EDITORIAL (SEE DYCK ET AL., P. 2619)

Whither Clinical Research in Diabetic Sensorimotor Peripheral Neuropathy?

Problems of end point selection for clinical trials

Neuropathies are among the commonest of long-term diabetes complications, and the management of chronic sensorimotor distal symmetric polyneuropathy (DPN) presents a significant therapeutic challenge (1,2). DPN may manifest with several diverse clinical presentations, including troublesome, neuropathic pain and, at the other end of the spectrum, the insensitive foot at risk of ulceration. Whereas the former gives rise to many unfamiliar and uncomfortable painful and paresthetic symptoms that impact quality of life (3), foot ulceration, which may lead to amputation, has major social and economic implications for the health care system (4,5).

There are currently two main approaches to DPN therapy. First, there are those treatments that alleviate the persistent painful symptoms in the lower limbs. These include the tricyclic antidepressants, anticonvulsants, opioids, and opioid-like agents; the efficacy of these is supported by multiple randomized controlled trials (RCTs) and, in some cases (e.g., the tricyclic drugs), meta-analyses (1,2,6). The newer agents duloxetine and pregabalin also have confirmed efficacy in several RCTs. However, none of these interventions has any impact on the natural history of the condition, which, until recently, was believed to comprise a progressive loss of nerve fibers.

The second group of therapies consists of those that primarily target the putative pathogenetic mechanisms (1). Included in this group are a number of mainly experimental treatments, such as the antioxidant α-lipoic acid (1,7), which, although not available in the U.S., is approved in a number of countries, and the aldose-reductase inhibitor epalrestat, which is only available in Japan (8). Unlike most agents in this group, α-lipoic acid may also alleviate neuropathic symptoms when administered parentally (7). Many other agents have been tested extensively in animal models and humans, with disappointing results when given to patients with early DPN (1).

One therefore has to ask why no pathogenetic therapy for DPN has demonstrated sufficient efficacy to achieve U.S. regulatory approval. Ziegler and Luft (9) addressed this question some years ago in a review. They stated that there is no doubt that both clinical and neurophysiological surrogate end points (especially electrophysiological studies [10]) used in such trials predict the ultimate end points (foot ulceration and amputation) but that trials until the mid-1990s were generally of poor design, being of short duration and prone to accept patients with advanced DPN. They concluded that trials enrolling patients with early (mild) DPN, conducted over 3–5 years, that assessed slowing or halting of progression rather than reversal were most likely to result in clinically meaningful results. Earlier this year, Tesfaye at al. (11) reported on the placebo-treated arms of two large 12-month RCTs of ruboxistaurin in DPN. They demonstrated significant improvement not only in symptoms but also in signs and quantitative vibration testing, whereas there was deterioration in some electrophysiological measures. They concluded that to demonstrate deterioration in any placebo-treated DPN group, studies of >12 months are needed.

In the current issue of *Diabetes Care*, Dyck et al. (12) further debate the challenges in selecting appropriate end points in clinical trials of new agents for DPN. Assessed were the performances of end points in the placebo arms of two large pharmaceutical trials (one of 4-years' and the other of 1-year's duration) and the 10-year Rochester DPN epidemiological study. They concluded that the main reasons for failure of these combined studies to demonstrate progressive worsening of end points included a strong placebo effect for symptoms and signs, measurement noise, and the fact that DPN actually progresses more slowly than previously believed.

I would add to the authors' list of potential explanations for difficulties in confirming efficacy of new treatments for DPN (12) the possibility that other concomitant medications might impact on nerve function. It is increasingly recognized that the incidence of DPN is associated with a number of potentially modifiable cardiovascular risk factors (13). Because most diabetic patients with early DPN are likely to be on agents such as ACE inhibitors and lipid-lowering agents, all of which might positively impact on peripheral nerve function (14,15), concomitant medications may well be further confounding variables in such trials.

Where do we go from here in clinical trial design? Dyck et al. conclude that future trials should do the following: *1*) include patients with developing rather than established DPN, *2*) recruit patients with suboptimal control, *3*) select end points known to show worsening, and *4*) preferably include patients with type 1 diabetes. The last proposal is unlikely to be adopted in large clinical trials of potential pathogenetic treatments; only a small minority of patients has type 1 diabetes, and any indication would need to be for both main types of diabetes. The question of end points is important. Many currently selected end points, including quantitative sensory testing and composite clinical scores, rely on patient responses and are therefore prone to variability. Electrophysiological measures, however, especially sural nerve amplitudes and peroneal nerve conduction velocities, performed well in recent studies (11,12).

There is clearly a need for new, robust end points for future studies; at present, there are many drugs in phase 2 and 3 studies (1,2,6), and recent experimental evidence suggests that more gene therapies may soon be in clinical trials (16). Two recently developed techniques for assessing peripheral nerve function might usefully serve as surrogate end points for future clinical trials. The assessment of intra-epidermal nerve fibers taken from minimally invasive punch skin biopsies is currently being used in practice (17) and

in clinical trials (18). Similarly, the noninvasive corneal confocal microscopy has been developed and might be an ideal technique that can be repeatedly performed to assess progression of DPN in future trials (19). Corneal confocal microscopy was recently used to confirm early small fiber repair after pancreas transplantation (20).

In summary, previous trials of potential pathogenetic treatments for DPN have failed for many reasons, but it is now apparent that the rate of progression of established DPN may not be as fast as previously believed. New promising therapies cannot be allowed to fail in clinical trials because inappropriate surrogate end points were selected to judge their efficacy.

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