ARA290 : a novel treatment for neuropathic pain in sarcoidosis

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CHAPTER 7

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EXPERT OPINION

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ARA 290 for treatment of small fiber neuropathy in sarcoidosis

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Introduction: Painful peripheral neuropathy is a common, difficult-to-treat complication associated with a variety of diseases, including diabetes mellitus and sarcoidosis. It is caused by damage of small and autonomic nerve fibers, resulting in potentially debilitating symptoms of neuropathic pain and autonomic dysfunction. The limited efficacy of current treatment options dictates a rationalized design of novel compounds.
Areas covered: The authors present the recent data from two Phase II clinical trials on ARA290, an erythropoietin derivative with tissue protective and healing properties that does not stimulate erythropoiesis. ARA 290 treatment was consistently associated with a significant improvement of neuropathic pain symptoms in sarcoidosis patients, evidenced by a decrease in pain scores on validated questionnaires. Moreover, ARA 290 treatment resulted in significant increases in corneal nerve fibers, improved sensory pain thresholds, improved quality of life and physical functioning.
Expert opinion: Current treatment modalities of neuropathy are based on a trial-and-error approach, have limited efficacy and come with significant side effects. Given the excellent safety profile while reducing neuropathy symptoms, the prospects of ARA 290 treatment in sarcoid neuropathy seem promising. The long-lasting beneficial effects of ARA 290 on both pain-related and non-pain-related symptoms in sarcoidosis patients prompt additional studies on potential disease-modifying properties of ARA 290.

Keywords: ARA 290, innate repair receptor, neuropathy, pain, Phase II study, sarcoidosis, small fiber neuropathy.

Expert Opin. Investig. Drugs [Early Online]

1. Introduction

Many chronic diseases and syndromes (including diabetes, sarcoidosis, HIV, paraneoplastic syndromes, alcoholism) can result in damage to peripheral nerves [1,2]. The neuropathy is often limited to small and autonomic nerve fibers, that is, small fiber neuropathy (SFN), which leads to the destruction and/or retraction of the small diameter nerve fibers in the skin and dysfunctional autonomic fibers, although in some patients a small and large fiber neuropathy coexists. While some SFN patients remain relatively symptom-free, the majority of patients develop complaints that significantly affect their quality of life (QoL). Most frequently, pain and autonomic symptoms dominate the clinical picture. Unfortunately, SFN remains repeatedly under-diagnosed by the physician specialists involved in treatment of the underlying disease [2]. Pain from SFN has specific characteristics, which include spontaneous (burning, itching, shooting, or electrical) pain, allodynia (touch-evoked pain) and hyperalgesia (increased pain sensitivity), often in combination with fasciculations or paresthesias [3]. Comorbid conditions may be present in some patients, including insomnia, anxiety, depression and catastrophization, tiredness and obesity. These comorbidities further deteriorate the physical and mental

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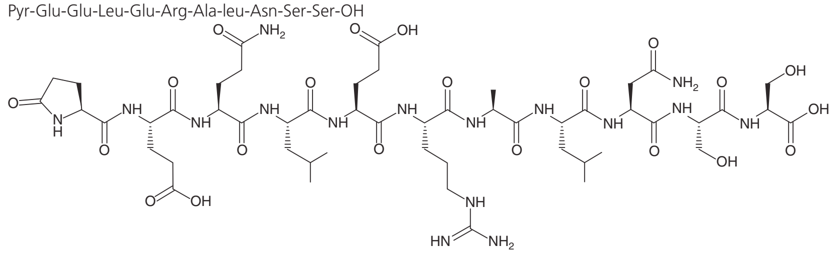
Box 1. Drug summary.

Drug name	ARA 290
Phase	II
Indication	Small fiber neuropathy (SFN) related to sarcoidosis
Mode of action	Activation of the innate repair receptor (IRR)
Route of administration	Intravenous or subcutaneous
Chemical structure	Pyr-Glu-Glu-Leu-Glu-Arg-Ala-leu-Asn-Ser-Ser-OH 
Pivotal trial(s)	NARA and NERVARA trials [6,10,11]

state of the patient, and may affect his or her socioeconomic status often with grave consequences, such as unemployment and social isolation.

