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Switching from pathogenetic treatment with α-lipoic acid to gabapentin and other analgesics in painful diabetic neuropathy: a real-world study in outpatients

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Abstract

In this retrospective real-world study, we aimed to evaluate whether switching from the pathogenetic treatment option α-lipoic acid to drugs for symptomatic treatment of neuropathic pain such as gabapentin would be associated with changes in efficacy, safety, and cost-effectiveness. A cohort of 443 diabetic patients with chronic painful neuropathy were treated with α-lipoic acid 600 mg qd orally for a mean period of 5 years. After stopping this treatment, 293 patients were switched to gabapentin (600–2400 mg/day), while 150 patients remained untreated because of no acute symptoms. In the untreated group, 110 (73%) patients developed neuropathic symptoms as soon as 2 weeks after the end of treatment with α-lipoic acid. In the group started on gabapentin, 131 (45%) patients had to stop taking the drug due to intolerable side effects. Among the patients treated with gabapentin 132 (45%) were responders on an average dose of 1200 mg/day, whereas 161 (55%) were nonresponders at gabapentin doses up to 2400 mg/day. These patients required an alternative treatment which consisted of pregabalin, carbamazepine, amitriptyline, tramadol, or morphine as monotherapy or in combination. The daily costs for α-lipoic acid were considerably lower than those for gabapentin or several frequently used drug combinations. The frequency of outpatient visits was 3.8 times per 3 months during the treatment period with α-lipoic acid, while it increased to 7.9 per 3 months after switching to gabapentin or the other pain medications. In conclusion, switching from long-term treatment with α-lipoic acid to central analgesic drugs such as gabapentin in painful diabetic neuropathy was associated with considerably higher rates of side effects, frequencies of outpatient visits, and daily costs of treatment. The pathogenic treatment option represents for the practicing diabetologist an effective, safe, and cost-effective treatment option for the majority of patients with diabetic polyneuropathy.

Keywords: α-lipoic acid; Diabetic neuropathy

1. Introduction

Pain associated with diabetic neuropathy exerts a substantial impact on the quality of life, particularly by causing considerable interference in sleep and enjoyment of life (Galer, Gianas, & Jensen, 2000). Chronic neuropathic pain is present in 16–26% of diabetic patients (Daousi, Benbow, Woodward, & MacFarlane, 2006; Davies, Brophy, Williams, & Taylor, 2006). Pain is a subjective symptom of major clinical importance as it is often this complaint that motivates patients to seek health care. However, in a recent survey from the United Kingdom, only 65% of diabetic patients received treatment for their neuropathic pain, although 96% had reported the pain to their physician (Daousi et al., 2006). Pain treatment consisted of antidepressants in 43.5% of the cases, anticonvulsants in 17.4%, opiates in 39%, and alternative treatments in 30%. Neuropathic pain may persist over several years (Boulton, Scarpello, Armstrong, & Ward, 1983), causing considerable disability and impaired quality of life in some diabetic patients (Galer et al., 2000), whereas it remits partially or completely in others (Young, Ewing, & Clarke, 1988;

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Benbow, Chan, Bowsher, MacFarlane, & Wiliams, 1993), despite further deterioration in small fiber function (Benbow et al., 1993). Although 77% of the patients reported persistent pain over 5 years, 23% were pain-free over at least 1 year (Daousi et al., 2006). Thus, neuropathic pain may persist in the majority of diabetic patients over periods of several years. Pain remission tends to be associated with sudden metabolic change, short duration of pain or diabetes, preceding weight loss, and less severe sensory loss (Young et al., 1988; Benbow et al., 1993).

Recent experimental studies suggest a multifactorial pathogenesis of diabetic neuropathy. From the clinical point of view, it is important to note that, based on the various pathogenetic mechanisms, therapeutic approaches could be derived, some of which have been evaluated in randomized clinical trials. These drugs have been designed to favourably influence the underlying neuropathic process and therefore represent disease-modifying therapy based on pathogenetic mechanisms rather than symptomatic pain treatment. Because free radical-mediated oxidative stress appears to play a major role in the pathogenesis of diabetic neuropathy, one of these options are antioxidants (Vincent, Russell, Low, & Feldman, 2004). Antioxidant treatment with α-lipoic acid has been shown to prevent these abnormalities in experimental diabetes, thus providing a rationale for a potential therapeutic value in diabetic patients (Ziegler, 2004). According to a meta-analysis comprising 1258 patients, infusions of α-lipoic acid (600 mg iv/day) ameliorated neuropathic symptoms and deficits after 3 weeks, while the Alpha-Lipoic-Acid-in Diabetic Neuropathy III Study (ALADIN) showed oral treatment with 600 mg tid resulted in a favorable effect on neuropathic deficits after 6 months (Ziegler, 2004; Ziegler, Nowak, Kempler, Vargha, & Low, 2004). Moreover, the Symptomatic Diabetic Neuropathie Study 2 (SYDNEY) trial suggests that treatment for 5 weeks using 600 mg of α-lipoic acid orally qd reduces the chief symptoms of diabetic polyneuropathy including pain, paresthesias, and numbness to a clinically meaningful degree (Ziegler et al., 2006). In a multicenter, randomized, double-masked, parallel-group clinical trial (Neurological Assessment of Thiotic Acid in Diabetic Neuropathy 1 [NATHAN]) including 460 diabetic patients with Stage 1 or 2a Distal Symmetrie Polyneuropathy (DSP) were randomly assigned to oral treatment with α-lipoic acid 600 mg qd or placebo for 4 years. After 4 years, some neuropathic deficits and symptoms, but not nerve conduction velocity, were improved (Ziegler et al., 2007).

