Single- versus dual-infusion of B-cell-depleting antibody ocrelizumab in rheumatoid arthritis: results from the Phase III FEATURE trial

Aim: To test the hypothesis that a therapeutic dose of ocrelizumab (200 mg × 2), can be administered as a single-infusion (400 mg × 1) to achieve clinical efficacy and safety in patients with active rheumatoid arthritis. **Patients & methods:** Three hundred and fourteen patients were randomized to double-blind placebo, ocrelizumab single-infusion or dual-infusion. The primary end point is American College of Rheumatology (ACR)20 response at week 24 for single-infusion ocrelizumab versus placebo. **Results:** At 24 weeks, ACR20 responses for patients treated with single-infusion ocrelizumab were not statistically significantly superior to placebo (37.6% [95% CI: 28.8–46.4%] vs 28.1% [95% CI: 17.1–39.1%]; p = 0.2253). ACR20 for dual-infusion ocrelizumab was 52.7% (95% CI: 44.1–61.2%). Initial depletion of peripheral B cells appeared comparable after single and dual-infusions. However, subsequent B-cell repletion occurred earlier after single-infusion. Adverse events were comparable across groups. **Conclusion:** Ocrelizumab 200 mg ×2 was efficacious, consistent with two other pivotal Phase III trials. The same drug amount administered as single-infusion was not significantly more efficacious than placebo and revealed differences in pharmacokinetic and pharmacodynamic profiles.

KEYWORDS: anti-CD20 ■ B cells ■ ocrelizumab ■ pharmacokinetics ■ rheumatoid arthritis

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B-cell activation is an important component of the manifestation of disease in rheumatoid arthritis (RA) and depleting B cells is now an established therapeutic approach for treating patients with RA. Rituximab, a chimeric monoclonal antibody that selectively targets $CD20^+$ B cells, has demonstrated clinical efficacy, in combination with methotrexate (MTX), in patients with active RA [1–4].

Ocrelizumab is a humanized anti-CD20 monoclonal antibody [5]. *In vitro* studies indicated that it has enhanced antibody-dependent cell-mediated cytotoxicity and reduced complement-dependent cytotoxicity compared with rituximab [Roche, Unpublished Data]. The clinical significance of these findings was unclear, but it was hypothesized that the reduced complement-dependent cytotoxicity activity could improve clinical safety, particularly with regards to infusion tolerability.

A Phase I/II dose-ranging study (ACTION) of ocrelizumab in patients with active RA established preliminary safety and suggested best clinical responses with lowest immunogenicity at doses of 200 mg and higher, administered as two infusions 2 weeks apart [6]. Infusions were generally well tolerated in this study without administration of preocrelizumab intravenous (iv.) steroids. Nevertheless, in Phase III studies, premedication with iv. steroids was administered to minimize risk of infusion-related adverse events (AEs) and maximize patient tolerability. The ocrelizumab Phase III program evaluated a dose of 200 mg × 2 and a higher dose of 500 mg × 2 in various RA patient populations (~2600 patients).

The current study (FEATURE) was designed to test the hypothesis that an ocrelizumab dose of 200 mg × 2 could be administered as a single-infusion of 400 mg × 1 with similar safety and efficacy in RA. This would represent an improved dosing regimen with several advantages for patients and treating physicians. The ocrelizumab dose of 200 mg × 2 was studied in two large pivotal Phase III RA trials, in an MTX-inadequate responder population (STAGE) as well as a TNF-α inhibitor-inadequate responder population (SCRIPT), and demonstrated robust efficacy with regards to improvement of signs and symptoms of RA in both studies [7,8].

Patients & methods

Patients

Patients (≥18 years of age) had active disease, defined as a diagnosis of RA using the 1987 American College of Rheumatology (ACR) criteria. The main inclusion criteria were: swollen joint count ≥4 (66-joint count) and tender joint count ≥4 (68-joint count) at screening and baseline; C-reactive protein ≥0.6 mg/dl or erythrocyte sedimentation rate ≥28 mm/h; and positivity for

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rheumatoid factor and/or anticitrullinated peptide antibodies (detected using the anticyclic citrullinated peptide test). All patients had an inadequate clinical response to at least 12 weeks of MTX at a dose of 7.5–25 mg/week, with the last 4 weeks prior to baseline at a stable dose. Patients who had failed other RA treatments including biologics, due to inefficacy or intolerance, were also eligible to participate in the study. As per the study protocol, all disease-modifying antirheumatic drug (DMARDs) except MTX were withdrawn at least 4 weeks prior to baseline (8 weeks for infliximab, adalimumab or abatacept; 4 weeks for etanercept; and 12 weeks for leflunomide or 4 weeks after 11 days of standard cholestyramine or activated charcoal drug removal).

