Cost-effectiveness of anti-tumor necrosis factor agents

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ABSTRACT

Rheumatoid arthritis can lead to substantial morbidity, disability and mortality. The development of anti-tumor necrosis factor antibodies from the bench to the bedside over the past 15 years has ushered in the new era of biologic therapies for rheumatic diseases. Etanercept, infliximab and adalimumab have all been approved for the treatment of rheumatoid arthritis on the basis of improved clinical outcomes. Because these treatments, however, are expensive and not uniformly effective, concerns have arisen regarding their cost-effectiveness. This paper reviews the disease burden of rheumatoid arthritis, costs of drug therapy, costs of rheumatoid arthritis and the economics and cost-effectiveness of anti-tumor necrosis factor antibody agents.

Introduction

Affecting about 1% of the population, rheumatoid arthritis occurs most commonly between 40-70 years of age with about 70% of patients being women (1). Anti-tumor necrosis factor antibodies have been found to be effective in relieving the signs and symptoms of active rheumatoid arthritis as assessed by improvements in the American College of Rheumatology (ACR) response criteria (2-10). Moreover, these agents have improved disease activity according to the EULAR response criteria and physical function measured by the Health Assessment Questionnaire (HAQ) or SF-36 and have halted radiographic progression. However, these agents have potential side effects, the long-term benefits beyond 4 years remain unknown, and their expense exceeds that of standard therapy, raising questions about whether the clinical benefit of these agents justifies their higher cost (11). As Hurst and Forbes pointed out, "economic evaluation . . . will enhance rheumatology's position in the competition for more resources . . . future levels of funding for rheumatic disease" (12). Indeed, a consortium of patients, physicians and medical organizations secured Euro 500,000 for anti-tumor necrosis factor treatment by placing it on their national political agenda (13), This paper reviews the disease burden of rheumatoid arthritis, costs of drug therapy, costs of rheumatoid arthritis and the economics and cost-effectiveness of anti-tumor necrosis factor antibody agents.

Cost-effectiveness analysis

The standard metric for the assessment of the economic and clinical value of new drugs or devices has become cost-effectiveness analysis (14). Although effectiveness can be any clinical measure, typically these analyses translate clinical benefit into both lifetime costs and effectiveness measures such as life expectancy or quality-adjusted life expectancy when performing a cost-utility analysis. By using a long time horizon, these analyses account for future benefits and economic savings or expense, and by standardizing the outcome metric, policymakers, physicians and patients can compare the relative cost-effectiveness of alternative medical interventions. The new therapies should always be compared to standard care (15, 16), so new therapies that are more effective and less costly over a lifetime are cost-saving and dominate the current standard. More often, new drugs extend quality-adjusted survival but also cost more, so the increased cost of the new therapy divided by its increased benefit yields the incremental or marginal cost-effectiveness. Typically, the outcome measure is expressed as the net additional lifetime cost to increase life expectancy by one discounted quality-adjusted life year. Approving or funding those interventions that are cost-saving or those that have the lowest marginal cost-effectiveness ratio should provide society with the greatest benefit for a given budgetary expenditure.

Decision analyses accounting for uncertainty have been developed to simulate the likely outcomes from anti-tumor necrosis factor treatment of rheumatoid arthritis (17-21). In general, these analyses consider the likelihood of mortality, response to rheumatoid arthritis therapy, discontinuation or change in therapy because of side effects or loss of efficacy, development of progressive disability, quality of life based on treatment and disability, and costs of drug treatment and of disease. These analyses differ in the underlying type of decision analysis: a decision tree that is individualized (21) or not (17) or Markov cohort simulation (18-20). These analyses also differ in their time horizon, i.e. the point in time that the analysis stops tracking disease outcomes (22): 6 months (17), 1 year (20), 10 years (19) or lifetime (18, 21). The majority of these analyses track HAQ outcomes (18-20), but some examine composite clinical responses such as the ACR20 in addition to the HAQ (21) or use only ACR20 responses (17). The ACR20, however, measures relative improvement, making the determination of absolute clinical benefit dependent on the initial disease status (23). EULAR or DAS criteria would account for initial disease status but comparative data for DMARDs are not available (21).

Quality of life

Because patients, physicians and policy makers increasingly recognize that quality of life may be as important as length of life, these pharmacoeconomic analyses (18-21) [except for Choi *et al*. (17)] also adjust for the morbidity of advanced rheumatoid arthritis. Instead of receiving full credit for each year of life, individuals with morbidity receive only partial credit. For instance, those patients developing severe disability (HAQ > 2) may receive credit for living 5 quality-adjusted months for each year they are alive (18). In these analyses the outcome measure becomes quality-adjusted life years (QALY). Specifically, a quality of life adjustment factor of 0.4 for severe disability (HAQ > 2) equates living a year of life with severe disability to living 5 months good health. Thus, a 10-year life expectancy with 2 years spent with severe disability would be equivalent to living 9.2 quality-adjusted life years in good health. The term "quality-adjusted life year gained" that is used in cost-effectiveness analyses then is equivalent to increasing life expectancy by one year of perfect health. The pharmacoeconomic analyses of anti-tumor necrosis factor differ in their choice of quality of life assessment methods: the patient-derived visual analog scale (18); EQ5D (19, 20); and HAQ (21).

