ARA290 : a novel treatment for neuropathic pain in sarcoidosis

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CHAPTER 8

Summary and conclusions/ Samenvatting en conclusies

Chapter 8. Summary, General Discussion and Future Perspectives

Small-fiber neuropathy (SFN) selectively affects the thinly-myelinated A-δ and unmyelinated C-fibers. These fibers have their neurons in the dorsal root ganglia (DRG) and are involved in various functions ranging from autonomous functions to the conduction of specific sensations (*e.g.* temperature, itch, pain, touch). Afferent information from the epidermis, where the sensory small-fibers end (*i.e.* as nociceptors), travels via the DRG to spinal cord dorsal horn. SFN, irrespective of its cause, is characterized by specific symptoms such as burning pain (often restricted to the extremities), allodynia (*e.g.* sheet intolerance), hyperalgesia but sometimes also hypoesthesia, often accompanied by signs of autonomous dysfunction (dry mouth, diarrhea, erectile dysfunction, etc.). In this thesis I discuss SFN due to sarcoidosis and propose a treatment with the tissue-healing peptide ARA290 in 6 distinct chapters.

In **Chapter 2** sarcoidosis and pain caused by small-fiber neuropathy is discussed. SFN is one of the disabling and often chronic manifestations of the disease. SFN presents with peripheral pain and symptoms of autonomic dysfunction. The character of the pain can be burning or shooting. Besides, allodynia and hyperesthesia can exist. Diagnosis is usually made on the basis of clinical features, in combination with abnormal specialized tests. The aim of treatment is often to reduce pain; however, total pain relieve is seldom achieved. The role of TNF-α in the pathogenesis of SFN in sarcoidosis appears interesting to explore. TNF- α is an proinflammatory cytokine that may be crucial in the pathogenesis of SFN in sarcoidosis. Novel therapeutic agents such as ARA290, a non-hematopoietic erythropoietin analogue with potent anti-inflammatory and tissue protective properties, are interesting novel treatment options of SFN in sarcoidosis. This agent binds, similar to hypoglycosylated erythropoietin, to the innate repair receptor and as such activates pathways leading to healing and tissue repair.

In **Chapter 3** a case series is presented of patients with sarcoidosis and neuropathic pain due to the presence of small-fiber neuropathy. Various testing modalities have been designed to characterize nerve fiber dysfunction affected patients. In the current study, we characterized the sensory phenotype of sarcoidosis patients with neuropathy using quantitative sensory testing (QST), skin biopsy, and cornea confocal microscopy (CCM). On average, patients displayed sensory abnormalities and decreased nerve fiber densities. However, some cases are discussed that show distinct disease characteristics. We identified an abnormal albeit heterogeneous sensory phenotype in sarcoidosis patients with neuropathic pain. Discrepancies between used methods, such as the assessment of nerve fiber density using skin biopsies *vs.* CCM, indicate that combinatory techniques should be used to link disease features with symptom expression. The sensitivity and specificity of cornea microscopy should be determined and correlated to skin-biopsy-obtained intra-epidermal nerve fiber densities in a larger cohort of neuropathic pain patients. The construction of sensory profiles or subgroups aids in the identification of commonalities in neuropathy phenotypes and will guide personalized, more successful therapy. Current pain treatment is symptomatic with limited efficacy.

The occurrence of severe side effects often prevents effective treatment at the required dose and decreases patient compliance. To improve outcome, future therapeutic trials should take into account both the heterogeneity of neuropathy symptoms, as well as the sensory profile in which patients could be stratified.

