Supplementary material for Tanaka Y. et al. Efficacy and safety of tofacitinib as monotherapy in Japanese patients with active rheumatoid arthritis: a 12-week, randomized, phase 2 study, Modern Rheumatology, 2015;25:514–21.

Supplementary Table 1. 12-week ACR20 response rates, calculated using LOCF and NRI (FAS).

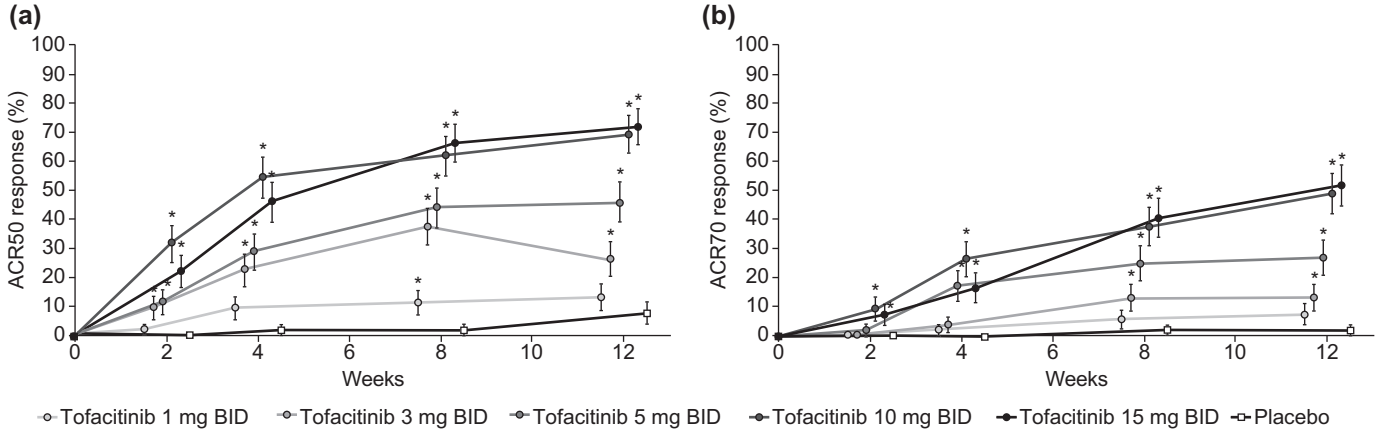
ACR20 Response Rate, n (%)	Tofacitinib 1 mg BID (n = 53)	3 mg BID (n = 53)	5 mg BID (n = 52)	10 mg BID (n = 53)	15 mg BID (n = 54)	Placebo BID (n = 52)
LOCF	20 (37.7)*	36 (67.9)†	38 (73.1)†	45 (84.9)†	49 (90.7)†	8 (15.4)
NRI	20 (37.7)*	36 (67.9)†	37 (71.2)†	43 (81.1)†	47 (87.0)†	8 (15.4)

*$p < 0.01$; †$p < 0.0001$ vs placebo.
ACR20, American College of Rheumatology 20% improvement criteria; BID, twice daily; FAS, full analysis set; LOCF, last observation carried forward; NRI, non-responder imputation.

