

Original article

Safety and tolerability of subcutaneous sarilumab and intravenous tocilizumab in patients with rheumatoid arthritis

Paul Emery¹, Juan Rondon², Janie Parrino³, Yong Lin⁴, Claudia Pena-Rossi⁴, Hubert van Hoogstraten⁴, Neil M. H. Graham³, Nancy Liu⁴, Anne Paccaly³, Richard Wu^{3,*} and Alberto Spindler⁵

Abstract

Objectives: Safety and efficacy of mAbs blocking the IL-6 receptor have been established in RA. This is the first analysis examining safety and tolerability of sarilumab and tocilizumab administered as single or multiple doses in patients with RA within the same study.

Methods: In ASCERTAIN, patients were randomized 1: 1: 2 to 24 weeks' double-blind sarilumab 150 or 200 mg every 2 weeks s.c. or tocilizumab 4 mg/kg every 4 weeks i.v., increased to 8 mg/kg if clinically indicated. In Study 1309, patients were randomized 1: 1: 1 to single-dose open-label sarilumab 150 or 200 mg s.c. or tocilizumab 4 or 8 mg/kg i.v.

Results: In ASCERTAIN, incidence of treatment-emergent adverse events was similar between sarilumab and tocilizumab. The most common treatment-emergent adverse events were the following: sarilumab: neutropenia [6 patients (12.2%) in the 150 mg group and 8 (15.7%) in the 200 mg group], nasopharyngitis [6 (12.2%) and 3 (5.9%)], and injection-site erythema [4 (8.2%) and 4 (7.8%)]; tocilizumab: accidental overdose [9 (8.8%)], upper respiratory tract infection [7 (6.9%)] and nausea [7 (6.9%)]. Laboratory changes in both studies included decreased neutrophils and platelets and increased transaminases and lipids. In Study 1309, incidence of absolute neutrophil count <1.0 giga/l was similar between sarilumab and tocilizumab, and occurred more frequently in the higher dose groups. No association between decrease in absolute neutrophil count and increased incidence of infection was observed in either study.

Conclusion: No clinically meaningful differences in treatment-emergent adverse events were observed between sarilumab and tocilizumab. Laboratory changes with sarilumab were within the same range as those with tocilizumab.

Trial registration numbers: ASCERTAIN (NCT01768572); Study 1309 (NCT02097524).

Key words: RA, sarilumab, tocilizumab, subcutaneous, intravenous

Rheumatology key messages

- There were no clinically meaningful differences in safety between sarilumab and tocilizumab.
- Laboratory changes observed with sarilumab were within the same range as those observed with tocilizumab.
- Decreases in absolute neutrophil count were not associated with increased infection risk.

¹Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals Trust, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK, ²Arthritis and Rheumatic Diseases of South Florida, Pembroke Pines, FL, USA, ³Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA, ⁴Sanofi Genzyme, Bridgewater, NJ, USA and ⁵Rheumatology, Universidad Nacional de Tucumán, Tucumán, Argentina

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*Former employee at Regeneron.

Correspondence to: Paul Emery, 2nd Floor, Chapel Allerton Hospital, Chapeletown Road, Leeds, LS7 4SA, UK. E-mail: p.emery@leeds.ac.uk

Introduction

The introduction of biologic DMARDs that target inflammatory cytokines, such as TNF or IL-6, has greatly expanded therapeutic options for the treatment of RA and improved treatment outcomes for these patients [1–3]. One of the key cytokines involved in mediating the underlying disease pathophysiology and clinical manifestations of RA is IL-6. The role of IL-6 in the pathophysiology of RA is not completely understood; however, pleiotropic effects of the cytokine have been correlated with disease activity and joint destruction [2]. Furthermore, IL-6 may mediate induction of acute-phase reactants and play a role in activating autoimmune response [1, 2]. Consistent with these observations, blockade of IL-6 signalling mitigates the underlying disease pathophysiology and clinical manifestations of RA [3]. Subsequently, multiple biologics targeting the IL-6 signalling pathway have been developed for the treatment of RA [4–8].

Sarilumab and tocilizumab are monoclonal antibodies directed against the IL-6 receptor (IL-6R). Sarilumab is a human IgG1 monoclonal antibody that binds specifically to both soluble and membrane-bound IL-6R, and it has been shown to inhibit IL-6-mediated signalling through these receptors [8]. Tocilizumab is a recombinant humanized monoclonal antibody also directed against the IL-6R [6]. The efficacy of sarilumab and tocilizumab has previously been demonstrated in patients with moderate-to-severe RA [9, 10]. ASCERTAIN and Study 1309 are the first studies in which sarilumab and tocilizumab were evaluated within the same study.

The Phase 3 ASCERTAIN study was designed to assess the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of sarilumab administered s.c. and tocilizumab administered i.v. in a population of patients who had an inadequate response to a prior TNF inhibitor and were receiving conventional synthetic DMARD (csDMARD) background therapy. The Phase 1b Study 1309 was designed to assess the PK and PD, as well as the safety and tolerability, of a single dose of sarilumab s.c. or tocilizumab i.v. in patients with RA who were receiving background MTX. The safety and tolerability assessments of the single-dose study complement the data from the multiple-dose ASCERTAIN study, and together allow for a better understanding of the overall safety profiles of the anti-IL-6R monoclonal antibodies sarilumab and tocilizumab. These studies were designed to report multiple- and single-dose safety and tolerability of sarilumab administered s.c. and of tocilizumab administered i.v. in adults with RA. No inferential statistics were planned.

