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ORIGINAL RESEARCH

The Clinical Impact of Seropositivity on Treatment Response in Patients with Rheumatoid Arthritis Treated with Etanercept: A Real-World Iraqi Experience

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Purpose: To assess the clinical impact of rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (ACPA)'s seropositivity on treatment response in patients with rheumatoid arthritis (RA) treated with etanercept.

Patients and Methods: A retrospective analysis of patients with RA registered in Baghdad Teaching Hospital Registry from May 2012 to August 2019 was conducted. Patients aged ≥18 years, meeting the ACR/EULAR 2010 criteria for RA, being treated with etanercept, and followed up at ≥1 year after etanercept initiation were included; patients who received any other biologics for RA were excluded. Patients were classified as seropositive (RF- and ACPA-positive), seronegative (RF- and ACPA-negative), RF-positive, RF-negative, ACPA-positive, and ACPA-negative. The primary outcomes included Clinical Disease Activity Index (CDAI) and Disease Activity Score 28 (DAS28) which were measured at one year after treatment initiation.

Results: At baseline, a total of 1318 (88.3%) patients were seropositive; 1122 (75.2%) and 1054 (70.6%) patients were RF- and ACPA-positive, respectively. Baseline mean CDAI scores were significantly ($P = 0.001$) higher among seropositive patients compared with seronegative patients. The baseline mean DAS28 score was also significantly higher in ACPA-positive group compared with the ACPA-negative group ($P = 0.021$). At baseline, the number of patients who had high CDAI scores was significantly higher among the seropositive, RF-positive, and ACPA-positive groups ($P = 0.001$, $P = 0.001$, and $P = 0.002$, respectively). After one year of treatment with etanercept, among seropositive versus seronegative and ACPA-positive versus ACPA-negative groups, there was a significant improvement in terms of the mean CDAI score ($P = 0.004$ and $P = 0.017$, respectively) and CDAI response ($P = 0.011$ and $P = 0.048$, respectively). At one year, the proportion of patients among the seropositive versus seronegative group who reached remission were 566 (42.9%) versus 78 (44.6%) and 642 (47.3%) versus 83 (47.4%), for CDAI and DAS28 response, respectively.

Conclusion: The results imply that seropositivity and ACPA-positivity may influence the treatment response in patients with RA, who were treated with etanercept.

Keywords: anti-cyclic citrullinated peptide antibody, Iraq, real-world, rheumatoid factor

Introduction

Rheumatoid arthritis (RA) is a chronic debilitating inflammatory disease in which the peripheral joints are the primary sites of inflammation, often leading to impairment of these joints.[1] The global prevalence of RA was estimated in a recent meta-analysis as 0.46%, with a 95% prediction interval of 0.06% to 1.27%.[2] The disease has also been found to be more prevalent in women.[3,4]

Rheumatoid factor (RF) has long been a component of the diagnostic criteria for RA. About 70% of patients with RA test positive for RF at onset, and 85% become positive during the first 2 years of the disease.[5] RF and its association

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with a more severe disease course of RA have been extensively studied.[6] Anti-cyclic citrullinated peptide antibody (ACPA) is another important serological biomarker of RA and studies have found ACPA to be positive in 60% to 80% of patients with RA.[1,7,8] The ACPA serological status provides important prognostic information regarding patients with RA.[1,9,10] One of the studies showed that ACPA-positive patients had more active disease during follow-up than ACPA-negative patients.[11] Based on the available evidence, ACPA was included in the diagnostic criteria for RA in 2009.[12]

During the last two decades, there has been a paradigm shift in the treatment patterns of RA. Previously, early treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) was followed by progressive addition of disease-modifying antirheumatic drugs (DMARDs); however, the present treatment modality starts with aggressive DMARD therapy soon after the diagnosis of RA. The initiation of DMARD therapy early in the course of a symptomatic disease has been substantiated with improved prognosis and disease outcomes in several studies.[13,14] Although several patients with RA respond to the conventional synthetic DMARDs (such as methotrexate), a large proportion of RA remains active despite such treatments. Immunotherapy with biological agents has significantly enhanced treatment outcomes in patients with RA.[15] Tumor necrosis factor-α (TNF-α) antagonists, such as etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol have been widely used for the treatment of RA.[12] Etanercept is the first anti-TNF agent to be approved for the treatment of RA. Over the last few years, numerous clinical studies have shown the efficacy and safety of etanercept in established and early RA, as a monotherapy or in combination with methotrexate.[16,17]

