Safety and efficacy of ARA290 in sarcoidosis patients with symptoms of small fiber neuropathy: a randomized, double blind, pilot study.

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ABSTRACT.

ARA290, a peptide designed to activate the innate repair receptor that arrests injury and initiates cytoprotection, anti-inflammation, and healing, reduces allodynia in preclinical neuropathy models. We studied the safety and efficacy of ARA 290 to reduce symptoms of small fiber neuropathy (SFN) in patients with sarcoidosis. Twenty two patients diagnosed with sarcoidosis and symptoms of SFN were enrolled in a double blind, placebo-controlled exploratory trial of three times weekly intravenous dosing of ARA 290 (2 mg; n=12) or placebo (n=10) for 4 weeks. Inclusion criteria were a diagnosis of neuropathy and a spontaneous pain $\geq$ 5 score (Brief Pain Inventory; BPI). Endpoints assessed were changes in pain intensity and the small fiber neuropathy screening list (SFNSL) score, quality of life (SF-36), depressive symptoms (Inventory of Depressive Symptomatology; IDS), and fatigue (Fatigue Assessment Scale; FAS). No safety concerns were raised by clinical or laboratory assessments. The ARA 290 group showed significant ($p < 0.05$) improvement at week 4 in the SFNSL score compared to placebo (Δ -11·5 $\pm$ 3·04 versus Δ -2·9 $\pm$ 3·34; SEM) . Additionally, the ARA 290 group showed a significant change from baseline in the pain and physical functioning dimensions of the SF-36 (Δ -23·4 $\pm$ 5·5 and Δ -14·6 $\pm$ 3·9 respectively). The mean BPI and FAS scores improved significantly but equivalently in both patient groups. No change was observed in the IDS. ARA 290 appears to be safe in patients with sarcoidosis and to reduce neuropathic symptoms.

Introduction.

Sarcoidosis is an inflammatory disease that targets many tissues. In common with a number of other conditions, e.g., Sjogren's disease (1), one prominent clinical manifestation is a dysfunction of small nerve fibers that occurs in a patchy, non-length dependent manner (small fiber neuropathy; SFN). Pathological investigation of sarcoid SFN has documented a loss of small myelinated (Aδ) and unmyelinated (C) fibers of the sensory and autonomic nervous systems (2), as well as both sensory and motor fibers (3). The clinical sequela of these changes is the development of sharp shock-like or burning pain characterized by dysesthesia and allodynia, and loss of cutaneous sensation and autonomic function. These symptoms significantly reduce the quality of life and are often very disabling and difficult to control (2).

SFN can be diagnosed in patients with neuropathic symptoms using quantitative sensory testing, quantitative sudomotor axon testing, and by skin biopsies that show a decreased density of intra-epidermal sensory nerve fibers within affected body regions. Additionally, a questionnaire (4) has been designed and validated in Dutch patients having sarcoidosis (the small fiber neuropathy screening list; SFNSL) which is useful in following the clinical course of SFN.

Recent studies have shown that the prevalence of SFN has been grossly underestimated. Unlike granulomatous large neuron involvement of neurosarcoidosis, which has a prevalence of < 10 % (5), painful SFN is more common, with a prevalence of 40%(6) to 60% (7) of patients. The etiology of SFN is unknown, but inflammation is believed to play a prominent role in the generation and maintenance of the symptoms (8). Current therapy of sarcoidosis is primarily via immune suppression, which is generally ineffective for SFN (2).

In recent years, an endogenous system has been identified that antagonizes the production and action of proinflammatory cytokines involved in promoting tissue injury, while simultaneously activating repair processes. The primary mediator of this system is locally-produced hypo-glycosylated erythropoietin (EPO) that acts through a distinct receptor isoform, the innate repair receptor (IRR), which is a combination of EPO receptor and beta common receptor

subunits (9). EPO acting through the IRR has been shown to improve recovery and function following nerve injury in a variety of preclinical models, including small fiber neuropathy caused by uncontrolled diabetes mellitus (10).