Methods

Study design

ASCERTAIN (NCT01768572) was an international, multicentre, 24-week, randomized, double-blind, double-dummy,

parallel-group, three-arm study assessing the safety and tolerability of sarilumab and tocilizumab in patients with RA and inadequate response to or intolerance of TNF inhibitor (TNF-IR) receiving background csDMARDs. The primary objective of ASCERTAIN was to assess the safety and tolerability of sarilumab and tocilizumab in TNF-IR patients with RA. Patients were randomized 1: 1: 2 to sarilumab 150 or 200 mg every 2 weeks (q2w) s.c., or tocilizumab 4 mg/kg every 4 weeks (q4w) i.v., which could be increased to 8 mg/kg if clinically indicated, consistent with US prescribing information at the time of the study (October 2012) [6]. Patients were also allowed to decrease the dose of tocilizumab from 8 to 4 mg/kg during the course of the study at the discretion of the investigator. Dose adjustments were not allowed for sarilumab. Safety assessments included incidences of treatment-emergent adverse events (TEAEs), adverse events (AEs) of special interest, serious AEs, and potentially clinically significant laboratory abnormalities. During the study, patients who experienced AEs and prespecified laboratory abnormalities [e.g. decreased absolute neutrophil count (ANC), decreased platelet count, elevated alanine aminotransferase (ALT)] could temporarily or permanently discontinue the study drug in accordance with protocol requirements. Laboratory assessments were made at predetermined time points throughout the study (e.g. complete blood count every 2 weeks).

Study 1309 was a multicentre, 6-week, open-label, parallel-group, single-dose safety, PK and PD study of sarilumab and tocilizumab in patients with RA receiving a stable background of MTX. Patients were randomized 1: 1: 1 to sarilumab 150 mg s.c., sarilumab 200 mg s.c., tocilizumab 4 mg/kg i.v. or tocilizumab 8 mg/kg i.v. The primary objective of the study was to describe the PD of ANC, CRP, IL-6 and soluble IL-6R after a single dose of sarilumab s.c. or tocilizumab i.v. in patients with RA receiving a stable dose of MTX. The PK, safety and tolerability of a single dose of active treatment were secondary objectives. Changes in ANC were considered as both a safety parameter and a PD marker as they provide an indication of immediate effects related to circulating drug concentrations. Detailed analyses of all PD markers, PK parameters and the PK/PD relationship will be discussed in a separate article. Laboratory and safety assessments were performed predose and 1, 4 and 8 h after study drug administration on day 1; daily through day 7; every 2 days through day 15; and on days 19, 22, 29 and 43.

Neither ASCERTAIN nor Study 1309 included an s.c. administration arm for tocilizumab as tocilizumab had not been approved for s.c. administration when the studies were designed.

ASCERTAIN and Study 1309 were conducted in accordance with the principles laid down in the Declaration of Helsinki and the International Conference on Harmonisation guidelines for Good Clinical Practice. All protocols and amendments were submitted to independent ethics committees and/or institutional review boards for review and written approval

(see Acknowledgements for details). Informed consent was obtained from all patients before the conduct of any study-related procedures.

Patient population

Eligible patients in both studies were ≥18 years of age with an RA diagnosis for ≥3 months as determined by the 2010 revised ACR criteria [11] as well as functional class I-III as categorized by the 1991 revised ACR criteria [12]. All patients had continuous treatment with one or a combination of csDMARDs (ASCERTAIN) or with MTX 10–25 mg/week (Study 1309) for ≥12 consecutive weeks before screening and were on a stable dose for ≥6 (ASCERTAIN) or ≥8 consecutive weeks (Study 1309). Key exclusion criteria included a history of severe systemic RA (e.g. vasculitis, pulmonary fibrosis); juvenile idiopathic arthritis or onset of arthritis before age 16; and past or current autoimmune, inflammatory systemic or localized joint disease other than RA (Supplementary Table S1, available at *Rheumatology* online).

Statistical analysis

There were no formal hypotheses being tested in these studies and therefore no formal sample-size power calculations. The sample size for these safety studies was based on practical considerations and clinical judgement. In both studies, all randomized patients who received any study drug were included in the analysis and analysed according to the treatment received. Data were analysed using descriptive statistics, and no formal statistical comparisons were performed between groups.

Results

Patient demographic and baseline characteristics

Patients enrolled in ASCERTAIN and Study 1309 were predominantly female (>80% for both studies), with a mean age of 52 and 55 years, respectively (Table 1). ASCERTAIN included patients from the USA, South America, Western Europe, Eastern Europe and Russia (Supplementary Table S2, available at *Rheumatology* online). All patients in Study 1309 were from the USA. Baseline disease characteristics were generally well balanced among treatment groups in ASCERTAIN; while imbalances in disease characteristics were noted in Study 1309, these were not expected to affect end point analyses in this single-dose study. The most common recorded medical history terms were hypertension (32.2%), cholecystectomy (10.9%), hypothyroidism (10.4%) and tonsillectomy (10.4%) in ASCERTAIN, and postmenopause (49.5%), hypertension (47.5%) and gastrooesophageal reflux disease (24.8%) in Study 1309.