Chapter 4 describes the pharmacokinetics of ARA290, a novel treatment option in sarcoidosis-induced SFN. ARA290 is an 11-amino acid peptide with tissue protective properties. It is effective in the treatment of neuropathic pain in patients with sarcoidosis and diabetes mellitus type 2. Since ARA290 requires frequent parenteral administrations, various routes of administration are being examined that allow treatment outside the hospital setting with high patient compliance. In this study we determined the safety and pharmacokinetics of subcutaneous (SC) compared to intravenous (IV) ARA290 administration. 10 healthy volunteers received on one occasion 2 mg IV ARA290, and on another occasion 2 mg SC ARA290. On a third occasion, 5 subjects received 4 mg SC and the five others 6 mg SC ARA290. Serial plasma samples were obtained to determine the time-dependent plasma concentrations of ARA290. Safety parameters were obtained; the pharmacokinetics were assessed by non-compartmental analysis. No safety issues were identified. The mean peak plasma concentration after IV dosing was estimated at 111 ng/mL. After SC administration peak concentrations were observed between 12 and 15 min and were greater than 1.25 ng/mL for all SC doses, the minimum concentration believed to be necessary to trigger the receptor mediating ARA290 biological effects. The terminal half-life of the IV and SC doses were 1.1 min and 17-26 min, respectively. Based on the area-under the plasma-concentration curve the bioavailability of SC ARA290 ranged from 11 to 25%. ARA290 is safe and well tolerated up to 6 mg SC. All three SC doses exhibited peak concentrations greater than the assumed minimum effective concentration. Despite the short plasma residence time of ARA290 in this study, long-term pharmacodynamics effects have been observed in animals and in humans. These observations suggest that ARA290 initiates a cascade of events involving several steps. For neuropathic pain, the site of action of ARA290 is within the central nervous system, and is likely mediated via the innate repair receptor, triggering anti-inflammatory, neuroprotective and healing effects in the damaged tissue.

Chapter 5 describes a first phase II trial on the efficacy and safety of ARA290 in sarcoidosis-induced SFN. ARA290 (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 ARA290 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 ARA290 (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) and fatigue (Fatigue Assessment Scale [FAS]). No safety concerns were raised by clinical or laboratory assessments. The ARA290 group showed significant ($p < 0.05$) improvement at week 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 ARA290 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 depressive symptoms. ARA290 appears to be safe in patients with sarcoidosis and can reduce neuropathic symptoms, , as assessed by questionnaires focused on pain and quality of life. The most robust effect of ARA290 was on the SFNSL score, indicating an effect on symptom severity rather than frequency. Notably, in the current study an improvement of autonomous symptomatology was observed. Autonomous nerve fibers show a faster regeneration pattern than sensory nerve fibers. The less robust effects of ARA290 treatment on pain suggests that prolonged or intensive dosing regimens are required.

Chapter 6 describes a next phase II trial studying SFN symptoms and cornea nerve fiber density in patients with painful sarcoidosis. Small nerve fiber loss and damage (SNFLD) is a frequent complication of sarcoidosis that is associated with autonomic dysfunction and sensory abnormalities, including pain syndromes that severely degrade the quality of life. SNFLD is hypothesized to arise from the effects of immune dysregulation, an essential feature of sarcoidosis, on the peripheral and central nervous systems. Current therapy of sarcoidosis-associated SNFLD consists primarily of immune suppression and symptomatic treatment; however, this treatment is typically unsatisfactory. ARA290 is a small peptide engineered to activate the innate repair receptor that antagonizes inflammatory processes and stimulates tissue repair. Here we show in a blinded, placebo-controlled trial that 28 days of daily subcutaneous administration of ARA290 in a group of patients with documented SNFLD significantly improves neuropathic symptoms. In addition to improved patient-reported symptom-based outcomes, ARA290 administration was also associated with a significant increase in corneal small nerve fiber density, changes in cutaneous temperature sensitivity, and an increased exercise capacity as assessed by the 6-minute walk test. On the basis of these results and of prior studies, ARA290 is a potential disease-modifying agent for treatment of sarcoidosis-associated SNFLD. The cornea appears to be an especially useful location to evaluate potential nerve regrowth, and assessment of cornea nerve fiber density is fast, non-invasive and can be used in longitudinal, interventional studies. It is currently unclear what sensory changes may be associated with the nerve regeneration that occurs during the short time frame of the trial, but it is likely that any changes have not reached a steady state. Moreover, most patients had longstanding sarcoidosis with failing existing therapy. Possible synergistic effects of concomitant medication should be evaluated in the future.

Finally, in **Chapter 7**, the results of the various ARA290 trials in painful sarcoidosis are discussed. 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. 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. ARA290 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, ARA290 treatment resulted in significant increases in corneal nerve fibers, improved sensory pain thresholds, improved quality of life and physical functioning. 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 ARA290 treatment in sarcoidosis-related neuropathy seem promising. The long-lasting beneficial effects of ARA290 on both pain-related and non-pain-related symptoms in sarcoidosis patients prompt additional studies on potential disease-modifying properties of ARA290. We argue that ARA290 should not be considered an analgesic but rather a disease-modifying drug that intervenes in the disease process responsible for SFN-related symptoms. There are no indications that ARA290 actually interferes with the underlying disease itself (*i.e.* sarcoidosis). The data collected so far suggest that ARA290 will be equally effective in SFN associated with other syndromes, including diabetes mellitus.

