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Original article

Long-term safety of sarilumab in rheumatoid arthritis: an integrated analysis with up to 7 years' follow-up

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Abstract

Objective. Sarilumab is a human monoclonal antibody that blocks IL-6 from binding to membrane-bound and soluble IL-6 receptor-α. We assessed the long-term safety of sarilumab in patients from eight clinical trials and their open-label extensions.

Methods. Data were pooled from patients with rheumatoid arthritis who received at least one dose of sarilumab in combination with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs; combination group) or as monotherapy (monotherapy group). Treatment-emergent adverse events (AEs) and AEs and laboratory values of special interest were assessed.

Results. 2887 patients received sarilumab in combination with csDMARDs and 471 patients received sarilumab monotherapy, with mean exposure of 2.8 years and 1.7 years, maximum exposure 7.3 and 3.5 years, and cumulative AE observation period of 8188 and 812 patient-years, respectively. Incidence rates per 100 patient-years in the combination and monotherapy groups, respectively, were 9.4 and 6.7 for serious AEs, 3.7 and 1.0 for serious infections, 0.6 and 0.5 for herpes zoster (no cases were disseminated), 0.1 and 0 for gastrointestinal perforations, 0.5 and 0.2 for major adverse cardiovascular events, and 0.7 and 0.6 for malignancy. Absolute neutrophil counts <1000 cells/mm^3 were recorded in 13% and 15% of patients, respectively. Neutropenia was not associated with increased risk of infection or serious infection. Analysis by 6-month interval showed no signal for increased rate of any AE over time.

Conclusion. The long-term safety profile of sarilumab, either in combination with csDMARDs or as monotherapy, remained stable and consistent with the anticipated profile of a molecule that inhibits IL6 signalling.

Key words: sarilumab, IL-6 inhibition, integrated safety analysis, long-term safety, biologic DMARD

CLINICAL SCIENCE

Rheumatology key messages

- This analysis represents the most comprehensive long-term safety report of sarilumab in RA to date.
- Sarilumab's long-term safety profile was consistent with phase III studies, with no new safety concerns.
- Neutropenia was not associated with increased risk of infection or serious infection.

Introduction

IL-6 is a pleiotropic cytokine that plays a role in metabolic, homeostatic and regenerative processes [1]. IL-6 levels increase in response to infection or injury, promoting and coordinating pro-inflammatory activities. In autoimmune conditions such as RA, persistently elevated IL-6 levels can contribute to chronic inflammation and disease progression [2].

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Sarilumab is a human monoclonal antibody that binds membrane-bound and soluble IL-6 receptor (IL-6R)-α to inhibit IL-6 *cis*- and *trans*-signalling [3]. Sarilumab is approved for the treatment of adults with moderately to severely active RA [3]. The efficacy and tolerability of sarilumab administered subcutaneously as monotherapy and in combination with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) have been demonstrated in active-comparator- and placebo-controlled phase III trials in adults with RA [4–6]. Long-term data on sarilumab as monotherapy and in combination with csDMARDs are being collected in patients with RA originally enrolled in eight trials, including those who continued into extension trials [4–11].

The aim of this *post hoc* analysis, the first integrated safety report of sarilumab in patients with RA, including up to 7.3 years of sarilumab exposure in combination with csDMARDs and up to 3.5 years as monotherapy, was to provide precise adverse event (AE) incidence rates (IRs) and to investigate changes in IRs over time for AEs of special interest (AESIs).

Methods

Data were pooled from patients with RA who received $\geqslant$1 dose of sarilumab in combination with csDMARDs, or as monotherapy. Details of the contributing trials (MOBILITY, NCT01061736; TARGET, NCT01709578; ASCERTAIN, NCT01768572; MONARCH, NCT02332590; ACT11575, NCT01217814; ONE, NCT02121210; COMPARE, NCT01764997; and EASY, NCT02057250) [4–11] and open-label extensions (including EXTEND) [12] are provided in Supplementary Fig. S1, available at *Rheumatology* online. All trials were conducted in accordance with Good Clinical Practice and the principles laid down in the Declaration of Helsinki. All study protocols and patient information materials were approved by appropriate ethical review boards, and all patients provided written informed consent. Key exclusion criteria shared across the trials were prior treatment with an anti-IL-6R antagonist; history of malignancy; and history of inflammatory bowel disease, severe diverticulitis, or previous gastrointestinal perforation. At randomization, sarilumab dosage was 150 mg or 200 mg in monotherapy trials and predominantly 150 mg or 200 mg in csDMARD combination trials. In EXTEND, sarilumab starting dosage was 200 mg and dose reduction to 150 mg was permitted for protocol-specified laboratory abnormalities or at investigator discretion. Protocol-specified sarilumab dose modifications for neutropenia, thrombocytopenia and increased alanine aminotransferase (ALT) were consistent with recommendations in the sarilumab prescribing information (Supplementary Table S1, available at *Rheumatology* online) [3, 13]. Exposure was calculated as last dose date minus first dose date plus 14 days, regardless of unplanned intermittent discontinuations. The AE observation period included 60 days after the last dose of sarilumab.

