Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo-controlled trial

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Summary

Background Multicentric Castleman's disease is a rare lymphoproliferative disorder driven by dysregulated production of interleukin 6. No randomised trials have been done to establish the best treatment for the disease. We assessed the safety and efficacy of siltuximab—a chimeric monoclonal antibody against interleukin 6—in HIV-negative patients with multicentric Castleman's disease.

Methods We did this randomised, double-blind, placebo-controlled study at 38 hospitals in 19 countries worldwide. We enrolled HIV-negative and human herpesvirus-8-seronegative patients with symptomatic multicentric Castleman's disease. Treatment allocation was randomised with a computer-generated list, with block size six, and stratification by baseline corticosteroid use. Patients and investigators were masked to treatment allocation. Patients were randomly assigned (2:1) to siltuximab (11 mg/kg intravenous infusion every 3 weeks) or placebo; all patients also received best supportive care. Patients continued treatment until treatment failure. The primary endpoint was durable tumour and symptomatic response for at least 18 weeks for the intention-to-treat population. Enrolment has been completed. The study is registered with ClinicalTrials.gov, number NCT01024036.

Findings We screened 140 patients, 79 of whom were randomly assigned to siltuximab (n=53) or placebo (n=26). Durable tumour and symptomatic responses occurred in 18 (34%) of 53 patients in the siltuximab group and none of 26 in the placebo group (difference 34·0%, 95% CI 11·1–54·8, p=0·0012). The incidence of grade 3 or more adverse events (25 [47%] *vs* 14 [54%]) and serious adverse events (12 [23%] *vs* five [19%]) was similar in each group despite longer median treatment duration with siltuximab than with placebo (375 days [range 1–1031] *vs* 152 days [23–666]). The most common grade 3 or higher were fatigue (five *vs* one), night sweats (four *vs* one), and anaemia (one *vs* three). Three (6%) of 53 patients had serious adverse events judged reasonably related to siltuximab (lower respiratory tract infection, anaphylactic reaction, sepsis).

Interpretation Siltuximab plus best supportive care was superior to best supportive care alone for patients with symptomatic multicentric Castleman's disease and well tolerated with prolonged exposure. Siltuximab is an important new treatment option for this disease.

Funding Janssen Research & Development.

Introduction

Castleman's disease is a rare lymphoproliferative disorder first described in the 1950s in patients with localised mediastinal lymphadenopathy.[1,2] Multicentric Castleman's disease is characterised by systemic symptoms including fever, night sweats, fatigue, anorexia, and cachexia, and was first recognised in 1978.[3] It constitutes roughly 30% of cases of Castleman's disease.[4] Common signs of multicentric Castleman's disease include enlarged lymph nodes in multiple anatomical sites, laboratory test abnormalities (eg, anaemia, hypoalbuminaemia), and increased concentrations of acute-phase proteins including C-reactive protein and fibrinogen.[5,6] The effects of multicentric Castleman's disease vary, and, in severe cases, multiorgan failure and death can occur.[5,6] Interleukin 6 plays a central part in the pathophysiology of multicentric Castleman's disease. Excess production of interleukin 6 leads to constitutional symptoms, growth of B lymphocytes and plasma cells, secretion of VEGF, and autoimmune phenomena.[7]

Multicentric Castleman's disease can affect HIV-seropositive patients, in whom viral interleukin 6 can trigger disease; however, many patients with multicentric Castleman's disease are HIV-negative, and the role of human interleukin 6 is well established.[5,8] There is no standard of care for multicentric Castleman's disease,[7] and roughly two-thirds of patients survive for more than 5 years after diagnosis.[6]

Siltuximab is a chimeric (human–mouse) immunoglobulin G1κ monoclonal antibody against human interleukin 6. Preliminary evidence from a phase 1 study suggests that it might have single-agent activity for Castleman's disease.[9,10] We assessed the efficacy and safety of siltuximab for HIV-negative patients with multicentric Castleman's disease in a randomised controlled trial.

Methods

Study design and patients

We did this randomised, double-blind, placebo-controlled study at 38 hospitals in 19 countries (Australia, Belgium, Brazil, Canada, China, Egypt, France, Germany, Hong Kong, Israel, New Zealand, Norway, Russia, Singapore, South Korea, Spain, Taiwan, UK, and USA).

Eligible patients (age ≥18 years, no upper age limit) had multicentric Castleman's disease based on a detailed patient history, physical examination, assessment of laboratory abnormalities, pathological diagnosis, and radiological imaging, and a histologically confirmed diagnosis of multicentric Castleman's disease using pre-specified criteria[11] by a central pathology laboratory (University of Washington School of Medicine, Seattle, WA, USA) from an excisional lymph node biopsy sample taken before enrolment. Patients had to have measurable disease not limited to cutaneous lesions, grade 1 or greater disease symptoms according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0, and Eastern Cooperative Oncology Group Performance Status score of 0–2. Patients could be newly diagnosed or previously treated, except those who had received interleukin-6 targeted treatment. Those receiving corticosteroids were given a stable or decreasing dose of no more than 1 mg/kg per day of prednisone or equivalent for more than 4 weeks before randomisation. Patients were excluded if they were HIV-seropositive, had evidence of human herpesvirus-8 infection by quantitative PCR in plasma by a central laboratory (see appendix for details), had other clinically significant infections including hepatitis B or C, or had a history of or concurrent lymphoma.

All patients provided written informed consent. The institutional review board or independent ethics committee at each site approved the protocol. The study was done according to the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice.

Randomisation and masking

Patients were centrally randomised (2:1) to receive either intravenous infusions of siltuximab (11 mg/kg) or matched placebo (appendix) every 3 weeks (one cycle). We used block randomisation (block size six) with a computer-generated randomisation schedule prepared under the supervision of the sponsor before the study and stratified by baseline concomitant corticosteroid use.

