Evidence Based Medicine in Dermatology: Minocycline and Acne: from Clinical to Literature Review

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ABSTRACT
Minocycline is one of the tetracyclines frequently used in the treatment of acne. There is a lack of consensus over the relative risk and benefits of minocycline in the treatment of acne. Starting from a clinical scenario, a literature search was initiated for the best available evidence on this subject. A Cochrane systemic review located 27 randomized controlled trials on the efficacy and risk of minocycline in treating mild to moderate acne. The trials were generally of insufficient size and quality to meet requirements of the systemic review. Although minocycline is an effective treatment for mild to moderate acne vulgaris, there was no reliable randomized controlled trial evidence to justify its continued first line use, given the price and concerns about safety that still remains.

Keywords: *Acne, minocycline, randomized controlled trials*

INTRODUCTION

Minocycline is one of the tetracycline antibiotics frequently used in the treatment of acne vulgaris. It can be taken in a more convenient once or twice daily dose compared with the generally more frequent dosing of other tetracyclines, but it is more expensive. There have also been concern about the safety of minocycline following case reports of death after taking the drug.[1] As there is a lack of consensus among dermatologists on the relative risk and benefits of minocycline in treating acne, a review on this subject should be based on the best available evidence. The material presented in this article was based on journal presentation of articles by author in April 2001, including Cochrane Systemic Review on this subject.[2]

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Steps in practicing Evidence Based Medicine

Evidence based medical practice can be divided into the following phases:[3]

1. To ask the clinical question in a format that can be answered. This identifies gaps or area of deficiencies in clinical knowledge that further search of evidence is required.
2. Search for the best external evidence.
3. Critically appraise evidence for the validity and importance.
4. Apply the evidence into clinical practice.
5. Evaluate self-performance in the practice of evidence based medicine.

In this review article, we shall concentrate on the first three steps in evidence based medical practice.

CLINICAL SCENARIO

A 20-year-old university student had mild acne for several years, requiring no therapy or intermittent 2.5% benzoyl peroxide aqueous obtained over the counter.

Two months ago he experienced a flare up of acne while preparing for his final examination. He visited a general practitioner who prescribed minocycline 100 mg daily and referred him to the dermatology clinic. Now his acne has improved, but he wishes to know whether to continue with minocycline for his acne?

ASKING AN ANSWERABLE CLINICAL QUESTION

The questions that may arise from daily clinical practice can be divided broadly into the following areas:[4]

1. Clinical findings
2. Aetiology
3. Differential diagnosis
4. Diagnostic tests
5. Prognosis
6. Therapy, harm and cost
7. Prevention
8. Self improvement

From the clinical scenario above, the clinical problem and question is obviously about therapy, harm and cost. The patient had received two months of minocycline already. Now he wishes to know whether to continue with oral minocycline for full six months or to substitute with an alternative, such as another oral tetracycline or topical antibiotic therapy, after taking into consideration the relative efficacy, side effects, and cost of the therapies.

Elements of the clinical question

The components of a clinical question on therapy can be divided into the following areas:[4] (1) The patient is a male student with mild acne who had recent flare up. (2) The intervention being investigated is acne therapy with oral minocycline. (3) Comparative intervention will, for example, be other oral tetracyclines, or topical antibiotics such as clindamycin. (4) The outcome measures will be improvement in acne, with objective and subjective scores as assessed by the physician and the patient himself, as well as quality of life scores. In addition, the safety and tolerability of minocycline is also assessed.

SEARCH FOR THE BEST EXTERNAL EVIDENCE

The types of evidence available can be broadly classified into the following areas:

1. Systemic review of well designed studies, including meta-analysis
2. Well designed studies – randomized controlled trials, cohort studies, case control studies
3. Results of large case series
4. Expert opinion

Evidence resource

External evidence from the literature may come from a variety of sources.

Hand searched review articles from recent or current issues of major dermatology journals, such as the Archives of Dermatology, Journal of American Academy of Dermatology, British Journal of Dermatology, and International Journal of Dermatology. Although these may provide useful information of topical interest, they do not necessarily cover the intended search topic unless by chance.

Standard textbooks generally provide comprehensive coverage on a wide range of topics, unfortunately the information they contained become rapidly outdated after publication.

Electronic databases such as the Medline allow rapid search over many journals indexed by the US National Library of Medicine in the Index Medicus. Other electronic databases available on CD-ROM or on the internet world wide web include Cochrane Systemic Review of Randomized Controlled Trials, Journal of Evidence Based Medicine, and American College of Physician Journal Club.

