Alternative Treatments for Rheumatoid Arthritis

by Alan R. Gaby, MD

Abstract
Conventional treatments for rheumatoid arthritis (RA) present a number of problems, in terms of both safety and efficacy. A number of different alternative therapies have been studied, including dietary modifications, nutritional supplements, botanicals, and antibiotics. While the response to these treatments is variable and often unpredictable, some patients have shown dramatic improvement or even complete and long-lasting remission. Moreover, alternative therapies, with the exception of antibiotics, have a low incidence of adverse effects. Consideration of these treatment options has the potential to benefit many patients with RA.
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Introduction

Rheumatoid arthritis (RA) is a chronic systemic disease, usually manifesting as inflammation of multiple joints. The severity of the disease varies from person to person, ranging from minor pain and discomfort to severe inflammation, with joint damage and deformity. RA can also present with a number of extra-articular manifestations, including rheumatoid nodules, vasculitis, heart or lung disease, anemia, and peripheral neuropathy. Although the cause of RA is unknown, it is generally considered an autoimmune disease. It has been suggested that RA may be a manifestation of the immune response to an infectious agent. However, while a number of possible causative agents have been investigated, none has been convincingly demonstrated to cause RA.

Conventional therapy for RA usually begins with nonsteroidal anti-inflammatory drugs (NSAIDs) or, more recently, with a similar class of drugs known as COX-2 inhibitors. In more severe cases, glucocorticoids or so-called "disease-modifying drugs" (such as gold or methotrexate) may be prescribed. None of these medications cures the disease, and they all have the potential to cause significant adverse effects, although the COX-2 inhibitors have a lower incidence of gastrointestinal side effects than NSAIDs.

Because of the limitations and risks of conventional therapy, many patients and practitioners are seeking other ways to treat the disease. Commonly used alternative approaches include dietary modifications, nutritional supplements, botanicals, and antibiotics. In the author's clinical experience, the response to these treatments varies considerably from one patient to the next. Some patients experience little or no benefit, whereas others show dramatic improvement to the point of becoming symptom-free for many years. Alternative treatments have been used both as an adjunct and an alternative to conventional therapy. Most of the treatments described in this review, with the exception of antibiotics, are relatively free of side effects.

Alan R. Gaby, MD — Professor of Nutritional Medicine, Bastyr University; Author, *The Patient's Guide to Natural Medicine.* Townsend Letter for Doctors and Patients; Contributing Editor, Alternative Medicine Review.
Correspondence address: 125 NE 61st Street, Seattle, WA 98115

The Role of Food Allergy

Food allergy has been reported to play a role in a number of inflammatory and autoimmune conditions, including RA. In one study, 22 patients with RA consumed a diet that excluded common allergens. Twenty patients (91%) experienced an improvement in symptoms, and 19 found that specific foods repeatedly exacerbated their symptoms. The mean time on the elimination diet before improvement occurred was 10 days, and the longest time was 18 days. The mean number of food sensitivities per patient was 2.5; the most common symptom-provoking foods were grains, milk, nuts, beef, and egg.[1]

In a study by Darlington et al, 53 patients with RA were randomly assigned to consume a diet that avoided common allergens or their usual diet (control group) for six weeks. After one week, the patients on the exclusion diet began reintroducing one food at a time; any foods producing symptoms were removed from the diet. The hypoallergenic diet group fared significantly better than the control group for each of 13 different subjective or objective parameters of disease activity. The patients in the control group then underwent the same elimination-and-challenge procedure that the diet group had, and experienced similar, though somewhat less pronounced, improvements.[2] See Table 1 for the foods most commonly causing symptoms, and their respective percentages.[3] Long-term follow-up of 100 patients who underwent dietary therapy at Darlington's clinic revealed that one-third remained well on diet alone, without any medication, for up to 7.5 years after starting treatment.[4] The enduring nature of these clinical improvements suggests something more than a placebo effect was involved. Although some patients treated by Darlington's group lost weight, there was no significant correlation between weight loss and clinical improvement.