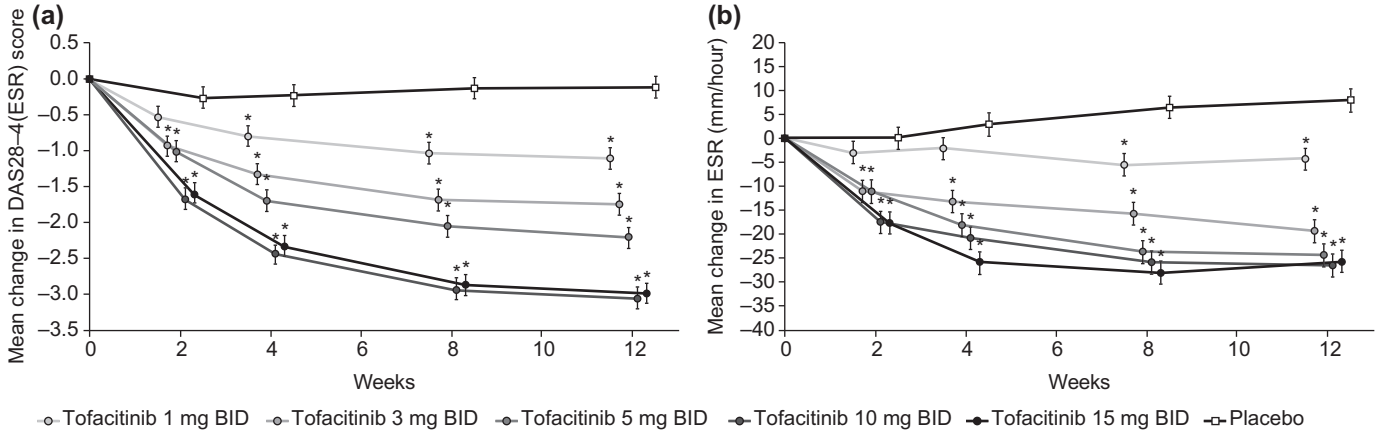
Supplementary Table 2. Proportion of patients achieving MCID in patient-reported outcomes.

Patient-Reported Outcome	Tofacitinib 1 mg BID (n = 51)	3 mg BID (n = 49)	5 mg BID (n = 50)	10 mg BID (n = 49)	15 mg BID (n = 52)	Placebo BID (n = 48)
HAQ-DI, n (%)§	24 (47.1)†	31 (63.3)†	37 (74.0)†	40 (81.6)†	38 (73.1)†	10 (20.8)
SF-36 physical component score, n (%)¶	29 (56.9)‡	33 (67.4)‡	41 (82.0)‡	42 (85.7)‡	43 (82.7)‡	12 (25.0)
SF-36 mental component score, n (%)¶	21 (41.2)	24 (49.0)*	33 (66.0)‡	24 (49.0)*	29 (55.8)*	13 (27.1)

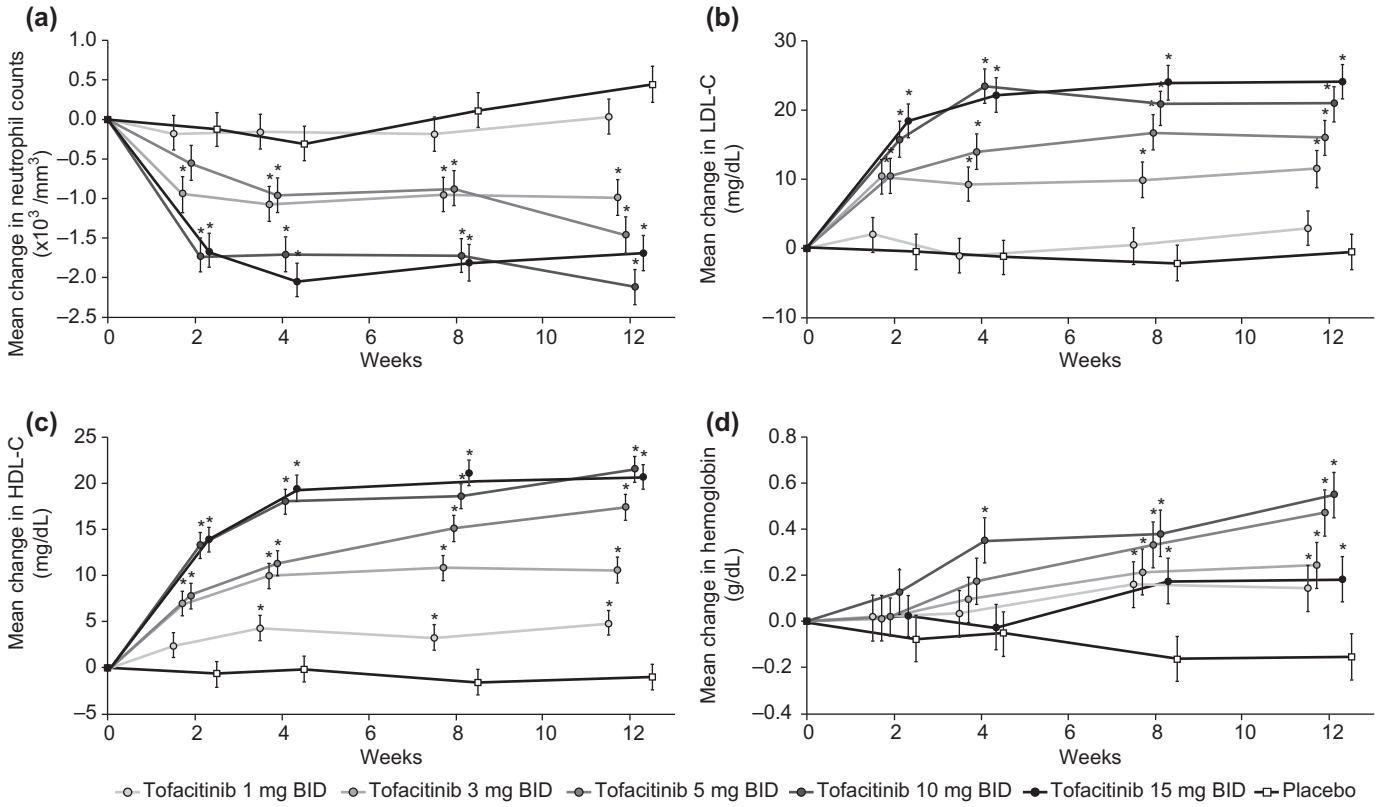
*$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$ vs placebo.
§MCID in HAQ-DI ≥ 0.22 units.
¶MCID in SF-36 component scores ≥ 2.5 points.
BID, twice daily; HAQ-DI, Health Assessment Questionnaire-Disability Index; MCID, minimum clinically important difference; SF-36, Medical Outcomes Study Short-Form (36-item) Health Survey.



