Safety and efficacy of ustekinumab or golimumab in patients with chronic sarcoidosis

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ABSTRACT Sarcoidosis is characterised by non-caseating granulomas that secrete pro-inflammatory cytokines, including interleukin (IL)-12, IL-23, and tumour necrosis factor (TNF)-α. Ustekinumab and golimumab are monoclonal antibodies that specifically inhibit IL-12/IL-23 and TNF-α, respectively.

Patients with chronic pulmonary sarcoidosis (lung group) and/or skin sarcoidosis (skin group) received either 180 mg ustekinumab at week 0 followed by 90 mg every 8 weeks, 200 mg golimumab at week 0 followed by 100 mg every 4 weeks, or placebo. Patients underwent corticosteroid tapering between weeks 16 and 28. The primary end-point was week 16 change in percentage predicted forced vital capacity (ΔFVC % pred) in the lung group. Major secondary end-points were: week 28 for ΔFVC % pred, 6-min walking distance, St George's Respiratory Questionnaire (lung group), and Skin Physician Global Assessment response (skin group).

At week 16, no significant differences were observed in ΔFVC % pred with ustekinumab (-0.15, p=0.13) or golimumab (1.15, p=0.54) compared with placebo (2.02). At week 28, there were no significant improvements in the major secondary end-points, although a nonsignificant numerically greater Skin Physician Global Assessment response was observed following golimumab treatment (53%) when compared with the placebo (30%). Serious adverse events were similar in all treatment groups.

Although treatment was well tolerated, neither ustekinumab nor golimumab demonstrated efficacy in pulmonary sarcoidosis. However, trends towards improvement were observed with golimumab in some dermatological end-points.

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For editorial comments see page 1123.

Introduction

Sarcoidosis is a systemic, granulomatous disease with highly variable clinical manifestations, natural history, and prognosis that primarily affects the lungs and lymphatic systems [1]. Sarcoidosis is diagnosed by clinical findings and corroborating histological evidence of non-caseating epithelioid cell granulomas [2]. Over 90% of patients have lung involvement [3], while skin lesions are observed in ~25% of patients [4]. Although spontaneous remissions occur in almost two-thirds of patients, chronic or progressive disease is seen in 10–30% [5], with permanent pulmonary or extrapulmonary sequelae in at least 10–20% of patients. The disease is fatal in 1–5% of patients, typically due to progressive respiratory insufficiency, central nervous system, or myocardial involvement [5].

Currently, no therapy is approved for the treatment of sarcoidosis. The standard of care is oral corticosteroids (OCS), which has been shown to stabilise or improve the disease, although relapse commonly occurs once OCS therapy is tapered or discontinued [6]. Alternatives, such as antimalarial, cytotoxic, and biological agents, have shown variable efficacy [7], although treatment with these agents has also been associated with a relapse upon discontinuation, toxicity, and/or potentially serious adverse effects [1, 8]. There is a substantial need for safer and more effective therapies for sarcoidosis.

Although the aetiology of sarcoidosis is unknown, the inflammatory cytokine, tumour necrosis factor (TNF)-α, is instrumental to the formation and maintenance of the non-caseating granuloma that characterises sarcoidosis [9]. Macrophage inflammatory protein (MIP)-1β, an immune cell chemoattractant (CCL4), is regulated by TNF-α [10] and higher levels of this inflammatory chemokine in some but not all sarcoidosis patients may indicate heightened activation of the TNF pathway in the subset of patients with the highest levels. TNF-α inhibition in patients with sarcoidosis has been shown to reduce disease signs and symptoms [11, 12]. In a phase II, multicentre, randomised, double-blind, placebo-controlled study of 138 patients with chronic sarcoidosis, treatment with infliximab (a chimeric monoclonal antibody that inhibits TNF-α) resulted in a statistically significant improvement in the percentage predicted forced vital capacity (FVC) compared with placebo [1]. Improvement was also observed in other disease activity measures, such as chest radiograph reticulation (R) scores [13], MIP-1β levels [10], and serum angiotensin-converting enzyme (ACE) levels [1]. In a case series of 54 patients with lupus pernio, near or complete resolution was achieved in 77% of patients who received infliximab treatment compared with only 19% of patients receiving systemic corticosteroids [14].

Although the potential pathogenic role of excess TNF-α in granulomatous disease [9, 15–18] is well documented, TNF-α does not solely account for the T-helper cell type 1 (Th-1) dominated cytokine environment in the sarcoid lung; in particular, high levels of interferon (IFN)-γ have also been implicated in the pathogenesis of sarcoidosis [19]. In addition, alveolar macrophages from patients with sarcoidosis have been shown to produce interleukin (IL)-12 in addition to TNF-α, IL–1β, and IL–6 [20–29]. Over-expression of IL-12, by activated alveolar macrophages, results in enhanced Th-1 cell proliferation and activation, leading to the increased expression of the pro-inflammatory mediators IFN–γ and TNF-α, and the secretion of cytokines and chemotactic factors that could, in turn, recruit and activate additional T-cells. Macrophages also produce profibrotic mediators, such as fibronectin [30], and transforming growth factor-β [31] that contribute to fibrotic granuloma development. Collectively, these data suggest that IL-12 may be involved in both initiating and perpetuating granulomatous inflammation of sarcoidosis. Recently, transcriptomic analysis of biopsies of sarcoid skin lesions demonstrated upregulation of TNF-α and IL-12 as well as IL-21 and IL-23, suggesting Th-1 and possibly Th-17 upregulation in sarcoidosis [32].Thus, inhibition of either TNF-α or IL-12/IL-23 could, potentially, be effective in the treatment of chronic sarcoidosis.

