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Editorial

Treatment Related Mortality versus Quality of Life — A Balancing Act

With increasing pressures on health care budgets worldwide, the desire for demonstration of value for money from new and existing therapies has escalated\(^1,2\). 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\(^3\). 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”\(^4\). 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\(^5\). 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, \textit{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?\(^7\) Theoretically HDC/ASCT has the potential to cure RA\(^8\), but practical considerations and early data suggest that partial, time limited remissions are much more realistic expectations\(^9,10\). 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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tion probabilities, and cycle length within a model should be based on our current understanding of the disease process. Thus, if past projections do not match reality the discordance may be a result of past data deficiencies rather than inherent defects in the modeling methods. Also, the modeling outcomes of particular interest to individual patients with RA (e.g., quantity and quality of life) may be different than those deemed important to society such as dollar costs/savings of HDC/ASCT.11,12

Although MM has become increasingly popular in the conduct of economic analysis, it has also been used to assess the longterm clinical effectiveness of therapies, such as the recent study by Albert and colleagues that assessed the clinical effectiveness of therapeutic strategies in the management of RA.13 In reference to MM these authors state that “the complexity of this analysis is evident.” They conclude that “treatment strategies in RA are difficult to model because of uncertainty in both the structure of the model and the data needed to perform the analysis.”

Ideally, potential risks and benefits should be expressed in terms of the effect of therapies (experimental vs standard of care) on both quantity and quality of life. This is the primary focus of the study by Verburg and colleagues. Quality and quantity of life may be measured using the concept of the quality adjusted life-year (QALY), which is the sum of annual utility scores for an individual.14 Utilities are a measure of health related quality of life measured on a scale calibrated with a score of 1 for perfect health and 0 for death. QALY can be measured by a number of techniques, and there is evidence that techniques often give different valuations and may be less responsive for specific diseases.15 However, use of direct measurement tools such as the time trade off and standard gamble have been argued to be the gold standard measures. In the study by Verburg and colleagues, QALY have been measured through the use of both time trade off and standard gambles. The utility values provided for health states relating to response are one of the first documented utility values for health states for RA. Thus, these values are of great benefit as they can be used for future modeling studies.

Data from observational studies have suggested that RA therapies tend to lose their effectiveness over time.16,17 Thus, although Markov modeling is useful in allowing estimates of accrued benefits beyond trial duration, it is necessary that such models employ reasonable estimates of a therapy’s effectiveness over time. Thus, models employing constant transition probabilities tend to overestimate both the clinical benefits and the cost effectiveness of therapies. In the study by Verburg and colleagues constant transition probabilities were applied for the period from 6 months to 5.5 years. This may be a minor cause for concern.

How does HDC/ASCT compare to continuing disease modifying antirheumatic drugs according to Verburg, et al? 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 longterm 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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