

Another DMARD Option in Rheumatoid Arthritis?



Rheumatologists have ample evidence that early treatment with disease modifying antirheumatic drugs (DMARD) slows or may even halt radiological progression and that disability is also reduced. Most rheumatologists, while using DMARD early in the course of rheumatoid arthritis (RA), also recognize the importance of sustained suppression of synovitis and that many available options are poorly tolerated. As in hypertension evidence is accumulating that using combinations of DMARD has an additive benefit rather than using more of the same DMARD or class of drug. In those with an inadequate response, the use of anti-tumor necrosis factor- α (TNF- α) agents provides additional clinical benefit in a proportion of patients, and even in the absence of clinical benefit there may be a radiological advantage. However, biologics are prohibitively expensive for widespread clinical use and exploring alternative uses for an existing agent is of value. It is in this context then that we need to examine the data for tetracyclines.

Initial interest in the use of tetracyclines in RA arose from the belief that a mycoplasma-like organism was implicated in its etiology. Subsequent studies, however, showed that both minocycline and doxycycline are metalloproteinase inhibitors *in vitro*. So, could such readily available agents that are relatively non-toxic and cheap provide us with a rational approach to inhibiting the final common pathway for cartilage breakdown and bone erosion? The metaanalysis published in this issue of *The Journal* suggests that there is some evidence for the efficacy of the available tetracycline compounds but that minocycline data provide the most convincing evidence of clinical benefit. Clinical trial evidence disappointingly suggests that despite the findings that tetracyclines inhibit metalloproteinase synthesis *in vitro*, this is not achieved in patients. Are the tetracyclines therefore more like nonsteroidal antiinflammatory drugs (NSAID) than DMARD because they have no effect on radiographs?

That tetracyclines do not affect radiological disease was

noted in the MIRA study¹. In this multicenter randomized placebo-controlled trial over 48 weeks, 219 patients received either 200 mg/day of minocycline or placebo. Using an intention-to-treat analysis, no difference in the progression of erosions or joint space narrowing was seen. Although there was a trend toward the appearance of newly eroded joints being less frequent in the active group, this too failed to achieve statistical significance.

One of the most comprehensive studies of radiological outcome in RA is the study by Wolfe and Sharp². Their study showed, using hand radiographs, that the rate of progression of joint space narrowing increases with time but that the rate of progression for erosions does not change with time. There was no difference in the rate of progression on radiographs and disease duration. It was also observed that joint space narrowing and erosions are not good markers to accurately document progression in patients with milder disease. The rate of progression in the MIRA cohort appears to be slower than that described in the Wolfe and Sharp study, an aspect noted by the investigators. In part this may have been due to fewer patients in both the active and placebo groups being seropositive for rheumatoid factor (56%), and the mean erythrocyte sedimentation rate (ESR) at the outset in both groups being similar, 34 mm/h. The initial ESR as a single reading, however, is a poor correlate of radiological progression, whereas cumulative inflammatory burden as measured by the mean ESR or as an area under the curve calculation is better associated. Seventy percent of patients in the MIRA study had erosive disease and joint space narrowing at onset. To detect a significant difference the investigators calculated that to achieve 80% significance, 376 and 478 patients would have to show a change in erosive disease and joint space narrowing, respectively.

The failure to show beneficial effect on radiological progression may be due to a true lack of effect, a lack of study power, or biases in patient selection.

See Should tetracycline treatment be used more extensively for rheumatoid arthritis? page 2112

Is disease duration of importance in predicting likelihood of response?

Median disease duration in the report from Tilley, *et al*³ was 8.6 years and convincing evidence of response to minocycline was seen in that study. It is of interest, however, to compare the American College of Rheumatology (ACR) responses in early RA with a drug such as minocycline⁴ and those achieved by Dougados, *et al*⁵ with sulfasalazine or methotrexate (MTX) and with MTX versus etanercept (Bathon, *et al*⁶) (Table 1). The numbers studied by O'Dell were relatively small but the effects achieved with hydroxychloroquine are much as one would expect clinically and from other studies. By contrast the benefits he and his colleagues reported with minocycline were similar in terms of ACR 20 response compared with sulfasalazine, MTX, and etanercept and greater in terms of ACR 50. Confirmation of such results and evidence of tolerability beyond the short to medium term will be of importance.

Is there a niche market for minocycline in RA?

Despite recent advances in managing RA including the evidence relating to the benefit of early DMARD introduction and an increasing range of options, not all patients tolerate available agents or are suitable for new drugs such as anti-TNF- α options. An additional hurdle for many is the US dollar/euro cost of therapies. Hence, the evidence relating to minocycline, which costs just 3% of a TNF- α blocker, is of importance.

RA is also associated with an increased risk of major sepsis or comorbidity such as bronchiectasis, and in these circumstances caution is often necessary when using high dose MTX or contemplating an anti-TNF- α drug.

Utilization of agents with antibacterial properties is an attractive option both theoretically and practically.

What is the extent of toxicity?