Current treatment of SFN pain is symptomatic, and conventional therapy consists of antidepressants, anticonvulsants, prolonged-release opioids and local applications of lidocaine or capsaicin. Irrespective of the treatment or the underlying disease, the efficacy is limited, with just 30 – 40% of patients showing adequate-to-good pain relief [4,5]. In the remaining patient population, the occurrence of severe side effects prevent effective treatment at the required dose or patients have no effect or very limited effect of treatment at all. In some diseases, the initial neuropathic pain treatment is aimed at intervening with the underlying disease process. In the case of sarcoidosis, although conventional immunosuppressive and experimental immune-modulatory and cytotoxic therapies are frequently applied, little relief of neuropathic pain symptoms is seen [3]. We recently initiated a program evaluating the response of patients diagnosed with sarcoidosis and SFN with a new treatment option: ARA 290, an erythropoietin-derivative with tissue protective and healing properties [6]. Sarcoidosis is an orphan disease with ORPHA number ORPHA797 (www.orpha.net) and ARA 290 has received designation as Orphan Drug Product for the treatment of neuropathic pain in sarcoidosis from both the FDA and European Medicines Agency.

A series of experimental studies showed that ARA 290 is effective in the reduction of allodynia in animal models of peripheral nerve injury (which coincided with a reduction in spinal cord inflammation) and inflammatory neuritis [7,8]. Furthermore, administration of related non-erythropoietic tissue protective derivatives have resulted in regrowth of intra-epidermal nerve fibers (IENF) in diabetes mellitus (DM)- and cisplatinum-induced SFN in animals [9]. An initial open-label trial in humans showed that ARA 290 is without side effects, caused relief of neuropathic pain, and improved the QoL of patients with SFN related to diabetes type 2 and sarcoidosis [6]. These positive results prompted the development of the program on ARA 290 in SFN in sarcoidosis patients. Currently, two Phase II trials have been completed and analyzed (the NARA and NERVARA trials [10,11]) and one Phase II trial is ongoing (the DOSARA trial). A first Phase III trial is planned for 2014. We previously reported on the safety, pharmacokinetics and pharmacodynamics of ARA 290 in animals and humans and discussed the open-label trial in DM and sarcoidosis patients [6,11]. Here we will discuss SFN in sarcoidosis and briefly reiterate the mechanism of action and pharmacological properties of ARA 290. Our main focus is the discussion of the two completed and analyzed Phase II trials on the effect of ARA 290 in sarcoidosis patients with painful peripheral neuropathy.

2. Painful small fiber neuropathy in sarcoidosis

Sarcoidosis is a multisystem inflammatory disease of unknown origin, characterized by the development of noncaseating granulomas in various tissues [12,13]. More than 50% of patients have symptoms of pulmonary involvement (dyspnea, coughing), while the majority of patients have nonspecific complaints including fatigue, general feelings of malaise, pain, and symptoms of autonomic dysfunction [14]. The incidence of the disease varies between the sexes and ranges from 1:5300 in females to 1:6300 in males [13,14]. A considerable percentage of patients with persistent sarcoidosis have symptoms consistent with SFN and the diagnosis of SFN is made

Table 1. The small fiber neuropathy screening list.

Part 1: These questions are aimed at finding out how often you experience the following complaints:	
I have painful arms	Never/sometimes/fluctuating/often/always
I suffer from palpitations	Never/sometimes/fluctuating/often/always
I have problems with bowel movements	Never/sometimes/fluctuating/often/always
I have difficulty urinating (either in emptying my bladder or being able to hold my water)	Never/sometimes/fluctuating/often/always
My food does not seem to go down well	Never/sometimes/fluctuating/often/always
I suffer from muscle cramps	Never/sometimes/fluctuating/often/always
My feet and/or hands are colder than I am use to	Never/sometimes/fluctuating/often/always
I have chest pain	Never/sometimes/fluctuating/often/always
Part 2: These questions are aimed at finding out how serious your complaints are:	
I have the feeling that my food gets stuck in my throat	Not at all/slightly/fluctuating/moderately/seriously
At night I throw the bedclothes off my legs	Not at all/slightly/fluctuating/moderately/seriously
I have difficulty urinating (either in emptying my bladder or being able to hold my water)	Not at all/slightly/fluctuating/moderately/seriously
I have dry eyes	Not at all/slightly/fluctuating/moderately/seriously
I have blurred vision	Not at all/slightly/fluctuating/moderately/seriously
I feel dizzy when I get up	Not at all/slightly/fluctuating/moderately/seriously
I have sudden hot flushes	Not at all/slightly/fluctuating/moderately/seriously
My feet and/or hands are colder than I am use to	Not at all/slightly/fluctuating/moderately/seriously
I have painful arms	Not at all/slightly/fluctuating/moderately/seriously
The skin of my leg is over-sensitive	Not at all/slightly/fluctuating/moderately/seriously
I have a tingling sensation in my hands (pins and needles)	Not at all/slightly/fluctuating/moderately/seriously
I have a tingling sensation in my legs (pins and needles)	Not at all/slightly/fluctuating/moderately/seriously
I have chest pain	Not at all/slightly/fluctuating/moderately/seriously