Patients and investigators giving treatment were masked to allocation until protocol-defined treatment failure. Laboratory assessments that could reveal treatment allocation (eg, C-reactive protein concentrations) were assessed centrally, and results were not provided to investigators during the masked phase. Investigators and independent assessors who evaluated outcomes were masked to allocation.

Procedures

All patients received best supportive care, which included management of effusions, use of antipyretic, antipruritic, antihistamine, and pain drugs, management of infections, transfusions, and standard management of infusion-related reactions as specified in institutional guidelines. Use of erythropoietin-stimulating agents, anti-tumour treatments, biological treatments, or an increase from baseline or a new course of corticosteroids were not allowed. Before each dose, patients had to meet retreatment criteria (absolute neutrophil count ≥$1{\cdot}0\times10^9$/L, platelets ≥50×10^9/L, and recovery of other clinically significant toxic effects to grade ≤2 or baseline) or dosing would be delayed by no more than 3 weeks until retreatment criteria were met. Dose reductions were not permitted.

Patients assigned to siltuximab discontinued study treatment at treatment failure (defined as sustained increase in grade ≥2 disease-related symptoms persisting ≥3 weeks; new disease-related grade ≥3 symptoms; sustained >1 point increase in ECOG-PS persisting for ≥3 weeks; radiological progression by modified Cheson criteria[12] or initiation of another treatment for multicentric Castleman's disease). At first treatment failure, patients assigned to placebo could crossover to receive open-label siltuximab plus best supportive care until second treatment failure. Patients who discontinued study treatment were followed up until the primary analysis.

CT imaging was done at screening, every 9 weeks during the first 6 months, and every 3 months thereafter. Disease signs and symptoms were assessed at each cycle on day 1. All tumour and symptomatic responses were confirmed on repeat assessment. We assessed safety on the basis of

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See **Online** for appendix

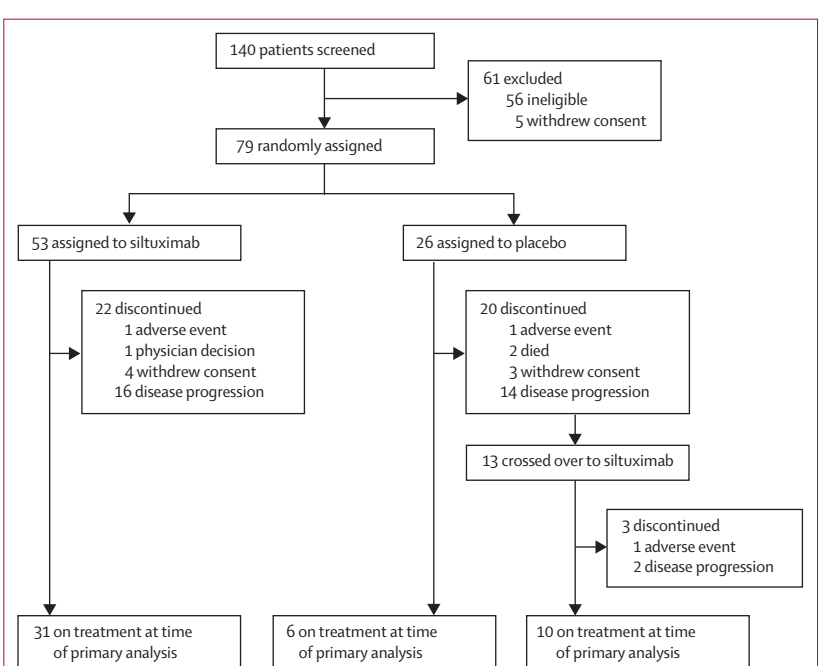

Figure 1: **Trial profile**

adverse events and serious adverse events graded by National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) and clinical laboratory testing. An independent data monitoring committee monitored safety data on an ongoing basis.

Outcomes

The primary endpoint was durable tumour and symptomatic response, defined as a complete response or partial response by modified Cheson criteria[12] (adjusted to include assessment of cutaneous lesions caused by multicentric Castleman's disease) with improvement or stabilisation of disease-related symptoms for at least 18 weeks during masked treatment. Because no specific response criteria exist to evaluate multicentric Castleman's disease, and since the disease is lymphoproliferative, we used Cheson criteria[12] because they can be used to evaluate lymph nodes. Tumour response was assessed by investigators and independent radiological review, masked to treatment failure (Biocor, Princeton, NJ, USA). Symptomatic response was assessed by investigators based on the sum of the severity of 34 disease-related signs and symptoms (disease-related overall symptom score; appendix).

Secondary endpoints were duration of tumour and symptomatic response, tumour response, time to treatment failure, 15 g/L or greater increase of haemoglobin concentration between baseline and week 13, discontinuation of corticosteroids, treatment failure rate (data not shown), improvement of multicentric Castleman's disease-related symptoms, overall survival at 1 year, and patient-reported outcomes including changes from baseline in Functional Assessment of Chronic Illness Therapy—Fatigue score, Short Form-36 Health Survey subscale scores (data not shown), and Multicentric Castleman's Disease Signs and Symptom Scores (data not shown). We also did pre-specified sensitivity (appendix) and subgroup analyses for the primary endpoint.

