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**Author:** Heij, L.
**Title:** ARA290 : a novel treatment for neuropathic pain in sarcoidosis
**Issue Date:** 2016-11-03
CHAPTER 5

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Molecular Medicine

Safety and Efficacy of ARA 290 in Sarcoidosis Patients with Symptoms of Small Fiber Neuropathy: A Randomized, Double-Blind Pilot Study

Lara Heij,1 Marieke Niesters,1 Maarten Swartjes,1 Elske Hoitsma,2 Marjolein Drent,3 Ann Dunne,4 Jan C Grutters,5,6 Oscar Vogels,7 Michael Brines,4 Anthony Cerami,1,4 and Albert Dahan1

1Department of Anesthesiology, Leiden University Medical Center, Leiden, the Netherlands; 2Department of Neurology, Diaconessenhuis, Leiden, the Netherlands; 3Faculty of Health, Medicine and Life Science, University of Maastricht, Maastricht, and Department of Interstitial Lung Diseases, Hospital Gelderse Vallei, Ede, the Netherlands; 4Araim Pharmaceuticals, Ossining, New York, United States of America; 5Department of Pulmonology, St. Antonius Hospital Nieuwegein, Nieuwegein, the Netherlands; 6Division of Heart and Lungs, University Medical Center Utrecht, Utrecht, the Netherlands; and 7Department of Neurology, St. Antonius Hospital, Nieuwegein, the Netherlands

ARA 290 (a peptide designed to activate the innate repair receptor that arrests injury and initiates cytoprotection, antiinflammation 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. A total of 22 patients diagnosed with sarcoidosis and symptoms of SFN were enrolled in a double-blind, placebo-controlled exploratory trial consisting of three times weekly intravenous dosing of ARA 290 (2 mg; n = 12) or placebo (n = 10) for 4 wks. Inclusion criteria were a diagnosis of neuropathy and a spontaneous pain score of ≥5 (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 wk 4 in SFNSL score compared with placebo (Δ -11.5 ± 3.04 versus Δ -2.9 ± 3.34 [standard error of the mean]). 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 ± 5.5 and Δ -14.6 ± 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 can reduce neuropathic symptoms.

Online address: http://www.molmed.org
doi: 10.2119/molmed.2012.00332

INTRODUCTION

Sarcoidosis is an inflammatory disease that targets many tissues. In common with a number of other conditions, for example, Sjogren 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 disabling and difficult to control (2).

SFN can be diagnosed in patients with neuropathic symptoms by using quantitative sensory testing or quantitative sudomotor axon testing and by performing skin biopsies that show a decreased density of intraepidermal sensory nerve fibers within affected body regions. Additionally, a questionnaire (4) was designed and validated in Dutch patients with sarcoidosis (the small fiber neuropathy screening list [SFNSL]) and is useful in following the clinical course of SFN.

Recent studies have shown that the prevalence of SFN is 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 was 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 β common receptor subunits (9). EPO acting through the IRR was shown to improve recovery and function after nerve injury in a variety of preclinical models, including SFN caused by uncontrolled diabetes mellitus (10).

ARA 290 is a novel peptide modeled from the three-dimensional structure of EPO that specifically activates anti-inflammation and tissue protection through the innate repair receptor. Preclinical toxicity 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 (11; unpublished data, Arai 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.

**MATERIALS AND METHODS**

**Study Design**

This study was a single-site, double-blind study carried out at Leiden University Medical Center (LUMC) and is summarized in the Consolidated Standards of Reporting Trials (CONSORT) flow diagram (Figure 1). A total of 26 patients (24 study and 2 alternates) diagnosed with sarcoidosis and as 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 individuals with confirmed sarcoidosis were included. For inclusion, chronic neuropathic symptoms consistent with SFN required at least two of the following: (a) distal symmetrical dys-/paresthesias, (b) burning feet or (c) intolerance of sheets touching the legs or feet. Additionally, a patient’s spontaneous pain level was ≥5 (visual analog scale 0–10, with 10 being the worst pain imaginable). Patients also underwent quantitative sensory testing (QST) (Medoc Advanced Medical Systems, Ramat Yishai, 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 as follows: capable of reading Dutch (n = 1 excluded) and aged between 18 and 65 years, with a body mass index ≤34 kg/m², since ARA 290 dosing was not scaled to body size. Women of childbearing potential (n = 1) were required to have a negative pregnancy test and use acceptable contraception for 2 months during the study. Exclusion criteria included the following: receiving a
vaccination or immunization within the last month; participation in an investigational drug trial in the 3 months before administration of the initial dose of ARA 290 or more than four times per year; major surgery within 6 months before screening; or use of anti–tumor necrosis factor (TNF)–α or EPO or treatment with immunoglobulin drugs 6 months before 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) (EudraCT 2010-021518-45). All patients gave written informed consent before 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 (for example, tricyclic antidepressants or selective serotonin reuptake inhibitors) were also continued. Patients were randomly assigned (1:1) by the study pharmacist by using a computer-generated randomization code to either ARA 290 or matching placebo (vehicle only). All other study personnel were blinded to the treatment. ARA 290 (pyroglu-glu-glu-leu-arg-ala-leu-asn-ser-ser) was manufactured by Bachem (Bubendorf, Switzerland) by using standard Fmoc solid-phase peptide synthesis. The characteristics of each patient group are summarized in Table 1.

