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Model-based evaluation of cost-effectiveness of nerve growth factor inhibitors in knee osteoarthritis: impact of drug cost, toxicity, and means of administration

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SUMMARY

Objective: Studies suggest nerve growth factor inhibitors (NGFi) relieve pain but may accelerate disease progression in some patients with osteoarthritis (OA). We sought cost and toxicity thresholds that would make NGFi a cost-effective treatment for moderate-to-severe knee OA.

Design: We used the Osteoarthritis Policy (OAPol) model to estimate the cost-effectiveness of NGFi compared to standard of care (SOC) in OA, using Tanezumab as an example. Efficacy and rates of accelerated OA progression were based on published studies. We varied the price/dose from $200 to $1000. We considered self-administered subcutaneous (SC) injections (no administration cost) vs provider-administered intravenous (IV) infusion ($69–$433/dose). Strategies were defined as cost-effective if their incremental cost-effectiveness ratio (ICER) was less than $100,000/quality-adjusted life year (QALY). In sensitivity analyses we varied efficacy, toxicity, and costs.

Results: SOC in patients with high levels of pain led to an average discounted quality-adjusted life expectancy of 11.15 QALYs, a lifetime risk of total knee replacement surgery (TKR) of 74%, and cumulative discounted direct medical costs of $148,700. Adding Tanezumab increased QALYs to 11.42, reduced primary TKR utilization to 63%, and increased costs to between $155,400 and $199,500. In the base-case analysis, Tanezumab at $600/dose was cost-effective when delivered outside of a hospital. At $1000/dose, Tanezumab was not cost-effective in all but the most optimistic scenario. Only at rates of accelerated OA progression of 10% or more (10-fold higher than reported values) did Tanezumab decrease QALYs and fail to represent a viable option.

Conclusions: At $100,000/QALY, Tanezumab would be cost effective if priced ≤$400/dose in all settings except IV hospital delivery.

Introduction

Knee osteoarthritis (OA) is a painful debilitating disease that affects more than 9 million American adults[1]. Current medications for knee OA pain, such as non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, are limited in their long-term efficacy and safety[2–9]. Consequently, over half of patients with knee OA elect to receive total knee replacement surgery (TKR) within their lifetimes[10]. With knee OA patients estimated to spend an average of

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13.3 years without adequate pain relief prior to TKR[11], additional pharmacologic therapies with increased efficacy and safety could improve quality of life (QOL) and reduce the number of TKRs in this population[12].

Nerve growth factor (NGF) represents a potential target for treatment of pain, and several antibodies have been developed to inhibit NGF[13,14], the most thoroughly studied of which was developed by Pfizer under the trade name Tanezumab. Clinical trials documented impressive relief of knee OA pain, but in 2010, the FDA suspended all trials for anti-NGF drugs in OA due to concerns about rapidly progressing OA leading to joint replacement in some patients[15–22]. In 2012, the FDA's Arthritis Advisory Committee (AAC) approved continued testing of anti-NGF drugs provided that certain safety recommendations are met[16].

Tanezumab is a biologic drug delivered via intravenous (IV) infusion or subcutaneous injection[23]. Biologics, such as those used in rheumatoid arthritis (RA), have high costs due to the resources needed to produce the drugs themselves and to their mode of administration[23]. Because OA is more prevalent than RA (12.1% vs 0.6% in the US), Tanezumab and other drugs in its class could conceivably be priced lower than biologics for RA[1,24].

Given the promising results surrounding the efficacy of Tanezumab, we sought to address several open questions: At what price might Tanezumab be cost-effective in the treatment of OA pain? How might the risk of accelerated OA progression affect the value of Tanezumab? Does Tanezumab have the potential to reduce primary and revision TKR utilization? Early clinical trials showed promising results regarding the attractiveness of Tanezumab for knee OA with some concerns about safety and no information about potential costs. Given the FDA's most recent decision to continue testing of anti-NGF drugs, it makes sense at this point to ask what clinical outcomes, side-effect profiles, and costs might make Tanezumab a cost-effective option for the treatment of OA pain. Such information would provide practical guidance to practitioners, payers, and designers of future trials regarding performance benchmarks and standards of evidence for treatment and reimbursement decisions.