	Siltuximab group (n=53)	Placebo group (n=26)
Age (years)	47 (20–74)	48 (27–78)
Sex (male)	30 (57%)	22 (85%)
Ethnic origin		
White	19 (36%)	12 (46%)
Asian	27 (51%)	11 (42%)
Black	3 (6%)	0 (0%)
Other or unknown	4 (8%)	3 (12%)
Region		
North America	10 (19%)	5 (19%)
EMEA	13 (25%)	8 (31%)
Asia Pacific	26 (49%)	11 (42%)
Latin America	4 (8%)	2 (8%)
ECOG-PS score		
0	22 (42%)	10 (38%)
1	24 (45%)	16 (62%)
2	7 (13%)	0 (0%)
Disease-related overall symptom score	6 (2–31)	10 (1–30)
Disease histology*		
Hyaline vascular	18 (34%)	8 (31%)
Plasmacytic	13 (25%)	5 (19%)
Mixed	22 (42%)	13 (50%)
Patients who received previous systemic treatment	29 (55%)	17 (65%)
Corticosteroids	28 (97%)	15 (88%)
Chemotherapy	17 (59%)	12 (71%)
Rituximab	5 (17%)	3 (18%)
Immunosuppressants†	1 (3%)	3 (18%)
Interferon	1 (3%)	1 (6%)
Patients concomitantly taking corticosteroid	13 (25%)	9 (35%)
Haemoglobin concentration (g/L)	118 (65–170)	134 (85–181)
Interleukin 6 concentration (pg/mL)	7·13 (0·38–50·6)	4·94 (1·03–19·8)
C-reactive protein concentration (mg/L)	17·6 (0·10–181·0)	4·2 (0·4–107·0)
Erythrocyte sedimentation rate (mm/h)	62·0 (4–120)	23·5 (1–112)
Fibrinogen concentration (μmol/L)	15·14 (6·9–29·4)	12·08 (7·3–29·4)
Albumin concentration (g/L)	35 (15-49)	36 (28–46)

Data are median (range) or n (%). ECOG-PS=Eastern Cooperative Oncology Group performance status. EMEA=Europe, Middle East, and Africa. *By central pathological review. †Azathioprine, ciclosporin, or thalidomide.

Table 1: **Baseline characteristics**

Statistical analysis

We did the primary efficacy analysis for the intention-to-treat population. Assuming a durable tumour and symptomatic response of 5% with placebo and 30% with siltuximab, 78 patients (26 placebo, 52 siltuximab) were required to show a difference between treatment groups with a two-sided significance level of 5% and 80% power. We analysed the primary endpoint with an exact Cochran-Mantel-Haenszel test adjusted for baseline concomitant corticosteroid use; we calculated the difference between the proportions in each group and the corresponding 95% CIs.

We did secondary efficacy analyses for the intention-to-treat population except for duration of response (assessed in responders only) and for haemoglobin response (assessed in treated patients with baseline haemoglobin concentration below the lower limit of normal and ≥1 post-baseline haemoglobin evaluation). We assessed durations of response and time to event with the Kaplan-Meier method; patients who did not meet the endpoint by the time of analysis were censored to the last assessment before unmasking. We used Fisher's exact test to assess corticosteroid discontinuation.

We did a post-hoc analysis of patients with durable symptomatic improvement (>50% decrease in disease-symptom score) and with durable complete symptomatic resolution for at least 18 weeks. The safety population was defined as all randomly assigned patients who received at least one dose of study drug. All analyses were done 48 weeks after the last patient started study treatment and were done with SAS (version 9.2).

This study is registered at ClinicalTrials.gov, number NCT01024036.

Role of the funding source
Representatives of the study sponsors were involved in the study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

We screened 140 patients, of whom 56 were ineligible and five withdrew consent. From Feb 9, 2010, to Feb 3, 2012, we enrolled 79 patients (53 assigned to siltuximab, 26 assigned to placebo; figure 1). Baseline characteristics were well balanced between groups except for sex (table 1). According to central pathological review, patients had mixed, hyaline vascular, or plasmacytic histological subtypes. The median age was 48 years (range 20–78). All patients had symptomatic disease, with 62 (78%) having more than three symptoms including fatigue (86%), malaise (61%), night sweats (52%), peripheral sensory neuropathy (38%), anorexia (37%), pruritus (37%), dyspnoea (35%), oedema of limbs (30%), hyperhidrosis (30%), or weight loss (30%). A wide range of inflammatory laboratory values was recorded in both groups. Most patients had received previous systemic treatment (table 1).

Median duration of masked treatment was 375 days (range 1–1031) with siltuximab and 152 days (range 23–666) with placebo. Median duration of follow-up for the intention-to-treat population was 422 (range 55–1051) days. At the time of analysis, 31 (59%) patients were still receiving masked siltuximab and six (23%) were receiving placebo.

18 patients (34%; one CR, 17 PR) taking siltuximab versus none taking placebo had durable tumour and symptomatic response (difference between groups 34·0%, 95% CI 11·1–54·8, p=0·0012; table 2), with a median response duration of 383 days (range 232–676). At the time of primary analysis, only one of 18 initial responders had subsequently progressed. We obtained similar results when the primary analysis was repeated without adjustment for the stratification factor (p=0·0004). Median time to treatment failure with siltuximab was not estimable (NE; 95% CI 378–NE) and with placebo was 134 days (95% CI 85–NE, p=0·0084; figure 2A, table 2). 16 (30%) of 53 patients taking siltuximab and 14 (54%) of 26 taking placebo discontinued because of treatment failure. 13 (50%) patients assigned to placebo received open-label siltuximab after treatment failure for a median of 295 days (range 128–852), including three who discontinued siltuximab because of a second treatment failure (n=2) or adverse event (n=1, thrombocytopenia). Among patients in the placebo group who crossed over, one had a durable tumour and symptomatic response (partial response) 120 days after starting siltuximab and nine had not had treatment failure at the time of analysis.