Patient disposition

In ASCERTAIN, 202 patients were randomized (tocilizumab 4/8 mg/kg q4w i.v., n=102; sarilumab 150 mg q2w s.c., n=49; sarilumab 200 mg q2w s.c., n=51). While dose adjustments were not allowed for sarilumab, 62 of 102 patients (60.8%) randomized to tocilizumab

TABLE 1 Demographics and baseline characteristics in the multiple-dose, 24-week ASCERTAIN study and single-dose, 6-week Study 1309

Characteristic	ASCERTAIN			Study 1309			
	Tocilizumab q4w i.v. + csDMARDs (n = 102) ^a	Sarilumab 150 mg q2w s.c. + csDMARDs (n = 49)	Sarilumab 200 mg q2w s.c. + csDMARDs (n = 51)	Tocilizumab 4 mg/kg i.v. + MTX (n = 25)	Tocilizumab 8 mg/kg i.v. + MTX (n = 24)	Sarilumab 150 mg s.c. + MTX (n = 26)	Sarilumab 200 mg s.c. + MTX (n = 26)
Age, mean (s.d.), years	50.4 (13.0)	54.8 (12.1)	51.7 (13.1)	52 (14.0)	53 (11.4)	58 (11.1)	58 (9.2)
Female, n (%)	82 (80.4)	41 (83.7)	39 (76.5)	22 (88.0)	23 (95.8)	20 (76.9)	22 (84.6)
Race, white, n (%)	94 (92.2)	47 (95.9)	46 (90.2)	21 (84.0)	20 (83.3)	22 (84.6)	21 (80.8)
Weight, mean (s.d.), kg	73.2 (15.4)	72.6 (17.6)	77.2 (20.6)	82.3 (18.8)	83.4 (18.2)	82.6 (18.0)	83.2 (16.9)
BMI, mean (s.d.), kg/m ²	27.3 (5.2)	27.3 (5.7)	28.1 (6.6)	31.6 (6.1)	30.8 (6.6)	31.6 (6.8)	31.1 (6.9)
Duration of RA, mean (s.d.), years	10.8 (8.9)	13.6 (8.2)	10.5 (7.6)	7.2 (8.7)	12.8 (11.0)	11.7 (14.0)	10.7 (11.8)
Prior biologic use, n (%)	102 (100)	49 (100)	51 (100)	2 (8.0)	7 (29.2)	4 (15.4)	3 (11.5)
Rheumatoid factor positive, n (%) ^b	79 (78.2)	39 (83.0)	29 (58.0)	11 (44.0)	14 (58.3)	10 (38.5)	20 (76.9)
ACCPA positive, n (%) ^b	82 (84.5)	41 (87.2)	36 (70.6)	10 (40.0)	11 (45.8)	14 (53.8)	18 (69.2)
CRP, mean (s.d.)	24.9 (30.4)	23.1 (32.1)	23.8 (29.8)	7.1 (7.7)	12.4 (14.1)	13.1 (18.7)	8.9 (8.5)
Tender joint count (0–68), mean (s.d.)	23.5 (12.2)	23.9 (13.0)	24.7 (12.8)	Not assessed	Not assessed	Not assessed	Not assessed
Swollen joint count (0–66), mean (s.d.)	15.2 (7.6)	16.0 (8.9)	16.0 (8.1)	Not assessed	Not assessed	Not assessed	Not assessed
HAQ-DI, mean (s.d.)	1.78 (0.63)	1.63 (0.66)	1.71 (0.60)	Not assessed	Not assessed	Not assessed	Not assessed
DAS28-CRP, mean (s.d.)	5.91 (1.01)	5.85 (0.92)	5.88 (0.97)	Not assessed	Not assessed	Not assessed	Not assessed

^aTocilizumab q4w i.v. starting at 4 mg/kg could be increased to 8 mg/kg based on clinical response as assessed by the investigator. ^bDenominator for percentage is number with assessment. ACCPA: anti-cyclic citrullinated peptide autoantibody; csDMARD: conventional synthetic DMARD; HAQ-DI: HAQ-Disability Index; q2w: every 2 weeks; q4w: every 4 weeks.

TABLE 2 Overview of treatment-emergent AEs in the multiple-dose, 24-week ASCERTAIN study and single-dose, 6-week Study 1309

AE	ASCERTAIN			Study 1309			
	Tocilizumab 4 mg/kg i.v. + csDMARDs (n = 102) ^a	Sarilumab 150 mg q2w s.c. + csDMARDs (n = 49)	Sarilumab 200 mg q2w s.c. + csDMARDs (n = 51)	Tocilizumab 4 mg/kg i.v. + MTX (n = 25)	Tocilizumab 8 mg/kg i.v. + MTX (n = 24)	Sarilumab 150 mg s.c. + MTX (n = 26)	Sarilumab 200 mg s.c. + MTX (n = 26)
AE	68 (66.7)	33 (67.3)	36 (70.6)	8 (32.0)	12 (50.0)	10 (38.5)	12 (46.2)
SAE	7 (6.9)	1 (2.0)	3 (5.9)	0	1 (4.2)	0	0
Serious infection	2 (2.0)	0	1 (2.0)	0	0	0	0
AE leading to death	1 (1.0)	0	0	0	0	0	0
AE leading to treatment discontinuation	4 (3.9)	6 (12.2)	8 (15.7)	0	0	0	0

Values are *n* (%). ^aTocilizumab 4 mg/kg i.v. starting at 4 mg/kg could be increased to 8 mg/kg based on clinical response as assessed by the investigator. AE: adverse event; csDMARD: conventional synthetic DMARD; q2w: every 2 weeks; q4w: every 4 weeks; SAE: serious AE.

