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MEDICAL HYPOTHESES

USE OF TAMOXIFEN FOR THE TREATMENT OF NEPHROGENIC SYSTEMIC FIBROSIS

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Versión en español

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SUMMARY

Nephrogenic systemic fibrosis is (NSF) a rare entity which develops in patients with renal failure undergoing dialysis, and its etiology is related to several factors such as the use of intravenous gadolinium, vascular surgeries, etc.

Tamoxifen, is a selective modulator (competitive inhibition) of estrogen receptors, and it has antifibrotic properties which are used for treating retroperitoneal fibrosis, peritoneal sclerosis associated to peritoneal dialysis, desmoids tumors and in some cases of sclerodermia.

In the present article, it is presented the hypothesis of a potential use of tamoxifen as a non immunosuppressant treatment for NSF in patients who have no contraindication for receiving it.

KEY WORDS: Tamoxifen. Nephrogenic systemic fibrosis.

RESUMEN La fibrosis sistémica nefrogénica (FSN) es una entidad infrecuente, que se desarrolla en pacientes insuficientes renales en diálisis, vinculándose su etiopatogenia con diversos factores tales como el uso de gadolinio intravenoso, el antecedente de cirugías vasculares, etc. El

Tamoxifeno, es un modulador selectivo (inhibición competitiva) de los receptores estrogénicos, que posee propiedades antifibróticas las cuales se emplean para el tratamiento de entidades tales como: fibrosis retroperitoneal, esclerosis peritoneal asociada a diálisis peritoneal, tumores desmoides y en algunos casos de esclerodermia.

En el presente articulo presentamos la hipótesis original de que el tamoxifeno, por su propiedades fibrinolíticas, podría ser una terapia no inmunosupresora potencialmente útil para el tratamiento de la fibrosis sistémica nefrogénica, evitándose desde ya su uso en pacientes portadores de contraindicaciones para su uso.

PALABRAS CLAVE: Tamoxifeno. fibrosis sistémica nefrogénica

NEPHROGENIC SYTEMIC FIBROSIS

Nephrogenic systemic fibrosis is (NSF) a rare entity which develops in patients with renal failure undergoing dialysis, and its etiology is related to several factors such as the use of intravenous gadolinium, certain types of medication (erythropoietin, etc), previous vascular surgeries, hyperphosphatemia, liver disease, hypercoagulability and proinflammatories states.

Clinically, this pathology is characterized by firm plaques in the superior/inferior limbs, which harden and thicken, and could later extend to the trunk, and cause muscle contraction when the joints of such limbs are bended, thus resulting in a progressive reduction of joint mobility. The NSF usually begins in the limbs and then progresses to the trunk, and it can involve the subcutaneous tissue, as well as the muscular one. This disease can developed in a period of days or weeks, and even having a potential systemic compromise, with a fast and severe evolution in 5% of the cases (1-10).

Regarding gadolinium, it is believed that in patients with renal failure, gadolinium chelates would suffer a process of transmetilation, this process would lead to an increase of free gadolinium in the plasma, and to its precipitation in the dermis and other organs. The hypothesis that the deposit of these compounds would cause tissue injury and could attract circulating fibrocytes to the dermis. These fibrocytes could come from the bone marrow. Of all the variants of gadolinium, gadodiamide, has been the one most related to the development of such entity.

This sort of gadolinium has a lineal structure, which would enable the release of gadolinium in its tissue binding sites. Patients suffering from severe renal insufficiency (glomerular filtration rate lower than 30 mi/min/1,73 m_2) are in a greater danger of developing FSN due to an increase in gadolinium elimination time: from 1.3 hours in healthy people to 34.3 hours in severe chronic renal failure patients (11-19).

TAMOXIFEN

Tamoxifen is a selective modulator (competitive inhibition) of estrogen receptors (MSRE or SERMs) which has a simultaneous estrogenic and antiestrogenic effect on the various types of tissues. When estrogen binds to its receptor, it causes a series of molecular changes and molecular interaction which finally produce protein transcription, among which we can mention some that are essential to stimulate cellular multiplication, besides, it can inhibit the transcription of other proteins which negatively module the progression of the cellular cycle and mitotic division.

