EXTENDED REPORT

A phase 1b clinical trial evaluating sifalimumab, an anti-IFN-α monoclonal antibody, shows target neutralisation of a type I IFN signature in blood of dermatomyositis and polymyositis patients

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ABSTRACT

Objective To assess the pharmacodynamic effects of sifalimumab, an investigational anti-IFN-α monoclonal antibody, in the blood and muscle of adult dermatomyositis and polymyositis patients by measuring neutralisation of a type I IFN gene signature (IFNGS) following drug exposure.

Methods A phase 1b randomised, double-blind, placebo controlled, dose-escalation, multicentre clinical trial was conducted to evaluate sifalimumab in dermatomyositis or polymyositis patients. Blood and muscle biopsies were procured before and after sifalimumab administration. Selected proteins were measured in patient serum with a multiplex assay, in the muscle using immunohistochemistry, and transcripts were profiled with microarray and quantitative reverse transcriptase PCR assays. A 13-gene IFNGS was used to measure the pharmacological effect of sifalimumab.

Results The IFNGS was suppressed by a median of 53–66% across three time points (days 28, 56 and 98) in blood (p=0.019) and 47% at day 98 in muscle specimens post-sifalimumab administration. Both IFN-inducible transcripts and proteins were prevalently suppressed following sifalimumab administration. Patients with 15% or greater improvement from baseline manual muscle testing scores showed greater neutralisation of the IFNGS than patients with less than 15% improvement in both blood and muscle. Pathway/functional analysis of transcripts suppressed by sifalimumab showed that leucocyte infiltration, antigen presentation and immunoglobulin categories were most suppressed by sifalimumab and highly correlated with IFNGS neutralisation in muscle.

Conclusions Sifalimumab suppressed the IFNGS in blood and muscle tissue in myositis patients, consistent with this molecule’s mechanism of action with a positive correlative trend between target neutralisation and clinical improvement. These observations will require confirmation in a larger trial powered to evaluate efficacy.

INTRODUCTION

The inflammatory myopathies dermatomyositis and polymyositis are rare autoimmune disorders affecting skeletal muscle function.1–3 Conventional treatment options for these diseases include immunosuppressant drugs associated with a wide range of side effects. There is a strong unmet medical need for better therapeutic alternatives.4–6

The role of type I IFN in the pathogenesis of myositis has been well documented. Immunohistochemical studies demonstrate that IFN is elevated in muscle tissue,7 and plasmacytoid dendritic cells (DC) are present in the muscle and skin of dermatomyositis patients.8–9 Measuring free IFN-α in the serum is less sensitive compared to measuring type I IFN-inducible transcripts, as has been reported in many studies.10–13 These type I IFN-inducible transcripts measured in the blood of myositis patients correlate with disease activity in dermatomyositis.14–18 Reports have recently indicated that the type I IFN signature in the blood of dermatomyositis patients correlates with IFN-β, not IFN-α protein expression.19

In a phase 1b clinical trial (MI-CP151) in adult patients with dermatomyositis or polymyositis evaluating the safety and tolerability of multiple intravenous doses of sifalimumab, an investigational anti-IFN-α monoclonal antibody (MI-CP151), we report here the clinical utility of the type I IFN gene signature (IFNGS) as a pharmacodynamic marker in both blood and muscle of patients treated with sifalimumab, similar to the approach used in systemic lupus erythematosus (SLE).19 20–23 Blood and/or muscle tissues from a total of 26 dermatomyositis and 25 polymyositis patients were transcript profiled at baseline (pre-dose) and up to 98 days post initial dose with either placebo or one of four dose levels for sifalimumab. We also examined the effects of sifalimumab on pathways downstream of type I IFN. Finally, correlative trends were examined between neutralisation of the IFNGS and changes in disease activity following administration of sifalimumab.

METHODS

Myositis patients and controls
MI-CP151 was a phase 1b randomised, double-blind, placebo controlled, dose-escalation, multicentre study to evaluate multiple intravenous doses of sifalimumab, in adult patients with dermatomyositis or polymyositis (NCT00533091). Primary trial objectives were to evaluate the safety and tolerability of
sifalimumab in dermatomyositis or polymyositis patients, while one of the exploratory objectives included the assessment of the effects of sifalimumab on pharmacodynamic markers in blood and disease tissue. A description of the latter objective is the scientific focus of this paper. Fifty-one patients were enrolled with seven, eight, 16 and eight patients dosed with sifalimumab at 0.3, 1, 3 and 10 mg/kg, respectively, and 12 received placebo. Patients received treatment for 6 months with 14 doses (every other week dosing), while patients receiving placebo were dosed for 3 months, then switched to sifalimumab for 3 months with seven doses beginning at day 98.

