ROAD BACK FOUNDATION

Update and Succinct Review of Antibiotic Protocols for the Treatment of Rheumatoid Disease

INTRODUCTION; *Reference is made to the comprehensive protocol provided by the Road Back Foundation to instruct physicians and other health care providers in the use of antibiotics in the treatment of rheumatoid arthritis (RA). This treatise remains an important benchmark in recording the origination, rationale, and early history of this approach. Other accounts can be found in the medical literature (Rheum Dis Clin N Am 21: 817-834, 1995 and Rheum Dis Clin N Am 24: 489-500, 1998). As is always the case in medicine, updates are regularly needed and this account will try to do so in a brief fashion.*

USE OF MINOCIN FOR RA* Modern trials have provided sufficient evidence of the effectiveness and safety of tetracycline derivatives that should allow an almost certain approval by the FDA for the use of minocycline in the treatment of RA if a formal application were submitted to the agency. Unfortunately, the oldness and generic availability of tetracyclines make it commercially non-viable for drug companies to pursue this FDA track. Physicians are thus left with an "off-label" usage designation for the use of tetracyclines in the treatment of RA.

Recently conducted controlled studies have concentrated on oral preparations because of their safety and ease of administration. So the use of parenteral, i.e., IM or IV administrated antibiotics such as clindamycin will not be commented upon in this review.

The most extensive experience has been with oral minocycline. It can actually be used in any stage of RA, although patients are more apt to do better when the disease is relatively early and major joint damage has not yet occurred. Minocycline can be used as a single "disease modifying" drug or in combination with other agents. Effective experience has been acquired in scleroderma and juvenile RA as well.

DETERMINING DOSE Patients who are otherwise healthy and not elderly or quite diminutive in size may be started on 100 mg of minocycline given on two occasions during the day. Physicians should clearly inform patients that minocycline is a somewhat difficult drug to absorb. If tolerated, it is ideal to take it on an empty stomach. Some physicians use the successful NIH-sponsored MIRA protocol. Here patients take the first pill at mid-morning (2 hours after breakfast) with a glass of water. The stomach is empty by this time and lunch can be taken in an hour or so. The second dose occurs at bedtime. (Sensitive patients may not tolerate this protocol and it can be adjusted as indicated to a lower dose and/or an intermittent schedule.) Snacking after dinner is discouraged. Brand name Minocin®** is a pelletized version of minocycline designed to foster bioabsorption. Even on an empty stomach, minocycline is unlikely to cause gastrointestinal side effects.

SIDE EFFECTS Early encountered problems are infrequent and most often can consist of headaches or dizziness. Both problems usually abate with time or can be eliminated by deletion of the morning dose until he/she has acclimatized to the low dose. Some patients remain on this lower dose and respond well. Patients should anticipate that a period of time will pass before they begin to improve and they may temporarily experience an increase in some symptoms. Increased energy levels along with a reduction in pain and morning stiffness are signs that the drug is working.

Other side effects, though uncommon, may occur. Following liver and kidney function with laboratory testing every few months can insure the lack of toxicity; most RA patients need a CBC checked as well. Quite rarely minocycline can cause drug-induced hepatitis or pneumonitis.

The most frequent long-term side effect usually encountered after prolonged (over)

administration is minocycline-induced hyperpigmentation. Most often the skin at either sun-exposed or non-exposed sites may develop patchy or generalized darkening. Any area of the body can be involved. Characteristically it has a slate-like hue. The gums, teeth or even the conjunctiva of the eyes can also darken. The problem, with the exception of the teeth, appears reversible with drug discontinuation and the passage of time. Since the hyperpigmentation is purely cosmetic in nature, some patients choose to stay on minocycline due to its beneficial effects on their RA. In an animal model of minocycline-induced hyperpigmentation, high dose vitamin C therapy improved the state for some. Decreased sun exposure can help the problem, at least in part.

ALTERNATIVE An alternative oral tetracycline derivative for RA is doxycycline. It may not be as strong as minocycline for RA although this point is by no means proven. A particular advantage of doxycycline use is its lessened likelihood of hyperpigmentation. Patients who have experienced hyperpigmentation with minocycline can be converted to doxycycline and followed for what hopefully will be an improvement in the darkening and continued arthritis benefit.

LENGTH OF TREATMENT As patients with RA improve on antibiotic therapy, other drugs, including NSAIDs, additional DMARDs or steroid preparations sometimes can be reduced in dose or even eliminated in their entirety. In some patients, minocycline therapy for a year or more can be associated with full clinical remission of disease often accompanied by a decline in rheumatoid factor titer. It is always difficult to decide whether a patient under excellent control can have their dose of minocycline/doxycycline decreased or even discontinued. The drugs are safe and many patients fear a return of disease if they were to stop. Others choose to follow a tapering/elimination program. If such patients flare, disease control may once again be achieved by reinstating the drug. Sometimes long-term minocycline responders flare on drug. This phenomenon is seen with many other drugs and is termed tachyphylaxis. Its mechanism is unclear. Sometimes conversion to another drug that controls the inflammatory response can provide a bridge to the return to minocycline at a later date. After this "minocycline rest", it may become effective again.

In a report (JAMA 291:827-835,2004) an association between the use of antibiotics and risk of breast cancer was described; this potential link did not apply to patients on chronic tetracycline use for acne or rosacea. Over the last 15 years of extensive use of minocycline in RA by many physicians, there have been no definitive reports whatsoever of an increased risk of breast cancer.

Lastly, several cases of what appears to be drug-induced lupus in patients on chronic minocycline treatment for acne have been reported, principally from Europe. However, there is no evidence to date that minocycline treated RA patients are predisposed to lupus.

**This protocol review is based on experience through an NIH sponsored clinical trial.*

***For the NIH MIRA clinical trial that proved minocycline as safe and effective, the brand (pelleted version) of the drug was used and has remained the form of choice. Bioequivalence data published on FDA's web site shows AUC and Cmax values for generic minocycline to be the same as for branded Minocin. Some patients use brand or a generic form of doxycycline with positive effect. Patients also report success with antibiotic protocols as treatment for other rheumatic diseases.*