Rheumatoid arthritis

Rheumatoid arthritis is a chronic (long-term) disease that causes inflammation of the joints and surrounding tissues. It can also affect other organs. The cause of rheumatoid arthritis (RA) is unknown. It is considered autoimmune disease. The body's immune system normally fights off foreign substances, like viruses. But in an autoimmune disease, the immune system confuses healthy tissue for foreign substances. As a result, the body attacks itself.

RA can occur at any age. It usually occurs in people between 25 and 55. Women are affected more often than men. The course and the severity of the illness can vary considerably. Infection, genes, and hormones may contribute to the disease. RA usually affects joints on both sides of the body equally. Wrists, fingers, knees, feet, and ankles are the most commonly affected.

The disease usually begins gradually with fatigue, morning stiffness (lasting more than one hour), widespread muscle aches, loss of appetite, and weakness. Eventually, joint pain appears. When the joint is not used for a while, it can become warm, tender, and stiff. When the lining of the joint (synovium) becomes inflamed, it gives off more fluid and the joint becomes swollen. Joint pain is often felt on both sides of the body, and may effect the wrist, knees, elbows, fingers, toes, ankle or neck. Additional symptoms include:

- Loss of appetite
- Low-grade fever
- Limited range of motion
- Deformities of hands and feet
- Round, painless nodules under the skin (usually a sign of more severe disease)
- Inflammation of the lung (pleurisy)
- Skin redness or inflammation
- Paleness
- Swollen glands
- Eye burning, itching, and discharge
- Numbness or tingling

Anemia may occur due to failure of the bone marrow to produce enough new red cells. Joint destruction may occur within 1-2 years after the appearance of the disease.

RA usually requires lifelong treatment, including medications, physical therapy, exercise, education, and possibly surgery. Early, aggressive treatment for RA can delay joint destruction. Rheumatoid arthritis is not solely a disease of joint destruction. It can involve almost all organs. A life-threatening joint complication can occur when the cervical spine becomes unstable as a result of RA. Rheumatoid vasculitis (inflammation of the blood vessels) is a serious , potentially life-threatening complication of RA. It can lead to skin ulcerations and infections, bleeding stomach ulcers, and nerve problems that cause pain, numbness, or tingling. Vasculitis may also affect the brain, nerves, and heart, which can cause stroke, heart attack, or heart failure.

RA may cause the outer lining of the heart to swell (pericarditis) and cause heart complications. Inflammation of heart muscle, called myocarditis, can also develop. Both of these conditions can lead to congestive heart failure.

Current Medications

Current standard of care (in addition to rest, strengthening exercises, and anti-inflammatory drugs) is aggressive therapy with **disease-modifying anti-rheumatic drugs (DMARDs).** Methotrexate (Rheumatrex) is the most commonly used DMARD for rheumatoid arthritis. Others include leflunomide (Arava), gold thiomalate (Myochrysine), aurothioglucose (Solganal), or auranofin (Ridaura).

Anti-inflammatory agents are used to treat RA include aspirin and non-steroidal anti-inflammatory drugs (NSAIDS), such as ibuprofen (Motrin, Advil), fenoprofen, indomethacin, and naproxen (Naprosyn). NSAIDS are commonly used to relieve joint pain and inflammation. Although NSAIDs work well, long-term use can cause stomach problems, such as ulcers and bleeding, and possible heart problems. In April 2005, the FDA asked drug manufacturers of NSAIDs to include a warning label on their product that alerts users of an increased risk for cardiovascular events and gastrointestinal bleeding.

COX-2 inhibitors block an inflammation-promoting enzyme called COX-2. This class of drugs was initially believed to work as well as traditional NSAIDs, but with fewer stomach problems. However, numerous reports of heart attacks and stroke have prompted the FDA to re-evaluate the risks and benefits of the COX-2s. Rofecoxib (Vioxx) and valdecoxib (Bextra) have been withdrawn from the U.S. market following reports of heart attacks in patients taking the drugs. Celecoxib (Celebrex) is still available, but labeled with strong warnings and a recommendation that it be prescribed at the lowest possible dose for the shortest duration possible.

Antimalarial medications such as hydroxychloroquine (Plaquenil) and sulfasalazine (Azulfidine) are also beneficial, usually in conjunction with methotrexate. This medications.are slow acting and are associated with toxic side effects.

Tumor necrosis factor (TNF) inhibitors are a relatively new class of medications used to treat autoimmune disease. They include etanercept (Enbrel), infliximab (Remicade), and adalimumab (Humira). Adalimumab and etanercept are injectable medications. Infliximab is given by IV.