For each question, scores range from 0 (never or not at all) to 4 (always or seriously). The highest score possible is 21 × 4 = 84 (40 points for pain-related symptoms, 44 for autonomic symptoms). The cutoff for SFN is set at 22.
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in about one-third of sarcoid patients with pain [15]. SFN is characterized by dysfunction, damage and/or destruction of thinly myelinated Aδ and unmyelinated C fibers of the sensory and autonomic nerve system that is not due to granuloma formation [2,3,16]. The symptoms of SFN related to sarcoidosis are similar to SFN from other systemic, inflammatory and autoimmune diseases with complaints of spontaneous pain, allodynia, hyperalgesia and symptoms of autonomic dysfunction (diarrhea or constipation, hypo or hyperhidrosis, urinary incontinence or retention, gastroparesis, dry eyes and mouth, blurry vision, flushes, orthostatic hypotension, erectile dysfunction) [2]. Moreover, sleep-related problems (allodynia-related insomnia from bedsheet intolerance) and restless legs are frequent symptoms of SFN. All symptoms may initially be episodic but gradually become permanent with exacerbations during the nightly hours. In many patients pain is the dominant complaint and varies in presentation between patients (but also within patients) ranging from spontaneous burning and shooting to vibration and electrical shock-like sensations. Finally, the distribution of sensory symptoms can vary between patients, such as a nerve fiber length-dependent stocking/glove presentation or a more patchy, scattered distribution of SFN-related symptoms.

Diagnosis of SFN is primarily based on existing symptoms. The Small-Fiber Neuropathy Screening List (SFNSL) is specifically developed and validated for SFN in sarcoidosis [17]. The SFNSL consists of 21 questions related to neuropathic pain and to autonomic dysfunction (**Table 1**). The latter is important as until recently autonomic complaints were seldom associated with SFN. The specificity of the SFNSL is very high, as a cutoff score has been defined identifying patients with SFN [17]. Additional tests for SFN are also of importance and include quantitative sensory testing (QST), autonomic function testing, and skin biopsies or corneal confocal microscopy, the latter two to assess nerve fiber density.

QST consists of a battery of psychophysical tests where the patient is requested to respond to a specific sensory stimulus to the skin [18]. Tests include cold and warm detection threshold (WDT), cold and warm pain threshold, paradoxical heat sensation, allodynia, and vibration detection threshold. Loss of function (i.e., an increased response threshold) for cold and WDT are indicative of SFN (**Figure 1A**). More objective QST measures include laser-evoked potentials and contact heat-evoked potentials where a short stimulus results in activation of thermo-nociceptive cutaneous nerve fibers. The electroencephalography-potentials (amplitude and delay) give a measure of the functionality of small nerve fibers although more central pathology cannot be excluded. Experimental new tests are being developed to increase specificity and patient compliance. One such example is offset-analgesia, a 30-s test quantitative sensory test in which a disproportionally large