ARA 290 is a novel peptide modeled from the three dimension structure of erythropoietin that specifically activates anti-inflammation and tissue protection through the innate repair receptor. Preclinical toxicology studies of ARA 290, as well as single and multiple ascending repeated dosing of human volunteers and patients with kidney disease, diabetes mellitus, or sarcoidosis have raised no safety issues (ref (11) and unpublished data, Araim Pharmaceuticals).

ARA 290 is highly effective in preclinical models of neuropathic pain (12). We hypothesized that patients with symptomatic SFN would benefit from administration of ARA 290. The current trial was undertaken to determine the safety and activity of repeated intravenous dosing of ARA 290 in painful neuropathy.

Study Design.

This was a single site, double-blind study carried out at Leiden University Medical Center (LUMC) and summarized by the CONSORT Flow Diagram (Figure 1). Twenty six patients (twenty four study and two alternates) diagnosed with sarcoidosis and having chronic neuropathic symptoms consistent with SFN were recruited. The diagnosis of sarcoidosis was confirmed as being consistent with the criteria set out in the international guidelines previously reported (13). Only those with confirmed sarcoidosis were included. For inclusion, chronic neuropathic symptoms consistent with SFN required at least two of the following: 1) distal symmetrical dys/paresthesias; 2) burning feet; 3) intolerance of sheets touching the legs or feet. Additionally, a patient's spontaneous pain level was $\geq$ 5 (visual analogue scale 0-10, 10 being the worst pain imaginable). Patients also underwent Quantitative Sensory Testined (QST; Medoc Advanced Medical Systems, Israel) according to the protocol of the German Research Network on Neuropathic Pain (14) with published reference values (15). The results showed a prominent loss of temperature and vibration detection thresholds (Table 1). Additional inclusion criteria were capable of reading Dutch (n=1 excluded) and to be between 18 and 65 years of age with a body mass index (BMI) $\leq$ 34 kg/m^2, as ARA 290 dosing was not scaled to

body size. Females of childbearing potential (n= 1) were required to have a negative pregnancy test and use acceptable contraception for two months during the study. Exclusion criteria included receiving a vaccination or immunization within the last month, participation in an investigational drug trial in the 3 months prior to administration of the initial dose of ARA 290 or more than 4 times per year, major surgery within 6 months prior to screening, or use of anti-TNFα, EPO, or treatment with immunoglobulins 6 months prior to or during ARA 290 administration and in the follow-up phase. The study was approved and monitored by the Ethics Committee of LUMC and is registered with the International Clinical Trials Registry (NCT 3081), Netherlands Trial Registry (trialregister.nl, NRT 3081) and is EudraCT 2010-021518-45. All patients gave written informed consent prior to entering into the study.

During the study, patients were maintained on a variable regimen of sarcoidosis therapeutics by their physicians, including oral glucocorticoids. Neuropathic symptom-directed agents, e.g., tricyclic antidepressants or selective serotonin reuptake inhibitors were also continued. Patients were randomly assigned (1:1) by the study pharmacist using a computer generated randomization code to either ARA 290 or to matching placebo (vehicle only). All other study personnel were blinded to the treatment. ARA 290 (pyroglu-glu-gln-leu-glu-arg-ala-leu-asn-ser-ser) was manufactured by Bachem AG, Bubendorf, Switzerland, using standard Fmoc solid phase peptide synthesis. The characteristics of each patient group are summarized in Table 2.

Baseline blood samples were obtained for routine chemistry, high sensitivity C-reactive protein, and hematology determinations. Repeat blood samples were obtained at week 1, and also just before the last intravenous infusion (day 25). Samples were centrifuged, separated, stored, and analyzed according to LUMC Clinical Laboratory protocols.

