Doxycycline and osteoarthritis: what does it show us?

Original article Brandt KD *et al.* (2005) Effects of doxycycline on progression of osteoarthritis. Results of a randomized, placebo-controlled, double-blind trial. *Arthritis Rheum* **52:** 2015–2025

SYNOPSIS

KEYWORDS doxycycline, joint-space narrowing, osteoarthritis

BACKGROUND

Previous laboratory studies have suggested that the tetracycline antibiotic doxycycline can be effective in slowing the progression of osteoarthritis (OA) of the knee.

OBJECTIVE

The objective of this trial was to determine whether or not doxycycline can reduce disease progression in patients with OA as determined by radiography.

DESIGN AND INTERVENTION

This randomized, double-blind, placebo-controlled trial included obese women aged between 45 and 64 years with unilateral knee OA diagnosed by radiography. Patients with secondary knee OA, inflammatory arthritis or a history of tetracycline allergy were excluded from this trial. Following a 30-day run-in period of placebo treatment, participating patients were randomized to receive either doxycycline or placebo over 30 months. Radiographic examinations of tibiofemoral joint-space narrowing (JSN) were performed at baseline, 16 months and at the end of the trial. Joint pain was assessed at 6-month intervals throughout the study.

OUTCOME MEASURES

The primary outcome measure in this study was the rate of JSN in the medial tibiofemoral compartment of the knee. Changes in knee pain and function were used as secondary outcome measures.

RESULTS

A total of 431 patients were deemed eligible for this trial after successfully completing the run-in period and were subsequently randomized to receive 100 mg doxycycline ($n=218$) or placebo ($n=213$) twice daily. A total of 307 patients completed the study, 149 from the doxycycline group and 158 from the placebo group. At baseline, there were no significant differences in BMI, radiographic severity, minimum JSN, pain and functional impairment in the knee and previous treatment for OA between groups. Assessment of the index knee showed significant difference between the two treatment groups with respect to overall rate of JSN ($P=0.009$), baseline joint-space width (JSW; $P<0.001$) and baseline pain ($P<0.0001$). At 16 months, the mean ± SD loss of JSW in patients in the doxycycline group was 0.15 ± 0.42 mm, compared with 0.24 ± 0.54 mm in the patients receiving placebo (adjusted $P=0.027$). At the end of the trial, the mean ± SD loss of JSW was 33% less in the doxycycline group, compared with the placebo group of patients. Analysis of data on the contralateral knee showed that both at 16 months and at the end of the study, loss of JSW was similar to that observed in the index knee. Reports of a mean increase in pain greater than 20% in the index knee at follow-up (as measured on the WOMAC pain scale) were fewer in the patients receiving doxycycline. No significant effect of doxycycline was observed in JSN or pain of the contralateral knee.

CONCLUSION

The authors conclude that doxycycline is effective in reducing the rate of JSN in patients with established knee OA, but does not reduce JSN or pain in the contralateral knee.

COMMENTARY

Tim D Spector

The article by Brandt and colleagues details the long-awaited findings of a placebo-controlled study of doxycycline in obese women with moderate knee OA. A small (33%), but significant, beneficial change in JSN was found in the index, more severely affected, knee and trends towards symptomatic differences were also observed. No effects of doxycycline were found in the mildly affected contralateral knee, however, which was one of the primary outcome measures. Also, the mode of action of doxycycline is still unclear and might involve cartilage, bone, or both.

This study is important for several reasons. Firstly, this is a proof-of-concept study that shows that a drug can reduce cartilage changes in the knee in less than 3 years. Studies of glucosamine have inconsistently reported similar effects, but have not been widely accepted for reasons of methodology and biology, and a study of diacerhein showed a smaller effect on the hip; treatment reduced JSN but did not affect symptoms.[1]

Secondly, the authors illustrate how difficult it is to perform such studies effectively. This study took almost 15 years, from planning to publication, using 'state-of-the-art' X-ray techniques which now look outdated. The study coincided with the lack of success of the large and expensive risedronate OA program, which might have been partly explained by the sensitivity of the X-ray methods and lack of progressors;[2] it is likely that this will be one of the last large X-ray therapeutic studies performed. Meanwhile, the FDA and the European Medicines Agency (EMEA) have yet to decide on rules for a therapeutic alternative using MRI and the field is left in limbo.

Thirdly, it is difficult to correlate improvements in JSW with symptoms. Until recently there was little supporting natural-history data, although larger studies are now rectifying this.[3] Any lack of correlation might be caused by lack of efficacy or X-ray sensitivity,[4] but is more likely to be because of case selection. Patients with early-stage disease have sufficient cartilage and measurable, but only mild or intermittent, symptoms; end-stage patients might have little or no cartilage and constant pain. Future trials might have to be performed on both ends of the clinical spectrum unless MRI allows greater sensitivity to bone and cartilage changes.

Finally, having demonstrated that these drugs can retard joint damage, the following question needs to be addressed: is there a need for new drugs and would patients adhere to new treatment? Although a few patients adhere to treatment with long-term antibiotics, most patients and their doctors would feel uneasy about doxycycline, even if patients coped with the gastrointestinal symptoms, unless they had inoperable disease and severe pain. It has been argued that this 'successful' trial might lead to further futile efforts to develop drugs for a condition that can be easily treated with sticking plaster, osteotomies and joint replacement.[5] The millions of patients who take long-term daily glucosamine or chondroitin without symptomatic relief, in the hope that it will eventually help, suggest that there is a real demand for disease-modifying drugs and this nihilistic future view of pharmaceuticals for OA is not shared by most. This author would rather take a hypothetical safe drug for years, such as a monthly bisphosphonate, than take any chances with the surgeon's knife. Further drug studies in OA are, therefore, eagerly anticipated.

References

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Competing interests
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PRACTICE POINT
Doxycycline could be effective in reducing disease progression in established osteoarthritis of the index knee; however, further trials are needed establish its use in common practice