4 mg/kg q4w in ASCERTAIN increased their dose from 4 to 8 mg/kg q4w at least once during the treatment period (Supplementary Fig. S1, available at *Rheumatology* online); 42 patients (41.2%) increased dose from 4 to 8 mg/kg q4w at week 4. Of the 62 patients who increased their tocilizumab dose to 8 mg/kg q4w, 39 patients who increased dose at week 4 remained at 8 mg/kg q4w for the remainder of the study (identified as the tocilizumab 4/8 mg/kg subset). The other 23 patients were up-titrated to the 8 mg/kg q4w dose at another time (*n* = 19) and/or did not remain at the 8 mg/kg q4w dose for the duration of the study as they were down-titrated to tocilizumab 4 mg/kg q4w primarily because of adverse safety findings (*n* = 4). In Study 1309, 101 patients were randomized and treated with single doses of tocilizumab 4 mg/kg i.v. (*n* = 25), tocilizumab 8 mg/kg i.v. (*n* = 24), sarilumab 150 mg s.c. (*n* = 26) or sarilumab 200 mg s.c. (*n* = 26). In both studies, all patients received concomitant csDMARDs (Supplementary Table S3, available at *Rheumatology* online).

Safety

Adverse events

Within each study, the incidence of TEAEs was similar between the sarilumab and tocilizumab groups (Table 2). There were few serious AEs in either study, with no discernible patterns. In ASCERTAIN, there were two serious infections in the tocilizumab group and one in the sarilumab 200 mg q2w group; no serious infections were reported in Study 1309. No opportunistic infections were reported in either study. In ASCERTAIN, the most frequently reported TEAEs were neutropenia, injection-site erythema and nasopharyngitis in the sarilumab groups and accidental overdose, upper respiratory tract infection and nausea in the tocilizumab group (Table 3).

In ASCERTAIN, a numerically higher incidence of TEAEs leading to treatment discontinuation was observed with sarilumab [150 mg q2w, *n* = 6 (12.2%); 200 mg q2w, *n* = 8 (15.7%)] than with tocilizumab [*n* = 4 (3.9%)]. Five patients who received sarilumab discontinued because

of laboratory abnormalities (neutropenia, leucopaenia and increased transaminases), which met protocol-defined criteria for discontinuation; none of these laboratory changes were associated with clinical manifestations. Three of these five patients had resumed their s.c. sarilumab injections but were discontinued because their i.v. infusion (placebo for tocilizumab) could not be resumed within the protocol-specified window. No discontinuations due to laboratory abnormalities were reported in the tocilizumab group. Two patients in each of the sarilumab groups and one patient in the tocilizumab group discontinued because of infections. Two patients who received sarilumab 200 mg q2w discontinued because of injection-site reactions and one patient who received sarilumab 200 mg q2w discontinued because of an infusion-related reaction while receiving i.v. placebo. No clinical patterns were observed for the remaining events that led to discontinuation of sarilumab. Two patients discontinued tocilizumab while receiving 8 mg/kg q4w because of worsening RA (*n* = 1) and acute renal failure (*n* = 1), and one patient discontinued after one dose of tocilizumab 4 mg/kg because of tremors. There was one death, which was due to septic shock and occurred after one dose of tocilizumab 4 mg/kg. The patient, a 64-year-old woman with history of prior abdominal exploratory laparotomy in 2005 (reason unknown) began to experience bloody diarrhoea and intense abdominal pain 18 days after receiving a single dose of tocilizumab. The patient died the following day despite treatment with antibiotics, vasopressors and mechanical ventilation. ANC 3 days before the event was 4.75 giga/l (baseline 5.33 giga/l). Concomitant medication included prednisone (7.5 mg oral) and naproxen (500 mg oral). The medical report indicated bowel infarction, and the death was adjudicated to be due to septic shock in the context of most probable mesenteric infarction.

In Study 1309, the rates of TEAEs were comparable in the sarilumab and tocilizumab groups and were numerically higher for the higher doses compared with the lower doses of sarilumab (200 mg, 46.2%; 150 mg, 38.5%) and

TABLE 3 Frequently reported treatment-emergent AEs in ASCERTAIN^a

AE	Tocilizumab q4w i.v. + csDMARDs (n = 102) ^b	Sarilumab 150 mg q2w s.c. + csDMARDs (n = 49)	Sarilumab 200 mg q2w s.c. + csDMARDs (n = 51)
Infection	32 (31.4)	20 (40.8)	11 (21.6)
Nasopharyngitis	4 (3.9)	6 (12.2)	3 (5.9)
Urinary tract infection	6 (5.9)	4 (8.2)	2 (3.9)
Upper respiratory tract infection	7 (6.9)	2 (4.1)	1 (2.0)
Gastroenteritis	1 (1.0)	3 (6.1)	0
Neutropenia	4 (3.9)	6 (12.2)	8 (15.7)
Injection-site erythema	1 (1.0)	4 (8.2)	4 (7.8)
Accidental overdose ^c	9 (8.8)	1 (2.0)	3 (5.9)
Dizziness	4 (3.9)	1 (2.0)	3 (5.9)
Hypercholesterolaemia	6 (5.9)	2 (4.1)	1 (2.0)
Nausea	7 (6.9)	1 (2.0)	1 (2.0)
RA	6 (5.9)	1 (2.0)	0