General Discussion of the Data

Heterogeneity of patient population

Despite the fact that all patients treated with ARA290 in Chapters 5 and 6 had neuropathy related to sarcoidosis, therapy efficacy was limited both in magnitude and responder rate. For example, just 50% of patients in Chapter 5 and 40% of patients in Chapter 6 showed a reduction in SFNSL score of 50% or greater at the end of the ARA290 treatment period. From Chapter 3 it becomes clear that different patients present with different phenotypes with respect to cornea fiber and skin fiber abnormalities, responses to the different questions in the neuropathic-pain related questionnaires, and outcome of sensory tests. Possibly multiple well defined specific subgroups of patients exist that may respond differently to therapy. For example, Martini et al.[1] showed previously that pain ratings in the days prior to therapy predicts the response to topical capsaicin or placebo in patients with post-herpetic neuralgia. A large placebo response was predicted by a high variability in the pain ratings in the days prior to treatment. Another example is the observation that patients with diabetic polyneuropathy respond best to treatment with tapentadol when they have defects in their endogenous pain modulatory system.[2] Tapentadol is an analgesic with a dual mode of action, it activates the mu-opioid receptor system and inhibits re-uptake of neuronal noradrenaline at spinal and supraspinal sites. Consequently, postsynaptic α_2-adrenergic

receptors are activated causing inhibition of nociceptive trafficking. Especially patients with defects in their endogenous pain modulatory system (as measured by conditioned pain modulation) are sensitive to the noradrenergic enhancement of opioid analgesia. These data suggest that indeed individualized pain management based on specific biomarkers is possible. Hence, identification of biomarkers may be a step forward towards understanding the pathophysiology of chronic pain and individualized pain medicine.

In this thesis sarcoidosis patients were all profiled prior to treatment with ARA290. Specific tests were performed to assess whether these patients present with abnormalities in intra-epidermal nerve fibers and cornea nerve fibers (as measured by cornea confocal microscopy, CCM). Additionally, quantitative sensory tests were performed to get an indication of the presence of gain- or loss-of-function of specific sensory modalities. And finally the small-fiber-neuropathy screening list (SFNSL) questionnaire was completed by all patients. Figure 1 is a summarizing box plot of the data. Each column represents a single patient and a colored square indicates a value for that biomarker that deviates from a sex- and age-matched “normal” reference population without pain (see the legend of Figure 1 for further explanation). This population clearly had abnormal functioning of their peripheral small nerve fibers as more than 90% of patients had an abnormal cold, warm or mechanical detection threshold (CDT, WDT and MDT, in Fig 1). Interestingly, quantification of the intra-epidermal nerve fibers (IENF) showed a normal density in 72% of the population and more than half (56%) had normal cornea C-fibers. Forty percent of patients had allodynia (ALL) or an increased wind-up ratio (WUR), indicative of central sensitization. Phenotyping patients based on CCM and the presence/absence of central sensitization results in 4 groups: (1) Abnormalities in CCM with central sensitization (n = 6/26); (2) Abnormalities in CCM without central sensitization (n = 20/26); (3) Normal CCM with central sensitization (n = 18/32); and (4) Normal CCM without central sensitization (n = 14/32). The absence of abnormalities in the cornea confocal nerve morphology data does not indicate that small nerves in the skin are unaffected. The abnormalities in CDT, WDT and MDT suggest otherwise and 9/36 of patients had abnormal skin fibers while the CCM indicated no abnormalities. Several conclusions may be drawn from the data presented in Figure 1: (i) Sensory testing based on CDT, WDT and MDT suggests abnormalities of small fibers in most tested patients; (ii) IENF abnormalities overlap with CCM abnormalities in just 50% of patients with IENF (7 of 16); (iii) neither IENF nor CCM quantification may correspond with clinical (or preclinical) small fiber abnormalities; (iv) the SFNL showed signs of small fiber neuropathy in 10/26 patients with CCM abnormalities and 6/32 patients without CCM abnormalities; (v) central sensitization is observed in about half of the population. I am aware that this is a first approach to profile the rather complex sarcoidosis patient with chronic pain. Various other factors have not been accounted for such as sex, age, duration of disease, medication, progression of the underlying disease and genotype. Further studies in a much larger population are required to allow a more complete profile of this patient population.

