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N-of-1 Trials of Expensive Biological Therapies:

A Third Way?

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Abstract

In developing policies for use of expensive agents, such as those used for the treatment of rheumatoid arthritis, managed care organizations have invoked “stepped care,” in which physicians and patients must first try more established and less costly agents. N-of-1 clinical trials are multiple crossover trials in a single patient. In this cost-minimization analysis, we show that offering patients with rheumatoid arthritis the opportunity to participate in an n-of-1 trial comparing methotrexate with etanercept could save costs relative to open access while preserving clinical freedom relative to mandatory stepped care. In the primary model, the n-of-1 trial option was 15% more expensive than stepped care but 47% cheaper than open access to etanercept. More research is needed on the acceptability, safety, and generalizability of this promising approach.

Biopharmaceuticals such as monoclonal antibodies, receptor blockers, and fusion proteins have unique mechanisms of action and are often singularly effective, but they can be expensive.¹⁻³ In developing policies for the use of these therapies, managed care organizations have frequently invoked the principle of “stepped care.” This strategy requires physicians and patients to try more established and less costly treatments before turning to biological agents.^{4,5} The stepped-care approach to chronic disease management has clinical and economic appeal, affording patients the opportunity to benefit from standard therapy without taking on the costs and risks of newer treatments.⁶ Nevertheless, opposition to stepped care has arisen from several quarters, including patient advocacy organizations and pharmaceutical companies.⁷

The therapeutic paradigm for rheumatoid arthritis emphasizes early use of disease-modifying antirheumatic drugs to avert joint deformity and dysfunction.^{8,9} Modern stepped-care regimens begin with methotrexate. If the response is suboptimal, other disease-modifying antirheumatic drugs are used alone or in combination (eg, methotrexate, hydroxychloroquine sulfate, and sulfasalazine are frequently combined as “triple therapy”).¹⁰ In addition to these agents, there are 6 biological disease-modifying antirheumatic drugs approved for use in rheumatoid arthritis in the United States.¹¹ Etanercept, the market leader, is a soluble tumor necrosis factor receptor

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linked to the Fc portion of an IgG molecule. It is subcutaneously selfinjected once or twice weekly, at a cost approaching \$20 000 per year.¹²

As new biological agents come to the market, the controversy surrounding stepped-care guidelines is likely to persist. Herein, we suggest that offering patients access to n-of-1 trials could provide a way forward by using an approach less costly than open access and less restrictive than mandatory stepped care. N-of-1 trials are single-patient experiments in which the patient receives a randomized sequence of treatments.^{13,14} The results can be used to estimate individual treatment effects and to guide individual therapy.

N-of-1 trials are feasible when the condition under study is chronic or recurrent, the treatment has a relatively rapid on-set and washout, and patients and physicians are willing to undertake the experiment.¹⁵ During the past 20 years, n-of-1 trials have been used to evaluate therapies for chronic obstructive pulmonary disease, fibromyalgia, osteoarthritis, gastroesophageal reflux, and numerous other conditions.¹⁶ N-of-1 trials rode a wave of popularity in the early 1990s that crested by decade's end. Here, we address whether n-of-1 trials might represent a "third way," a reasonable approach to balancing the interests of patients and payers when establishing policies for the use of expensive biopharmaceuticals.

CASE STUDY

In developing this argument, we used a case study approach comparing the costs of 3 strategies for the treatment of rheumatoid arthritis. We performed a cost-minimization analysis, which focuses on costs and assumes substantially equivalent clinical outcomes. In this illustrative analysis, the purpose is to explore the feasibility of using n-of-1 trials to solve a policy conundrum, not to generate definitive cost estimates.

Assumptions

Using a 3-year time horizon for costs and outcomes, we measured treatment effectiveness in terms of ACR50, a 50% reduction in signs and symptoms as assessed using the American College of Rheumatology response measure.¹⁷ The ACR50 response probabilities (35% for methotrexate, 40% for etanercept, and 50% for both combined) were obtained from recent systematic reviews.^{4,8,9,14,18} Weekly treatment costs (\$8.40 for methotrexate, \$330 for etanercept, and \$20.50 for triple therapy) were estimated by taking median 2005 prices (including injection supplies) posted on the RxUSA, homemed.com, Wal-Mart, Walgreens, and Costco Web sites. Nonrecurring n-of-1 trial packaging costs were estimated to be \$150 per patient.¹⁴

Model Structure

The basic decision tree (available at: http://repositories.cdlib.org/chsrpc/reports/n1_suppl_1) compares 3 clinical strategies. In strategy A, mandatory stepped care, the patient is given methotrexate for 13 weeks. If the patient achieves an ACR50 response, methotrexate is continued for the remaining 143 weeks to complete 3 years of treatment. If the response is inadequate, etanercept is added, and if successful, therapy with the combination of methotrexate plus etanercept is continued. If the response to combination therapy during 13 weeks is inadequate, salvage with oral triple therapy is initiated and continued for the remaining 99 weeks.

