Association Between Biologic Therapies for Chronic Plaque Psoriasis and Cardiovascular Events

A Meta-analysis of Randomized Controlled Trials

Caitriona Ryan, MB, BAO, BCh
Craig L. Leonardi, MD
James G. Krueger, MD, PhD
Alexa B. Kimball, MD, MPH
Bruce E. Strober, MD, PhD
Kenneth B. Gordon, MD
Richard G. Langley, MD
James A. de Lemos, MD
Yahya Daoud, MA
Derek Blankenship, PhD
Salahuddin Kazi, MD
Daniel H. Kaplan, MD, PhD
Vincent E. Friedewald, MD
Alan Menter, MD

Context Ustekinumab and briakinumab, monoclonal antibodies to the shared p40 subunit of interleukin (IL)-12 and IL-23, have shown efficacy in treating chronic plaque psoriasis (CPP). Preliminary reports of major adverse cardiovascular events (MACEs) in psoriasis patients receiving anti–IL-12/23 agents have prompted concern.

Objective To evaluate a possible association between biologic therapies for CPP and MACEs via meta-analysis.

Data Sources Randomized controlled trials (RCTs) of anti–IL-12/23 (ustekinumab and briakinumab) agents and anti–tumor necrosis factor α (TNF-α) agents (adalimumab, etanercept, and infliximab) used in treating CPP were reviewed using the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and Ovid MEDLINE from database inception to May 2011. The results of registered nonpublished completed studies were procured through abstract publications or poster presentations.

Study Selection Randomized, placebo-controlled, double-blind, monotherapy studies (with safety outcome data for MACE) of IL-12/23 antibodies and anti–TNF-α agents in adults. Studies of psoriatic arthritis were excluded.

Data Extraction Two investigators independently searched data while 6 investigators reviewed the abstracted data.

Results A total of 22 RCTs comprising 10 183 patients met the predefined inclusion criteria. The primary outcome measure was MACE, a composite end point of myocardial infarction, cerebrovascular accident, or cardiovascular death during the placebo-controlled phase of treatment in patients receiving at least 1 dose of study agent or placebo. Absolute risk differences were used as an effect measure. There was no evidence of statistical heterogeneity across the studies using the I^2 statistic (I^2=0), allowing for combination of trial results using the Mantel-Haenszel fixed-effects method. During the placebo-controlled phases of the anti–IL-12/23 studies, 10 of 3179 patients receiving anti–IL-12/23 therapies experienced MACEs compared with zero events in 1474 patients receiving placebo (Mantel-Haenszel risk difference, 0.012 events/person-year; 95% confidence interval [CI], −0.001 to 0.026; P=.12). In the anti–TNF-α trials, only 1 of 3858 patients receiving anti–TNF-α agents experienced a MACE compared with 1 of 1812 patients receiving placebo (Mantel-Haenszel risk difference, −0.0005 events/person-year; 95% CI, −0.010 to 0.009; P=.94).

Conclusions Compared with placebo, there was no significant difference in the rate of MACEs observed in patients receiving anti–IL-12/IL-23 antibodies or anti–TNF-α treatments. This study may have been underpowered to identify a significant difference.

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IN THE PAST DECADE, IMPORTANT NEW findings have emerged linking autoimmune diseases including rheumatoid arthritis (RA), psoriasis, and Crohn disease with chronic systemic inflammation and a subsequent increase in occlusive vascular disease and cardiovascular risk.[1-3] It has been proposed that control of inflammation could help reduce cardiovascular morbidity. Indeed, a cardioprotective effect has been suggested with systemic agents such as methotrexate and anti–tumor necrosis factor α (TNF-α) agents in RA and psoriasis populations.[4,5]

See also Patient Page.

CME available online at www.jamaarchivescme.com and questions on p 888.

Given this context, we were concerned about preliminary reports of a numerical excess of major adverse car-

Author Affiliations are listed at the end of this article.
Corresponding Author: Caitriona Ryan, MB, BAO, BCh, Department of Dermatology, Baylor Research Institute, 3900 Junius St, Ste 125, Dallas, TX 75246 (caitriona.ryan@baylorhealth.edu).