Interleukin 1 Inhibitor: Another relatively new medication is injectable anakinra (Kineret), which is a protein that blocks the inflammatory protein interleukin-1. The drug is used to slow the progression of moderate to severe active RA in patients over 18 who have not responded to one or more of the DMARDs. Kineret can be used with other DMARDs or TNF inhibitors.

Immunosuppresants: Other drugs that suppress the immune system, like azathioprine (Imuran) and cyclophosphamide (Cytoxan), are sometimes used in people who have failed other therapies. These medications are associated with toxic side effects and usually reserved for severe cases of RA.

Corticosteroids: have been used to reduce inflammation in RA for more than 40 years. However, because of potential long-term side effects, corticosteroid use is usually limited to short courses and low doses where possible. Side effects may include bruising, psychosis, cataracts, weight gain, susceptibility to infections, diabetes, high blood pressure, and thinning of the bones (osteoporosis). A number of medications can be administered with steroids to minimize osteoporosis.

ParActin® Rheumatoid Arthritis Research

In previous research, we have shown the anti-inflammatory property of ParActin®. Our research has shown ParActin® to naturally activate PPAR gamma, thereby inhibit NF kappa B, deactivate T cell proliferation, and reduce pro-inflammatory cytokines such as Interleukin 2, Interferon gamma, TNF α, and COX 2. In our previous in vitro and in vivo research with mice with Multiple Sclerosis (MS), we have shown ParActin® to effectively reduce clinical scores of the symptoms, significantly inhibit the Interferon gamma, Interleukin 2, and T cell proliferation within 3 weeks. Since rheumatoid arthritis (RA) is also an auto-immune disease like MS, and ParActin® has the same mechanism of action like most current medications for RA, such as NSAIDs (NFkappaB inhibitor), COX-2 inhibitors, TNF α inhibitor, Interleukin inhibitor, we hypothesis that ParActin® may be useful for reducing symptoms in RA.

Method:

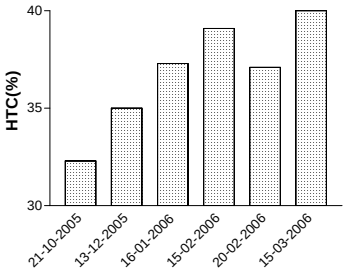
10 patients diagnosed with RA were given 200mg of ParActin®, once daily for 18 weeks. A complete blood test is conducted. Hemacrit, hemoglobin, C-reactive Protein, and Rheumatoid Factor value were tested at the beginning, week 3, 7, 11, 15, and 18.

Hematocrit (HCT)

The hematocrit is the percent of whole blood that is composed of red blood cells. The hematocrit is a measure of both the number of red blood cells and the size of red blood cells. The hematocrit is almost always ordered as part of a complete blood count, which measures the number of red blood cells, the number of white blood cells, the total amount of hemoglobin in the blood, and the fraction of the blood composed of red blood cells (hematocrit).

Normal Hematocrit level may varies with altitude:

- Male: 40.7-50.3%
- Female: 36.1-44.3%



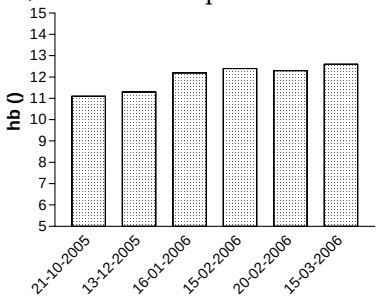
Low hematocrit level may indicate anemia, bone marrow failure, destruction of red blood cells, leukemia, malnutrition, and rheumatoid arthritis.
In this study, patients taking ParActin® is showing improvement of hematocrit level from below normal level of around 32.4% (pre-treatment) to a normal average level of ~40% at the end of the 18 weeks clinical study.

Hemoglobin

Hemoglobin is the protein molecule in red blood cells that carries oxygen from the lungs to the body's tissues and returns carbon dioxide from the tissues to the lungs. The normal ranges for hemoglobin depend on the age and, beginning in adolescence, the sex of the person. The normal ranges are:

- Men after middle age: 12.4-14.9 gm/dl
- Women after middle age: 11.7-13.8 gm/dl

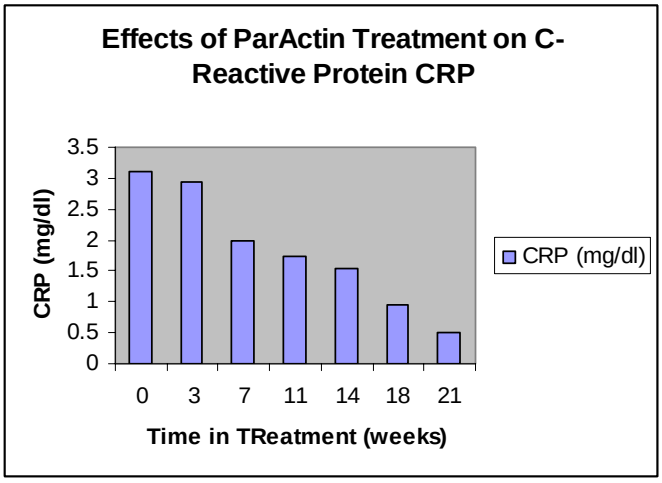
In this study, patients taking ParActin® is showing gradual improvement in hemoglobin level from below normal level of 11% (pre-treatment) to healthy normal level of 12.6% at the end of study.