This study was carried out in the outpatient clinic of the Department of Anesthesiology, Leiden University Medical Center. ARA 290 (2 mg) or placebo was infused intravenously in 6 mL of normal saline over two minutes using a calibrated infusion pump on Monday, Wednesday, and Friday for 4 consecutive weeks. Patients were monitored for 60 minutes following infusion for adverse effects and instructed to contact the research staff if delayed adverse effects were

suspected. The endpoints of this exploratory study were change at week four in 1) pain level as assessed by the BPI and SF-36, 2) neuropathic symptoms as assessed by the small fiber neuropathy screening list (4) (SFNSL), and 3) quality of life assessments by the SF-36, Inventory of Depressive Symptomatology (ISD), and the fatigue assessment scale (FAS) that has been validated for sarcoidosis patients (16). These questionnaires were completed at baseline and then weekly for the four weeks of dosing. Each patient independently completed the weekly questionnaires using the Project Manager Internet Server maintained by LUMC that provided a record that could not be modified.

One patient from the ARA 290 treatment group and two from the placebo group withdrew from the study because of the inconvenience of intravenous infusions and were replaced with the two alternates that had been previously recruited as backups for the study. A total of twelve ARA 290 patients and 10 placebo patients completed the study.

The trial sample size was chosen based on the robust efficacy of ARA 290 in a rodent model of neuropathy (12) and from the observations derived from a prior small, non-blinded trial of 20 patients with symptoms of small fiber neuropathy who received ARA 290 (2 mg intravenously) for three doses every two days over one week (11). Responses from the weekly patient questionnaires were calculated as change from baseline values. Individual missing data points were assigned using a last observation carried forward approach (number of missing data points summarized below for each variable). Normality of data distribution was assessed and confirmed using the Kolmogorov-Smirnov test. Statistical significance ($p<0.05$) of change from baseline value was calculated at week four using a two sample t-test comparing change at week 4 over baseline (two tailed distribution). Because no data points were missing from the SFNSL questionnaire, these data were analyzed using repeated measures ANOVA. A cumulative proportional responders graph was constructed according to Farrar et al. (17).

Results.

There were no documented changes in concomitant drug treatment, including analgesic use, during the 4 week dosing period. Patients tolerated repeated intravenous infusions of ARA 290 without adverse events noted by study personnel or self-reported. ARA 290 recipients and

placebo patients exhibited no significant differences between chemistry and hematology values at baseline and week four. Hemoglobin concentrations (mmol/L) of ARA 290 patients compared to placebo were 8·9 ± 0·21 (SEM) versus 8·6 ± 0·26 at baseline and 8.7 ± 0·19 versus 8·7 ± 0·34 at the end of dosing on week 4.

The SFNSL score (no missing data points) showed a time-dependent, significant difference between treatment groups, reaching a maximum difference by week 4 (Figure 2). The SFNSL data obtained at the end of dosing at week 4 are expressed as a cumulative proportion of responders plot in Figure 3. As illustrated, 60 % of placebo patients experienced an improvement from baseline at week 4 between 1 and 5 points, versus 83 % of ARA 290 patients. In contrast, while none of the placebo patients experienced an improvement of 15 points or more, 42% of the ARA 290 recipients did. The SFNSL assesses both the frequency and the severity of symptoms. As shown in Figure 4A, the frequency of SFN symptoms decreased moderately in both groups to a similar extent. In contrast, the severity of neuropathic symptoms remained constant in the placebo group over the dosing period, whereas it significantly improved in the ARA 290 group (Figure 4B). The SFNSL can also be separated into components that assess symptoms referable to autonomic dysfunction (questions 2-5, 9, 11-16) or to pain (questions 1, 6-8, 10, 17-21). Patients that received ARA 290 reported a significant improvement in their autonomic symptoms, in contrast to the placebo group (Figure 5). Although a similar improvement was noted for the pain dimension, the magnitude was not significantly different from that observed for the placebo group. Assessing for change from baseline for individual questions showed that significant changes occurred in 6 questions for the ARA 290 group and 1 question for the placebo group (Table 3).

Similarly, quality of life as assessed by the SF-36 (1 patient had a total of 4 data points missing) showed significant improvements from baseline in the active treatment group for pain and physical functioning in contrast to the placebo group (Figure 6). Both groups showed significant improvements from baseline in general health (ARA 290: 35·4 ± 8·3; placebo: 22·7 ± 7·9). There were no significant changes from baseline between active and placebo groups in the remaining dimensions of SF-36. The mean pain score for the BPI (3 patients had a total of 5 data points

missing) and FAS (3 patients had a total of 1 data point each missing) decreased to a similar extent for both ARA 290 and the placebo group (Table 2), which were not significantly different from each other. The Inventory of Depressive Symptomatology (4 patients had a total of 1 data point each missing) did not change from baseline for either group (Table 2).