In a double-blind study, 94 patients with RA were randomly assigned to consume one of two elemental (hypoallergenic) diets for four weeks, followed by a return to their usual diets for another four weeks. One diet ("allergen free") was free of common allergens, additives and preservatives. The other diet ("low allergen") was similar to the allergen-free diet, but contained milk allergens and azo dyes. Seventy-eight patients completed the study. The effects of food elimination and rechallenge varied considerably among patients. Nine patients (11.5% of the total; 6 in the allergen-free group, 3 in the low-allergen group) had a favorable response to the elimination diet, followed by marked disease exacerbation during rechallenge. In these patients, subjective improvements were confirmed by improvements in objective parameters of disease activity.[5]

In another double-blind study, two of 11 RA patients showed a favorable response to an elimination diet and experienced exacerbation after ingesting offending foods. In that study, the elimination diet did not exclude certain common allergens (wheat, corn, egg whites, sugar, and coffee). It is possible the response rate would have been higher if the elimination diet had been more restrictive.[6]

These studies indicate avoidance of allergenic foods is beneficial for a subset of patients with RA, although the proportion of patients responding to dietary modification varied considerably from one study to the next. The difference in response rates may be related in part to the patient populations studied. In this author's experience, younger female patients (aged 25-40 years) with less severe cases of RA had the best response to avoidance of allergens. Indeed, of the approximately 15 or so patients who fit that description, every one improved markedly with dietary modification alone. Older patients and those with relatively severe RA were less likely to improve, and dramatic changes were infrequent in those patients. The divergent results

Table 1: Allergenic Foods and Rheumatoid Arthritis

Food	Percent of patients experiencing symptoms
corn	56%
wheat	54%
bacon/pork	39%
oranges	39%
milk	37%
oats	37%
rye	34%
egg	32%
beef	32%
coffee	32%
malt	27%
cheese	24%
grapefruit	24%
tomato	22%
peanuts	20%
cane sugar	20%
butter	17%
lamb	17%
lemon	17%
soy	17%

in published studies may also be explainable in part by different degrees of dietary restriction and/or compliance. For example, some highly allergic or chemically sensitive individuals have been reported to develop arthritic reactions to pesticides or to other food-derived chemicals.[7] The extent to which these chemicals were avoided in the various studies may have influenced the results.

Other Dietary Interventions

Twenty-seven patients with RA participated in a 7-10 day partial fast, during which they consumed only herbal teas, garlic, vegetable broth, decoction of potato and parsley, and juices from carrots, beets and celery. After the fast, they introduced one food every second day. Foods that provoked symptoms were removed from the diet. During the first 3.5 months gluten, meat, fish, eggs, dairy products, refined sugar, citrus fruits, preservatives, coffee, tea, alcohol, salt, and strong spices were avoided. After that time, dairy products and gluten were allowed if they did not provoke symptoms. A control group of 26 patients consumed their usual diet. After four weeks, the diet group showed significant improvements in the number of tender joints, Ritchie's articular index, number of swollen joints, pain score, duration of morning stiffness, grip strength, sedimentation rate, C-reactive protein, and a health assessment questionnaire score. In the control group, only the pain score improved significantly.[8] Among those who continued on the diet, the improvements were maintained for up to two years.[9]

In another study (reported only in abstract form), 40 patients with RA were randomly assigned to consume an uncooked vegan diet (n = 20) or a control diet (n = 20) for three months. Patients on the vegan diet reported relief of stiffness and joint swelling and an improvement in general well being; but they became worse after resuming an omnivorous diet. The response in the control group was not reported, with the exception of the Ritchie index of tender joints, which remained unchanged.[10]

In another trial, 46 patients with RA consumed a diet rich in raw foods and containing no cereals or dairy products for periods of 1-3 years. Thirty-six patients (78%) showed significant improvements in joint pain and swelling, morning stiffness, sedimentation rate, and other parameters. Of the 36 responders, 19 were in complete remission for 1-5 years. Among those who responded to the diet, improvements were seen by the end of the third month in approximately 90 percent of cases. Improvement typically was progressive and often occurred rapidly. Seven responders who abandoned the diet relapsed, but improved again after resuming the diet.[11]

In another report, 15 patients with RA fasted for 7-10 days on fruit and vegetable

juices and then consumed a lactovegetarian diet for nine weeks. Ten patients consuming a normal diet served as controls. One-third of the patients showed objective signs of improvement while fasting, compared with only one of 10 individuals consuming the control diet. The fasting patients also experienced a reduction in pain and stiffness, and required fewer analgesics than previously. However, by the end of the lactovegetarian diet period, only one patient continued to show objective improvement.[12]

Proposed mechanisms by which vegetarian diets might benefit patients with RA include: 1) a reduction in the intake of the fatty acid, arachidonic acid (found mainly in animal foods), that is metabolized to inflammatory prostaglandins; 2) avoidance of common allergens (such as wheat and dairy products), as was done in some of these studies; or 3) consumption of potential anti-inflammatory compounds (such as enzymes) that are present in raw plant foods.

