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ORIGINAL ARTICLE

Efficacy of a fixed combination of palmitoylethanolamide and acetyl-l-carnitine (PEA+ALC FC) in the treatment of neuropathies secondary to rheumatic diseases

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ABSTRACT

BACKGROUND: The neurologic complications of rheumatic diseases (RDs) are highly variable, and their manifestations are linked to the pathogenesis and clinical phenotype of the specific RDs. In rheumatoid arthritis, for example, the peripheral nervous system is most commonly involved and mononeuritis multiplex, nerve entrapment and vasculitic sensorimotor neuropathies are not uncommon. Often the therapy for these disorders is not easy and is characterized by the use of different drugs. Palmitoylethanolamide (PEA) has been tested in a wide variety of animal models and has been evaluated in several clinical studies for nerve compression syndromes, demonstrating that PEA acts as an effective and safe analgesic compound. Acetyl-L-Carnitine (ALC) has also been shown to be an effective and safe treatment in painful peripheral neuropathy. In the last years the synergistic effect between PEA and ALC has been demonstrated. The aim of our study was to evaluate the efficacy of supplementation of standard therapy (STh) with Kalanit® (Chiesi Italia Spa; Parma, Italy) in patients with peripheral neuropathy secondary to RDs.

METHODS: Patients at the time of enrollment were affected by RDs with neuropathy from <12 months, documented by electromyography. The analyzed patients were treated with the STh chosen according to their rheumatic disease (RA or SpA) and for their neuropathy (*e.g.* analgesic, NSAIDs, pregabalin or gabapentin) as per clinical practice. The sample was divided into 2 groups: group 1, patients treated with STh, to which a fixed combination of PEA (600 mg) + ALC (500 mg) (Kalanit®) was added twice a day for 2 weeks and then once a day for 6 months; group 2, patients treated only with STh. Each patient underwent clinical evaluations and questionnaires were administered in order to evaluate their neuropathy and the efficacy of the therapy.

RESULTS: In group 1, 18 patients suffering from sciatic pain, 16 patients from carpal tunnel syndrome and 8 patients with peripheral neuropathy of the lower limbs were included and PEA + ALC FC was added to STh. These patients were compared with patients from group 2, who had the same pathology and demographic characteristics: 20 patients with sciatic pain, 15 with carpal tunnel syndrome and 5 with peripheral neuropathy of the lower limbs, respectively; this group was treated with STh only. Patients treated with PEA + ALC FC had a significant improvement in pain VAS compared to patients treated with group 2 in all the diseases analyzed (P value: sciatic pain 0.032, carpal tunnel syndrome 0.025 and lower limbs neuropathy 0.041). Patients in group 1 showed a significant improvement compared to patients treated in group 2 also from a specific score. Specifically, LBP-IQ showed significant improvement in group one (P value: 0.031), as did CHFD (P=0.011) and NPQ (P=0.025).

CONCLUSIONS: The synergistic effect of PEA and ALC seems to have a further advantage in the treatment of this type of pathology, including the anti-inflammatory effect but also in terms of therapy optimization and therefore of better adherence to treatments. Our study shows that it is important to identify the type of pain to follow an accurate diagnostic algorithm, considering the clinical characteristics of the patient and carefully evaluate the indication, preferring a multimodal approach.

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KEY WORDS: Nerve compression syndromes; Rheumatic diseases; Complications.

Inflammation is a complex biological response which allows to limit primary causes of injuries and infections. Inflammation in the nervous system (called neuroinflammation) can be particularly serious when prolonged. While inflammation *per se* may not cause a disease, it can certainly contribute to its gravity in both peripheral and central nervous systems. Cell-derived inflammatory molecules are critical for the regulation of host responses to inflammation; although these mediators can originate from various non-neuronal cells, microglia, mast cells, astrocytes and possibly oligodendrocytes are important sources. Understanding neuroinflammation also requires understanding that interactions between both glia and mast-cells and glia-to-glia cells are an integral part of the inflammation process. Within this context, the mast-cell plays an important role in the initiation as well as in its pursuance.[1]