Tumour response was achieved by 20 (38%) patients in the siltuximab group and one (4%) in the placebo group according to independent review (p=0·0022) and 27 (51%) versus none according to investigator assessment (p<0·0001; table 2). Figure 2 shows best tumour response according to central review (figure 2B) and investigator assessment (figure 2C). Median disease-related overall symptom score improved compared with baseline at every cycle, with a greater improvement with siltuximab than with placebo (figure 3A). A durable symptomatic response was significantly more common with siltuximab than with placebo (p=0·0018), as was durable complete symptomatic response (p=0·0037; table 2). Median time to durable symptomatic response was 170 days (95% CI 67–274) with siltuximab and not reached (95% CI 227–NE) with placebo (p=0·0288; table 2, figure 3B). Median time to next treatment was not reached (95% CI NE–NE) with siltuximab and 280 days (95% CI 161–NE) with placebo (p=0·0013; table 2, figure 3C). Among the 31 patients taking siltuximab and 11 patients taking placebo who had anaemia at baseline, a more than 15 g/L increase in haemoglobin concentration occurred in 19 (61%) versus no patients at week 13 (p=0·0002), with 13 (42%) versus

	Siltuximab group (n=53)	Placebo group (n=26)	Difference or HR (95% CI)	p value
Primary endpoint				
Durable tumour and symptomatic response by independent review*	18 (34%)	0 (0%)	34·0% (11·1 to 54·8)	0·0012
Complete response	1 (2%)	0 (0%)	..	..
Partial response	17 (32%)	0 (0%)	..	..
Duration of durable tumour and symptomatic response* (days)	383 (232 to 676)	..	..	..
Secondary endpoints				
Tumour response by independent review†	20 (38%)	1 (4%)	33·9% (11·1 to 54·8)	0·0022
Complete response	2 (4%)	0 (0%)	..	..
Partial response	18 (34%)	1 (4%)	..	..
Tumour response by investigator assessment†	27 (51%)	0 (0%)	50·9% (29·2 to 70·1)	<0·0001
Complete response	3 (6%)	0 (0%)		
Partial response	24 (45%)	0 (0%)		
Time to tumour response by independent review for responders† (days)	155 (44 to 742)	65 (65 to 65)	..	..
Durable symptomatic response rate*	30 (57%)	5 (19%)	37·4% (14·9 to 58·2)	0·0018
Complete symptom response	13 (25%)	0 (0%)	24·5% (1·4 to 46·2)	0·0037
Time to durable symptomatic response* (days)	170 (67 to 274)	NE (227 to NE)	2·774 (1·068 to 7·206)	0·0288
Time to treatment failure* (days)	NE (378 to NE)	134 (85 to NE)	0·418 (0·214 to 0·815)	0·0084
Time to next treatment* (days)	NE (NE to NE)	280 (161 to NE)	0·298 (0·137 to 0·652)	0·0013
Haemoglobin concentration increase of ≥15 g/L at week 13 compared with baseline‡	19 (61%)	0 (0%)	61·3 (28·3 to 85·1)	0·0002
Patients who discontinued corticosteroids§	4 (31%)	1 (11%)	19·7 (−23·6 to 56·7)	0·3602

Data are n (%) or median (range). *Intention-to-treat population. †Response-evaluable population. ‡Haemoglobin response-evaluable population (31 in siltuximab group *vs* 11 in placebo group). §Patients taking corticosteroids at baseline: 13 *vs* nine. NE=not evaluable.

Table 2: **Key efficacy endpoints**

none (0%) achieving normalised haemoglobin concentrations in a post-hoc analysis (figure 4A). 1-year survival was 100% (95% CI 100–100) in the siltuximab group and 92% (95% CI 72–98) in the placebo group.

Although no patients with the hyaline vascular subtype in either treatment group had durable tumour and symptomatic responses by independent review (figure 5), durable tumour and symptomatic response by investigator assessment occurred in three (17%) of 18 siltuximab-treated patients but in none of eight placebo-treated patients during the masked treatment period. Furthermore, we consistently recorded a positive treatment effect across all endpoints among siltuximab-treated patients in the hyaline vascular subgroup (appendix).

Median baseline serum interleukin-6 concentration was greater in the siltuximab group than in the placebo

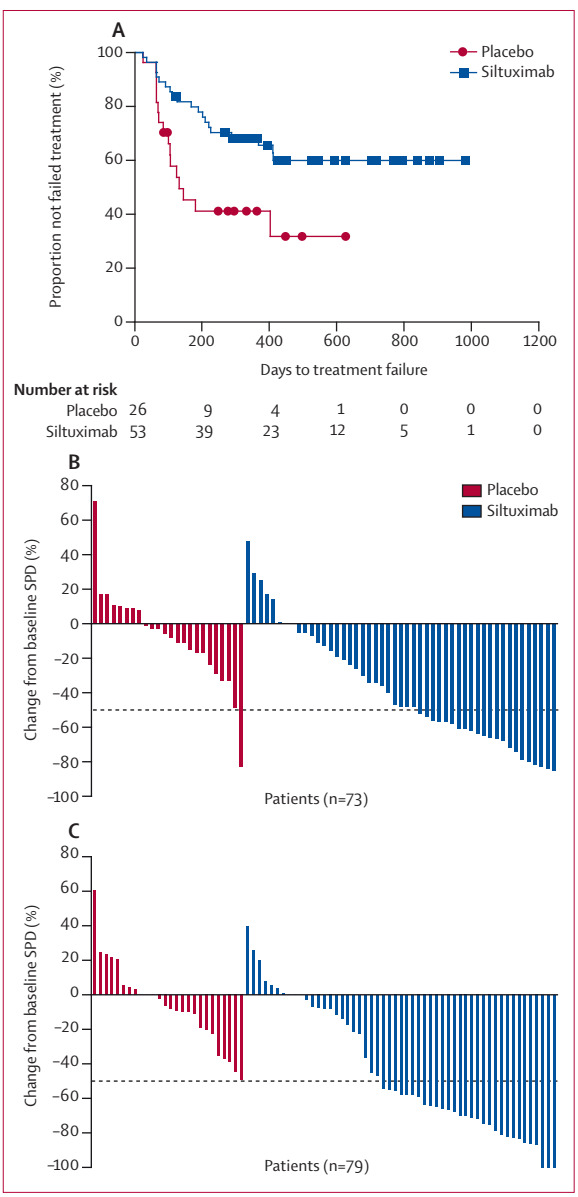

Figure 2: **Analyses of time to treatment failure and best tumour response**
(A) Kaplan-Meier plot of time to treatment failure for the intention-to-treat population. Waterfall plots for best tumour response in the response-evaluable population, by central review (B) and investigator assessment (C). For six patients, measurable lesions were identified by investigator but patients were not deemed measurable by central reviewer. SPD=sum of the product of the diameters of index lesions.