Key exclusion criteria included a history of rheumatic autoimmune disorders other than RA and significant systemic involvement secondary to RA (i.e., extra-articular manifestations of RA such as vasculitis, pulmonary fibrosis or Felty's syndrome). Patients with active tuberculosis were excluded. Patients were eligible after tuberculosis screening and prophylaxis, if required, according to local/national guidelines. Screening for hepatitis B (HepB) and hepatitis C was also conducted. Patients with active HepB or hepatitis C were excluded; those with a serological status of HepB surface antigen negative, HepB core antibody positive and HepB viral DNA negative were eligible for inclusion with regular monitoring of HepB viral DNA.

Study design

WA20496/FEATURE was a randomized, double-blind, parallel-group, Phase IIIb study conducted at 96 centers in 14 countries worldwide (59 centers in the USA) (Figure 1A). At baseline, patients were randomized 1:2:2 to placebo (two iv. infusions of placebo given on days 1 and 15), dual-infusion ocrelizumab (two iv. infusions of ocrelizumab 200 mg given on days 1 and 15) or single-infusion ocrelizumab (iv. infusion of ocrelizumab 400 mg on day 1 and placebo infusion on day 15). Patients and investigators were blinded to group assignment and dose. Before each infusion, patients received iv. methylprednisolone 100 mg. Acetaminophen (1 g) and an antihistamine (diphenhydramine HCl 50 mg or its equivalent) were recommended for additional premedication. At 24 weeks, patients in the placebo and dual-infusion ocrelizumab groups entered an exploratory 24-week period and were re-randomized to ocrelizumab 400 mg × 1 or ocrelizumab 200 mg × 2; single-infusion patients continued to receive single-infusion ocrelizumab. After 48 weeks, patients were eligible for open-label treatment with ocrelizumab 400 mg × 1. Patients who discontinued treatment for any reason were followed-up for a minimum of 48 weeks from the first infusion of their last course of treatment or until return of B-cell counts to their baseline level or to the lower limit of normal. This was considered safety follow-up for B-cell depletion. Any rescue therapy was allowed at any time for control of disease activity at the discretion of the investigator. Patients who received rescue therapy could remain in the study and were eligible for open-label treatment at 48 weeks, but were counted as nonresponders for statistical efficacy analyses after initiation of rescue therapy.

Approval from the local ethics committees was obtained before the study started. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and all patients provided written informed consent. This study is registered with ClinicalTrials.gov, identifier NCT00673920 [101].

Efficacy assessments

The primary end point compared the proportion of ACR20 responders [9] at week 24 in the single-infusion ocrelizumab group versus the placebo group. Planned secondary end points included the proportion of patients achieving ACR50 and ACR70 responders at week 24.

Pairwise comparison of efficacy between dual-infusion ocrelizumab and placebo was also conducted in secondary and exploratory analyses.

Pharmacokinetics/ pharmacodynamics

Blood samples for pharmacokinetic analysis were obtained at baseline and weeks 2 and 4, then every 4 weeks thereafter. Conventional fluorescence-activated cell sorting was used to assess B-cell (CD19-positive) counts.

Safety

Clinical AEs and serious AEs (SAEs) were recorded throughout the study.

Statistical analyses

A sample size of 300 patients was estimated to provide at least 80% power to detect a difference of 23% in the primary end point between single-infusion ocrelizumab and placebo using the Cochran–Mantel–Haenszel test, stratified by region (USA or rest of world) and with a two-sided significance level of 0.05.