Acute and chronic pain are fundamental features of inflammation. The former is given by a specific disease or injury as it serves a useful biologic purpose, and it is self-limited. Chronic pain, on the other hand, may be considered a disease state that outlasts the normal time of healing and is thought to result from alterations in neuronal cell plasticity. Such alterations include sensitization of peripheral nociceptors in dorsal root and trigeminal ganglia and central nociceptive neurons in the spinal cord, trigeminal nucleus, brain stem, and cortex.[2] Neuropathic pain is either peripheral or central and it is caused by a disease (*e.g.* diabetes mellitus), a medical intervention (chemotherapy, surgery), or an injury; its prevalence is thought to be between 6.9 and 10%.[3] Peripheral neuropathic pain (painful neuropathy) is a condition in which alterations in neural networks affect multiple aspects of brain function, structure, and chemistry. Analgesics continue to focus on reducing pain transduction and transmission, which likely accounts for their limited success in controlling its progression.[4] This "neuron-centric" view fails to consider that neuropathic pain relies on Schwann cells, spinal microglia, and astrocytes, together with elements of the peripheral immune system.[5]

Mast cells and microglia are primary interlocutors for pain neurons, in the periphery as well as at the spinal/supraspinal levels; Kissel *et al*. demonstrated that spinal nerve ligation corresponds temporally and functionally with the degranulation of thalamic mast cells.[6] Peripheral nerve-resident mast cells (and not microglia) are the responders in the damaged site, where they promote the recruitment of neutrophils and macrophages.[7] In addition, not only can mast cell-derived Nerve Growth Factor (NGF) sensitize nociceptors, but mast cells themselves may respond to NGF through a paracrine/autocrine mechanism.[8] Mast cells could also help in recruiting other immune cell types (*e.g.*, T-cells) which, in turn, release pro-nociceptive mediators. Glia cells are important interlocutors of pain processes at the spinal level.[9] Spinal microglia, upon activation by either cell surface molecules or pro-inflammatory signals elaborate IL-1b to modulate neuronal cell activity; dorsal horn microglia become activated in pathological conditions (*e.g.* peripheral nerve injury) accompanied by up-regulation of P2X and P2Y receptors to participate in neuropathic pain.[10] Inhibiting the function or expression of these microglial receptors strongly attenuates neuropathic pain.[10] Interactions between mast-cells and glia might contribute to amplification of peripheral pain signals at the spinal level. Astrocytes are a key contributor to neuropathic pain too.[4]

Nerve roots and bodies can get inflamed by pressure therefore causing neuritis and radiculitis as they progress into a more chronic pathological state due to the induction of inflammatory reactions.[11] Inflammatory cells, such as activated mast cells, play an important role in nerve compression syndromes and they are one of the main sources of prostaglandins (PG) and cytokines. These compounds trigger the synthesis of nitrogen monoxide (NO), a strong vessel dilator.[12] In the next step, many pro-inflammatory compounds are produced; amongst them, metalloproteinases play an important role as they are enzymes inducing connective tissue around the nerves to expand and get hyperactivated. This cascade is followed by enhanced pain sensitivity in peripheral areas; these elements lead to cell migration, oedema, erythema, pain, hyperalgesia, and allodynia. Glial cells, mast cells, and non-neuronal cells contribute to pain perceptions such as in sciatic compression and carpal tunnel

syndrome, due to neurons transmitting pain signals and upregulating pain-circuits in the spinal medulla.[13, 14]

