

Postmarketing effectiveness and safety of Heberprot-P for diabetic foot ulcer treatment in Cuba

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RESEARCH

ABSTRACT

Postmarketing effectiveness and safety of Heberprot-P for diabetic foot ulcer treatment in Cuba. Heberprot-P is a novel and unique drug developed in Cuba to treat diabetic foot ulcers. Its efficacy has been demonstrated in clinical trials, those data requiring to be enriched with the evidences coming from the common medical practice. For that purpose, an observational, longitudinal and multicentered phase IV trial was carried out in 1851 adult patients, who were treated in 85 health institutions where this product is being applied since June 2007. At the end of treatment, 75.6% (IC 95%, 73.6-77.6) of patients showed their lesions completely granulated. One or more adverse events were present in 47.2% of cases during treatment, predominantly mild. The most frequent adverse events included malaise and disorder at the administration site. The clinical evolution of patients treated with Heberprot-P in Cuba together with its drug safety elements contributed to establish its pharmacoepidemiological profile within the context of the common medical practice. All these corroborate the therapeutic window of opportunity for using Heberprot-P to treat diabetic foot ulcers and the relevance of the postmarketing surveillance for patients, manufacturers, sanitary systems and all the society.

Keywords: Heberprot-P, pharmacovigilance, postmarketing

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RESUMEN

Efectividad y seguridad del Heberprot-P en el tratamiento de la úlcera de pie diabético durante la etapa de poscomercialización en Cuba. Heberprot-P es un fármaco desarrollado en Cuba, novedoso y único de su tipo para la terapia de úlceras en pies diabéticos. En estudios clínicos se ha comprobado su eficacia y seguridad, datos que necesitan ser enriquecidos con las evidencias de su uso en la práctica médica habitual. Con tal propósito se efectuó un estudio observacional, longitudinal y multicéntrico, fase IV con 1851 pacientes adultos, que acudieron a recibir tratamiento en 85 instituciones de salud donde se administra el medicamento desde junio de 2007. Al finalizar el tratamiento, las lesiones del 75.6% (IC 95%, 73.6-77.6) de los pacientes habían granulado completamente. El 47.2% del total de casos presentaron al menos un evento adverso durante el ciclo de tratamiento, con predominio de los de intensidad leve. Los sistemas de órganos que agrupan los mayores porcentajes de eventos adversos fueron: trastornos generales del organismo y trastornos en el punto de aplicación. En el contexto de la práctica médica habitual, la evolución clínica de los pacientes tratados con Heberprot-P en Cuba y los elementos de seguridad del medicamento, han contribuido a conformar su perfil pharmacoepidemiológico y corroboran el espacio terapéutico del Heberprot-P en el tratamiento de la úlcera de pie diabético, así como la importancia de la vigilancia poscomercialización desde la perspectiva de los pacientes, los productores, los sistemas sanitarios y la sociedad.

Palabras clave: Heberprot-P, farmacovigilancia, poscomercialización

Introduction

The randomized clinical study is considered a reference to evaluate the efficacy of therapeutic interventions. The evidences accumulated by clinical research during the development of new drugs are essentials for the regulatory authorities to determine whether the sanitary registration is granted or not [1].

At the moment that a new registered drug starts its commercialization, the results accumulated during the different clinical assays stages are essentially the main available knowledge about the product effects. However there are differences between the conditions where the clinical assays are conducted and the normal practical medicine regarding: a) type of patient, treatment extension, way to apply the drug, conditions for subjects following up and other aspects. This needs the continuation of a research process to fill it up the degree of unknown regarding the results of any specific treatment in the real clinical practice [2].

The pharmacoepidemiology as discipline studies the use of drugs and their medical, economical and social

impact, offering the tools to analyze from an integrated perspective the drug effects on populations. This branch from public health, covers two huge areas as some authors referred: the use of drug studies and the Pharmacovigilance, both with the objective to identify, quantify, evaluate and prevent the risks generated by the use of drugs once their commercialization started [3].

In Cuba, the Pharmacoepidemiology keeps a measured development since 1996 with the founding of the Center for the Pharmacoepidemiology Development (CDF) and a network formed by provincial and municipal centers. All of them have the duty to maintain the surveillance regarding the use, effectiveness and safety of all drugs commercialized within the national territory, including the biotechnological drugs, an area where Cuba has shown huge development [4].

