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ORIGINAL ARTICLES

Tofacitinib 5 mg *Twice Daily* in *Patients with Rheumatoid Arthritis* and *Inadequate Response* to Disease-Modifying *Antirheumatic Drugs*

A *Comprehensive Review* of *Phase* 3 *Efficacy* and *Safety*

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Abstract

Background

Tofacitinib is an oral Janus kinase inhibitor for the treatment of ***rheumatoid arthritis*** (RA). We performed a ***comprehensive review*** of ***phase*** 3 studies of ***tofacitinib*** 5 mg ***twice daily*** (BID) (approved dose in many countries) in ***patients with*** moderate to severe RA and ***inadequate response*** to prior disease-modifying ***antirheumatic drugs***.

Methods A search of PubMed and ClinicalTrials.gov identified 5 studies: ORAL Solo (NCT00814307), ORAL Sync (NCT00856544), ORAL Standard (included adalimumab

40 mg once every 2 weeks; NCT00853385), ORAL Scan (NCT00847613), and ORAL Step (NCT00960440). ***Efficacy*** and ***safety*** data for ***tofacitinib*** 5 mg BID, placebo, and adalimumab were analyzed.

Results Across the 5 studies, 1216 ***patients*** received ***tofacitinib*** 5 mg BID, 681 received placebo, and 204 received adalimumab. At month 3, ***tofacitinib*** demonstrated significantly higher 20%, 50%, and 70% improvement in American College of Rheumatology ***response*** criteria (ACR20, ACR50, and ACR70, respectively) ***response*** rates, greater improvement in Health Assessment Questionnaire-Disability Index, and a higher proportion of Disease Activity Score-defined remission than placebo. Frequencies of adverse events (AEs), serious AEs, and discontinuations due to AEs were similar for ***tofacitinib*** and placebo at month 3; serious infection events were more frequent for ***tofacitinib***. In ORAL Standard, although not powered for formal comparisons, ***tofacitinib*** and adalimumab had numerically similar ***efficacy*** and AEs; serious AEs and serious infection events were more frequent ***with*** ***tofacitinib***.

Conclusions

Tofacitinib 5 mg BID reduced RA signs and symptoms and improved physical function versus placebo in ***patients*** ***with*** ***inadequate*** ***response*** to prior disease-modifying ***antirheumatic*** ***drugs***. ***Tofacitinib*** 5 mg BID had a consistent, manageable ***safety*** profile across studies, ***with*** no new ***safety*** signals identified.

Rheumatoid ***arthritis*** (RA) is a chronic and debilitating autoimmune disease associated ***with*** considerable morbidity and diminished quality of life and characterized by persistent synovitis, systemic inflammation, and ultimately joint destruction.[1–4] Conventional synthetic disease-modifying ***antirheumatic*** ***drugs*** (csDMARDs), such as methotrexate (MTX), are recommended as first-line therapy for RA and are often followed by biologic DMARDs (bDMARDs), such as tumor necrosis factor inhibitors (TNFi), for ***patients*** who have an ***inadequate*** ***response*** (IR).[5,6] Earlier and more aggressive use of csDMARDs and the introduction of bDMARDs have improved outcomes for ***patients***.[4] However, existing treatment regimens are not effective in all ***patients***, and bDMARDs that require parenteral administration are not universally available.[7] In addition, only between 24% and 58% of ***patients*** achieve 20% improvement in American College of Rheumatology ***response*** criteria (ACR20) after 1 year of treatment.[8–11] Despite the variety of targeted bDMARDs available (e.g., TNFi, interleukin inhibitors, and T- and B-cell inhibitors), some ***patients*** ***with*** active, uncontrolled disease are unable to receive these treatments, additional ***patients*** lose clinical ***response***, and some are subject to unacceptable risks.[8–10,12] Therefore, a need remains for RA therapies ***with*** alternative mechanisms of action to provide ***patients*** ***with*** additional therapeutic options to manage this chronic and progressive condition.

Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of RA. The JAK family of kinases mediates intracellular signal transduction of cytokines involved in immune regulation and has been linked to regulation of the intensity and

duration of inflammatory responses, implicating it in chronic inflammatory diseases, including RA.[13,14] ***Tofacitinib*** preferentially inhibits signaling via JAK3 and JAK1 ***with*** functional selectivity over JAK2.[15,16] JAK inhibition blocks the signaling pathways involved in lymphocyte activation, proliferation, and function and may thus modulate the immune ***response***, including reducing inflammation.[15,17] ***Phase*** 2, dose-ranging, randomized controlled trials provided sufficient evidence for ***phase*** 3 studies of ***tofacitinib*** in ***patients*** ***with*** RA administered as monotherapy or in combination ***with*** MTX.[18–22] Long-term extension (LTE) studies (1 complete and 1 ongoing) to evaluate ***tofacitinib*** ***safety*** and ***efficacy*** over longer periods have been reported for ***patients*** who completed ***phase*** 2 and 3 studies.[23,24]

While the ***phase*** 3 studies examined 2 separate doses of ***tofacitinib***—5 and 10 mg ***twice*** ***daily*** (BID)—based on the results of the ***phase*** 3 program, ***tofacitinib*** has been approved in many countries at a 5-mg BID dose for ***patients*** ***with*** active RA and an IR or intolerance to prior DMARD treatment.[25–30] We present a ***review*** of ***tofacitinib*** 5 mg BID ***phase*** 3 data in ***patients*** ***with*** RA and prior IR to DMARDs (DMARD-IR), in order to provide a ***comprehensive*** summary of the ***efficacy*** and ***safety*** of the widely approved dose in the ***phase*** 3 program and to allow comparison of results across the pivotal ***phase*** 3 registration studies, including ***patients*** ***with*** IR to csDMARDS and bDMARDs.

METHODS

Search Strategy

In order to identify all relevant articles to include in this ***review***, a search was conducted in the PubMed and ClinicalTrials.gov databases to identify primary reports of ***phase*** 3 randomized controlled trial data for ***tofacitinib*** 5 mg BID in ***patients*** ***with*** active RA and DMARD-IR. We used the search string "***tofacitinib*** AND ***phase*** III AND ***rheumatoid*** ***arthritis***" to interrogate both databases and identified 38 articles in PubMed and 12 studies in ClinicalTrials.gov. Search results were then assessed for eligibility based on the following inclusion criteria: ***phase*** 3 study, ***patients*** received ***tofacitinib*** 5 mg BID, ***patients*** had active RA, ***patients*** had previously received DMARDs and were DMARD-IR, and the study was completed and results were available. In total, 5 studies and corresponding articles were identified that matched all of these criteria: ORAL Solo (NCT00814307, A3921045)[28]; ORAL Sync (NCT00856544, A3921046)[25]; ORAL Standard (NCT00853385, A3921064)[26]; ORAL Scan (NCT00847613, A3921044)[30]; and ORAL Step (NCT00960440, A3921032).[29]

Further information about the design of the 5 studies analyzed is presented in Table 1. Data are reviewed from ***patients*** who were randomly assigned to receive ***tofacitinib*** 5 mg BID, placebo advanced to ***tofacitinib*** 5 mg BID, or adalimumab 40 mg once every 2 weeks (Q2W; ORAL Standard only). Placebo-treated ***patients*** advanced to ***tofacitinib*** 5 mg BID at month 3 or month 6, depending

on disease activity and according to randomization. The 5 studies also included ***tofacitinib*** 10 mg BID and placebo advanced to ***tofacitinib*** 10 mg BID treatment arms, which are not included in this ***review***. ***Patients*** received stable background DMARDs in all studies, except ORAL Solo.