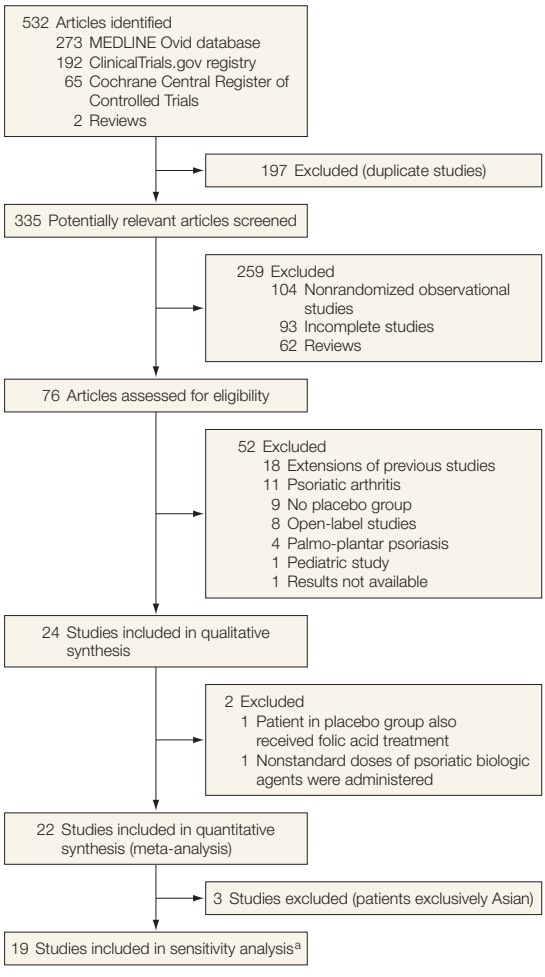
diovascular events (MACEs [a composite end point of myocardial infarction, cerebrovascular accident, or cardiovascular death]) in randomized controlled trials (RCTs) of psoriasis patients treated with ustekinumab (Centocor Ortho Biotech Inc, Horsham, Pennsylvania) and briakinumab (Abbott Laboratories, Abbott Park, Illinois)—highly effective monoclonal antibodies to the p40 subunit common to interleukin 12 (IL-12) and IL-23.[6-16] There were 10 MACEs in anti–IL-12/23–treated patients in the placebo-controlled phases of phase 2 and 3 studies of ustekinumab (n=5) and briakinumab (n=5) compared with zero events in placebo-treated patients, and a paucity of events reported from studies of anti–TNF-α–treated psoriasis patients with similar disease severity. A total of 53 MACEs have occurred to date across all phases of these studies; 26 MACEs, including 1 cardiovascular death in studies of ustekinumab (additional cases confirmed by Centocor)[6-11] and 27 MACEs, including 4 cardiovascular deaths, in studies of briakinumab (additional cases confirmed by Abbott).[12-16]

METHODS

A meta-analysis was conducted to evaluate cardiovascular outcomes in studies comparing biologic agents with placebo for the treatment of psoriasis. We reviewed all RCTs of anti–IL-12/23 agents (ustekinumab and briakinumab) and anti–TNF-α agents (adalimumab, etanercept, and infliximab) for the treatment of chronic plaque psoriasis (CPP) and performed a meta-analysis using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2009 guidelines.[17] Analysis methods were specified in advance and documented in a review protocol. Randomized, placebo-controlled, double-blind, monotherapy studies of IL-12/23 antibodies and anti–TNF-α agents for the treatment of CPP in adults that had publicly available safety outcome data for MACEs were included in the meta-analysis. Studies of psoriatic arthritis were excluded. No language, publication date, or publication status restrictions were imposed.

Studies were identified by systematic electronic literature searches in the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and Ovid MEDLINE from inception to June 2010 using combinations of the terms *psoriasis*, *trial*, and the names of each of the study drugs (including former names if applicable eg, CNT0-1275, ABT-874). An updating search was performed in May 2011. Two investigators independently searched data while 6 investigators reviewed the abstracted data. Abstractors were not blinded to study drug, authors, institutions, or journals when reviewing the studies. A data abstraction form included information on treatment allocation, methods of randomization, concealment and blinding, inclusion and exclusion criteria, duration and severity of disease, and patient characteristics. This information was used to assess quality and to compare the eligibility criteria of studies. A quantitative quality assessment was performed using a predefined scoring system devised by the Cochrane Collaboration, which allocated categories (present, absent, or not stated) for adequacy of randomization, conceal-

Figure 1. PRISMA Flowchart of Studies Included in Meta-analysis



[a]A sensitivity analysis excluding these 3 studies was also performed. PRISMA indicates Preferred Reporting Items for Systematic Reviews and Meta-analyses.

ment of allocation, and blinding of patients.[18] All included studies were deemed to be of high quality according to this quantitative assessment (eTable available at http://www.jama.com; studies were designed for efficacy). Disagreements were resolved by consensus of the 6 reviewers. To avoid publication bias, the results of all suitable nonpublished completed studies registered with the Cochrane Central Register of Controlled Trials and ClinicalTrials.gov were procured through abstract publications or poster presentations and a funnel plot was generated to assess the possibility of publication bias.[19] The individual sponsor companies were contacted if ambiguity existed regarding the definitions of cardiovascular events reported and in each case this information was provided.

