Should tetracycline treatment be used more extensively for rheumatoid arthritis: metaanalysis demonstrates clinical benefit with reduction in disease activity

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CRD summary
This review compared the effect of tetracyclines versus placebo or conventional therapy for rheumatoid arthritis. The authors concluded that tetracyclines given for more than 3 months lead to a reduction in disease activity and acute phase reactants. The review was well-conducted, although apparent clinical differences were not considered in the analysis. Hence, the conclusion should be viewed with caution.

Authors' objectives
To compare the effectiveness of tetracycline antibiotics with placebo or conventional treatment for patients with active rheumatoid arthritis (RA) in the prevention or reduction of disease activity, as defined by the American College of Rheumatology.

Searching
MEDLINE (from 1966 to 2002), EMBASE (from 1980 to 2002), and the Cochrane Controlled Trials Register (Issue 1, 2002) were searched for potential studies. The search terms used were reported and no language restrictions were applied. Additional studies were sought in the reference lists of retrieved trials and presentations at scientific meetings. Only published reports were eligible for inclusion.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies that compared tetracycline antibiotics with placebo or conventional, disease-modifying antirheumatic therapy were eligible for inclusion. Tetracycline (250 mg/day), minocycline (100 to 200 mg/day) and doxycycline (50 mg twice daily to 200 mg/day) were evaluated in the included studies. The route of administration, duration of treatment and comparator group varied across the included studies. Further details were given in the report.

Participants included in the review
Studies of participants aged 16 years or older, who satisfied the 1987 modified American Rheumatism Association criteria for active RA, were eligible for inclusion. Active RA was defined by the presence of tender or swollen joints, morning stiffness, and increased acute phase reactants including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The average duration of disease ranged from 0.5 to 14 years.

Outcomes assessed in the review
Studies that reported on American College of Rheumatology disease activity measures for clinical trials of RA were eligible for inclusion. These included the following: tender joints (tender joint count), swollen joints (swollen joint count), patient perception of pain level, patient global assessment of disease activity, physician global assessment of disease activity, ESR, CRP, and radiographic change of bone and joint damage (erosions and joint space narrowing).

The secondary outcome measures were the adverse events profile and disability measured by the Health Assessment Questionnaire.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed the eligibility of the identified studies and resolved any disagreements by consensus.
Assessment of study quality
Each of the included studies was assigned a quality score based on: the adequacy of allocation concealment; blinding of the outcome assessor and patients for all outcomes; blinding of the patient and caregiver to the intervention; and follow-up data on at least 80% of the enrolled participants. The studies were considered high quality if all 4 criteria were met, medium if 3 were met, and poor if 2 or fewer were met. The authors also noted the use of intention-to-treat analysis. The authors did not state how the papers were assessed for quality, or how many reviewers performed the quality assessment.

Data extraction
Two reviewers extracted the data using a pre-designed form and resolved any differences by consensus with a third reviewer. The mean and standard deviation were extracted from each individual study to derive a weighted mean difference (WMD) or standardised mean difference (SMD), along with 95% confidence intervals (CIs), for outcomes that reported continuous data. Studies reporting only a median value were not included in the analysis. The occurrence of an event was extracted from each individual study and used to derive a relative risk (RR) or absolute risk reduction (ARR), along with 95% CIs, for outcomes that reported binary data. Data were extracted from each study using an intention-to-treat format where possible.

Methods of synthesis
How were the studies combined?
The results from the individual studies were combined using fixed- and random-effects meta-analysis. A pooled WMD, SMD, RR, or ARR with 95% CIs was calculated depending on the type of data available. A narrative summary was provided for those outcomes where the studies could not undergo statistical pooling.

How were differences between studies investigated?
Homogeneity was investigated using the chi-squared test with a significance level of P less than 0.1. Subgroup analyses were also performed. These excluded trials using an active comparator, those that used doxycycline, and those that included patients with an early onset of disease or who were exclusively seropositive.

Results of the review
Ten RCTs (n=535) were included in the review.

Disease activity.
Tetracycline was associated with a statistically significant reduction in tender joint count compared with the control; the SMD was -0.39 (95% CI: -0.74, 0.05, P=0.03) based on 494 patients in 7 RCTs (random-effects). However, there was evidence of significant statistical heterogeneity (chi-squared 17.74, d.f.=6, P=0.0069). The subgroup analysis of tetracycline compared with placebo trials did not alter the results, although the removal of trials evaluating doxycycline found a greater reduction in tender joint count.

Tetracycline was associated with a statistically significant improvement in swollen joint count compared with the control; the SMD was -0.23 (95% CI: -0.41, 0.05, P=0.01) based on 494 patients in 7 RCTs (random-effects). There was no evidence of significant statistical heterogeneity (chi-squared 5.99, d.f.=6, P=0.42). Subgroup analyses of tetracycline compared with placebo, and the exclusion of trials evaluating doxycycline, did not affect the results obtained.

