Evaluation of US2019070266 patent, treatment diabetic foot ulcers with Liraglutide

Martin Perez-Santos[*1]

Dirección de Innovación y Transferencia de Conocimiento, Benemérita Universidad Autónoma de Puebla, Ciudad Universitaria, San Manuel, Puebla, México. C. P. 72570.
*Email autor corresponsal: martin.perez@correo.buap.mx

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Abstract

Diabetic foot ulcers are clinical complications that affect to a 15-25% of patients of type-2 diabetes mellitus and are responsible for more hospitalizations than any other complication of diabetes. Authors of US2019070266 patent propose a method for treatment of diabetic foot ulcers. US2019070266 describes a method that consists of the administration of Liraglutide, at a dose of 1.2-1.8 mg, in patients with type 2 diabetes and with at least one risk factor for vascular disease, such as microalbuminuria, proteinuria, hypertension, left ventricular hypertrophy, left ventricular systolic dysfunction, left ventricular diastolic dysfunction and ankle/brachial index <0.9. The results of the clinical trials support the therapy's efficacy; however, the invention is not new considering art state, whereby, new studies will be necessary to determine other administration routes, e.g. topical, dose and time of administration of Liraglutide.

Keywords: Liraglutide, diabetic foot, patent, diabetes, ulcer

Introduction

Globally, diabetes mellitus has been recognized as the third cause of premature mortality due to hyperglycemia. The data suggests that about 415 million people live with diabetes, of which 75% live in low- and middle-income countries [1]. Similarly, it is estimated that by 2040 there will be 642 million people with diabetes [2]. Various clinical complications are observed in patients with type 2 diabetes mellitus, including cardiovascular disease [3], diabetic foot ulcer [4], retinopathy [5], neuropathy [6] and nephropathy [7].

It has been estimated that 15-25% of diabetic patients will develop ulcerations in their lower limbs [8]. Diabetic foot ulcers are the initial cause of a dramatic process that, if not treated, will lead to the amputation of the affected limb. Neuropathy, neuroischemia and infections play an important role in the healing or worsening of ulcers, and amputations are usually preceded by

an ulceration that can lead to severe gangrene or infection [9-11].

There are several treatment modalities for diabetic foot ulcers, which include the topical application of growth factors, synthetic drugs and natural products. For example, platelet-derived growth factor increases cell proliferation and consequently angiogenesis and epithelialization [12-13]. Similarly, fibroblast growth factor improved the adhesion, proliferation and migration of fibroblasts, causing angiogenesis and epithelialization [14-15]. In turn, epidermal growth factor induces fibroblast proliferation [16-17]. On the other hand, several synthetic drugs, such as Pravastin, improve the resistance to wound breakage by positive regulation of eNOS and the expression of NO [19]. On the other hand, Azelnidipine stimulate the production of NO thus improving histological processes [20]. Pentoxifylline by decreasing the expression of MMP and increasing the expression of TIMP-1, accelerates healing [21].

Continuous development of new alternatives for the treatment of diabetic foot ulcers is necessary, and consequently this article evaluates the US2019070266 patent application [22], which describes the application of Liraglutide as an alternative for healing diabetic foot ulcers. Liraglutide is a long-acting human GLP-1 (Glucagon-like peptide-1) analogue that causes, through the messenger intracellular cyclic adenosine monophosphate, insulin to be secreted in presence of elevated glucose levels [23]. Liraglutide is 97% homologous to native human GLP-1 by substituting arginine for lysine at position 34 and is made by attaching a C-16 fatty acid (palmitic acid) with a glutamic acid spacer on the remaining lysine residue at position 26 of the peptide precursor [24-25]. Liraglutide has different therapeutic applications, such as atherosclerosis, hepatocellular carcinoma, endometrial cancer, and breast cancer, [26-29]. This drug is owned by Novo Nordisk and its application in humans was approved in United States, Europe and Japan as an adjunctive therapy to diet and exercise in adults with type-2 diabetes.

Chemistry and Biology

US2019070266 patent was published on March 7, 2019. In addition to being filed in the United States, the patent is filed in Worldwide (WO2017149109) and China (CN108883159). US2019070266 patent claims and describes a method to reduce or delay the development of diabetic foot ulcer. Said method includes the administration of liraglutide in a therapeutically effective amount to a patient with type 2 diabetes and with at least one risk factor for vascular disease, such as microalbuminuria, proteinuria, hypertension, left ventricular hypertrophy, left ventricular systolic dysfunction, ventricular

diastolic dysfunction left and ankle/brachial index <0.9. Further claims cover the doses, administration regimen, and pharmaceutical compositions containing them, and their applications in diabetic foot ulcers (Table I).