The primary outcome measure was the number of MACEs during the placebo-controlled phase of treatment. Numbers were based on patients who received at least 1 dose of study agent or placebo. All doses of study agents were combined for comparison.

Statistical Analysis

Absolute risk differences were used as an effect measure, measuring the excess probability of MACEs in those receiving active treatment compared with those receiving placebo. All statistical tests were 2 sided and conducted at a significance level of .05. The statistical analysis was performed by independent academic biostatisticians from Baylor University Medical Center. Data were analyzed with Review Manager (RevMan) 5.1 developed by the Cochrane Collaboration, Baltimore, Maryland.

Based on a background rate of 0.0012 events per patient-year (aggregate rate in the placebo group for all 22 studies), a sample size of 4284 patient-years would be required to demonstrate a 0.5% absolute increase in the frequency of MACEs with 80% power

Table 1. Baseline Patient Characteristics

		No. of Patients		Mean (SD)[a]		Baseline, Mean (SD)	
Source	Biologic Agent	Biologic Agent	Placebo	Patient Age, y	Duration, y[b]	Percentage of Affected BSA	PASI[c]
Krueger et al,[6] 2007	Ustekinumab	254	64	45 (13.3)	18.2 (12.1)	27.2 (17.6)	19.1 (7.6)
Leonardi et al,[7] 2008	Ustekinumab	510	255	45.3 (11.7)	19.9 (11.5)	26.7 (16.7)	20.2 (8.3)
Papp et al,[8] 2008	Ustekinumab	820	410	46.2 (12.3)	20.1 (12.1)	26.4 (16.8)	19.6 (7.3)
Igarashi et al,[10] 2010[d]	Ustekinumab	126	31	46.7[e]	16.6[e]	46.8[e]	29.4[e]
Youn et al,[11] 2010[d]	Ustekinumab	61	60	40.6[e]	12.9[e]	38.8[e]	24.05[e]
Kimball et al,[12] 2008	Briakinumab	150	30	46 (14.1)	21 (13.0)	26 (14.5)	19 (6.6)
Gordon et al,[13] 2010	Briakinumab	981	484	45.5 (13.3)	19.0 (12.2)	25.1 (16.5)	19.2 (7.4)
Menter et al,[14] 2010[f]	Briakinumab	138	68	43.4 (13.4)	17.03 (12.7)	23.8 (15.7)	18.8 (7.5)
	Etanercept	141					
Strober et al,[15] 2010[f]	Briakinumab	139	72	45.1 (13.8)	15.7	24.2 (15.5)	18.8 (6.9)
	Etanercept	139					
Chaudhari et al,[20] 2001	Infliximab	22	11	43.7 (14)	NA	NA	23 (9.9)
Gottlieb et al,[21] 2004	Infliximab	197	51	44 (35-53)[g]	17 (11-24)[g]	27 (19-45)[g]	19 (15-27)[g]
Reich et al,[22] 2005	Infliximab	301	77	42.8 (11.9)	18.7 (11.1)	34.0 (19.0)	22.9 (9.2)
Menter et al,[23] 2007	Infliximab	627	208	44.1 (12.7)	18.4 (12.0)	28.4 (16.7)	20.1 (8.8)
Leonardi et al,[24] 2003	Etanercept	486	166	44.9 (3.7)	18.6 (1.8)	28.6 (2.8)	18.3 (1.6)
Gottlieb et al,[25] 2003	Etanercept	57	55	47.4 (18-77)[h]	21.5 (2.2)	32.0 (3.3)	18.6 (1.5)
Papp et al,[26] 2005	Etanercept	390	193	45.0 (18.0-75.0)[h]	19.0 (0.8-64.6)[h]	23.0 (7.8-95)[h]	16.4 (4-62.4)[h]
Tyring et al,[27] 2006	Etanercept	311	307	45.7 (12.4)	19.9 (11.9)	27.2 (17.7)	18.2 (7.5)
van de Kerkhof et al,[28] 2008	Etanercept	96	46	45.2 (12.7)	18.7 (10.4)	27.7 (16.0)	21.3 (9.1)
Bagel et al,[29] 2010	Etanercept	59	62	42.1 (13.8)	17.7 (11.5)	22.3 (15.9)	17.5 (7.2)
Gordon et al,[30] 2006	Adalimumab	95	52	44.3 (20-86)[h]	19.3 (1.0-57.9)[h]	27.3 (7-75)[h]	15.7 (5.5-40.4)[h]
Menter et al,[31] 2008	Adalimumab	814	398	44.5 (13.3)	18.2 (11.9)	25.7 (10.3)	18.9 (7.1)
Asahina et al,[32] 2010[d]	Adalimumab	123	46	44.8 (12.59)	13.9 (8.31)	46.2 (19.69)	28.38 (10.84)
Total		**7037**	**3146**				