Given the optionality of biological treatment for patients with RA, it is important to identify a predictor for treatment response, which in turn can guide early treatment decisions.[18,19] RF and ACPA are well studied, and their associations with a more severe disease course have been described in western countries. However, there are limited data available from the Middle East region.[20–22] The present study was conducted to determine the clinical impact of RF and ACPA seropositivity on the treatment response in patients with RA treated with etanercept in Iraq.

Patients and Methods

Study Design

This is a retrospective, observational, real-world study performed on data collected from all the patients diagnosed with RA in the Baghdad Teaching Hospital registry, between May 2012 and August 2019. The rheumatology patient registry was an initiative established in 2012 to build a prospective, longitudinal, multicenter cohort. The registry captures data pertaining to all the patients treated with biologic therapies in the Rheumatology unit, Baghdad Teaching Hospital. The treatment decisions for patients with RA were guided by the American College of Rheumatology (ACR) recommendations. Data captured in the study included patient demographics (age and gender) and disease duration (in years); Disease Activity Score 28 (DAS28), Clinical Disease Activity Index (CDAI) at baseline and at one year after initiation of etanercept treatment, RF, and ACPA status. The treatment response was determined by measuring the change between baseline and one-year scores of DAS28 and CDAI. A patient with a DAS28 score of <2.6 denotes remission,[23] ≥2.6 to <3.1 indicates low activity, ≥3.1 to <5.1 indicates moderate activity, and ≥5.1 indicates high activity.[24,25] A CDAI score of <2.8 indicates remission, 2.9 to 10 indicates low activity, 10.1 to 22 indicates moderate activity, and 22.1 to 76 indicates high activity.[26]

The study was conducted in accordance with legal and regulatory requirements, scientific purpose, value and rigor; it followed generally accepted research practices described in the Guidelines for Good Pharmacoepidemiology Practices (GPP) by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines by the International Epidemiological Association (IEA), and Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

All patients had signed individual consent forms before including their data in the Baghdad Teaching Hospital Registry. The study was approved by the Ethics Committee, Baghdad Teaching Hospital. Our study is in full compliance with the Declaration of Helsinki.

Study Population

The eligibility criteria for the study included all patients aged ≥18 years with a diagnosis of RA based on the criteria defined by the ACR/The European League Against Rheumatism (EULAR) 2010, patients referred for treatment with etanercept (as monotherapy or combination therapy with any other concomitant conventional DMARDs), and those who had ≥1 year of follow-up after initiating etanercept. All patients with RA receiving any biologic therapy other than etanercept during their entire treatment period were excluded.

Outcomes and Statistical Analysis

The response variable was defined as DAS28 and CDAI response at 1 year. Clinical response to etanercept treatment was assessed by evaluating mean changes in CDAI and DAS28 scores from baseline to 1 year after initiation of treatment. A *P*-value of <0.05 without multiplicity adjustment is considered statistically significant for this post hoc analysis. Patients were classified as seropositive (RF- and ACPA-positive), seronegative (RF- and ACPA-negative), RF-positive, RF-negative, ACPA-positive, and ACPA-negative. Categorical covariates were described by frequency distribution, whereas continuous covariates were expressed in terms of their mean and standard deviation or median and interquartile range, as appropriate. The unadjusted comparisons between groups of the covariates and the outcomes were evaluated using Chi-square test for categorical data, while for continuous data, the Student's *t*-test was used for normally distributed variables and the Kruskal–Wallis test for non-parametric data. SPSS (version 23) was used for statistical analysis.