A disappointing aspect of the report by Stone and colleagues was the relative lack of information relating to toxicity in the primary studies. The first question many patients with RA ask when offered additional therapy relates to the risk of side effects. While the consort structure of reporting clinical studies is relatively recent, the lack of toxicity information from some studies is a concern (an indictment of investigators and also of peer reviewers who have assessed such studies). Information about toxicity should be routinely and meticulously documented in any prospective study and all clinicians need to maintain vigilance when using a new drug or initiating therapy for an unlicensed indication.

Table 2 lists the side effects recorded in those studies where this information is available. However, use of minocycline in clinical practice reveals far more side effects than these studies have reported. The British National Formulary, for instance, includes anorexia, pancreatitis, dizziness, tinnitus, vertigo (more common in females), acute renal failure, pigmentation that may be irreversible, discoloration of conjunctivae, tears and sweat, drug induced systemic lupus erythematosus (SLE), and hepatotoxicity as possible side effects. Known rare adverse events attributed to tetracycline include benign intracranial hypertension^{7,8}. Gastrointestinal upset, dizziness, skin pigmentation, and hepatitis are thought to be dose-related whereas rashes, headache, SLE, benign intracranial hypertension, or Stevens-Johnson syndrome are more likely to be idiosyncratic.

Table 1. ACR response in early RA: comparative figures from recent studies.

Drug/Dose	Author Study, Year	n	Median Disease Duration, yrs	Duration of Study, yrs	Proportion ACR 70(%)
Minocycline 200 mg/day	O'Dell, 2001	30	< 1	2	67
Hydroxychloroquine 400 mg/day	O'Dell, 2001	30	< 1	2	43
Sulfasalazine 2-3 g/day	Dougados, 1999	68	1	1	59
Methotrexate 7.5-15 mg/wk	Dougados, 1999	69	1.5	1	59
Methotrexate 7.5-20 mg/wk	Bathon, 2000	217	1	1	65
Etanercept 10 g twice weekly subcutaneously	Bathon, 2000	218	1	1	64

Table 2. Adverse events with minocycline.

Author, year	Total n, n per Group	Duration	Minocycline Side-Effects Leading to Discontinuation
Kloppenborg ⁹ , 1994	80, 40 minocycline 40 placebo	26 wks	Gastrointestinal symptoms 10%; dizziness 10%; allergic pneumonitis 2.5%; total 12.5% off because of toxicity
Tilley ³ , 1995	219, 109 minocycline 110 placebo	48 wks	6% withdrew because of toxicity: dizziness, rash, headache, stomatitis, severe itching, diarrhea, recurrent vaginitis
O'Dell ¹⁰ , 1997	46, minocycline vs placebo	6 mos	No minocycline withdrawals because of toxicity; no dizziness reported; one GI bleed on placebo
O'Dell ⁴ , 2001	60, 30 minocycline 200 mg/day 30 HCQ 400 mg/day	2 yrs	Dizziness 3%; fingernail discoloration 3%; erythematous rash 3%

HCQ: hydroxychloroquine.

In their study of 40 patients receiving minocycline, Kloppenburg, *et al* noted that 2 patients developed dizziness of such severity that they fell, leading to fracture of elbow in one and fracture of humerus in another⁹. Although total discontinuations because of toxicity were relatively low in that study (12.5%), there was a life-threatening allergic pneumonitis in one patient. Other study toxicity reports are noted in Table 2.

In view of the potential usefulness of minocycline, rheumatologists need answers to issues of toxicity. For instance, does gradual dose escalation mitigate the dizziness? Could onset of skin pigmentation be delayed by using a smaller dose? Similarly, can one predict which individuals are more likely to develop skin problems? The extent to which this slate gray skin discoloration is of concern to patients varies greatly. Some will tolerate extensive discoloration, others are less willing to do so despite a good effect from the drug.

Clinicians caring for such patients need to be committed to full blood count and biochemistry checks every 3 months while therapy is continued. Tetracyclines are known to be teratogenic and therefore appropriate pre-pregnancy advice should be given. There are also potential interactions with warfarin, oral contraception, antacids, iron preparations, and penicillins. It is of importance to be alert to these possible side effects.

While data relating to adverse events may be sparse, this metaanalysis provides a useful summary of the value of tetracyclines in RA for the practicing physician considering their use. The finding that drugs in the same class differ *in vivo* despite similar *in vitro* effects suggests that further study may be useful. Minocycline appears to achieve benefit similar to drugs that we accept as useful DMARD. It is important, however, to recognize that to show radiological change, significantly larger studies than rheumatologists usually undertake will be necessary.

HILARY A. CAPELL, MB, Mch, MD, BA, FRCP,
Consultant Rheumatologist;

RAJAN MADHOK, FRCP, MD,
Centre for Rheumatic Diseases,
Wards 14/15,
Glasgow Royal Infirmary,
Castle Street,
Glasgow G4 0SF Scotland.

Address reprint requests to Dr. Capell.

E-mail: hiliary.capell@northglasgow.scot.nhs.uk

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