Sixty-one different immunosuppressant agents or corticosteroids were used among 37 patients, with prednisone (n=30) and methotrexate (n=15) being the two most common. No correlation was observed between baseline prednisone or methotrexate dose and baseline IFNGS.

MI-CP151 was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the institutional review board at each site. All patients provided written informed consent before study-related procedures were performed. IFNGS scores in blood were prescreened to stratify patients. The baseline clinical characteristics and IFNGS status summaries are provided in table 1.

For the detailed study inclusion and exclusion criteria, IFNGS calculation, RNA extraction, transcript and protein assays, and immunohistochemistry see supplementary material (available online only).

RESULTS

Safety profile of sifalimumab
Before day 98, a total of 49 treatment-emergent adverse event (TEAE) occurred in 10/12 subjects (83.3%) in the placebo group and 172 TEAE occurred in 34/39 subjects (87.2%) in the any sifalimumab group. The most frequent adverse event in either group was headache. During open-label sifalimumab administration or after day 98, 306 TEAE occurred in 47/51 (92.2%) subjects in all cohorts. Anti-drug antibodies to sifalimumab were detected in less than one-fifth of the subjects across the sifalimumab dose groups. Anti-drug antibody titres did not have an obvious impact on sifalimumab pharmacokinetics. The combination of the safety database size and trial design limits the interpretation of the safety profile of this molecule; however, a larger study (N=161) that characterises the safety profile of sifalimumab in SLE has recently been accepted.24

No deaths occurred in this study (see supplementary material, available online only, for a detailed safety summary).

Target modulation of an IFNGS by sifalimumab in the blood and muscle of myositis patients

Dermatomyositis (n=26) or polymyositis (n=25) patients enrolled in this study were screened using their baseline 13 IFNGS described previously15 (detailed in supplementary material, available online only), then randomly assigned to either placebo or sifalimumab groups. Of the 51 patients enrolled, 75% (38/51) had a positive baseline IFNGS (table 1 and see supplementary material (available online only)). A previous study showed that approximately 60% of deramotymositis or polymyositis patients demonstrate an elevated IFNGS in the blood.15 The baseline IFNGS in dermatomyositis or polymyositis patients calculated using microarrays were confirmed by taqMan quantitative reverse transcriptase PCR (r=0.95; p<0.001; see supplementary figure S2, available online only).

The same 13 type I IFN-inducible genes were also used to evaluate the pharmacodynamics of sifalimumab on target neutralisation in IFNGS-positive patients. The total numbers of dermatomyositis or polymyositis patients who had specimens available for correlative studies at baseline were 26 and 21 for blood, and 23 and 25 for muscle, respectively (see supplementary material, available online only, for patient counts at each time point).

In blood, target neutralisation was observed in sifalimumab-dosed patients in three dose groups relative to placebo-dosed patients after the first dose and sustained to day 98 (figure 1A,B). After day 98, placebo-dosed patients crossed over and received sifalimumab. Graphs displaying target neutralisation up to day 196 post initial dosing are provided in supplementary figure S3 (available online only). The IFNGS in the blood is maximally neutralised in the 0.3 mg/kg cohort (91% at day 98; p=0.002 at all time points). At day 98, the IFNGS is neutralised from 54% to 91% in 0.3, 1.0 and 3.0 mg/kg cohorts (p=0.002, 0.05 and 0.014, respectively). The 10 mg/kg cohort did not show a significant difference from placebo at day 98 (p=0.28), although this cohort had the smallest sample size (n10mg/kg=4 vs nplacebo=4). As expected, the placebo-dosed patients showed no target neutralisation across all time points. The median of all four dose cohorts combined show that the IFNGS is neutralised from 53% to 66% across the three time points, compared to the placebo (figure 1B; Hotelling’s T2 p=0.019). Dose-dependent target neutralisation was not observed in the blood.

All four sifalimumab cohorts show dose-dependent target neutralisation in muscle that differs from the placebo cohort (figure 1C) with a median for combined sifalimumab cohorts of 47% target neutralisation (figure 1D), although the difference was not statistically significant. The medians do, however, show a trend towards a difference from placebo, noting that the sample sizes for the muscle specimens were generally lower than those available from the blood.