Values are n (%). ^aAt least 5% in any treatment group. ^bTocilizumab q4w i.v. starting at 4 mg/kg could be increased to 8 mg/kg based on clinical response as assessed by the investigator. ^cAn overdose was defined as the administration of ≥ 2 sarilumab doses in <11 calendar days or ≥ 2 tocilizumab doses in <21 calendar days or at least twice of the intended dose within the intended therapeutic interval for sarilumab or tocilizumab. AE: adverse event; csDMARD: conventional synthetic DMARD; q2w: every 2 weeks; q4w: every 4 weeks.

tocilizumab (8 mg/kg, 50.0%; 4 mg/kg, 32.0%). TEAEs occurring in >1 patient in any treatment group were neutropenia, upper respiratory tract infection, headache, thrombocytopenia and RA (Supplementary Table S4, available at *Rheumatology* online). One patient in the tocilizumab 8 mg/kg group had a serious AE (hip fracture), which was not considered treatment related. No deaths were reported during the study, and no patients in any treatment group discontinued because of an AE.

Laboratory changes

Laboratory changes in both ASCERTAIN and Study 1309 were consistent with IL-6R signalling blockade and included decreases in neutrophil and platelet counts and increases in transaminases and lipids (Table 4).

In ASCERTAIN, in which haematology assessments were performed q2w, a numerically higher incidence of ANC <1.0 giga/l was observed with sarilumab administered q2w compared with tocilizumab administered q4w, although the mean change in ANC in the sarilumab groups was within the range observed with tocilizumab (Fig. 1A). At week 24, the mean change in ANC was comparable between patients receiving sarilumab 200 mg q2w and those who increased their tocilizumab dose to 8 mg/kg q4w. There was no evidence of an association between decrease in ANC and increased incidence of infections.

In Study 1309, a dose-dependent effect on ANC <1.0 giga/l was observed, with a higher incidence reported in the high-dose sarilumab and tocilizumab groups compared with the low-dose groups (Table 4). Over days 1–7, there was no meaningful difference across all treatment groups in the ANC parameters assessed. The time to onset for decreased ANC and magnitude of decrease were similar across the sarilumab and tocilizumab groups for all doses. ANC decreased within a few hours of dosing (Fig. 1B and C). The median time to ANC nadir ranged from 3 to 5 days after administration;

mean nadir values ranged from 1.55 to 1.78 giga/l across all treatment groups. The timing of the trend for return to baseline was consistent with the dosing interval for both sarilumab (q2w) and tocilizumab (q4w). By day 15, the approximate time that a second dose of sarilumab would be given in a q2w dosing regimen, ANC values in the sarilumab groups had increased but had not yet returned to baseline. By day 29, the approximate time that a second dose of tocilizumab would be given in a q4w dosing regimen, ANC values had essentially returned to baseline in the tocilizumab 4 mg/kg group but not in the 8 mg/kg group. Decreases in ANC did not appear to be associated with an increased incidence of infections.

Increased levels of ALT >3 \times upper limit of normal occurred in few patients in either study. In ASCERTAIN, the mean increase in ALT at week 24 was comparable between the tocilizumab 4/8 mg/kg q4w and sarilumab 200 mg q2w groups, and increases in both groups were slightly greater than in the sarilumab 150 mg q2w group (Fig. 2). Incidence of ALT increases of 3–5 \times upper limit of normal was comparable among the treatment groups and reversible upon discontinuation of study treatment. Platelet count <100 giga/l was reported in a single patient receiving sarilumab 150 mg q2w in ASCERTAIN and in two patients receiving sarilumab 150 mg in Study 1309; none of the patients experienced bleeding related to decreased platelet count. Incidence of total cholesterol ≥ 6.2 mmol/l in the sarilumab and tocilizumab groups was generally similar in both studies. In ASCERTAIN, mean increases in low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides at week 24 were of similar magnitude in all treatment groups. Lipid-modifying agents (including statins) were initiated on the same day or after the first dose in eight patients (7.8%) in the tocilizumab group, two patients (4.1%) in the sarilumab 150 mg q2w group and two

TABLE 4 Overview of laboratory changes in the multiple-dose, 24-week ASCERTAIN study and single-dose, 6-week Study 1309

Patients	ASCERTAIN			Study 1309			
	Tocilizumab q4w i.v. + csDMARDs (n = 102) ^a	Sarilumab 150 mg q2w s.c. + csDMARDs (n = 49)	Sarilumab 200 mg q2w s.c. + csDMARDs (n = 51)	Tocilizumab 4 mg/kg i.v. + MTX (n = 25)	Tocilizumab 8 mg/kg i.v. + MTX (n = 24)	Sarilumab 150 mg s.c. + MTX (n = 26)	Sarilumab 200 mg s.c. + MTX (n = 26)
ANC ^b							
0.5–<1.0, giga/l	1 (1.0)	2 (4.2)	5 (9.8)	3 (12.0)	6 (25.0)	4 (15.4)	6 (23.1)
<0.5, giga/l	0	1 (2.1)	0	0	0	0	1 (3.8)
ALT ^c							
>3–5 × ULN	3 (3.0)	2 (4.3)	2 (3.9)	0	1 (4.2)	0	1 (3.8)
>5 × ULN	0	0	1 (2.0)	0	1 (4.2)	0	0
Platelet count ^d							
<100, giga/l	0	1 (2.1)	0	0	0	2 (7.7)	0