Methods

Analytic overview

We used the Osteoarthritis Policy (OAPol) Model to project the clinical and economic implications of adding Tanezumab monotherapy to the current standard of care (SOC). Outcomes included lifetime medical costs, quality-adjusted life years (QALYs), incremental cost-effectiveness ratios (ICERs), and utilization of primary and revision TKR. We determined the efficacy, toxicity, and cost ranges for Tanezumab that would be required to satisfy accepted, societal willingness to pay (WTP) thresholds. To implement trial-reported data into the OAPol model, we generated a sample with pain scores based on the distribution reported in the trial (mean pain 67.1, standard deviation (SD) 12.7)[17] and then grouped the generated values by the pain group categories used in the OAPol model. We stratified the change in pain score by the initial pain groups, assuming a correlation between the initial and the final pain scores of 0.39, obtained from a meta-analysis comparing the pain relief between NSAIDs and opioids[25]. We considered three WTP thresholds often used in the US: $50,000/QALY, $100,000/QALY, and $150,000/QALY[26–28]. Results are presented in 2014 USD with costs and QALYs discounted at 3% per year[29].

The OAPol model

The OAPol model is a validated, state transition, Monte Carlo simulation of the natural history and management of knee OA[30–32]. The model generates cohorts of hypothetical subjects and assigns them initial characteristics from pre-specified distributions of age, sex, race/ethnicity, obesity, comorbid conditions, knee OA severity, and pain severity. The OAPol model accounts for the interrelationships among key variables. For example, QOL is a function of pain, obesity and comorbidities; background medical costs are based on sex, age and comorbidities; and pain reduction depends on baseline pain.

In the model, subjects progress through health states in 1-year intervals, during which they may develop comorbidities, increase body mass index (BMI), progress in OA severity, change in pain severity, and/or die. Five comorbidities were considered: cancer, cardiovascular disease (CVD), chronic obstructive pulmonary disease, diabetes mellitus, and musculoskeletal conditions other than OA. Prevalence and incidence rates for these diseases were stratified by age, sex, race/ethnicity, and obesity. We used underlying mortality rates derived from the 2010 CDC life tables, accounting for increased mortality due to specific comorbidities[33–37]. The initial BMI distribution was stratified by sex and race/ethnicity with obesity defined as a BMI $\geq$30 kg/m^2. Progression in OA severity was defined as an increase in Kellgren–Lawrence (K–L) radiographic grade and was stratified by sex and obesity[31,38]. Pain severity in the OAPol model is measured on a 0–100 scale and is assigned to one of five pain groups. There are no well-established cut-offs for defining mild, moderate, and severe OA pain. Several lines of inquiry guided our effort. Kapstad *et al.* defined thresholds between mild/moderate and moderate/severe at 4 and 7 out of 10 on the Body Pain Index (BPI)[39]. Since most of our data come from clinical trials that use the WOMAC Pain scale, we transformed the WOMAC Pain scale to a 0–100 scale with 100 = worst. We did a similar transformation with BPI, and established thresholds of 40 and 70 for moderate and severe pain. To distinguish mild from moderate pain we drew upon studies of TKR efficacy showing WOMAC <15 reflects mild pain[40]. This designation has face validity in that pain scores between 0 and 1 (none and mild) across 5 items correspond to the 1–15 group, scores between 1 and 2 (mild and moderate) correspond roughly to the 16–40 group, and pain scores in the 3–4 (severe, extreme) range correspond to the >70 group. Downgrading by one group level corresponds to a clinically meaningful difference in pain[41,42]. QOL decrements corresponding to each pain group were derived using data from the Osteoarthritis Initiative (OAI)[43,44]. Table I contains select cohort and treatment characteristics.

Subjects in the model undergo OA treatments that reduce pain severity, incur a cost, and may be associated with toxicity. Each year subjects eligible for treatment have the opportunity to accept or reject it. Pain reduction is drawn from published data and its magnitude depends on pain severity at the start of treatment. Success of treatment is defined as reduction from a higher to a lower pain group. In subsequent years, pain relief may end based on a defined probability (late failure) at which point the subject's pain severity is set to an estimate of what their pain severity would have been had they not received treatment. Subjects are removed from non-surgical regimens when their pain severity worsens to pre-treatment levels. Treatment regimens carry a risk of major (e.g., myocardial infarction) and minor (e.g., rash) toxicity, each with an associated decrease in QOL and increase in cost. Major toxicities lead to regimen discontinuation and may carry a risk of death. TKR eligibility criteria of pain severity >40 was defined based on published literature[45].

Cohort characteristics

Initial age, sex, race/ethnicity, pain severity, and K–L distributions were derived from Lane *et al.* (2010; Table I)[17]. Subjects' age at baseline was drawn from the normal distribution with a mean age