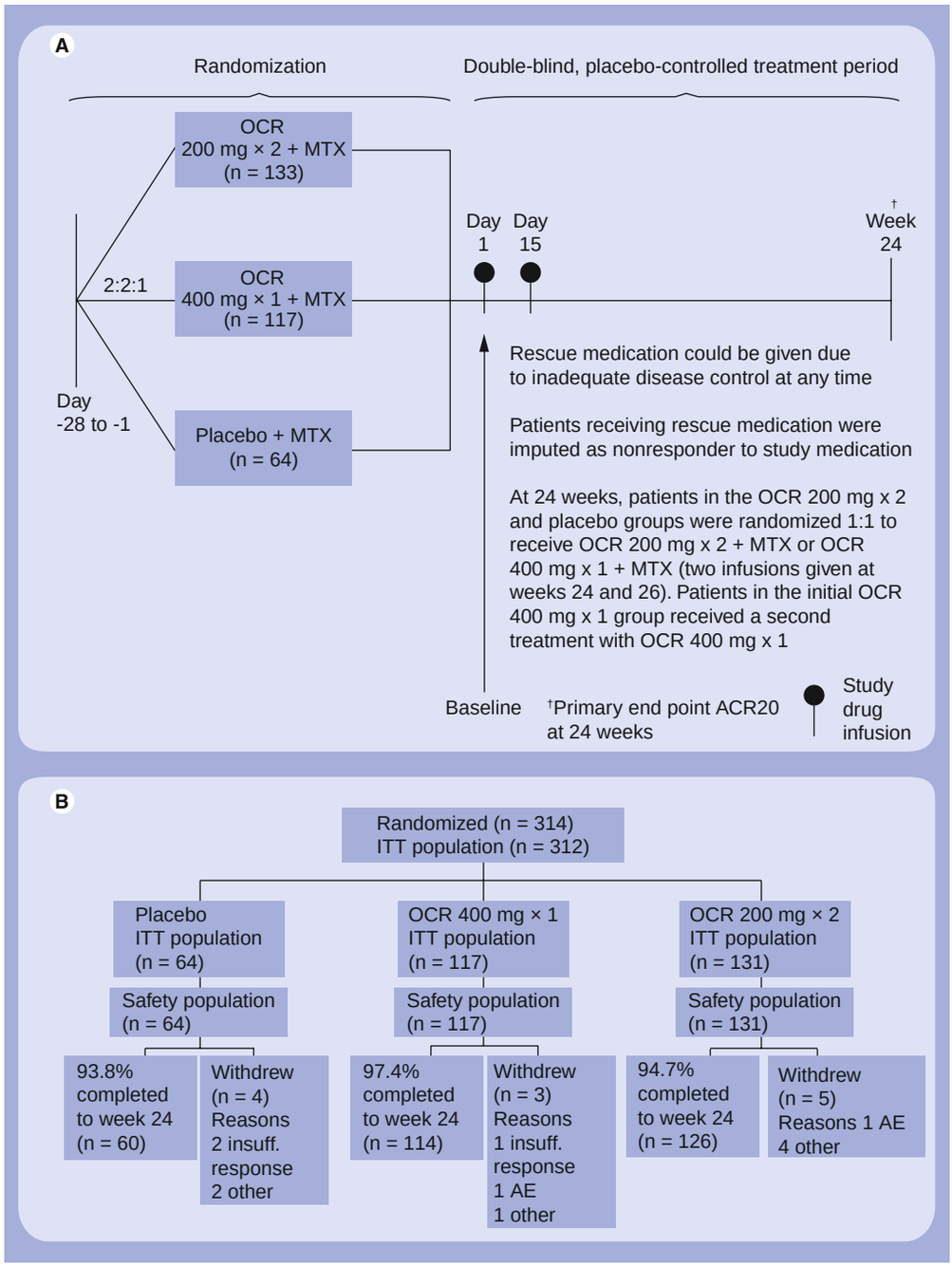

Figure 1. Ocrelizumab FEATURE trial. (A) Study design. **(B)** Patient disposition.
ACR: American College of Rheumatology; AE: Adverse event; insuff.: Insufficient; MTX: Methotrexate; OCR: Ocrelizumab.

In the analysis of the primary end point, missing data were imputed using the nonresponder method. Patients were considered nonresponders if they withdrew prematurely from the study, received rescue therapy or had insufficient data available. All efficacy analyses to 24 weeks were performed using the intention to treat population, defined as all patients who were randomized and received any part of an infusion of study drug prior to week 24. The safety population was defined as all patients (including those not randomized) who received any part of a study drug infusion drug prior to week 24 and had at least one safety assessment.

Results

Patient population

A total of 314 patients were randomized. The intention to treat and safety populations comprised 312 patients (placebo, n = 64;

single-infusion ocrelizumab, n = 117; dual-infusion ocrelizumab, n = 131). Two patients randomized to dual-infusion ocrelizumab did not receive any dose of ocrelizumab. Patient disposition is summarized in Figure 1B. Prior to week 24, 21 patients received rescue therapy (13, seven and one from the placebo, single-infusion ocrelizumab and dual-infusion ocrelizumab groups, respectively). Twelve patients withdrew from study treatment prior to week 24: two for safety reasons (n = 1 in both ocrelizumab groups), three because of insufficient therapeutic response (placebo, n = 2; single-infusion ocrelizumab, n = 1) and seven for other reasons (placebo, n = 2; single-infusion ocrelizumab, n = 1; dual-infusion ocrelizumab, n = 4).

The three treatment groups were generally well balanced in terms of baseline demographics and disease characteristics (Table 1). A total of 248 patients (79.5%) had previously been exposed to DMARDs other than MTX. A higher proportion of patients in the placebo group had received prior biologic DMARD therapy (placebo, 51.6%; single-infusion ocrelizumab, 37.6%; dual-infusion ocrelizumab, 38.9%), mostly TNF inhibitors.