Clinical and postmarketing surveillance studies have revealed a highly favorable safety profile of α-lipoic acid, which has been licensed and used for treatment of symptomatic diabetic neuropathy for more than 40 years.

We report here the results of an observation study in which diabetic patients with painful neuropathy were treated with α-lipoic acid 600 mg qd for 5 years on average and then were switched to gabapentin. We aimed to evaluate whether switching from α-lipoic acid to symptomatic pain treatments such as gabapentin would be associated with changes in efficacy, safety, and cost-effectiveness.

2. Patients and methods

A total of 443 diabetic patients with chronic painful neuropathy from large private practices specialized in diabetes treatment were treated with 600 mg α-lipoic acid given orally qd (Thioctacid 600 HR, Meda Pharma, Bad Homburg, Germany) for 5 years on average. Immediately after stopping this treatment, 293 patients were switched to gabapentin (600–2400 mg/day), while 150 patients remained untreated. Responders to gabapentin treatment were defined as those who had least moderate pain relief or were free of pain no later than 6 months after starting the treatment. Nonresponders were patients who reported no or only slight pain relief at doses up to 2400 mg/day, and therefore stopped treatment.

Responders to α-lipoic acid treatment were defined to those who had symptom relief and showed improvement in neuropathic deficits. Nonresponders were defined as those who had no symptom relief after 3 weeks treatment.

Neuropathic symptoms and deficits were assessed using the Neuropathy Symptom Score and the Neuropathy Disability Score according to Young, Boulton, Macleod, Williams, and Sönksen (1993), respectively.

3. Results

Among 443 diabetic patients [(mean age: 65 years, duration of diabetes: 13.6 years, hemoglobin A_{1c}: 7.1% (normal range: 4.3–6.1%)] with chronic painful neuropathy who were treated with 600 mg α-lipoic acid qd for 5 years on average, n=333 were responders, while n=110 were nonresponders. The rates of side effects during treatment with α-lipoic acid were 3%, mainly consisting of nausea or postprandial fullness. Immediately after stopping this treatment, 293 patients were switched to gabapentin, while 150 patients remained untreated. In the untreated group, 110 (73%) patients developed neuropathic symptoms as soon as 2 weeks after the end of treatment with α-lipoic acid. In the group started on gabapentin 131 (45%), patients had to stop taking the drug due to intolerable side effects consisting of dizziness, somnolence, vertigo, and tendency to fall. Among the patients treated with gabapentin 132 (45%) were responders on an average dose of 1200 mg/day, whereas 161 (55%) were nonresponders at gabapentin doses up to 2400 mg/day. Of the patients, 109 (68%) had predominantly parasthesia and numbness, in which gabapentin showed no efficacy. These patients required an alternative treatment which consisted of pregabalin, carbamazepine (200 mg tid or 300 mg bid), amitriptyline (75 mg/day), tramadol (100 mg

Table 1
Comparison of daily therapy costs

Product	Daily dosage in mg	Daily costs in Euro
Thioctacid 600 HR	600	0.95
Gabapentin Stada	1200	2.28
Neurontin	1200	2.53
Carbamazepine+ tramadol+amitriptyline	600, 200, 75	1.97 (total)
Lyrica+tramadol	150, 200	2.67 (total)
Durogesic+carbamazepine	75 μg/h, 600	10.52 (total)

bid), or morphine. These drugs were frequently used in combination.

The daily costs for α-lipoic acid (1 tablet of Thioctacid HR 600 per day) were €0.95 ($1.15) and differed very much from other treatment options used (Table 1).

The frequency of outpatient visits was 3.8 times per 3 months during the treatment period with α-lipoic acid, while it increased to 7.9 per 3 months after switching to gabapentin or the other pain medications.