TABLE 1:

Study Design Information for the 5 ***Phase*** 3 Studies

We also identified 5 pooled analyses of ***safety*** outcomes covering the ***tofacitinib*** clinical development program, which included data from the ***phase*** 3 trials.[23,31–35] We also requested and received further information regarding laboratory parameters for each study, as there was wide variation in reporting within the identified primary and ***safety*** articles. These reports supplemented our ***safety*** analyses of ***tofacitinib*** 5 mg BID.

End Points Evaluated

The ***phase*** 3 studies identified in the literature search were reviewed, and data for ***efficacy*** and ***safety*** end points were extracted. Co-primary end points in all 5 studies were ACR20 rate, least-squares (LS) mean change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI), and Disease Activity Score (DAS)-defined remission (DAS28-4 erythrocyte sedimentation rate [ESR] <2.6). Radiographic progression, assessed by LS mean change from baseline in modified Total Sharp Score (mTSS), was also a co-primary end point in ORAL Scan. Secondary study end points included ACR50 and ACR70 rates and the proportion of ***patients with*** no radiographic progression (change from baseline in mTSS ≤0.5; ORAL Scan only).

Co-primary end points were measured at month 3 or month 6 and were assessed using a step-down procedure: statistical significance could be claimed only if the prior end point in the sequence met significance requirements. For this ***review***, we primarily evaluated end points at month 3, because this was the most consistent time point across the studies, that is, before placebo-treated ***patients*** advanced, so all ***patients*** had received their assigned study medication for 3 months. Missing values for binary ***efficacy*** variables (e.g., ACR ***response*** rates and DAS28-4 [ESR] <2.6) were imputed using nonresponder imputation. The normal approximation was used to test the treatment difference in proportions. Missing values for HAQ-DI were handled using a linear mixed-effects model ***with*** treatment effect assessed from the same model. For mTSS, missing values were imputed using linear extrapolation.

In all 5 studies, ***safety*** end points included adverse event (AE) reports, discontinuations due to AEs, serious AEs (SAEs), and clinical laboratory abnormalities. For this ***review***, the most frequent AEs/SAEs were determined by first identifying the AEs/SAEs ***with*** the 3 highest percentage values for each study; those AEs/SAEs

occurring in 2 or more studies were then identified as the most frequent. In each study, AEs of special interest were analyzed in further detail. These related to ***safety*** signals associated ***with*** RA treatment and those identified during the ***tofacitinib*** clinical development program, including serious infection events (SIEs), opportunistic infections (OIs), malignancies, lymphomas, lymphocyte and neutrophil levels, and changes in levels of liver transaminases, hemoglobin, lipids, and serum creatinine.

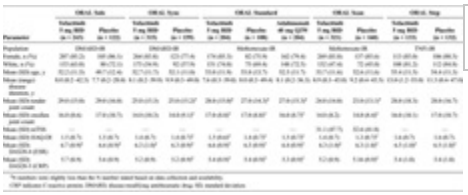
RESULTS

Patients

Across the 5 studies, 1216 ***patients*** received ***tofacitinib*** 5 mg BID, 681 received placebo, and 204 received adalimumab 40 mg Q2W. Patient selection criteria were similar across the studies, ***with*** all 5 studies enrolling ***patients*** 18 years or older, ***with*** active RA based on the ACR 1987 Revised Criteria, and active disease defined by at least 4 (ORAL Sync) or at least 6 (all other studies) tender/painful joints, at least 4 (ORAL Sync) or at least 6 (all other studies) swollen joints, and ESR greater than 28 mm/h or C-reactive protein greater than 7 mg/L. Additional criteria that applied to ORAL Scan were evidence of 3 or more distinct joint erosions or, if radiographic evidence of joint erosions was unavailable, ***rheumatoid*** factor or anti-cyclic citrullinated peptide (anti-CCP) positive. Requirements for prior DMARD use varied across studies, ***with*** ORAL Scan and ORAL Standard enrolling MTX-IR ***patients***, ORAL Sync and ORAL Solo enrolling csDMARD-IR or bDMARD-IR ***patients***, and ORAL Step enrolling TNFi-IR ***patients***. Patient exclusion criteria relating to AEs and laboratory parameters were similar across studies.

Baseline demographics and disease characteristics were generally well balanced between the treatment arms of individual studies and similar across all 5 studies (Table 2); the only exception was longer disease duration in ORAL Step (TNFi-IR) than the other 4 studies (DMARD-IR, MTX-IR) (Table 2).

TABLE 2:



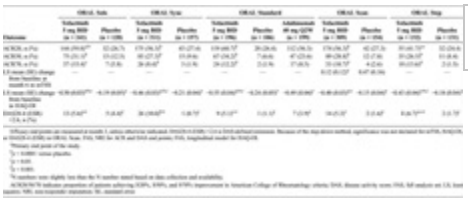
Baseline Demographics and Patient Characteristics across ***Phase*** 3 Studies

Efficacy

Across the ***phase*** 3 studies at month 3, ACR20 rates were significantly higher ***with*** ***tofacitinib*** 5 mg BID versus placebo, either as monotherapy or ***with*** background DMARDs (Table 3, Fig. 1). Significantly higher ACR20 rates for ***tofacitinib*** 5 mg BID versus placebo were observed at the first evaluable time point in each study (week 2 or month 1; Fig. 1). The ACR50 and ACR70 rates followed

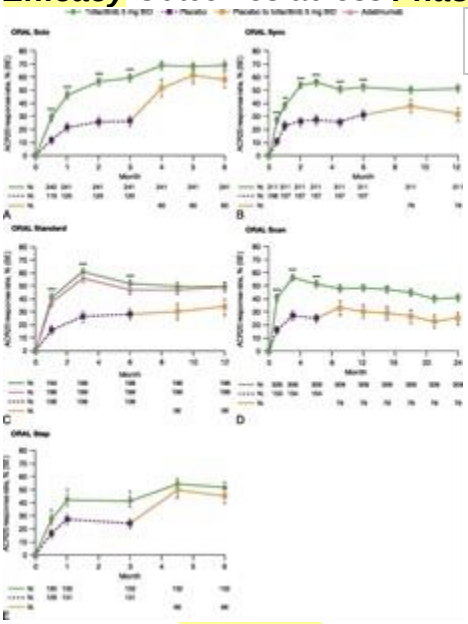
similar patterns (Table 3). The ACR20 rates were sustained over the remaining study periods for the ***tofacitinib*** 5 mg BID group, and similar ACR20 rates were observed after switching for ***patients*** who advanced to ***tofacitinib*** after 3 or 6 months on placebo (Fig. 1).