Table I. Claims of US2019070266

Number claim	Claim type	Technical feature
1	**Method** of treatment for reducing or delaying the development of diabetic foot ulcer	Administer Liraglutide in a **therapeutically effective** amount to a subject in need
2	**Method** of treatment for reducing or delaying the development of diabetic foot ulcer	**Reduces** or delays severe or moderate diabetic foot ulcer
3	**Method** of treatment for reducing or delaying the development of diabetic foot ulcer	**Reduces** or delays severe or moderate diabetic foot ulcer
4	**Method** of treatment for reducing or delaying the development of diabetic foot ulcer	**Reduces** or delays serious diabetic foot ulcer
5	**Method** of treatment for reducing or delaying the development of diabetic foot ulcer	**16 months** of chronic administration of liraglutide
6	Method of treatment for reducing or delaying the development of diabetic foot ulcer	Liraglutide is administered **once daily**.
7	**Method** of treatment for reducing or delaying the development of diabetic foot ulcer	Liraglutide is administered once daily in an amount in the range of **0.4-4.0 mg** per day
8	**Method** of treatment for reducing or delaying the development of diabetic foot ulcer	Liraglutide is administered at **0.6 mg** per day.
9	**Method** of treatment for reducing or delaying the development of diabetic foot ulcer	Liraglutide is administered at **1.2 mg** per day.
10	**Method** of treatment for reducing or delaying the development of diabetic foot ulcer	liraglutide is administered at **1.8 mg** per day.
11	**Method** of treatment for reducing or delaying the development of diabetic foot ulcer	Liraglutide is administered in the form of a pharmaceutical composition comprising about **1-20 mg/ml liraglutide**, about **2-15 mM phosphate buffer**, about **2-25 mg/ml propylene glycol**, about **1-18 mg/ml phenol**, and has a **pH in the range of 7.5-9.0**.
12	**Method** of treatment for reducing or delaying the development of diabetic foot ulcer	Liraglutide is administered in the form of a pharmaceutical composition comprising about **6 mg/ml liraglutide**, about **1.42 mg/ml disodium phosphate dihydrate**, about **14.0 mg/ml propylene glycol**, about **5.5 mg/ml phenol**, and has **pH of about 8.15**.
13	**Method** of treatment for reducing or delaying the development of diabetic foot ulcer	liraglutide is administered in the form of a pharmaceutical composition comprising **6 mg/ml liraglutide**, **1.42 mg/ml disodium phosphate dihydrate**, **14.0 mg/ml propylene glycol**, **5.5 mg/ml phenol**, and has **pH of 8.15**.

Two experimental studies were reported in patent US2019070266 as support of the proposed methodology. In the first study, the therapeutic efficacy of bumetanide in treating cancer was evaluated in long-term (3.5-5 year), multicenter, randomized, double-blind, placebo-controlled trial with 9340 human subjects to evaluate the efficacy and safety of liraglutide for which subjects were given an initial dose of 0.6 mg of liraglutide or placebo, increasing to 1.2 mg after one week, and 1.8 mg after another week. Formulations with liraglutide were administered as an aqueous solution containing 6.0 mg/ml of liraglutide, 1.42 mg/ml of disodium phosphate dehydrate, 14.0 mg/ml of propylene glycol, 5.5 mg/ml of phenol, and pH of 8.15.

In the second study, which validates the method proposed in the invention, a clinical trial to test the effectiveness of treatment with liraglutide was conducted in 9340 patients, half of whom were administered liraglutide and the second half were given a placebo. The results show that liraglutide, compared to placebo, reduces the frequency of diabetic foot ulcer. Liraglutide reduced both the frequency of severe ulcer and severe or moderate ulcer of the diabetic foot. Similarly, chronic administration of liraglutide, compared to placebo, for at least 16 months reduced the risk of developing diabetic foot ulcer. Thus, US2019070266 patent shows the scientific support that makes it possible to claim the method of treating diabetic foot ulcers.

Expert opinion

US2019070266 patent describes the potential application of liraglutide for the treatment of diabetic foot ulcer. As mentioned in the Biology section, the inventors do show data regarding the safety and efficacy of liraglutide's treatment. Therefore, the patent is shown scientific data concerning efficacy. In the state of the art, the inventors have published the same data regarding

efficacy [30], and clinical trials to establish the safety of the treatment are still being tested (NCT01179048) [31]. However, despite these positive premises, data supporting the invention are still limited; further studies aimed at investigating other administration ways and defining the optimal pharmaceutical composition, delivery method, dose–response relationship, long-term effects, are indeed necessary to assess the clinical applicability of the invention.

However, there is a publication that describe the application of Liraglutide for treatment of diabetic foot ulcer. Tzanetakos et al. describe the use of liraglutide for the treatment of diabetic foot ulcers [32]. Tzanetakos *et al*, shown an analysis of Liraglutide versus sitagliptin or exenatid. Patient's characteristics relative a microalbuminuria, proteinuria and left ventricular hypertrophy are describes in the Tzanetakos's work; thus, claim 1 of US2019070266 lacks novelty. In relation to claims 2-4 (Reduces or delays severe/moderate/serious diabetic foot ulcer), Tzanetakos describes that baseline foot ulcer complications, whereby these claims lack inventive activity. Likewise, in that clinical trial 1.2 mg liraglutide was administered once a day to diabetic patients with foot ulcer. Similarly, in this clinical trial, 1.8 mg of liraglutide was administered once daily in diabetic patients with foot ulcers; thus, claims 6, 9-10 lack inventive activity. Finally, claims 11-13 relative to pharmaceutical composition containing Liraglutide (disodium phosphate dehydrate, propylene glycol, phenol, and pH 8.15), Pedersen et al. [33] describes formulations of Liraglutide mixed with disodium phosphate dihydrate, propylene glycol and phenol; therefore, said claims have no inventive activity, a primary requirement for the granting of a patent.

In conclusion, the application of Liraglutide for the treatment of diabetic foot ulcers is not new or has inventive activity, so additional studies are necessary that include the topical application of Liraglutide in the ulcer as well as other types of additives that allow a greater permanence of the drug in the damaged tissue. Similarly, new studies will be necessary to determine, at the topical level, the dose and time of administration of Liraglutide.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials

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