Discussion.

This is the first study to demonstrate that ARA 290 appears to be safe when administered repeatedly over a 4 week period to sarcoidosis patients with symptoms of small fiber neuropathy. During and following dosing, no abnormalities were noted in the laboratory or clinical evaluations, and the patients reported no potentially drug-related adverse effects. Notably, ARA 290 appears to improve symptoms of SFN, as assessed by the SFNSL, as well as on quality of life as assessed by the pain, physical functioning dimensions of the SF-36. Pain, as assessed by the BOI decreased significantly but to the same degree in both patient groups.

Primary treatment of diseases complicated by SFN has been reported to variably improve the symptoms of SFN. Sarcoidosis is a disease mediated by a complex interaction involving tissue injury and the responses of immune-competent cells. High dose glucocorticoids have been the predominant therapeutic approach for all forms of this disease. However, use of glucocorticoids is frequently associated with unacceptable adverse effects, and appears to be generally ineffective in improving the symptoms of SFN (2). Substitution of other immunosuppressants, e.g., methotrexate, also fails to improve symptomatic SFN. Consequently, sarcoid patients who suffer from chronic symptomatic SFN currently lack effective treatment.

A recent development has been the availability of agents that directly inactivate the pro-inflammatory cytokine TNFα. Use of anti-TNFα therapy in refractive pulmonary sarcoidosis has been shown to directly reduce systemic pro-inflammatory cytokine concentrations and has successfully induced a sustained improvement in lung function in some patients (18, 19). Case studies have also reported that direct antagonism of proinflammatory cytokines in patients with symptomatic SFN has been associated with significant and sustained improvement in neuropathic symptoms, including dysautonomia (20), as well as on cognitive function and

fatigue (18, 21). The results of these studies directly support the concept that proinflammatory cytokines play a major etiologic role in the development of specific organ involvement in sarcoidosis and that anti-proinflammatory cytokine therapy may constitute an effective treatment. However, the high costs and side effects of anti-TNFα therapy currently limit its widespread use. Finally, intravenous immunoglobulin infusions have been effective in a small number of patients with sarcoidosis and SFN (22), as well as in other diseases with associated SFN (23).

In the absence of strong effects of primary therapy of sarcoidosis on the symptoms of SFN, alternative therapies utilized for treating the symptoms of SFN include those utilized for other peripheral neuropathies. These include antidepressants, anticonvulsants, topical analgesics, and/or opioids. Each of these classes of therapeutic agents have specific adverse effects, sometimes severe, and further, typically do not adequately treat the symptoms of SFN (24).

ARA 290 is a peptide designed to mitigate inflammation by activating the innate repair receptor (IRR), which in turn inhibits pro-inflammatory cytokine production and action. In preclinical models of injury, ARA 290 not only inhibits TNFα, but also other components of the pro-inflammatory cytokine cascade (25). Although ARA 290 has a short serum half-life of a few minutes (11), the peak plasma concentrations attained following the administration of 2 mg intravenously in normal human volunteers in pharmacokinetic studies reached ~ 50 ng/mL, exceeding the minimum effective peak concentration of ~1 ng/mL (26). ARA 290 at concentrations exceeding ~ 1ng/mL activates the IRR which functions as a molecular swtich to provide long lasting effects, similar to other effector molecules in the immune response. In this clinical trial, administration every other day for one month appears sufficient to produce a significant biological response, similar to the finding in a preclinical rodent model in which every other day treatment with ARA 290 is very effective in preventing neuropathic pain (12). ARA 290 therefore constitutes an attractive candidate for treatment of symptomatic SFN.

