Liquid Cartilage Extract Decreases Symptoms of Rheumatoid Arthritis

by Alain Thibodeau, PhD and Stephen Behr, PhD
Atrium Biotechnologies Inc., Québec, Canada, GIP 4P5

Abstract

Liquid cartilage extract (LCE) manufactured by means of a specific molecular extraction and enrichment method is anti-inflammatory and antiangiogenic, and inhibits matrix metalloproteinases (MMPs). These biological activities suggest a potential benefit of LCE in arthritis. In addition, human studies have demonstrated that, when taken orally, the antiangiogenic components of LCE are bioavailable. The objective of this open label study was to document the effects of LCE on key endpoints of rheumatoid arthritis. Twenty-nine subjects with documented stable rheumatoid arthritis (RA) and a well established medication regimen were selected for the study. Without changing their medications, the subjects consumed LCE for a period of 6 months. The benefits of supplementation were evaluated using the American College of Rheumatology (ACR) clinical parameters as assessed by a rheumatologist. For each of the clinical parameters, the results are presented as the percentage of subjects who had an improvement of at least 20% compared to baseline, as specified by the ACR (ACR20 results). Over 50% of the subjects improved in joint swelling and joint tenderness, the key parameters of clinical improvement. Over 60% of the subjects also registered improvement in their physical capabilities and relief from pain during the study. The ACR50 results (percentage of subjects who had improvement of at least 50% compared to baseline) for joint pain and swelling obtained with the LCE exceeded the placebo response by approximately 3-fold, and were similar in magnitude to the effects of auranofin provided orally and gold sodium thiomalate administered parenterally, when comparing independent studies. Unlike previous medications used for the treatment of arthritis, there was no evidence of toxicity or lack of tolerance to LCE. The results suggest that LCE has significant potential as a component of nutritional supplementation for joint health. In addition, because of its anti-inflammatory and anti-MMP features, LCE merits investigation in osteoarthritis where these mechanisms play a crucial role in cartilage degradation.

Introduction

Matrix metalloproteinases (MMPs) are an important group of zinc enzymes responsible for degradation of the extracellular matrix (ECM) components such as collagen and proteoglycans in tissue turnover and remodeling and in many disease processes, including arthritis (Woessner JF 1991). MMPs are known to play an important role in angiogenesis (Norrby, 1997). In adults, angiogenesis usually occurs only for a limited period of time, for example during wound healing, but it becomes a chronic condition in many diseases such as rheumatoid arthritis (RA). In rheumatoid arthritis, MMP production and angiogenesis are driven by cytokines and other inflammatory growth factors, and account for the progressive destruction of cartilage and the development of new capillaries in the synovial pannus (Ahrens et al, 1989; Konttinen et al, 1998; Walsh, 1999).

Cartilage is an avascular tissue which has been shown to inhibit MMPs and the formation of new blood vessels, without however affecting the existing vasculature. Cartilage has been shown to inhibit collagenases and other proteases (MMPs) in vitro and to prevent the degradation of the extracellular matrix (Moses et al., 1992; Kuettner and Pauli, 1983). Cartilage has also been shown to interrupt the angiogenic process, as demonstrated by the inhibition of neovascularization in the chick embryo (Dupont et al, 1998; Brem and Folkman, 1975; McGuire et al, 1996). In addition, the antiangiogenic effect of cartilage may be due to the inhibition of endothelial cell proliferation, which has been demonstrated in vitro (McGuire et al, 1996; Moses et al., 1992; Kuettner and Pauli, 1983). A liquid cartilage extract (LCE) obtained using a specific extraction method inhibits several members of the matrix metalloproteinase class, inhibits endothelial cell proliferation, and is antiangiogenic in several experimental models of angiogenesis (Dupont et al, 1997 and 1998). This extract is also antiangiogenic in vivo, after oral administration, in human subjects (Berbari et al., 1999).