Abbreviations: BSA, body surface area; IQR, interquartile range; NA, not available; PASI, Psoriasis Area and Severity Index; SD, standard deviation.
[a] Data are presented as mean (SD) unless otherwise specified. For categories showing no place value to the right of the decimal point, none were provided in the original publication of the study.
[b] Duration indicates time since onset of plaque psoriasis.
[c] Composite score measuring the grade of erythema, induration, scaling of plaques, and the BSA involved; PASI score is based on a scale of 0 when BSA is clear to a maximum severity of 72.
[d] Asian studies excluded in sensitivity analysis.
[e] Median supplied where mean is not available.
[f] Briakinumab was compared to treatment with etanercept and placebo and each biologic agent was compared with the same placebo group.
[g] Data are presented as median (IQR) where mean is not available.
[h] Data are presented as median (range) where mean is not available.

during the placebo-controlled phase using the typical ratio of 2:1 (biologic treatment:placebo study design; eFigure 1) demonstrates the increasing number of patients required to achieve higher degrees of statistical power, SiZ statistical software, Cytel Inc, Cambridge, Massachusetts). For 3 of the studies, which included exclusively Asian patients, an additional sensitivity analysis excluding these 3 studies was also performed.

RESULTS

The initial literature search was completed in June 2010. An updating search was performed in May 2011. Of the 532 citations screened, a total of 22 RCTs comprising 10 183 patients met the predefined inclusion criteria (PRISMA flow diagram, FIGURE 1).[6-8,10-15,20-32] Minimal individual study bias was observed with regard to the methodological quality of the studies (quantitative quality assessment, eTable) and eligibility criteria for all studies were very similar. Baseline patient characteristics were highly comparable between studies including patient age, duration of psoriasis, severity of baseline psoriasis as defined by the Psoriasis Area and Severity Index (PASI), and percentage of body surface area (BSA) affected (TABLE 1). Cardiovascular risk factors were listed as exclusion criteria for a phase 2 briakinumab study and a phase 4 etanercept study (which excluded patients with diabetes, unstable ischemic heart disease, and congestive heart failure).[12,29] There was no evidence of statistical heterogeneity across the studies using the I^2 test (I^2=0),[33] allowing for combination of trial results using the Mantel-Haenszel fixed-effects method.

TABLE 2 lists the number of MACEs during the placebo-controlled phase of these studies. The risk difference of MACE between patients treated with study drug and those receiving placebo is shown in FIGURE 2 and FIGURE 3. During the placebo-controlled phases of the anti–IL-12/23 studies, 10 of the 3179 patients treated with anti–IL-12/23 therapies had a MACE compared with no events in the 1474 patients treated with placebo (Mantel-Haenszel risk difference, 0.012 events/person-year; 95% confidence interval [CI], –0.001 to 0.026; *P*=.12; Figure 2). In studies of anti–TNF-α agents, 1 of the 3858 patients receiving anti–TNF-α treatments had a MACE compared with 1 of the 1812 treated with placebo (Mantel-Haenszel risk difference, –0.0005 events/person-year; 95% CI, –0.010 to 0.009; *P*=.94; Figure 3). A sensitivity analysis excluding 3 studies of Asian patients treated with ustekinumab and adalimumab did not appreciably alter these results (Mantel-Haenszel risk difference in the anti–IL-12/23 group compared with placebo, 0.013; 95% CI, –0.001 to 0.027; *P*=.09; eFigure 2, and Mantel-Haenszel risk difference in the anti–TNF-α group compared with placebo, –0.0005; 95% CI, –0.010 to 0.009; *P*=.94; eFigure 3). There was no evidence of publication bias (eFigure 4), although many of the studies had zero results, making this measure of bias less reliable.