The most robust effect of ARA 290 observed in this pilot trial was on the SFNSL score which appeared to be primarily on symptom severity, rather than frequency. It is notable that this instrument, which was specifically developed and validated in sarcoidosis patients (4),

incorporates prominent symptoms of autonomic dysfunction, as well as pain. In the current study, patients receiving ARA 290 appeared to improve specifically with respect to autonomic symptomatology, e.g., with respect to dry eyes, blurred vision, and orthostatic symptoms. In this regard it is interesting to note that ARA 290 has been observed to reverse neuropathic changes in the sympathetic ganglia of a mouse model of type 2 diabetes (27). Additionally, results of experiments performed on normal volunteers in whom intra-epidermal nerve fibers have been denervated by the application of capsaicin show that cutaneous autonomic nerve fibers regenerate much faster than sensory nerve fibers (28). This observation could explain, in part, the less robust effects that are noted in the pain dimension, which may require more prolonged or intensive dosing. The results also suggest that future studies in symptomatic SFN that focus on autonomic dysfunction may yield especially informative data.

The primary limitations of this trial are the small sample size, patient variability of neuropathic involvement, and lack of skin biopsy or sudomotor testing evidence definitively establishing SFN. Also, a sizeable fraction of the study group also exhibited abnormalities in mechanoreception as determined by QST in addition to the sensory and autonomic abnormalities attributable to SFN. Therefore, the observed reduction in the severity of symptoms as assessed by the SFNSL cannot be attributed with certainty only to effects of ARA 290 on small fiber function alone.

In conclusion, the acceptable safety profile noted for ARA 290 in this patient group having sarcoidosis, as well as an apparent reduction of symptoms of SFN, encourages a larger study of the potential effects of ARA 290 for this unmet medical need.

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A. Dunne, M. Brines, and A. Cerami are employees and officers of Araim Pharmaceuticals and own stock and/or stock options.

Figure Legends.

Figure 1. CONSORT flow diagram of the study of ARA 290 in sarcoidosis-associated chronic neuropathic pain.

Figure 2. ARA 290 administration is associated with a time-dependent improvement of the Small Fiber Neuropathy Screening List score.

Reduction is SFNSL score from baseline (improvement) in the ARA 290 group occurs within the first week and continues for the whole duration of the dosing period. In contrast, a small, non-significant change in placebo patients appeared to reach a plateau. (Curves (mean ± SEM) are significantly different at the $p<0{\cdot}05$ level based on repeated measures ANOVA).

Figure 3. A higher proportion of ARA 290 patients exhibited a superior improvement than did placebo patients in the Small Fiber Neuropathy Screening List score at all levels of response.

Cumulative proportion of responder analysis summarizes that across a wide range of score improvements a greater proportion of ARA 290 patients reached a specific level of reduction in the SFNSL score than did placebo patients.

Figure 4. Small Fiber Neuropathy Screening List subscore analysis.

A) A decrease in frequency of symptoms occurred in both groups over the dosing period, which did not differ significantly.

B) Severity of symptoms remained unchanged in the placebo group, whereas a decrease was noted in the ARA 290 ($p<0{\cdot}05$).

Figure 5. ARA 290 administration was associated with a significant improvement in the autonomic component of the SFNSL.

ARA 290 administration was associated with a significant improvement in the autonomic component of the SFNSL at week 4 compared to baseline (* $p<0.05$). Although a similar change was noted in the pain subcategory, the magnitude did not differ significantly from that of the placebo group.

Figure 6. ARA 290 patients demonstrated a significant improvement from baseline in the pain and physical functioning dimensions of the SF-36 quality of life questionnaire.

In contrast to the placebo patients, those receiving ARA 290 showed significant improvement from baseline in the dimension of pain and physical functioning at week 4 (** $p<0.01$).

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Table 1. Results of baseline quantitative sensory testing.