Efficacy

The single-infusion cohort did not meet the primary end point. The proportion of ACR20 responders at week 24 in the single-infusion ocrelizumab group was not statistically significantly higher than the placebo group (37.6% [95% CI: 28.8–46.4%] vs 28.1% [95% CI: 17.1–39.1%]) (Figure 2); the weighted difference was 8.6% (95% CI: -5.3–22.4%; p = 0.2253). As the primary end point was not met, all secondary end points were analyzed for exploratory and descriptive purposes only.

The proportion of patients in the dual-infusion ocrelizumab group who achieved ACR20 response was 52.7% (95% CI: 44.1–61.2%). ACR50 and ACR70 response rates are shown in Figure 2.

Pharmacokinetics/ pharmacodynamics

The pharmacokinetic profile of ocrelizumab appeared generally linear, with comparable half-life ($T_{1/2}$) values for the two dosing regimens (Figure 3). For the first course of single-infusion ocrelizumab, mean (± standard deviation [SD])

Table 1. Baseline characteristics in the intent-to-treat population.

Characteristic	Placebo (n = 64)	Ocrelizumab 400 mg × 1 (n = 117)	Ocrelizumab 200 mg × 2 (n = 131)
Female, n (%)	56 (87.5)	93 (79.5)	105 (80.2)
Mean (SD) age, years	53.1 (11.4)	52.3 (11.1)	53.0 (11.2)
White race, n (%)	44 (68.8)	85 (72.6)	99 (75.6)
Recruited at US center	33 (51.6)	54 (46.2)	67 (51.1)
Serologic status, n (%)[†]			
– $RF^+/ACPA^+$	54 (84.4)	93 (80.2)	101 (77.1)
– $RF^-/ACPA^-$	0	0	1 (0.8)[‡]
– $RF^-/ACPA^+$	5 (7.8)	13 (11.2)	20 (15.3)
– $RF^+/ACPA^-$	5 (7.8)	10 (8.6)	9 (6.9)
Median (range) RA disease duration, years	7.2 (0.3–38.5)	7.1 (0.4–36.5)	6.5 (0.3–47.5)
Previous DMARDs, n (%)[§]	53 (82.8)	95 (81.2)	100 (76.3)
– Biologics	33 (51.6)	44 (37.6)	51 (38.9)
– TNF inhibitors	26 (40.6)	35 (29.9)	43 (32.8)
SJC (66 joints), mean (SD)	18.0 (11.8)	16.5 (11.3)	17.6 (11.8)
TJC (68 joints), mean (SD)	29.4 (16.8)	27.8 (16.9)	26.6 (15.3)
CRP (mg/dl), mean (SD)	2.6 (3.4)	1.8 (1.7)	1.9 (2.2)
ESR (mm/h), mean (SD)	49.5 (27.3)	46.7 (22.8)	47.4 (24.7)
DAS28-ESR, mean (SD)	6.8 (1.1)	6.4 (1.0)	6.5 (0.9)
Corticosteroid dose (mg/day), mean (SD)	6.7 (2.9)	7.5 (2.8)	7.2 (2.8)
Methotrexate dose (mg/week), mean (SD)	16.3 (4.9)	16.7 (8.7)	15.1 (4.7)

[†]Ocrelizumab 400 mg × 1, n = 116.
[‡]All but one patient in the ocrelizumab 200 mg × 2 group had confirmed seropositive disease. This patient was a protocol violator and was excluded from the per protocol population.
[§]Except methotrexate.
ACPA: Anticitrullinated protein antibody; CRP: C-reactive protein; DAS28-ESR: Disease Activity Score in 28 joints using erythrocyte sedimentation rate; DMARD: Disease-modifying antirheumatic drug; ESR: Erythrocyte sedimentation rate; RA: Rheumatoid arthritis; RF: Rheumatoid factor; SD: Standard deviation; SJC: Swollen joint count; TJC: Tender joint count.

$T_{1/2}$ was 16.51 ± 4.80 days compared with 17.41 ± 5.93 days for dual-infusion ocrelizumab. After the first infusions of the first course, the C_{max} for single-infusion ocrelizumab was nearly double that seen with dual-infusion ocrelizumab (mean [± SD] 133 ± 38.5 vs 73.1 ± 63.8 µg/ml). Following the second infusion of ocrelizumab 200 mg, C_{max} was similar to the value observed after the first infusion (mean [± SD] 71.7 ± 18.0 µg/ml).

A rapid reduction in peripheral CD19-positive B cells was observed in both ocrelizumab groups as early as the first evaluation time point, in other words, study week 2 (single-infusion: mean ± SD 5.6 ± 9.48; median [range] 3.0 [0–85]; dual-infusion: mean ± SD 4.2 ± 4.25; median [range] 3.0 [0–24] compared with placebo: mean ± SD 193.6 ± 135.2; median [range] 172 [26–875]).