PEA is an endogenous fatty acid amide, first described in 1957 and evaluated for the treatment of neuropathic and chronic pain since 1975.[15, 16] It regulates many physiological processes such as nerve compression pain, respiratory inflammation, neuroinflammation, neurotoxicity, and central nervous ischemia.[17] PEA reduces mast cell migration and degranulation and reduces over-activation of astrocytes and glial cells.[18] Both mast cells and glial cells shift under influence of PEA from activated immune cells to resting phenotypes.[19] However, the mast cell is not the main pathogenetic factor, as PEA has a number of mechanisms of action, probably more important in nerve compression and impingement syndromes. On the molecular level, it reduces the activity of the pro-inflammatory enzyme cyclooxygenase (COX), as well as endothelial NOS and inducible NOS.[20] PEA has a number of other properties, related to its affinity for various receptors: the orphan cannabinoid receptors GPR55 (G protein-coupled receptor) and GPR119, the vanilloid receptor TRPV1 (Transient receptor potential cation channel subfamily V member 1) and the nuclear PPAR-α (peroxisome proliferator-activated receptor alpha).[21] The latter is clearly expressed in glial cells and neurons, and most probably PEA's most important mechanism of action. These mechanisms of action of PEA are related to its analgesic and anti-inflammatory actions in nerve compression syndromes.

ALC represents another opportunity to approach neuropathic pain therapy. This molecule is an acetyl-group donor and plays an important role on mitochondrial energy homeostasis and detoxification[22] while increasing the actions of NGF[23] and promoting peripheral nerve regeneration.[24] ALC revealed a neuroprotective function *in vitro*, *in vivo* and in animal models of diabetic neuropathy.[25-27] It has antiapoptotic effects in peripheral mononeuropathy models as well as antioxidant activities and it increases acetylcholine production.[28] Due to its analgesic effect, ALC has gained a growing clinical interest in different forms of chronic-pain neuropathy, not only for the treatment itself but also for pain prevention. Several experimental models of neuropathic pain documented the antinociceptive effect of ALC.[29] Moreover, ALC provides a significant antinociceptive effect even after the development of neuropathic pain. These analgesic properties result from different mechanisms; ALC is the only drug whose analgesic effect is due to an epigenetic mechanism, based on the acetylation of p65/RelA, a transcription factor belonging to the NFkB family. Acetylation of p65/RelA leads to a strengthened expression of type-2 metabotropic glutamate (mGlu2) receptors in the dorsal root ganglia and dorsal horns of the spinal cord, thus reducing the glutamate release from primary afferent sensory fibers.[30] The effect on pain of ALC is also modulated by nicotinic and muscarinic antagonists, as shown in a number of animal studies, thus suggesting the role of the cholinergic pathway in the antinociceptive activity of this drug.[31] ALC may raise the uptake of acetyl-CoA into the mitochondria and, due to its similarity in structure to acetylcholine, it may also produce cholinomimetic effects.[32]

Controlled trials in large cohorts of patients with peripheral neuropathy of different etiologies tested the effect of ALC on neurophysiological measures. In the double-blind RCT of De Grandis *et al.*, involving 333 patients with diabetic neuropathy, the mean nerve conduction velocity and amplitude significantly improved, in comparison with placebo.[33] A short-term, double-blind clinical study involving 426 patients with peripheral neuropathy of different etiologies, showed statistically meaningful differences between the ALC and placebo groups in terms of mean conduction velocity improvement.[34] A double-blind, randomized placebo-controlled study, totaling 239 patients with chemotherapy-induced peripheral neuropathy, reported a meaningful increase of sural nerve conduction velocity after ALC treatment.[35]

In the last years the synergistic effect between PEA and ALC has been demonstrated.[36] The inventors of this patent have surprisingly found that the association between PEA and ALC can provide a highly synergistic effect between the two molecules, an effect that is particularly clear on neuropathic pain. They have also found that

the addition of a molecule with antioxidant activity with PEA and ALC further enhances the synergy between these two components. Experiments were carried out using male mice of the C57BL/6J breed; 10 animals were used per group as they underwent surgical intervention for sciatic nerve ligation to induce neuropathic pain. The results showed that ALC alone or PEA alone cause significant relief of neuropathic pain when used at doses of 100 mg/kg and 10 mg/kg, respectively, while doses of 10 mg/kg for ALC alone and 5 mg/kg for PEA alone failed to cause significant differences. On the other hand, PEA at a dose of 5 mg/kg, in association with ALC at a dose of 10 mg/kg, causes a very high decrease in neuropathic pain after 8 days of treatment. Lastly, the association of PEA (5 mg/kg) together with polydatin (0.5 mg/kg) and ALC (10 mg/kg) causes an almost complete remission of neuropathic pain after 8 days of treatment. Therefore, the data showed a remarkably synergistic effect of the combination of PEA and ALC, especially when in association with an antioxidant.