Golimumab is a human monoclonal antibody that binds TNF-α with high affinity and specificity and is approved for the treatment of moderate-to-severe rheumatoid arthritis, ulcerative colitis, active psoriatic arthritis, and ankylosing spondylitis [33]. Ustekinumab is a human immunoglobulin G1κ monoclonal antibody that binds, with high affinity, to the shared p40 subunit of human IL-12 and IL-23 and is approved for the treatment of moderate-to-severe plaque psoriasis [34]. Here we report the results from a multicentre, randomised, double-blind, placebo-controlled study using ustekinumab or golimumab in patients with chronic pulmonary and/or cutaneous sarcoidosis.

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Material and methods

Patients

Patients aged between 18 and 85 years were eligible for enrolment if they had histologically proven pulmonary or skin sarcoidosis diagnosed a minimum of 2 years before screening took place and no history of latent or active tuberculosis. In addition, a negative Quantiferon-GOLD assay was required at the screening visit in order for a patient to be enrolled. Entry into the lung group required evidence of lung parenchymal disease on a chest radiograph (stage II, III, or IV, but without cavitary disease), % pred FVC 45–80%, Medical Research Council dyspnoea score of >2, and a 6-min walking distance (6MWD) of between 100 and 550 m. These criteria were chosen based on the results of a previous randomised, placebo-controlled trial of infliximab for chronic pulmonary sarcoidosis, where a significant response was observed and the subgroup of patients with the aforementioned criteria had a more robust response [1]. Entry into the skin group required: active, unresolved, chronic skin lesions for $\geqslant$3 months, despite use of current systemic/local therapies; a single lesion of $\geqslant$2 cm or multiple lesions ($\geqslant$3) with at least one lesion $\geqslant$1 cm in size at its longest dimension; and a Skin Physician's Global Assessment (SPGA) score $\geqslant$2. The SPGA score is based on the physician's assessment of induration and erythema of the patient's skin lesions, each graded on a 0 (none) to 4 (very severe) scale. Patients meeting entry criteria for both the lung and skin groups could be entered into both groups. All patients required treatment with 10–25 mg·day^{-1} of prednisone or its equivalent orally and/or $\geqslant$1 immunomodulator for $\geqslant$3 months with a stable dose for $\geqslant$4 weeks before screening. Key exclusion criteria were: a smoking history of $\geqslant$20 pack-years; treatment with any other anti-TNF-α agent, anakinra, IL-12- or IL-23-targeted agent; previous cyclophosphamide use; local therapy or injections within 3 months or topical therapy within 1 month for skin sarcoidosis; clinically significant pulmonary hypertension receiving vasodilator therapy; and current or history of congestive heart failure.

This study was conducted according to the principles of the Declaration of Helsinki. The Institutional Review Board or Ethics Committee for each site approved the study and all patients provided written informed consent.

Study design

This was a phase II, multicentre, randomised, double-blind, placebo-controlled, three-arm study to evaluate the safety and efficacy of ustekinumab or golimumab in patients with chronic pulmonary and/or skin sarcoidosis. Following 1–4 weeks of screening, patients were randomly assigned in a 1:1:1 ratio stratified by baseline disease (pulmonary involvement only, skin involvement only, and both pulmonary and skin involvement) and prior anti-TNF-α biological use (yes/no) using an interactive voice-response system, to receive subcutaneous injections of ustekinumab, golimumab, or placebo. Patients assigned to ustekinumab received 180 mg at week 0 and 90 mg at weeks 8, 16, and 24 (with placebo at weeks 4, 12, and 20 to maintain blinding). Patients assigned to golimumab received 200 mg at week 0, followed by 100 mg every 4 weeks through to week 24 (fig. 1). Patients receiving background OCS were maintained on a stable dose through week 16, if clinically possible, to enable the evaluation of the effect of treatment on the primary end-point on a stable background regimen. Then, if clinically stable, patients had their OCS dose tapered through week 28, with dose reductions of 50% at weeks 16, 20, and 24. Information on the dose of OCS and other sarcoid medications at baseline and post baseline are included in the online supplementary tables S1–S3.

The primary end-point was the change from baseline at week 16 in % pred FVC in the lung group (*i.e.* those with lung only and lung and skin involvement). Major secondary end-points at week 28 were the change from baseline in the 6MWD (Δ6MWD), the St. George's Respiratory Questionnaire (SGRQ) total score, percentage predicted FVC in the lung group, and the proportion of SPGA responders (score $\leqslant$1, refer to online supplementary material) in the skin group (*i.e.* those with skin only and lung and skin involvement. The skin group was also assessed by the Sarcoidosis Activity and Severity Index (SASI), which was modified from BAUGHMAN *et al.* [35], (fig. S1). Samples were also collected at weeks 0, 4, 8, 16, 28, and 44 to explore the levels of ACE (R&D Systems, Minneapolis, MN, USA), C-reactive protein (CRP) (Siemens Nephelometry, Deerfield, IL, USA), MIP-1β (MesoScale Discovery, Rockville, MD, USA), and other inflammatory biomarkers. An assessment of overall organ involvement, extrapulmonary physician organ severity tool (ePOST) [36], was performed at each visit, using all information available to the physician. Patients also completed several additional patient reported outcomes (PRO) questionnaires, including the 36-item short form health survey (SF-36) [37], the Fatigue Assessment Scale (FAS) [38], the sarcoidosis assessment tool (SAT) [39], and a patient global assessment (PGA) of overall wellbeing on a visual analogue scale. An Independent Data Monitoring Committee reviewed all available data after the 15th randomised patient had completed the week-16 visit and, periodically, thereafter. Patients were followed through to week 44.