Heberprot-P is a novel drug, unique in its type and addressed to treat Diabetic Foot Ulcers (DFU), pro-

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duced at the Center for Genetic Engineering and Biotechnology (CIGB) of Havana, Cuba [5]. Since April of 2007 the drug was introduced at the Basic Drug Frame of Cuba after being approved by the National Drug Formulation Commission. Since this moment started a drug extension strategy headed by the Public Health National System which maintain among their main milestones the early surveillance to determine the effectiveness and safety of Heberprot-P in the daily clinic practice. With this purpose CIGB and FED since May 2007 are carrying out a post commercialization Phase IV observational, prospective and multicenter study, to determine the effectiveness and safety of this drug through intensive pharmaco surveillance. Up to June 2010 more than 3000 DFU diabetic patients holding DFU has received treatment and care with Heberprot-P in 85 Cuban institutions located at the Primary and Secondary Health Care level. Now it is shown the results in more than 1851 patients having complete information dossiers about their follow up since the moment they received the drug.

Results

The average age of treated patients with Heberprot-P was 63.6 ± 11.2 years. In 50% of the cases age varied between 57 and 71 years. The major patient proportion regarding sex was women with 53.5%. 60.7% showed a previous antecedent of arterial hypertension and 22.9% ischemic cardiopathy. Diabetes mellitus type 2 were in higher proportion among the patients 76.1%. the disease evolution time was about 14.0 ± 10.4 years average. Patients with previous amputation were 24.2% (448 cases), among this group minor amputation (316 patients) were predominant. Patients with previous ulcers in their legs were the 38%.

The 81% of DFU correspond with Ulcers grade 3, 4 and 5 according Wagner classification. According Mc Cook classification, 44.1% were ischemic ulcers. The 38.5% received the Heberprot-P vial of 25 µg; meanwhile the other 58.3% used the 75 µg dose. In 2.7% both Heberprot-P doses were combined, and in 0.5% of them the dose was not reported.

Total granulation was achieved in 75.6% of the patient ulcers. After finishing the treatment with Heberprot-P 73.6 and 77.6% showed 95% of trust. In 86.9% of the patients carrying neuropathic ulcers showed total granulation at the end of the treatment. In ischemic patients total granulation was achieved in 65.6%. According the lesion position in the legs; 65.6% of 227 patients with ulcers located at the calcaneus region ended with the wound totally covered by granulation tissue. The average time for total granulation was 28.1 ± 19.8 days.

During the treatment with Heberprot-P, in 873 patients it was recorded at least one adverse event (47.2%) being predominant those with minor intensity. In table 1, it is shown 7 different types of recorded adverse event presented with proportions higher than 1.0% as well as the highest repetition number per patient. In 93.3% adverse events are compiled according affected organ/system recorded as: adverse reaction at the application point and general adverse reaction in the organism.

Table. Adverse reaction events distribution according its type

Type of Event	%*	Maximum number of repetitions
Pain at the administration site	21.7	24
Shivering	19.9	23
Ardor at the administration site	16.1	17
Chills	9.3	16
Local infection	3.8	4
Fever	2.4	7
Vomiting	1.5	10
Ischemic zone augmentation	1.4	2
Headache	1.0	12

*Percentage calculated from the total number of patients.

Discussion

The behavior according age and sex in patients that received treatment with Heberprot-P in hospitals and policlinics in Cuba is related, regarding the sex, with the rate of dispensed patients with Diabetes mellitus in Cuba in 2009, data that, according the Annual Statistic from the Cuban Health Minister is 48.7 x 1000 female habitants and 32.2 x 1000 male inhabitants [6]. Regarding the age, there is a coincidence with other studies using the drug that report a median of 60 years, which might be linked with the type of UPD lesion that deserve treatment and the extended life expectancy of Cuban citizens. The patient age and the disease evolution time contribute to the coexistence of other affections as arterial hypertension and ischemic cardiopathy, both presented also in patients included in clinical trials phase III carried out with Heberprot-P [7-9].

The higher percent of patients having DFU grade 3 and 4 Wagner classification and ischemic ulcers (Mc Cook) coincide with other previous studies [8, 9]. These results, as well as those referred to granulation percent achieved after using the drug in the post commercialization corroborate with the results showed in Clinical Trial Phase III [9] and confirm the therapeutic effectiveness of Heberprot-P in patients with extended and complicated DFU.

During the active patients surveillance in the state of administering the drug, it was corroborated that adverse event maintain a coincident patron with those previously reported in pre-commercialization studies regarding type and severity of reported adverse reactions. It has been identified other type of percentages very low but contribute to enrich the safety frame of Heberprot-P at the same time it might serve as reference for further studies.

Conclusions

In the frame of daily practical medicine, the clinic evolution of treated patients with Heberprot-P have helped to conform the pharmaco epidemiological frame of the drug and corroborate the therapeutic space of Heberprot-P in the treatment of DFU, as well as to remark the importance of post commercialization surveillance of the product, from the patients, producers, sanitary system and society perspectives.

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