The neurologic complications of rheumatic diseases (RDs) are highly variable, and their manifestations are linked to the pathogenesis and clinical phenotype of the specific RDs.[37] In active rheumatoid arthritis (RA), the peripheral nervous system is most commonly involved and mononeuritis multiplex, nerve entrapment and vasculitic sensorimotor neuropathies are not uncommon. In spondyloarthropathies (SpA), neurologic complications are more frequent in long-standing advanced disease and include atlantoaxial subluxation, cauda equina syndrome, spinal stenosis, and acute vertebral fractures.[38]

The aim of our observational study was to evaluate the efficacy of supplementation of standard therapy (STh) with PEA + ALC FC in patients with peripheral neuropathy secondary to RDs.

Materials and methods

Patients at the time of enrollment were affected by RDs (diagnosis of RA or SpA) with neuropathy from <12 months, documented by electromyography. The analyzed patients were treated with the STh chosen according to their rheumatic disease (RA or SpA) and for their neuropathy (*e.g.* analgesic, NSAIDs, pregabalin or gabapentin) as per clinical practice.

The sample was divided into 2 groups: group 1, patients treated with STh, to which a fixed combination of PEA (600 mg)+ALC (500 mg) (Kalanit® Chiesi Italia Spa; Parma, Italy) was added twice a day for 2 weeks and then once a day for 6 months; group 2, patients treated only with STh.

In addition, all patients had to have stable therapy for at least 3 months. Each patient underwent clinical evaluations and questionnaires were administered in order to evaluate their neuropathy and the efficacy of the therapy.

The assessment at baseline, after 3 months and after 6 months of treatment included:

- VAS pain (0-10);
- LBP-IQ: Low Back Pain Impact Questionnaire (0-100);[39]
- CHFD: cochin hand functional disability (0-90);[40, 41]
- NPQ: Neuropathic Pain Questionnaire (1-12).[42]

Statistical analysis

Data are presented as mean±standard deviation for continuous variables, and number and percentage for categorical data. Non-parametric and parametric tests (Kruskal-Wallis Test, Mann-Whitney U test and $\chi 2$ test) were properly used to compare subgroup characteristics (clinical characteristics, clinical assessment, T0, T1 and T2). A P value ≤ 0.05 was considered statistically significant. Statistical analyses were performed using SPSS statistical software, version 20.0 (SPSS Inc.; Chicago, IL, USA).

Results

In the first group (group 1), 18 patients suffering from sciatic pain, 16 patients from carpal tunnel syndrome and 8 patients with peripheral neuropathy of the lower limbs were included and PEA+ALC FC was added to STh. These patients were compared with patients from group 2, who had the same pathology and demographic characteristics: 20 patients with sciatic pain, 15 with carpal tunnel syndrome and 5 with peripheral neuropathy of the lower limbs, respectively; this group was treated with STh only.

TABLE I.—*Patients' characteristics (group 1: standard of therapy + PEA + ALC FC/group 2: standard of therapy).*

Variables	Patients (N.)	Age (years)	Sex (M/F)	Duration of RD (years)	Duration of Neuropathy (months)	P value
Sciatic pain (group 1)	18	65.2±7.3	11/7	7.2±5.5	6.4±2.1	0.132
Sciatic pain (group 2)	20	66.1±6.4	12/8	6.9±6.5	6.1±2.0	
Carpal tunnel syndrome (group 1)	16	57.5±5.1	8/8	6.5±5.1	5.2±1.9	0.877
Carpal tunnel syndrome (group 2)	15	56.4±6.6	6/9	6.8±5.2	4.9±2.1	
Lower limbs neuropathy (group 1)	8	68.4±3.1	5/4	10.3±8.2	7.5±3.2	0.543
Lower limbs neuropathy (group 2)	5	68.2±4.5	3/2	11.1±6.5	7.8±2.8	

Both group of patients did not show significant differences in demographic characteristics and pathology at baseline. (Table I). Both group of patients did not show significant differences in specific score (VAS pain, LBP-IQ, CHFD, NPQ) at baseline (Table II).