COMMENT

This meta-analysis did not show a significant increase in the risk of MACEs associated with the use of anti–IL-12/23 agents. Limitations of this study, however, prevent us from determining whether these drugs expose psoriasis patients to increased cardiovascular risk. Access to patient-level data for these studies was not granted by any of the study sponsors, which precluded the use of a more statistically robust time-to-event analysis. The small number of MACEs that occurred

Table 2. Summary of the Randomized Controlled Trials Included in the Meta-analysis

Source	Biologic Agent	Length of Placebo-Controlled-Phase, wk	Biologic Agent[a]	
			No. of Events	Events per Person-Year
Krueger et al,[6] 2007	Ustekinumab	20	3	0.031
Leonardi et al,[7] 2008	Ustekinumab	12	1	0.009
Papp et al,[8] 2008	Ustekinumab	12	1	0.005
Igarashi et al,[10] 2010[b]	Ustekinumab	12	0	0.000
Youn et al,[11] 2010[b]	Ustekinumab	12	0	0.000
Kimball et al,[12] 2008	Briakinumab	12	0	0.000
Gordon et al,[13] 2010	Briakinumab	12	5	0.022
Menter et al,[14] 2010[c]	Briakinumab	12	0	0.000
	Etanercept	12	0	0.000
Strober et al,[15] 2010[c]	Briakinumab	12	0	0.000
	Etanercept	12	0	0.000
Chaudhari et al,[20] 2001	Infliximab	10	0	0.000
Gottlieb et al,[21] 2004	Infliximab	10	0	0.000
Reich et al,[22] 2005	Infliximab	24	0	0.000
Menter et al,[23] 2007	Infliximab	14	0	0.000
Leonardi et al,[24] 2003	Etanercept	12	0	0.000
Gottlieb et al,[25] 2003	Etanercept	24	0	0.000
Papp et al,[26] 2005	Etanercept	12	0	0.000
Tyring et al,[27] 2006	Etanercept	12	0	0.000
van de Kerkhof et al,[28] 2008	Etanercept	12	0	0.000
Bagel et al,[29] 2010	Etanercept	12	0	0.000
Gordon et al,[30] 2006	Adalimumab	12	1	0.046
Menter et al,[31] 2008	Adalimumab	16	0	0.000
Asahina et al,[32] 2010[b]	Adalimumab	24	0	0.000

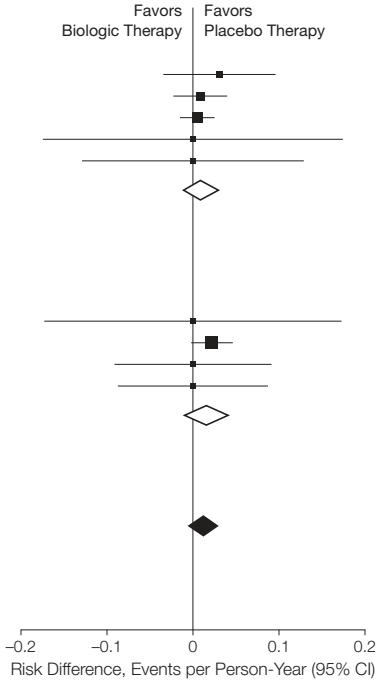
Abbreviations: BSA, body surface area; IQR, interquartile range; NA, data not available; PASI, Psoriasis Area and Severity Index; SD, standard deviation.
[a] Number of events and events per person-year for placebo group for Gottlieb et al,[25] were 1 and 0.040, respectively. For other studies, values for placebo groups were 0 and 0.00, respectively.
[b] Asian studies excluded in sensitivity analysis.
[c] In studies where briakinumab was compared to treatment with etanercept and placebo, each biologic agent was compared with the same placebo group.