AEs, including serious AEs (SAEs: including AEs that required inpatient hospitalization or prolongation of existing hospitalization) and prespecified AESIs, were collected at every visit. Samples for laboratory analysis, including haematology and clinical chemistry, were collected during screening, and pre-dose on treatment day 1, then at least every 2 weeks until week 12, at least every 12 weeks up to week 96, and at least every 24 weeks thereafter. AEs and AESIs were categorized according to Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries (narrow definitions) and High-Level Terms, except for infection (MedDRA primary system organ class), opportunistic infection (case-report form checkbox), and overdose (administering $\geqslant$2 doses in $<$11 calendar days [once every 2 weeks (q2w) schedule] or $<$6 days [weekly (qw) schedule]; case-report form checkbox; reported as an AE per protocol). Serious infections were defined as infections requiring hospitalization and/or intravenous antibiotics. Major adverse cardiovascular events (MACE) were reviewed by an independent cardiovascular adjudication committee, and suspected gastrointestinal perforations were confirmed by medical review. Thromboembolic events were not prespecified as an AESI in the study protocols but are reported here *post hoc* based on the MedDRA high-level group term 'Embolism and thrombosis'. IR by 6-month interval was analysed for serious AEs, serious infections, AEs leading to discontinuation, malignancies, MACE, injection-site reactions, absolute neutrophil count (ANC) $<$1000 cells/mm^3, ALT $>3\times$ upper limit of normal (ULN), and platelet count $<$100 giga/L. The exact method was used to calculate 95% confidence intervals (95% CI) for proportions. For ANC, ALT and platelet count, the largest abnormality during follow-up is reported. Incidences of infection and serious infection were calculated by maximum neutropenia grade recorded at any time during the study. In addition, for infections that occurred within 12 weeks after an ANC assessment, incidences of infection and serious infection were calculated by the last ANC assessment before onset of the infection.

Results

Patient population and exposure

At the data cutoff of 15 January 2018, a total of 2887 patients had received at least one dose of sarilumab in combination with csDMARDs (predominantly methotrexate) and 471 patients had received at least one dose of sarilumab monotherapy (Supplementary Table S2, available at *Rheumatology* online). Most patients received sarilumab 200 or 150 mg q2w subcutaneously, except 151 patients from MOBILITY Part A (in combination with methotrexate) who received 100 mg qw, 150 mg qw, or 100 mg q2w subcutaneously. Both pooled study populations included patients with intolerance or inadequate response to csDMARDs, and the combination group also included those with inadequate response or intolerance to tumour necrosis factor antagonists and those with inadequate response to adalimumab plus methotrexate. Patients in the combination group had longer disease

Table 1 Demographics and baseline characteristics

Characteristic	Combination $n = 2887$	Monotherapy $n = 471$
Age, mean (S.D.), years	51.8 (12.2)	52.0 (12.6)
Female, *n* (%)	2346 (81.3)	389 (82.6)
Weight, mean (S.D.), kg	75.6 (18.9)	73.1 (17.5)
BMI $\geqslant$30 kg/m^2, *n* (%)	974 (33.8)	127 (27.0)
Duration of RA, mean (S.D.), years	9.4 (8.4)	8.3 (8.4)
Prior biologic DMARD use, *n* (%)	1118 (38.7)	40 (8.5)
Baseline medications, *n* (%)		
MTX without other csDMARD	2654 (91.9)	0
MTX with or without other csDMARD	2730 (94.6)	0
$\geqslant$2 other csDMARDs	94 (3.3)	0
Oral corticosteroids	1727 (59.8)	253 (53.7)
NSAIDs	2019 (69.9)	323 (68.6)
Mean (S.D.) dose of csDMARDs at baseline		
MTX, mg/week	16.2 (5.1)	N/A
Leflunomide, mg/day	19.3 (2.6)	N/A
Sulfasalazine, g/day	1.65 (0.66)	N/A
Hydroxychloroquine, mg/day	474 (258)	N/A

csDMARD: conventional synthetic DMARD; N/A: not applicable.

duration and greater prior exposure to biologic disease-modifying antirheumatic drugs (DMARDs) than those in the monotherapy group (Table 1).

Mean exposure to sarilumab in the combination group was 2.8 years, cumulative exposure was 7985.5 patient-years, maximum exposure was 7.3 years, and 773 patients (27%) were treated for $\geqslant$240 weeks ($\sim$5 years). In the monotherapy group, mean exposure was 1.7 years, cumulative exposure was 798.7 patient-years, maximum exposure was 3.5 years, and 384 patients (82%) were treated for $\geqslant$60 weeks. Cumulative duration of observation for AEs was 8187.7 patient-years in the combination group and 812.4 patient-years in the monotherapy group.

Adverse events

The overall incidence and exposure-adjusted IR of AEs were similar between combination and monotherapy (Table 2). The incidence and exposure-adjusted rate of SAEs and AEs leading to discontinuation were numerically lower with monotherapy compared with combination therapy. The most common AEs were neutropenia, injection-site erythema and upper respiratory tract infection with combination therapy, and neutropenia, injection-site erythema and nasopharyngitis with monotherapy. The most common SAEs were pneumonia, osteoarthritis and RA with combination therapy, and osteoarthritis, atrial fibrillation, neutropenia and RA with monotherapy. The most common AEs leading to discontinuation were neutropenia, ALT increased and herpes zoster (all non-disseminated) with combination therapy, and neutropenia, injection-site erythema and RA with monotherapy. There was no signal for an increased rate over time for any of the AEs analysed by 6-month interval (Fig. 1).