Values are *n* (%). ^aTocilizumab q4w i.v. starting at 4 mg/kg could be increased to 8 mg/kg based on clinical response as assessed by the investigator. ^bFor ANC in ASCERTAIN, *n* = 48 for sarilumab 150 s.c. ^cFor ALT in ASCERTAIN, *n* = 101 for tocilizumab q4w i.v. and *n* = 47 for sarilumab 150 mg q2w s.c. ^dFor platelets in ASCERTAIN, *n* = 48 for sarilumab 150 mg q2w s.c. ALT: alanine aminotransferase; ANC: absolute neutrophil count; csDMARD: conventional synthetic DMARD; ULN: upper limit of normal.

patients (3.9%) in the sarilumab 200 mg q2w group. In Study 1309, small mean increases from baseline in total cholesterol, low-density lipoprotein cholesterol and triglycerides observed at day 15 returned to baseline by day 29 in the sarilumab groups and remained slightly elevated in the tocilizumab groups. There were no notable differences in mean high-density lipoprotein cholesterol values.

Discussion

ASCERTAIN and Study 1309 were the first studies in which sarilumab and tocilizumab were evaluated in patients with RA within the same study using multiple and single doses, respectively, providing an opportunity to understand the safety and tolerability of these two agents within the same therapeutic class of IL-6R inhibitors. Overall, no clinically meaningful differences were observed regarding safety between sarilumab and tocilizumab in either study. The incidence and type of TEAEs were similar for the sarilumab and tocilizumab groups in each study.

In ASCERTAIN, the incidence of TEAEs leading to treatment discontinuation was numerically higher with sarilumab than with tocilizumab, but some of these discontinuations were due to protocol-mandated criteria related to laboratory changes; these laboratory changes occurred without clinical manifestations. While most patients in the sarilumab groups who interrupted therapy because of laboratory abnormalities resumed treatment as these abnormalities resolved, three patients were discontinued because the protocol-mandated interval between i.v. infusions had been exceeded. There was no clinical pattern for the non-laboratory TEAEs that led to discontinuation, but the low number of events limits assessment and interpretation of these data.

Upper respiratory tract infections and neutropenia were among the most frequent TEAEs in both studies.

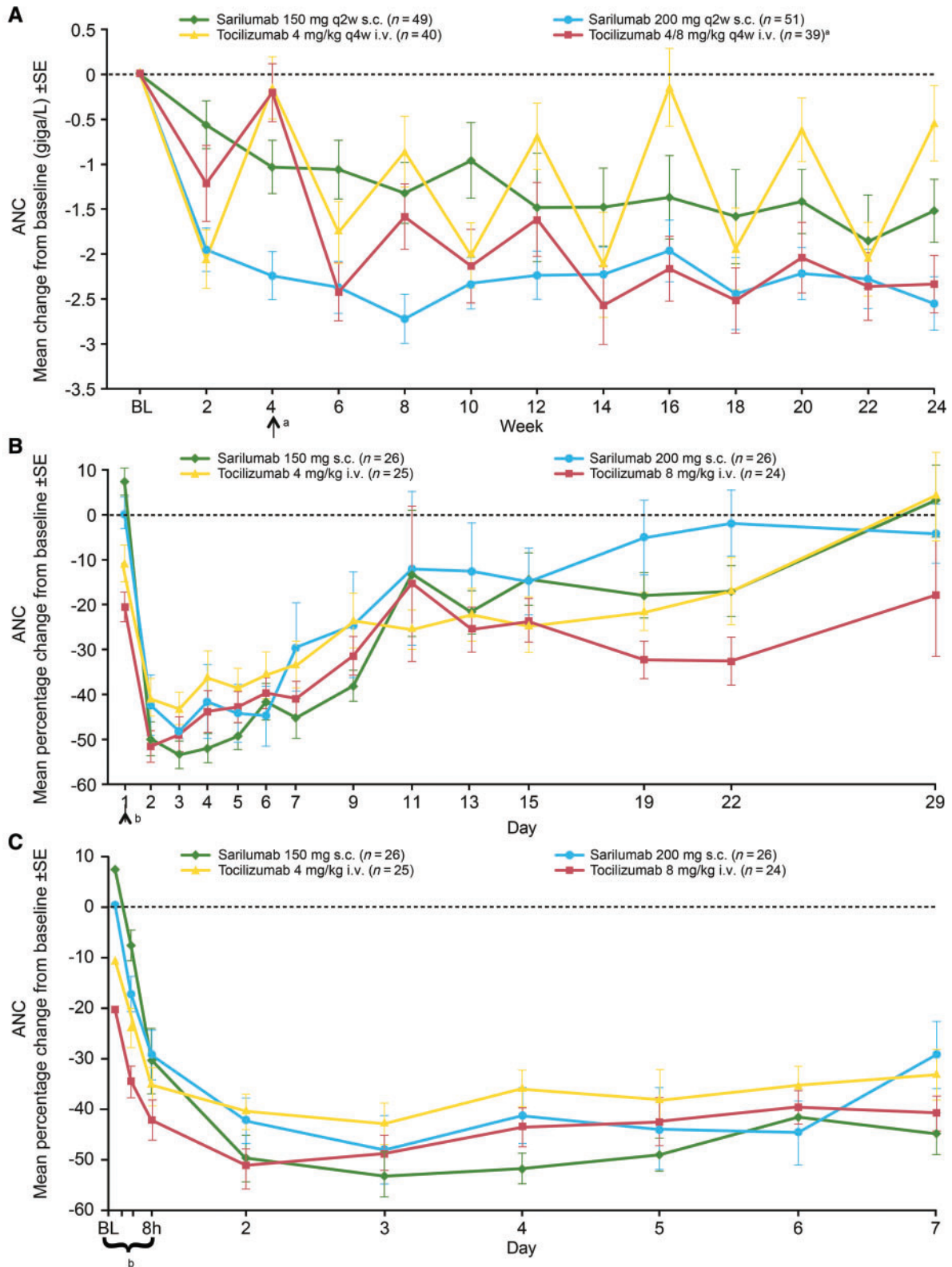
Laboratory changes in both studies were consistent with IL-6R inhibition and included increases in lipids and transaminases and decreases in neutrophil counts. Mean changes in ANC in the sarilumab groups were within the ranges observed in the tocilizumab groups.