Although the symptoms of RA can be controlled to some extent with medication, major side effects remain a problem (Harris, 1994). Therefore, research is focused on the development of preventive therapies with fewer or no side effects. Given the basic role of MMPs and angiogenesis in the pathogenesis of RA, the use of LCE has been investigated in the present study.

Materials and Methods

Study Design

The design of this prospective, open label pilot study was to evaluate subjects with documented rheumatoid arthritis (RA) at baseline and for 6 months during which they consumed LCE. The study was conducted at St. Mary’s Hospital, Catholic University Medical College, Seoul, S. Korea, by Dr. Ho Youn Kim, Department of Internal Medicine, Rheumatology and Immunology. The subjects were asked to add LCE to their daily therapeutic regimen, without changing their medications during the study. The subjects were evaluated at baseline and monthly for 6 months by the rheumatologist according to clinical evaluation parameters of RA established by the American College of Rheumatology (ACR). Study inclusion was based on the...
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ACR criteria, using the classification tree of Arnett et al. (1988). Subjects were included only if their condition had remained stable or progressed during the three months preceding the study. Secondary causes of RA as defined by Harris (1994) were ruled out and only subjects whose medication had not been changed during three months prior to the study were included.

Product Description and Dosage

The clinical product used in this study was LCE #CI-0406, manufactured according to US Patent 5616925 by Atrium Biotechnologies Inc., Québec, Canada. The product had the following physio-chemical parameters: pH of 6.9, extract dry weight of 14.3 mg/ml. Following microbiological verification according to USP XXIII, the product was bottled under aseptic conditions and frozen until use. For use, the product was thawed and consumed within 30 minutes. The subjects were asked to consume 21 ml of product per day (10.5 ml twice per day), which corresponds to approximately 300 mg dry weight of extract per day.

Clinical Evaluations and Methods of Analysis

The following five well characterized parameters were monitored at baseline and monthly during the study: tender joint count, swollen joint count, subject's assessment of pain, subject's global assessment of disease activity, and physician's global assessment of disease activity. The tender joint count was supplemented by a complete assessment of joint tenderness, the Ritchie index or Ritchie score (Ritchie et al. 1968). Finally, a complete assessment of physical function, emotional status and social well being was done using the Arthritis Impact Measurement Scale (AIMS) questionnaire (Meenan et al. 1980).

Only the results for physical functions are presented. Results are presented according to a modification of the current ACR20 definition of clinical improvement (Felson et al. 1995, Felson et al. 1998). According to this definition, clinical improvement consists of a 20% improvement compared to the baseline values for selected parameters. For the purposes of discussion, the results of the tender and swollen joint counts are also presented according to the ACR50 definition of clinical improvement.

Results

Of these 29 subjects who completed the study, 27 were women. The subjects had the following characteristics (mean and range): age of 46 (range: 27-64 years), weight of 50 kg (38-72 kg), height of 159 cm (152-178 cm), ponderal index of 19.8 kg/m2 (15.6-23.8). Eleven of the subjects changed medications during the study. In one case, the change consisted only of a formulation change. Seven subjects decreased their medication intake and 3 subjects increased their medication intake. All of these subjects were included in the "intent to treat" analysis of results which are presented below. A comparison of the intent to treat results and the "compliance" or "as per protocol" results is presented in the discussion.

Results for tender joint count and swollen joint count, as well as subject and physician global assessment, pain, and disability are shown in Figures 1-6. According to a modification of the ACR20 definition of improvement (Felson et al. 1995), these results are expressed as the percentage of subjects for whom a 20% improvement over baseline was noted. All figures are compared to the baseline measured at Month 0 (M0).

The results for the two most widely used clinical variables in arthritis, the tender joint count and swollen joint count, are shown in Figs. 1 and 2. During the first two months (M1 and M2), the number of subjects responding increased rapidly to plateau after three months of treatment with slightly more than 50% of the subjects showing a clinically significant response to the treatment. The results obtained with the Ritchie score were more positive (Fig. 3). After only 2 months of treatment, over 80% of subjects had responded positively according to this index, and 2/3 of the subjects improved throughout the study.