in placebo-controlled phases of these studies and the limited duration of the placebo-controlled phases reduce the power of this meta-analysis to detect a change in risk. Moreover, the difficulty in obtaining accurate *P* values for rare and no-event data makes this analysis less reliable.[18] The abstractors were not blinded to authors, institutions, or journals when reviewing studies to be included in the meta-analysis, leading to another potential source of bias. The results of all suitable nonpublished completed studies registered with the Cochrane Central Register of Controlled Trials and ClinicalTrials.gov were procured through abstract publications or poster presentations in the public domain. Although publications of all studies included reported adverse events, including serious adverse events, failure to report serious adverse events in these publications may constitute another source of publication bias. A myocardial infarction in an infliximab-treated patient and a myocardial infarction in a placebo-treated patient were not reported in the serious adverse event sections of publications of phase 3 infliximab studies (data on file, Centocor).[34] There also may be a temporal effect biasing the results of our meta-analysis, as the majority of the anti–TNF-α studies were conducted in a time when there was less vigilance for adverse cardiac events in clinical studies. For example, all potential cardiovascular events that occurred in phase 2 and 3 studies of anti–IL-12/23 agents were adjudicated by a team of cardiology experts.

We remain concerned about the MACE rate of 1.33 per 100 patient-years (95% CI, 0.43-3.10) in the placebo-controlled phase of the phase 3 briakinumab study, with an overall rate of 0.60 events per 100 patient-years (95% CI, 0.35-0.94) across all treatment periods.[16] Indeed, after identification of these cases, a statistical analysis was performed by the manufacturers of briakinumab to determine whether a specific subset of treated patients may be at particularly high risk of a MACE. This analysis led to an amendment to the study protocol for the open-label continuation phase of this study in May 2010 to adjust the exclusion criteria, visit procedures, and discontinuation criteria for the enrolled patients. Patients with 2 or more predefined cardiovascular risk factors who had not previously experienced failure or intolerance to anti–TNF-α therapies or other systemic therapies were withdrawn from the study. Subsequently, in July 2011, all clinical trials of briakinumab were discontinued by Abbott, pending further investigations particularly relating to possible mechanistic links to MACEs. Until more definitive data become available, we believe that dermatologists should exercise height-

Figure 2. Risk Difference of MACEs in Patients Treated With Anti–IL-12/23 Agents Compared With Placebo in RCTs

Source	Biologic Therapy Events, No.	Biologic Therapy Person-Years	Placebo Events, No.	Placebo Person-Years	Weight, %	Risk Difference, Events per Person-Year (95% CI)
Ustekinumab						
Krueger et al,[6] 2007	3	97	0	25	8.4	0.03 (–0.03 to 0.09)
Leonardi et al,[7] 2008	1	117	0	59	16.6	0.01 (–0.02 to 0.04)
Papp et al,[8] 2008	1	189	0	94	26.5	0.01 (–0.01 to 0.02)
Igarashi et al,[10] 2010	0	29	0	7	2.4	0.00 (–0.17 to 0.17)
Youn et al,[11] 2010	0	14	0	14	3.0	0.00 (–0.13 to 0.13)
Subtotal (95% CI)		446		199	56.9	0.01 (–0.01 to 0.03)
Total events	5		0			
Heterogeneity: $\chi^2 = 0.65$, $df = 4$; $P = .96$; $I^2 = 0\%$						
Test for overall effect: $z = 0.96$; $P = .34$						
Briakinumab						
Kimball et al,[12] 2008	0	35	0	7	2.5	0.00 (–0.17 to 0.17)
Gordon et al,[13] 2010	5	226	0	111	31.5	0.02 (–0.002 to 0.04)
Menter et al,[14] 2010	0	32	0	16	4.5	0.00 (–0.09 to 0.09)
Stober et al,[15] 2010	0	32	0	17	4.7	0.00 (–0.09 to 0.09)
Subtotal (95% CI)		325		151	43.1	0.02 (–0.01 to 0.04)
Total events	5		0			
Heterogeneity: $\chi^2 = 0.54$, $df = 3$; $P = .91$; $I^2 = 0\%$						
Test for overall effect: $z = 1.27$; $P = 0.20$						
Overall		771		350	100.0	0.012 (–0.001 to 0.026)
Total events	10		0			
Heterogeneity: $\chi^2 = 1.79$, $df = 8$; $P = .99$; $I^2 = 0\%$						
Test for overall effect: $z = 1.58$ $P = .12$						
Test for subgroup differences: $\chi^2 = 0.17$; $df = 1$; $P = .68$; $I^2 = 0\%$						



Mantel-Haenszel fixed-effects method used to calculate risk difference, person-years of events. MACE indicates major adverse cardiovascular event; IL, interleukin; RCTs randomized controlled trials; CI, confidence interval.

ened vigilance for cardiovascular risk factors when initiating anti–IL-12/23 agents in psoriasis patients.