Baseline blood samples were obtained for routine chemistry, high-sensitivity C-reactive protein and hematology determinations. Repeat blood samples were obtained at wk 1 and also just before the last intravenous infusion (d 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 normal saline over 2 min by using a calibrated infusion pump on Monday, Wednesday and Friday for 4 consecutive weeks. Patients were monitored for 60 min after 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 wk 4 in (a) pain level, as assessed by the BPI and SF-36; (b) neuropathic symptoms, as assessed by the SFNSL (4); and (c) quality of life assessments by the SF-36, Inventory of Depressive Symptomatology (IDS) and the Fatigue Assessment Scale (FAS), which has been validated for sarcoidosis patients (16). These questionnaires were completed at baseline and then weekly for the 4 wks of dosing. Each patient independently completed the weekly questionnaires by using the Project Manager Internet Server maintained by LUMC, which provided a record that could not be modified.

One patient from the ARA 290 treatment group refused qST. 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.

**Table 1. Results of baseline quantitative sensory testing.**

| Variable                        | ARA 290*          | Placebo          |
|---------------------------------|------------------|------------------|
| Nerve fibers involved          | Change           | Number of patients (%) | Change           | Number of patients (%) |
| Cold detection threshold       | Decrease         | 7 (64)           | Decrease         | 9 (90)             |
| Warm detection threshold       | Decrease         | 7 (64)           | Decrease         | 6 (60)             |
| Thermal sensory limen          | Decrease         | 3 (27)           | Decreased, increased | 2 (20), 1 (10) |
| Paradoxical heat sensation     | Decrease         | 1 (9)            | —                | 0                  |
| Cold pain threshold            | —                | 0                | Increase         | 1 (10)             |
| Heat pain threshold            | Increase, decrease | 2 (18), 1 (9)   | Decrease, increase | 1 (10), 2 (20) |
| Mechanical detection threshold | Increase, decrease | 2 (18), 1 (9)   | Decrease         | 1 (10)             |
| Mechanical pain threshold      | Decrease         | 2 (18)           | Decrease         | 3 (30)             |
| Mechanical pain sensitivity    | Decrease         | 1 (9)            | Increase         | 4 (40)             |
| Dynamic mechanical allodynia   | Increase         | 1 (9)            | Increase         | 1 (10)             |
| Windup ratio                   | —                | 0                | Increase         | 1 (10)             |
| Vibration detection threshold  | Decrease         | 6 (55)           | Decrease         | 6 (60)             |
| Pressure pain threshold        | Increase         | 2 (18)           | Increase         | 8 (80)             |

*One patient in the ARA 290 treatment arm refused qST. 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.
from the weekly patient questionnaires were calculated as change from baseline values. Individual missing data points were assigned by 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 by using the Kolmogorov-Smirnov test. Statistical significance (p < 0.05) of change from baseline value was calculated at wk 4 by using a two-sample t test comparing change at wk 4 over baseline (two-tailed distribution). Because no data points were missing from the SFNSL questionnaire, these data were analyzed by using repeated-measures analysis of variance (ANOVA). A cumulative proportional responders graph was constructed according to Farrar et al. (17).

