ORIGINAL ARTICLE

# Poor early response to methotrexate portends inadequate long-term outcomes in patients with moderate-to-severe psoriasis: Evidence from 2 phase 3 clinical trials

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***Background:*** Most methotrexate-treated psoriasis patients do not achieve a long-term PASI75 (75% reduction from baseline Psoriasis Area and Severity Index score) response. Indications of nonresponse can be apparent after only 4 weeks of treatment.

***Objective:*** To develop a prediction rule to identify patients unlikely to respond adequately to methotrexate.

***Methods:*** Patient-level data from CHAMPION (NCT00235820, N = 110) was used to construct a prediction model for week 16 PASI75 by using patient baseline characteristics and week 4 PASI25. A prediction rule was determined on the basis of the sensitivity and specificity and validated in terms of week 16 PASI75 response in an independent validation sample from trial M10-255 (NCT00679731, N = 163).

***Results:*** PASI25 achievement at week 4 (odds ratio = 8.917) was highly predictive of response with methotrexate at week 16. Patients with a predicted response probability <30% were recommended to discontinue methotrexate. The rates of week 16 PASI75 response were 65.8% and 21.1% ($P < .001$) for patients recommended to continue and discontinue methotrexate, respectively.

***Limitations:*** The CHAMPION trial excluded patients previously treated with biologics, and the M10-255 trial had no restrictions.

***Conclusion:*** A prediction rule was developed and validated to identify patients unlikely to respond adequately to methotrexate. The rule indicates that 4 weeks of methotrexate might be sufficient to predict long-term response with limited safety risk. ( J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2017.08.017.)

***Key words:*** discontinuation; methotrexate; moderate-to-severe psoriasis; Psoriasis Area and Severity Index (PASI); prediction; response.

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Funding sources: Supported by AbbVie. AbbVie participated in the interpretation of data, review, and approval of the manuscript.

Conflicts of interest: Dr Gordon receives research support from AbbVie, Amgen, Jannsen, Eli Lilly, Boerhinger Ingelheim, Dermira, and Celgene and serves as consultant for AbbVie, Amgen, Boerhinger Ingelheim, Jannsen, Eli Lilly, Celgene, Pfizer, Sun Pharmaceuticals, and Novartis. Drs Betts, Signorovitch, Li, and Wu and Ms Xie are employed by Analysis Group Inc, which received payment from AbbVie Inc for participation in this research. Dr Sundaram is a former employee of AbbVie and may own AbbVie stock or stock options. Dr Okun is a former employee of AbbVie and serves as a consultant for AbbVie, Gilead Science, and Crescendo Biosciences.

Accepted for publication August 8, 2017.

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Published online October 6, 2017.
0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2017.08.017

Methotrexate is one of the most commonly utilized systemic treatments for psoriasis, having been successfully used for >50 years in the clinical setting.[1,2] Randomized controlled trials have demonstrated that methotrexate has lower efficacy than cyclosporine but can be used continuously for years.[3-7] Recommendations for the dosing, scheduling, monitoring, and folic acid supplementation approaches vary. Generally, methotrexate is given as a single weekly oral dose. Often low doses are given initially, and then adjusted based on the individual patient's disease control and side effect profile.[8]

Limitations of methotrexate treatment for psoriasis include slow onset of action, modest efficacy, and toxicity. Rare side effects include hepatotoxicity, hematotoxicity, and allergic pneumonitis, and common side effects include nausea, malaise, diarrhea, and headaches.[9] Identifying the characteristics of patients unlikely to respond to methotrexate would allow clinicians to limit patient exposure to this medication, thereby avoiding the risk for toxicity and unnecessary delays in initiating more effective treatment. The benefit-risk balance of methotrexate would be enhanced because the patients who continue methotrexate would have an enhanced probability of response.

The CHAMPION clinical trial (NCT00235820) was a phase 3, randomized, double-blind trial that compared the treatments adalimumab, oral methotrexate, and placebo for subjects with moderate-to-severe psoriasis.[10] The M10-255 clinical trial (NCT00679731) was a phase 3, randomized, double-blind clinical trial that compared methotrexate and briakinumab.[11] By using the methotrexate treatment arms in these 2 controlled clinical trials, we developed and evaluated a prediction model for a patient's probability of response to methotrexate on the basis of patient characteristics and early clinical improvements in Psoriasis Area and Severity Index (PASI).[12,13] Even though initial methotrexate doses were low and increased gradually in these trials, outcomes at week 4 proved to be a powerful predictor of long-term treatment success. In addition, the risk of serious hepatotoxic or hematologic adverse events was low at the methotrexate doses used up to week 4, so patients experienced little risk of acute toxicity while determining whether methotrexate would be beneficial for them.

**CAPSULE SUMMARY**

- Most methotrexate-treated psoriasis patients fail to achieve a PASI75 (75% reduction from baseline Psoriasis Area Severity Index score) response.
- A parsimonious scoring algorithm to predict a patient's probability of response to methotrexate was developed and validated.
- This decision rule allows for early identification of patients unlikely to respond adequately to methotrexate.

## METHODS

### Study population

Data from the CHAMPION randomized controlled trial was used to develop the model, and data from the M10-255 randomized controlled trial was used to evaluate the model. Subjects randomized to methotrexate in CHAMPION were assigned the following dosing regimen: 7.5 mg on weeks 0-1, 10 mg on weeks 2-3, and 15 mg on weeks 4-7, with dose escalation to 20 mg on weeks 8-11 and 25 mg on weeks 12-15 if PASI50 (50% reduction from baseline PASI) response was not achieved at weeks 8 or 12. Subjects randomized to methotrexate in M10-255 were assigned the following dosing regimen: 5 mg on week 0, 10 mg on week 1, and 15 mg on weeks 2-9, with dose escalation to 20 mg on weeks 10-15 and 25 mg on weeks 16-24 if PASI75 (75% reduction from baseline PASI) response was not achieved or Physician's Global Assessment (PGA) score was worse than minimal on weeks 10 or 16. This study analyzed the intent-to-treat (ITT) population for the methotrexate arm in each trial. This study was a retrospective analysis of deidentified clinical trial data, and did not require institutional review board approval.

### Model development and validation

The primary outcome was PASI75 response at week 16. A patient's PASI score is a measure of body surface area involvement and psoriasis severity[14]; PASI75 is defined as ≥75% improvement in PASI score from baseline.

A prediction model for PASI75 response with methotrexate at week 16 was developed by using the patients randomized to methotrexate in CHAMPION. The prediction model included baseline patient and disease characteristics, as well as achievement of PASI25 (25% reduction from baseline PASI) at week 4 (an early indication of patient response to methotrexate). Model selection was performed via best subsets regression and clinical input. The best prediction model was chosen on the basis of the area under the curve (AUC) and the Hosmer-Lemeshow test[15] in M10-255. The full set of considered baseline characteristics is shown in