The association between IL-6 signalling and the PD marker ANC after a single dose of sarilumab or tocilizumab was assessed in Study 1309. This assessment indicated that despite differences in PK profiles due to route of administration and 10-fold lower drug peak concentrations with sarilumab s.c. compared with tocilizumab i.v. (data not shown), similar rapid decreases in ANC (within 4 h), nadir values and median time to nadir values were observed across all four treatment groups. ANC returned towards baseline earlier with sarilumab than with tocilizumab, which is consistent with drug concentration-time profiles. A dose-dependent effect on ANC <1.0 giga/l was observed, with a higher incidence reported in the high-dose sarilumab and tocilizumab groups *versus* the low-dose groups. Decreased ANC was not associated with an increased incidence of infections.

In ASCERTAIN, tocilizumab was administered i.v. according to US product labelling [6]; patients were treated with 4 mg/kg and the dose was increased at the discretion of the investigator. In the study, 60% of patients received at least one dose of tocilizumab 8 mg/kg. Because of differences in the route of administration (s.c. for sarilumab, i.v. for tocilizumab), PK profiles and dosing intervals (q2w for sarilumab, q4w for tocilizumab) in relation to the sampling schedule (q2w for haematology assessments), numeric differences were observed in the incidence of ANC <1.0 giga/l, a PD marker of IL-6 inhibition, between the sarilumab and tocilizumab groups. Regardless, there was no difference in the rates of infection or serious infection between the tocilizumab and sarilumab groups.

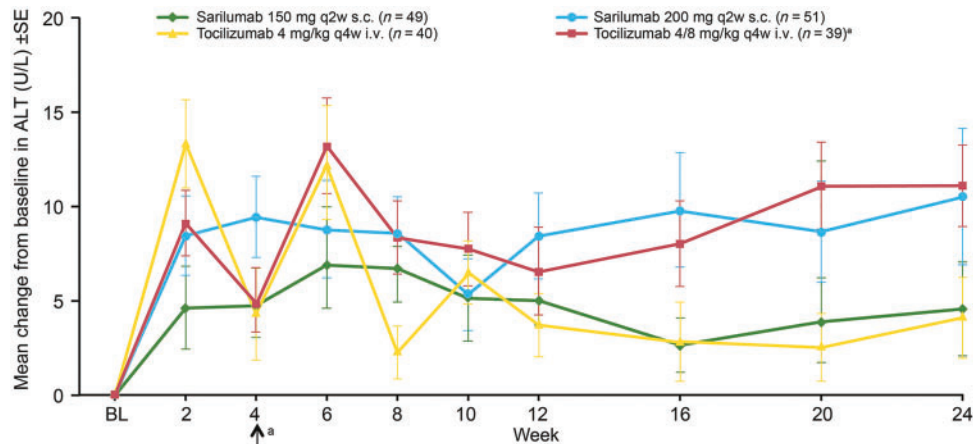
The rapid and similar decrease in ANC with these IL-6R inhibitors is potentially explained by redistribution from the

Fig. 1 Mean change from baseline in ANC \pm s.e. by treatment and visit in **(A)** ASCERTAIN (weeks 1–24), **(B)** Study 1309 (days 1–29) and **(C)** Study 1309 (days 1–7)



^aPatients in the 4/8 mg/kg q4w i.v. group increased their dose to 8 mg/kg at week 4 and remained on 8 mg/kg for the remainder of the study. ^bThere were four sampling points on day 1: baseline, 1 h, 4 h and 8 h after dosing. ANC: absolute neutrophil count; BL: baseline; q2w: every 2 weeks; q4w: every 4 weeks.

Fig. 2 Mean change from baseline in ALT \pm s.e. in ASCERTAIN



^aPatients in the 4/8 mg/kg q4w i.v. group increased their dose to 8 mg/kg at week 4 and remained on 8 mg/kg for the remainder of the study. ALT: alanine aminotransferase; BL: baseline; q2w: every 2 weeks; q4w: every 4 weeks.

vascular compartment and results in the uptake and removal of circulating neutrophils without affecting their function [13]. *In vitro* evidence suggests that IL-6 increases circulating neutrophils by releasing them from marginated pools in bone marrow [14]. Thus, an anti-IL-6R agent may potentially reverse this effect. The rapid onset and recovery of the decrease in neutrophil count observed in Study 1309 provides support for this mechanism, and a PD model that implemented neutrophil margination with ANC-specific tolerance describes the mechanism of transient decreases in ANC observed with IL-6R inhibitors [15].