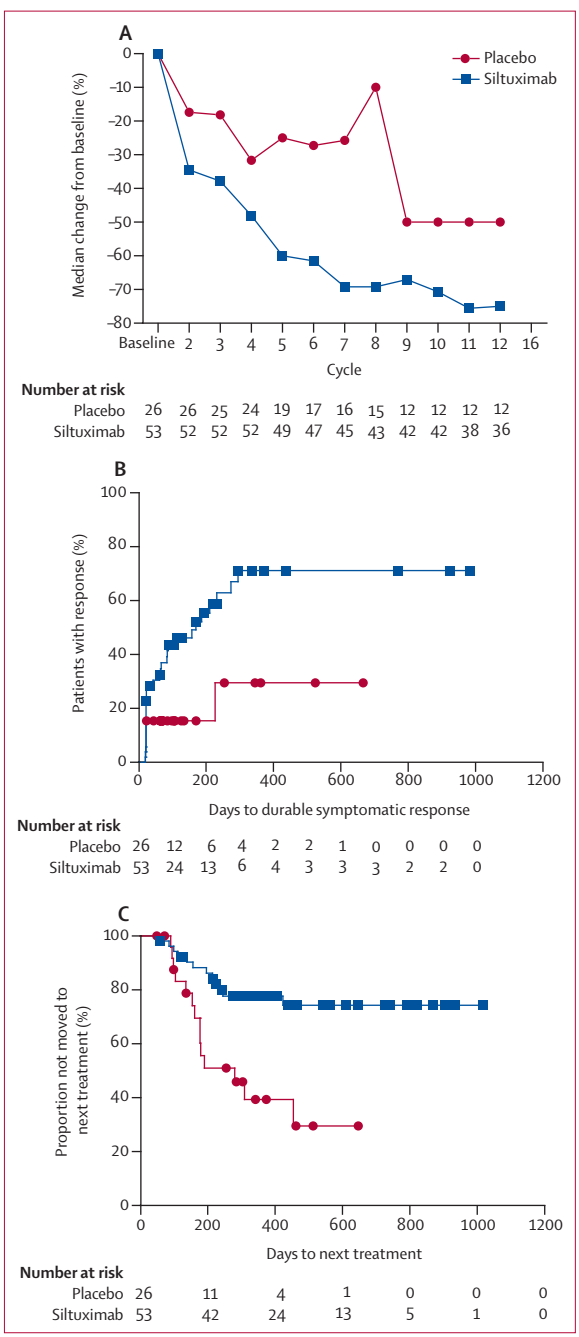

Figure 3: **Symptom score, time to durable symptomatic response, and time to next treatment**
Median percent change from baseline for multicentric Castleman's disease-related overall symptom score on day 1 of each cycle (A). Kaplan-Meier plot of time to durable symptomatic response (B) and time to next treatment in the intention-to-treat population during the masked treatment period (C).

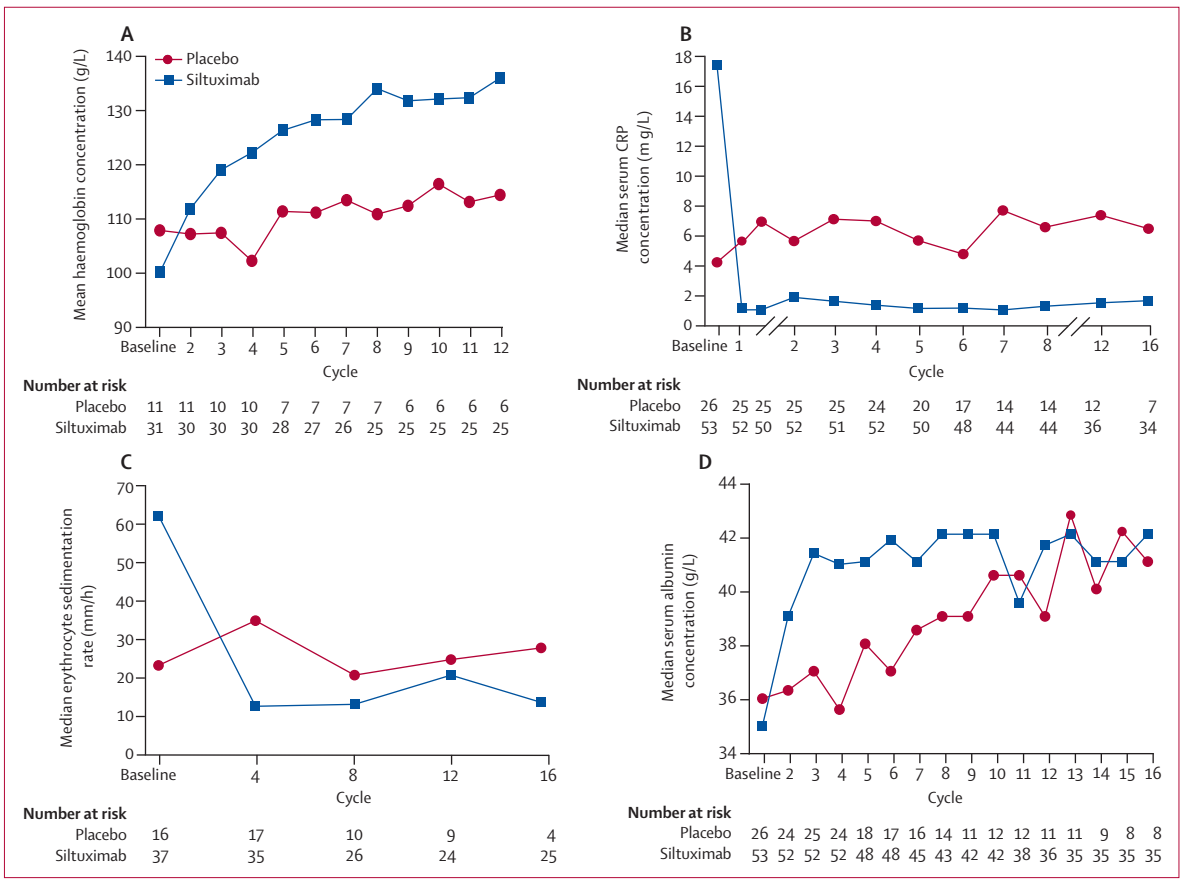

Figure 4: **Haemoglobin, serum C-reactive protein, erythrocyte sedimentation rate, and serum albumin concentration**
Data are for day 1, unless stated otherwise. (A) Mean haemoglobin concentration by study visit in anaemic patients at baseline. Median serum concentration of C-reactive protein (B), erythrocyte sedimentation rate (C), and serum concentration of albumin (D) by study visit in the intention-to-treat population. In panel B, the earliest three timepoints show baseline, cycle 1 day 8, and cycle 1 day 15.