4. Discussion

In this real-world observation study, we observed that long-term therapy with α-lipoic acid is a safe and effective treatment option in outpatients with diabetic polyneuropathy as previously described in placebo controlled double blind studies (Ziegler, 2004, Ziegler et al., 2004, 2006, 2007). Switching from long-term treatment with α-lipoic acid to available pain treatments for painful diabetic neuropathy such as gabapentin was associated with considerably higher rates of side effects, frequencies of outpatient visits, and daily costs of treatment. Notably, 45% of the patients who were switched to gabapentin had to stop taking the drug due to intolerable side effects, although the dose was not titrated to as high as 3600 mg/day, which was the target dose reached in 76% of the patients in the only available larger trial of gabapentin in painful diabetic neuropathy (Backonja et al., 1998). It is obvious that the setting of a controlled clinical trial may not mirror the real-world situation. The main concerns are that populations enrolled in trials are more selected than those treated in the "real world" and whether the treatment effects observed in trials will also be observed in clinical practice. Extrapolating treatments to different health care settings from the trial can result in important variations in treatment effects (Flather, Delahunty, & Collinson, 2006).

Gabapentin was chosen because, at the time this study was conducted, this was the most widely used and recommended drug for treatment of neuropathic pain,

It is important to note that treating patients with predominantly parasthesia and numbness showed no efficacy under treatment with gabapentin.

However, our study shows that the compliance with gabapentin is poor due to the high rates of adverse events associated with its use, even when the drug is titrated to only two thirds of its maximum dose. A recent trial compared the compliance with gabapentin and selective serotonin reuptake inhibitors (SSRIs) in patients with painful diabetic neuropathy. On the pill count, significantly more patients on SSRIs (93.5%) than on gabapentin (82.9%) were taking over the 75% of their medication (Giannopoulos et al., 2007). Our study adds to this finding, suggesting that the low compliance with gabapentin seems to be due to the relatively high rates of side effects, particularly somnolence and dizziness. However, metabolic side effects of gabapentin such as weight gain may aggravate the cardiovascular risk profile specifically in diabetic patients who in general carry a high risk for cardiovascular disease. However, the use of alternative drugs for gabapentin such as the tricyclic agent amitriptyline, which was used in this study, was associated with an increased risk of myocardial infarction. After adjusting for age, gender, baseline heart disease, diabetes, hypertension, hyperlipidemia, anxiety, and cancer, the relative risk of myocardial infarction was 2.2 (95% CI 1.2–3.8) in users of tricyclic agents (Cohen, Gibson, & Alderman, 2000).

Another recent study could show that 20% of diabetic patients aged >65 years receiving pain related medications who had diagnosis of peripheral neuropathy within 30 days of such prescriptions were prescribed tricyclic antidepressants (TCAs). Among these patients, nearly one half had comorbidities and/or received other medications that could render the prescribing of TCAs potentially inappropriate (i.e., contraindications, warnings, or precautions listed in product labeling). Thus, many older diabetic patients with peripheral neuropathy who receive TCA therapy may be inappropriately treated. Safer agents such as α-lipoic acid may be more appropriate in the older diabetic population (Berger, Dukes, Edelsberg, Stacey, & Oster, 2007). It should also be emphasized that the daily costs of treatment with α-lipoic acid are only half of those for gabapentin and much lower than for pregabalin or transdermal fentanyl. A recent US study compared the cost-effectiveness of duloxetine vs. routine treatment over 1 year in painful diabetic neuropathy. As in our study, routine treatment most frequently used included gabapentin (56%), while amitriptyline was the third most frequently used drug (15%) (Wu et al., 2006). Simulation modeling has recently been employed to allow for formal cost-effectiveness evaluations of treatments for painful neuropathies when with data on health-state utilities and treatment costs (Vera-Llonch et al., 2006). Such a stochastic simulation model was recently applied to results from clinical trials of gabapentin and pregabalin in painful diabetic neuropathy and postherpetic neuralgia. Following 12-week treatment, compared with pregabalin (150–600 mg), gabapentin (900–3600 mg) was projected to result in 6 and 9 fewer days with no or mild pain for patients with painful diabetic neuropathy and postherpetic neuralgia, respectively. Gabapentin therapy was estimated to provide a fewer 0.0047 quality-adjusted life year (QALY) and 0.0086 QALY over pregabalin administration, for painful diabetic neuropathy and postherpetic neuralgia,

respectively (Tarride, Gordon, Vera-Llonch, Dukes, & Rousseau, 2006).

In conclusion, in this real-world study switching from long-term treatment with α-lipoic acid to available pain treatments for painful diabetic neuropathy was associated with considerably higher rates of side effects, frequencies of outpatient visits, and daily costs of treatment. Thus, α-lipoic acid has several advantages over drugs like gabapentin: (1) its use is associated with much lower rates of side effects, (2) it is less expensive, and (3) it is a disease modifying treatment option which not only improves neuropathic symptoms but also neuropathic deficits such as impaired sensory function. Thus, switching from long-term treatment with α-lipoic acid to gabapentin or other central analgesic drugs in patients with painful diabetic neuropathy is not warranted.

Recurrence of symptoms after 2 weeks, when not being treated with α-lipoic acid, showed that treatment of diabetic polyneuropathy is a long term treatment, even at symptom-free intervals, which requires a drug with pathogenetic properties like α-lipoic acid.

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