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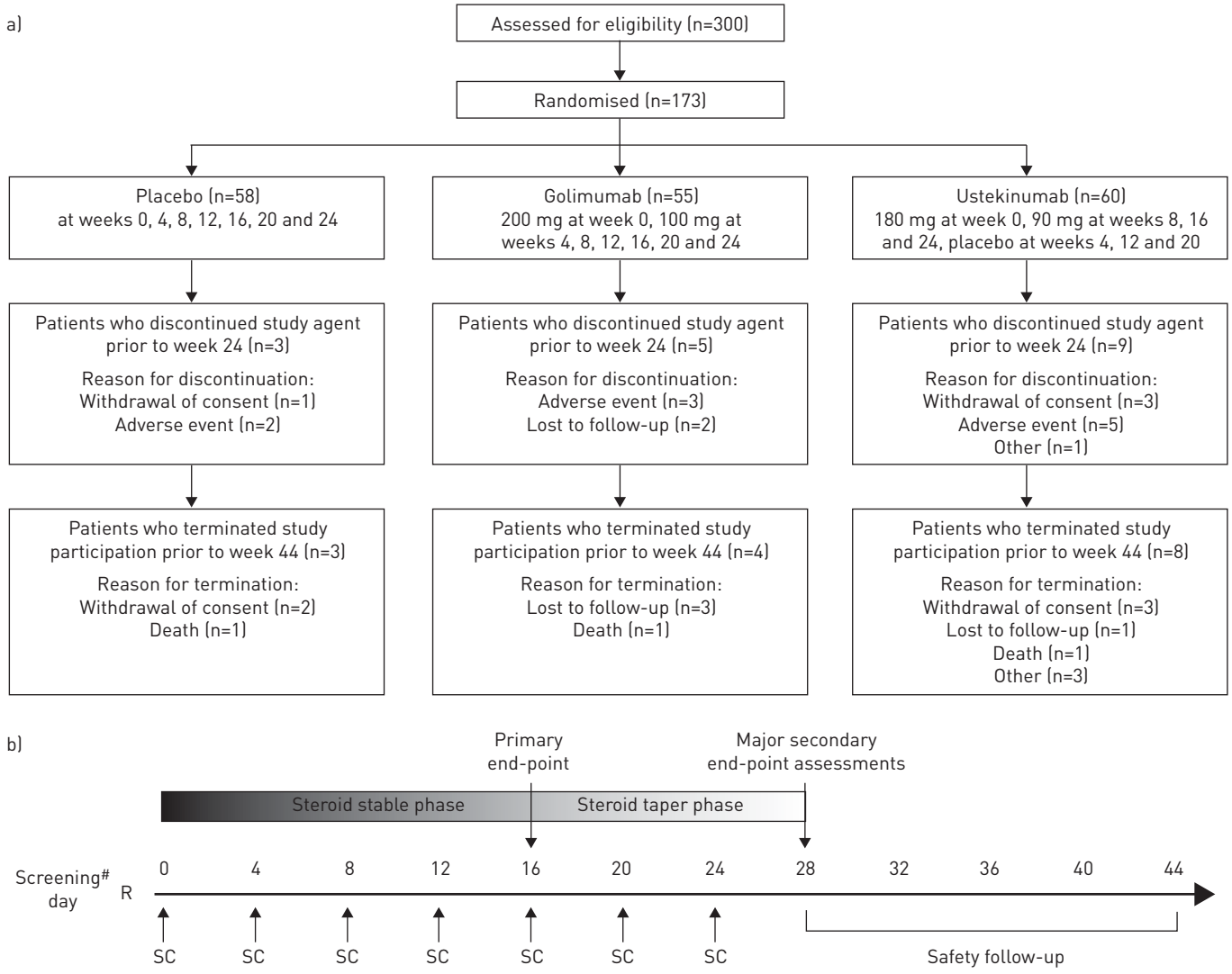

FIGURE 1 a) Study design and b) patient flow through the study. R: randomisation; SC: subcutaneous injections of study agent at weeks 0, 4, 8, 12, 16, 20 and 24. #: screening from day -28 to day -1.

Statistical analyses

The planned total sample size of 180 patients included a lung population of ⩾135 patients and a skin population of ⩾45 patients. Assuming a standard deviation of 7%, 45 lung patients per treatment arm provided 86.4% power to detect a 5% difference in the change from baseline in % pred FVC at week 16 among the three treatments at an overall 0.05 significance level, with Bonferroni adjustment. ANCOVA was used for the primary end-point analysis. The testing procedure comprised an overall test among placebo, ustekinumab, and golimumab, followed by two comparisons between ustekinumab and placebo, and golimumab and placebo. The significance level used for all analyses was 0.05. The study would be considered positive if the overall test achieved statistical significance and at least one of the golimumab or ustekinumab arms was significantly better than placebo.