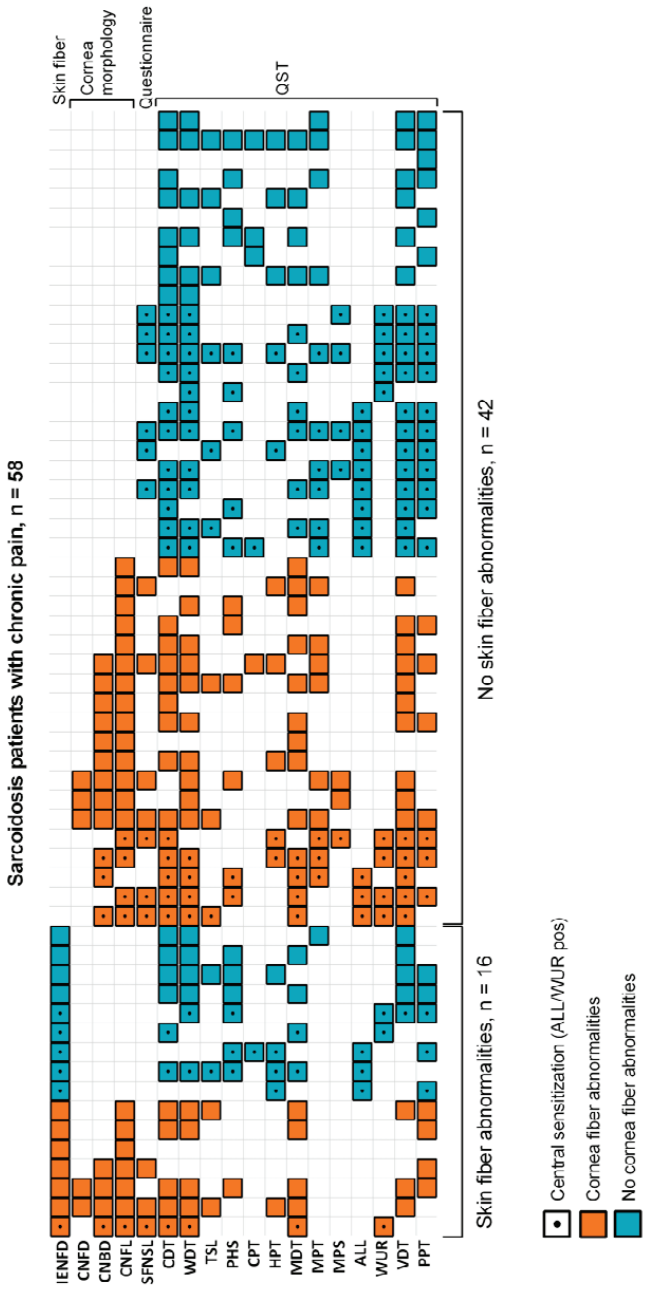

Figure 1. Fire plot of 58 sarcoidosis patients with chronic pain. Each column represents 1 patient. On the y-axis the following biomarkers are presented: IENFD = intra-epidermal nerve fiber density; CNFD cornea nerve fiber density; CNBD = cornea nerve branching density; CNFL=cornea nerve fiber length; SFNSL = small fiber neuropathy screening list; CDT= cold detection threshold; WDT= warm detection threshold; TSL= thermal sensory limen; PHS= paradoxical heat sensation; CPT= cold pain threshold; HPT= heat pain threshold; MDT= mechanical detection threshold; MPT= mechanical pain threshold; MPS= mechanical pain sensitivity; ALL= dynamic mechanical allodynia; WUR= wind-up ratio; VDT= vibration detection threshold; PPT= pressure pain threshold. Colored squares indicate abnormalities in the tests: for cornea testing values outside the 95% interval of normal reference data are considered abnormal; for quantitative sensory tests (QST) values less than –2 (loss of function) or greater than 2 (gain of function) x the SD of normal reference data are considered abnormal, for the questionnaires values > 37 (indicative of neuropathic pain) are colored. In blue lines the CCM data and the data indicative of central sensitization (ALL and WUR).