Patients treated with PEA+ALC FC (group 1) had a significant improvement in pain VAS compared to patients treated with group 2 in all the diseases analyzed (respectively P value: sciatic pain 0.032, carpal tunnel syndrome 0.025 and lower limbs neuropathy 0.041) (Table III).

Patients in group 1 showed a significant improvement compared to patients treated in group 2 also from a specific score. Specifically, LBP-IQ showed significant improvement in group one (P=0.031), as did CHFD (P=0.011) and NPQ (P=0.025) (Table IV).

Patients treated with PEA+ALC FC did not show an increase in the intake of other pain control drugs such as analgesics or NSDAIDs compared to the comparison population, but the data was not statistically significant (P=0.082). However, there was no significant change from standard therapy in either group over the 6-month follow-up (data not showed).

TABLE II.—*VAS pain, LBP-IQ, CHFD, NPQ at baseline (group 1 standard of therapy + PEA + ALC FC/group 2 standard of therapy).*

groups	VAS pain (0-10)	P value VAS pain Gr 1*vs.* Gr 2
group 1	7.1±1.3	0.812
group 2	6.8±0.7	
LBP-IQ (0-100)		P value LBP-IQ pain Gr 1 *vs.* Gr 2
group 1	35.5±2.8	0.755
group 2	37.2±3.9	
CHFD (0-90)		P value CHFD Gr 1 *vs.* Gr 2
group 1	27.4±2.4	0.924
group 2	25.3±3.1	
NPQ (1-12)		P value NPQ Gr 1 *vs.* Gr 2
group 1	8.5±0.6	0.634
group 2	8.7±0.9	

LBP-IQ: Low Back Pain Impact Questionnaire; CHFD: cochin hand functional disability; NPQ: Neuropathic Pain Questionnaire.

TABLE III.—*Improvement (%) of VAS pain at T1 and T2 (group 1 standard of care + PEA + ALC FC/group 2 standard of therapy).*

Variables	VAS 3 (T1) %	VAS 6 (T2) %	P value
Sciatic pain			
group 1	+22	+28	0.032
group 2	+17	+21	
Carpal tunnel syndrome			
group 1	+20	+33	0.025
group 2	+21	+28	
Lower limbs neuropathy			
group 1	+34	+41	0.041
group 2	+23	+29	

TABLE IV.—*Improvement (%) of LBP-IQ, CHFD and NPQ at T1 and T2 (group 1 standard of care + PEA + ALC FC/group 2 standard of care).*

Variables	LBP-IQ 3 (T1)%	LBP-IQ 6 (T2)%	P value
Sciatic pain			
group 1	+18	+28	0.031
group 2	+10	+18	
Carpal tunnel syndrome	CHFD 3 (T1)%	CHFD 6 (T2)%	
group 1	+28	+37	0.011
group 2	+18	+23	
Lower limbs neuropathy	NPQ 3 (T1)%	NPQ 6 (T2)%	
group 1	+27	+38	0.025
group 2	+21	+28	

LBP-IQ: Low Back Pain Impact Questionnaire; CHFD: cochin hand functional disability; NPQ: Neuropathic Pain Questionnaire.