However, at week 24, B-cell counts in the single-infusion group were higher than in the dual-infusion group (single-infusion: mean ± SD 30.8 ± 38.2; median [range] 15.0 [0–186]; dual-infusion: mean ± SD 22.3 ± 34.7; median [range] 11.0 [0–301]).

Safety

The 24-week safety data are summarized in Table 2. The incidence of AEs was similar across the treatment groups. The most common AEs were infections, with an incidence of 32.5, 39.7 and 37.5% in the single-infusion ocrelizumab, dual-infusion ocrelizumab and placebo groups, respectively. SAEs were reported in three patients (2.6%) who received single-infusion ocrelizumab, two patients (1.5%) who received dual-infusion ocrelizumab and five patients (7.8%) who received placebo.

Infusion-related reactions (IRRs) were the second most frequent AE and were reported at a higher incidence in both ocrelizumab groups compared with placebo (Table 2). All IRRs were mild or moderate in intensity. There were no serious IRRs, and no significant difference in IRRs between single- and dual-infusion groups. The incidence of IRRs was highest during the first infusion of ocrelizumab and decreased with the second infusion. Overall, 25 (21.4%), 28 (21.4%) and seven (10.9%) patients in the single-infusion ocrelizumab, dual-infusion ocrelizumab and placebo groups, respectively, reported IRRs. The corresponding incidences by infusion (first/second) were 21.4/7.1%, 19.1/7.9% and 10.9/3.2%, respectively. It should be noted that the second infusion administered to patients in the single-infusion ocrelizumab group contained placebo alone.

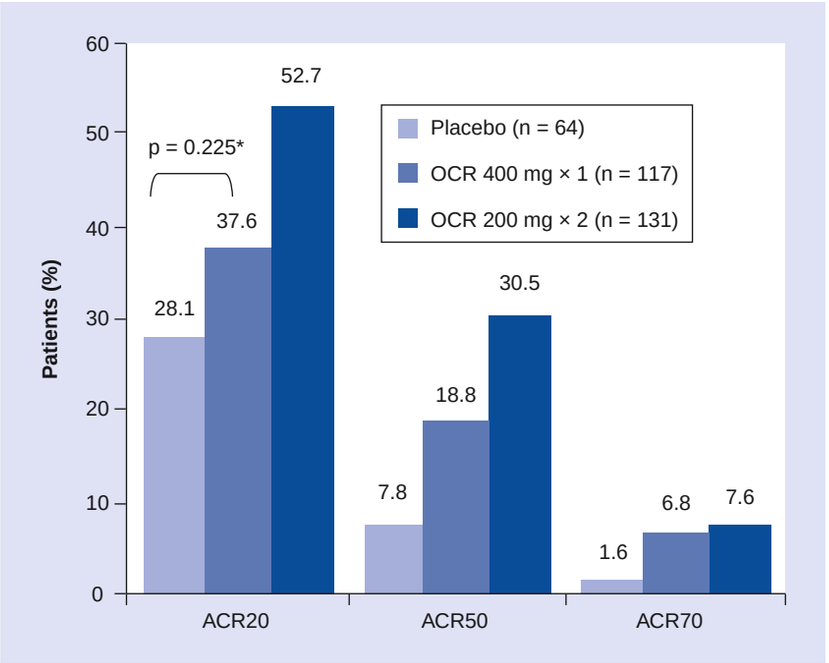

Figure 2. Proportion of patients achieving American College of Rheumatology 20/50/70 responses at week 24 in the intent-to-treat population.
p-values shown only for primary efficacy comparison of OCR 400 mg × 1 versus placebo.
*Cochran–Mantel–Haenszel test, stratified by region (US vs non-US).
ACR: American College of Rheumatology; OCR: Ocrelizumab.

Serious infections were reported with similar frequency in each treatment group, with three (2.6%), two (1.5%) and two (3.1%) patients recorded as having serious infections in the single-infusion ocrelizumab, dual-infusion ocrelizumab and placebo groups, respectively (Table 2). There was one opportunistic infection reported in the placebo group (a cutaneous *Mycobacterium abscessus* infection of the thigh in a patient in Thailand that resolved after appropriate antibiotic treatment) and none in the active treatment arms. There were no cases of progressive multifocal leukoencephalopathy.

No deaths occurred during the 24-week, placebo-controlled period. There was no imbalance with regards to malignancies between the treatment arms.