Although the roles of IL-12/23 in the development and progression of atherosclerosis have yet to be clearly elucidated, preliminary evidence suggests that IL-12 is proatherogenic and that its inhibition should confer cardioprotection.[35-37] In the phase 2 study of ustekinumab, however, serum levels of the p40 subunit of IL-12 were shown to paradoxically increase 13-fold in the first 12 weeks of treatment with a gradual decrease to above-baseline levels at week 32.[38] Contrary to traditional understanding of antibody-cytokine interactions, the binding of antibody may produce agonistic rather than antagonistic activity.[39-43]

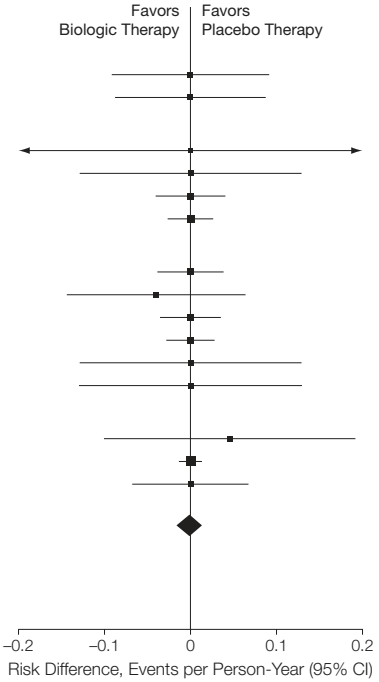
There is conflicting evidence regarding the role of IL-17, an IL-23–induced cytokine, in atherosclerotic plaque inflammation.[37,44-51] Recent evidence has suggested that IL-17 and signal transducer and activator of transcription (STAT) 3, a transcription factor downstream of IL-23, may have counterregulatory roles in atherosclerosis.[50,51] With numerous therapeutics agents inhibiting IL-17 and IL-23 currently in development, it is essential that the effect of these cytokines on vascular inflammation be fully explored.

Although meta-analysis is a strategy to increase power for the detection of rare events, this cannot correct for limitations in quality of the original clinical trials, most notably the absence of a systematic strategy to screen for, capture, and adjudicate cardiovascular events. This has been recently highlighted by the international controversy surrounding rosiglitazone, a drug used to treat type 2 diabetes.[52] Although individual RCTs detected no increase in cardiovascular events, observational studies and meta-analyses suggested an increased risk of MACEs associated with the drug.[53] More concerning, however, is the time delay between the detection of potential safety signals and their reporting to regulatory agencies or to the medical community at large. This was also highlighted in the case of rofecoxib, in which safety concerns regarding the risk of thrombotic events existed approximately 4 years before the drug was ultimately withdrawn from the market. Although a manufacturer-driven pooled analysis of more than 28 000 patients from 23 RCTS did not show evidence of an excess of cardiovascular events for rofecoxib relative to placebo,[54] a large RCT of 2586 patients finally confirmed a 2-fold increase in thrombotic events and was stopped prematurely.[55] The overwhelming question was why it took a relatively small trial to identify this risk several years after the drug had been prescribed to more than 80 million patients, with continued aggressive marketing by the pharmaceutical company despite warnings

Figure 3. Risk Difference of MACEs in Patients Treated With Anti–TNF-α Agents Compared With Placebo in RCTs