TABLE 3:



Efficacy Outcomes across ***Phase*** 3 Studies

FIGURE 1:



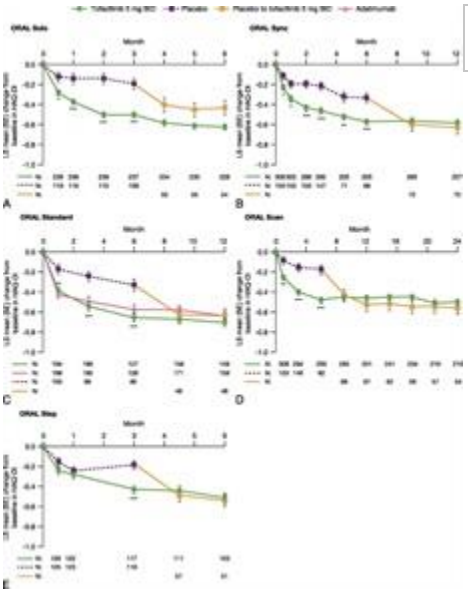
The ACR20 ***response*** rates (% [SE]) over time in the ***phase*** 3 studies (FAS, NRI). *p < 0.05, **p < 0.001, ***p < 0.0001 versus placebo. The ACR20 ***response*** rate at month 3 was a primary end point in the ORAL Solo and ORAL Step studies, and the ACR20 ***response*** rate at month 6 was a primary end point in the ORAL Sync, ORAL Scan, and ORAL Standard studies. ACR20 indicates ≥20% improvement in American College of Rheumatology criteria; FAS, full analysis set; N, number of ***patients*** included in analysis; NRI, non-responder imputation; SE, standard error. Color online-figure is available at http://www.jclinrheum.com.

The LS mean increases from baseline in mTSS (measured in ORAL Scan only) were numerically greater for placebo-treated ***patients*** compared ***with*** those receiving ***tofacitinib*** 5 mg BID at month 6, but this difference was not statistically significant (Table 3). Post hoc analyses of the interim study data demonstrated that ***patients with*** prognostic factors predictive of greater progression of joint damage (anti-CCP positivity, DAS28-4 [ESR] >5.1, anti-CCP and/or ***rheumatoid*** factor positivity ***with*** erosion score ≥3, and baseline total mTSS greater than the baseline median) had more pronounced effects ***with tofacitinib*** 5 mg BID versus placebo.[30] The proportion of ***patients with*** no radiographic progression at month 6 was significantly

greater in the ***tofacitinib*** 5 mg BID group (88.8%) compared ***with*** the placebo group (77.7%; $p \leq 0.01$).

Greater LS mean improvements from baseline in HAQ-DI were observed across the ***phase*** 3 studies at month 3 for ***patients*** treated ***with*** ***tofacitinib*** 5 mg BID than placebo (Table 3; Fig. 2). These improvements were significant for ***tofacitinib*** versus placebo, except in ORAL Scan, where significance was not declared because of the step-down procedure. Improvements were observed for ***tofacitinib*** 5 mg BID administered as monotherapy or ***with*** background csDMARDs. ***Patients*** advancing to ***tofacitinib*** 5 mg BID after 3 or 6 months on placebo reported HAQ-DI improvements following advancement (Fig. 2). Observed HAQ-DI improvements from baseline ***with*** ***tofacitinib*** 5 mg BID were sustained over the remaining study periods (Fig. 2).

FIGURE 2:



Least-squares mean (SE) change from baseline in HAQ-DI over time in the ***phase*** 3 studies (FAS, longitudinal model). *$p < 0.05$, **$p < 0.001$, ***$p < 0.0001$ versus placebo. Least-squares mean change from baseline at month 3 was the primary end point across studies. Because of the step-down method, significance was not declared in ORAL Scan. FAS indicates full analysis set; HAQ-DI, Health Assessment Questionnaire-Disability Index; LS, least squares; N, number of ***patients*** included in analysis; SE, standard error. Color online-figure is available at http://www.jclinrheum.com.

Across the 5 ***phase*** 3 studies, more ***patients*** receiving ***tofacitinib*** 5 mg BID achieved DAS-defined remission (DAS28-4 [ESR] <2.6) at month 3 compared ***with*** placebo-treated ***patients*** (Table 3). These differences were significant in ORAL Sync, ORAL Standard, and ORAL Step; because of the step-down procedure, significance was not declared in ORAL Scan.

In ORAL Standard, ***efficacy*** responses were numerically similar for ***patients*** receiving ***tofacitinib*** 5 mg BID or adalimumab 40 mg Q2W, although ORAL Standard was not designed for noninferiority or superiority comparisons between ***tofacitinib*** and adalimumab (Figs. 1 and 2, Table 3).

Safety

As expected for active treatment arms, frequencies of AEs and SAEs were slightly higher ***with*** ***tofacitinib*** compared ***with*** placebo groups across all of the ***phase*** 3 studies between baseline and month 3 (patient-years of exposure for ***tofacitinib*** 5 mg BID vs. placebo for ORAL Solo, ORAL Sync, ORAL Standard, ORAL Scan, and ORAL Step: 30.1 vs. 15.0, 77.8 vs. 39.3, 49.0 vs. 26.5, 154.5 vs. 77.0, 16.5 vs. 16.4; Fig. 3). In total, 51.6% and 53.0% of ***patients*** receiving ***tofacitinib*** 5 mg BID and placebo, respectively, had AEs in the first 3 months. During this period, the most frequent AEs were diarrhea (2.2%–6.0%), headache (1.3%–5.6%), nasopharyngitis (1.6%–5.9%), and upper respiratory tract infection (2.8%–10.5%) for ***patients*** receiving ***tofacitinib*** 5 mg BID; and arthralgia (0.0%–3.8%), cough (0.0%–3.8%), peripheral edema (0.0%–3.8%), and upper respiratory tract infection (0.9%–4.9%) for placebo-treated ***patients***. There were no frequent SAEs (all ≤1%) reported in either the ***tofacitinib*** 5 mg BID or placebo groups; SAEs were experienced by 2.9% of ***tofacitinib***-treated ***patients*** and 4.1% of placebo-treated ***patients***. During the first 3 months of treatment, 4.2% and 3.2% of ***tofacitinib***- and placebo-treated ***patients*** discontinued because of AEs, respectively (Fig. 3). In ORAL Standard, ***tofacitinib***- and adalimumab-treated ***patients*** reported generally similar AE rates: 52.0% for ***tofacitinib*** and 51.5% for adalimumab (patient-years of exposure to month 3 for ***tofacitinib*** 5 mg BID vs. adalimumab 40 mg Q2W: 49.0 vs. 49.8; Fig. 3). Although there were few SAEs or discontinuations due to AEs ***with*** both ***tofacitinib*** (5.9% and 6.9%, respectively) and adalimumab (2.5% and 4.9%, respectively), SAEs and discontinuations due to AEs were numerically higher ***with*** ***tofacitinib*** than adalimumab.

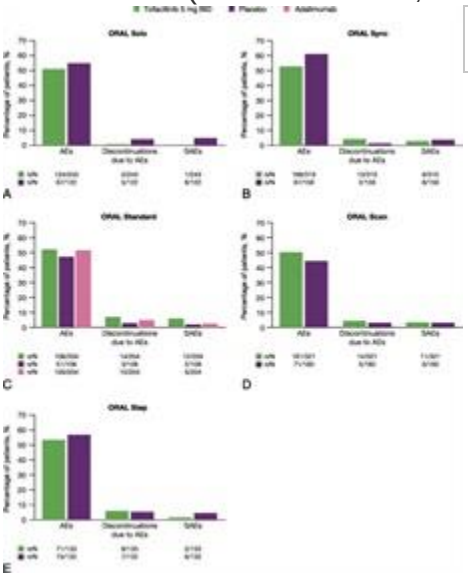


FIGURE 3:

Safety outcomes at month 3 across the ***phase*** 3 studies. n, number of ***patients*** ***with*** event; N, number of ***patients*** included in analysis; SAE, serious adverse event. Color online-figure is available at http://www.jclinrheum.com.