Discussion

The FEATURE trial was designed to optimize dosing of ocrelizumab in RA. The overall Phase III program included approximately 2600 patients across multiple patient populations. In all other ocrelizumab Phase III trials, dose levels of 200 mg × 2 and 500 mg × 2 were investigated to establish safety and efficacy. With the assumption that 200 mg × 2 would likely be an effective dose, FEATURE tested the

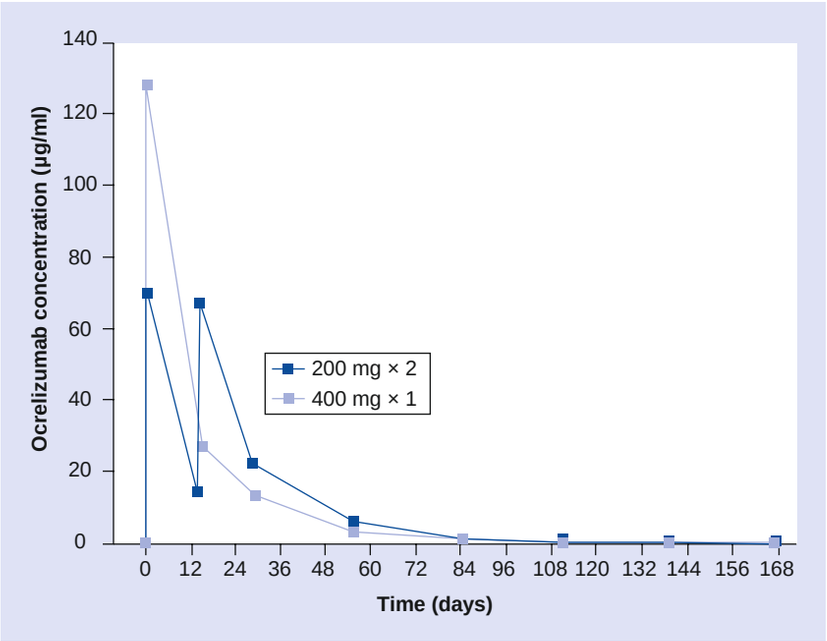

Figure 3. Pharmacokinetic profile over 24 weeks after one course of single-infusion (400 mg × 1) and dual-infusion (200 mg × 2) ocrelizumab.

hypothesis that this dose level could be administered as a single-infusion of 400 mg and yield comparable efficacy and safety results.

FEATURE failed to meet the primary efficacy end point of a statistically significant difference in ACR20 response rate at 24 weeks for a single 400-mg infusion of ocrelizumab compared with placebo. Exploratory analyses showed that ACR20 response rates in the dual-infusion arm compared with placebo was robust and generally consistent with the rates observed in the two pivotal Phase III ocrelizumab RA trials: STAGE (conducted in DMARD-inadequate responder patients) [8] and SCRIPT (conducted in TNF-inhibitor inadequate responders) [9]. No study conduct issues were identified to explain the failure of the single-infusion regimen to meet the primary end point. Baseline demographics and compliance with protocol-specified drug administration schedules (drug exposure) were well balanced across treatment arms. The efficacy difference between the two dose regimens was also observed in efficacy subgroup analyses across geographic regions.

Pharmacokinetic analyses demonstrated, as expected, that C_{max} after the first infusion of ocrelizumab was approximately twice as high with the 400-mg infusion compared with the 200-mg infusion. The second infusion of 200 mg at week 2 resulted in drug concentrations similar to levels observed after the first infusion of 200 mg. However, at that time point, overall drug concentration levels were higher in the dual-infusion 200 mg × 2 group than in the single-infusion 400 mg × 1 group and remained above threshold levels for a longer duration during the 24-week treatment period. In the single-infusion cohort, ocrelizumab mean drug concentrations fell below threshold levels sooner than in the dual-infusion cohort. This translated into faster repletion of CD19-positive B cells at week 24. Mean and median values in the dual-infusion group at week 24 were lower compared with the single-infusion group. It is noteworthy

Table 2. Summary of overall safety profile over 24 weeks.

Patients with at least one event, n (%)	Placebo (n = 64)	Ocrelizumab 400 mg × 1 (n = 117)	Ocrelizumab 200 mg × 1 (n = 131)
All AEs	40 (62.5)	75 (64.1)	87 (66.4)
All SAEs	5 (7.8)	3 (2.6)	2 (1.5)
All infections	24 (37.5)	38 (32.5)	52 (39.7)
Serious infections	2 (3.1)	3 (2.6)	2 (1.5)
– Bronchiectasis	0	1 (0.9)†	0
– Cellulitis	1 (1.6)	0	0
– Influenza-like illness	0	0	1 (0.8)†
– *Mycobacterium abscessus* infection	1 (1.6)†	0	0
– Pneumonia	0	1 (0.9)	0
– Prostate infection	0	1 (0.9)	0
– Urinary tract infection	0	0	1 (0.8)†
All IRRs	7 (10.9)	25 (21.4)	28 (21.4)
Serious IRRs	0	0	0
Deaths	0	0	0