Results

Baseline patient characteristics

Between September 2009 and August 2012, 173 patients entered the study and were treated at 47 sites in nine countries. Of the 173 patients randomised, approximately half of the population (50.9%, n=88) was male and the majority were Caucasian (61.3%, n=106) (table 1). A total of 15 patients terminated their study participation prior to the final study visit (placebo n=3, golimumab n=4, ustekinumab n=8) (fig. 1).

Baseline characteristics were well balanced across treatment arms. Approximately 67% of patients had lung involvement only, 24% had skin involvement only, and 10% had both lung and skin involvement.

TABLE 1 Baseline demographics and disease characteristics

	Placebo	Golimumab	Ustekinumab	Total
Total patients#	58	55	60	173
Age mean±SD years	49.5±9.5	50.0±9.4	49.8±10.2	49.8±9.7
Male	29 (50.0)	28 (50.9)	31 (51.7)	88 (50.9)
Ethnicity				
White	32 (55.2)	36 (65.5)	38 (63.3)	106 (61.3)
Black or African American	23 (39.7)	16 (29.1)	19 (31.7)	58 (33.5)
Asian	0	1 (1.8)	0	1 (0.6)
Other	1 (1.7)	2 (3.6)	2 (3.3)	5 (2.9)
Unknown	1 (1.7)	0	0	1 (0.6)
Multiple	1 (1.7)	0	1 (1.7)	2 (1.2)
Weight mean±SD kg	88.7±20.4	87.9±19.3	92.2±21.5	89.6±20.4
Lung group#				
Patients	44	42	46	132
FVC L	2.69	2.84	2.62	2.72
FVC % predicted	68.4	68.0	64.3	66.9
FEV_1 L	1.83	1.89	1.82	1.84
FEV_1 % predicted	57.6	57.0	55.9	56.8
D_{LCO} (mL·min^{-1}·mmHg^{-1})	13.2	10.3	12.6	12.1
SGRQ total score	53.1	51.1	50.2	51.4
6MWD m	389.5	401.9	396.0	395.7

Data presented as n or n (%), unless otherwise stated. FVC: forced vital capacity; FEV_1: Forced expiratory volume in 1 s; D_{LCO}: diffusing capacity of the lung for carbon monoxide; SGRQ: St George's Respiratory Questionnaire; 6MWD: 6-min walking distance. #: patients were randomised.

Efficacy

At week 16, there were no observed statistical differences in the primary end-point (the change from baseline in % pred FVC) in the lung group with either active treatment compared to placebo (ustekinumab -0.15, p=0.126; golimumab 1.15, p=0.543; placebo 2.02) (fig. 2 and table 2). The sensitivity and subgroup analyses on the primary end-point showed consistent results with the primary analysis (fig. S2) and included smoking status (yes/no), body mass index (BMI) ($\geqslant$30 *versus* <30), ethnicity (white/non-white), sex (male/female), and age ($\geqslant$50 *versus* <50 years). Of note is that patients with lower BMI tended to show improvement in FVC with golimumab treatment as opposed to patients with higher BMI, who tended toward worsening. An analysis of trough golimumab serum levels by quartiles, suggested that the change from baseline in FVC at week 16 tended to be increased in the two higher quartiles, but not the two lower quartiles (fig. S3). Subgroup analysis, based on the median levels of baseline biomarkers, failed to demonstrate any significant improvement in response in FVC (table S4).

At week 28, the active treatments demonstrated no statistically significant improvements compared with the placebo in any major secondary end-points (table 2). No significant differences were observed in the change

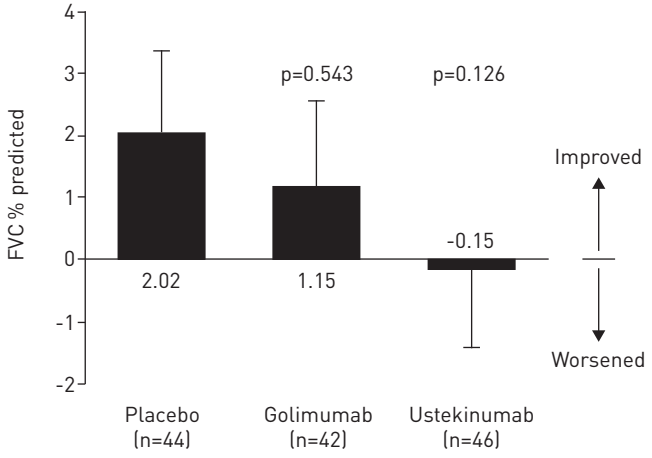

FIGURE 2 Primary end-point for the lung group at week 16, the change from baseline in the mean±SE % predicted forced vital capacity (FVC). Analysis uses last observation carried forward to input missing values.