Overall, the most frequently reported infections for ***tofacitinib*** 5 mg BID and placebo across the full reported study periods (6 or 12 months) of the ***phase*** 3 studies were bronchitis (n = 14 and n = 10, respectively), herpes zoster (HZ; n = 5 and n = 2, respectively), influenza (n = 8 and n = 5, respectively), nasopharyngitis (n = 47 and n = 19, respectively), upper respiratory tract infection (n = 53 and n = 23, respectively), and urinary tract infection (n = 25 and n = 12, respectively) (patient-years of exposure for ***tofacitinib*** 5 mg BID vs. placebo: 1311.5 vs. 696.5).[34] As expected for active treatment, SIEs were numerically more frequent in ***tofacitinib*** groups than in placebo groups; 29 ***patients*** receiving ***tofacitinib*** 5 mg BID and 3 placebo-treated ***patients*** reported SIEs.[34] A total of 4 OIs were reported ***with*** ***tofacitinib*** 5 mg BID: 1 case each of disseminated HZ and *Pneumocystis jirovecii* pneumonia and 2 cases of esophageal candidiasis.
Any ***patients*** ***with*** evidence of active, latent, or inadequately treated tuberculosis (TB) at screening were excluded from the studies, and no cases of TB were reported in ***patients*** receiving ***tofacitinib*** 5 mg BID or placebo during any of the ***phase*** 3 studies.[36]

Malignancies (excluding nonmelanoma skin cancer [NMSC]) were reported in 8 ***patients*** in the ***tofacitinib*** 5 mg BID groups across the full reported study periods (6 or 12 months) of the ***phase*** 3 studies (incidence rate, 0.55 [95% confidence interval, 0.27–1.09]; patient-years of exposure for ***tofacitinib*** 5 mg BID vs. placebo: 1311.5 vs. 696.5).[31] Six ***patients*** in the ***tofacitinib*** 5 mg BID groups reported NMSC (incidence rate, 0.41 [95% confidence interval, 0.19–0.92]).[31] Eight ***patients*** receiving ***tofacitinib*** 5 mg BID had more than 1 malignancy (1 patient had esophageal carcinoma and colon carcinoma, 1 patient had prostate cancer and basal cell carcinoma, 3 ***patients*** had 2 basal cell carcinomas, 2 ***patients*** had 2 squamous cell carcinomas, and 1 patient had squamous cell carcinoma and basal cell carcinoma).[31] Two ***patients*** receiving ***tofacitinib*** 5 mg BID were reported to have lymphoma, and 2 placebo-treated ***patients*** reported NMSC.[31] In ORAL Standard, malignancy (excluding NMSC) was reported in 1 patient (lung cancer) receiving adalimumab 40 mg Q2W (199 patient-years of exposure).

Four cardiovascular events were reported across the full reported study periods (6 or 12 months) for ***patients*** receiving ***tofacitinib*** 5 mg BID (1 each of transient ischemic attack [ORAL Sync], cerebrovascular accident [ORAL Sync], angina pectoris [ORAL Scan], coronary artery disease [ORAL Scan]) and none in placebo-treated ***patients*** (patient-years of exposure for ***tofacitinib*** 5 mg BID vs. placebo: 1311.5 vs. 696.5). One patient receiving adalimumab 40 mg Q2W in ORAL Standard reported 3 cardiovascular events (myocardial infarction, cardiac arrest, myocardial ischemia; 199 patient-years of exposure).

For ***patients*** receiving ***tofacitinib*** 5 mg BID, 5 deaths occurred up to 30 days from the last dose of study drug; 2 further deaths were reported after this time (1311.5 patient-years of exposure).[34] One death was considered treatment related (pneumonia n = 1), 4 were considered possibly treatment related (*P. jirovecii* n = 1, septic syndrome n = 1, acute respiratory distress and pneumonia n = 1, metastatic lung cancer n = 1), and 2 were considered unrelated to study treatment (traumatic brain injury n = 1, viral infection n = 1).[34] One death was reported in the placebo groups (696.5 patient-years of exposure).

Across the 5 ***phase*** 3 studies, decreases from baseline in neutrophil and lymphocyte counts and increases in hemoglobin and lipid levels, relative to placebo, were observed by month 3 ***with*** ***tofacitinib*** 5 mg BID (297.23 patient-years of exposure) and stabilized thereafter. Dose-dependent decreases in neutrophil counts were seen ***with*** ***tofacitinib*** and adalimumab, ***with*** similar magnitudes of change, in ORAL Standard and stabilized for all treatment groups thereafter. Neutropenia was more frequently reported in ***tofacitinib*** groups than in placebo groups, although no life-threatening cases of neutropenia were reported, and no SIEs were associated ***with*** neutropenia. The frequency of occurrence of lymphopenia was similar between ***tofacitinib***- and placebo-treated ***patients***.[34] One placebo-treated patient withdrew from ORAL Step because of decreased hemoglobin levels. Four ***patients*** receiving ***tofacitinib*** 5 mg BID had confirmed greater than 50% increase in serum creatinine from baseline. One patient in the placebo to ***tofacitinib*** 5 mg BID group discontinued because of this, ***with*** levels subsequently stabilizing.

DISCUSSION

A large clinical program comprising ***phase*** 3 data from more than 4000 ***patients***[23] resulted in the approval of ***tofacitinib*** for the treatment of RA in many countries at a 5-mg BID dose. In 5 ***phase*** 3 studies enrolling ***patients*** ***with*** various treatment histories (Table 1), ***tofacitinib*** 5 mg BID rapidly reduced the signs and symptoms of RA and improved physical function when administered as monotherapy or ***with*** background csDMARDs. ***Tofacitinib*** 5 mg BID provided clinically meaningful improvements, as well as clinical and functional superiority to placebo, in ***patients*** ***with*** prior DMARD-IR. The variety of treatment backgrounds in these ***phase*** 3 studies (i.e., MTX, csDMARD, TNF-bDMARDs, and non-TNF-bDMARDs) demonstrated that ***tofacitinib*** could be effective for ***patients*** ***with*** a range of treatment histories in clinical practice. Across the 5 ***phase*** 3 studies, ***patients*** who advanced to ***tofacitinib*** 5 mg BID after 3 or 6 months on placebo had improvements in ***efficacy*** following the switch. These ***phase*** 3 results are consistent ***with*** ***efficacy*** results from ***phase*** 2 trials of ***tofacitinib*** 5 mg BID in DMARD-IR ***patients***.[18–20,22] ***Tofacitinib*** 5 mg BID had numerically similar ***efficacy*** results to adalimumab ***with*** MTX in ORAL Standard. The objectives of the ORAL Standard study were to compare the ***efficacy*** of ***tofacitinib*** ***with*** placebo and to compare adalimumab ***with*** placebo. It was not powered to detect noninferiority or superiority between ***tofacitinib*** and

adalimumab, but the inclusion of this active control group allowed estimates of the relative ***efficacy*** of ***tofacitinib***.

Identified ***safety*** events up to month 3 (patient-years of exposure for ***tofacitinib*** 5 mg BID vs. placebo: 297.25 vs. 167) were consistent across the 5 studies and generally consistent ***with*** ***phase*** 2[18–20,22] and LTE[23] studies. The proportions of ***patients*** reporting AEs, SAEs, SIEs, and discontinuing due to AEs were numerically higher for ***tofacitinib*** than adalimumab in ORAL Standard.