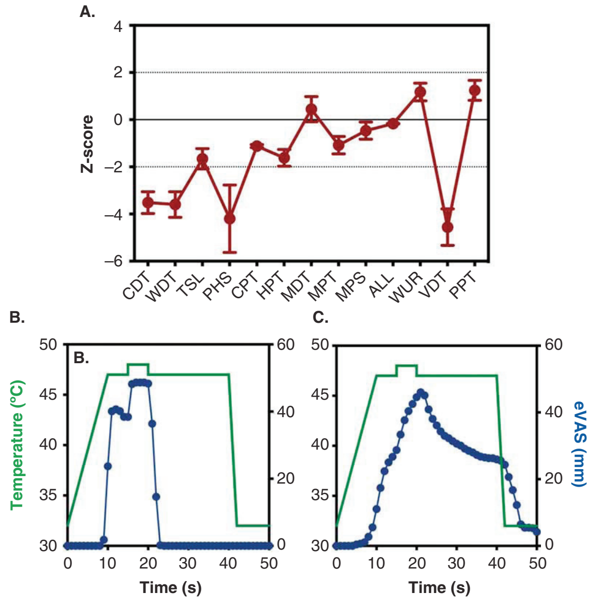

Figure 1. A. Quantitative sensory testing in a mixed population of patients with small fiber neuropathy (n = 10). Values are *z*-scores (mean ± SEM). Values below -2 or above 2 indicate a significant deviation relative to a healthy control population ($p < 0.05$). Abnormal values at the painful extremity were observed for CDT and WDT, PHS and VDT. TSL, CPT, HPT, MDT, MPT, MPS, ALL dynamic mechanical allodynia, WUR, and PPT. **B.** Offset analgesia in a healthy male volunteer 60 years of age. The green line is the temperature change at the skin of the volar surface of the underarm induced by a thermode. Blue dots represent the electronic visual analogue scores. Following the 1°C decrease in temperature a large analgesic response is observed with VAS = zero despite a heat stimulus of 45°C. **C.** An offset analgesia response in a patient with SFN showing no analgesic response following the 1°C decrease in temperature. VAS scores follow closely the noxious temperature stimulus.

A. Data adapted from [45] with permission of Oxford University Press.

B. and **C**. Data adapted from [21] with permission of Wolters Kluwer Health.

ALL: Dynamic mechanical allodynia; CDT: Cold detection thresholds; CPT: cold pain threshold; HPT: Heat pain threshold; MDT: Mechanical detection threshold; MPS: Mechanical pain sensitivity; MPT: Mechanical pain threshold; PHS: Paradoxical heat sensation; PPT: Pressure pain threshold; tsl: Thermal sensory limen; VAS: visual analog scale; VDT: Vibration detection threshold; WDT: Warm detection thresholds; WUR: Windup ratio.

amount of analgesia becomes apparent upon a slight decrease in noxious heat stimulation (**Figure 1B** and **C**) [19-22]. We recently showed that this test has a > 90% sensitivity and specificity to discriminate between healthy volunteers and patients with SFN [21].

Skin biopsies are considered the gold standard for diagnosis of SFN [23,24]. The technique, which involves a 3-mm punch biopsy of the skin (most commonly a site 10 cm above the lateral malleolus chosen), identifies the presences of the small Aδ and C-nerve fibers that penetrate the dermal-epidermal junction (**Figure 2**). Several studies show that SFN in sarcoidosis is associated with a reduction of the intraepidermal nerve fiber density (IENFD) albeit with high specificity and low sensitivity [2]. The punch biopsy is an invasive, time-consuming test, and few medical centers offer this technique. Furthermore, there is a dependence on age and gender and high variability of normal values. Also, diseased patients (up to 60% in sarcoidosis) may have a normal IENFD despite severe SFN pain-like complaints [25]. These numbers indicate that small nerve loss of function precedes actual destruction or retraction (**Figure 2A**). Moreover, sarcoidosis-related SFN can have a non-length-dependent, patchy bodily distribution, so that the detection of SFN could be missed by a single ankle skin biopsy [26,27].

A relatively new technique involves the quantification of C-fibers between the layer of Bowman and basal epithelium of the cornea [28-31]. Using cornea confocal microscopy (CCM), the nerve fibers of the cornea are systematically photographed and quantified with respect to length, density, branching, and tortuosity. Recently we demonstrated that in sarcoidosis patients with SFN, corneal nerve fibers density and length are reduced and, in contrast to intraepidermal fiber

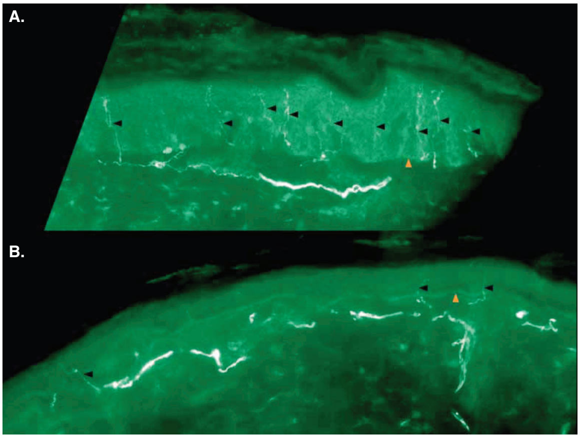

Figure 2. Skin biopsies obtained 10 cm above the lateral malleolus of two patients (A and B) with sarcoidosis and small fiber neuropathy. Both patients had moderate to severe neuropathic pain with pain scores > 5. Note the difference in intraepidermal nerve fiber density. Orange arrowheads point toward the basal membrane between dermis and epidermis, the black arrowheads point toward the small nerve fibers (white). In the dermis the nerve plexus are visible (white).

density, the CCM data correlated with pain-interference score (i.e., the degree at which pain interferes with activities of daily living) derived from the Brief Pain Inventory (BPI) questionnaire [28]. These results, together with the fact that CCM allows rapid and noninvasive assessment of the cornea nerve fibers, this technique may be a further aid in the diagnosis and follow-up of SFN. The corneal nerve plexus is a highly dynamic structure, allowing easy detection of density changes in time [32]. Furthermore, the association between cornea fiber density and pain interference designates this measure as a promising biomarker of SFN pain.