group (table 1, appendix). Because baseline interleukin-6 and C-reactive protein concentrations correlated well (r=0·7; appendix) and only baseline interleukin 6 could be measured because of assay interference in the presence of siltuximab, we measured C-reactive protein as an indirect assessment for inhibition of interleukin 6 bioactivity.[13] Median C-reactive protein concentrations decreased rapidly from baseline for patients taking siltuximab and were stable in patients taking placebo (figure 4B) and decreases in erythrocyte sedimentation rate (figure 4C) and fibrinogen. Serum albumin concentration increased rapidly in the siltuximab group (figure 4D), whereas improvement in albumin concentration in patients in the placebo group without treatment failure occurred in later cycles. Baseline interleukin 6 concentration was not associated with durable tumour and symptomatic response or best tumour response. Analysis using log-transformed baseline C-reactive protein concentrations (because the values were not normally distributed and inter-patient variability was large) showed a difference between responders and non-responders by durable tumour and symptomatic response (median 34·50 *vs* 6·32 mg/L; p=0·0522) and by best tumour response (median 38·00 *vs* 5·09 mg/L; p=0·0118) in the siltuximab group; however, we could not identify baseline C-reactive protein concentrations predictive of tumour response.

During masked treatment, patients completed a median of 19 cycles of siltuximab and eight cycles of placebo. At least one dose was delayed in 21 (40%) siltuximab-treated patients. 34 (3%) of 1113 siltuximab doses were delayed, including for 15 patients because of adverse events, most often neutropenia (n=2).

Adverse events occurred in similar proportions of patients in each treatment group despite treatment duration being more than twice as long in the siltuximab group than in the placebo group. Serious adverse events occurred in 12 (23%) patients in the siltuximab group *vs* five (19%) in the placebo group (table 3). Common adverse events that were much more frequent (>10 percentage points) in the siltuximab group than in the placebo group were pruritus, maculopapular rash, weight gain, upper respiratory tract infection, and localised oedema (table 3). Four (8%) of 53 patients reported siltuximab infusion reactions of low grade, except for one grade 3 anaphylactic reaction. Adverse events leading to discontinuation of

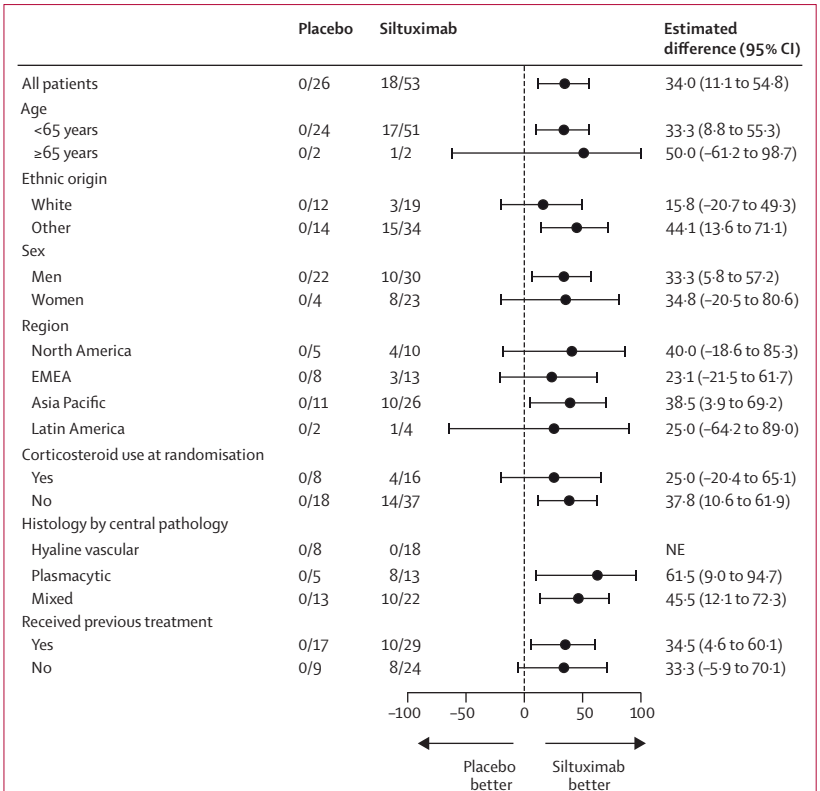

Figure 5: **Subgroup analyses of durable tumour and symptomatic response**
Estimated difference is %. EMEA=Europe, Middle East, and Africa.

siltuximab and placebo (12 [23%] *vs* ten [38%]) were related to treatment failure, except for one patient in each group (myelodysplastic syndrome on placebo; anaphylactic reaction on siltuximab).

Grade 3 or higher events reported in more than 5% of siltuximab-treated patients were fatigue and night sweats and, in participants receiving placebo, anaemia (table 3); treatment-emergent adverse events of grade 4 or higher are shown in the appendix. Grade 3 haematological and laboratory abnormalities were infrequent and manageable; no grade 4 or higher haematological and chemistry abnormalities occurred with siltuximab. No grade 3 or higher liver function test abnormalities or gastrointestinal perforations occurred.