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TABLE 2 End-point analyses

	Placebo	Golimumab	Ustekinumab	p-value[#]
Patients in the lung group n	44	42	46	
ΔFVC % predicted at week 16				
Mean±SE[¶]	2.02±1.350	1.15±1.413	-0.15±1.279	0.305
95% CI	-0.65–4.69	-1.64–3.95	-2.68–2.38	
p-value[+]		0.543	0.126	
ΔFVC % predicted at week 28				
Mean±SE[¶]	1.59±1.621	0.29±1.679	0.56±1.536	
95% CI	-1.62–4.79	-3.07–3.65	-2.48–3.60	
p-value[+]		0.451	0.546	
Δ6MWD at week 28				
Mean±SE[¶] m	14.52±14.223	12.53±14.919	-13.22±13.584	
95% CI	-13.63–42.66	-16.99–42.06	-40.10–13.67	
p-value[+]		0.896	0.063	
ΔSGRQ total score at week 28				
Mean±SE[¶]	-9.50±2.790	-6.86±2.921	-4.25±2.662	
95% CI	-15.02– -3.98	-12.64– -1.08)	-9.52–1.01	
p-value[+]		0.374	0.073	
Patients in the skin group n	20	17	21	
Patients with a SPGA score ⩽1 n				
Responders n (%)	6 (30)	9 (52.9)	3 (14.3)	
p-value[§]		0.1931	0.2772	

ΔFVC%: change from baseline in forced vital capacity; Δ6MWD: change from baseline in 6-min walking distance; ΔSGRQ: change from baseline in the St. George's Respiratory Questionnaire; SPGA: Skin Physician Global Assessment. [#]: the overall p-value is based on the F-test; [¶]: means are reported as least square means; [+]: treatment comparisons are based on linear contrasts; [§]: treatment comparisons are based on Fisher's exact test.

from baseline in % pred FVC at week 28 in either of the active treatment arms (golimumab 0.29, p=0.451; ustekinumab 0.56, p=0.546) compared to 1.59 for the placebo lung group. The Δ6MWD was 12.53 m in the golimumab arm (p=0.896) and -13.22 m in the ustekinumab arm (p=0.063) compared to 14.52 m in the placebo arm. At week 28, the mean change from baseline in the SGRQ total score in the lung group was: -9.50 for the placebo, -6.86 for golimumab (p=0.374), and -4.25 for ustekinumab (p=0.073). In addition, no significant improvements were observed in the active treatment arms relative to the placebo arm in the scores from the PRO questionnaires completed by the patients (SF-36, FAS, SAT, and PGA).

For the lung group who received OCS at baseline, a nominally greater proportion of golimumab-treated patients, but not ustekinumab-treated patients, were able to reduce their OCS dose by at least 50% during the taper-phase (golimumab 81.6%, p=0.01; ustekinumab 57.9%, p=0.63) compared with the placebo arm (51.6%). For the golimumab arm, the results were mainly driven by patients with a BMI <30 (golimumab 85%, placebo 36%, p=0.0134) consistent with the general trend towards improved results in patients with a lighter weight. Among the skin group, both arms tended to reduce OCS dose by at least 50% (golimumab 70.0%, p=0.23; ustekinumab 83.3%, p=0.047) compared with placebo (40%). The proportion of patients in both the lung and skin groups with complete withdrawal of OCS use prior to week 28 was low and similar to that of the placebo: golimumab 11 (28.9%) out of 38 (p=0.41), ustekinumab 7 (18.4%) out of 38 (p=1.0), placebo 6 (19.4%) out of 31 in the lung group; golimumab 3 (30.0%) out of 10 (p=0.36), ustekinumab 1 (8.3%) out of 12 (p=1.0), and placebo 2 (13.3%) out of 15 in the skin group.

In the skin group, a nonsignificant improvement in SPGA response following golimumab treatment was observed (52.9%, p=0.19) compared with placebo (30.0%), but not with ustekinumab treatment (14.3%, p=0.28) (fig. 3a) at week 28. The target lesion score tended to improve with golimumab but not ustekinumab over time (golimumab -2.3, p=0.07, ustekinumab -1.2, p=NS, placebo -1.4) at week 28. A similar pattern was seen with SASI scores (golimumab -2.57, p=0.38; ustekinumab -0.50, p=0.89) compared with placebo (-0.52) (fig. 3b). Greater numerical improvement was also observed in the skin domain of the ePOST for golimumab-treated patients but not ustekinumab-treated patients (fig. 3c) (p=NS, for both). In the skin group, there was a significant improvement in extrapulmonary involvement overall measured by the ePOST with golimumab, at weeks 20, 24, and 28 (p=0.004, 0.016, 0.005, respectively), but not with ustekinumab (fig. 3d).