Even with librarian or experienced searchers of electronic databases, a Medline search does not always locate all the relevant articles indexed. The sensitivity of search unfortunately decreases further with lack in search experience.

A search of the Medline using the keywords acne and minocycline therapy yielded over 200 published articles, mostly uncontrolled trials or case reports. To narrow down the search to randomized controlled trials only, Medline search yielded two articles. One article was a systemic review of randomized controlled trials on minocycline for acne vulgaris: efficacy and safety (Cochrane Review) published by Cochrane Skin Group in Cochrane library.[2] The abstract was available on the following web address: http://www.update-software.com/default.htm. The second article was a randomized controlled trial comparing doxycycline with minocycline in the treatment of acne vulgaris.[5] It was one of the studies included by Cochrane Systemic Review mentioned above for analysis.

Cochrane Collaborative Review Groups consist of a panel of international experts initiated and coordinated by health care epidemiologists at Oxford University UK, to perform systemic reviews of randomized controlled trials in a specific field. There were 50 different groups starting alphabetically from acute respiratory infections to wound care. Cochrane Skin Group (Group 46) was responsible for systemic reviews in dermatology.

CRITICAL APPRAISAL OF EVIDENCE FOR VALIDITY AND IMPORTANCE

The criteria used to assess the validity of a systemic review are listed in Table 1.[6]

The objectives of the Cochrane systemic review on minocycline for acne vulgaris: efficacy and safety, were to collate and evaluate evidence on the clinical efficacy of minocycline in the treatment of inflammatory acne vulgaris. It also compared the efficacy of minocycline with other drug treatments for acne and estimated the incidence of adverse drug reactions.

Table 1. Assessing the validity of systemic overview

1.	Did the overview address a focused question? (What is the objective?)
2.	Were the criteria used to select articles for inclusion appropriate?
3.	Is it unlikely that important relevant studies were missed?
4.	Were the methodology and validity of included studies appraised?
5.	Were the results similar from study to study?

The studies included in the systemic review were randomized controlled trials, assessing the efficacy of minocycline at any dose in comparison with control, which may be a placebo or another active acne treatment. The participants should have inflammatory acne vulgaris on face and/or upper trunk, which may be papulopustular, polymorphic or nodular acne. The outcome measures evaluate clinical efficacy and patient acceptability in a defined way (for example, lesion counts, acne severity scores, physician's global evaluation and patients' self-assessment).

Trials were not excluded on the basis of language. Non-English studies were translated to English if it was not apparent from their original language whether they were randomized control trials or not. The resources and databases on which the studies were located include MEDLINE, EMBASE, Biosis, Biological Abstracts, International pharmaceutical abstracts, Cochrane Skin Groups Trial Register, Thesis Online, BIDS ISI Science Citation Index, BIDS Index to Scientific and Technical proceedings. Other methods to ensure that important studies were not missed included scanning references of articles already retrieved, hand searching of major dermatology journals; last but not least personal communication with trialist and drug companies on unpublished data to reduce publication bias.

Description of studies

There were a total of 72 studies of minocycline in acne, 32 studies were randomized control trials, two studies were duplicate, two were interim report, and one study compared minocycline with streptokinase versus placebo. Therefore only 27 studies met the primary inclusion criteria, with 3031 subjects in total, and sample sizes varying from 18 to 325 subjects (median 85).

Methodological quality of studies

Two reviewers independently assessed each study to see if it met the inclusion criteria for review. The methodology and validity of included studies were appraised according to assessment criteria listed in Tables 2 and 3.[7,8] The methodological components concern overall trial design and execution.[7] The substantive components are specific to the topic under discussion.[8]

Table 2. Appraisal of included studies-methodological components

1. Adequate sample size enrolled
2. Correct randomization protocol, allocation concealed
3. Baseline comparability of groups
4. Withdrawals (number and reason) clearly stated; all patients enrolled in the trial accounted for
5. Appropriate method of analysis (for example, Intention to Treat analysis)

Table 3. Appraisal of included studies-substantive components

1. Adequate study duration
2. Explicit and appropriate inclusion/exclusion criteria
3. Concomitant medication prohibited, monitor patient compliance
4. Standardize skin hygiene routine, control for ultraviolet light exposure
5. Uniform site of evaluation
6. Number and timing of assessments standardized
7. Evaluation of inter-assessor variability

The main theme was heterogeneity among the 27 trials, with variety and differences rather than consensus and standardization. Fourteen studies were conducted in more than one center (Dermatology clinics, Air Force, college and university volunteers, and general practice). Only two studies performed power calculation to estimate sample size of trial. Twenty of 27 trials were of insufficient size to detect any real difference between treatments if one existed. Only five trials mentioned how the randomization procedure was carried out. Eleven studies were not blinded, these were not excluded but analyzed in consideration of bias associated with open trials. The duration of trials varied from five to 24 weeks, the majority of trials (14/27) were for 12 weeks only.