Discounting

In addition to quality of life adjustments, pharmacoeconomic analyses typically discount costs and outcome projections to reflect the higher present value of money. This is consistent with health care policies hoping to minimize current fiscal year drug budgets. For example, spending $1000 this year would be comparable to spending $970 a year from now or $554 in 20 years, when using the currently recommended 3% annual discount rate. Discounting is particularly relevant to these analyses because anti-tumor necrosis factor treatment costs occur now, and the costs of endstage rheumatoid arthritis complications occur in the future. Analyses for the United Kingdom (UK) applied their recommended 6% annual discount rate for costs and a 1.5% rate for health benefits (19, 21), but other analyses applied the recommended standard 3% annual discount rate for both costs and clinical benefits (18, 19).

By discounting, economic outcomes are all valued as current 2004 expenses. Similarly, because costs are discounted, health benefits are also discounted, so future health benefits are valued less than benefits that would accrue now. Thus, the outcome term “cost per discounted quality-adjusted life year gained” used in cost-effectiveness analyses can be considered to be equivalent to the cost in 2004 dollars to increase life expectancy by a year of perfect health now in 2004. In general, incremental or marginal cost-effectiveness ratios falling below $50,000 to $100,000 per discounted quality-adjusted life year gained have been considered to be “cost-effective” because many well-accepted medical interventions fall within or below this range. For example, chronic facility-based hemodialysis costs about $55,000 to $80,000 per discounted life year gained (24). Therefore, if public health policymakers are willing to fund hemodialysis, they should be willing to fund medical treatments that are more cost-effective (i.e., those that have lower cost-effectiveness ratios).

Burden of disease

In 1953, rheumatoid arthritis decreased life expectancy by 8 to 11 years (25). Despite changes in care over the years, standardized mortality ratios ranged from 1.2 to 3.1 with little evidence of improvement (26-29). For patients with unfavorable rheumatoid arthritis profiles, the 5-year survival ranges from 45-55% and is comparable to patients with 3-vessel coronary artery disease (30). Because a higher HAQ, poorer functional status, advanced age, and co-morbidity lead to higher mortality (26), preventing the development of functional loss may improve survival.

Besides mortality, rheumatoid arthritis leads to morbidity and disability. Depending on the national social support system, early retirement ranged from 37% to 64% from 2 to 8 years following onset (31, 32). About 50% of Germans with rheumatoid arthritis under age 60 were unemployed (33). Compared to patients with osteoarthritis or those without arthritis, Gabriel *et al*. found that patients with rheumatoid arthritis were more likely to have worked reduced hours, lost their job or retired early (34). Recently, patients with rheumatoid arthritis were found to be 7 times more likely to have disability than the general population (35).

When assessing the quality of life with rheumatoid arthritis, global instruments such as the SF-36 demonstrate marked decreases in both the physical and mental dimensions of health, with considerable reductions when compared to other diseases (36, 37). Trials with anti-tumor necrosis factor agents have demonstrated improvement in the HAQ (9, 10, 38) and in the physical component of the SF-36 (9).

Therapeutic need

For the majority of the randomized controlled trials involving anti-tumor necrosis factor therapy, patients had over 20 to 30 swollen and tender joints despite disease-modifying anti-rheumatic drug (DMARD) use and HAQ scores ranging from 1.6 to 1.8 (9, 10, 38). Compared to norms for the general rheumatoid arthritis population, these patients fall into the 15-25% with the highest disease activity and severity (39). Some 5-6% of rheumatoid arthritis patients would have qualified for an anti-tumor necrosis factor agent based on the entry criteria for the Anti-tumor necrosis factor Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) or the British Society of Rheumatology criteria (40, 41).

These patients had usually failed multiple DMARDs with 70% treated with 3 or more (38). Anti-tumor necrosis factor treatment has usually been compared to methotrexate plus placebo for patients who only partially respond to methotrexate or other DMARDs (9, 10). Withdrawal of methotrexate (42) or other DMARDs would likely have increased disease activity and magnified the effect of anti-tumor necrosis factor agents. An increasing duration of disease decreased the likelihood of a DMARD response (43). Similarly, the durability of a response depends on the order in which the DMARDs are given as opposed to the specific DMARD, so regardless of which DMARD, the second one given is less likely to be durable than the first one (43-46).