The neutralisation of the IFNGS was represented in a heat map for each patient at days 28, 56 and 98 post-administration in blood and day 98 in muscle specimens with either sifalimumab or placebo (figure 2). The majority of sifalimumab-dosed patients exhibit strong, sustained and durable target neutralisation in blood and muscle, while the majority of the placebo-dosed patients do not. Of sifalimumab-dosed patients showing greater than 20% target neutralisation at day 98 in muscle, 75%, 55% and 72% of patients at days 28, 56, and 98, respectively are concordant in the blood.

The IFN-α protein was not measurable in all but a few patients in the blood with luciferase reporter assay.

Transcripts and proteins most neutralised in the blood and serum by sifalimumab

The specificity of the transcripts most neutralised by sifalimumab administration was evaluated on a patient-by-patient level, using at least 50% neutralisation in the blood for each patient visit. Transcripts neutralised in over 25% of sifalimumab-dosed patients were ranked across all post-dose time points up to day 98. The top 200 transcripts most neutralised by this criterion are provided in supplementary table S1 (available online only). Among them, 48% are type I IFN inducible, including all 13 genes in the pharmacodynamic biomarker for this trial.14 20 21 25 A similar observation was reported in a sifalimumab trial in SLE.10 23 Among measured serum proteins, five of 11 that were significantly suppressed by sifalimumab (false discovery rate (FDR) p<0.05) are IFN inducible (IL2R, MCP1,
MCP2, BAFF and Ferritin). Immunohistochemistry analysis was also performed on a small subset of paired patient muscle tissue to assess general signs of inflammation using BDCA2, a marker for plasmacytoid DC; CD83, a marker for myeloid DC; and IP-10, an IFN-inducible protein. A representative polymyositis patient showing decreases in BDCA2, CD83 and IP-10 98 days post-dosing with sifalimumab is shown in supplementary figure S4 (available online only), although with the heterogeneity of the specimens and small patient subset, no significant conclusion can be drawn.

### Table 1  MI-CP151 patient summary information

<table>
<thead>
<tr>
<th></th>
<th>Sifalimumab (all doses, N=39)</th>
<th>Sifalimumab (0.3 mpk, N=7)</th>
<th>Sifalimumab (1.0 mpk, N=8)</th>
<th>Sifalimumab (3.0 mpk, N=16)</th>
<th>Sifalimumab (10 mpk, N=8)</th>
<th>Placebo (N=12)</th>
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<td>Age, years</td>
<td>51.3 (20–77)</td>
<td>47.3 (29–59)</td>
<td>52.4 (20–77)</td>
<td>51.8 (21–76)</td>
<td>52.8 (37–67)</td>
<td>51 (33–67)</td>
</tr>
<tr>
<td>% Female</td>
<td>74 (29/39)</td>
<td>88 (4/7)</td>
<td>88 (7/8)</td>
<td>69 (11/16)</td>
<td>88 (7/8)</td>
<td>58 (7/12)</td>
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<tr>
<td>% Caucasian</td>
<td>79 (31/39)</td>
<td>100 (7/7)</td>
<td>63 (5/8)</td>
<td>82 (13/16)</td>
<td>75 (6/8)</td>
<td>67 (8/12)</td>
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<tr>
<td>% Hispanic</td>
<td>15 (6/39)</td>
<td>14 (1/7)</td>
<td>13 (1/8)</td>
<td>25 (4/16)</td>
<td>0 (0/8)</td>
<td>17 (2/12)</td>
</tr>
<tr>
<td>% Dermatomyositis</td>
<td>54 (21/39)</td>
<td>29 (2/7)</td>
<td>38 (3/8)</td>
<td>81 (13/16)</td>
<td>38 (3/8)</td>
<td>42 (5/12)</td>
</tr>
<tr>
<td>Viral reactivation history</td>
<td>6 (15.4%)</td>
<td>1 (14.3%)</td>
<td>2 (25.0%)</td>
<td>2 (12.5%)</td>
<td>1 (12.5%)</td>
<td>2 (16.7%)</td>
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<tr>
<td>Mean baseline MMT8</td>
<td>117.7</td>
<td>123.6</td>
<td>113.8</td>
<td>112.9*</td>
<td>125.9</td>
<td>119.8</td>
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<tr>
<td>% Corticosteroid use at baseline</td>
<td>84.6</td>
<td>85.7</td>
<td>87.5</td>
<td>100</td>
<td>50</td>
<td>66.7</td>
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<tr>
<td>Disease duration, months, median (range)</td>
<td>40.3 (3–361.5)</td>
<td>31.5 (3–153.9)</td>
<td>23.6 (15.3–361.5)</td>
<td>53.1* (13.8–217.2)</td>
<td>35.4 (4.3–109.9)</td>
<td>36.9 (10.8–76.9)</td>
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<td>% Signature positive</td>
<td>72 (28/39)</td>
<td>86 (6/7)</td>
<td>100 (8/8)</td>
<td>63 (10/16)</td>
<td>50 (4/8)</td>
<td>83 (10/12)</td>
</tr>
</tbody>
</table>