### Table 2. Patient characteristics.

| Variable                              | ARA 290 | Placebo |
|---------------------------------------|---------|---------|
| n                                     | 12      | 10      |
| M/F                                   | 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 nonsteroidal antinflammatory drugs (NSAIDs) | 2/12     | 1/10    |
| Use of psychological drugs            | 2/12    | 2/10    |
| Use of oral steroids                  | 4/12    | 2/10    |
| Use of opioids                        | 1/12    | 0/10    |
| Use of analgesics                     | 2/12    | 2/10    |
| Use of anticonvulsants                | 3/12    | 3/10    |
| Use of systemic antinflammatory drug  | 1/12    | 2/10    |
| Currently smoking                     | 2/12    | 2/10    |
| ARA 290 dose (µg/kg)                  | 24.6 ± 1.1 | 0      |
| ARA 290 dose (µg/m²)                  | 997.1 ± 26.9 | 0    |
| C-reactive protein (pretreatment versus posttreatment; NS) | 3.0 ± 1 versus 3.7 ± 1.5 | 3.1 ± 1.2 versus 4.1 ± 1.6 |
| SFNSL score (pretreatment versus posttreatment; p < 0.05) | 41.0 ± 4.6 versus 30.6 ± 4.2 | 29.8 ± 3.5 versus 26.2 ± 4.0 |
| BPI mean score (pretreatment versus posttreatment; NS) | 7.1 ± 0.2 versus 6.2 ± 0.9 | 4.8 ± 0.4 versus 4.1 ± 0.3 |
| SF-36 mean score (pretreatment versus posttreatment; NS) | 37.6 ± 2.8 versus 44.5 ± 2.8 | 37.9 ± 2.6 versus 52.3 ± 3.1 |
| FAS (pretreatment versus posttreatment; NS) | 37.9 ± 2.6 versus 33.6 ± 2.3 | 33.3 ± 2.8 versus 29.8 ± 3.3 |
| IDS (pretreatment versus posttreatment; NS) | 28.7 ± 4.9 versus 24.1 ± 4.3 | 24.7 ± 4.2 versus 22.1 ± 4.3 |

Data are mean ± SEM. BPI score consisted of most pain, average pain and pain now. NS, nonsignificant differences.

### RESULTS

There were no documented changes in concomitant drug treatment, including analgesic use, during the 4-wk 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 wk 4. Hemoglobin concentrations (mmol/L) of ARA 290 patients compared with placebo were 8.9 ± 0.21 (standard error of the mean [SEM]) versus 8.6 ± 0.26 at baseline and 8.7 ± 0.19 versus 8.7 ± 0.34 at the end of dosing on wk 4.

The SFNSL score (no missing data points) showed a time-dependent, significant difference between treatment groups, reaching a maximum difference by wk 4 (Figure 2). The SFNSL data obtained at the end of dosing at wk 4 are expressed as a cumulative proportion of the responders plot in Figure 3. As illust-
ARA 290 in sarcoid small fiber neuropathy

Treated, 60% of placebo patients experienced an improvement from baseline at wk 4 compared with baseline (*p < 0.05). Although a similar change was noted in the pain subgroup, the magnitude did not differ significantly from that of the placebo group.

![Figure 4. SFNSL subscore analysis.](image)

(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 < 0.05).

**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 wk 4 compared with baseline (*p < 0.05). Although a similar change was noted in the pain subgroup, the magnitude did not differ significantly from the placebo group.

![Figure 5.](image)

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 wk 4 compared with baseline (*p < 0.05). Although a similar change was noted in the pain subgroup, the magnitude did not differ significantly from the placebo group.

Primary treatment of diseases complicated by SFN was reported to variably improve the symptoms of SFN. Sarcoidosis is a disease mediated by a complex

**Table 3.** Significant changes in individual questions of the SFNSL.

| 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.

**DISCUSSION**

This is the first study to demonstrate that ARA 290 appears to be safe when administered repeatedly over a 4-wk period to sarcoidosis patients with symptoms of SFN. During and after 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 and physical functioning dimensions of the SF-36. Pain, as assessed by the BPI, decreased significantly, but to the same degree in both patient groups.
The development of specific organ inter
port the concept that proinflammatory cytokines in patients (18,19). Case studies have also re-
tested the proinflammatory cytokine cascade at concentrations exceed-
in the clinical trial, administration every other day for 1 month appears suf-
ctions as a molecular switch to pro-
itive in improving the symptoms of SFN (24).
ARA 290 for this unmet medical need.
the improvement in neurologic abnormalities attributable to SFN. Therefore, the observed reduction in the severity of symptoms as assessed by the SFNSL score, which appeared to be pri-
AR A290 provides 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.

CONCLUSION
The acceptable safety profile noted for ARA 290 in this patient group with sarco-
idosis, as well as an apparent reduc-
sion of symptoms of SFN, encourages a larger study of the potential effects of ARA 290 for this unmet medical need.

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 wk 4 (**p < 0.01).
ACKNOWLEDGMENTS
The authors thank patients, and their families as well as F Breedveld, A Rabelink, I. Aarts, E. Lansink and E. Sarton for support and assistance in making this study possible. This was an investigator-initiated study. ARA 290 was supplied by Araim Pharmaceuticals.

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

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