Supplementary Figure 1. Response rates for patients receiving tofacitinib monotherapy or placebo over time. (a) ACR50 response (± SE), FAS, LOCF; (b), ACR70 response (± SE), FAS, LOCF. *$p < 0.05$ vs placebo; ACR50/70, American College of Rheumatology 50%/70% improvement criteria, respectively; BID, twice daily; FAS, full analysis set; LOCF, last observation carried forward; SE, standard error.



Supplementary Figure 2. Mean (± SE) changes from baseline to weeks 2–12 in (a) DAS28-4(ESR), FAS; (b) ESR, FAS. *$p < 0.01$ vs placebo; DAS28-4(ESR), 28-joint disease activity score using erythrocyte sedimentation rate; FAS, full analysis set; SE, standard error.



Supplementary Figure 3. Mean (± SE) changes from baseline in (a) absolute neutrophil counts; (b) LDL-C levels; (c) HDL-C levels; (d) hemoglobin levels, FAS. *$p < 0.05$ vs placebo; FAS, full analysis set; HDL-C, high-density lipoprotein cholesterol; LDL-C, lowdensity lipoprotein cholesterol; SE, standard error.

Supplementary Text

Details on 6 patients with treatment-related serious adverse events

Patient 1: rheumatoid vasculitis

This 58-year-old male was randomized to tofacitinib 3 mg twice daily (BID). He had a medical history including Raynaud's phenomenon, diabetes mellitus, and impaired blood flow. Two months prior to randomization, he underwent an incisional drainage due to an excessive toenail cut which had become infected. His lymphocyte count and absolute neutrophil count (ANC) on study day 1 were 1,860/mm^3 and 10,570/mm^3, respectively.

On study day 15, a left toe turned purple with a chilblain-like rash. The patient received sarpogrelate hydrochloride. On study day 28, a black color portion was observed on the left sole of the foot, and the patient received alprostadil and Berasus LA (beroprost sodium prolonged release). On study day 36, he had necrosis of the left foot, which biopsy revealed as a subcorneal abscess with vasculitis, and *Staphylococcus aureus* (+ 3) was detected. The patient was hospitalized, treated for necrosis, and permanently withdrawn from the study, and tofacitinib discontinued, on study day 38. His lymphocyte and ANC counts 6 days after study withdrawal were 1,090/mm^3 and 8,830/mm^3, respectively. Despite treatment for the necrosis, the necrotic site continued to expand, and vasculitis of the deep vein was identified 13 days after study withdrawal. The necrosis of the left lower limb was caused by cholesterol crystal emboli. Eighty-five days after study withdrawal he tested positive for cytomegalovirus, which was treated with ganciclovir and valganciclovir. From 126 days after study withdrawal the patient's necrosis began to improve, and was still improving at the last follow-up date (163 days after study withdrawal). In the opinion of the investigator, wash-out of the patient's pre-treatment methotrexate and salazosulfapyridine could have caused a temporary worsening of the rheumatoid arthritis, which might have led to the vasculitis. This could have been exacerbated by tofacitinib.