In the ***phase*** 3 studies, SIEs were generally more frequent ***with*** ***tofacitinib*** 5 mg BID than placebo (1311.5 vs. 696.5 patient-years of exposure, respectively), and rates were similar to those in ***phase*** 2 studies.[18–20,22] A pooled analysis of infections across ***phase*** 2, ***phase*** 3, and LTE studies of ***tofacitinib*** found the overall SIE rate ***with*** ***tofacitinib*** (5 and 10 mg BID) to be 3.1 events per 100 patient-years.[34] The SIE rate was 3.2 events per 100 patient-years for ***tofacitinib*** 5 mg BID versus 1.5 events per 100 patient-years for placebo from pooled ***phase*** 3 study data.[34] Serious infection events have been reported at similar rates (1.5–9.2 events per 100 patient-years) in ***safety*** analyses of DMARDs,[37–42] TNFi observational studies,[43–47] and a meta-analysis of DMARD data.[48]

Five cases of HZ were reported in ***patients*** receiving ***tofacitinib*** 5 mg BID in the first 3 months of the ***phase*** 3 studies, ***with*** 2 cases reported for placebo-treated ***patients*** (327.9 vs. 174.1 patient-years of exposure, respectively); no cases of HZ were reported in adalimumab-treated ***patients*** in ORAL Standard. This is consistent ***with*** higher nonserious HZ rates observed ***with*** all ***tofacitinib*** doses compared ***with*** placebo throughout the clinical development program.[32,49] Herpes zoster has generally been reported more frequently ***with*** ***tofacitinib*** than other DMARDs,[37,38] and it is interesting to note that HZ rates in ***phase*** 3 studies and LTE studies (after ***phase*** 3 study participation) were higher for ***patients*** receiving placebo (***phase*** 3 studies only), adalimumab (***phase*** 3 studies only), and ***tofacitinib*** (5 and 10 mg BID; ***phase*** 3 and LTE studies) compared ***with*** rates reported for other DMARDs.[23,34] Although the reasons for higher rates remain unclear, HZ incidence may vary by race and region,[50] ***with*** more frequent reports among ***patients*** from Japan and Korea.[32,34] ***Rheumatoid*** ***arthritis*** is known to increase HZ infection risk, and some RA therapies may further increase this risk.[51,52] However, conflicting reports exist, and it remains unclear whether direct associations exist between RA therapies and HZ risk.[32]

Although no TB cases were reported in the ***tofacitinib*** 5 mg BID groups in the 5 ***phase*** 3 studies, cases have been reported in LTE studies,[33] and TB incidence across the ***tofacitinib*** clinical development program (5 and 10 mg BID) is known to be generally similar to TNFi and csDMARDs[33,34,53–62] and higher in countries ***with*** high background prevalence.[33] Comparisons of OI rates between studies are not straightforward because different studies use varying definitions of OI, and endemic infections vary by country.

Across the 5 ***phase*** 3 studies, 8 ***patients*** had malignancies (excluding NMSC), 6 ***patients*** had NMSC, and 2 ***patients*** had lymphoma in the ***tofacitinib*** 5 mg BID groups (1311.5 patient-years of exposure). Increased risks and incidence rates for malignancies and lymphomas have been associated ***with*** RA.[31,37,39,63–76] The types of malignancies reported in these studies and across the whole ***tofacitinib*** clinical development program[31,77] were similar to those reported for RA and general populations.[31,64]

No cases of gastrointestinal (GI) perforation were reported in ***patients*** treated ***with*** ***tofacitinib*** 5 mg BID across the 5 ***phase*** 3 studies (5945 patient-years of exposure). However, cases have been reported in other ***tofacitinib*** studies (3, 5, and 10 mg BID), including open-label LTE studies.[23] The background incidence rate for GI perforation ***with*** ***tofacitinib*** is similar to reported rates for csDMARDs and bDMARDs.[23,78,79]

Initial changes in laboratory parameters in the ***phase*** 3 studies were generally consistent ***with*** ***phase*** 2b observations,[18,20] and stabilization continues ***with*** longer-term treatment.[23,80] It is unclear whether neutrophil count decreases ***with*** ***tofacitinib*** and adalimumab are associated ***with*** increases in infectious AE rates, although, where reported in the ***phase*** 3 studies, none of the moderate to severe neutropenia cases ***with*** ***tofacitinib*** 5 mg BID were associated ***with*** SIEs. Decreases in mean lymphocyte levels were observed in the ***phase*** 3 studies, and although not assessed in ***phase*** 3 studies, in LTE studies rates of SIEs were increased in ***patients*** ***with*** confirmed lymphocyte counts of less than $0.5 \times 10^3/mm^3$.[34] It remains unclear whether lipid level changes associated ***with*** immune-modulatory therapy are associated ***with*** increased cardiovascular risks or whether increases in cardiovascular events are due to RA. Cardiovascular event rates in ***tofacitinib*** LTE studies are similar to published csDMARD and bDMARD rates.[23,81–83] Changes in serum creatinine and liver aminotransferase levels were small and consistent across all groups in all 5 studies. Pooled analyses and LTE studies have shown that reported ***tofacitinib***-associated changes in serum creatinine levels and liver transaminases are reversible.[23] In addition, ***tofacitinib***-related serum creatinine changes do not appear to be associated ***with*** acute renal failure or progressive worsening of renal function.[23,84,85]

These studies are limited by the relatively short placebo-controlled period, making analysis and interpretation of differences between active treatment and placebo difficult. However, this is an inherent issue when active treatment cannot be reasonably withheld for ethical reasons. These ***phase*** 3 studies were also relatively short in duration compared ***with*** the chronic duration of RA; however, long-term ***tofacitinib*** ***safety*** and ***efficacy*** continue to be monitored in an ongoing LTE study,[23] postmarketing surveillance,[86] and analyses of real-world data.[87] In addition, no specific screening methods were used to detect malignancies in any of these trials, so underlying malignancies may not be captured in the data. ***Patients*** who developed malignancies were required to discontinue, so it was not possible to assess the risk of ***tofacitinib*** treatment on the development of additional malignancies.

Although we have observed and discussed similarities and differences in the ***safety*** and ***efficacy*** profiles of ***tofacitinib*** 5 mg BID to csDMARDs and bDMARDs reported in the literature, our comparisons are not based on head-to-head studies and should be interpreted ***with*** caution.

This ***comprehensive*** ***review*** of ***phase*** 3 data demonstrates that, in ***patients*** ***with*** DMARD-IR, ***tofacitinib*** 5 mg BID reduced the signs and symptoms of RA and improved physical function during the first 3 months of treatment. Improvements were sustained to month 6, similar to adalimumab ***with*** MTX in ORAL Standard and to other DMARDs across studies. ***Tofacitinib*** 5 mg BID demonstrated a consistent, manageable ***safety*** profile across the ***phase*** 3 studies. ***Patients*** should be monitored for AEs of special interest, including SIEs, OIs, malignancies and lymphomas, GI perforations, cardiovascular events, and changes in laboratory parameters. Monitoring of long-term ***tofacitinib*** ***safety*** and ***efficacy*** is ongoing in LTE studies, postmarketing surveillance, and analyses of real-world data.

KEY POINTS

- We performed a ***comprehensive*** ***review*** of ***phase*** 3 studies of ***tofacitinib*** 5 mg BID, the widely approved dose, in ***patients*** ***with*** moderate to severe RA and DMARD-IR.
- In ***phase*** 3 studies, ***tofacitinib*** 5 mg BID reduced the signs and symptoms of RA and improved physical function.
- ***Tofacitinib*** 5 mg BID demonstrated a consistent, manageable ***safety*** profile across the ***phase*** 3 studies.

