Development of New Drug, Epidermal Growth Factor for Chronic Diabetic Foot Ulcer

Young-hyo Yoo Ph.D.
R&D Center, Daewoong Pharmaceutical Co., Ltd.

Abstract

Of 16 million diabetic patients in the USA, 2.4 millions have experienced diabetic foot ulcer and 67,000 have amputations every year. For treatment of diabetic foot ulcer, Americans spend more than $1 billion each year, including $36,000 per patient for complete treatment and $60,000 for each amputation.

Neuropathy and ischemia, two common complications of diabetes mellitus, are the primary underlying risk factors for development of diabetic foot ulcers. Ischemic ulcers develop as a result of low perfusion pressure in the foot with inadequate blood supply, whereas neuropathic ulcers develop from loss of protective sensation. In addition, diabetes also increases the risk of infection by impairing the body's ability to eliminate bacteria. From these circumstances, results are chronic wounds with impaired healing ability.

In a normal wound healing process, epidermal growth factor (EGF) is present in the blood to aid normal healing process where it works as chemoattractant and mitogen for epithelium, dermis and fibroblast, and to help formation of transforming growth factor-α (TGF-α) and other growth factors' activities, which promotes proliferation of epithelium and fibroblast, and as a result collagen syntehsis occurs (Assioan et al., 1984; Coffey et al., 1987; McAuslan et al., 1985; Nakagawa et al., 1985). EGF has already been recognized to enhance wound healing in ischemic ulcers, donor sites of skin graft, partial and full thickness burns and excimer laser keratectomy injuries (Iwakawa et al., 1994; Ahn et al., 1995; Callahan et al., 1995; Kim et al., 1995)

DWP401, recombinant human epidermal growth factor (rhEGF), is a novel wound-healing topical formulation developed by Daewoong Pharmaceutical Co., Ltd., whose indications include various wounds. DWP401 consists of complete 53 amino acid residues and is physicochemically and biologically identical to intact human EGF found in various body fluids and tissues such as breast milk, urine, semen, saliva and tears (Carpenter et al., 1976). The superiority of DWP401 to other EGF's is characterized by its high-level expression and large-scale purification technology, which yields mass production of recombinant EGF with high purity and great specific activity. Thus DWP401 exhibits higher mitogenic and receptor-binding activities than other

EGF's.

From non-clinical specific effect studies of DWP401, it was found to facilitate healing of non-healing wounds significantly. It also increased neodermis, neovascularization, thickness and maturation of the collagen bundles, and reepithelialization compared to control.

The general pharmacological studies showed that DWP401 had no effect on the central and autonomic nervous systems. In addition, DWP401 had no effect on leukocyte migration and renal function, as well as no effect on the cardiovascular system except a temporary increase of blood pressure. DWP401 increased the intestinal propulsion rate significantly, which may result in the promotion of intestinal content excretion. Finally, DWP401 decreased gastric secretion, and was presumed to have an insulin-like activity.

Pharmacokinetic studies of DWP401 proved no significant changes or indications of accumulation in the system after repeated treatment. Although EGF was found to be more permeable through damaged skin, no significant metabolism was found in the damaged skin model and it was indicated that EGF receptor binding plays a role in determining the skin permeability. In addition, pretreatment with DWP401 changed the permeability of the damaged skin model to be as low as the normal skin model, which is thought to be related either to the phathophysiological changes of the skin or to down-regulation of the EGF receptors. Ocular administration studies found that DWP401 was more concentrated in the burned eye model than normal eye model except in the lens, and that DWP401 was hardly detected after a single dose but was detected significantly after repeated doses.

Toxicology studies of DWP401 reported favorable results. Mice and rats showed no toxic symptoms and LD_{50} was over 2 mg/kg in oral and subcutaneous acute toxicity tests. The subacute toxicity study of 13-week repeated *s.c* injection reported no-observed-adverse-effect-level (NOAEL) of 0.04 mg/kg in mice and below 1 μg/kg in rats. Furthermore, local, reproductive and genetic toxicology tests gave negative results, and rats did not develop antibody to rhEGF unless administered along with Freund's complete adjuvant, while male mouse had low- affinity and low-titer antibody response in the highest dose group (1,000μg/kg). Based on the results of the toxicity studies, possibility of DWP401 to elicit adverse reactions upon topical application to open wounds in clinical practice appears insignificant.

From the Phase I clinical trial of DWP401, we concluded that DWP401 is safe to be applied as a topical treatment. DWP401 was proven to have no significant systemic and local adverse effect when administered on normal skin and suction-blistered /

scotch-tape abraded wounds in 34 healthy adult male subjects. The plasma and urine concentration of EGF did not increase significantly, thus the test drug is thought to be either not absorbed to the blood stream or metabolized fast in the system.

The efficacy of DWP401 shall be further verified in Phase II clinical trial where administratin of DWP401 is expected to perform as an excellent wound healing agent for diabetic foot ulcers.

DWP401 is currently under Phase II clinical trial in Korea, as well as Phase IIa clinical trial in Germany, as a topical application with an indication of diabetic foot ulcer,. It has not been applied for approval or registration for marketing in Korea as well as in any other country yet, and it is expected to be on the market at the end of 2000 in Korea.

The present presentation is to discuss the process and strategies of development of EGF.