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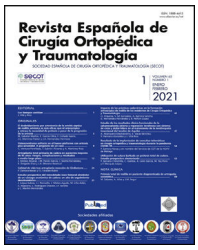

LETTER TO THE EDITOR

[Translated article] Colagenasa *Clostridium histolyticum* for Dupuytren's disease: A shooting star

Colagenasa *Clostridium histolyticum* para la enfermedad de Dupuytren: una estrella fugaz

Dear Editor:

The appearance on the market of collagenase clostridium histolyticum (CCH) in 2011 changed the perspective of treatment of Dupuytren's contracture (DC). The number of surgeons who preferred less aggressive treatment for this problem increased, and it was considered a common therapeutic alternative for DC until the end of 2019, when it suddenly ceased to be marketed in our country.

This decision carries several elements that should be noted and that affect us to a greater or lesser extent. In favour of the drug, and thus our consciences, it must be made clear that the decision was not due to medical problems such as side effects, toxicity, or carcinogenesis. On the contrary, the decision was made unilaterally from the US and purely for economic reasons. Although there has been no official statement, the main reason for all of this could be the price of the vial, which in the US is around $3250 and varies according to the country in Europe; the price in Spain being €725, resulting in much lower profits and part of the profits having to go to the distributor. The acquisition of Auxilium (Auxilium Pharmaceuticals Inc., Pennsylvania, USA) by Endo (Endo Pharmaceuticals Inc., Westbury, NY, USA) in January 2015 has probably led to a change in company policies. We saw in 2013 a first crisis in the marketing of CCH when Pfizer Europe (Pfizer Europe Inc., Surrey, UK) abandoned its project to establish CCH as almost the only treatment for DC through a very aggressive marketing and advertising policy. Therefore, an agreement was reached to establish the regulated use of CCH by orthopaedic surgeons, preferably specialists in hand surgery and with adequate training in administering the treatment.

I have been asked from various quarters whether another company or another pharmaceutical form would be available for collagenase treatment of DC. The chances are very slim for several reasons. Primarily, clinical studies in humans are for a patented and purified form of CCH, known as AUX-I and AUX-II (data sheet). Although the industrial and medical uses of CCH have been known for years, the application of other pharmaceutical forms is not possible as it is a biological product. It should be noted that the term collagenase refers only to the name of the effect of an enzyme (collagen degradation) and that the chemical composition of the collagenase produced may not be the same, like the specificity of Xiapex© (Endo Pharmaceuticals Inc., Westbury, NY, USA), for collagens I and III as substrates.

Secondly, but possibly more importantly, is the economic reason. The significant price difference is a major handicap and reintroduction in Europe at a higher price does not seem to have been welcomed by buyers, which include governments. The disease profile does not help either, as it is not a drug intended for a highly prevalent, fatal disease, or one with major social impact.

Thirdly, we must highlight the unilateral nature of the decision. SOBI (Swedish Orphan Biovitrum AB, Stockholm, Sweden) indicated that the decision was made solely and exclusively by Endo Pharmaceuticals, without negotiation or prior notice. This attitude seems unlikely to result in a change of perspective or reconsideration of the decision. From our perspective, we agree with the urologists[1] in questioning the extent to which the decision to withdraw the drug is ethical from a medical point of view.

Fourthly, the planned long-term assessment in Spain (SPAINCOL study) and abroad will not take place or will be ignored to an extent in the literature, as it comes from centres where CCH will no longer be elective treatment. This can result in conjecture without objective data, to the point of unofficially suggesting that the recurrence rate published in these studies would go against the use of CCH as we know it today, i.e., the long-term recurrence rate is much higher than expected.[2]

We are therefore again obliged to redefine our protocols for treating DC and are now faced with a situation where only in the USA is CCH treatment an alternative, while in Europe the minimally invasive treatment option will be needle aponeurotomy or fasciotomy. Withdrawal of the treatment has been global; having said only in the US, it has also been discontinued in Australia and New Zealand as indicated in a statement from Actelion (Actelion Pharmaceuticals Ltd, Allshwill, Switzerland), the Xiapex© distributor in those countries. This will make it difficult to reach a

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consensus, such as the recent unification of criteria on the definition of recurrence, affecting the validity of results as it will not be possible to compare them outside the USA, and could even prevent meta-analyses due to biases such as geographical dispersion.

In conclusion, John T. Hueston's quote paraphrasing Martin Luther King[3] ''I have a dream, that Dupuytren's contracture will be treated with no surgical procedures...'' will have to wait either for the end of the CCH patent in the USA and marketing by another pharmaceutical company, or for the appearance of a new treatment. However, in a disease in which changes in treatment have been so slow and hardly revolutionary over the last 100 years, this is going to be really complicated, if not utopian.

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Conflict of interests

The author has no conflict of interest to declare.

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