Nutritional Interventions for RA

Zinc

Because it is capable of inhibiting the inflammatory response,[13] zinc has been investigated as a possible treatment for RA. In a double-blind study, 24 patients with moderately severe RA, refractory to conventional therapy, were randomly assigned to receive zinc (50 mg elemental zinc three times daily in the form of zinc sulfate) or placebo for 12 weeks. Compared with placebo, zinc significantly reduced joint swelling, morning stiffness, and improved patients' subjective assessment of disease activity.[14] However, in three other controlled studies, zinc was not significantly more effective than a placebo.[15-17]

While it is not clear why the results differed in these studies, two possible explanations exist. First, in at least one of the negative studies, the disease was more severe than in the study that produced positive results. It is conceivable that zinc supplementation is helpful only for mild or moderately severe RA. Second, administration of large doses of zinc can result in a deficiency of copper,[18] a mineral that may be even more important for arthritis than zinc. While the evidence does not indicate supplementation of zinc alone will produce great benefit, it is possible that combining zinc with copper and other nutritional treatments would be more effective.

Copper

Copper is also known to have anti-inflammatory activity. Rats fed a copper-deficient diet had an increased inflammatory response in two models of acute inflammation.[19] The role of copper complexes as anti-arthritic agents has been reviewed by Sorenson.[20-22] Between 1940 and 1971 a small number of rheumatologists used copper complexes safely and effectively to treat rheumatoid diseases. Studies have shown that copper complexes of NSAIDs are more potent anti-inflammatory agents and are less toxic than the parent compounds. For example, in animal models of inflammation, the copper chelate of aspirin was active at one-eighth the effective dose of aspirin. Moreover, whereas NSAIDs can cause peptic ulcer, copper chelates of these same drugs have potent anti-ulcer activity in animal studies. It has been suggested that NSAIDs become active *in vivo* by forming complexes with copper. If that is true, then the ulcerogenic effect of NSAIDs may be due, at least in part, to their tendency to pull copper from certain tissues (copper depletion leads to impaired tissue integrity).

Copper complexes of NSAIDs have not been approved by the U.S. Food and Drug Administration and are difficult to obtain in the United States. In addition, the long-term safety of administering copper complexes to humans has not been studied. While it is conceivable that supplementing with "nutritional" doses of copper (e.g., 2-4 mg per day) could

increase the efficacy and reduce the toxicity of NSAIDs, that possibility has not been tested.

Folk wisdom teaches that wearing a copper bracelet can relieve arthritic symptoms. While most conventional doctors consider that claim to be nonsense, a pilot study indicated that copper bracelets may, indeed, be helpful. Some 160 individuals with arthritis, half of whom had previously worn a copper bracelet, were randomly assigned to one of two groups. Group 1 wore a copper bracelet for one month, and then a placebo bracelet (anodized aluminum resembling copper) for a second month. Group 2 wore the same bracelets in reverse order. Of those patients who noticed a difference between the two bracelets, significantly more preferred copper ($p < 0.01$) than placebo.[23] Previous users of copper bracelets deteriorated significantly during the time they were wearing the placebo bracelet. Interestingly, the weight of the copper bracelets fell by an average of 13 mg during the month they were being worn, suggesting that some copper from the bracelet may have been absorbed through the skin.

Combining Zinc and Copper

Some nutritionally-oriented practitioners prescribe 30-90 mg zinc and 2-4 mg copper daily as part of an overall nutritional program for RA. Both of these supplements can cause nausea, particularly if taken on an empty stomach. Since taking large amounts of zinc alone can promote copper deficiency, these minerals probably should be used in combination. There is no good evidence that taking zinc and copper at separate times of the day enhances their efficacy. Although studies on zinc as a treatment for RA typically used 150 mg of elemental zinc per day (as zinc sulfate), some doctors recommend lower doses of better-absorbed forms of zinc (such as zinc picolinate[24] or zinc citrate[25]).