Discussion

In recent years, several studies have been carried out regarding PEA and its efficacy in different nerve compression syndromes. Canteri *et al.*[43]

reported the results of a placebo-controlled, double blind, randomized study in 111 patients suffering from lumbo-sciatic pain. All patients were allowed to continue their established medication. After 3 weeks, there was a significant decrease of pain in which the high dose (600 mg PEA/day) was seen to be the most effective (p: 0.03) compared to lower doses and placebo group. The use of co-analgesics did not change the outcome. Gatti *et al.* performed an observational study with 610 patients suffering from chronic pain states, among which 331 patients suffered from sciatic pain.[44] Patients received 600 mg, twice daily for 3 weeks followed by single daily dosing for 4 weeks. PEA was added to established analgesic therapies, or as single therapy. PEA decreased the mean pain on the VAS from 6.4±1.4 to 2.5±1.3 in the patients who completed the study. In patients without concomitant analgesics, PEA was equally efficacious in reducing chronic pain. Moreover, Desio *et al*.[45] reported the effects of PEA in an open study in 20 non-responders to previous analgesic pharmacotherapy with sciatic pain, low back pain, hernia, and vertebral stenosis. Other studies[46, 47] showed the efficacy of PEA in the treatment of neuropathic low back pain. Assini *et al.*[48] and Congiliaro *et al.*[49] investigated the effect PEA carpal tunnel syndrome showing significant difference in reduction of pain at endpoint between treatment with PEA and control group.

According to preclinical and clinical studies, ALC can be considered both an etiological and symptomatic treatment in patients with peripheral neuropathy, with a good safety profile. ALC operates *via* several mechanisms, inducing regeneration of injured nerve fibers, reducing oxidative stress, promoting DNA synthesis in mitochondria, and increasing NGF concentrations in neurons, thus promoting neurite extensions.[50] A lack of carnitine reduces energy synthesis by impairing fatty acid degradation: this condition was reported in association with diabetes and its complications.[51, 52] ALC showed analgesic properties, by relieving acute and in chronic pain. Several clinical studies reported an improvement in symptoms after ALC supplementation in patients with peripheral neuropathy of different etiologies.[53-55] Several studies, describing different neuropathic pain models, confirmed the antinociceptive effect of ALC. Such an effect results from different mechanisms, including the activation of muscarinic cholinergic receptors, and the increased expression of mGlu2 receptors in dorsal root ganglia neurons, by using an acetylation mechanism involving transcription factors of the nuclear factor (NF)-kappaB family.[56] Noteworthy, the analgesic effect of ALC exceeds by several days or weeks the end of treatment in models of chronic inflammatory and neuropathic pain. This enforces the role of ALC as an analgesic drug and supports the role of the epigenetic mechanisms in the treatment of chronic pain.[56, 57]

Both PEA and ALC also seem to act by causing the downregulation of peculiar cytokines which are typically involved in RDs such as IL-1, TNF-alpha and IL-6.[58, 59] This could justify the favorable effect shown in our study in patients treated with PEA + ALC FC in both improving neuropathic pain and joint mobility (Table IV).

Limitations of the study

This study, to our knowledge, is the first to evaluate the efficacy of the synergistic effect of PEA and ALC in a clinical subset of patients suffering from neuropathy secondary to RDs. However, there are some limitations as the sample appears to have a limited number of patients and the study is not randomized and controlled even if 2 groups were compared.

Conclusions

PEA has been tested in a wide variety of animal models for nerve compression and has been evaluated in several clinical studies involving a total of more than 1000 patients with nerve compression syndromes. Both preclinical and clinical findings agree that PEA acts as a safe analgesic compound in nerve compression. Its safety and efficacy profile supports its clinical use in neuropathic compression syndromes such as sciatic pain and carpal tunnel syndrome. ALC has also been shown to be an effective and safe treatment in painful peripheral neuropathy. Furthermore, ALC-induced pain relief can be mediated by both a neuroprotective mechanism and a central *anti*-nociceptive mechanism. However, future studies

are needed to evaluate the duration of therapeutic efficacy and the optimal dose in larger populations, possibly with longer follow-up periods. Finally, the synergistic effect of PEA and ALC in Kalanit® (Chiesi Italia Spa) seems to have a further advantage in the treatment of this type of pathology, including the anti-inflammatory effect but also in terms of therapy optimization and therefore of better adherence to treatments. Our study shows that it is important to identify the type of pain to follow an accurate diagnostic algorithm, considering the clinical characteristics of the patient and carefully evaluate the indication, preferring a multimodal approach.

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