Assessment of pain by the subject is another one of the key parameters evaluated by the ACR. As shown in Fig. 4, approximately half of the subjects indicated that they had significantly improved by the second month of the trial. These results were quantitatively similar to the tender and swollen joint count, but occurred more rapidly. According to the AIMS questionnaire, over 50% of the subjects improved significantly for at least 3 consecutive months in overall physical ability (data not shown). The results of this overall assessment of physical disability are that 50% of the subjects improved for at least 3 consecutive months (data not shown).

According to the subjects' own evaluation, 20%-30% had actual improvements in global disease, and these improvements remained throughout the study (Fig. 5). According to the rheumatologist's evaluation, over 30% of the subjects had improvements in global disease after 3 months of treatment and until the end of the study (Fig. 6).

In order to compare the present results to previously published results for auranofin and gold sodium thiomalate, the ACR50 results for joint tenderness and joint swelling are presented in Fig. 7. Historical placebo responses were 9% and 11% for joint tenderness and joint swelling. When treated with LCE, responses in this category were 31% and 32%, very close to the responses obtained with auranofin and GST.
Discussion

ACR Parameters and Definition of Improvement in RA

The criteria used to determine clinical response to RA in the U.S. have evolved somewhat over the past 20 years, as shown in the publications of Pinals et al. 1981, Paulus et al. 1990, Anderson et al. 1989 and Felson et al. 1995 and 1998. The two publications by Felson et al. represent the “official” parameters of the American College of Rheumatology (ACR) for clinical improvement in RA. As specified by Felson et al., the results of the present trial are reported as the proportion of subjects who improved according to a modification of the ACR 20 standards (Figs. 1-6). European parameters are similar to the US parameters, though not identical (van der Heide et al. 1994).

There is general agreement that the tender and swollen joint counts are the most useful outcome parameters in RA. The tender joint count also correlates highly with the Ritchie index, which is widely used in Europe (van Zeben et al. 1993). For each of these key parameters, over half the subjects had clinically significant improvements from month 3 until the end of the study. Other parameters that are recognized by the ACR include assessment of pain, and global assessments of disease by the subject and by the physician. Results obtained from the AIMS questionnaire confirm the improvement pattern obtained using the other measures. Using this tool, physical disability is assessed by combining the normalized numeric scores for mobility, physical activity, activities of daily living, household activities and dexterity (Meenan et al. 1980).

Comparison of Present Results with Several Pharmaceutical Approaches

The data shown in Fig. 7 summarizes the results obtained in the present study and in a study of Ward et al. (1983) when expressed at the ACR50 level of response. Approximately 10% of the subjects responded to the placebo in this study. Auranofin and gold sodium thiomalate led to improvements in joint tenderness in 30-35% of the subjects and improvements in joint swelling in 25-27% of the subjects. These results with LCE are very similar to these results, with 31% of the subjects showing improvements in joint tenderness and 32% of the subjects with improvements in joint swelling. This result is all the more interesting, considering that parenteral treatment with gold produces serious side effects (Ward et al. 1983).

In a study by Williams et al. (1983), subjects treated with D-penicillamine did not show any statistically significant improvements in any joint count variables compared to the placebo group (although there were improvements in other parameters). In addition, D-penicillamine therapy causes numerous side effects (Williams et al. 1983). Another pharmaceutical approach to RA is the treatment with methotrexate (MTX), an antimetabolite of folic acid which is used to decrease the proliferation of synovial cells by blocking DNA synthesis. MTX is used in patients who do not respond or are intolerant to gold salts or penicillamine. It is more effective than gold salts (Weinblatt et al. 1990), but has no analgesic effect and considerable toxicity. A more recent and highly sophisticated therapeutic approach using an antagonist to tumor necrosis factor yielded a positive ACR50 result in over half the subjects, as compared to a positive placebo effect in 7% (Moreland LW et al., 1997). However, this approach requires twice per week injections. In addition to the antirheumatic drugs above, the drugs most often used in RA are NSAIDs. These drugs do relieve pain, but tend to irritate the gastric mucosa and cause the development of ulcers.