Strategy B provides immediate access to subcutaneous etanercept. As in strategy A, those in whom treatment has failed are treated with combination therapy (methotrexate plus etanercept) for 13 weeks. If the combination succeeds, it is continued; otherwise, the patient switches to

triple therapy (more information is available at:
http://repositories.cdlib.org/chsrpc/reports/n1_suppl_1).

In strategy C, the patient is entered into a 44-week, double-blind, n-of-1 clinical trial comparing subcutaneous methotrexate with subcutaneous etanercept. Although methotrexate can be given orally, subcutaneous injection is safe and effective and obviates the need for providing an injectable placebo to patients in the methotrexate arm (and an oral placebo to patients in the etanercept arm).¹⁸ Unlike oral methotrexate, the subcutaneous form is not associated with nausea (which could enable patients taking an oral form of methotrexate to distinguish it from placebo). In addition, methotrexate and etanercept cause minor burning when injected subcutaneously.

The n-of-1 trial consists of four 8-week treatment episodes separated by three 4-week washout periods (44 weeks total). This washout period is consistent with reported response durations for methotrexate and etanercept.¹⁹⁻²¹ Once each week, patients assigned to receive methotrexate inject 15 mg subcutaneously and patients assigned to receive etanercept inject 50 mg subcutaneously. (In an actual single-patient trial, the dose of each agent could be adjusted based on individual patient characteristics, such as body mass or comorbid disease.) Patients are assessed at the beginning and end of each treatment episode; each episode is declared a “success” or “failure” depending on whether an ACR50 response (relative to the beginning of the treatment episode) is achieved. To account for possible ordering effects, patients entering the n-of-1 trial are randomized to 1 of 4 treatment sequences (ie, MEME, EMEM, MEEM, or EMME, where M indicates methotrexate and E indicates etanercept).

In the present hypothetical n-of-1 trial, there are 16 possible permutations of treatment success and failure (outcome sequences) for the 4 treatment episodes (SSSS, SSSF, SSFS . . . FFFF, where S indicates success and F indicates failure). Two successes for methotrexate combined with 0 or 1 success for etanercept is declared a “win” for methotrexate. We also declare a winner when the trial results in 1 success for one treatment and no success for the other. An equal number of successes for methotrexate and etanercept is declared a “tie,” except when all 4 episodes do not result in an ACR50 response. In the event of a tie, the patient defaults to methotrexate, the less expensive treatment. If both treatments fail individually, the patient receives combination therapy for 13 weeks. Depending on the response, the patient either continues combination therapy or switches to triple therapy.

The expected proportion of cases represented by each n-of-1 outcome sequence is given by multiplying through the probabilities of an ACR50 response for the individual treatment episodes under the assumption that the outcome for each episode is statistically independent of the outcomes for the other episodes. When the probability products are summed, methotrexate wins 27% of the time, etanercept wins 34% of the time, there is a tie 24% of the time, and both treatments fail 15% of the time. To assess the stability of the model, sensitivity analyses evaluated the impact of (1) assuming nonindependence among treatment episode outcomes by applying a random-effects model, (2) treating ties in the n-of-1 trial with methotrexate plus etanercept combined (rather than defaulting to methotrexate only), and (3) using an ACR20 response criterion rather than ACR50. (Details of the random-effects model can be found at http://repositories.cdlib.org/chsrpc/reports/n1_suppl_2.)

Results of the Model

In the primary model, the expected cost of the mandatory stepped-care strategy for 3 years, including drug acquisition and packaging costs, was \$18 538. In contrast, the cost of the immediate access to etanercept strategy was \$39 770 and the cost of the n-of-1 strategy was \$22 078 (Table). The n-of-1 approach, thus, offers potential savings of \$17 692 over the immediate access strategy while allowing patients and their physicians to make more informed

decisions about treatment selection. Using random-effects models to allow for nonindependence of outcomes across treatment episodes had little effect on costs (Table). Treating ties with combination therapy rather than with methotrexate alone cut the putative savings in half, whereas using ACR20 rather than ACR50 as the response criterion nearly doubled the savings (Table).