One limitation of ASCERTAIN is that robust characterization of the neutrophil kinetics (including identification of the nadir) after multiple doses of sarilumab and tocilizumab, as was done in Study 1309 after single-dose administration, could not be performed because of less frequent PK and PD sampling. Therefore, Study 1309 provides valuable insight into the similarities in changes in neutrophil parameters that occur with the two IL-6R inhibitors.

In summary, IL-6R inhibition leads to transient decreases in ANC, likely due to margination of neutrophils from the circulation where the neutrophils remain present and maintain their functionality if triggered. This phenomenon of margination is further supported by the fact that no clinically meaningful consequence of the decrease in ANC by IL-6R inhibitors has been identified.

Conclusions

Overall, no clinically meaningful differences were observed with regard to safety between sarilumab and tocilizumab in either study, including the incidence and types of TEAEs. Laboratory changes (e.g. decrease in ANC and increase in ALT) noted in the sarilumab groups were within the same range as those noted in the tocilizumab groups. Although numeric differences in incidence of ANC <1.0 giga/l between the sarilumab and tocilizumab groups were observed in ASCERTAIN, considering the results of Study 1309, this most likely reflects

differences in PK (related to route of administration; s.c. for sarilumab and i.v. for tocilizumab) and dosing interval (q2w for sarilumab versus q4w for tocilizumab) in relation to the sampling schedule (q2w). Decreased ANC was not associated with an increased incidence of infection.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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Clinical vignette

Rheumatology 2019;58:858

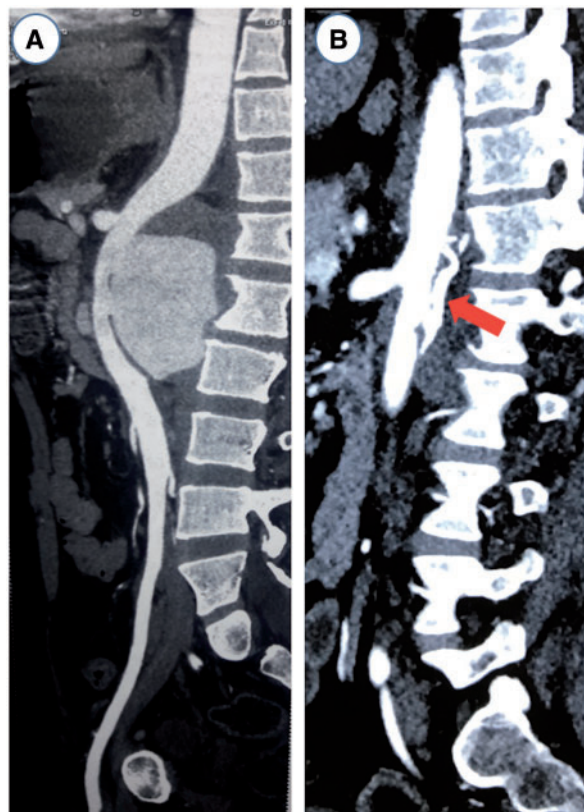
doi:10.1093/rheumatology/key351

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A blind man with an acute abdomen

A 32-year-old male presented to the emergency service with acute periumbilical pain. He had a history of recurrent oral and scrotal ulcers for the past 3 years and loss of vision in both eyes for the past 2 years. On ophthalmological evaluation, he was found to have right hypopyon and bilateral retinal vasculitis. Abdominal ultrasonography revealed a large globular mass at the umbilical region suggestive of an aneurysm. A computed tomographic angiogram of abdominal vessels revealed a large

Fig. 1 (A) CT angiogram (sagittal view) of abdominal vessels showing a large (7.3 cm×5.4 cm×7.9 cm) pseudoaneurysm arising from the posterior wall of the aorta at the level of origin of the right renal artery, with self-contained rupture. (B) Postoperative CT angiogram (sagittal view) showing intact repair. Radio-opaque area behind repaired rent is Teflon felt (polytetrafluoroethylene material) used for reinforcement of repair (arrow).



(7.3 cm×5.4 cm×7.9 cm) pseudoaneurysm arising from the posterior wall of the aorta at the level of origin of the right renal artery, with self-contained rupture (Fig. 1(a)). A diagnosis of vascular Behçet's disease was made and he was started on pulse methylprednisolone and cyclophosphamide, and subsequently surgical repair of the aneurysm was performed (Fig. 1(b)).

Arterial involvement in Behçet's disease is rare and almost exclusively found in young males. Although pulmonary artery aneurysm is a classical symptom of Behçet's disease, the abdominal aorta is the most common site [1]. Arterial involvement is a potentially fatal complication. Early aggressive immunosuppressive therapy is essential for good outcome. For aortic and peripheral artery involvement, treatment with corticosteroid and cyclophosphamide is necessary before surgical intervention [2].

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Arghya Chattopadhyay^{1,*}, Ajay Savlania^{2,*}, Sanjay Jain¹ and Aman Sharma¹

¹Clinical Immunology and Rheumatology Services, Department of Internal Medicine and ²Department of General Surgery, Postgraduate Institute of Medical Education and Research, Chandigarh, India

*Arghya Chattopadhyay and Ajay Savlania contributed equally to this study as first authors.

Correspondence to: Aman Sharma, Professor, Clinical Immunology and Rheumatology Services, Department of Internal Medicine, Post Graduate Institute of Medical Education and Research, Chandigarh, India. E-mail: amansharma74@yahoo.com

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