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LETTER TO THE EDITOR

What were the adverse events for Dupuytren's patients treated with Xiaflex who had contractures less than 20°?

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Dear Sir:
I read with interest the online first article "Nonsurgical treatment of Dupuytren's contracture: 1-year US post-marketing safety data for collagenase clostridium histolyticum" that reports the 270 adverse incidents voluntarily reported to the FDA during the first 12 months that the drug had been used after approval in the USA [3].

I believe that transcript of the FDA's Arthritis Advisory Committee's September 16, 2009 meeting underscores the importance of my question for the authors. All of my page references are to the transcript pages for that hearing [2].

Auxilium's senior vice-president of quality and regulatory affairs clearly stated (pp. 21–2):

> "The proposed indication is the treatment of advanced Dupuytren's disease, and that can be defined as a progressive disease resulting in a fixed flexion deformity or a contracture in one of several joints, most commonly the last two digits of the hand."

Auxilium's chief medical officer presented data to support the proposed indication. He said (pp. 40–1):

> "The three double-blind placebo-controlled trials were all identically designed …The key inclusion criteria, these were adults at least 18 years of age who were affected with Dupuytren's disease and a palpable cord, *causing a contracture of at least 20 degrees*." (emphasis mine)

He stated that the objective measurement of "clinical success was reduction of the joint contracture from at least 20 degrees (the inclusion criterion) to no more than 5 degrees" (pp. 42–3):

> "Now, the primary endpoint, the primary outcome of all of the studies, was the proportion of subjects who achieved that correction to within zero to 5 degrees after their last injection, and this was defined as 'clinical success' in the protocol."

The severity of Dupuytren's contracture is extremely important. Most of us are familiar with and use Hueston's Table Top test to counsel patients who arrive with nodules and cords [1]. Even Auxilium's own presenter stated (p. 31):

> But we reserve treatment of the contracture until the contracture is bad enough, because there's limitations with all of our treatments. A quick test is when a patient can't get their hand flat on a table anymore, we typically think that their contracture has advanced to the point that intervention is warranted.

Agreeing with the Auxilium speaker was William Swartz MD, a member of the FDA's Arthritis Advisory Committee. He noted that most of his patients with Dupuytren's disease do not develop contractures that required any treatment (pp. 104–5).

> "Most patients who come to my office with this condition have it in a mild form. They may have a nodule that may or may not be painful. They may have an early contracture. And our advice to these patients is that we don't know if it's going to be progressive or not. And so observation, as has been mentioned earlier, is the most often the first encounter and the first advice to these patients, and they come back when it's more significant.

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Swartz was concerned about the possible off-label use of Xiaflex for milder cases (pp. 105–6):

> But with this medication, I can envision that our inclination is going to be to recommend that we treat them without knowing that in fact, they will have a progressive condition, and treat them before the contracture of the MP joint is more than 30 degrees or the PIP joint more than 20 degrees. So my question to the FDA panel as well as to the Auxilium people is would this be considered an off-label treatment, and is this going to be—and I guess, a better question, will there be a long-term focus and study of these patients to see if in fact, it does prevent progressive disease? That's my first question."

It appears that Dr. Swartz's concern about "off-label" use of Xiaflex has happened, but not for the reason that he expected. Despite the fact that by a unanimous vote of 12 to 0 the Committee recommended (p. 244):

> "Approval of Auxilium's clostridial collagenase for the treatment of patients with *advanced Dupuytren's disease*" (emphasis mine).

Xiaflex's "Current Indication and Usage" states:

> "XIAFLEX is indicated for the treatment of adult patients with Dupuytren's contracture with a palpable cord."

In other words, Xiaflex is indicated for any degree of contracture no matter how mild it may be despite the absence of any data on its safety and efficacy for contractures less than 20°.

My question for the authors is:

> Since none of the published prospective trials included patients with contractures less than 20°, what were the adverse events for patients with contractures less than 20° in your study?

References

1. Hueston JT. The table top test. The Hand. 1982;14:100–3.
2. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisDrugsAdvisoryCommittee/UCM186962.pdf Accessed 16 Apr 2012.
3. Peimer CA, McGoldrick CA, Fiore GJ. Nonsurgical treatment of Dupuytren's contracture: 1-year US post-marketing safety data for collagenase clostridium histolyticum. Hand. 2012;7(2):143–6. doi:10.1007/s11552-012-9407-3.