Results

Baseline Characteristics

A total of 1493 patients with RA were included in this analysis, and the majority were female patients (1234; 82.7%) (Table 1). The mean duration of RA symptoms prior to the initiation of etanercept treatment was 9 ± 8.1 years (Table 1). At baseline, a total of 1318 (88.3%) patients were seropositive and 1122 (75.2%) and 1054 (70.6%) patients were RF- and ACPA-positive, respectively (Table 2). Significantly higher baseline mean CDAI scores were observed among seropositive patients as compared to seronegative patients (*P*=0.001) (Table 2). The baseline mean DAS28 score was also significantly higher in ACPA-positive group compared to ACPA-negative group (*P*=0.021) (Table 2). At baseline, the number of patients who had high disease activity according to CDAI (high CDAI score) was significantly higher among seropositive, RF-positive, and ACPA-positive groups (*P*=0.001, *P*=0.001, and *P*=0.002, respectively) (Table 2).

Table 1 Demographics and Baseline Disease Characteristics of the Study Population

Demographics	**Mean ± SD**
N	1493
Mean age	48.34 ± 11.7 years (range: 23–95 years)
Gender distribution n (%)	
Males	259 (17.3%)
Females	1234 (82.7%)
Mean disease duration	8.9 ± 8.1 years (range: 1–37 years)
Rheumatoid factor (positive)	1122 (75.2%)
ACPA (Positive)	1054 (70.6%)
MTX (Yes)	970 (65.0%)
Baseline disease characteristics	**Mean ± SD**
CDAI	28.6 ± 9.8 (range 12.0–70.0)
DAS28-ESR	6.48 ± 10.3 (range 3.3–9.05)

Abbreviations: ACPA, anti-cyclic citrullinated peptide; CDAI, clinical disease activity index; DAS28-ESR, 28-joint disease activity score calculated using erythrocyte sedimentation rate; MTX, methotrexate; SD, standard deviation.

Table 2 Baseline Characteristics Data of Patients with Rheumatoid Arthritis

Variables	Seropositivity			RF			ACPA		
	Positive (N = 1318)	Negative (N = 175)	P value	Positive (N = 1122)	Negative (N = 371)	P value	Positive (N = 1054)	Negative (N = 439)	P value
Age (mean ± SD)	48.4 ± 11.7	47.7 ± 12.1	0.44	48.5 ± 11.7	47.5 ± 11.9	0.14	48.4 ± 11.6	48.0 ± 12.0	0.52
Disease duration, years (mean ± SD)	9 ± 8.1	8.4 ± 7.8	0.38	8.9 ± 8	8.8 ± 8.2	0.79	9.1 ± 8.1	8.4 ± 7.8	0.12
Baseline CDAI (mean ± SD)	29.3 ± 10.1	23.1 ± 5.3	0.001	30.3 ± 10.1	23.5 ± 6.7	0.001	29.6 ± 10.6	26.2 ± 7.1	0.001
Baseline DAS28 (mean ± SD)	6.4 ± 1.03	6.5 ± 1.07	0.72	6.5 ± 1.0	6.4 ± 1.1	0.065	6.5 ± 1	6.3 ± 1	0.021
MTX (No. %*)									
Yes	859 (65.2)	111 (63.4)	0.64	733 (65.3)	237 (63.9)	0.61	687 (65.2)	283 (64.5)	0.79
No	459 (34.8)	64 (36.6)		389 (34.7)	134 (36.1)		367 (34.8)	156 (35.5)	
Baseline CDAI (No. %*)									
Moderate (10.1–22)	380 (28.8)	87 (49.7)	0.001	292 (26.0)	175 (47.2)	0.001	305 (28.9)	162 (36.9)	0.002
High (22.1–76)	938 (71.2)	88 (50.3)		830 (74.0)	196 (52.8)		749 (71.1)	277 (63.1)	
Baseline DAS28 (No. %*)									
Moderate (≥3.1–<5.1)	126 (9.6)	20 (11.4)	0.43	100 (8.9)	46 (12.4)	0.050	97 (9.2)	49 (11.2)	0.24
High (≥5.1)	1192 (90.4)	155 (88.6)		1022 (91.1)	325 (87.6)		957 (90.8)	390 (88.8)	

Note: *The percentage presented as column percentage.

Abbreviations: ACPA, anti-cyclic citrullinated peptide antibody; CDAI, Clinical Disease Activity Index; DAS28, 28-joint Disease Activity Score; RF, rheumatoid factor; SD, standard deviation.