Source	Biologic Therapy Events, No.	Biologic Therapy Person-Years	Placebo Events, No.	Placebo Person-Years	Weight, %	Risk Difference, Events per Person-Year (95% CI)
Etanercept						
Menter et al,[14] 2010	0	32	0	16	3.4	0.00 (–0.09 to 0.09)
Strober et al,[15] 2010	0	32	0	17	3.4	0.00 (–0.09 to 0.09)
Infliximab						
Chaudhari et al,[20] 2001	0	4	0	2	0.4	0.00 (–0.50 to 0.50)
Gottlieb et al,[21] 2004	0	38	0	10	2.4	0.00 (–0.13 to 0.13)
Reich et al,[22] 2005	0	139	0	35	8.6	0.00 (–0.04 to 0.04)
Menter et al,[23] 2007	0	168	0	56	12.9	0.00 (–0.03 to 0.03)
Etanercept						
Leonardi et al,[24] 2003	0	112	0	38	8.7	0.00 (–0.04 to 0.04)
Gottlieb et al,[25] 2003	0	26	1	25	3.9	–0.04 (–0.14 to 0.06)
Papp et al,[26] 2005	0	90	0	44	9.0	0.00 (–0.03 to 0.03)
Tyring et al,[27] 2006	0	72	0	71	10.9	0.00 (–0.03 to 0.03)
Van de Kerkhof et al,[28] 2008	0	22	0	11	2.2	0.00 (–0.13 to 0.13)
Bagel et al,[29] 2010	0	14	0	14	2.1	0.00 (–0.13-0.13)
Adalimumab						
Gordon et al,[30] 2006	1	22	0	12	2.4	0.04 (–0.10 to 0.19)
Menter et al,[31] 2008	0	250	0	122	25.1	0.00 (–0.01 to 0.01)
Asahina et al,[32] 2010	0	57	0	21	4.7	0.00 (–0.07 to 0.07)
Overall		1078		494	100.0	–0.0005 (–0.01 to 0.009)
Total events	1		1			

Heterogeneity: $\chi^2 = 0.96$, $df = 14$; $P > .99$; $I^2 = 0\%$
Test for overall effect: $z = 0.07$ $P = .94$
Test for subgroup differences: $\chi^2 = .07$; $P = .94$



Mantel-Haenszel fixed-effects method used to calculate risk difference, person-years of events. CI indicates confidence interval; MACE, major adverse cardiovascular event; RCTs, randomized controlled trials; TNF, tumor necrosis factor.

of a safety signal.[56-58] A new statement from the US Food and Drug Administration in September 2010, however, issued a final rule clarifying that companies must report safety issues occurring during clinical trials within 15 days, including data that suggest the occurrence of serious adverse reactions at higher-than-expected rates, to expedite the review of critical safety information and protect patients enrolled in clinical trials.[59]

This analysis highlights the inherent limitations of placebo-controlled clinical trials to reliably interpret the significance of rare events given their current design. Although RCTs are currently the criterion standard for measuring clinical efficacy in psoriasis therapies, these studies are designed to detect differences in the severity of psoriasis in response to therapy over short periods of treatment and are often underpowered and of too short duration to detect rare or long-term adverse events. Careful consideration of these issues is warranted to best serve patients in these studies and those who are treated once drugs are approved.

Author Affiliations: Department of Dermatology, Baylor Research Institute, Dallas, Texas (Drs Ryan and Menter); Department of Dermatology, St Louis University, Saint Louis, Missouri (Dr Leonardi); Laboratory for Investigative Dermatology, The Rockefeller University, New York, New York (Dr Krueger); Department of Dermatology, Massachusetts General Hospital, Boston (Dr Kimball); Department of Dermatology, University of Connecticut, Farmington (Dr Strober); Division of Dermatology, University of Chicago, Pritzker School of Medicine, Chicago, Illinois (Dr Gordon); Department of Dermatology, Dalhousie University, Halifax, Canada (Dr Langley); Donald W. Reynolds Cardiovascular Research Center and Division of Cardiology, University of Texas Southwestern Medical Center, Dallas (Dr de Lemos); Department of Research and Improvement Education, Baylor University Medical Center, Dallas, Texas (Mr Daoud and Dr Blankenship); Department of Rheumatology, VA North Texas Health Care System, Dallas (Dr Kazi); Department of Dermatology, Center for Immunology, University of Minnesota, Minneapolis (Dr Kaplan); and Department of Cardiology, University of Notre Dame, Notre Dame, Indiana (Dr Friedewald).

Author Contributions: Dr Ryan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Ryan, Leonardi, Krueger, Kimball, Strober, Menter.
Acquisition of data: Ryan, Strober, Gordon, Langley, Menter.
Analysis and interpretation of data: Ryan, Leonardi, Krueger, Kimball, Strober, Gordon, Langley, de Lemos, Daoud, Blankenship, Kazi, Kaplan, Friedewald, Menter.
Drafting of the manuscript: Ryan, Leonardi, Krueger, Kimball, Strober, Daoud, Blankenship, Menter.
Critical revision of the manuscript for important intellectual content: Ryan, Leonardi, Krueger, Strober, Gordon, Langley, de Lemos, Kazi, Kaplan, Friedewald, Menter.
Statistical analysis: Ryan, Leonardi, Krueger, Gordon, Daoud, Blankenship, Menter.
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