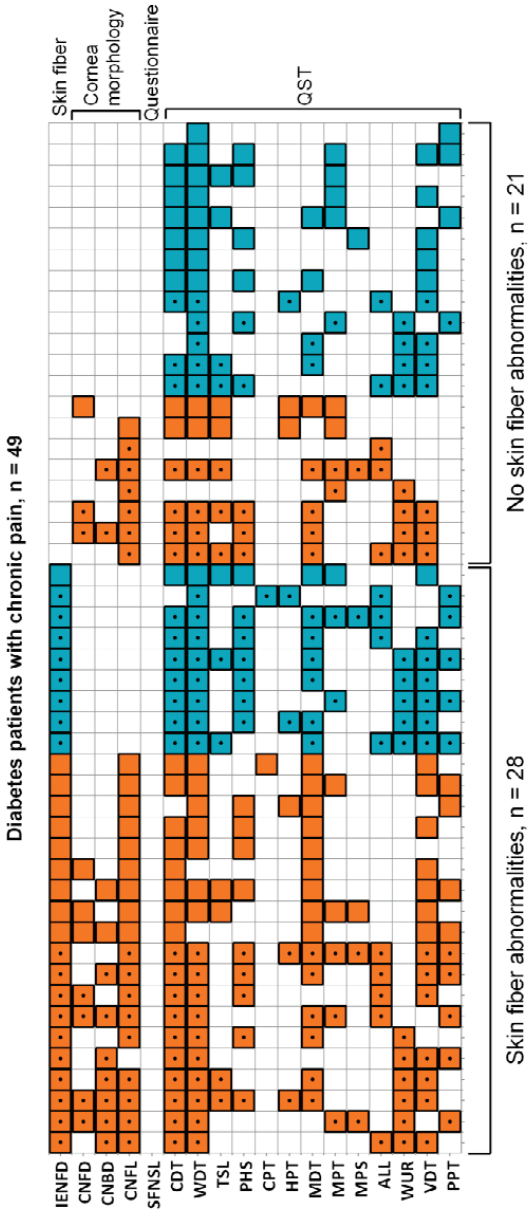

Figure 2. Fire plot of 49 diabetes mellitus type 2 patients with chronic pain. See legend of Figure 1 for explanation.

It is of interest to compare the sarcoidosis data set to small-fiber neuropathies of other origins. In Figure 2, I present a summarizing box plot of data obtained from 49 patients with diabetes mellitus type 2 and chronic neuropathic pain that were tested in our laboratory at LUMC. The plot is comparable to the data obtained in sarcoidosis patients. Again CDT, WDT and MDT abnormalities were present in the complete population with just 1 exception. Twenty-nine of 49 patients had signs of central sensitization. Again the data are well described by 4 phenotypes (absence/presence of CCM abnormalities with and without central sensitization) in close agreement to the sarcoidosis data. A similar observation was made in patients with fibromyalgia (data not shown).

These data collectively indicate that chronic pain is a complex entity with similar phenotypes determined from a small subset of biomarkers, regardless of the underlying disease (and consequently the initial cause of the chronic pain). The 4 phenotypes that I present here may indicate that the progression of disease or involvement of specific systems differs between patients. In cases with central sensitization prolonged afferent input to central sites may have caused upregulation of excitatory receptors at the spinal levels and/or may have caused a profound spinal inflammatory response. In cases without ALL and WUR the disease appears to be restricted to the periphery, without (as yet) any central involvement. Perhaps more importantly, these 4 phenotypes may require different treatment approaches. For example patients with just signs of central sensitization may need a centrally acting drug such as pregabalin; patients with just signs of small fiber abnormalities may benefit from a drug that causes tissue repair such as ARA290; patients with combinations of the two may require a combination therapy targeting peripheral and central pathology. An interesting group is the population without abnormalities of peripheral nerve fibers (CCM) and absence of signs of central sensitization (most of them also have a normal IENF density, Fig. 1). Since most of these patients have an abnormal CDT, WDT or MDT the peripheral nerves respond abnormal to cold, warm or pressure stimulation. Possibly the morphology of the relevant nerves is still intact, which may be due to a less aggressive underlying disease progression, or the disease has just recently manifested. Irrespective, these results indicate the importance of sensory testing in diagnosing neuropathic pain from small-fiber pathology.