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Primary Outcomes

At one year after initiating treatment with etanercept, there was a significant improvement in terms of the mean CDAI scores among seropositive versus seronegative (P=0.004) and ACPA-positive versus ACPA-negative groups (P=0.017). Similarly, improvement of the CDAI response was observed in seropositive versus seronegative groups (P=0.011) and ACPA-positive versus ACPA-negative groups (P=0.048) (Table 3). However, there was no significant difference between RF-positive and RF-negative groups in terms of CDAI scores (P=0.27) and CDAI response (P=0.23).

At one year, there was no observable difference in terms of DAS28 scores and DAS response (statistically insignificant, P>0.05) among all the three comparative analyses: seropositive versus seronegative (P=0.53), RF-positive versus RF-negative (P=0.81), and ACPA-positive versus ACPA-negative groups (P=0.55) (Table 3).

The proportion of patients among the seropositive versus seronegative groups reaching remission within a year of etanercept treatment initiation based on CDAI scores was 566 (42.9%) and 78 (44.6%); it was 642 (47.3%) and 83 (47.4%) for DAS28 response (Table 2 and Figure 1).

At one year compared to baseline, both CDAI and DAS28 scores improved across the patient groups, irrespective of the baseline serological status of RF and ACPA. CDAI scores (baseline vs one year) were as follows: seropositive (29.3 vs 8.1), seronegative (23.1 vs 5.7), RF-positive (30.3 vs 8.0), RF-negative (23.5 vs 7.3), ACPA-positive (29.6 vs 8.2), and ACPA-negative (26.2 vs 6.8). DAS28 scores (baseline vs one year) were as follows: seropositive (6.4 vs 3.1), seronegative (6.5 vs 3.0), RF-positive (6.5 vs 3.1), RF-negative (6.4 vs 3.1), ACPA-positive (6.5 vs 3.1), and ACPA-negative (6.3 vs 3.1) (Tables 1 and 2).

Discussion

The introduction of anti-TNF-α biological agents has contributed significantly to the advancement in the treatment of RA. However, the possible risk of serious toxicity and substantial treatment expenses associated with biologics have emphasized the need for reliable treatment response predictors for anti-TNF-α treatments.[27,28] A predictor for treatment response is essential in guiding early treatment decisions. ACPA and RF are widely used in the diagnosis and classification of RA.[29] Patients with RA, who are seropositive for RF or ACPA, are considered to manifest an aggressive disease course compared with seronegative patients. However, the association between seropositivity and measures of disease severity (CDAI and DAS28) remains unclear.[30] The present study investigated the clinical impact of RF and ACPA seropositivity on treatment response in patients with RA, who were treated with etanercept for at least 1 year. The results of our analysis show that patients with RA who received treatment with etanercept for 1 year had clinical improvements in CDAI and DAS28 scores, versus baseline, irrespective of baseline serological status for RF and ACPA. Further, seropositive versus seronegative and ACPA-positive group versus ACPA-seronegative groups showed a significant impact on the CDAI score and CDAI response (Table 3).

Although the present study did not measure the ACPA and RF levels, it confirmed that a substantial proportion of patients reached remission in terms of CDAI and DAS28 response within a year of treatment with etanercept. These findings are comparable to a previous study that demonstrated a significant decrease in the ACPA and RF levels in the sera of rheumatoid patients after three months of etanercept treatment. The same study also reported a reduction in DAS28 score, indicating a decline in disease activity.[31] However, in the present study, there is no significant difference at one year in terms of DAS28 scores and DAS28 response between the seropositive and seronegative groups.