Tetracycline was associated with a statistically significant improvement in ESR compared with the control; the WMD was -8.96 (95% CI: -14.51, 3.42, P=0.002) based on 494 patients in 7 RCTs (random-effects). There was no evidence of statistical heterogeneity (chi-squared 8.96, d.f.=6, P=0.18). The subgroup analysis of tetracycline compared with placebo trials did not alter the results, although the removal of trials using doxycycline found a greater reduction in
ESR.

The studies evaluating CRP were inconclusive. One RCT found no significant difference between tetracycline and the control, while one RCT found a significant difference.

There was no statistically significant improvement in the patient global assessment of disease activity in those given tetracycline compared with those given the control; the SMD was -0.15 (95% CI: -0.036, 0.5) based on 425 patients in 5 RCTs.

There was no statistically significant improvement in the physician global assessment of disease activity in patients given tetracycline compared with those given the control; the SMD was 0.00 (95% CI: -0.7, 0.7) based on 360 patients in 4 RCTs (random-effects). Subgroup analyses of tetracycline compared with placebo did not affect the results obtained.

Tetracycline was associated with a statistically significant reduction in self-reported pain levels compared with the control; the SMD was -0.68 (95% CI: -1.03, 0.33) based on 140 patients in 2 RCTs. However, a subgroup analysis of trials comparing tetracycline with placebo did not find a statistically significant reduction in self-reported pain.

Disease damage.

No statistically significant reduction in erosions was reported in patients given tetracycline compared with the control; the SMD was 0.17 (95% CI: -0.29, 0.64; P=0.5) based on 299 patients in 2 RCTs (random-effects). There was evidence of significant statistical heterogeneity (chi-squared 3.30, d.f.=1, P=0.069).

No statistically significant improvement in joint space narrowing was found in patients given tetracycline compared with those given the control; the SMD was 0.04 (95% CI: -0.19, 0.27).

Disability.

Tetracycline was associated with a significant improvement in the Health Assessment Questionnaire compared with the control; the SMD was -0.15 (95% CI: -0.28, 0.02) based on 394 patients in 4 RCTs. Subgroup analyses of tetracycline compared with placebo did not affect the results obtained.

Adverse events.

No statistically significant difference in the absolute risk of adverse events was found between patients given tetracycline compared with those given the control; the ARR was 0.10 (95% CI: -0.01, 0.21) based on 381 patients in 8 RCTs (random-effects). Subgroup analyses of tetracycline compared with placebo did not affect the results obtained.

Response to treatment.

The number of patients responding to treatment was significantly higher in the tetracycline group than in the control group; the RR was 1.78 (95% CI: 1.0, 3.16) based on 421 patients in 4 RCTs (random-effects). This remained significant after the exclusion of 2 RCTs of patients with early onset RA.

Authors’ conclusions

Tetracyclines, in particular minocycline, administered for more than 3 months lead to a clinically significant reduction in disease activity and acute phase reactants with no absolute increased risk of side-effects. The treatment effect was more pronounced in patients with short duration of disease (less than one year) who were also seropositive.

CRD commentary

The review addressed a clear question and the inclusion criteria appear to have been appropriate. The search to identify relevant trials was comprehensive and an attempt was made to limit language bias. However, unpublished studies were excluded from the review; the potential of publication bias cannot, therefore, be ruled out. Procedures to minimise bias...
in the study selection and data extraction processes were used. The quality of each of the included studies was assessed systematically and considered in the discussion of the results.

Details of the patients' demographics and clinical characteristics were given in the report, although the results of individual outcomes of individual studies were restricted to those pooled and depicted in forest plots. No results were reported for those studies not included in the statistical pooling. In addition, although the authors used a random-effects model, the decision to pool might not have been clinically appropriate given the different types of tetracycline used, variation in the duration of treatment, and different patient characteristics. Consequently, the clinical and statistical heterogeneity across the individual studies mean that the authors' conclusions should be viewed with caution. Furthermore, there was insufficient evidence to support the conclusion that the treatment effect was more pronounced in patients with a short duration of disease.

**Implications of the review for practice and research**

**Practice:** The authors stated that tetracyclines have a potentially important role in the treatment of RA.

**Research:** The authors stated that studies are needed to compare the efficacy, safety and cost-effectiveness of tetracyclines with newer, disease-modifying antirheumatic drugs. In particular, an RCT should be performed to evaluate potential additive or multiplicative effects associated with the use of tetracyclines in combination with disease-modifying antirheumatic drugs.

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