Entry (inclusion) criteria were reported in all trials, but were not standardized across trials. Eight trials specified whether mild, moderate, severe and nodular acne were included, six trials had no statement of disease status as an entry criterion, and one trial simply stated acne that merited antibiotic therapy. Exclusion criteria were mentioned in all but five trials. These included hypersensitivity, pregnancy, and lactation.

The washout period of previous acne treatments on entry to trials varied from 48 hours to four months. Five studies failed to mention stopping previous medications prior to entry into trial. Nine trials specifically disallowed concomitant therapy that might affect acne severity.

Most trials tried to show that different treatment groups were comparable at baseline. For example, age (16/26 trials), sex (15/23 trials), weight (6/26 trials), lesion count or scores (15/26 trials), duration of acne (5/26 trials), and acne grade or severity (11/26 trials).

In the 27 studies a total of 50 different outcome measures were used. Most trials used more than one outcome measure. Ten trials used some acne grade or overall severity score, 20 trials used some form of lesion count, 15 trials included separate counts for inflamed and non-inflamed lesions. Categorical outcome measures such as physicians global evaluation and patients global assessments were reported respectively in 10 trials. Three trials used visual analogue scale to obtain patients assessment, two trials used quality of life questionnaire, and one trial evaluated patient satisfaction.

It was unclear how withdrawals or patients who failed to attend one or more visits were dealt with. Few studies specified how many of the patients enrolled had been included in the final analysis. Most studies were analyzed on a per protocol basis, only 7/26 trials used intention to treat analysis, and three used both methods.

Twenty-six trials reported data on adverse events, side effects or tolerance. How unwanted effects were identified were often not given or rarely adequate. Sometimes they were obtained by asking the patient directly, by patients' spontaneous reporting of subjective symptoms such as dizziness, or physicians observation of objective signs such as urticaria. There was confusion about definition, with arbitrary decisions about which adverse reactions were possibly drug related. In six studies, side effects were only reported if it led to withdrawal of therapy.

Minocycline comparators

Among the 27 trials, one trial compared minocycline versus placebo, another trial was a minocycline dose response study. Seven trials compared minocycline with other tetracyclines or oxytetracycline. Five trials compared minocycline with doxycycline, and three trials compared minocycline with topical

clindamycin. Other comparators include isotretinion, Diane, topical fusidic acid, topical erythromycin and zinc. The methodological deficiencies of individual trials were discussed in the Cochrane Review.[4]

Minocycline versus placebo

This study compares minocycline 200 mg daily for one week followed by 100 mg daily for four weeks with placebo treatment of identical appearance. It was a randomized double-blind cross-over study of five weeks for each arm, with no washout period in between.[9] During the first phase, minocycline demonstrated significant reduction in summed weighted acne lesion score, but placebo group did not.

Dose response of minocycline

This was a randomized double-blind control trial comparing minocycline 100 mg daily for eight weeks with minocycline 100 mg daily for two weeks followed by 50 mg daily for six weeks.[10] The study found no significant difference between dosage regimens in outcome measures using either per protocol or intentional to treat analysis. However, due to the short duration of study (eight weeks only), inference could not be made concerning the relative efficacy in long term treatment. There were no adequate dose response studies to confirm that 200 mg and 100 mg per day were equivalent in terms of clinical efficacy.

Minocycline versus other tetracyclines

One trial found that significantly more patients show improvement in their acne after receiving four weeks of minocycline instead of oxytetracycline.[11] Two trials showed statistically significant difference in favour of minocycline over tetracycline in acne after six weeks.[12,13] In all cases where initial response to minocycline was faster, the magnitude of reduction in acne severity at the end of treatment (12-24 weeks) was similar.

All five trials that compared patients receiving minocycline and doxycycline showed no overall difference in acne improvement between the drugs.[5,14-17] There was no evidence of earlier onset of acne improvement with minocycline compared with doxycycline. However, pooling of data was impossible due to variability of dosage and methodological design.