IMPLICATIONS

This case study suggests that n-of-1 trials offer a way of balancing clinical judgment, consumer choice, and pharmaceutical cost containment in selected circumstances. Prescription drug costs continue to increase faster than the overall rate of health care inflation,²² and biopharmaceutical agents are responsible for an increasing proportion of these costs. All known methods of pharmaceutical cost containment, including the exclusion of entire drug classes, patient cost sharing, and “payment for results,” have limitations.²³⁻²⁵ Stepped care, although sensible under many circumstances, may not be clinically efficient or politically palatable.

Under these circumstances, the results of this modeling suggest that offering patients who want to circumvent stepped care the opportunity to enroll in an n-of-1 trial may yield considerable cost savings relative to immediate access. Under the primary model, the n-of-1 trial option was 15% more expensive than mandatory stepped care but 47% cheaper than open access to etanercept. This result was robust to assumptions examined in the sensitivity analyses.

In addition, there may be other noneconomic benefits of the n-of-1 strategy. Patients may have an increased probability of receiving what is, for them, the optimal treatment. Stepped care can be viewed as an informal, abbreviated, n-of-1 trial, with long-term treatment selection based on 1 uncontrolled trial episode using standard therapy. For reasons adduced by Senn,²⁶ the empirical information from such an informal “trial” is limited. Thus, it is plausible that the n-of-1 strategy might lead not only to reduced costs relative to immediate access but also to better clinical outcomes relative to stepped care.

Switching from one (effective) treatment to another (less effective) treatment in the course of a single-patient trial carries some risk of an increase in symptoms (and, in the case of rheumatoid arthritis, a small chance that bony erosions could advance irreversibly). However, treatment withdrawal also has a potential upside. Patients who experience a symptom flare-up when they discontinue therapy may have increased tolerance of risk, enhanced willingness to undergo monitoring, and improved treatment adherence in the long run.

It is conceivable that therapeutic precision could be improved by using additional treatment episodes. We chose a 4-episode trial lasting 44 weeks based on the assumption that few patients (or physicians) will tolerate a trial lasting much longer than 6 to 8 months. Even so, this modeling suggests that almost a quarter of hypothetical 4-episode n-of-1 trials will result in a tie between methotrexate and etanercept. Extending the trial to 6 episodes would break 47% of ties but would alter treatment in only 26% of ties (approximately 6% of all patients).

One limitation of this analysis is that it did not take into consideration benefits (eg, reduced joint erosions) or risks (eg, serious infections and lymphoma) accruing beyond 3 years.^{27,28} In addition, the acceptability of n-of-1 trials to patients and physicians is uncertain.¹⁵ Several academic n-of-1 trial units have been established to great fanfare, only to fade away once start-up funds were exhausted.^{13,14} One factor that distinguishes this proposal from previous ventures is that patients would have a direct incentive to participate.

In conclusion, this analysis suggests that n-of-1 trials may constitute a reasonable compromise between mandatory stepped care and immediate access to expensive biological agents. Giving patients with complex chronic diseases a choice between stepped care and an n-of-1 trial of

expensive biological therapies could reduce costs while providing more precise information on individual treatment response. Before implementation of such policies can be recommended, however, more research is needed to establish the acceptability and safety of the approach and its potential extension to other treatments and conditions.

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Table
Cost Projections for 3 Treatment Policies

Treatment Policy	Projected Cost, \$		
	Primary Model	Treat Ties With Combination Therapy	ACR20 Response
Mandatory stepped care	18 538	18 538	16 040
Immediate access to etanercept	39 770	39 770	50 360
N-of-1 trial	22 078 ^a	29 953	18 650
Savings (n-of-1 vs immediate etanercept)	17 692	9817	31 710

Abbreviation: ACR20, a 20% reduction in signs and symptoms as assessed using the American College of Rheumatology response measure.

^aThe value shown represents expected costs assuming independence of outcomes among treatment episodes in each n-of-1 trial. Using random-effects models assuming nonindependence of outcomes, expected costs for the n-of-1 trial arm in the primary model were \$22 510 assuming 20% shared variance and \$22 743 assuming 50% shared variance.