Patients in both treatment groups showed functional impairment in the function of both small fibers (Aδ and C) as well as larger sensory fibers (Aβ). Data are expressed as either increased or decreased function in those patients deviating 2 or more standard deviations from measurements obtained from a normal population.

variable	Nerve fibers involved	ARA 290*		Placebo	
		change	Number of patients (%)	change	Number of patients (%)
Cold detection threshold	Aδ & C	decrease	7 (64)	decrease	9 (90)
Warm detection threshold	Aδ & C	decrease	7 (64)	decrease	6 (60)
Thermal sensory limen	Aδ & C	decrease	3 (27)	decreased increased	2 (20) 1 (10)
Paradoxical heat sensation	Aδ	decrease	1 (9)	-	0
Cold pain threshold	Aδ & C	-	0	increase	1 (10)
Heat pain threshold	C	decrease increase	2 (18) 1 (9)	decrease increase	1 (10) 2 (20)
Mechanical detection threshold	Aβ	decrease increase	2 (18) 1 (9)	decrease	1(10)
Mechanical pain threshold	Aβ	decrease	2 (18)	decrease	3(30)
Mechanical pain sensitivity	Aβ + C	decrease	1 (9)	increase	2 (20)

Dynamic mechanical allodynia	Aβ	increase	1 (9)	increase	4 (40)
Windup ratio	Aδ & C	-	0	increase	1 (10)
Vibration detection threshold	Aβ	decrease	6 (55)	decrease	6 (60)
Pressure pain threshold	Aδ & C	increase	2 (18)	increase	8 (80)

*One patient in the ARA 290 treatment arm refused QST.

Table 2. Patient Characteristics.

variable	ARA 290	Placebo
number	12	10
males/females	6/6	6/4
weight (kg)	83·2 ± 3·7	85·5 ± 5·9
age	48·1 ± 2·7	49·1 ± 2·7
height (cm)	177·8 ± 2·8	177·4 ± 3·3
Pulmonary involvement	10/12	9/10
Fatigue	12/12	10/10
Use of NSAIDs	2/12	1/10
Use of psychological drugs	2/12	2/10
Use of oral steroids	4/12	2/10
Use of opiods	1/12	0/10
Use of analgesics	2/12	2/10
Use of anticonvulsants	3/12	3/10
Use of systemic anti-inflammatory drug	1/12	2/10
Currently smoking	2/12	2/10
ARA 290 dose (mcg/kg)	24·6 ± 1·1	0
ARA 290 dose (mcg/ m^2)	997·1 ± 26·9	0
C-reactive protein (pre- vs post; NS)	(3·0 ± 1) vs (3·1 ± 1·2)	(3·7 ± 1·5) vs (4·1 ± 1·6)
SFNSL score (pre- vs post; NS)	(41·0 ± 4·6) + (29·8 ± 3·5)	(30·6 ± 4·2) vs (26·2 ± 4·0)
BPI mean score (pre- vs post; NS)	(7·1 ± 0·2) vs (4·8 ± 0·4)	(6·2 ± 0·9) vs (4·1 ± 0·3)
SF-36 mean score (pre- vs post; NS)	(37.6 ± 2.8) vs (50.7 ± 3.1)	(44.5 ± 2.8) vs (52.3 ± 3.1)
Fatigue Assessment Score (pre- vs post; NS)	(37·9 ± 2·6) vs (33·3 ± 2·8)	(33·6 ± 2·3) vs (29·8 ± 3·3)
Inventory of Depressive Symptomatology (pre- vs post; NS)	(28·7 ± 4·9) vs (24·7 ± 4·2)	(24·1 ± 4·3) vs (22·1 ± 4·3)

± SEM; BPI score consisted of most pain, average pain, and pain now

NS; non-significant differences

Table 3. Significant changes in individual questions of the Small Fiber Neuropathy Screening List.

Patient group	Question	Symptom subgroup	Change from baseline (mean ± SEM)	Significance*
ARA 290	6 (muscle cramps)	frequency	-1.1 + 0.36	0.012
ARA 290	8 (chest pain)	frequency	-0.5 + 0.19	0.026
ARA 290	12 (dry eyes)	severity	-1.33 + 0.33	0.002
ARA 290	13 (blurred vision)	severity	-1.17 + 0.32	0.004
ARA 290	14 (dizzy when rising)	severity	-0.83 + 0.32	0.025
ARA 290	21 (chest pain)	severity	-0.58 + 0.19	0.012
placebo	6 (muscle cramps)	frequency	-0.7 ± 0.30	0.045

*determined by two tailed paired t-test

CONSORT 2010 Flow Diagram