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Dupuytren and Collagenase: Are they really as Simple as they Seem?

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1. EDITORIAL

In the treatment of Dupuytren's disease (DD), the use of Collagenase Clostridium Histolyticum (CCH) represents a new therapeutic alternative for this condition which currently has no definitive cure. Since the publication of the study by Hurst et al. [1] in which the immediate clinical results were very positive, several studies have validated the efficacy of CCH using different drug administration protocols with the same safety values [2-5]. Clinical results appear promising, with recurrence rates similar to those after surgery [6]. The cost-effectiveness ratio is favorable, compared to fasciectomy [7], and outpatient treatment improves the quality of healthcare for both orthopedic surgeons and for patients [8]. Functional recovery frequently takes place immediately, and evolution is generally more favorable.

However, some authors [9] find the rate of adverse events associated with CCH alarming. Although adverse events affect more than 85% of patients, most complications are minor, transient and mild [10]. Major and severe complications occur much less frequently than with other types of treatment, such as fasciectomy or dermofasciectomy.

There is little available material published on the mechanism of action and the adverse events associated with CCH. The CCH administered for DC consists of two isoforms: AUX I and AUX II, obtained from the purification of Clostridium Histolyticum toxins. CCH anchors in fibrillar collagen, especially types I and III, causing degradation and digestion. This leads to a chemical digestion of the DC cord [11]. Undoubtedly, the adverse events reported are related to treatment administration and the mechanism of action. But, what exactly is the mechanism of action? In a short communication, De Carlo [12] proposes that the inflammatory effects are a consequence of CCH administration. Likewise, studies performed in the 80s using Nucleolisyn© [13] with the use of CCH for the treatment of herniated disks and Peyronie's disease [14] also confirmed this process through an increase in vascular permeability and a healing response of the wound with inflammatory phenomena. The appearance of CCH adverse events is based on the facts that: A) CCH is a protein with bacterial and exogenous origin that activates the immunological mechanisms in the organism; and B) the degradation of collagen causes a response similar to the healing of any other wound. The latter process is the basis for much current investigation: collagen degradation activating the mediators for complete digestion [15] (endogenous metalloproteinases (MMP)). In turn, these MMP are regulated by certain inhibitors (α2-macroglobulin [16] and TIMPs [15]). This entire ensemble relates to molecules which, since they act on the extracellular matrix, may be considered paracrine factors (interleukins [17], IGF2 [18], etc.) under these circumstances. There is also interaction with molecules related to the cell surface (MT-MMPs or matrix metalloproteins) or the degradation of the rest of the extracellular matrix (ADAMTs acting as aggrecanases, for example [19]). The interrelations among these processes are very complex and variable, depending on the particular phase of Dupuytren's disease (cellular or nodular phases vs. acellular or fibrotic phases). Proof thereof is the fact that the research methods here under discussion have been applied to studies on the physiopathology Dupuytren's disease [20-23], the healing process of wounds [24-26], pathologic fibrosis [27-29], or cancer [30,31]. It should be noted that the processes involved are active both physiologically and pathologically. Indeed, the current situation regarding DC seems a bit chaotic. Apart from these areas of research into the processes within the cell [32] and those mentioned above that occur inside the extracellular matrix, there are other very different lines of investigation awaiting study: the

relationship of paracrine factors with regard to myofibroblasts, the relationship between myofibroblasts and the extracellular matrix [33], self-regulation of the extracellular matrix, distant factors or relationships such as the connection between DC and adhesive capsulitis [34], and others. Unifying all the various research lines is a complicated process, since professionals approaching the subject from the standpoint of so many different specialties frequently have little contact with each other (clinicians, pathologists, biochemists, orthopedic surgeons,...), and assessing results in clinical terms is difficult and leads to enormous uncertainties of opinion within the community of orthopedic surgeons For example, there is no universal agreement as to the definition of DC recurrence [35]. Recent advances, such as the possibility of sustaining pathological DC tissue in live rats [36] may help to establish models for carrying out more uniform research. These multiple investigative lines are encouraging, and the advances are promising.

To conclude, much more research into the pharmacological aspects of CCH needs to be carried out, both regarding its positive side (the possibility of reapplication in patients after satisfactory initial treatment) and its negative side (analysis of adverse events and options to reduce them). In this regard the knowledge of the mechanism of action of the CCH is essential to development and approach to clinical trials. Knowing these mechanisms could help determine which developments after CCH administration are not complications, but rather processes intrinsic to the administration of CCH, as it has been similarly established for the surgical wounds in fasciectomy or for fat removal through liposuction in percutaneous aponeurotomy and lipofilling (PALF) [37].

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