Taken the fact that autonomic dysfunction is an important symptom occurring in SFN, autonomic tests are important for diagnosis as well as assessment of the clinical condition of the patient [2]. Apart from specific questionnaires aimed at diagnosing dysautonomy [17], specific tests are available, including quantitative sudomotor axon reflex testing where the sweat output is measured in response to acetylcholine iontophoresis at the upper and lower extremities [23,24]. Other tests involve cardiac testing, including heart rate variability tests.

3. ARA 290

There is ample evidence that the anti-inflammatory cytokine erythropoietin (EPO) has tissue protective properties [33]. For example, recombinant human EPO (5000 IU/kg) reduces concussive injury in an animal model of blunt head trauma [34]. In humans, EPO (40,000 IU/week) reduces mortality by 50% in trauma patients admitted to the intensive care [35]. In various animal nerve injury models (including SFN due to DM), EPO improved nerve recovery and function [9,36]. The anti-inflammatory property of EPO is exerted through activation of the innate repair receptor (IRR). The IRR is a hetero-complex composed of β-common receptor and erythropoietin receptor subunits. The IRR has a low affinity for EPO, but is expressed on the cell surface in response to local tissue injury and inflammation and is effectively activated by locally produced EPO. IRR activation results in engagement of multiple anti-inflammatory and tissue protective pathways and ultimately results in reduced apoptosis, tissue restoration, and nitric oxide formation by endothelial cells (hence improving tissue perfusion). The EPO-IRR system is programmed to increase the probability of non-hematopoietic cell and tissue survival.

Since a high dose of exogenous EPO, required to activate the IRR, concurrently stimulates erythropoiesis and results in various serious side effects (including pro-thrombotic effects, hypertension, myocardial infarction), novel molecules have been developed that exclusively activate the IRR [37]. One such molecule is ARA 290 (Araim Pharmaceuticals Inc., Ossining, NY), an 11-amino acid linear peptide (molecular weight 1257 Da, amino acid sequence: Pyr-Glu-Glu-Leu-Glu-Arg-Ala-leu-Asn-Ser-Ser-OH [**Box 1**]), which mimics the spatial configuration of EPO that interacts with the IRR. Like EPO, derivative peptides, such as ARA 290 reduce apoptosis, are anti-inflammatory and promote healing in a variety of animal nerve injury models (including peripheral nerve injury and SFN in DM) [9,36,38,39]. In animals (maximum dose given 11,000 μg/kg ARA 290), healthy volunteers (up

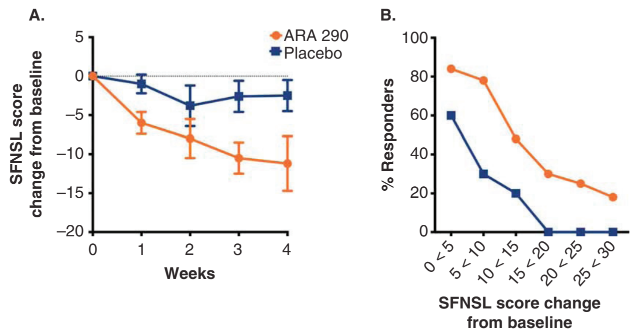

Figure 3. A. Effect of ARA 290 in the first Phase II trial (NARA). ARA 290 produces a time-dependent improvement of the small fiber neuropathy screening list (SFNSL) score, significantly greater than placebo ($p < 0.05$; values are mean ± SEM). **B.** Cumulative percentage responder analysis at six SFNSL score ranges. At each range, the responder percentage of ARA 290-treated patients exceeds that of placebo-treated patients.

Data adapted from [11] with permission of Molecular Medicine.

to 30 µg/kg), and patients (25 – 50 µg/kg) no safety issues were identified (Araim, data on file [6]). In healthy volunteers, ARA 290 has a short intravenous half-life (2 min following intravenous and 20 min following subcutaneous administration). This indicates a rapid passage of ARA 290 eliciting a long-lasting effect. Indeed, the pharmacodynamic analysis of pain relief data of the Phase I trial (data obtained in sarcoidosis and diabetes type 2 patients following a 3-day intravenous treatment with 2 mg ARA 290 on Monday, Wednesday, and Friday) yielded an effect half-life, of 2 – 3 days [6].