Selenium

The trace mineral selenium is also known to have anti-inflammatory effects.[26] Serum selenium levels were significantly lower in a group of 87 patients with RA than in healthy individuals. The reduction in serum selenium was greatest among patients with the most severe disease.[27] In a double-blind trial, 15 women with RA received either 200 mcg selenium daily (from selenium-rich yeast) or a placebo for three months. Pain and joint inflammation were reduced in six of eight women treated with selenium, but there was no significant change in the placebo group.[28] Selenium was ineffective in another study,[29] possibly because the patients in that study had more severe arthritis.

Essential Fatty Acids

RA has been shown to respond to supplementation with several different oils containing omega-6 or omega-3 fatty acids, or both. Each of these classes of fatty acids has been shown to have both immunosuppressive and anti-inflammatory effects.[30-33] The most dramatic results have been seen with borage seed oil, a potent source of the omega-6 fatty acid gamma-linolenic acid (GLA). In a double-blind trial, 37 patients with active RA were randomly assigned to receive borage seed oil (providing 1.4 g of GLA per day) or a placebo (cottonseed oil) for 24 weeks. Treatment with borage seed oil resulted in a statistically significant and clinically important reduction in disease activity; the number of tender joints was reduced by 36 percent, the tender-joint score by 45 percent, and the swollen-joint score by 41 percent. In contrast, patients in the placebo group experienced no change or a worsening of disease activity. No serious side effects occurred, although a few patients reported minor intestinal discomfort from borage seed oil.[34]

In a follow-up double-blind study, 56 patients with active RA were randomly assigned to receive 2.8 g GLA per day (twice the dose as in the previous study) from a concentrate of borage seed oil or placebo (sunflower oil) for six months. All patients then received GLA in single-blind fashion for an additional six months. After the first six months, the improvements in the following parameters were significantly greater in the GLA group than in the placebo group: swollen joint count, tender joint count, tender joint score, pain, and Health Assessment Questionnaire score. Meaningful clinical improvement (at least 25 percent improvement in four measures) occurred in 14 (63.6%) of 22 patients in the GLA group, compared with 4 (21.1%) of 19 patients in the placebo group ($p = 0.015$). During the second six months, both groups showed improvement in disease activity. Of the 21 patients who received GLA for 12 months, 16 (76.2%) showed meaningful improvement at 12 months, compared with baseline.[35] Adverse reactions included belching (three in the GLA group, two in the placebo group) and diarrhea (four in the GLA group, one in the placebo group).

Black currant seed oil (BCSO), which contains both GLA and the omega-3 fatty acids alpha-linolenic and stearidonic acid, has also been tested as a treatment for RA. Thirty-four patients with RA and active synovitis were randomly assigned to receive, in double-blind fashion, 10.5 g BCSO daily or placebo (soybean oil) for 24 weeks. Fourteen patients (seven in each group) completed the study; the main reason for withdrawal was difficulty swallowing 15 large capsules each day. Compared with placebo, treatment with BCSO resulted in a modest but statistically significant improvement in pain and joint tenderness.[36]

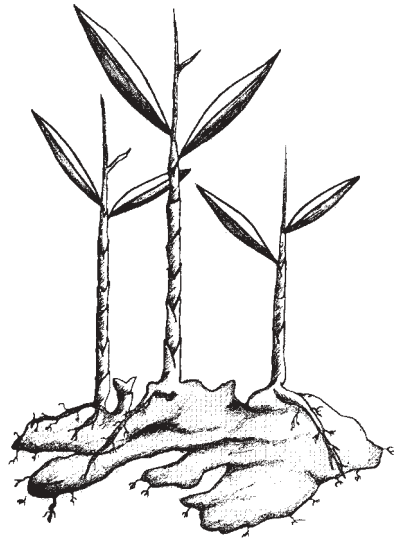
Evening primrose oil (EPO), the other major dietary source of GLA, has produced equivocal results in patients with RA. Forty patients were randomly assigned to receive, in double-blind fashion, 6 g EPO (providing 540 mg GLA) per day or placebo (olive oil) for six months. There was a significant reduction in morning stiffness in the EPO group after three months, and there were significant improvements in pain and articular index at six months in the olive oil group.[37] Although EPO did not appear to be more effective than placebo, this study did not rule out the possible benefit of EPO. The dosage of GLA employed in this study (61 percent less than the amount used in the successful study with borage seed oil) may have been too low to produce a clear effect. In addition, olive oil may have been a poor choice for a placebo, as it has been reported to relieve symptoms in patients with RA.[38] On the other hand, since borage seed oil is a less expensive source of GLA than is EPO, the former seems preferable to the latter as a treatment for RA.