Three (6%) of 53 patients had serious adverse events reasonably related to siltuximab (lower respiratory tract infection, anaphylactic reaction, sepsis). Two (4%) of 53 patients taking siltuximab died because of disease progression, and four (15%) of 26 patients taking placebo who did not crossover died (three as a result of disease progression and one because of broncho-pneumonia and congestive cardiac failure). One of 66 siltuximab-treated patients with appropriate samples had detectable, non-neutralising antibodies to siltuximab 45 days after last dose. No treatment-related deaths were reported.

	Siltuximab group (n=53)		Placebo group (n=26)	
	All grades	Grade ≥3	All grades	Grade ≥3
Patients with ≥1 adverse event	53 (100%)	25 (47%)	25 (96%)	14 (54%)
Pruritus	22 (42%)	0 (0%)	3 (12%)	0 (0%)
Upper respiratory tract infection	19 (36%)	0 (0%)	4 (15%)	1 (4%)
Fatigue	18 (34%)	5 (9%)	10 (38%)	1 (4%)
Maculopapular rash	18 (34%)	0 (0%)	3 (12%)	0 (0%)
Peripheral oedema	17 (32%)	1 (2%)	6 (23%)	0 (0%)
Malaise	15 (28%)	0 (0%)	5 (19%)	0 (0%)
Dyspnoea	13 (25%)	1 (2%)	9 (35%)	1 (4%)
Peripheral sensory neuropathy	13 (25%)	0 (0%)	5 (19%)	1 (4%)
Diarrhoea	12 (23%)	0 (0%)	5 (19%)	1 (4%)
Localised oedema	11 (21%)	2 (4%)	1 (4%)	0 (0%)
Weight gain	11 (21%)	2 (4%)	0 (0%)	0 (0%)
Hyperhidrosis	10 (19%)	2 (4%)	4 (15%)	0 (0%)
Decreased appetite	9 (17%)	1 (2%)	4 (15%)	0 (0%)
Night sweats	9 (17%)	4 (8%)	3 (12%)	1 (4%)
Cough	8 (15%)	0 (0%)	6 (23%)	0 (0%)
Abdominal pain	8 (15%)	0 (0%)	1 (4%)	1 (4%)
Thrombocytopenia	8 (15%)	2 (4%)	1 (4%)	1 (4%)
Nasopharyngitis	8 (15%)	0 (0%)	1 (4%)	0 (0%)
Hyperuricaemia	7 (13%)	2 (4%)	0 (0%)	0 (0%)
Neutropenia	7 (13%)	2 (4%)	2 (8%)	1 (4%)
Nausea	5 (9%)	1 (2%)	5 (19%)	0 (0%)
Anaemia	5 (9%)	1 (2%)	4 (15%)	3 (12%)
Weight loss	4 (8%)	0 (0%)	4 (15%)	0 (0%)
Tumour pain	4 (8%)	0 (0%)	4 (15%)	0 (0%)
Hypertension	4 (8%)	2 (4%)	1 (4%)	0 (0%)
Hyperkalemia	2 (4%)	2 (4%)	0 (0%)	0 (0%)

Data are n (%). Events occurred in at least 15% of patients in either group, although grade ≥3 events shown occurred in at least 4% of patients in either group.

Table 3: **Adverse events**

Discussion

We report the results of the first randomised, double-blind, placebo-controlled trial for the treatment of HIV-negative and human herpesvirus-8-negative multicentric Castleman's disease (panel). These results are the basis of the US Food and Drug Administration's approval[16] and of the European Medicines Agency's[17] positive opinion for siltuximab as a treatment in this setting. Siltuximab plus best supportive care was superior to best supportive care alone as measured by durable tumour response, amelioration of symptoms, and improvement in laboratory parameters. Since no established criteria for response in multicentric Castleman's disease were available, we used stringently defined endpoints encompassing standardised comprehensive symptom assessment and central review of CT scans to assess tumour size.

Overall, almost three-fifths of patients had a durable symptomatic response to siltuximab, with a median time

to response of 33 days for responders. Laboratory parameters, including haemoglobin concentration, erythrocyte sedimentation rate, and fibrinogen concentration, also normalised rapidly. By contrast, involution of lymphadenopathy with siltuximab was more gradual, with a median time to response of 155 days and an overall tumor response rate of 38%. 11 (21%) patients assigned to siltuximab were still taking masked treatment without tumour response at the time of the primary analysis, and as anti-interleukin-6 treatment is not expected to be directly cytolytic, more patients might achieve tumour response with longer treatment. Although we recorded no difference in survival, the duration of follow-up was short and the crossing over of patients from placebo to siltuximab treatment might limit our conclusions. It seems unlikely that differences in baseline characteristics explained the different responses between treatment groups, which were well matched.

The hyaline vascular histological type was originally thought to be localised and thus associated with unicentric Castleman's disease; however, many patients with multicentric Castleman's disease have distinct hyaline vascular characteristics,[6,7,10] although the plasmacytic type tends to be more common.[6] In patients with hyaline vascular disease, durable tumour and symptomatic responses were reported by investigator assessment, and we reported a benefit for secondary endpoints (appendix). In a phase 1 study, durable tumour and clinical responses were reported in patients with the hyaline vascular subtype,[9] suggesting that such patients might benefit from treatment with siltuximab. Viral interleukin 6 is postulated to trigger multicentric Castleman's disease in patients with HIV or human herpesvirus-8, and because results of in-vitro studies showed that siltuximab does not bind to viral interleukin 6 (unpublished data), we excluded these patients from the study. There is, however, emerging evidence of a contribution of human interleukin 6 to the pathogenesis of HIV-associated and human herpesvirus-8-associated multicentric Castleman's disease,[18] and the role of siltuximab in this disease might be established in future studies.