Previous studies with anti-TNFα agents (infliximab, adalimumab, etanercept, and golimumab) showed that there is a differential treatment response to biological therapies based on the RF or ACPA serological status.[32–34] Some studies have suggested that the seropositive status of RF or ACPA in patients with RA is associated with a clinical response to treatment,[27,28,35–40] while there was no correlation between treatment response and RF and ACPA seropositivity in other studies.[30,41,42]

Similar to the findings of the present study, the ACTION study demonstrated clinical efficacy in biologic-naïve patients with RA, who were treated with abatacept for six months, irrespective of baseline serostatus for RF or ACPA. Additionally, a significantly superior clinical efficacy of abatacept was observed in seropositive (RF- and ACPA-positive) patients compared to those who were seronegative (RF- and ACPA-negative) at baseline.[43] Harrold et al demonstrated in

Table 3 Response After 1 Year of Etanercept Treatment in Patients with Rheumatoid Arthritis

Variables	Seropositive			RF			ACPA		
	Positive (N = 1318)	Negative (N = 175)	P value	Positive (N = 1122)	Negative (N = 371)	P value	Positive (N = 1054)	Negative (N = 439)	P value
1-year CDAI (mean ± SD)	8.1 ± 10.5	5.7 ± 5.6	0.004	8.0 ± 10.4	7.3 ± 9.0	0.27	8.2 ± 10.9	6.8 ± 7.5	0.017
1-year DAS28 (mean ± SD)	3.13 ± 1.6	3.05 ± 1.6	0.53	3.13 ± 1.6	3.10 ± 1.59	0.81	3.1 ± 1.58	3.16 ± 1.6	0.55
1-year CDAI (No. %*)									
Remission (<2.8)	566 (42.9)	78 (44.6)		487 (43.4)	157 (42.3)	0.23	461 (43.7)	183 (41.7)	0.048
Low (2.9–10)	472 (35.8)	75 (42.9)	0.011	405 (36.1)	142 (38.3)		368 (34.9)	179 (40.8)	
Moderate (10.1–22)	162 (12.3)	18 (10.3)		130 (11.6)	50 (13.5)		128 (12.2)	52 (11.8)	
High (22.1–76)	118 (9.0)	4 (2.3)		100 (8.9)	22 (5.9)		97 (9.2)	25 (5.7)	
1-year DAS28 (No. %*)									
Remission (<2.6)	642 (47.3)	83 (47.4)	0.19	537 (47.9)	170 (45.8)	0.64	502 (47.6)	205 (46.7)	0.8
Low (≥2.6–< 3.1)	292 (22.2)	49 (28.0)		248 (22.1)	93 (25.1)		239 (22.7)	102 (23.2)	
Moderate (≥3.1–<5.1)	165 (12.5)	15 (8.6)		134 (11.9)	46 (12.4)		131 (12.4)	49 (11.2)	
High (≥5.1)	237 (18.0)	28 (16.0)		203 (18.1)	62 (16.7)		182 (17.3)	83 (18.9)	

Note: *The percentage presented as column percentage.

Abbreviations: ACPA, anti-cyclic citrullinated peptide antibody; CDAI, Clinical Disease Activity Index; DAS28, 28-joint Disease Activity Score; RF, rheumatoid factor; SD, standard deviation.

