Comparative Effectiveness Without Head-to-Head Trials
A Method for Matching-Adjusted Indirect Comparisons Applied to Psoriasis Treatment with Adalimumab or Etanercept

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Supplemental Digital Content
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APPENDIX A: SAMPLE SELECTION DETAILS

A PubMed search was conducted to identify randomized trials of adalimumab or etanercept versus placebo for the treatment of psoriasis in North America. Since individual patient data were not available for etanercept trials, only etanercept trials with published summaries of patient baseline characteristics were considered.

For etanercept treatment, the randomized, placebo-controlled trial described in Leonardi et al.\(^{28}\) was selected for analysis. This trial included patients who were naïve to biologic therapy for psoriasis, had \(\geq 10\%\) body surface area (BSA) involvement, and a PASI score \(\geq 10\). Only the placebo arm and the highest-dosage etanercept arm (50 mg twice weekly for the first 12 weeks) of Leonardi et al.\(^{28}\) were included in the current analyses. This dosage is consistent with the current FDA label for etanercept, which recommends for adult patients a 50 mg dose given twice weekly (administered 3 or 4 days apart) for 3 months followed by reduction to a maintenance dose of 50 mg weekly.

The pivotal randomized, placebo-controlled trial of adalimumab vs. placebo for psoriasis, REVEAL,\(^{27}\) included patients with baseline BSA \(\geq 10\%\), PASI \(\geq 12\), and a Physician’s Global Assessment (PGA) of “moderate” or worse. Since these inclusion criteria are more restrictive than those of Leonardi and coworkers\(^{28}\) (i.e., a higher PASI threshold and a PGA requirement), REVEAL patients were pooled with patients drawn from the Phase II randomized, placebo-controlled trial M02-528,\(^{30}\) which included patients with BSA \(\geq 5\%\) and required no minimum PASI or PGA scores. From these pooled data, the final adalimumab- and placebo-treated study population with IPD (referred to here as REVEAL/528) was selected to include only patients with baseline BSA \(\geq 10\%\), PASI \(\geq 10\) and no prior use of biologics, matching the inclusion criteria in the etanercept trial of Leonardi et al.\(^{28}\) Patients were also excluded from REVEAL/528 if they had been randomized to weekly dosing of adalimumab 40 mg in M02-528, as this dose was not consistent with the FDA-approved label for adalimumab. All adalimumab-treated patients in REVEAL/528 received adalimumab 40 mg every other week (eow) starting at Week 1 after an 80 mg induction dose at Week 0. This dosing schedule is consistent with the current FDA label for adalimumab treatment in patients with psoriasis.

The trials of Saurat et al.\(^{26}\) and Papp et al.\(^{29}\) both enrolled non-North American patients, and hence were excluded from the present study. Additionally, the trial of Saurat et al.\(^{26}\) was unique in requiring folate supplementation for all patients.
APPENDIX B: STATISTICAL METHODS

To apply the method of moments to estimate $\beta$ in [2], we find the value of $\beta$ such that re-weighting the IPD for patients receiving treatment $T=0$ by $w_t = \exp(x_t' \beta)$ exactly matches their mean baseline characteristics to the aggregate data for treatment $T=1$. That is, we estimate $\beta$ as the $\hat{\beta}$ solving the equation

$$0 = \sum_{i \in T=0} x_i \exp(x_i' \beta) - \overline{x}_T,$$

[A1]

This estimator works because a correct logistic regression model for the odds of receiving $T=1$ vs. $T=0$ would, by definition, provide the correct weights for balancing the trial populations. If the $x_i$’s contains all confounders and the logistic model for $w_t$ is correctly specified, then $\hat{\beta}$ in [3] provides a consistent estimate of the causal effect of treatment $T=0$ vs. $T=1$ on the mean of $Y$ among patients actually receiving treatment $T=1$.

To show that this method of moments estimator can behave well in practice, we note that finite solutions to [A1] are unique, and, if the logistic regression model is correct, will converge to the true $\beta$ as the sample size increases. To see this, note that the estimator in [A1] is equivalent to solving

$$0 = \sum_{i \in T=0} (x_i - \overline{x}_T) \exp(x_i' \beta).$$

Without loss of generality it can be assumed that $\overline{x}_T = 0$ (e.g., we could transform all baseline characteristics in both trials by subtracting $\overline{x}_T$), leaving the estimator

$$0 = \sum_{i \in T=0} x_i \exp(x_i' \beta).$$

Note that the right-hand side of this estimator is the first derivative of $Q(\beta) = \sum_{i \in T=0} x_i \exp(x_i' \beta)$, which has second derivative $Q''(\beta) = \sum_{i \in T=0} x_i x_i' \exp(x_i' \beta)$. Since $Q''(\beta)$ is positive-definite for all $\beta$, $Q(\beta)$ is convex and any finite solution to [A1] is unique and corresponds to the global minimum of $Q(\beta)$. In SAS version 9.2, $\hat{\beta}$ can be obtained by minimizing $Q(\beta)$ using Newton-Raphson optimization as implemented in the NLPNRA subroutine of PROC IML, with the gradient specified using the GRD option.

Placebo arm data can be incorporated by applying a standard adjusted indirect comparison\cite{1} after first matching baseline characteristics across trials. In particular, the setting described in Section 3.3 can be extended to observations of $(X, T, Z, Y)$ where $X$, $T$ and $Y$ are defined as in Section 3.3 and $Z=0$ for the placebo arm and $Z=1$ for the treatment arm (the particular type of treatment still depends on $T$, which can now be thought of as the trial indicator). As in Section 3.3, IPD for $(X, T, Z, Y)$ are observed only when $T=0$, however when $T=1$ we observe aggregate baseline and outcome data, respectively, for both arms: $\overline{x}_0^{(T)}$ and $\overline{y}_0^{(T)}$ when $Z=0$ and $\overline{x}_1^{(T)}$ and
can be obtained as described above by ignoring Z. (Pooled average baseline characteristics across trial arms may need to be computed from the aggregate data as \[ n_2 = \frac{(n_2^{(0)} + n_2^{(1)})}{n_1^{(0)} + n_1^{(1)}}, \]
where \( n_2^{(0)} \) and \( n_2^{(1)} \) are the numbers of patients in trial \( T=1 \) with \( Z=0 \) and \( Z=1 \), respectively.) The estimated treatment effect, based on a matching-adjusted indirect comparison, is then

\[
\hat{\delta} = \frac{\sum_{i=1}^{n_2^{(0)}} y_i \exp \left( x_i^{(0)} \beta \right)}{\sum_{i=1}^{n_2^{(0)}} \exp \left( x_i^{(0)} \beta \right)} - \frac{\sum_{i=1}^{n_2^{(1)}} y_i \exp \left( x_i^{(1)} \beta \right)}{\sum_{i=1}^{n_2^{(1)}} \exp \left( x_i^{(1)} \beta \right)}. \]

This estimator can be obtained using PROC GENMOD in SAS version 9.2 with patient weights entered through the WEIGHT option, and use of the REPEATED statement to ensure that the weights are correctly interpreted in the estimation of standard errors. Standard errors for \( \hat{\delta} \) can be obtained from published summary statistics.

To gauge the impact of re-weighting on the available statistical information in the IPD, an effective sample size can be computed as the square of the summed weights divided by the sum of the squared weights. If the weights are treated as fixed, this effective sample size provides the correct sample size for converting the standard deviation of the re-weighted outcome to a standard error. The maximum effective sample size occurs when all patients have equal weight. The occurrence of a small effective sample size can indicate that some patients are receiving extreme weights, and there may be little statistical power to detect differences between treatments.

References