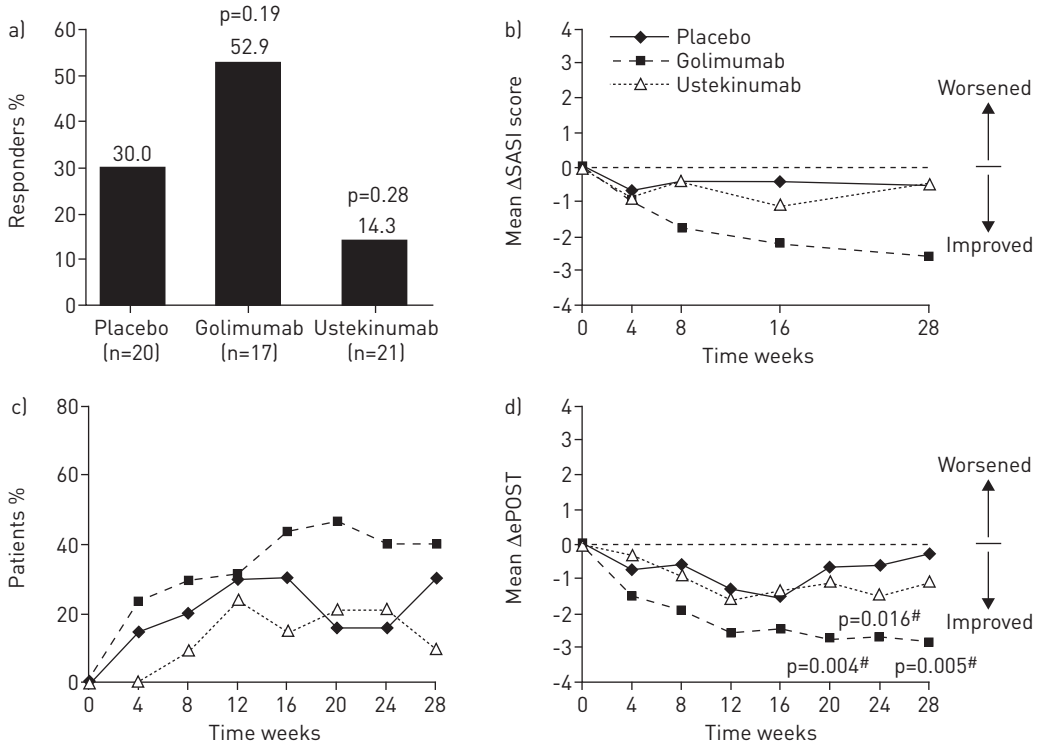

FIGURE 3 Skin group population assessments. a) Skin Physician Global Assessment Responders at week 28. b) Change from baseline in the Sarcoidosis Activity and Severity Index (ΔSASI) score over time. c) Skin domain of the extrapulmonary Physician Organ Severity Tool (ePOST) defined as the percentage of patients with a score improvement of ⩾2 points over time. d) Change from baseline in ePOST (ΔePOST) over time. #: nominal p-value *versus* placebo.

Of the serum inflammatory markers measured, (ACE, MIP-1β, and CRP), MIP-1β, an immune cell chemoattractant and pharmacodynamic marker of anti-TNF-α treatment, demonstrated a significant decrease from baseline by week 4, and this difference was maintained through to week 28, following treatment with golimumab (-84.57) when compared with placebo (24.48, ($p<0.001$). There was no difference observed with the treatment of ustekinumab (fig. 4). Statistically significant decreases in ACE were observed in both treatment arms at weeks 4, 8, and 16. ACE levels tended to rise in all 3 arms after week 16 during the steroid taper phase measured at week 28 (fig. S4).

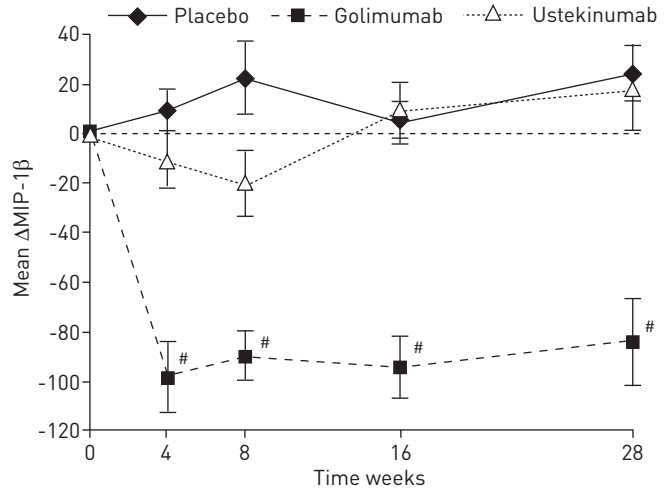

FIGURE 4 Macrophage inflammatory protein (MIP)-1β levels, response to treatment over time. #: $p<0.0001$ for golimumab *versus* placebo. Δ: change from baseline.

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Safety

Serious adverse events were reported throughout the course of the study in 15.5% (n=9), 12.7% (n=7), and 16.7% (n=10) for the placebo-treated, golimumab-treated, and ustekinumab-treated patients, respectively (table 3). The highest reported event was pneumonia (golimumab n=1, ustekinumab n=3). The occurrence of treatment emergent adverse events in patients throughout the course of the study were 93.1% (n=54), 96.4% (n=53), and 93.3% (n=56) in the placebo-treated, golimumab-treated, and the ustekinumab-treated patients, respectively (table 4). Injection site reactions occurred in 3.4% (n=2), 20% (n=11), and 5.0% (n=3) for placebo-treated, golimumab-treated, and ustekinumab-treated patients, respectively, and were mostly mild. There was no increased incidence of infection with either of the active-treatment arms of the study (golimumab 61.8%, ustekinumab 65.0%) compared with placebo arm (65.5%). One case of tuberculosis was reported in a golimumab-treated patient.

Three deaths were reported during the study: a golimumab-treated patient died from sepsis 5 months after the first and only dose of golimumab, subsequent to being withdrawn from study drug administration due to dyspnoea; a ustekinumab-treated patient died due to acute respiratory failure 5 months after the last dose of ustekinumab at week 12; and one placebo-treated patient died, suddenly, 3 months after the last dose of study agent. Two reported malignancies included one event of recurrent squamous cell carcinoma (SCC) in a patient with a history of basal cell carcinoma and SCC (ustekinumab arm), and one case of breast cancer in a patient with a family history of breast cancer (placebo arm). One additional malignancy (chronic myeloid leukaemia) was reported in a female patient with a family history of malignancy, 2 months after completion of drug dosing (ustekinumab arm). Retrospective review of laboratory values and analyses of banked blood samples indicated that the malignancy was pre-existing at study entry and, therefore, was not recorded as a treatment-emergent event. There were no reports of possible anaphylactic reactions or possible delayed hypersensitivity (serum sickness-like) reactions through to week 44.