†*Considered by the investigators to be related to study treatment.*
AE: Adverse event; IRR: Infusion-related reaction; SAE: Serious adverse event.

that the pharmacodynamic effect seen with ocrelizumab 200 mg × 2 in FEATURE is almost identical to the effects observed with the same dose in the Phase III SCRIPT and STAGE trials [8,9]. Furthermore, those trials showed that B-cell counts in the 500 mg × 2 dose groups were even lower than in the 200 mg × 2 groups. This suggests that a dose–response relationship with regards to B-cell repletion exists for 400 mg × 1, 200 mg × 2 and 500 mg × 2. Although the differences in the peripheral blood B-cell counts between the ocrelizumab regimens in FEATURE appear numerically small (mean values of 30.8 and 22.3 cells/µl), it is conceivable that these differences could translate into much greater differences in B-cell counts in relevant secondary lymphoid organs or synovial tissue and thereby impact disease activity.

No new safety concerns were identified with ocrelizumab therapy up to 24 weeks. The overall incidences of AEs and SAEs were similar among the three study groups. Furthermore, there were no clear differences in the incidences of infections, including serious infections, between the treatment groups. Infusions were generally well tolerated. The incidence of IRRs decreased between the first and second infusions and no serious IRRs were reported.

In conclusion, this study demonstrated a difference in clinical efficacy between ocrelizumab 400 mg given as a single-infusion and the same dose administered as 200 mg × 2 administered 2 weeks apart. The pharmacodynamic differences of B-cell depletion and repletion patterns translate into clinically meaningful efficacy differences in this trial. The results suggest that not only the dose level of ocrelizumab but also the dosing regimen impact clinical outcomes, in particular when therapeutic doses are close to the minimal efficacious dose level.

The overall evaluation of all four Phase III studies in RA led the sponsors to decide not to file an application for regulatory approval of ocrelizumab in RA. Ocrelizumab remains in development for multiple sclerosis and other indications are being considered.

Executive summary

Background

- Ocrelizumab is a humanized anti-CD20 antibody with enhanced antibody-dependent cell-mediated cytotoxicity and reduced complement-dependent cytotoxicity compared with the mouse–human chimeric anti-CD20 antibody rituximab.
- FEATURE was a Phase IIIb, randomized, double-blind clinical trial designed to test the hypothesis that an ocrelizumab dose of 200 mg × 2 can be given as single-infusion of 400 mg × one to achieve efficacy and safety in patients with rheumatoid arthritis (RA).
- Ocrelizumab 200 mg × two was efficacious in two large Phase III trials in RA.

Patients & methods

- Three hundred and fourteen RA patients on background methotrexate were randomized 1:2:2 to placebo, dual-infusion ocrelizumab or single-infusion ocrelizumab.
- The primary end point was American College of Rheumatology (ACR)20 response at week 24 for single-infusion ocrelizumab versus placebo.

Results & discussion

- Single-infusion ocrelizumab failed to meet the primary end point. ACR20 response at week 24 in the single-infusion ocrelizumab group was not statistically significantly better than placebo (37.6% [95% CI: 28.8–46.4%] vs 28.1% [95% CI: 17.1–39.1%]).
- In an exploratory analysis, ACR20 in the dual-infusion ocrelizumab group was 52.7% (95% CI: 44.1–61.2%), consistent with two other Phase III ocrelizumab trials.
- Drug half-life values were comparable between the two dosing regimens. The C_{max} for single-infusion ocrelizumab (400 mg) was approximately double that for dual-infusion ocrelizumab (200 mg). The second infusion of ocrelizumab 200 mg resulted in a C_{max} value similar to that observed after the first infusion.
- A rapid reduction in peripheral CD19-positive B cells to essentially undetectable levels was observed in almost all patients in both ocrelizumab groups as early as week 2. However, at week 24, mean and median B-cell counts in the single-infusion group were higher than in the dual-infusion group, suggesting earlier return of B cells with the single-infusion arm.
- The incidences of adverse events (AEs) and serious AEs were generally similar in the three treatment groups. The most common AEs were infections and infusion-related reactions. All infusion-related reactions were mild or moderate in intensity. Serious infections were similar across groups.

Conclusion

- The results suggest that not only the dose level of ocrelizumab but also the dosing regimen impact clinical outcomes, in particular when therapeutic doses are close to the minimal efficacious dose level.
- Pharmacokinetic (drug concentration levels) and pharmacodynamic differences (B-cell depletion and repletion patterns) between the two dosing regimens translated into clinically meaningful efficacy differences.
- The data suggest that for B-cell-depleting therapies to be effective, drug concentrations above threshold levels for longer duration are more important than initial C_{max}.