*Indicates average from cohorts 3 mpk IFN gene signature (IFNGS) positive (N=7) and 3 mpk IFNGS negative (N=9).

See supplementary material (available online only) for IFNGS-positive blood and muscle patient counts at each time point. IFNGS-positive patient counts above are provided for those with available microarray data at day 0 in either blood or muscle specimens, or both. Only these IFNGS-positive patients are used in the analyses presented.

Target neutralisation correlates with MMT8 improvement in IFNGS-positive myositis patients

To evaluate any trend between neutralisation of the IFNGS by sifalimumab and improvement in disease activity, we evaluated the proportion of signature-positive patients dosed with sifalimumab with neutralisation at day 98 (the last dose before placebo crossing over) relative to pretreatment in 5% increments. Patients were classified into two groups: showing 15% or greater improvement in Manual Muscle Testing (MMT8) (US Food and Drug Administration accepted clinical endpoint for disease activity) from baseline to day 98.

**Figure 1** Median target neutralisation (with median absolute deviation error bars) of the IFN gene signature (IFNGS) as calculated based on the expression of 13 genes (see supplementary material, available online only) pre-dose and post-dose up to day 98 for dose cohorts of 0.3 mg/kg (green), 1 mg/kg (blue), 3 mg/kg (orange), 10 mg/kg (purple) and placebo (red) in (A) blood and (C) muscle specimens, as well as median combined dose cohorts (blue) versus placebo treatment cohorts (red) in (B) blood and (D) muscle specimens from dermatomyositis or polymyositis patients. The y-axis represents the percentage of IFNGS remaining following treatment; each line is the median of the respective dose cohort. p Values at each time point for each dose cohort are provided in supplementary material (available online only), while those with p<0.05 are marked with an asterisk.
efficacy in dermatomyositis and polymyositis) at day 98 compared to predose or showing less than 15%. Figure 3 shows the results in both blood and muscle specimens from 14 dermatomyositis and 10 polymyositis patients. In the blood sifalimumab dose group (figure 3A), there is a clear separation between the 15% or greater MMT8 improvers and the less than 15% MMT8 improvers at each IFNGS neutralisation threshold value after 20%—the largest gap existing between 45% and 100%. This indicates that for the 15% and greater MMT8 improvers at day 98, a larger proportion (y-axis) showed greater
neuralisation of the IFNGS, compared to the less than 15% MMT8 improvers. A few patients dosed with placebo also showed MMT8 improvement of 15% or greater at day 98, although no appreciable modulation of the IFNGS was observed in these patients and they did not demonstrate a substantial target modulation difference between 15% or greater MMT8 improvers and less than 15% MMT8 improvers.

For the muscle biopsy specimens (figure 3B), a similar trend exists, although not as pronounced as in blood, with a slightly higher intersection between the curves at the IFNGS neutralisation threshold less than 40%. The placebo-dosed muscle specimens have a more defined difference in IFNGS neutralisation between 15% and greater MMT8 improvers and less than 15% MMT8 improvers, although it is restricted to between 20% and 40% target modulation thresholds. Overall, sample sizes for the placebo-dosed specimens are much smaller than sifalimumab-dosed specimens, so trends should be interpreted with caution until confirmed in a larger trial. Similar analysis for dermatomyositis or polymyositis patients alone are not shown, as the results are unlikely to be meaningful due to the small sample size. One representative patient with an improvement of the MMT8 score of greater than 2 relative to placebo-dosed patients were retained for pathway enrichment analysis. In all, 86 pathways were suppressed by sifalimumab. Among the top enriched pathways were antigen pathway signalling (33 transcripts; B αH p=0.003), its contribution to the disease