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Compliance and Intake of Concomitant Medication

The intake of concomitant medication in the present study was supposed to remain constant during the entire period of the protocol. However, there were documented changes in the medication intake in 11 subjects. One subject changed the formulation of the product she was taking. Of the remaining 10 subjects who made real changes in their medication intake, 7 subjects decreased their medication and 3 subjects increased their medication. This result by itself indicates that 7 of the 10 subjects experienced sufficient improvement or relief during the study that they were able to decrease their intake of concomitant medication. The result suggests that a documentation of decreases in concomitant medication might be an outcome parameter to be measured in future clinical studies.
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decrease in NSAIDs would be of particular benefit in this population, both in order to decrease the gastrointestinal risk of NSAIDs (Bagge et al. 1997, Simon 1998), but also because of the potential negative effect of certain NSAIDs in chondrocyte metabolism (Smith et al. 1995, Wright 1995).

Mechanism of Action

The clinical benefits of LCE presented in this report may not be explained entirely by the anti-MMP-and/or antiangiogenic effect of liquid cartilage extract. The decreases in joint tenderness and swelling and in the pain measurements are also consistent with the documented anti-inflammatory effect of LCE. This anti-inflammatory effect was demonstrated in a mouse model of contact hypersensitivity, in which LCE decreased the production of several cytokines, including TNF (Zhuang et al. 1997). In this model, the results were similar, although not identical, to results obtained with cortisol administered intraarticularly. Anti-inflammatory and analgesic effects of a liquid cartilage extract have also been demonstrated in rats with paw edema induced by injection of carrageenan and dextran (Fontenelle et al. 1996).

LCE is known to inhibit several enzymes of the matrix metalloproteinase class of enzymes. The anti-MMP effect has been demonstrated in vitro (Dupont et al. 1998) and may be part of the antiangiogenic effect which has been demonstrated in humans (Berbari et al. 1999). The anti-MMP activity of LCE may have particular relevance in arthritides. MMPs are active in the tissue destruction and remodeling of the synovial tissue and cartilage of the joint that is a hallmark of rheumatoid arthritis (Konttinen et al. 1998, Ahrens et al. 1996). The present results were obtained in rheumatoid arthritis subjects, but may well be relevant for osteoarthritis subjects. In osteoarthritis, synthesis of cartilage is inhibited by IL-1 (Dingle 1991), one of the interleukins that is known to be decreased by LCE (Zhuang et al. 1997).

Conclusion

The present results indicate that LCE can decrease joint swelling and pain in subjects with rheumatoid arthritis. The results confirm that this natural product has no side effects and, to the extent that the results are positive, that LCE is orally bioavailable. LCE is known to be anti-inflammatory, to inhibit MMPs and to be anti-angiogenic. These multiple activities are not found in other products and suggest that LCE administration may be appropriate for a wide array of angiogenic and inflammatory disorders, including rheumatoid arthritis and other conditions involving cartilage deterioration, such as osteoarthritis.

Correspondence:
Alain Thibodeau, PhD
Stephen Behr, PhD
Atrium Biotechnologies, Inc.
Quebec, Canada G1P 4P5

References

Comparison of LCE and Other Treatment Modalities:
proportion of subjects who improved by at least 50%

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<th>Treatment</th>
<th>Placebo</th>
<th>LCE</th>
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<td>Percentage of subjects</td>
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<td>Placebo</td>
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<td>LCE</td>
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Legend:
Tender Joint Count
Swollen Joint Count

Duration of study

62

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