Discussion

In this randomised, double-blind, placebo-controlled trial, neither golimumab nor ustekinumab demonstrated a significant effect on the primary end-point, the change from baseline at week 16 in % pred FVC at week 16 in the lung group, compared with the placebo. In addition, neither drug met any secondary study end-points at week 28 (Δ6MWD, ΔSGRQ total score, ΔFVC % pred in the lung group, and the proportion of SPGA responders in the skin group). Additional sensitivity and subgroup analyses failed to demonstrate a significant difference between active study drug and placebo, although trends of improvement were consistently observed in the skin group end-points (SPGA, SASI, and ePOST) of patients treated with golimumab. Both golimumab and ustekinumab demonstrated a safety profile comparable to placebo in this cohort of patients with chronic sarcoidosis.

TABLE 3 Number of patients with ⩾1 treatment-emergent serious adverse events throughout the course of the study

	Placebo	Golimumab	Ustekinumab
Treated patients	58	55	60
Patients with events	9 (15.5)	7 (12.7)	10 (16.7)
Infections and infestations	3 (5.2)	3 (5.5)	5 (8.3)
Respiratory, thoracic and mediastinal disorders	1 (1.7)	3 (5.5)	1 (1.7)
Cardiac disorders	0	1 (1.8)	1 (1.7)
General disorders and administration site conditions	1 (1.7)	1 (1.8)	0
Metabolism and nutrition disorders	0	1 (1.8)	0
Musculoskeletal and connective tissue disorders	0	1 (1.8)	2 (3.3)
Psychiatric disorders	1 (1.7)	1 (1.8)	1 (1.7)
Gastrointestinal disorders	1 (1.7)	0	1 (1.7)
Immune system disorders	1 (1.7)	0	1 (1.7)
Injury, poisoning and procedural complications	1 (1.7)	0	0
Investigations	0	0	1 (1.7)
Neoplasms benign, malignant and unspecified, inclusive of cysts and polyps	1 (1.7)	0	0
Nervous system disorders	1 (1.7)	0	0
Renal and urinary disorders	1 (1.7)	0	0
Vascular disorders	0	0	1 (1.7)

Data presented as n or n (%). Percentages were calculated with the number of patients treated in each arm as the denominator. Incidence is based on the number of patients experiencing at least one serious adverse event, not the number of events.

TABLE 4 Number of patients with ⩾1 treatment-emergent adverse events ⩾10% through the end of the study

	Placebo	Golimumab	Ustekinumab
Treated patients	58	55	60
Patients with events	54 (93.1)	53 (96.4)	56 (93.3)
Cough	15 (25.9)	11 (20.0)	13 (21.7)
Arthralgia	16 (27.6)	13 (23.6)	9 (15.0)
Fatigue	8 (13.8)	11 (20.0)	12 (20.0)
Headache	12 (20.7)	7 (12.7)	12 (20.0)
Upper respiratory tract infection	13 (22.4)	6 (10.9)	10 (16.7)
Dyspnoea	11 (19.0)	11 (20.0)	4 (6.7)
Diarrhoea	11 (19.0)	6 (10.9)	9 (15.0)
Bronchitis	9 (15.5)	8 (14.5)	8 (13.3)
Pain in extremity	11 (19.0)	3 (5.5)	8 (13.3)
Back pain	6 (10.3)	6 (10.9)	9 (15.0)
Nausea	6 (10.3)	7 (12.7)	8 (13.3)
Rash	6 (10.3)	6 (10.9)	6 (10.0)
Sarcoidosis	3 (5.2)	4 (7.3)	11 (18.3)
Sinusitis	9 (15.5)	3 (5.5)	5 (8.3)
Oedema peripheral	5 (8.6)	8 (14.5)	4 (6.7)
Vomiting	7 (12.1)	4 (7.3)	6 (10.0)
Nasopharyngitis	2 (3.4)	4 (7.3)	9 (15.0)
Skin lesion	8 (13.8)	1 (1.8)	6 (10.0)
Oropharyngeal pain	4 (6.9)	2 (3.6)	7 (11.7)

Data presented as n or n (%). Percentages were calculated with the number of patients treated in each arm as the denominator. Incidence was based on the number of patients experiencing at least one adverse event, not the number of events.