Treatment effect of ARA290

Virtually all pharmacotherapy for chronic pain causes 30 to 50% pain relief in just 30 to 50% of patients.[3] One way of improving medication efficacy is by phenotyping patients and treating patients on a mechanistic basis (see above) or by determining responder groups and linking specific biomarkers or covariates to these responder groups. Martini et al.[1] identified 5 responder groups to treatment with topical capsaicin in patients with post-herpetic neuralgia; the responder groups ranged from non- to super-responders. Specific covariates such as age, baseline pain and duration of disease predicted the super-response to capsaicin treatment. The data presented in Chapters 5 and 6 point towards the same principle, a limited effect of treatment in a limited portion of the population. However, the ARA290 data are more complex than data from “regular” analgesic trials as ARA290 is not an analgesic in the sense that morphine is an analgesic

but it is rather a disease modifier. Morphine blocks nociceptive trafficking from the periphery to spinal and supra-spinal areas involved in pain processing. ARA290 through its actions at the innate repair receptor (Chapter 7) causes tissue healing and repair of affected small nerve fibers. Animal data further indicate profound anti-inflammatory effects at the level of the spinal cord.[4] ARA290's effects on pain are therefore more indirect and pain relief may not be the first disease symptom to be alleviated. The reduction of autonomic symptoms and increase in activity level that was observed in Chapters 5 and 6 point towards a more general (healing) effect of ARA290 on the diseased system. Moreover, pain relief from pharmacotherapy may be a rather insufficient and possibly even illogical end-point in chronic pain trials. Pain perception is a multifactorial process that is influenced by various often-interacting complex bio-psychosocial factors such as the pathophysiology of the underlying disease, activity level, energy level, inflammation, nociceptive damage, presence of a neuropathic component, spinal inflammation, central sensitization, ability to activate descending inhibition, presence of psychiatric symptoms (depression and/or anxiety), physical and mental resilience, previous painful diseases/symptoms, medication, sex, socioeconomic and marital status, etc. While some drugs may affect one factor (*e.g.* nociceptive afferent input to the brain) many of the other factors remain undertreated. Hence, a composite end-point in trials of chronic pain is needed.

Future perspectives

The results from the presented trials indicate that ARA290 is beneficial to some extent but much more work is needed before we can definitively conclude that ARA290 is effective in alleviating sarcoidosis-induced neuropathic pain.

Future ARA290 trials should focus on:

(1) More prolonged exposure to ARA290. Current trials that have been performed on ARA290 (in sarcoidosis and diabetes mellitus) were relatively short in duration. The studies presented in this thesis (Chapters 5, 6 and 7) and one additional trial in diabetes mellitus patients (Ref. 5) were performed in patients treated for 28 days. One later trial was performed in sarcoidosis patients treated for 3 months (unpublished observation). It is difficult to imagine that such a short treatment period is beneficial with respect to the many factors involved in pain perception in a complex disease such as sarcoidosis. Assuming that ARA290 affects the disease process I suggest a much longer treatment duration, such as 6-12 months and only then re-assess the pain as well as other related factors (activity as assessed by the 6-min walk, depression, autonomic function, etc.).

(2) Dose finding studies. Just one small multicenter dose-finding study has been performed so far suggestive that once daily ARA290 4 mg sc. is the optimal dose (unpublished observation). However, taken the short half-life of ARA290 in the body (Chapter 4), possibly multiple exposures during the day are even more beneficial. ARA290 is given by subcutaneous injections very similar to insulin injections. Studies on

repeated injections with multiple doses in large populations are required focusing on efficacy and toxicity. The current data shows little toxicity but the data set is small and the exposure doses and durations limited.

(3) Treatments based on body weight. ARA290 dosing is currently based on a fixed dose (2-4 mg) irrespective of the patient's body weight. This approach is based on the fact that ARA290 is rapidly transported to its main target, the innate repair receptor, and that it initiates a cascade of events that do not require prolonged and intense stimulation of the receptor. In fact, ARA290 likely loses its necessity once the cascade is activated (Chapter 7). Still I predict that fixed doses of ARA290 may be less efficacious in morbidly obese patients. Hence dosing based on total body weight seems a logical step in improving the efficacy of ARA290.

(4) Multicenter studies in large patient populations. The number of patients so far dosed with ARA290 is limited (< 100 patients). Hence, a true indication of ARA290's efficacy is lacking. Large multicenter trials are needed to determine a true treatment effect. However, as suggested above, first the study's end-points have to be defined. It may be clear that the end-point pain perception will require large patient numbers and that, irrespective of study size, the effect-sizes will be relatively limited. This is especially true taken the relatively large placebo effect that is currently observed in pain trials.[6] Also in the ARA290 trials the effect of placebo treatment was substantial. A composite end-point, combining pain symptoms with improvement in physical function, autonomic function and mental state may be the more optimal end-point.