Laboratory abnormalities

Leucopenia was reported as an AE in 21% and 20% of patients treated with combination therapy and monotherapy, respectively (IR 18.1 and 30.0 per 100 patient-years, respectively; Table 3). ANC values $<$1000 cells/mm^3, the level at which dose interruption/reduction is recommended, were recorded in 13% and 15% of patients treated with combination therapy and monotherapy, respectively (Supplementary Table S3, available at *Rheumatology* online). Analysis by 6-month interval showed that incidence of ANC $<$1000 cells/mm^3 was greatest during the first 6 months of treatment and declined thereafter (Fig. 2). ANC normalized on treatment in 257 (70%) of the 365 patients with ANC $<$1000 cells/mm^3 in the combination group, and in 57 (81%) of the 70 patients with ANC $<$1000 cells/mm^3 in the monotherapy group (Supplementary Table S2, available at *Rheumatology* online).

ALT increase was reported as an AE in 11% and 6% of patients treated with combination therapy and monotherapy, respectively (IR 5.0 and 3.8 per 100 patient-years, respectively; Table 2). ALT elevations were observed in 65% and 48% of patients with combination therapy and monotherapy, respectively (Supplementary Table S4, available at *Rheumatology* online). ALT elevations $>3\times$ ULN, the level at which dose interruption is recommended, were observed in 10% and 6% of patients with combination therapy and monotherapy, respectively. Analysis by 6-month interval showed that incidence of ALT $>3\times$ ULN was greatest during the first 6 months of treatment and declined thereafter (Fig. 2). ALT normalized on treatment in 162 (55%) of the 296 patients with ALT $>3\times$ ULN in the combination group and in 17 (65%) of the 26 patients with ALT $>3\times$ ULN in the monotherapy group (Supplementary Table S4, available at *Rheumatology* online). Bilirubin

Table 2 Investigator-reported all-cause AEs

Cumulative total AE observation period, PY	Combination ($n = 2887$) 8187.7		Monotherapy ($n = 471$) 812.4	
	n (%)	IR/100 PY (nE)	*n* (%)	IR/100 PY (nE)
Summary[a]				
Any AE	2489 (86.2)	144.2 (2489)	386 (82.0)	151.8 (386)
SAE	685 (23.7)	9.4 (685)	52 (11.0)	6.7 (52)
AE leading to discontinuation	705 (24.4)	8.7 (705)	53 (11.3)	6.6 (53)
AE leading to death	31 (1.1)	0.4 (31)	5 (1.1)	0.6 (5)
AEs with IR $\geqslant$5.0 per 100 PY in either group[b]				
Neutropenia	536 (18.6)	13.8 (1132)	85 (18.0)	27.7 (225)
Injection-site erythema	216 (7.5)	13.3 (1091)	38 (8.1)	25.6 (208)
URTI	386 (13.4)	7.7 (634)	37 (7.9)	5.9 (48)
Accidental overdose[c]	381 (13.2)	6.7 (552)	41 (8.7)	6.6 (54)
Urinary tract infection	309 (10.7)	5.9 (481)	33 (7.0)	5.9 (48)
Nasopharyngitis	294 (10.2)	5.2 (426)	55 (11.7)	9.8 (80)
ALT increased[d]	309 (10.7)	5.0 (412)	26 (5.5)	3.8 (31)
Bronchitis	250 (8.7)	4.3 (349)	46 (9.8)	7.1 (58)
SAEs with IR $\geqslant$0.3 per 100 PY in either group[b]				
Pneumonia	44 (1.5)	0.6 (47)	1 (0.2)	0.1 (1)
Osteoarthritis	36 (1.2)	0.5 (43)	4 (0.8)	0.5 (4)
Rheumatoid arthritis	34 (1.2)	0.4 (35)	2 (0.4)	0.2 (2)
Cellulitis	23 (0.8)	0.3 (25)	0	0
Neutropenia	22 (0.8)	0.3 (23)	2 (0.4)	0.2 (2)
Atrial fibrillation	9 (0.3)	0.1 (10)	3 (0.6)	0.5 (4)
AEs leading to discontinuation with IR $\geqslant$0.3 per 100 PY in either group[b]				
Neutropenia	90 (3.1)	1.1 (90)	10 (2.1)	1.5 (12)
ALT increased	67 (2.3)	0.8 (67)	3 (0.6)	0.4 (3)
Herpes zoster[e]	38 (1.3)	0.5 (38)	3 (0.6)	0.4 (3)
Rheumatoid arthritis	25 (0.9)	0.3 (25)	4 (0.8)	0.5 (4)
Pneumonia	24 (0.8)	0.3 (24)	1 (0.2)	0.1 (1)
Injection-site erythema	13 (0.5)	0.2 (13)	6 (1.3)	0.7 (6)

[a]IR over time at risk of first event. [b]IR over cumulative total AE observation period. [c]Overdose was defined as administering $\geqslant$2 doses in <11 calendar days (once every 2 weeks schedule) or <6 days (weekly schedule). [d]Individual events were reported and laboratory abnormalities were not necessarily persistent. [e]All cases of herpes zoster were non-disseminated. AE: adverse event; ALT: alanine aminotransferase; IR: incidence rate; nE: number of events; PY: patient-years; SAE: serious adverse event; URTI: upper respiratory tract infection.

elevations >1.5× ULN were observed in 135 patients (4.7%) and 25 patients (5.3%) with combination therapy and monotherapy, respectively, of whom 43 (1.5%) and 6 (1.3%) had elevations >2× ULN. There were no cases of Hy's law attributable to sarilumab treatment.