**DISCUSSION**

In this phase 1b trial evaluating sifalimumab in myositis, we showed that a 13-gene IFNGS can monitor the level of type I IFN activity in both the peripheral blood and muscle of dermatomyositis or polymyositis patients, similar to that observed in a sifalimumab trial in SLE10 (see supplementary figure S1, available online only). Sifalimumab shows strong neutralisation of the IFNGS in blood up to day 98 at three dose levels and is distinct from the placebo-dosed cohort, although the 10 mpk cohort in blood does not reflect this difference (figures 1 and 2). The activation of the type I IFN pathway is concordant in blood and muscle, supporting a pharmacodynamic marker to evaluate the mechanism of action of sifalimumab. Although the safety database is small, the adverse events were of low severity and serious adverse events were uncommon.

Type I IFN-inducible transcripts make up 48% of those most neutralised in blood (see supplementary table S1, available online only), and five of 11 proteins significantly suppressed are IFN inducible in serum, demonstrating the specificity of sifalimumab to suppress the type I IFN pathway in myositis.

There is no clear dose-dependent target neutralisation in blood, as opposed to the trend observed in the muscle (albeit not statistically significant). The small sample size accompanied by patient-to-patient variability could contribute to this observation. Furthermore, neutralisation by sifalimumab may be partly bypassed via IFN-β or other type I IFN family members besides IFN-α. Sifalimumab binds to the majority of the IFN-α subtypes with high affinities, but not to other type I IFN. The prevalence of IFN-β compared to IFN-α, and its contribution to the disease

**Sifalimumab suppressed pathways downstream of type I IFN in muscle from myositis patients**

Pathways besides type I IFN that were significantly affected following administration of sifalimumab in muscle specimens from dermatomyositis or polymyositis patients were evaluated. Transcripts suppressed by at least 37.5% in at least five sifalimumab-dosed patients and displaying an odds ratio (calculated as patients with target neutralisation >37.5% or <37.5% for each transcript) greater than 2 relative to placebo-dosed patients were retained for pathway enrichment analysis. In all, 86 pathways were suppressed by sifalimumab. Among the top enriched pathways were antigen presentation (11 transcripts; B–H αp=0.003), leucocyte extravasation signalling (33 transcripts; B–H αp=0.0009) and B-cell development (10 transcripts; B–H αp=0.004) (figure 4A–C; see supplementary figure S6A–C, available online only).

To confirm these results, we compared these pathways suppressed by sifalimumab to four primary gene signatures that were elevated in muscle biopsies in a previous study evaluating 31 dermatomyositis or polymyositis patients26 (see supplementary material, available online only). Briefly, a leucocyte index, a MHC class I signature, an immunoglobulin signature and an IFNGS were able to characterise and quantify the inflammatory cell infiltration in the muscle of myositis patients at the molecular level. The leucocyte signature was correlated with the three other signatures and was concordant with H&E staining results from the same patient biopsies in that study. We evaluated the effects of sifalimumab on these signatures in muscle. The neutralisation of the leucocyte index was significantly correlated with the neutralisation of the IFNGS in muscle (Spearman test r=−0.93, p<0.001; figure 5A), as was the signatures of MHC class I and immunoglobulin (Spearman test r=−0.84, p<0.001 and r=−0.64, p=0.001, respectively; figure 5B,C).

**Figure 4** Three of the pathways most suppressed by sifalimumab at day 98 in muscle specimens from dermatomyositis or polymyositis patients and unique to type I IFN signalling. Each point indicates a gene in either the (A) leucocyte extravasation pathway, (B) antigen presentation pathway, or (C) B-cell development pathway treated with either sifalimumab (blue squares) or placebo (red triangles). The y-axis represents the percentage of patients with at least 37.5% neutralisation of pathway-enriched transcripts at day 98 in muscle tissue specimens.
pathogenesis in myositis, is less clear. The IFN-α level in the blood has been shown to be both unique to and correlate with an elevated IFNGS in dermatomyositis. Cappelletti et al. showed that IFN-β and not IFN-α transcripts were overexpressed in polymyositis as well as dermatomyositis and juvenile dermatomyositis muscle, suggesting a local source of IFN-β that might contribute to the lack of stronger target neutralisation by sifalimumab in muscle compared to blood beyond the variation in pharmacokinetic profile in individual patients. Furthermore, type III IFN signalling can similarly bypass effects of sifalimumab and induce activation of IRF-9 and transcription of IFN-inducible genes, although IFN-λ induces a much smaller effect on IFNGS in blood (data not shown). Stimulation of purified human placental cord DC with virus or Toll-like receptor 9 agonist, CpG A showed that one subset of cells produced IFN-α only, while another subset produced IFN-α and IFN-λ. A larger study, particularly one comparing sifalimumab to an anti-type I IFN receptor (IFNAR) monoclonal antibody, will help to explain if blockage of the type I IFN pathway would clinically benefit myositis patients, and what type I IFN contributes to the pathogenesis and drives the disease progression.