Fish oil, a source of the anti-inflammatory omega-3 fatty acids, has been investigated in several controlled trials. In one study, 51 patients with active RA were randomly assigned to receive, in double-blind fashion, fish oil (providing 3.6 g omega-3 fatty acids per day) or placebo (a mixture of fatty acids comparable to that found in an average diet) for 12 weeks. In the fish oil group there was a significant reduction in the duration of morning stiffness, whereas there was no change in the placebo group. Joint tenderness improved to a similar degree in both groups. Grip strength increased by 24 percent in the fish oil group and decreased by 8 percent in the placebo group, but no statistical comparison was made between the two groups.[39]

In another double-blind study, 66 patients with RA were randomly assigned to receive omega-3 fatty acids or placebo (corn oil) for 26-30 weeks. The dose of omega-3 fatty acids was 130 mg/kg body weight/day, in the form of ethyl esters of eicosapentaenoic and docosahexaenoic acids. In the group taking fish oil there were significant decreases from baseline in the mean number of tender joints,

duration of morning stiffness, physicians' and patients' assessment of global arthritis activity, and physicians' evaluation of pain. In the placebo group no clinical parameters improved.[40] Similar results were obtained in a 12-week, double-blind, crossover trial involving 16 patients with RA.[41]

Figure 1: Zingiber officinalis (Ginger)



Which Oils to Use?

It should be noted that different fatty acids exert different biochemical effects in the body. Some individuals may respond best to omega-3 fatty acids, others to omega-6, and still others to a combination. The optimal fatty acid supplement for any particular individual would presumably depend in part on his or her previous diet (i.e., the ratio of omega-6 to omega-3 fatty acids), as well as genetic or acquired differences in the metabolism of each class of fatty acids. Although we still have a great deal to learn about fatty acid treatment of RA, measuring fatty acid concentrations in the blood may provide some guidance.

Herbal Therapies for RA

Ginger Root

Ginger (Figure 1) has been used for thousands of years in Ayurvedic medicine and other systems of traditional medicine as an anti-inflammatory agent. Five constituents of ginger have been identified as inhibitors of prostaglandin synthesis,[42] the same mechanism by which aspirin and other NSAIDs exert their anti-inflammatory effect. Oral administration of ginger oil suppressed the induction of adjuvant-induced inflammation in rats.[43] In a pilot study, six patients with RA consumed 5 g of fresh ginger or 0.5-1.0 g of powdered ginger per day. After three months, every patient reported a reduction in pain, better joint mobility, and less swelling and morning stiffness, even though they had stopped taking their anti-inflammatory medications.[44]

In another study, 28 RA patients who had tried ginger for their symptoms completed a questionnaire. The usual dose was 1-2 g per day and the duration of treatment ranged from 3 months to 2.5 years. More than 75 percent of those completing the questionnaire reported varying degrees of improvement in joint pain and swelling. In most of the responders, improvements were seen within 1-3 months of starting treatment. No patient in either study experienced side effects from ginger.

Although these reports suffer from lack of a placebo group and from the selection bias inherent in a questionnaire study, ginger shows promise as a treatment for RA.

Bromelain

Twenty-nine patients with moderate or severe arthritis (25 with RA) received oral bromelain, an extract of pineapple stem that contains proteolytic enzymes. The dosage was 20 or 40 mg, 3 or 4 times daily, of an enteric-coated tablet (Ananase; Rorer) for 3 weeks to 13 months. All patients had had residual joint swelling for many months or years despite glucocorticoid therapy, which was continued during bromelain treatment. Eight patients (28%) experienced a resolution of swelling, pain, and soreness soon after starting bromelain, and an additional 13 patients (45%) improved. Overall, 72 percent of the patients receiving bromelain had good or excellent results. No side

effects were seen.[45] Although the absence of a control group makes it difficult to interpret the results, the reported benefits are consistent with the known anti-inflammatory effect of bromelain.[46]

Ananase is no longer commercially available, and most bromelain products currently on the market are not enteric-coated. Because enteric-coating presumably protects the protein molecules in bromelain from being inactivated by hydrochloric acid and pepsin, non-enteric-coated products may be less potent and/or less effective than the preparation used in the research cited above. However, it should also be noted most bromelain products on the market are offered in considerably higher dosages than those used in the study. The higher dosage may make up for the lack of enteric coating.