Financial & competing interests disclosure

F Hoffmann-La Roche Ltd, Genentech Inc. and Biogen Idec sponsored this clinical trial. JE Huffstutter has received consulting fees, speaker fees and honoraria from Genentech, Centocor, Takeda, Eli-Lilly and Amgen. J Schechtman has received consulting fees, speaker fees and honoraria from Abbott, Amgen, Novartis, Forest Pharmaceuticals and Warner Chilcot. D Moawad is an employee of Genentech. AV Kapp is an employee of Genentech, and owns stock or stock options in Roche. R Sudlow is an employee of, and owns stock or stock options in Roche. W Dummer is an employee of Genentech, and owns stock or stock options in Roche. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing assistance for this manuscript was provided by Neil Anderson, PhD and funded by Genentech, Inc. The authors were responsible for critical revisions of the manuscript and for important intellectual content.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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▪ of interest
▪▪ of considerable interest

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▪▪ **Details the 6-month efficacy and safety outcomes of the first Phase III randomized controlled trial with rituximab in patients with rheumatoid arthritis (RA) and an inadequate response to TNF inhibitors. Rituximab in combination with methotrexate (MTX) demonstrated significant clinical benefit over MTX alone, with a well-tolerated safety profile.**

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▪▪ **Details the efficacy outcomes of a Phase IIb randomized controlled trial with a single course of rituximab in patients with RA and an inadequate response to MTX. Rituximab alone, or in combination with MTX or cyclophosphamide, demonstrated significant clinical benefit over MTX alone at 24 and 48 weeks.**

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▪▪ **Details the efficacy outcomes of a Phase IIb randomized controlled dose-ranging trial evaluating two doses of rituximab with or without two different glucocorticoid premedication regimens in patients with RA and an inadequate response to disease-modifying antirheumatic drugs, including biologic agents. Both rituximab doses demonstrated significant clinical benefit over MTX alone. Glucocorticoids had no impact on achievement of an American College of Rheumatology (ACR)20 response. Intravenous glucocorticoids improved tolerability during the first rituximab infusion.**

4 Tak PP, Rigby WF, Rubbert-Roth A *et al.* Inhibition of joint damage and improved clinical outcomes with rituximab plus methotrexate in early active rheumatoid arthritis: the IMAGE trial. *Ann. Rheum. Dis.* 70(1), 39–46 (2011).

▪▪ **Details the outcomes of a Phase III randomized controlled trial evaluating efficacy of two doses of rituximab in the prevention of joint damage and its safety in combination with MTX in patients initiating MTX. Treatment with rituximab (1000 mg × 2) and MTX was associated with a reduction in joint damage progression and an improvement in clinical outcomes compared with MTX alone. Rituximab 500 mg × 2 and MTX improved clinical outcomes but did not significantly reduce joint damage progression.**

5 Kausar F, Mustafa K, Sweis G *et al.* Ocrelizumab: a step forward in the evolution of B-cell therapy. *Expert Opin. Biol. Ther.* 9(7), 889–895 (2009).

▪ **Describes current understanding of B-cell therapy, including the role of rituximab in the treatment of RA and potential future use of ocrelizumab.**

6 Genovese MC, Kaine JL, Lowenstein MB *et al.* Ocrelizumab, a humanized anti-CD20 monoclonal antibody, in the treatment of patients with rheumatoid arthritis: a Phase I/II randomized, blinded, placebo-controlled, dose-ranging study. *Arthritis Rheum.* 58(9), 2652–2661 (2008).

▪ **Details the safety and pharmacokinetics/pharmacodynamics of data from the first-in-human, Phase I/II dose-ranging trial with ocrelizumab in patients with RA and an inadequate response to at least MTX. Ocrelizumab in combination with MTX was well tolerated, with no serious adverse events reported. Doses of 200 mg (two infusions) and higher led to better clinical responses than lower doses.**

7 Rigby W, Tony H-P, Oelke K *et al.* Safety and efficacy of ocrelizumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: the Phase III STAGE trial. *Arthritis Rheum.* doi:10.1002/art.33317 (2011) (Epub ahead of print).

8 Tak PP, Mease PJ, Genovese MC *et al.* Safety and efficacy of ocrelizumab in patients with rheumatoid arthritis with an inadequate response to at least one TNF inhibitor: the Phase III SCRIPT trial. *Arthritis Rheum.* (2011) (In Press).

9 Felson DT, Anderson JJ, Boers M *et al.* American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum.* 38(6), 727–735 (1995).

■ Website

101 A study to evaluate ocrelizumab compared with placebo in patients with rheumatoid arthritis who have an inadequate response to methotrexate therapy (FEATURE). www.clinicaltrials.gov/ct2/show/NCT00673920?term=NCT00673920&rank=1