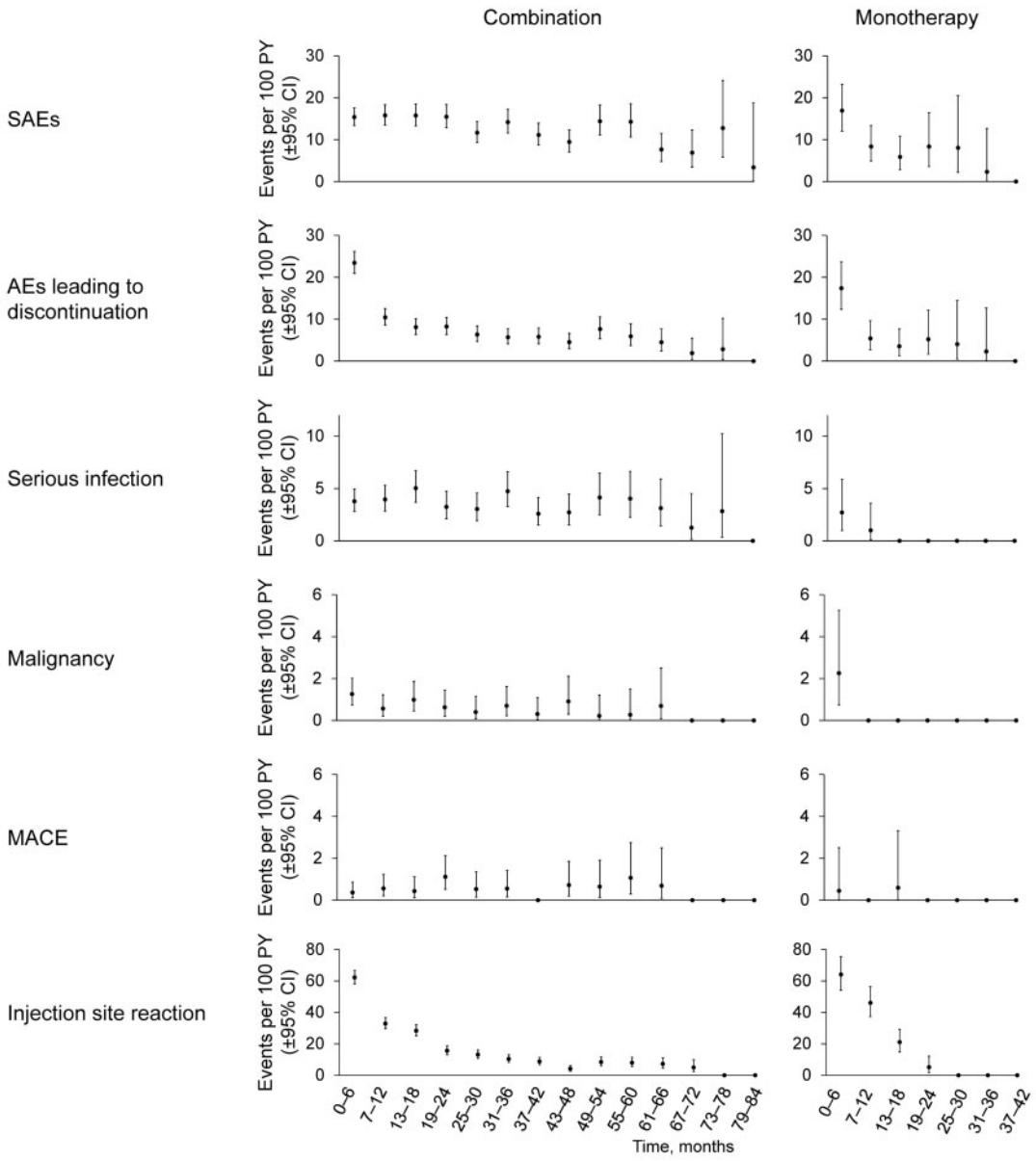
Thrombocytopenia was reported at a rate of 1.8 and 1.0 per 100 patient-years with combination therapy and monotherapy, respectively (Table 3). Platelet counts <100 giga/L, the level at which dose interruption is recommended, were observed in 2.8% and 1.3% of patients with combination and monotherapy, respectively (Supplementary Table S5, available at *Rheumatology* online). Analysis by 6-month interval showed no increased incidence of platelet count <100 giga/L over time (Fig. 2). Platelet counts normalized on treatment in 47 (59%) of the 80 patients with platelet count <100 giga/L in the combination group and in four (67%) of the six patients with platelet count <100 giga/L in the monotherapy group (Supplementary Table S5, available at *Rheumatology* online).

