

Editorial

Lipoxygenase inhibition in osteoarthritis: a potential symptomatic and disease modifying effect?

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See related research article by Sengupta *et al.*, <http://arthritis-research.com/content/10/4/R85>

Abstract

5-Loxin[®] is a compound extracted from an ancient herb that might be considered as a potent lipoxygenase inhibitor. The results observed in a preliminary trial suggest a highly intriguing clinically relevant symptomatic effect contrasting with a poor bioavailability of this compound. Moreover, in this trial, a statistically significant decrease in matrix metalloproteinase enzyme serum level suggests that, in addition to the observed symptomatic effect, such a compound might have a disease modifying effect in osteoarthritis. Further studies are required both to confirm the symptomatic efficacy and acceptable safety profile and to evaluate the potential chondromodulating effect of this compound.

In the previous issue of *Arthritis Research & Therapy*, Sengupta and colleagues [1] report the results of a short-term placebo randomized controlled trial evaluating both the symptomatic and biological effects of the compound 5-Loxin[®], which is a gum resin extracted from an ancient herb. Despite the small sample size (25 patients per arm) and the short duration of this trial (3 months), the reported results are interesting and intriguing for several reasons.

In the field of rheumatology, most new therapeutic compounds are based on our knowledge of the pathophysiological pathways of the disease (for example, targeted therapies against cytokines such as tumor necrosis factor (TNF), interleukin-6, and so on) or against some specific enzyme (for example, cyclooxygenases). The compound evaluated in the trial reported by Sengupta and colleagues [1] is in fact derived from an ancient herb, *Boswellia*. Because of the empirically observed anti-arthritic and analgesic effects of this compound, researchers have tried to understand its mechanism of action. *In vitro* data suggest that 5-Loxin[®] might be considered as a potent lipoxygenase inhibitor but also, at a lower magnitude, an inhibitor of the TNF α -induced gene expression of matrix metalloproteinases. Such *in vitro*

findings have to be kept in mind when interpreting the results of the trial. In particular, should we consider that the observed symptomatic treatment effect is related to the lipoxygenase inhibition, to the anti-TNF α inhibition, to both, or to an as yet unknown mechanism?

This trial has been conducted in India. The researchers have to be congratulated because of the high quality of both the design, the conduct, the analysis and the reporting of the trial.

The observed symptomatic placebo effect is of a similar magnitude as those observed in previous placebo randomized controlled trials in this condition [2,3]. The observed symptomatic effect (for example, the differences in the changes in the active minus the placebo groups) seems to be not only statistically relevant but also highly clinically relevant. In osteoarthritis, a symptomatic treatment effect of a least 10 on a scale of 0 to 100 is usually considered as clinically relevant [4]. In this reported trial, a treatment effect of 26 (for the VAS [Visual Analogue Scale] score), 18 (for the WOMAC [Western Ontario and MacMaster universities osteoarthritis questionnaire] pain subscale) and 15 (for the WOMAC function sub-scale) were observed in the group of patients taking the compound at a 250 mg daily dose when compared to placebo. Moreover, a trend in favor of a dose ranging effect (when comparing placebo, 5-Loxin[®] 100 mg and 5-Loxin[®] 250 mg) supports the relevance of these results. These results are intriguing since the oral bioavailability of the active ingredient of 5-Loxin[®] is very low [5]. Such findings concerning the symptomatic effect of this compound have now to be confirmed in larger trials conducted in different parts of the world.

More intriguing are the results observed for some biological markers, especially matrix metalloproteinase-3 serum levels.

TNF = tumor necrosis factor.

Such findings raise the question of whether we should consider this compound as an alternative to the currently available symptomatic drugs (for example, analgesics, cyclooxygenase inhibitors, and so on) because of potentially better efficacy and safety profiles, or whether we have to consider that, in addition to its symptomatic effect, such a compound might have an osteoarthritic disease modifying effect. The demonstration of a disease modifying effect requires long-term studies with hard end-points, such as the capacity to reduce the requirement for total articular replacement, to reduce cartilage loss, and so on. In this study, the researchers have evaluated an interesting surrogate biomarker in this area, for example, the level of matrix metalloproteinase-3, which is deeply involved in the degradation of cartilage [6].

In conclusion, because of obvious unmet needs in the treatment of osteoarthritis and because we have yet to develop an efficient and safe targeted therapy, the reported results observed with this new compound are very promising, although they need to be confirmed in other studies evaluating not only its symptomatic effect but also its potential chondromodulating effect.

Competing interests

The author declares that they have no competing interests.

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