Patient 2: gastric ulcer perforation

This 52-year-old female was randomized to tofacitinib 3 mg BID. She was also receiving diclofenac sodium and prednisolone. On study day 1, her lymphocyte count and ANC were 1,240/mm^3 and 7,650/mm^3, respectively, her hematocrit level was 29.6% (reference range 33.4–44.9%), and her hemoglobin level was 9.0 g/dL (reference range 11.3–15.2 g/dL).

On study day 9, the patient's hematocrit level had decreased > 30% from baseline and met the protocol-defined exclusion criteria. The patient was therefore withdrawn from the study and tofacitinib discontinued. Six days after study withdrawal, her hematocrit level was 24.9% and her hemoglobin level was 7.4 g/dL. At 18 days post-study withdrawal, the patient complained of pyrexia and left abdominal pain. A computed tomography scan revealed a gastric ulcer perforation and peritonitis in the anterior wall of the lower gastric body. The patient had the following risk factors associated with a gastric ulcer: history of laparotomy for gastric ulcer hemorrhage 10 years previously, tobacco smoking for 17 years, and treatment with diclofenac sodium and prednisolone. Concomitant medication at the time of gastric ulcer perforation included methotrexate and rabeprazole. She had no history of *Helicobacter pylori* infection.

The investigator considered that there was a reasonable possibility that the gastric ulcer perforation was related to tofacitinib and the concomitant drugs diclofenac sodium and prednisolone. Of note, the patient's hemoglobin levels decreased from 10 g/dL

at screening to 9.0 g/dL on study day 1, suggesting that the gastric ulcer was already bleeding prior to initiation of tofacitinib. Owing to the patient's history of gastric ulcer, use of diclofenac, short study drug duration, and long interval between discontinuation of study drug and developing gastric ulcer perforation, the event gastric ulcer perforation was assessed as unlikely to be related to study medication.

Patient 3: elevated alanine transaminase, aspartate transaminase, and creatine kinase

This 63-year-old female was randomized to tofacitinib 3 mg BID. Her medical history included uterine leiomyoma, insomnia, hepatic cyst, renal cyst, and interstitial lung disease. At 51 days prior to study start, she received celecoxib 200 mg as needed for 3 days for an aggravated joint symptom, and developed a generalized rash and face edema in response to celecoxib (neither serious). Her creatine kinase (CK) level was increased and the patient received methylprednisolone 8 mg/day. The patient's alanine transaminase (ALT) and aspartate transaminase (AST) levels were also elevated, and appeared associated with the increased CK levels.

Ten days before tofacitinib initiation, the patient's condition had improved sufficiently for her to be enrolled in the study. On study day 1, the patient's lymphocyte count and ANC were 1,020/mm^3 and 27,080/mm^3, respectively. Her ALT and AST levels were 64 units/L (reference range 5–40 units/L) and 56 units/L (reference range 10–40 units/L), respectively. On study day 33, the patient's methylprednisolone dose was reduced to 4 mg; the following day she had elevated CK, AST, and ALT levels, and was hospitalized. The CK levels decreased slightly after switching to prednisolone.

On study day 47, the patient withdrew from the study due to lack of effect. The following day, her lymphocyte count and ANC were 700/mm^3 and 17,920/mm^3, respectively. Her ALT and AST levels were 77 units/L and 78 units/L, respectively. The patient was treated with methotrexate and folic acid. At 17 days after study withdrawal, the CK levels had increased, and methotrexate and folic acid treatments stopped. At 24 days post-study withdrawal, prednisolone was discontinued and high-dose steroid therapy initiated (betamethasone sodium phosphate and intravenous Rinderon [betamethasone 17α-valerate] 6 mg/day). A magnetic resonance imaging test performed the following day suggested myositis as the cause of elevated CK, ALT, and AST levels, which at that point were 3,866 units/L (reference range 45–163) for CK, 121 units/L for ALT, and 120 units/L for AST. A day later, the patient experienced an inflammatory reaction, increased CK, and muscle weakness.