Infections

Overall infection rates were 54.4 and 54.9, and serious infection rates were 3.7 and 1.0 per 100 patient-years for combination therapy and monotherapy, respectively (Table 3). The most common serious infections with combination therapy were pneumonia ($n = 44$; 1.5%), cellulitis ($n = 23$; 0.8%), and erysipelas ($n = 9$; 0.3%). Incidence of serious infections was low with monotherapy ($n = 7$; 1.5%), and no type of serious infection occurred in more than one patient. The rates of opportunistic infections, including herpes zoster and tuberculosis, were 0.9 and 0.7 per 100 patient-years with combination therapy and monotherapy, respectively. All cases of herpes zoster were non-disseminated.

With both combination therapy and monotherapy, incidences of infection and of serious infection were similar between patients with and without a recorded event of neutropenia at any time during the study (Table 4). Moreover, incidence of infection and serious infection

Fig. 1 Incidence rates of selected AEs by 6-month interval



Time, months	0–6	7–12	13–18	19–24	25–30	31–36	37–42	43–48	49–54	55–60	61–66	67–72	73–78	79–84
Combination pool														
Number of patients at risk	2887	2376	1968	1654	1554	1474	1382	1203	1007	814	676	460	203	104
Total patient-years of exposure	1354	1065	915	804	758	720	658	552	460	373	289	160	71	30
Monotherapy pool														
Number of patients at risk	471	425	393	260	107	91	86							
Total patient-years of exposure	225	204	170	96	50	44	26			Not applicable				

AE: adverse event; csDMARD: conventional synthetic DMARD; MACE: major adverse cardiovascular event; PY: patient-years.

did not increase with increasing severity of neutropenia. Of the total 4451 and 446 infections observed with combination therapy and monotherapy, respectively, 3943 (89%) and 434 (97%) occurred within 12 weeks after an ANC assessment. ANC values were normal at the last ANC assessment before infection for the majority of infections occurring within 12 weeks after an ANC assessment (3452/3943 [88%] and 370/434 [85%] of infections with combination therapy and monotherapy, respectively; Supplementary Table S6, available at *Rheumatology* online). Similar results were observed for serious infection: ANC values were normal at the last ANC assessment

Table 3 Investigator-reported all-cause AEs of special interest

Cumulative total AE observation period, PY	Combination ($n = 2887$) 8187.7		Monotherapy ($n = 471$) 812.4	
	n (%)	IR/100 PY (nE)	*n* (%)	IR/100 PY (nE)
Infections	1582 (54.8)	54.4 (4451)	225 (47.8)	54.9 (446)
Serious infections	232 (8.0)	3.7 (301)	7 (1.5)	1.0 (8)
Opportunistic infections	72 (2.5)	0.9 (76)	6 (1.3)	0.7 (6)
Tuberculosis[a]	4 (0.1)	<0.1 (4)	1 (0.2)	0.1 (1)
Herpes zoster[b]	51 (1.8)	0.6 (53)	4 (0.8)	0.5 (4)
Leucopenia[c]	618 (21.4)	18.1 (1482)	92 (19.5)	30.0 (244)
Thrombocytopenia[c]	101 (3.5)	1.8 (147)	5 (1.1)	1.0 (8)
Hepatic disorders	448 (15.5)	8.9 (726)	39 (8.3)	7.1 (58)
Confirmed GI perforations	9 (0.3)	0.1 (9)	0	0
Upper	3 (0.1)	<0.1 (3)	0	0
Lower	6 (0.2)	0.1 (6)	0	0
GI ulcerations	33 (1.1)	0.5 (38)	1 (0.2)	0.1 (1)
MACE	41 (1.4)	0.5 (45)	2 (0.4)	0.2 (2)
Elevation in lipids[c]	334 (11.6)	6.1 (498)	17 (3.6)	2.2 (18)
Hypersensitivity	308 (10.7)	5.4 (444)	37 (7.9)	5.9 (48)
Anaphylaxis	0	0	0	0
Injection-site reactions	333 (11.5)	23.6 (1934)	48 (10.2)	34.3 (279)
Malignancy	52 (1.8)	0.7 (56)	4 (0.8)	0.6 (5)
Malignancy excluding NMSC	38 (1.3)	0.5 (38)	3 (0.6)	0.5 (4)
Lupus-like syndrome	5 (0.2)	0.1 (5)	0	0
Demyelinating disorders	0	0	1 (0.2)	0.1 (1)
Thromboembolic events[d]	46 (1.6)	0.8 (67)	3 (0.6)	0.4 (3)

[a]All cases of tuberculosis were reported as opportunistic infections. [b]Herpes zoster was reported as an opportunistic infection per protocol requirement; no cases of herpes zoster were disseminated. [c]Individual events were reported and laboratory abnormalities were not necessarily persistent. [d]Thromboembolic events were not prespecified as AEs of special interest and were summarized *post hoc* using a database search with the Medical Dictionary for Regulatory Activities System Organ Class 'Vascular disorders' and High-Level Group Term 'Embolism and thrombosis'. AE: adverse event; GI: gastrointestinal; IR: incidence rate; MACE: major adverse cardiovascular events (comprising cardiovascular death, myocardial infarction, stroke and hospitalization for either unstable angina and/or transient ischaemic attack); NMSC: non-melanoma skin cancer; PY: patient-years.

before serious infection for 244/261 (93%) and 8/8 (100%) serious infections occurring within 12 weeks of an ANC assessment with combination therapy and monotherapy, respectively.