REFERENCES

1. Scott DL, Wolfe F, Huizinga TW. ***Rheumatoid*** ***arthritis***. *Lancet*. 2010;376:1094–1108.

2. Strand V, Singh JA. Improved health-related quality of life ***with*** effective disease-modifying ***antirheumatic*** ***drugs***: evidence from randomized controlled trials. *Am J Manag Care*. 2007;13(suppl 9):S237–S251.

3. Hochberg MC, Johnston SS, John AK. The incidence and prevalence of extra-articular and systemic manifestations in a cohort of newly-diagnosed ***patients*** ***with*** ***rheumatoid*** ***arthritis*** between 1999 and 2006. *Curr Med Res Opin*. 2008;24:469–480.

4. Breedveld F. The value of early intervention in RA—a window of opportunity. *Clin Rheumatol*. 2011;30(suppl 1):S33–S39.

5. Smolen JS, Landewé R, Breedveld FC, et al. EULAR recommendations for the management of ***rheumatoid arthritis with*** synthetic and biological disease-modifying ***antirheumatic drugs***: 2013 update. *Ann Rheum Dis*. 2014;73:492–509.

6. Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying ***antirheumatic drugs*** and biologic agents in the treatment of ***rheumatoid arthritis***. ***Arthritis*** *Care Res (Hoboken)*. 2012;64:625–639.

7. Smolen JS, Aletaha D, Koeller M, et al. New therapies for treatment of ***rheumatoid arthritis***. *Lancet*. 2007;370:1861–1874.

8. Keystone EC, Kavanaugh AF, Sharp JT, et al. Radiographic, clinical, and functional outcomes of treatment ***with*** adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in ***patients with*** active ***rheumatoid arthritis*** receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. ***Arthritis*** *Rheum*. 2004;50:1400–1411.

9. Lipsky PE, van der Heijde DM, St Clair EW, et al. Infliximab and methotrexate in the treatment of ***rheumatoid arthritis***. Anti-Tumor Necrosis Factor Trial in ***Rheumatoid Arthritis with*** Concomitant Therapy Study Group. *N Engl J Med*. 2000;343:1594–1602.

10. Finckh A, Simard JF, Gabay C, et al. Evidence for differential acquired drug resistance to anti-tumour necrosis factor agents in ***rheumatoid arthritis***. *Ann Rheum Dis*. 2006;65:746–752.

11. Agarwal SK, Glass RJ, Shadick NA, et al. Predictors of discontinuation of tumor necrosis factor inhibitors in ***patients with rheumatoid arthritis***. *J Rheumatol*. 2008;35:1737–1744.

12. Rubbert-Roth A. Assessing the ***safety*** of biologic agents in ***patients with rheumatoid arthritis***. *Rheumatology (Oxford)*. 2012;51(suppl 5):v38–v47.

13. Egan PJ, Lawlor KE, Alexander WS, et al. Supressor of cytokine signaling-1 regulates acute inflammatory ***arthritis*** and T cell activation. *J Clin Invest*. 2003;111:915–924.

14. Egwuagu CE. STAT3 in $CD4^+$ T helper cell differentiation and inflammatory diseases. *Cytokine*. 2009;47:149–156.

15. Meyer DM, Jesson MI, Li X, et al. Anti-inflammatory activity and neutrophil reductions mediated by the JAK1/JAK3 inhibitor, CP-690,550, in rat adjuvant-induced ***arthritis***. *J Inflamm (Lond)*. 2010;7:41.

16. Changelian PS, Moshinsky D, Kuhn CF, et al. The specificity of JAK3 kinase inhibitors. *Blood*. 2008;111:2155–2157.

17. Ghoreschi K, Jesson MI, Li X, et al. Modulation of innate and adaptive immune responses by ***tofacitinib*** (CP-690,550). *J Immunol*. 2011;186:4234–4243.

18. Fleischmann R, Cutolo M, Genovese MC, et al. ***Phase*** IIB dose-ranging study of the oral JAK inhibitor ***tofacitinib*** (CP-690,550) or adalimumab monotherapy versus placebo in ***patients with*** active ***rheumatoid arthritis with*** an ***inadequate response*** to disease-modifying ***antirheumatic drugs***. ***Arthritis*** *Rheum*. 2012;64:617–629.

19. Kremer JM, Bloom BJ, Breedveld FC, et al. The ***safety*** and ***efficacy*** of a JAK inhibitor in ***patients with*** active ***rheumatoid arthritis***: results of a double-blind, placebo-controlled ***phase*** IIA trial of three dosage levels of CP-690,550 versus placebo. ***Arthritis*** *Rheum*. 2009;60:1895–1905.

20. Kremer JM, Cohen S, Wilkinson BE, et al. A ***phase*** IIB dose-ranging study of the oral JAK inhibitor ***tofacitinib*** (CP-690,550) versus placebo in combination ***with*** background methotrexate in ***patients with*** active ***rheumatoid arthritis*** and an ***inadequate response*** to methotrexate alone. ***Arthritis*** *Rheum*. 2012;64:970–981.

21. McInnes IB, Kim HY, Lee SH, et al. Open-label ***tofacitinib*** and double-blind atorvastatin in ***rheumatoid arthritis patients***: a randomised study. *Ann Rheum Dis*. 2014;73:124–131.

22. Tanaka Y, Suzuki M, Nakamura H, et al. ***Phase*** II study of ***tofacitinib*** (CP-690,550) combined ***with*** methotrexate in ***patients with rheumatoid arthritis*** and an ***inadequate response*** to methotrexate. ***Arthritis*** *Care Res (Hoboken)*. 2011;63:1150–1158.

23. Wollenhaupt J, Silverfield J, Lee EB, et al. ***Safety*** and ***efficacy*** of ***tofacitinib***, an oral Janus kinase inhibitor, for the treatment of ***rheumatoid arthritis*** in open-label, longterm extension studies. *J Rheumatol*. 2014;41:837–852.

24. Yamanaka H, Tanaka Y, Takeuchi T, et al. ***Tofacitinib***, an oral Janus kinase inhibitor, as monotherapy or ***with*** background methotrexate, in Japanese ***patients with rheumatoid arthritis***: an open-label, long-term extension study. ***Arthritis*** *Res Ther*. 2016;18:34.

25. Kremer J, Li Z-G, Hall S, et al. ***Tofacitinib*** in combination ***with*** nonbiologic disease-modifying ***antirheumatic drugs*** in ***patients with*** active ***rheumatoid arthritis***: a rando mized trial. *Ann Intern Med*. 2013;159:253–261.

26. Van Vollenhoven RF, Fleischmann R, Cohen S, et al. ***Tofacitinib*** or adalimumab versus

27. Lee EB, Fleischmann R, Hall S, et al. ***Tofacitinib*** versus methotrexate in ***rheumatoid arthritis***. *N Engl J Med*. 2014;370:2377–2386.

28. Fleischmann R, Kremer J, Cush J, et al. Placebo-controlled trial of ***tofacitinib*** monotherapy in ***rheumatoid arthritis***. *N Engl J Med*. 2012;367:495–507.

29. Burmester GR, Blanco R, Charles-Schoeman C, et al. ***Tofacitinib*** (CP-690,550) in combination ***with*** methotrexate in ***patients with*** active ***rheumatoid arthritis with*** an ***inadequate response*** to tumour necrosis factor inhibitors: a randomised ***phase*** 3 trial. *Lancet*. 2013;381:451–460.

