societal factors may affect the treatment of chronic diseases. Where should our efforts and expenditures as a society be directed? To the conception and development of new therapies, which are associated with enormous developmental and process costs, or to enhance the potential benefits of what we already have? Obviously the answer is not simple — both aspects are crucial in our quest to help patients with chronic disease, but often the importance of nonmedical or health system factors is forgotten in our search for the perfect cure.

It is clear that information on variables other than efficacy cannot be easily obtained from clinical trials, and that observational studies and surveys of practice patterns such as the ones presented in this issue have a major role in the assessment of the overall effectiveness of a therapeutic intervention. These types of studies need to be conducted on a continuing basis to provide a realistic view of the effectiveness of new therapies, in the context of usual practice in the community, and should be considered as a complement to clinical trials and a necessary component of evidence based medicine.

MARIA E. SUAREZ-ALMAZOR, MD, PhD,
Associate Professor of Medicine,
Baylor College of Medicine,
Houston Center for Quality of Care and Utilization Studies,
2002 Holcombe Boulevard (152),
Houston, Texas 77030, USA. E-mail: mes@bcm.tmc.edu

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Address reprint requests to Dr. Suarez-Almazor.

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