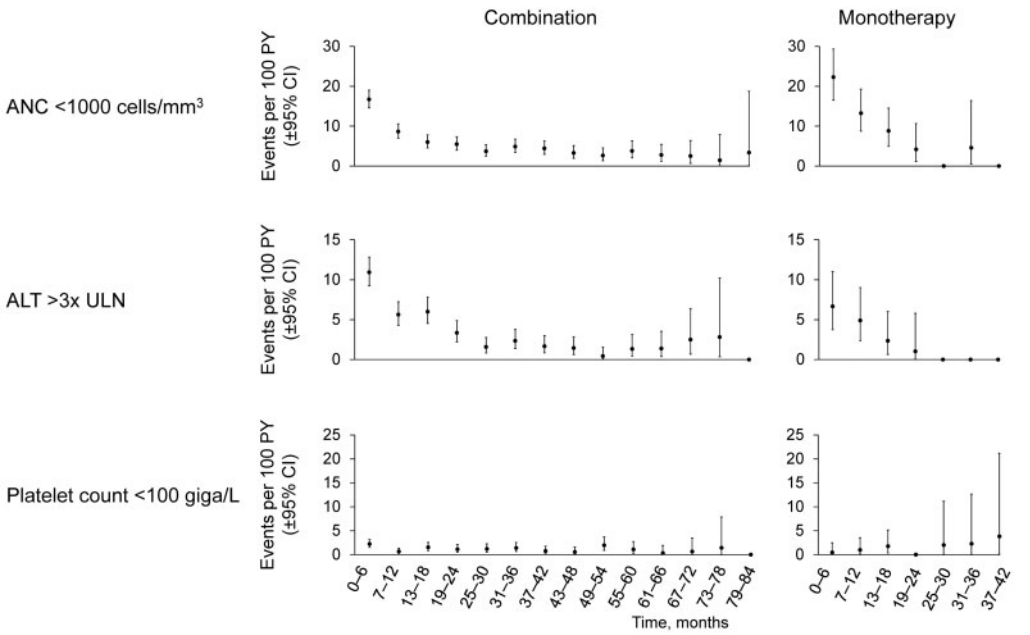
Adverse events of special interest

Injection-site reactions were reported in 12% and 10% of patients with combination therapy and monotherapy, respectively (Table 3). There was a marked decline in incidence of injection-site reaction over time (Fig. 1). AEs of hypersensitivity occurred in 11% and 8% of patients with combination therapy and monotherapy, respectively. The most common hypersensitivity events (⩾1.0% incidence) were injection-site rash ($n = 45$; 1.6%), rash ($n = 40$; 1.4%) and urticaria ($n = 29$; 1.0%) with combination therapy, and rash ($n = 5$; 1.1%) with monotherapy. There were no events of anaphylaxis.

The exposure-adjusted incidence of malignancy was 0.7 and 0.6 per 100 patient-years (Table 3). The most common malignancy types with combination were basal cell carcinoma ($n = 9$; 0.3%), squamous cell carcinoma of skin ($n = 4$; 0.1%), breast cancer ($n = 3$; 0.1%) and malignant melanoma ($n = 3$; 0.1%). No more than one patient (0.2%) had the same malignancy type with monotherapy. The age- and sex-adjusted standardized incidence ratio for all malignancy types *vs* the general population in the US National Cancer Institute Surveillance and Epidemiology and End Results database, 2015, was 1.10 (95% CI 0.85, 1.43) with combination therapy and 0.94 (0.39, 2.25) with monotherapy. Compared with a reference population of patients with RA (Clinformatics Data Mart, 2000–2014; OptumInsight, Eden Prairie, MN, USA), the SIRs for all malignancy types were 0.55 (95% CI 0.42, 0.71) and 0.47 (0.20, 1.14) with combination therapy and monotherapy, respectively, and for malignancies excluding non-melanoma skin cancer, the SIRs were 0.38 (0.28, 0.52) and 0.39 (0.151, 1.03), respectively.

Nine patients had gastrointestinal perforations (three upper and six lower gastrointestinal tract) with combination therapy, giving an overall IR of 0.1 per 100 patient-years. The mean age of these nine patients at enrolment was 60 years (range 47–77). Six of the nine patients had

Fig. 2 Incidence rates of selected laboratory abnormalities by 6-month interval



Time, months	0–6	7–12	13–18	19–24	25–30	31–36	37–42	43–48	49–54	55–60	61–66	67–72	73–78	79–84
Combination pool														
Number of patients at risk	2887	2376	1968	1654	1554	1474	1382	1203	1007	814	676	460	203	104
Total patient-years of exposure	1354	1065	915	804	758	720	658	552	460	373	289	160	71	30
Monotherapy pool														
Number of patients at risk	471	425	393	260	107	91	86							
Total patient-years of exposure	225	204	170	96	50	44	26				Not applicable			

ALT: alanine aminotransferase; ANC: absolute neutrophil count; csDMARD: conventional synthetic DMARD; PY: patient-years; ULN: upper limit of normal.