In a previous independent study of dermatomyositis or polymyositis patients, a leucocyte index, an MHC class I signature and an immunoglobulin signature were overexpressed in muscle biopsies and positively correlated with the IFNGS. Independent pathway analysis conducted across the transcriptome in this study identified three similar pathways—leucocyte extravasation, antigen presentation and B-cell development (figure 5A–C, respectively), which were preferentially suppressed in muscle biopsies following exposure to sifalimumab. The leucocyte index and immunoglobulin signature represented the level of leucocyte infiltration and abundance of plasma cells in the myositis muscle, respectively. Type I IFN plays a critical role in the self-sustaining inflammatory response, contributing to leucocyte infiltration as well as the upregulation of MHC class I expression on the cell surface of muscle fibres. For both dermatomyositis and polymyositis, the inflammatory cell infiltrates are primarily composed of CD4 cells, DC and macrophages, whereas polymyositis has an additional CD8 T-cell component. In addition, DC infiltrates may act as both antigen presenting cells and as a major source of type I IFN in the diseased tissue, and contribute directly to disease pathogenesis and sustained inflammation at the disease site. In this study, all three inflammation-related signatures were suppressed concordantly with the modulation of the IFNGS in muscle following administration of sifalimumab (figure 5), consistent with the biological function of IFN-α.

Modulation of the type I IFN signature in both blood and muscle of dermatomyositis or polymyositis patients dosed with sifalimumab positively correlates with MMT8 improvement at day 98. It should be noted that a few patients receiving placebo also showed clinical improvement at day 98 based on MMT8 with no target neutralisation in either blood or muscle. One likely explanation is that some patients respond favourably to standard of care (ie, immunosuppressive medications). As MI-CP151 was not designed to evaluate the clinical efficacy of sifalimumab, the true clinical benefit of sifalimumab (on top of standard of care) in myositis needs to be evaluated in a carefully designed trial with sufficient statistical power.

This study shows the utility of an IFNGS as a pharmacodynamic biomarker for sifalimumab in adult dermatomyositis or polymyositis patients. Although this clinical trial is modest sized, we observed substantial target neutralisation of this biomarker following administration of sifalimumab in blood with a trend in muscle tissue, as well as suppressed signalling activity in several important inflammatory pathways. Preliminary results indicate a positive trend between target neutralisation of the IFNGS and reduction in disease activity in dermatomyositis or polymyositis patients, an observation that needs additional confirmation. This potential association between the mechanism of action of sifalimumab and clinical benefit, coupled with the lack of complete target neutralisation by sifalimumab, raises the possibility that blockage of the IFNAR might show superior clinical benefit in myositis patients. This hypothesis, along with a better understanding of the potential contribution of other IFN types, needs to be rigorously evaluated in future clinical trials.

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**Contributors** Conception and design, acquisition of data or analysis and interpretation of data: BW, WZ, CM, YY, XG, MR, WG. Drafting the article or revising it critically for important intellectual content: BW, WZ, CM. Final approval of the version published: WW, PB, CL, AA, DF, SAG, YY, JD, LR, BI, WG. The first two authors contributed equally.

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**Competing interests** All authors with the MedImmune LLC affiliation are full time employees and have stock in AstraZeneca. AA, SAG, and DF were paid consultants on the sifalimumab program and MI-CP151 clinical trial.

**Ethics approval** The study protocol was approved by the institutional review board at each site.

**Patient consent** Obtained.

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**Figure 5** Correlation between target neutralisation of the IFN gene signature (IFNGS) and neutralisation of the (A) leucocyte index, (B) MHC class I signature and (C) immunoglobulin signature in dermatomyositis (DM; red squares) or polymyositis (PM; blue circles) patient muscle specimens. Red dashed lines flanking the black dotted least squares fit line indicate 95% CI. The plots indicate that the alterations of the three gene signatures display significant negative correlation with target neutralisation of the IFNGS in muscle.
REFERENCES