30. van der Heijde D, Tanaka Y, Fleischmann R, et al. ***Tofacitinib*** (CP-690,550) in ***patients with rheumatoid arthritis*** receiving methotrexate: twelve-month data from a twenty-four-month ***phase*** III randomized radiographic study. ***Arthritis*** *Rheum*. 2013;65:559–570.

31. Curtis JR, Lee EB, Kaplan IV, et al. ***Tofacitinib***, an oral Janus kinase inhibitor: analysis of malignancies across the ***rheumatoid arthritis*** clinical development programme. *Ann Rheum Dis*. 2016;75:831–841.

32. Winthrop KL, Yamanaka H, Valdez H, et al. Herpes zoster and ***tofacitinib*** therapy in ***patients with rheumatoid arthritis***. ***Arthritis*** *Rheumatol*. 2014;66:2675–2684.

- Cited Here

33. Winthrop KL, Park SH, Gul A, et al. Tuberculosis and other opportunistic infections in ***tofacitinib***-treated ***patients with rheumatoid arthritis***. *Ann Rheum Dis*. 2016;75:1133–1138.

34. Cohen S, Radominski SC, Gomez-Reino JJ, et al. Analysis of infections and all-cause mortality in ***phase*** II, ***phase*** III, and long-term extension studies of ***tofacitinib*** in ***patients with rheumatoid arthritis***. ***Arthritis*** *Rheumatol*. 2014;66:2924–2937.

35. Isaacs JD, Zuckerman A, Krishnaswami S, et al. Changes in serum creatinine in ***patients with*** active ***rheumatoid arthritis*** treated ***with tofacitinib***: results from clinical trials. ***Arthritis*** *Res Ther*. 2014;16: R158.

36. Winthrop KL, Novosad SA, Baddley JW, et al. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. *Ann Rheum Dis*. 2015;74:2107–2116.

37. van Vollenhoven RF, Emery P, Bingham CO III, et al. Long-term ***safety*** of rituximab in ***rheumatoid arthritis***: 9.5-year follow-up of the global clinical trial programme ***with*** a focus on adverse events of interest in RA ***patients***. *Ann Rheum Dis*. 2013;72:1496–1502.

38. Schiff MH, Kremer JM, Jahreis A, et al. Integrated ***safety*** in tocilizumab clinical trials. ***Arthritis*** *Res Ther*. 2011;13:R141.

39. Gottlieb AB, Gordon K, Giannini EH, et al. Clinical trial ***safety*** and mortality analyses in ***patients*** receiving etanercept across approved indications. *J* ***Drugs*** *Dermatol*. 2011;10:289–300.

40. Lacaille D, Smitten A, Simon T, et al. Hospitalized infections in the Abatacept ***Rheumatoid Arthritis*** Clinical Development Program: an epidemiological assessment ***with*** >10,000 person-years of exposure. *J Rheumatol*. 2009;36:2568.

41. Schiff M, Keiserman M, Codding C, et al. Clinical ***response*** and tolerability to abatacept in ***patients with rheumatoid arthritis*** previously treated ***with*** infliximab or abatacept: open-label extension of the ATTEST Study. *Ann Rheum Dis*. 2011;70:2003–2007.

42. Kay J, Fleischmann R, Keystone E, et al. Golimumab 3-year ***safety*** update: an analysis of pooled data from the long-term extensions of randomised, double-blind, placebo-controlled trials conducted in ***patients with rheumatoid arthritis***, psoriatic ***arthritis*** or ankylosing spondylitis. *Ann Rheum Dis*. 2015;74:538–546.

43. Kievit W, Fransen J, Adang EM, et al. Long-term effectiveness and ***safety*** of TNF-blocking agents in ***daily*** clinical practice: results from the Dutch ***Rheumatoid Arthritis*** Monitoring register. *Rheumatology (Oxford)*. 2011;50:196–203.

44. Curtis JR, Patkar N, Xie A, et al. Risk of serious bacterial infections among ***rheumatoid arthritis patients*** exposed to tumor necrosis factor alpha antagonists. ***Arthritis*** *Rheum*. 2007;56:1125–1133.

45. Dixon WG, Watson K, Lunt M, et al. Rates of serious infection, including site-specific and bacterial intracellular infection, in ***rheumatoid arthritis patients*** receiving anti–tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. ***Arthritis*** *Rheum*. 2006;54:2368–2376.

46. Favalli EG, Desiati F, Atzeni F, et al. Serious infections during anti-TNFalpha treatment in ***rheumatoid arthritis patients***. *Autoimmun Rev*. 2009;8:266–273.

47. Galloway JB, Hyrich KL, Mercer LK, et al. Anti-TNF therapy is associated ***with*** an increased risk of serious infections in ***patients with rheumatoid arthritis*** especially in the first 6

months of treatment: updated results from the British Society for Rheumatology Biologics Register ***with*** special emphasis on risks in the elderly. *Rheumatology (Oxford)*. 2011;50:124–131.

48. Ahadieh S, Checchio T, Tensfeldt T, et al. Meta-analysis of malignancies, serious infections, and serious adverse events ***with*** ***tofacitinib*** and biologic treatment in ***rheumatoid*** ***arthritis*** clinical trials. ***Arthritis*** *Rheum*. 2012;64(suppl 10): S726.

49. Winthrop KL, Curtis JR, Lindsey S, et al. Herpes zoster and ***tofacitinib***: clinical outcomes and the risk of concomitant therapy. ***Arthritis*** *Rheumatol*. 2017;69:1960–1968.

50. Nagasako EM, Johnson RW, Griffin DR, et al. Geographic and racial aspects of herpes zoster. *J Med Virol*. 2003;70(suppl 1):S20–S23.

51. Strangfeld A, Listing J, Herzer P, et al. Risk of herpes zoster in ***patients*** ***with*** ***rheumatoid*** ***arthritis*** treated ***with*** anti–TNF-alpha agents. *JAMA*. 2009;301:737–744.

52. McDonald JR, Zeringue AL, Caplan L, et al. Herpes zoster risk factors in a national cohort of veterans ***with*** ***rheumatoid*** ***arthritis***. *Clin Infect Dis*. 2009;48:1364–1371.

53. Burmester GR, Mariette X, Montecucco C, et al. Adalimumab alone and in combination ***with*** disease-modifying ***antirheumatic*** ***drugs*** for the treatment of ***rheumatoid*** ***arthritis*** in clinical practice: the Research in Active ***Rheumatoid*** ***Arthritis*** (ReAct) trial. *Ann Rheum Dis*. 2007;66:732–739.

54. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated ***with*** infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med*. 2001;345:1098–1104.

55. Wolfe F, Michaud K, Anderson J, et al. Tuberculosis infection in ***patients*** ***with*** ***rheumatoid*** ***arthritis*** and the effect of infliximab therapy. ***Arthritis*** *Rheum*. 2004;50:372–379.

56. Brassard P, Kezouh A, Suissa S. ***Antirheumatic*** ***drugs*** and the risk of tuberculosis. *Clin Infect Dis*. 2006;43:717–722.

57. Carmona L, Gómez-Reino JJ, Rodríguez-Valverde V, et al. Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in ***patients*** treated ***with*** tumor necrosis factor antagonists. ***Arthritis*** *Rheum*. 2005;52:1766–1772

58. Seong SS, Choi CB, Woo JH, et al.
Incidence of tuberculosis in Korean ***patients*** ***with*** ***rheumatoid*** ***arthritis*** (RA): effects of RA itself and of tumor necrosis factor blockers. *J Rheumatol*. 2007;34:706–711.