Minocycline versus topical clindamycin

Two trials had similar results for both minocycline and clindamycin, but it was uncertain whether the product was applied to all of the affected areas of face where spots were.[18,19] One trial showed superiority of topical clindamycin applied to entire face. But this did not reach statistical significance because large range of lesion counts and small number of patients were included.[20]

Adverse reactions

There were 1230 patients from 22 studies who received minocycline. The total adverse reactions were 137 (11.1%), with 36 (2.9%) led to withdrawal of therapy. The most common were gastrointestinal disturbance, followed by vertigo or dizziness, vaginal candidiasis, and abnormal pigmentation. However the reported incidence of common side effects may not be reliable due to inadequacies in collection and reporting methods. The lack of a denominator in nearly all studies means that risk for minocycline compared to other tetracyclines cannot be reliably compared.

Rare but serious side effects such as autoimmune disorders may not be detected. The study might not be large enough to detect rare adverse reactions (with incidence <1 in 1000) and was not controlled. Although case reports suggested that minocycline had greater risk of severe side effects, this might reflect current interest and selective reporting, for example, minocycline induced auto-immune hepatitis and LE-like syndromes.[1]

A case control study involving 27,688 acne patients from a primary care research database found that 29 (0.1%) developed LE-like syndromes, 27 of whom were females.[21] Comparing with age and sex matched controls, minocycline was associated with 8.5 fold risk (95% confidence interval 2.1-35) of developing lupus erythematosus, and other tetracyclines with 1.7 fold risk only (95% confidence interval 0.4-8.1). The absolute risk was 52.8 cases per 100,000 prescriptions.

Limitations of overview

Systemic overview attempts to review individual studies objectively, minimizing subjective bias in the selection of studies, analysis of data, and in drawing conclusions. It has clearly focused objectives, predetermined selection criteria to retrieve studies,

exhaustive search of literature to avoid publication bias, and translation of foreign languages to avoid language bias. At least two independent reviewers critically appraised the validity of studies, and where possible to pool study results in a systemic fashion (for example, mathematically in meta-analysis before drawing conclusions).

This Cochrane systemic overview was limited by the quality of the individual studies it could find; including heterogeneity of primary studies due to methodological insufficiencies, inadequacies of reported data, insufficient numbers of patients. The studies were generally of inadequate duration, majority lasted only 12 weeks, so that assumptions could not be reliably made on long-term therapy. The poor characterization of patients made subgroup analysis impossible. There was a lack of adequate outcome data for analysis. Standardized outcome measures were not available, and pooling of results was impossible. It was also not possible to examine the impact of study design on results (especially the degree of blinding), as many of the studies were inconclusive.

Conclusions of overview

The systemic review concluded that there was no clear cut and unbiased evidence to support the routine first-line use of minocycline in the treatment of acne. Minocycline 100 mg daily is an effective treatment of moderate acne, but no study has shown conclusively any important clinical difference in efficacy between the various tetracyclines in acne therapies. There was insufficient information to make any recommendations concerning the appropriate dose of minocycline that should be used. The relative safety of tetracyclines could not be adequately determined, and there was an inherent inability of the studies to detect rare events. However, one case control study suggested minocycline in acne therapy was associated with higher risk of lupus erythematosus syndromes than other tetracyclines.

APPLYING EVIDENCE IN CLINICAL PRACTICE

When applying the findings and conclusions of external evidence to patient care in the clinical setting, the combination of individual's clinical experience with best available external evidence is important. This personal experience is required to make judgement as to whether the external evidence found may be appropriately applied to the clinical situation in hand, taking into account individual patient characteristics and preferences (Table 4).[6,22]

Conclusion

Evidence based medical practice begins by asking an answerable question arising from daily clinical practice, continues with searching for the best available external evidence and critically appraising this evidence for its validity and importance, and eventually its application into clinical practice.

Starting from a clinical scenario, a literature search was initiated for the best available external evidence on the relative risk and benefits of minocycline in the treatment of acne vulgaris. A Cochrane systemic review located 27 randomized controlled trials. They were generally of inadequate size and quality to meet requirements of the systemic review. Although minocycline is an effective treatment for mild to moderate acne vulgaris, there was no reliable randomized controlled trial evidence to justify its continued first line use, given the price and concerns about safety that still remains.

Table 4. Applying evidence based medicine in clinical practice

Therapy
1. Can the results be applied to my patient care? *Is my patient so different from those in the trial that its result can't help me?* *How great would be the potential benefit of therapy actually be for my patient?*
2. Were all clinically important outcomes considered? *Are the benefit worth the harms and the costs?* *What alternative treatments are available?*
3. Is my patients' values and preferences satisfied by the regimen and its consequence? *Do my patient and myself have a clear assessment of their values and preferences?* *Are they met by this regimen and its consequences?*

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