ORIGINAL ARTICLE

Comparative efficacy and incremental cost per responder of methotrexate versus apremilast for methotrexate-naïve patients with psoriasis

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Background: To our knowledge, no clinical trials directly compare apremilast with methotrexate (the standard of care for initial systemic treatment of psoriasis).

Objective: We sought to compare apremilast's relative efficacy with that of methotrexate for moderate to severe psoriasis.

Methods: An anchor-based indirect comparison was conducted for 75% improvement in Psoriasis Area and Severity Index score from baseline to week 16 (PASI 75) rates for systemic-naïve patients from Efficacy and Safety Trial Evaluating the Effects of apreMilast in psoriasis (ESTEEM) 1 and 2 (apremilast vs placebo) and Comparative study of HumirA vs. Methotrexate vs Placebo In psOriasis patieNts (CHAMPION) (adalimumab vs methotrexate vs placebo) trials. The difference-in-difference in PASI 75 response rates was calculated as the difference between the ESTEEM apremilast and placebo rates and the CHAMPION methotrexate versus placebo rates. Number needed to treat and incremental drug cost per responder were also estimated.

Results: No statistically significant difference was found between apremilast and methotrexate in PASI 75 (risk difference 13.1%; 95% confidence interval −1.8% to 28.0%; P = .09). Number needed to treat with apremilast versus methotrexate to gain 1 additional PASI 75 responder was 7.6. Annual incremental drug cost of this responder was estimated at $187,888.33.

Limitations: Few trials compare systemic-naïve patients. Only direct medication costs were considered.

Conclusions: There was no statistical evidence of greater efficacy for apremilast versus methotrexate. The $187,888 incremental cost per PASI 75 may exceed what payers are willing to pay. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2016.05.040.)

Key words: apremilast; cost per responder; cost-effectiveness; indirect comparison; methotrexate; moderate to severe psoriasis; number needed to treat; Psoriasis Area and Severity Index.

Psoriasis is a chronic, autoimmune disease that causes skin irritation, which can have an ongoing impact on patient well-being and affects approximately 2% of the US population.[1] Symptoms of psoriasis include itchy, painful erythematous plaques on the body's surface and

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substantial impairment of health-related quality of life.[2,3] In addition, the inflammatory process of psoriasis is associated with numerous underlying comorbidities, including cardiovascular disease and diabetes. Simultaneously, it has been estimated that almost 25% of patients with psoriasis have clinical depression.[4] In the past decade, psoriasis treatment has been revolutionized by highly efficacious biologic therapies.[5,6] However, methotrexate remains the most commonly used treatment for psoriasis as it has been the standard of care in the clinical setting for over 50 years.[7,8] Methotrexate is recommended as one of the first-line therapies by both the American Academy of Dermatology (AAD) and the European Academy of Dermatology and Venerology.[9,10]

CAPSULE SUMMARY

- The relative effectiveness of apremilast and methotrexate in treating psoriasis is uncertain.
- This study used indirect comparison methods to investigate the efficacy and cost of apremilast relative to methotrexate.
- There was no statistical evidence of greater efficacy for apremilast versus methotrexate, although its cost was significantly higher.

Apremilast, a small-molecule inhibitor of phosphodiesterase 4, was approved by the Food and Drug Administration (FDA) on September 24, 2014, as a treatment for moderate to severe psoriasis. The clinical efficacy and safety of apremilast was evaluated in 2 large-scale, phase-III, randomized, placebo-controlled trials: ESTEEM 1 (NCT01194219) and ESTEEM 2 (NCT01232283).[11,12] These trials measured achievement of 75% improvement in Psoriasis Area and Severity Index (PASI) score from baseline to week 16 (PASI 75) as the primary end point. Both trials found that rates of PASI 75 achievement among patients treated with apremilast (30 mg) were significantly higher than those of patients treated with placebo. However, PASI 75 achievement rates (33.1% in ESTEEM 1 and 28.8% in ESTEEM 2) were lower than those typically observed in biologic treatments for moderate to severe psoriasis.[13-18] In fact, the observed PASI 75 rates for apremilast were closer to those observed for methotrexate (36.4% in the CHAMPION trial[19]) than to etanercept at 50 mg twice weekly (observed range 47%-49%[20-22]). However, apremilast has not been directly compared with methotrexate in a head-to-head randomized controlled trial. This lack of direct comparative trials represents a substantial evidence gap for health care decision makers, who need to make treatment and reimbursement decisions. For example, the German Institute for Quality and Efficiency in Health Care (IQWiG) recently concluded that the added benefit of apremilast could not be derived because of a lack of relevant data against appropriate comparator therapy.[23] To fill these gaps, indirect comparisons of treatment outcomes across separate randomized trials have become a standard and valuable source of comparative evidence. Detailed methodological reviews and implementation guidelines for indirect comparisons have been published, and indirect comparisons have become a preferred evidence source for researchers and medical decision makers.[24-27]

The purpose of this study is to formally evaluate the relative efficacy of apremilast and methotrexate via indirect comparison to support informed first-line psoriasis treatment decisions. In addition, because methotrexate is generically available and less expensive, the relative cost-effectiveness of apremilast and methotrexate will provide important information for clinical and economic decision making.

METHODS

A targeted literature review was conducted to identify clinical trials that satisfied the following inclusion criteria: (1) conducted among patients with moderate to severe plaque psoriasis; (2) placebo controlled; (3) reported PASI 75 response rates at week 16; (4) randomized patients to either methotrexate or apremilast; and (5) reported results stratified by experience with systemic therapy for psoriasis. This literature leveraged previously conducted systematic literature reviews.[16,18,28] As the majority of psoriasis trials are conducted among patients who were poorly controlled with systemic therapy, ESTEEM 1, ESTEEM 2, and CHAMPION were the only 3 trials that satisfied the inclusion criteria.

In the ESTEEM 1 (NCT01194219) and ESTEEM 2 (NCT01232283) trials, patients were randomized to apremilast (30 mg twice per day) or placebo. Patients in the CHAMPION trial (NCT00235820) were randomized to receive adalimumab (40 mg every other week after a starter dose of 80 mg), methotrexate (7.5 mg weekly increased as needed and as tolerated to 25 mg), or placebo. All active medication doses administered were FDA approved. CHAMPION was conducted among patients with moderate to severe (body surface area ≥10%, and PASI score ≥10)