Gradually the patient's condition improved, and the CK levels decreased. At 122 days after study withdrawal, ALT, AST, and CK were within the reference ranges.

The investigator and study sponsor concluded that a causal link between CK, ALT, and AST levels and tofacitinib could not be ruled out. The investigator recognized that celecoxib could also have been related to increased CK, ALT, and AST levels.

Patient 4: herpes zoster

This 60-year-old female was randomized to tofacitinib 5 mg BID. On study day 1, her lymphocyte count and ANC were 1,740/mm^3 and 4,180/mm^3, respectively.

On study day 33, the patient experienced painful blisters between her fourth and fifth toes of her right foot. On study day 38 she was hospitalized and diagnosed with herpes zoster. The patient was permanently withdrawn from the study and tofacitinib discontinued. Two days after study withdrawal, she developed a movement disorder in her right ankle which was considered a symptom of post-herpetic nerve paralysis; she received valaciclovir hydrochloride 1,000 mg and mecobalamin 500 μg 3 times daily for 6 days. Five days after study withdrawal, her lymphocyte and ANC counts were 1,470/mm^3 and 2,400/mm^3, respectively. The herpes zoster resolved 35 days after study withdrawal. The post-herpetic nerve paralysis was considered to have resolved 168 days after study withdrawal.

The investigator attributed the post-herpetic nerve paralysis to herpes zoster, and considered there was a reasonable possibility that both events were related to tofacitinib.

Patient 5: herpes zoster

This 64-year-old female was randomized to tofacitinib 10 mg BID. On study day 1, her lymphocyte count and ANC were 940/mm^3 and 7,190/mm^3, respectively.

On study day 42, the patient developed cystitis-like symptoms, and received levofloxacin hydrate 250 mg/day. On study day 46 she developed a pins and needles sensation in her groin, and on study day 50 developed a rash primarily occurring in the perineal region. On study day 51 the rash was widespread; the patient was hospitalized and diagnosed with herpes zoster. The patient was withdrawn from the study and tofacitinib discontinued on study day 51; her lymphocyte and ANC counts were 660/mm^3 and 4,240/mm^3, respectively. The patient received intravenous aciclovir with a maintenance medium (Fructlact). Nine days after study withdrawal she was discharged from hospital with only a slight rash. The patient was prescribed vidarabine 13 days after study withdrawal, and 49 days after study withdrawal was considered to have recovered from herpes zoster. The investigator considered the herpes zoster to be related to tofacitinib and not to concomitant therapy taken within 2 weeks of herpes zoster onset (which included methylprednisolone, sulindac, famotidine, rosuvastatin, and levofloxacin).

Patient 6: herpes zoster oticus, Ramsay Hunt syndrome

This 63-year-old female was randomized to tofacitinib 15 mg BID. On study day 1, her lymphocyte count and ANC were 2,090/mm^3 and 6,450/mm^3, respectively. She had a history of osteoporosis, low back pain, and a vertebral compression fracture.

On study day 75, the patient was diagnosed with a lumbar vertebral compression fracture, and received zaltoprofen 80 mg 3 times daily. On study day 85, the patient experienced a strange sensation on the left eyelid, lip weakness on the left side, and ear pain. She was diagnosed with Ramsay Hunt syndrome, a medically significant event caused by varicella virus infection, and was withdrawn from the study; tofacitinib was discontinued. Her lymphocyte count and ANC were 1,390/mm^3 and 6,170/mm^3, respectively. The patient was treated with stellate ganglion block and zaltoprofen 240 mg/day, troxipide 300 mg/day, amitriptyline hydrochloride 10 mg/day, adenosine triphosphate disodium 180 mg/day, and ophthalmic sodium hyaluronate without steroid therapy. She was still recovering at her last study visit (98 days from study withdrawal). As the Ramsay Hunt syndrome was due to a viral infection and developed after study start, a causal link with tofacitinib could not be ruled out.