da Costa BR, Nuesch E, et al. Doxycycline for osteoarthritis of the knee or hip. Cochrane Database Syst Rev. 2012 Issue 11. Article #:CD007323.

Design: meta-analysis of randomized clinical trials.

Study question: In the setting of hip or knee osteoarthritis (OA), is oral doxycycline an effective intervention to improve function, relieve pain, or slow the rate of joint space narrowing compared to placebo?

PICOS:

- Patients: Adults with OA of the hip of knee confirmed clinically or radiologically or both
- Interventions: Doxycycline at any dosage or in any formulation
- Comparison: Placebo or no intervention
- Outcomes: Primarily pain and function; joint space narrowing and the occurrence of adverse events were secondary outcomes; outcomes included:
    - Global pain
    - Pain on walking
    - Disability or pain scores on WOMAC or similar instruments
    - Lequesne OA index global score
- Study types: Randomized or quasi-randomized trials with a control group having placebo or no intervention

Study selection:

- Databases included the Cochrane Central Register, MEDLINE, EMBASE, and CINAHL through July 2008, with manual searches of conference proceedings, reference lists of studies, and several trial registries
- Two authors independently evaluated abstracts and titles for eligibility and extracted trial information on a standardized form, assessing the risk of bias on the basis of allocation concealment, blinding, intention-to-treat analysis, and selective outcome reporting
- Continuous outcomes such as for pain and function were analyzed in terms of standard deviation units, following the conventional interpretation of such units in which 0.2 SD differences between treatments is a small effect, 0.5 SD is a moderate effect size, and 0.8 SD is a large difference

Results:

- 288 potentially relevant articles were identified, but only 12 reports describing only 2 randomized trials (633 patients) were included in the meta-analysis

    - No ongoing trials were found in trial registries and no further trials were found in conference proceedings
    - Both trials were considered of moderate quality, with both trials lacking intention-to-treat analysis and one with unclear allocation concealment
- Both RCTs administered doxycycline at a dose of 100 mg twice daily; one trial lasted for 30 months and the other lasted for 24 weeks
- Pooling of data from both trials suggested that there is no difference between doxycycline and placebo for pain relief or function
    - The pooled effect size was 0.05 SD (95% confidence interval from 0.22 SD in favor of doxycycline to 0.13 SD in favor of placebo), which corresponds to a difference on a 10 point VAS pain scale of 0.1 points
    - WOMAC function from pooling outcome data from both trials was also nearly nonexistent, with an effect size of 0.07 SD (95% CI from 0.25 SD in favor of doxycycline to 0.10 points in favor of placebo), corresponding to a difference of 0.2 points on a 10 point disability scale
- The difference between doxycycline and placebo on joint space narrowing was small (0.23 SD in favor of doxycycline)
- Safety data showed that patients randomized to doxycycline were more than twice as likely to withdraw from a study because of adverse effects, even though no serious adverse events were deemed to be attributable to doxycycline
- One of the trials may have been susceptible to bias due to selective outcome reporting; the primary outcome in the registered trial protocol was joint space narrowing in the contralateral knee, but the published trial reported on reduced joint space narrowing in the index knee with no effect of doxycycline in the contralateral knee, rendering the effect of doxycycline on radiologic progression of OA even more dubious

Authors' conclusions:

- The benefits in terms of pain and function of doxycycline in patients with OA of the knee is minimal to non-existent
- The small benefit in terms of joint space narrowing was of questionable clinical relevance
- Any biases which were present in the studies would be expected to act in favor of showing a therapeutic effect of doxycycline rather than of placebo
- It is unlikely that any relevant articles were missed, and no trials in the future are likely to change the estimate of a null effect of doxycycline

Comments:

- The studies were large enough to exclude any but the smallest benefits of doxycycline; the best case scenarios (top end of the 95% confidence intervals) had an effect size of 0.22 SD for pain and 0.25 SD for function
- The trial showing no effect on pain/function and minimal effect on joint space narrowing was done in 431 obese patients, where doxycycline would be expected to have the best chance of demonstrating a therapeutic effect

Assessment: High quality meta-analysis providing good evidence that oral doxycycline has no therapeutic effect on knee OA