Overall, siltuximab had a favourable safety profile. Siltuximab was discontinued because of adverse events in only one patient, because of an anaphylactic reaction. Furthermore, prolonged treatment with siltuximab is reported to be well tolerated with no evidence of new or cumulative toxic effects or treatment discontinuations and with a low rate of serious adverse events in a study of extended treatment with siltuximab for patients with multicentric Castleman's disease.[19]

Response to drugs such as corticosteroids, chemotherapy, and immunomodulatory drugs has been described in case reports and small case series.[20,21] Rituximab has been widely used for the treatment in HIV-associated and human herpesvirus-8-associated multicentric Castleman's disease;[22] however, for patients without HIV and human herpesvirus-8, only incidental responses to rituximab treatment either alone or in combination treatment have been reported in single patient case reports[21,23,24] and a case series of three patients.[20] Two large retrospective studies done before the introduction of anti-interleukin-6 targeted treatment reported overall survival of 65% at 5 years[6] and disease-free survival of 46% at 3 years.[25] These studies are limited by their retrospective nature and incomplete testing (including HIV status) and treatment data. Tocilizumab, a monoclonal antibody targeting the interleukin-6 receptor, reduced lymphadenopathy and improved symptoms and interleukin-6-related laboratory markers in a single-group study[9] of 28 HIV-negative patients with plasmacytic multicentric Castleman's disease. However, this study did not have a control group, used less rigorous response criteria, and enrolled a homogeneous patient population.

Multicentric Castleman's disease waxes and wanes, which was another justification for our placebo-controlled trial design, and the implementation of strict protocol definitions of treatment failure. As expected, more patients on placebo had treatment failure. Siltuximab-treated patients with treatment failure might have discontinued siltuximab too early to assess treatment effect, or their disease might have needed treatment beyond siltuximab and best supportive care. Furthermore,

***Panel:* Research in context**

Systematic review

We searched PubMed (with no date restrictions) with the keywords "Castleman", "angiofollicular lymph node hyperplasia", "giant lymph node hyperplasia", "angiomatous lymphoid hamartoma", "lymph nodal hamartoma", and "IL-6 syndrome" for any report of treatment outcomes of multicentric Castleman's disease. We also characterised incidence and treatment practice of multicentric Castleman's disease in two US health insurance claims databases [14] and through review of medical records from two US multicentric Castleman's disease referral centres.[15] We developed a novel composite endpoint of durable radiological and symptom response based on the pilot phase 1 study of siltuximab[9,10] and after advice from regulatory agencies. Before our study, no treatments had been approved for multicentric Castleman's disease in either the USA or the European Union. Chemotherapy, rituximab, steroids, and other drugs are used; however, published studies are largely confined to case studies and retrospective series. One prospective Japanese single-group, phase 2 trial of the anti-interleukin-6 receptor antibody tocilizumab has led to the approval of this drug in Japan.[8]

Interpretation

We report the first randomised and largest trial ever done of HIV-negative, human herpesvirus 8-negative patients with multicentric Castleman's disease. We assessed the safety and efficacy of siltuximab, a high-affinity monoclonal antibody against human interleukin 6 for this disease. Siltuximab plus best supportive care was superior to best supportive care alone and well tolerated with prolonged exposure. It also had a favourable effect on radiological response in lymph nodes, anaemia and other disease symptoms, and inflammatory parameters. Siltuximab was well tolerated, with no increase in adverse events compared with placebo. These results provide further evidence that interleukin 6 has a central role in development of multicentric Castleman's disease. Based on these results, siltuximab has become the first treatment for HIV-negative, human herpesvirus-8-negative patients with multicentric Castleman's disease to be approved by the US Food and Drug Administration and the European Medicines Agency and is a valuable new treatment option.

activation of other cytokines apart from interleukin 6, including interleukin 1, interleukin 10, and tumour necrosis factor α has been reported,[26] which might explain the need for additional treatment in some patients. Future studies should address optimum treatment for patients with multicentric Castleman's disease, including combination treatments; however, siltuximab should be considered a valuable treatment option.

Contributors

FvR, AF, JC, RB, HvdV, CC, NM, and JV designed the study. RSW, NM, J-FR, X-YK, AF, MC, TL, RKH, JZ, S-GC, HR, JC, and CC collected data. FvR, RSW, NM, J-FR, AF, DS, MC, TL, RKH, YTG, JC, RB, MR, TAP, MR, HvdV, CC, and JV analysed and interpreted data. FvR, RSW, NM, J-FR, X-YK, AF, DS, MC, TL, RKH, YTG, JZ, S-GC, HR, JC, RB, MR, TAP, MR, HvdV, JV, and CC wrote the report.

Declaration of interests

RB, MRo, TAP, MRe, HvdV, and JV have been employed by Janssen Research & Development and own stock in Johnson & Johnson. AF has had an advisory role for and received honoraria from Janssen Pharmaceuticals. DS has received honoraria from Janssen Cilag. FvR has had an advisory role for and received research funding from Janssen Research & Development. J-FR has received speaker's fees from Beta Innovation and research funding from Janssen Research & Development. NM and JC have received research funding from Janssen Research & Development. YTG has received research funding from Janssen Research & Development and honoraria from Gilead Sciences, and Hospira, and has had an advisory role with Bristol-Myers Squibb, Gilead Sciences, and Hospira. CC has received research funding from Janssen Research & Development and the US National Institutes of Health, done consultancy with Janssen Research & Development, has had an advisory role for St Jude Children's Hospital and Research Center and Hutchinson Cancer Research Institute—Uganda, and has received royalties from UpToDate. RSW has received research funding from Janssen Research & Development, Amgen, Baxter, Bayer, Biogen-Idec, Bristol-Myers Squibb, GlaxoSmithKline, MSD, Novartis, Pfizer, and Roche, has been a consultant for Bayer, Biogen-Idec, GlaxoSmithKline, and Novartis, has had advisory roles with Biogen-Idec and Novartis, received speaker's fees from Novartis, and received honoraria from Alexion. X-YK, MC, TL, RKH, JZ, S-GC, and HR declare no competing interests.

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