4. Clinical efficacy

4.1 The NARA trial protocol [11]

The first exploratory Phase II study was designed in light of the findings from the open-label study. The NARA study was a double-blind, randomized, controlled trial (RCT) performed in sarcoidosis patients with moderate to severe neuropathic pain. Only patients with confirmed sarcoidosis were eligible to participate. Inclusion criteria related to the presence of painful SFN were: i) the presence of at least one of the following symptoms: distal symmetrical dysesthesia or paresthesia; burning feet and; allodynia at the lower extremities (bed sheet intolerance); and ii) spontaneous pain scores of 5 or greater (on an 11-point scale). Confirmation of SFN was further obtained by quantitative sensory testing. Patients could remain on their pain medication (e.g., corticosteroids, antidepressants) but were not allowed to change intake during the study. Patients were randomized to receive ARA 290 (intravenous dose of 2 mg dissolved in 6 ml of normal saline) or placebo (6 ml normal saline) three times weekly (Monday, Wednesday, Friday) for 4 weeks; follow-up period was 12 weeks. The main end points of the study included pain intensity scores from the BPI questionnaire, neuropathic symptoms as determined from the SFNSL questionnaire (**Table 1**), and QoL score from the short form of the RAND36 (SF-36).

4.2 The NARA trial results

A total of 13 patients of either sex were randomized to ARA 290 (12 analyzed, 1 patient did not receive allocated treatment), 13 to placebo (10 analyzed, 2 did not receive the allocated medication, 1 was excluded because of noncompliance). Mean age of the patients was 48.6 years. All patients were treated at home by the trial physician. The SFNSL scores showed a 30% decrease in ARA 290-treated patients (**Figure 3A**) compared to baseline with a maximum difference between treatments at week 4. SFNSL responder rate was greatest in the ARA 290-treated patients: 83 versus 60% of patients had a reduction in score of 1 – 5 points (ARA 290 vs placebo), 42 versus 0% had a reduction in score of at least 15 points (**Figure 3B**). The SFNSL reports on pain-related and autonomic symptoms; ARA 290 caused improvement in both dimensions (autonomic symptoms including dry eyes, blurred vision, orthostatic hypotension: $p < 0.05$ vs placebo; pain symptoms: NS). QoL improved in ARA 290-treated patients ($p < 0.05$ vs placebo). Interestingly, pain scores derived from the BPI reduced in both treatment groups similarly by 2.1 versus 2.3 points. Pain score and physical functioning score derived from the SF-36 improved significantly in ARA 290 treated patients than in placebo-treated patients (difference in score reduction > 50%, $p < 0.01$).

The first Phase II trial confirmed the observations made in the open-label study showing a significant improvement in neuropathic pain symptoms including autonomic symptoms. No safety issues were raised during or in the 3 months following treatment. As expected, ARA 290 had no effect on hemoglobin concentrations.

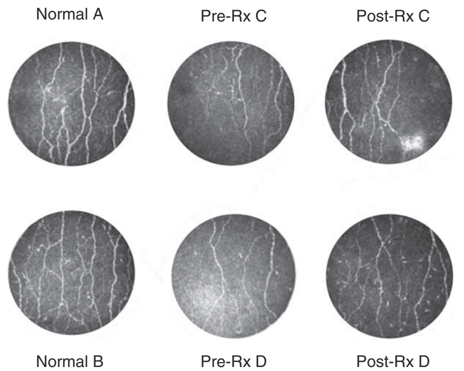

Figure 4. Cornea nerve fibers obtained via corneal confocal microscopy in two normal subjects (Normal A and Normal B) and two sarcoidosis patients with small fiber neuropathy before treatment (Pre-Rx C and Pre-Rx D) and after a daily 28 week 4 mg subcutaneous injection with 4 mg ARA 290 (Post-Rx C and Post Rx D). The paucity in nerve fibers before treatment and the improvement in nerve fiber density after treatment are evident.

Data are from [10] with permission of Molecular Medicine.

4.3 The NERVARA trial protocol [10]

The positive observations from the NARA trial prompted a second, larger Phase II trial, the NERVARA trial. This double-blind, randomized, placebo-controlled RCT was also performed in sarcoidosis patients with painful neuropathy. Inclusion criteria were: i) the confirmed diagnosis of sarcoidosis; ii) pain levels > 5, and SFNSL score > 22 (indicative of SFN-related neuropathic symptoms); and iii) the presence of at least one of the following symptoms: dysesthesias, burning or painful feet worsening at night, and bedsheet intolerance. In contrast to the NARA trial, patients were treated daily with 4 mg subcutaneous ARA 290 injections for 28 days; follow-up was 12 weeks. The primary end points of the study were treatment-induced changes in corneal nerve fiber density, intra-epidermal nerve fiber density, and cutaneous quantitative sensory sensitivity. The secondary end points of the study were treatment-induced changes in the SFNSL score, BPI score, exercise capacity determined by the 6-min walk test (6MWT).