Other Herbal Treatments

Feverfew, an herb recognized for its effectiveness in preventing recurrences of migraine, has also been tested in patients with RA. In a double-blind trial, 40 female patients were randomly assigned to receive dried feverfew (70-86 mg/day) or a placebo for six weeks. Compared with placebo, treatment with feverfew resulted in a significant increase in grip strength.[47]

Curcuma longa (turmeric), a commonly used spice, has been used in traditional Chinese and Indian (Ayurvedic) medicine, primarily as a tea.[48] A component of turmeric, curcumin has been investigated as an anti-inflammatory agent. In a preliminary study, 18 patients with RA were randomly assigned to receive curcumin (400 mg 3 times daily) or the NSAID phenylbutazone (100 mg 3 times per day) for two weeks, and then the alternate treatment for an additional two weeks. Compared with baseline, both treatments resulted in a significant improvement in morning stiffness, walking time, and joint swelling,[49] although phenylbutazone appeared to be slightly more effective than curcumin. As there was no placebo-treated control group in this study, the possibility of a placebo response to curcumin cannot be ruled out, particularly in view of the short duration of the study. In addition, it is not clear whether powdered curcumin, the form recommended by some doctors of natural medicine, would have the same effect as turmeric consumed as a tea (the traditional method of administration). For some herbs, extraction with hot water causes the release of active ingredients that would not otherwise be available. Additional research is therefore needed to determine whether curcumin is an effective treatment for RA.

Antibiotic Therapy for RA

Several antibiotics have been used with some success in the treatment of RA. Although antibiotics are used in conventional medicine to treat various infections, their use in RA is not discussed in major textbooks of internal medicine, and is therefore still considered "alternative."

In the 1960s, Wyburn-Mason isolated a free-living ameba, Naegleria, from the tissues of patients with RA and other autoimmune diseases. Administration of an anti-amebic drug (such as metronidazole or clotrimazole) to patients with rheumatoid diseases resulted either in a cessation of disease activity or a temporary exacerbation of symptoms, with or without a fever (Herxheimer reaction), followed by improvement or complete resolution of symptoms.[50] Other investigators have been unable to isolate the organism described by Wyburn-Mason, and anti-amebic therapy has remained controversial. However, a number of practitioners are convinced that metronidazole and related drugs are among the most effective treatments available for RA.

A typical protocol for metronidazole is 2 g on two consecutive days (taken in divided doses with meals) weekly for a total of six weeks. Individuals weighing less than 70

kg are given proportionately less medication. In some cases, patients with active inflammation are given an intramuscular injection of a long-acting glucocorticoid along with the initial dose of metronidazole, in order to reduce the severity of the Herxheimer reaction.

This author has administered metronidazole to a few dozen patients with rheumatoid disease; approximately one-third to one-half of these patients experienced worthwhile and long-lasting improvement. The most dramatic response was in a middle-aged man with moderately severe psoriatic arthritis, which had been present for about ten years and had fluctuated very little in severity. Five days after his first dose of metronidazole his symptoms of arthritis disappeared. He completed his six-week course of treatment and remained symptom-free for the next five years, after which he was lost to follow-up.

Additional information on anti-amebic therapy may be obtained by writing Arthritis Trust (formerly Rheumatoid Disease Foundation), P.O. Box 8949, Topeka, KS 66608-8949, or by visiting www.arthritistrust.org.

Three double-blind studies have shown that minocycline, a derivative of tetracycline, is beneficial in the treatment of RA.[51] In patients with long-standing disease, the clinical improvement was only modest. However, in those whose disease had been present for less than one year and who had not previously been treated with disease-modifying drugs or glucocorticoids, the results were more pronounced. In this latter group, after a mean follow-up period of 3.3 years, 44 percent of patients treated with minocycline were in or near remission, without having to take any other medication for their RA. While the beneficial effect of minocycline may be due to the eradication of one or more microorganisms, its mechanism of action remains uncertain.

Conclusion

RA can be a severe and sometimes crippling disease. Because of the limitations and risks of conventional therapy, many patients and practitioners are seeking other ways to treat the disease. Alternative therapies include dietary modifications, nutritional supplements, botanicals, and antibiotics. While not everyone responds to these approaches, many patients do improve, and some have experienced complete and long-lasting remission. Moreover, these therapies, with the exception of antibiotics, have a low incidence of adverse effects. The treatments described in this review should, therefore, be given more-serious consideration by the medical community.

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