Cost of anti-tumor necrosis factor agents

Based on the average US wholesale price, adalimumab 40 mg sc every other week costs $15,679, etanercept 25 mg sc biw costs $15,679 and infliximab for 70 kg person at 3 mg/kg (0, 2, 6 weeks and then every 8 weeks) costs $16,598 per year (47). These costs do not include pre-therapy testing for tuberculosis or monitoring for treatment complications. On the other hand, they also assume continued therapy and neglect the 26-34% of patients who discontinue in the first year due to side effects or ineffectiveness (48).

Cost of rheumatoid arthritis

In the absence of anti-tumor necrosis factor therapy or COX-2 inhibitors, annual rheumatoid arthritis care costs a mean of $7708 in direct care and $7845 in indirect or productivity losses in 1996 dollars inflated to 2004 dollars using the medical care component of the Consumer Price Index (49). The annual, 5-year and 10-year costs of care increase with increasing disability as measured by higher HAQ (50-52). Conceptually, improving the HAQ from between 1.6 and 2.1 to between 1.1 and 1.6 should reduce the annual direct care costs by $1900 to $2600 and indirect costs by $8290 when inflated to 2004 dollars (50, 52). In the ATTRACT study, patients whose HAQ improved by 0.25 or more were more likely to work and to have less time lost from work (53). Another study suggests that etanercept increased the likelihood of employment by 20% and the hours worked each week by 7.4 (54). These savings would partially but incompletely offset the cost of the anti-tumor necrosis factor agents.

Modeling the natural history of rheumatoid arthritis

Choi *et al*. only examined a 6-month time horizon for treatment toxicity and the ACR response (17). For 160 patients beginning anti-tumor necrosis factor therapy, Kobelt *et al*. compared quality of life and economic outcomes one year before and one year after starting therapy (20). Brennan *et al*. modeled the natural history of rheumatoid arthritis for those who had failed at least 2 DMARDs, as a sequence of drug treatments over 6-month intervals. For those responding to treatment, the ACR20 response was translated into an HAQ reduction (decreased disability) and quality of life benefit. Patients without an ACR20 response may die or have an adverse drug-related event. The absence of an ACR response or the presence of an adverse event prompted a change in treatment. Patients then developed worsened disability with an HAQ that was, at least initially, higher than that prior to starting the last therapy, similar to a "Sawtooth" model of the natural history of rheumatoid arthritis (55).

In the Markov model analyses (18, 19), a pre-defined and mutually exclusive set of health states represent the natural history of rheumatoid arthritis. Patients start the computer simulation in the appropriate state or states of health and treatment. Over time, represented by Markov cycles of a specified duration (e.g., one year), some of the patients may die, improve or worsen, with the remainder maintaining their same state of health. Depending on the state of health and the model, treatment may change. The analysis continues until all patients in the cohort die or until a fixed time has elapsed. By tracking survival and costs for each cohort member, the Markov model estimates life expectancy, quality-adjusted life expectancy and lifetime costs.

Based on ARAMIS data involving 17,085 patient-years of data, the Markov model by Wong *et al*. involved 21 health states with combinations of 5 alternative treatments (infliximab plus methotrexate, methotrexate, DMARD, methotrexate plus another DMARD and steroids or non-steroidal anti-inflammatory drugs) and 4 categories of HAQ disability (0, 0.1–1.0, 1.1–2.0 and > 2.0) along with death, the terminal state of health (18). Patients could worsen or improve their HAQ and depending on that change, they could change their treatment. In Kobelt *et al*., the Markov model had 7 health states with 6 levels of HAQ disability and the dead state (19). Using data involving 2068 patient-years of follow-up for Sweden and 7145 patient-years of follow-up for the UK, the likelihood of progression was based on ordered probit regression models, accounting for age, gender and time since rheumatoid arthritis onset (56).

Cost-effectiveness of anti-tumor necrosis factor antibodies

Although not uniformly effective in achieving improvement for all rheumatoid arthritis patients, anti-tumor necrosis factor therapy should reduce future medical care costs attributable to rheumatoid arthritis. However, when adding anti-tumor necrosis factor therapy and the costs of rheumatoid arthritis

complications together, the lifetime costs of the strategy to give anti-tumor necrosis factor therapy exceeds that of standard care. In such cases, if anti-tumor necrosis factor treatment also yields improved clinical outcomes, an incremental or marginal cost-effectiveness ratio can be calculated by dividing the additional cost by the additional benefit gained.