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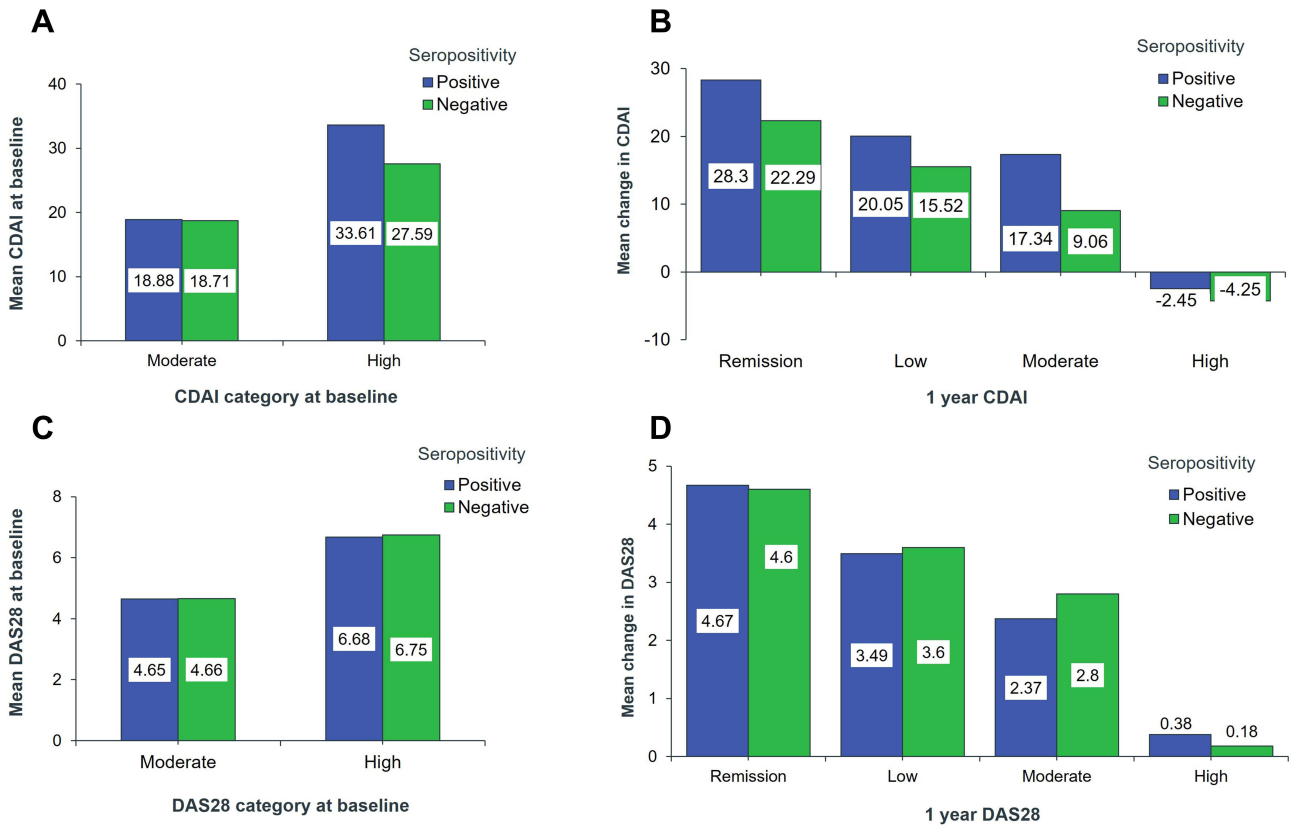

Figure 1 Seropositivity impact on baseline CDAI, DAS28 and one year after treatment with etanercept. **(A-D)** Mean change in CDAI and DAS28 scores from baseline to 1 year after initiation of treatment.
Abbreviations: CDAI, Clinical Disease Activity Index; DAS28, 28-joint Disease Activity Score.

the patients treated with abatacept that higher ACPA concentrations at baseline were associated with numerically greater improvements in CDAI and significant improvements in patient-reported outcomes after six months. However, there was no association between baseline ACPA concentration and treatment response in patients treated with a tumor necrosis factor inhibitor (TNFi).[1] Furthermore, a meta-analysis indicated that the status of RF and ACPA is not associated with the clinical response to anti-TNF-α treatment in patients with RA.[34] There is no definite conclusion on the impact of RF or ACPA serological status on the treatment response. However, the determination of RF and ACPA is useful for diagnostic and prognostic implications of early RA.[34,42]

To the best of our knowledge, this is the first study from the Middle East region examining the predictive role of ACPA and RF on etanercept treatment response in patients with RA. As with all real-world studies, there are limitations to our study. This study does not include a control group of patients with RA not treated with etanercept, limiting the comparison of treatment response with other anti-TNF-α agents or any other DMARD treatment. Additionally, there are missing data that could lead to inherent bias in the analysis.

Conclusion

The results of the present analysis show that seropositive and ACPA-positive Iraqi patients with RA, who received treatment with etanercept for one year, had significant improvements in CDAI scores and CDAI response. However, there was no observable difference between the groups in terms of DAS28 scores and DAS28 response. These results imply that seropositivity and ACPA positivity may influence the treatment response in patients with RA treated with etanercept. Further studies are needed to corroborate the definitive predictive role of ACPA and RF seropositivity on treatment response in patients with RA treated with etanercept or any other anti-TNF-α agents.

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Disclosure

AR, SH, FIG, and NAA declare no conflicts of interest in this work. AA and LMG are employees of Pfizer.

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