4.4 The NERVARA trial results

Twenty-one patients were randomized to ARA 290 treatment (21 analyzed), 20 patients to placebo treatment (17 analyzed, 2 did not receive allocated medication; 1 patient excluded because of noncompliance). Mean age of the patients was 49.5 years (range 28 – 65 years) with 18 men and 20 women. There were on average 7 (ARA 290) and 10 years (placebo) between the current study and the diagnosis of sarcoidosis. No safety issues became apparent during the study or the follow-up period.

The test results were as follows:

1) *Corneal Nerve Fiber Density (CNFD).* All patients exhibited a reduced CNFD, about 50% of that of healthy age- and sex-matched controls. ARA 290 treatment caused a significant increase in CNFD by 14.5% (compared to a small decrease in placebo treated patients, p = 0.02) (**Figure 4**).
2) *IENFD.* The IENF densities of the proximal (thigh) and distal leg were about 50% reduced compared to healthy age- and sex-matched controls. Treatment had no significant effect on the IENF densities.
3) *QST*. Pretreatment measurements showed loss of function of small fibers of the skin with abnormal cold and WDTs. ARA 290 but not placebo caused an increase in sensory pain thresholds: cold pain threshold increased by about 6°C, warm pain threshold by 3°C. Baseline values of these modalities were within the normal range.
4) *SFNSL.* Baseline scores of the SFNSL were 43 (pain component: 23, autonomic component 21). ARA 290 produced a 30% improvement of the SFNSL score at week 5 of the study versus a 9% improvement for placebo (p < 0.01). The improvement was most apparent for symptom severity than for symptom frequency. The observed changes persisted for at least 3 months post-treatment (**Figure 5A** and **B**). In a large subset of patients (36 patients) a final measurement was obtained at 9 months demonstrating a 6-point difference between treatment groups favoring the ARA 290 patients. Improvement in SFNSL score by ARA 290-treated patients occurred in both pain and autonomic symptom subscores.
5) *BPI.* Mean pain intensity scores were reduced similarly in ARA 290- and placebo-treated patients by a significant 9%. Pain interference scores improved significantly in ARA 290 patients by 36 versus 16% in placebo patients (p < 0.05).
6) *6 MWT.* On average patients were able to walk 470 m during the 6 min of the test. This is over 200 m less than predicted for the study population. After treatment, ARA patients increased the walking distance by almost 19 m versus a reduction of 15 m in placebo patients (p < 0.05). Responder analysis showed that an improvement of > 25 m occurred in 52% of ARA 290 patients versus 12% in placebo patients.

5. Conclusion

The picture that emerges from the first Phase II trials, NARA and NERVARA, is that the effect of the non-hematopoietic EPO analogue ARA 290 is consistent, showing improvement of pain, neuropathic symptoms (including symptoms related

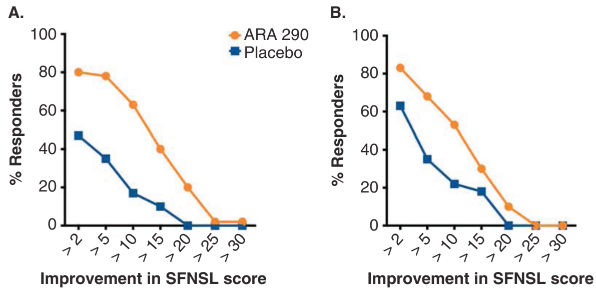

Figure 5. A. Cumulative responder percentage at study week 5 (i.e., the first week following treatment) of the small fiber neuropathy screening list (SFNSL) score. The responder percentage of ARA 290-treated patients exceeds that of placebo-treated patients. **B.** Responder percentage at week 16. The larger responder percentage of ARA 290-treated patients over placebo-treated patients is maintained at 12 weeks after termination of therapy.