For methotrexate-resistant rheumatoid arthritis patients, Choi *et al.* estimated the cost-effectiveness of 6 drug therapies and found that triple therapy (hydroxychloroquine, sulfasalazine and methotrexate) cost $1500 per additional ACR20 responder compared to no second-line agent, and etanercept plus methotrexate cost $42,600 per additional ACR20 responder compared to triple therapy (17). In the absence of head-to-head trials involving all 6 strategies, the drug efficacy estimates used in the analysis could be confounded by differences in patient characteristics across trials – for example, disease activity or duration at inclusion. Moreover, the use of cost per ACR20 responder or any other clinical rheumatologic outcome metric as the effectiveness measure makes it impossible to compare the cost-effectiveness of rheumatoid arthritis treatment to other non-rheumatologic medical interventions.

Using the standard effectiveness metric, all cost-utility analyses have found the incremental or marginal cost-effectiveness ratios of anti-tumor necrosis factor agents to be less than $50,000 to $100,000 per discounted quality-adjusted life year gained for rheumatoid arthritis patients with active disease when compared to the control arms of the randomized controlled trials (18, 19, 21) or compared to costs and quality of life in the year preceding anti-tumor necrosis factor therapy (20). When converted to US dollars (assuming $1 = Euro 1.2 = £1.8 British pound sterling), base-case estimates ranged from $30,500 in the US (18) to $34,320 in Sweden (19) and $29,394 per discounted quality-adjusted life year gained in the UK (21) when considering only direct medical care costs. When also including indirect or productivity costs, base-case incremental cost-effectiveness ratios improved (fell) to $9,100 in the US (18), $4,128 in Sweden (19) and $7,729 per discounted quality-adjusted life year gained in the UK (21). Two of these studies examined infliximab (18, 19) and the other etanercept (21). Two studies presented in abstract form only have found adalimumab to have incremental cost-effectiveness ratios ranging from $28,924 based on the ARMADA trial to $49,147 per discounted quality-adjusted life year gained when compared to a sequence of traditional DMARDs (57, 58).

Conclusion

"Biologic therapies offer improvements in disease activity, quality of life and radiological progression that are unmatched" (11). Similar to most medical prevention programs, all of these analyses suggest that some of the costs of anti-tumor necrosis factor treatment should be offset by the prevention of future disability from rheumatoid arthritis. Despite the methodological differences mentioned above, these studies report remarkably similar marginal cost-effectiveness ratios for anti-tumor necrosis factor treatment – ranging from $28,924 to $34,320 per discounted quality-adjusted life year gained compared to the trial control arms considering only direct medical care costs. When including indirect or productivity costs, these ratios fell below $10,000 per discounted quality-adjusted life year gained. In the absence of head-to-head trials of these anti-tumor necrosis factor agents, their relative cost-effectiveness cannot be assessed reliably from these analyses. Nonetheless, all of these ratios fall below the widely cited $50,000 to $100,000 per discounted quality-adjusted life year gained threshold below which therapies may be considered to be "cost-effective" (59). This is within the range of other widely accepted or mandated medical interventions such as colon cancer screening, highly active anti-retroviral therapy for HIV, intensive glycemic control for diabetes mellitus, and hemodialysis (24, 60-62), so that anti-tumor necrosis factor agents can be considered to be "cost-effective."

From another perspective, the net societal economic cost of anti-tumor necrosis factor treatment of patients with active rheumatoid arthritis would be at most $34,320 to increase life expectancy by one quality-adjusted life year, i.e., one year of perfect health, even with discounting. From a health budget perspective, $1 million spent entirely over the lifetime of a population to support hemodialysis would buy an additional 14 year increase in the population life expectancy at marginal cost-effectiveness ratio of $65,000 per discounted quality-adjusted life year gained, but if spent on anti-tumor necrosis factor antibody for treatment of active rheumatoid arthritis, the same amount would add 29 years of perfect health to the population at a cost-effectiveness ratio of $34,320 per discounted quality-adjusted life year gained. Thus, if one is willing to fund hemodialysis, one should be willing to fund anti-tumor necrosis factor antibody for treatment of active rheumatoid arthritis because it is even more "cost-effective" than hemodialysis.

Rheumatoid arthritis leads to substantial morbidity and mortality. Although long-term randomized trials for anti-tumor necrosis factor treatment are still lacking, numerous clinical studies show that treatment improves the signs, symptoms and function of patients with rheumatoid arthritis. Therapy, however, does entail the risk for infection (in particular, tuberculosis for which patients now undergo pre-treatment screening), developing antinuclear antibodies, worsening congestive heart failure and demyelinating disorders. Nonetheless, these therapies have ushered in a new era of treatment, enabling patients to attain levels of function and symptom relief that had been previously unobtainable with standard therapies. In 1999, Hurst and Forbes asked, "Does economic evaluation have anything to offer the rheumatologist?" (12) Multiple cost-effectiveness studies have now been performed and suggest that anti-tumor necrosis factor antibodies should be cost-effective.

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