The lack of efficacy of these two active drugs may provide insight into the immunopathogenesis and treatment of sarcoidosis. It is somewhat surprising that golimumab did not demonstrate a benefit *versus* placebo in this trial, as other TNF-α antagonists have shown favourable results for the treatment of sarcoidosis, including in randomised, double-blind, placebo-controlled trials [1, 14, 36, 40]. Furthermore, the entry criteria for the lung group in this trial matched that of a subgroup in a previous positive trial involving infliximab for pulmonary sarcoidosis that had a more robust response [1]. There are several potential explanations for the lack of response to golimumab in this trial. First, the limited clinical data available suggests that not all TNF-α antagonists are equally effective for sarcoidosis. In particular, etanercept has not been found to be particularly effective for various forms of sarcoidosis [41, 42] and has not been recommended for this condition [43]. Although limited data are available concerning the benefit of adalimumab for the treatment of sarcoidosis, it appears to require high dosing (administered subcutaneously) and to be administered over a longer period of time to maximize the benefit in comparison to infliximab, which is administered intravenously [43]. Secondly, it is possible that the dose of golimumab used in this trial was inadequate for the treatment of sarcoidosis. Although the additional sensitivity analyses were underpowered and conjectural, the fact that the cohort with a BMI <30 had a statistically nonsignificant greater improvement in FVC compared to those with a BMI ⩾30 suggests that the golimumab dose used may have been too low. This hypothesis is further supported by the tendency towards FVC improvement at higher golimumab trough levels (fig. S2). We also found that patients receiving golimumab with a lower BMI had a higher rate of corticosteroid tapering than the placebo arm. Thirdly, only a subset of sarcoidosis patients may have TNF-α driven disease. A subset analysis of the prior infliximab trial in pulmonary sarcoidosis showed better improvement in FVC in patients with measurable serum TNF-α levels at baseline (>lower limit of detection of 4 $pg \cdot mL^{-1}$) [10]. The median serum TNF-α level in patients at baseline in the current study was ~5 $pg \cdot mL^{-1}$, and those with higher levels at baseline had slightly greater improvement in FVC, but this was not consistent across all inflammatory biomarkers (table S1). Fourthly, because corticosteroids also antagonise the action of TNF-α, it is possible that the maintenance corticosteroid doses of the patients "masked" a benefit of golimumab. In support of this postulation, a recent re-analysis [44] of the positive infliximab trial for pulmonary sarcoidosis [1] demonstrated that patients receiving ⩾15 $mg \cdot day^{-1}$ of prednisone did not demonstrate an additional benefit from infliximab. This postulation may also explain why a nominally greater proportion of golimumab treated patients, in both the lung and skin groups, were able to reduce their corticosteroid dose by at least 50% during the taper-phase compared with the placebo arm. Fifthly, the 3-month corticosteroid taper phase of the trial may have been too short to demonstrate a maximum corticosteroid-sparing effect,

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although the mean corticosteroid dose between weeks 28 and 44 (period whilst patient was not on study drug treatment) tended to be lower in both the golimumab (7.2 mg) and ustekinumab (7.9 mg) arms compared to the placebo arm (12.2 mg). Finally, the skin group may have been inadequately powered to reach a conclusion concerning drug efficacy in this trial.

The lack of efficacy of ustekinumab was consistent, with no obvious signal of efficacy demonstrated in the primary end-point, secondary end-points, or sensitivity and subgroup analyses. This lack of efficacy may possibly indicate that the IL-12 p40 mechanism is not a major determinant of the disease process, although it is unknown if higher doses would have impacted on the disease. The lack of efficacy of ustekinumab must be reconciled against the findings that active sarcoidosis skin lesions showed upregulation of IL-12 and IL-23 relative to control tissue [32] and increased IL-12 has been detected in sarcoidosis serum [26], bronchoalveolar lavage [25] and lymph nodes [45]. IL-12, in particular, has been thought to be a key driver of the dysregulation in interferon demonstrated in sarcoidosis [25, 32, 46]. Possibly, these mediators are not integral in driving interferon production or mediating sarcoid granuloma formation. Since ustekinumab blocks both IL-12 and IL-23, it leaves open the questions as to whether the blockade of IL-12 or IL-23 alone might be effective.

The design of this trial reflects a problem inherent in all novel drug therapy trials for sarcoidosis. Corticosteroids are highly effective for sarcoidosis. Because of the effectiveness of corticosteroids, it may be problematic to demonstrate an additional benefit of a study drug over the corticosteroid effect [44]. Because the enrolment criteria for this trial were identical to a subgroup that had a robust improvement in FVC in the previous infliximab trial, we believed that it was likely to see a benefit of at least golimumab in the current trial. We added a corticosteroid taper phase in the current trial in an attempt to uncover benefits of the study drugs that might have been obscured by maintenance corticosteroid therapy. Other study designs could have included tapering corticosteroids off or to a dose where the patient exacerbated before entering them in the trial. However, these approaches would have lengthened the duration of the trial. Possibly, biomarkers may be useful to determine drug responders as C-reactive protein identified responders to infliximab in the previous randomised, double-blind, corticosteroid-dependent pulmonary sarcoidosis trial [47].

Data from this study may give insight into the relative importance of immunopathogenic pathways in sarcoidosis. A number of samples collected during the course of the study are currently being analysed to evaluate the impact of treatment on the molecular signature of the disease and to identify alternative pathways with potential for therapeutic intervention. In addition, considering the wide spectrum in antisarcoidosis activity of the various TNF-α antagonists currently available, these data may lead to further modification of these agents to improve their efficacy or evaluation of the combination of anti-TNF-α with other key pathogenic mechanisms

In conclusion, although treatment with ustekinumab or golimumab was well tolerated, neither demonstrated efficacy in pulmonary sarcoidosis. However, trends towards improvement were observed with golimumab in some dermatological end-points. This trial may have been underpowered to fully examine the role of the study drugs in the skin group.

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