Additional issues that require future discussion include:

(5) Are there alternatives for ARA290 with possibly an improved efficacy? ARA290 mimics the effect of erythropoietin (EPO) and as such is an agent that counteracts the effects of tumor necrosis factor α (TNF-α; Chapter 7). The literature indicates that administration of both EPO and TNF-α to chronic patients is an exception (see Chapters 2 and 7) due to the side-effects these drugs produce. Still both drugs are useful for other indications and it may well be worthwhile to compare ARA290 with either drug to parallel efficacy and toxicity.

(6) Is it preferable to combine ARA290 with an analgesic agent? In modern pain medicine patients are treated according to a multimodal approach. Pharmacotherapy is an often-important component of such an approach. Combining analgesic drugs with different mechanisms of action will cause enhanced efficacy with a reduced side effect profile. Since the overall treatment effect of ARA290 seems limited, combining ARA290 with an analgesic may result in a better outcome for the patient. The question then remains, which analgesic is the best choice? Given the prolonged treatment duration, the use of opioids seems less of an option due to its known negative or harmful effects such as the possibility of overdose, abuse and addiction, and tolerance development with reduced efficacy over time. The choice of co-medication should depend on the patient's phenotype. Two drug classes may be considered, GABAergic medication

(gabapentin or pregabalin) in case of central sensitization and drugs that (re-)activate descending inhibition (*eg.* drugs that increase serotonergic or noradrenergic neurotransmission in the spinal cord such as duloxetine, tapentadol and other serotonin-noradrenaline reuptake inhibitors). The phenotyping approach that was discussed above, however, does not assess descending inhibition. Additional tests for descending inhibition should therefore be added to the test battery. One such test is Conditioned Pain Modulation (CPM), which provides a surrogate marker for the presence or absence of descending inhibition. In CPM testing two painful stimuli are applied to the skin at remote areas. An active CPM response is when pain inhibits pain, *i.e.* the first painful stimulus decreases in intensity due to application of the second stimulus.[2] An alternative test is offset analgesia (OA; see also Chapter 7). Both CPM and OA tests are relatively simple to execute and will give the clinician an indication of the vitality of the endogenous pain modulatory system. In case of CPM or OA abnormalities, duloxetine or tapentadol may be added to the patient's pharmacotherapy. In cases in which CPM and OA responses are normal and also no central sensitization is detected, ARA290 may be combined with opioids for no longer than three months. The opioids will subdue the initial pain while ARA290 initiates a healing process that in the end will effectively reduce the neuropathic pain component on multiple levels. The confirmation of this hypothesis, however, requires future studies.

Conclusions

- SFN is one of the more disabling and often chronic manifestations of sarcoidosis.
- Using specific diagnostic tests such as quantitative sensory testing, skin biopsy, and cornea confocal microscopy allows determination of specific sensory phenotypes of sarcoidosis patients with SFN.
- Cornea confocal microscopy examines the densely innervated cornea as a surrogate for the small nerve fiber state, and can serve as a quantitative and qualitative measure of small fiber pathology in a reproducible, non-invasive manner.
- ARA290 is a small (11 amino acid) peptide engineered to activate the innate repair receptor that antagonizes inflammatory processes and stimulates tissue repair.
- Despite that fact that patients with sarcoidosis and SFN have less pain during treatment with ARA290, this peptide cannot be considered a classical analgesic. ARA290 is rather a disease-modifying molecule.
- ARA290 is a potential disease-modifying agent for treatment of sarcoidosis-

associated SFN. Whether it modulates the underlying disease process is currently unknown and merits further study.

- Using multiple biomarkers of chronic pain leads to identification of specific phenotypes that may require different treatments and as such may form the basis of individualized pain medicine.

- Pain perception is a multifactorial process that is influenced by various often-interacting factors. A composite end-point, combining pain symptoms with improvement in physical function, autonomic function and mental state may be the more optimal end-point in clinical trials.

- ARA290 may be used in combination with true analgesics to enhance treatment efficacy. The choice of co-medication depends on the patient's phenotype.

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