Data adapted from [10] with permission of Molecular Medicine.

to autonomic dysfunction), QoL, and exercise capacity during and following the 4-week treatment. In both trials, SFNSL showed robust changes with significant improvement in the two dimensions queried (pain or autonomic function), indicative of an effect of ARA 290 on sensory and autonomic nerve fibers. An important observation in the NERVARA trial is the observation of regrowth of corneal nerve fibers, a clear and visible consequence of the reparative properties of the ARA 290 peptide. The lack of effect on IENFD suggests that longer treatment periods may be needed before an effect on intra-epidermal nerves becomes visible. A caveat of these studies is evidently the small patient numbers studied with ARA 290 (33 patients in total). To further complete the ARA 290 dossier and to strengthen the evidence for a beneficial effect of ARA 290, additional studies are ongoing or being planned in SFN resulting from sarcoidosis or other origins (e.g., DM).

6. Expert opinion

Chronic pain and especially chronic neuropathic pain is difficult to treat. Common treatments are effective in just a portion of patients and efficacy is often limited. Furthermore, most (if not all) of these treatments come with side effects that significantly lower the QoL and consequently patient compliance. SFN is a form of neuropathy that is associated with a variety of common diseases and has a high incidence of occurrence in these diseases (e.g., DM, leprosy, HIV, alcoholism, chemotherapy-induced peripheral neurotoxicity, and sarcoidosis). SFN causes a series of debilitating symptoms that, besides neuropathic pain, includes autonomic symptoms ranging from dry mouth to erectile dysfunction, palpitations, and orthostatic hypotension.

ARA 290 is the first treatment option aimed at treatment of SFN in sarcoidosis. The search for compounds that produce relief of neuropathic symptoms (without producing toxic side effects) is important, as there is an unmet need for the treatment of pain and autonomic symptoms in this disease as well as other diseases. Given the first results obtained from Phase I and Phase II clinical trials, the prospects for SFN treatment in sarcoidosis seem promising, although further proof from larger trials is required. Safety data are promising as well but longitudinal data in large patient cohorts should be collected, especially during and following longer treatment periods (> 28 days).

Many pharmacological studies on chronic pain focus on simple quantitative pain-related end points [40]. This is not surprising as most treatments are symptomatic aimed at increasing pain detection thresholds without any modulatory role on the underlying disease process. The most common end point therefore is a pain score, either by numerical rating, visual analogue scale, or a pain score derived from a questionnaire (e.g., the BPI). However, many symptoms (pain- and non-pain-related) deserve investigation and treatment in chronic pain patients. For example, exercise capacity and autonomic symptoms are equally important as they may be affected causing an appreciable reduction in patients' QoL. Although treatment may produce pain relief, the lack of improvement of other symptoms (e.g., physical functioning, orthostatic hypotension) will reduce patient compliance, even more so when treatment causes annoying side effects or worsens present symptoms (e.g., lightheadedness upon standing up causing an increased probability of falling and trauma, especially in the elderly). In the NERVARA trial a systematic and extensive set of end points was chosen to assess pain-related, autonomic, and disease-modulating symptoms. End points were multiple and included neuropathic pain and autonomic scores from several questionnaires (e.g., SFNSL, BPI), nerve fiber density in the epidermis and cornea, sensory thresholds, and exercise capacity (as assessed by the 6MWT). Moreover, assessments were made prior to and at the end of treatment and during follow-up (at 3 months and an additional assessment was made at 9 months following the start of treatment). ARA 290 had long-lasting beneficial effects on a variety of these end points, suggesting long-lasting anti-inflammatory and tissue restorative effects. In this respect ARA 290 seems unique as other anti-inflammatory drugs that have recently been tested in neuropathic pain syndromes were either ineffective or did produce pain relief but were without improvement in functionality [3,41]. One such treatment is ketamine, which exclusively reduces pain but does not provide improvements in function in chronic pain patients with complex regional pain syndrome [42]. Anecdotal treatment of SFN in sarcoidosis with immune-modulating drugs, such as steroids or anti-tumor necrosis factor agents, suggest some improvement of pain symptoms and support anti-inflammatory mediated beneficial effects [3,43,44]. We argue that ARA 290 should not be considered an analgesic but rather a disease-modifying drug that intervenes in the disease process responsible for SFN-related symptoms. Note that at this point there are no indications that ARA 290 actually interferes with the underlying disease itself (i.e., sarcoidosis). The data presented here suggest that ARA 290 will be equally effective in SFN associated with other syndromes including DM. Indeed, the initial open-label trial showed efficacy in DM SFN similar to sarcoidosis SFN. A more extensive RCT of ARA 290 effect in DM-related SFN has recently been completed and presentation of the results is pending.

Declaration of interest

A Dunne and M Brines are employees of Araim Pharmaceuticals. A Dahan is on the scientific board of Araim pharmaceuticals. A Cerami is the CEO of Araim pharmaceuticals. All other authors declare no conflict of interest.

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