Table 4 Incidence of infection by lowest ANC during the study

Lowest ANC (neutropenia grade)	Combination ($n = 2879$)[a]			Monotherapy ($n = 470$)[a]		
	Lowest ANC *n* (%)	Infection *n* (%)	Serious infection *n* (%)	Lowest ANC *n* (%)	Infection *n* (%)	Serious infection *n* (%)
⩾LLN	1382 (48.0)	720 (25.0)	106 (3.7)	188 (40.0)	93 (19.8)	5 (1.1)
<LLN	1497 (52.0)	862 (29.9)	126 (4.4)	282 (60.0)	132 (28.1)	2 (0.4)
⩾1500 cells/mm^3 – LLN (1)	564 (19.6)	332 (11.5)	54 (1.9)	112 (23.8)	49 (10.4)	0 (0)
⩾1000–<1500 cells/mm^3 (2)	568 (19.7)	329 (11.4)	48 (1.7)	101 (21.5)	52 (11.1)	2 (0.4)
⩾500–<1000 cells/mm^3 (3)	318 (11.0)	186 (6.5)	22 (0.8)	64 (13.6)	29 (6.2)	0 (0)
<500 cells/mm^3 (4)	47 (1.6)	15 (0.5)	2 (<0.1)	5 (1.1)	2 (0.4)	0 (0)

been treated with concomitant corticosteroids, seven had been treated with nonsteroidal anti-inflammatory drugs (NSAIDs), four experienced AEs of diverticulitis during the study and none had a history of diverticulitis prior to baseline. There were no gastrointestinal perforations with monotherapy. Patients with a history of diverticulitis at baseline ($n = 24$ with combination [0.8%] and $n = 6$ with monotherapy [1.3%]) had no gastrointestinal-related AEs during sarilumab treatment. The majority of these patients were also receiving concomitant NSAIDs and/or corticosteroids (19/24 and 5/6, respectively).

Elevation in lipids was reported as an AE with an incidence of 6.1 and 2.2 per 100 patient-years with combination therapy and monotherapy, respectively (Table 3). Increases were observed in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and high-density

lipoprotein cholesterol (HDL-C; Supplementary Table S7, available at *Rheumatology* online). Mean HDL/LDL ratio remained generally stable throughout follow-up (Supplementary Fig. S2, available at *Rheumatology* online). At baseline, 319 (11%) and 56 patients (12%) in the combination and monotherapy groups, respectively, were receiving lipid-modifying agents (predominantly statins), of whom 236 and 46 had no change in prescription of lipid-modifying agent during the study, 68 and 9 changed medication, and 15 and 1 stopped their medication. A total of 307 (11%) and 21 patients (4%) in the combination and monotherapy groups, respectively, initiated lipid-modifying therapy after initiating study drug. There were 47 MACE in 43 patients overall (Supplementary Table S8, available at *Rheumatology* online).

Other medically relevant events

Thromboembolic events (reported by the investigators and evaluated *post hoc*; not a prespecified AESI) occurred at a rate of 0.8 and 0.4 per 100 patient-years with combination therapy and monotherapy, respectively, including 0.2 and 0.2 per 100 patient-years for pulmonary embolism and 0.2 and 0.1 per 100 patient-years for deep vein thrombosis.

Discussion

This integrated analysis of ~9000 patient-years of cumulative patient exposure to sarilumab represents the most comprehensive investigation of sarilumab long-term safety to date. Results were consistent with the safety findings of sarilumab phase III trials, and consistent with the anticipated safety profile of IL-6 signalling inhibition [4–6, 14]. No signal was observed for an increased IR of any of the AEs or laboratory assessments analysed over time by 6-month interval. For several AEs, including serious infections, thrombocytopenia, ALT elevation, MACE and lipid elevations, the incidence was markedly lower with monotherapy than with combination therapy. Moreover, incidences of SAEs and AEs leading to discontinuation were lower with monotherapy than with combination therapy. These disparities likely reflect differences in the patient populations recruited into the combination and monotherapy trials, and in the case of serious infections and thrombocytopenia, possibly also the additional burden of taking more than one immunomodulator.

The IRs for SAEs and serious infections observed with sarilumab were no greater than those observed with other biologic and targeted synthetic DMARDs in long-term studies [15–19]. Focussing on DMARDs that target IL-6 signalling, the IRs for AEs and SAEs with sarilumab monotherapy (151.8 and 6.7 per 100 patient-years, respectively) and sarilumab combination therapy (144.2 and 9.4, respectively) may compare favourably with those observed for tocilizumab (224.5 and 13.6, respectively; all-exposed population: all doses, combination and monotherapy, exposure >36 months) [18]. Similarly, the IRs for serious infection with sarilumab monotherapy and combination therapy, 1.0 and 3.7 per 100 patient-years, respectively, may compare favourably with the IR of 4.5 observed with tocilizumab (all-exposed population) [18].

Consistent with previous analyses and with this class of therapy [4–6, 14], neutropenia was common with sarilumab treatment, as evidenced by investigator-reported AEs of leucopenia as well as protocol-mandated study measures of ANC. However, in this dataset, patients with neutropenia at any time during the study were no more likely to develop infections or serious infections than patients without neutropenia. Furthermore, the last ANC recorded before onset of infection or serious infection was normal in most cases. The absence of an association between neutropenia and infection in the sarilumab clinical trial populations is supported by the analyses of infection rate by maximum grade of neutropenia during the study (lowest ANC), which found no increase in infection rate with increasing maximum grade of neutropenia. Moreover, although the IR for leucopenia was numerically greater with sarilumab monotherapy than with combination therapy, the IR for serious infection was lower with monotherapy than with combination therapy. Evidence from pharmacodynamic studies suggests that the disconnect between neutropenia and infection with sarilumab treatment might be a consequence of neutrophil margination, whereby blockade of the effects of IL-6 results in migration of neutrophils from the circulation into extravascular pools without impairing their function [20, 21]. *In vitro* and *in vivo* studies on the effect of inhibition of IL-6 signalling on neutrophils found no effect on apoptosis, priming of respiratory burst, expression of adhesion molecules or chemotaxis [22].

