Treatment related mortality versus quality of life--a balancing act.

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The Journal of Rheumatology is a monthly international serial edited by Earl D. Silverman featuring research articles on clinical subjects from scientists working in rheumatology and related fields.
With increasing pressures on health care budgets worldwide, the desire for demonstration of value for money from new and existing therapies has escalated. New biologic therapies for rheumatoid arthritis (RA) such as high dose chemotherapy followed by autologous stem cell transplantation (HDC/ASCT) are often costly, but are they cost effective? And, aside from cost considerations, how do these new therapies compare to traditional antirheumatic therapies in terms of potential risks and benefits? How best can these questions be answered using currently available data?

There have been a number of published studies assessing the cost effectiveness of therapies for RA. However, most evaluations have ignored both the quality of life effects of therapies and the associated long-term benefits and costs, mainly focusing on response rates within the duration of available clinical trials.

Measuring the range of risk patients with RA would be willing to accept in return for a cure (or sustained remission) provides an appropriate measure for the value placed on benefits from treatment. In previous studies the “standard gamble” and “willingness to pay” paradigms have been successfully used in such a context.

Thompson, in a study of 245 patients with RA, reported that a 27% risk of death would be acceptable for a hypothetical treatment that would either “kill them or cure them.” On average, the same cohort of patients would be willing to pay (in perpetuity) 22% of their household income for a cure.

In a more recent report, also using the standard gamble methodology, a 3.3% treatment related mortality was acceptable to 84% of the RA patients, in return for a hypothetical cure using HDC/ASCT. In both studies acceptance of higher risk was positively associated with increasing pain and/or disability and negatively associated with age.

The study by Verburg and colleagues in this issue of The Journal is a welcome attempt to assess the long-term quality of life effect of HDC/ASCT using Markov modeling (MM). The question posed by Verburg, et al is important: How might the usual standard of care for severe RA compare with HDC/ASCT in which the treatment related risks are better understood than the degree and duration of benefits? Theoretically HDC/ASCT has the potential to cure RA, but practical considerations and early data suggest that partial, time limited remissions are much more realistic expectations. MM provides an analytical approach for the estimation of a variety of long-term outcomes based on various assumptions relating to treatment effectiveness and disease progression.

Verburg and colleagues have employed MM to estimate the benefits of HDC/ASCT over a period of five and one-half years compared to continuing conventional treatment with disease modifying antirheumatic drugs. Markov modeling is an analytical approach whereby a hypothetical cohort of patients can be followed over a period of time to assess outcomes such as clinical effectiveness, health care costs, and quality of life. Patients are assumed to move between health states defining the clinical course of disease. Movement is based upon transition probabilities that depict the likelihood that a patient in one particular health state will be in another health state at the end of the next period of interest. In the model used by Verburg and colleagues patients are assumed first to move every 3 months for the first 6 months with subsequent transitions occurring on a yearly basis.

Whether from a societal or from a patient perspective there is a need to make the best informed decisions with the data that are currently available. MM is able to incorporate the available observational data with explicit assumptions to derive projections of various outcomes. These hypothetical projections can, in the future, be tested against reality. The value of defining and refining the modeling process may be as important as the actual projected outcomes per se. The design of a Markov model should reflect the current clinical knowledge. For example, the choice of health states, transi-

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Using MM for a hypothetical cohort of 50-year-old women with RA they concluded that for a treatment related mortality of 3.3% (or less) HDC/ASCT is the preferred treatment option. In most centers HDC/ASCT, when used to treat malignant disease, is associated with a treatment related mortality of less than 2%. To date there has been one treatment related mortality for the 43 adult patients with RA reported as receiving experimental HDC/ASCT worldwide.

Overall, the studies by Verburg and colleagues and by Albert and colleagues should be welcomed as an attempt to model the longer term implications of a new intervention. Markov modeling may be criticized for the lack of transparency within the model; although in this case the study authors should be complimented on the transparency of reporting of data employed. Unless clinical trials of RA therapies employ greater longterm followup of patients, the use of techniques such as Markov modeling will increase.

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