59. Dixon WG, Hyrich KL, Watson KD, et al. Drug-specific risk of tuberculosis in ***patients*** ***with*** ***rheumatoid*** ***arthritis*** treated ***with*** anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). *Ann Rheum Dis*. 2010;69:522–528.

60. Baldin B, Dozol A, Spreux A, et al. Tuberculosis and infliximab treatment. National surveillance from January 1, 2000, through June 30, 2003 [in French]. *Presse Med*. 2005;34:353–357.

61. Sichletidis L, Settas L, Spyratos D, et al. Tuberculosis in ***patients*** receiving anti-TNF agents despite chemoprophylaxis. *Int J Tuberc Lung Dis*. 2006;10:1127–1132.

62. Solovic I, Sester M, Gomez-Reino JJ, et al. The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement. *Eur Respir J*. 2010;36:1185–1206.

63. Weinblatt ME, Moreland LW, Westhovens R, et al. ***Safety*** of abatacept administered intravenously in treatment of ***rheumatoid*** ***arthritis***: integrated analyses of up to 8 years of treatment from the abatacept clinical trial program. *J Rheumatol*. 2013;40:787–797.

64. Simon TA, Smitten AL, Franklin J, et al.
Malignancies in the ***rheumatoid*** ***arthritis*** abatacept clinical development programme: an epidemiological assessment. *Ann Rheum Dis*. 2009;68:1819–1826.

65. Burmester GR, Panaccione R, Gordon KB, et al. Adalimumab: long-term ***safety*** in 23 458 ***patients*** from global clinical trials in ***rheumatoid*** ***arthritis***, juvenile idiopathic ***arthritis***, ankylosing spondylitis, psoriatic ***arthritis***, psoriasis and Crohn's disease. *Ann Rheum Dis*. 2013;72:517–524.

66. Bykerk VP, Cush J, Winthrop K, et al. Update on the ***safety*** profile of certolizumab pegol in ***rheumatoid*** ***arthritis***: an integrated analysis from clinical trials. *Ann Rheum Dis*. 2015;74:96–103.

67. Smolen JS, Kay J, Doyle MK, et al.
Golimumab in ***patients*** ***with*** active ***rheumatoid*** ***arthritis*** after treatment ***with*** tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, ***phase*** III trial. *Lancet*. 2009;374:210–221.

68. Keystone EC, Genovese MC, Hall S, et al.
Golimumab in ***patients*** ***with*** active ***rheumatoid*** ***arthritis*** despite methotrexate therapy:

results through 2 years of the GO-FORWARD study extension. *J Rheumatol*. 2013;40:1097–1103.

69. Wolfe F, Michaud K. Biologic treatment of ***rheumatoid arthritis*** and the risk of malignancy: analyses from a large US observational study. ***Arthritis*** *Rheum*. 2007;56:2886–2895.

70. Askling J, Fahrbach K, Nordstrom B, et al. Cancer risk ***with*** tumor necrosis factor alpha (TNF) inhibitors: meta-analysis of randomized controlled trials of adalimumab, etanercept, and infliximab using patient level data. *Pharmacoepidemiol Drug Saf*. 2011;20:119–130.

71. Askling J, Fored CM, Brandt L, et al. Risks of solid cancers in ***patients with rheumatoid arthritis*** and after treatment ***with*** tumour necrosis factor antagonists. *Ann Rheum Dis*. 2005;64:1421–1426.

72. Mellemkjaer L, Linet MS, Gridley G, et al. ***Rheumatoid arthritis*** and cancer risk. *Eur J Cancer*. 1996;32A:1753–1757.

73. Chakravarty EF, Michaud K, Wolfe F. Skin cancer, ***rheumatoid arthritis***, and tumor necrosis factor inhibitors. *J Rheumatol*. 2005;32:2130–2135.

74. Mariette X, Matucci-Cerinic M, Pavelka K, et al. Malignancies associated ***with*** tumour necrosis factor inhibitors in registries and prospective observational studies: a systematic ***review*** and meta-analysis. *Ann Rheum Dis*. 2011;70:1895–1904.

75. Baecklund E, Askling J, Rosenquist R, et al. ***Rheumatoid arthritis*** and malignant lymphomas. *Curr Opin Rheumatol*. 2004;16:254–261.

76. Baecklund E, Iliadou A, Askling J, et al. Association of chronic inflammation, not its treatment, ***with*** increased lymphoma risk in ***rheumatoid arthritis***. ***Arthritis*** *Rheum*. 2006;54:692–701.

77. Curtis JR, Lee EB, Martin G, et al. Analysis of non-melanoma skin cancer across the ***tofacitinib rheumatoid arthritis*** clinical programme. *Clin Exp Rheumatol*. 2017;35:614–622.

78. Curtis JR, Xie F, Chen L, et al. The incidence of gastrointestinal perforations among ***rheumatoid arthritis patients***. ***Arthritis*** *Rheum*. 2011;63:346–351.

79. Curtis JR, Lanas A, John A, et al. Factors associated ***with*** gastrointestinal perforation in a cohort of ***patients with rheumatoid arthritis***. ***Arthritis*** *Care Res (Hoboken)*. 2012;64:1819–1828.

80. Schulze-Koops H, Strand V, Nduaka C, et al. Analysis of haematological changes in ***tofacitinib***-treated ***patients*** ***with*** ***rheumatoid*** ***arthritis*** across ***phase*** 3 and long-term extension studies. *Rheumatology (Oxford)*. 2017;56:46–57.

81. Charles-Schoeman C, Wicker P, Gonzalez-Gay MA, et al. Cardiovascular ***safety*** findings in ***patients*** ***with*** ***rheumatoid*** ***arthritis*** treated ***with*** ***tofacitinib***, an oral Janus kinase inhibitor. *Semin* ***Arthritis*** *Rheum*. 2016;46:261–271.

82. Choy E, Sattar N. Interpreting lipid levels in the context of high-grade inflammatory states ***with*** a focus on ***rheumatoid*** ***arthritis***: a challenge to conventional cardiovascular risk actions. *Ann Rheum Dis*. 2009;68:460–469.

83. Saiki O, Takao R, Naruse Y, et al. Infliximab but not methotrexate induces extra-high levels of VLDL-triglyceride in ***patients*** ***with*** ***rheumatoid*** ***arthritis***. *J Rheumatol*. 2007;34:1997–2004.

84. Kremer JM, Kivitz AJ, Simon-Campos JA, et al. Evaluation of the effect of ***tofacitinib*** on measured glomerular filtration rate in ***patients*** ***with*** active ***rheumatoid*** ***arthritis***: results from a randomised controlled trial. ***Arthritis*** *Res Ther*. 2015;17:95.

85. Isaacs J, Zuckerman A, Krishnaswami S, et al. Changes in serum creatinine in ***patients*** ***with*** active ***rheumatoid*** ***arthritis*** treated ***with*** ***tofacitinib***: results from clinical trials. ***Arthritis*** *Res Ther*. 2014;16:R158.

86. Cohen S, Curtis JR, Fleishmann R, et al. 18-Month worldwide post-marketing surveillance experience of ***tofacitinib***. ***Arthritis*** *Rheumatol*. 2014;66:S199.

87. Harnett J, Curtis J, Gruben D, et al. Early experience ***with*** ***tofacitinib***: treatment patterns in two US healthcare claims databases. *Ann Rheum Dis*. 2015;74:740.

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