Effective treatment of RA is associated with an increase in TC, LDL-C and HDL-C levels, without a change in TC: HDL-C ratio and without concomitant increase in the risk of MACE [23]. Monitoring lipid levels is recommended 1–2 months after initiating sarilumab and every 6 months thereafter [3]. Owing to a disease–drug interaction involving anti-IL-6R agents and simvastatin [24], the LDL-lowering effect of simvastatin is reduced by 5–6% in patients with RA taking concomitant sarilumab [25]. In the present analysis, sarilumab treatment was associated with increases in TC, LDL-C and HDL-C, whereas HDL/LDL ratio remained generally stable. The changes were not associated with an elevated risk of MACE in this study population. Exposure-adjusted incidences of MACE with sarilumab combination and monotherapy (0.5 and 0.2 per 100 patient-years, respectively) were no greater than the incidence in the general RA population (1.4 per 100 patient-years without exposure to DMARDs, 1.1 with exposure to DMARDs, and 1.2 overall) [26]. The absence of an excess in MACE despite the increase in lipid levels might be a manifestation of the 'lipid paradox', which describes the weaker association between LDL-C level and cardiovascular risk among patients with RA compared with the general population [27]. Moreover, inhibition of IL-6 signalling might exert effects on cardiovascular risk outside any effects on lipid levels; advances in the understanding of the role of inflammation in atherosclerosis have led to the suggestion that targeting the actions of IL-6 might prove

beneficial in reducing the inflammatory response implicated in development of coronary artery disease [28, 29].

Gastrointestinal perforation is a rare but serious condition, and patients with RA may be at higher risk than the general population [30, 31]. The incidence of gastrointestinal perforations observed with sarilumab (IRs of 0.1 per 100 patient-years and 0 with combination therapy and monotherapy, respectively) was lower than reported with tocilizumab (0.3 per 100 patient-years) [32]. It is notable that the majority of patients who experienced gastrointestinal perforations with sarilumab were taking concomitant NSAIDs and/or corticosteroids, which are a known risk factor for gastrointestinal perforations in patients with RA [30]. Indeed, the IR of 0.1 per 100 patient-years for the sarilumab combination group irrespective of NSAID/corticosteroid use is similar to the rate reported for biologic DMARDs without glucocorticoids in an administrative database analysis of 143 000 patients with RA (0.10 per 100 patient-years without glucocorticoids and 0.19 per 100 patient-years with glucocorticoids) [30]. However, the protocol exclusion of patients with a history of severe diverticulitis, another recognized risk factor for gastrointestinal perforation [30], may have mitigated against the risk of gastrointestinal perforation in this population. Sarilumab prescribing information lists diverticulitis under warnings and precautions and recommends the prompt evaluation of acute abdominal signs or symptoms [3].

Patients with RA are at approximately two-fold greater risk of venous thromboembolism compared with the general population, and assessment of thromboembolic events has become an important factor in the assessment of drug safety in RA [33, 34]. The IRs for thromboembolic events with sarilumab combination therapy and monotherapy (0.8 and 0.4 per 100 patient-years, respectively) were within the range of IRs reported in population-level analyses of patients with RA treated with DMARDs (0.4–0.8 per 100 patient-years) [33].

The IR for malignancy with sarilumab was similar to the general population, lower than a reference population of patients with RA, and remained stable throughout the observation period, suggesting no excess of malignancies with sarilumab.

Elevation in liver enzymes is a recognized effect of IL-6 signalling inhibition, and the profile of ALT increases seen with sarilumab was similar to that reported with tocilizumab [35]. The approximately doubled incidence of AEs of ALT elevation with sarilumab in combination with csDMARDs (predominantly methotrexate) compared with sarilumab monotherapy might reflect the known hepatoxic effects of methotrexate [36].

One limitation of this analysis is that cumulative patient-years of exposure to sarilumab in combination with csDMARDs was ~10 times greater than exposure to sarilumab monotherapy; consequently, the level of evidence is lower for monotherapy than for combination therapy. Moreover, where the incidence of an adverse event is low, it is not possible to appropriately determine a differential rate between combination and monotherapy because too few events occurred with monotherapy to allow a meaningful comparison. Another limitation, common to all prospective long-term analyses, is that attrition of patients who develop AEs, SAEs or serious infections tends to enrich the long-term population with patients who are best able to tolerate treatment.

In conclusion, no new safety concerns emerged in this integrated analysis of up to 7 years' sarilumab treatment representing almost 9000 years cumulative exposure. The long-term safety profile of sarilumab, either in combination with csDMARDs or as monotherapy remained stable and consistent with the anticipated profile of an IL-6 signalling inhibitor. Safety follow-up is ongoing in the sarilumab clinical development programme for both combination treatment and monotherapy.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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