As far as tamoxifen is concerned, when it binds to its estrogen receptor, the complex tamoxifen-receptor binds to DNA, and this causes an agonist or antagonist message of estrogen according to the cellular type. So, for example, tamoxifen blocks the dominium activation activities of the receptor AF-2, thus, it will be an estrogen antagonist in all the cellular environments on genes which only need AF-2; nevertheless, in the environments where AF-1 is the dominant activator, tamoxifen will manifest its ability as a partial agonist. Due to its pharmacocynetic characteristics, this drug can be administered orally, reaching maximum serum concentrations 4-7 hours later.

It shows a strong binding to serum albumina (>99%), and it is extensively metabolized in the liver through the cytochrome P450. Its most important metabolite is N-desmetiltamoxifen, which has similar therapeutic properties to tamoxifene but half of its average life. Its metabolites are excreted mainly through faeces, and since it is not excreted through the kidney, it does not need adjustments of the doses in nephropathy.

The main clinical uses of tamoxifen based on its antiestrogen properties are: breast cancer, malign melanoma, mastalgia, etc.; while those based on antifibrotic properties are: retroperitoneal fibrosis, peritoneal sclerosis associated to peritoneal dialysis, desmoids tumors and in some cases of sclerodermia.

Its principal reported side effects are:

- **depression of the bone marrow**
- **appearance of venous thrombosis and/or pulmonary embolism**
- **stimulation of the endometrial hyperplasia and/or endometrial cancer. The possibility of having uterine cancer is higher in women older than 50 years old and with doses of 20-40 mg/day for more than 2 years.**
- **appearance of cataracts or retinopathies**
- **other: depression, cephalea, hypercalcemia, oedema, hot flashes, menstrual irregularities, vaginal flux, constipation, enzymatic mobilization in the liver and hypetriglyceridemia**

These side effects are the fundament of contraindication for its use as well as the types or monitoring which should be carried out during its use. It is not advisable to use it in combination with warfarin, or during pregnancy. Anafilactic reactions are extremely rare. Its main pharmacological interactions are of the inhibitor type of its metabolism (inhibitors of the anti-retroviral proteasa, cyclosporin, efavirenz, eritromicin, nevirapin, benzodiazepines, nifedipin, diltizem), as well as inhibitors of cytochrome P450: cyclofosfamide, isofosfamide, etoposide, paclitaxel and the alcaloids of the vinca.

Enzymatic inducers, such as carbamazepine, fenobarbital, rifampicine, etc reduce its average life.

PROPONED HYPOTHESIS:

In this article we present the original hypothesis that tamoxifen, due to its fibrinolitic properties could be a non immunosuppressant therapy, potentially useful for treating nephrogenic systemic fibrosis, but avoiding its use in patients who have contraindications to its use (prothrombotic status, etc), as well as implementing it by doing the corresponding controls: hemogram, lipidogram, oftalmological as well as gynecological evaluation. Of course, this hypothesis, as any one, must be scientifically confirmed before its clinical application.

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Even though, this hypothesis makes sense, there are already several conventional immunosuppressant drugs in use for treating FSN. Since tamoxifen also has immunosuppressant effect, if this medication would be useful for treating FSN, it would be difficult to identify which of its properties, anti fibrotic or immunosuppressant, would explain its effect. Regarding if tamoxifen could replace conventional immunosuppressant drugs for treating FSN, before that it might perform a clinical trial in this sense, something that seems to be impossible.

FSN is a new entity (first case in 1997), and there are currently just 200 cases described in the world. Its incidence seems to be going down due to kidney transplant practicing and better handling of acute renal failure. Since, there is no clear cause of FSN apart from gadolinium exposition, an adequate medical preventive behaviour could become this entity a historical one in the near future.

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Tamoxifen is authorized only for treating pre and post menopausal patients who suffer from breast carcinoma with positive receptors in Spain.

There are few cases in the literature regarding tamoxifen use in desmoid tumors, Peyronie disease, bone fibroses dysplasia, and retroperitoneal fibrosis, with scarce evidence for its use. Since this is just a hypothesis, it must take into account that it has to be

scientifically confirmed before its clinical use.

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