Both Hematocrit and Hemoglobin test indicates the capacity of ParActin® to revert one of the most relevant systemic complications of rheumatoid arthritis chronic inflammatory activity, such as myelosuppression, a condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets. During the period of myelosuppression, patients may be at an increased risk of infection or bleeding or may experience symptoms from anemia. Myelosuppression has the highest clinical value in RA, and is a common side effect from taking the current available RA medications. This research showed that ParActin® may normalized the hemoglobin and hematocrit level and avoid side effects associated with current RA medications.

C-Reactive Protein

C-Reactive Protein (CRP) is a test which measures the concentration in blood serum of a special type of protein produced in the liver that is present during episodes of acute inflammation or infection. In the body, CRP plays the important role in the immunologic defense mechanism. Normally there is no CRP in blood serum. A high or increasing amount of CRP in blood suggests an acute infection or inflammation. Although a result above 1 mg/dL is usually considered high for CRP, most infections and inflammations result in CRP levels above 10 mg/dL. A positive CRP may be an indicator of several conditions, including rheumatoid arthritis, cancer, tuberculosis, pneumonia, heart attack, and lupus.



CRP also has the highest clinical value in RA. Patients treated with ParActin® is showing improvement in CRP level from a above normal CRP level of over 3% at pre-treatment to a normal level of 0.5%. The result suggest the capacity of ParActin® to reduce C-reactive protein, which is one the most sensitive mediator reactants of acute and chronic inflammatory activity in RA, which also correlates with symptoms profile and systemic perception of either well being or worsening. NSAIDs, which exhibits NFkappaB inhibitory activity has been shown to effectively reduce CRP level. Corticosteroids and immunosupresive drugs only partially reduce CRP level. This research showed that ParActin, which also exhibits NFkappaB inhibitory activity, is effective in normalizing CRP level.

Rheutamoid Factor Test

This is a test that measures the presence and level of rheumatoid factor (RF) in the blood. The RF test is used mainly in the diagnosis of rheumatoid arthritis, although the test result can be positive in many other diseases as well as in healthy people. RF is an antibody that attaches to a substance in the body called immunoglobulin G (IgG), forming a molecule known as an immune complex. This immune complex can activate various inflammatory processes in the body. About 80% of patients with rheumatoid arthritis have positive RF tests.

Normal Value for RF Test is less than 60 u/ml (nephelometric method) or less than 1:80 titer (agglutination method). A positive test may indicate chronic hepatitis, chronic viral infection,

leukemia, dermatomyositis, infectious mononucleosis, rheumatoid arthritis, scleroderma, and systemic lupus erythematosus. In this study, we do not showed that ParActin has any effects on RF value. The changes of RF values observed during 21 weeks of treatment did not show any other laboratory parameter, clinical or any particular symptoms correlation.

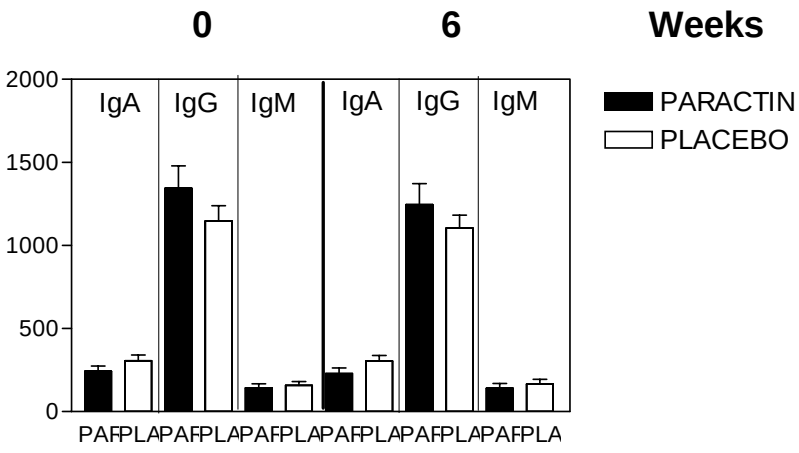
ParActin® Double Blind, Placebo Controlled, Rheumatoid Arthritis Research

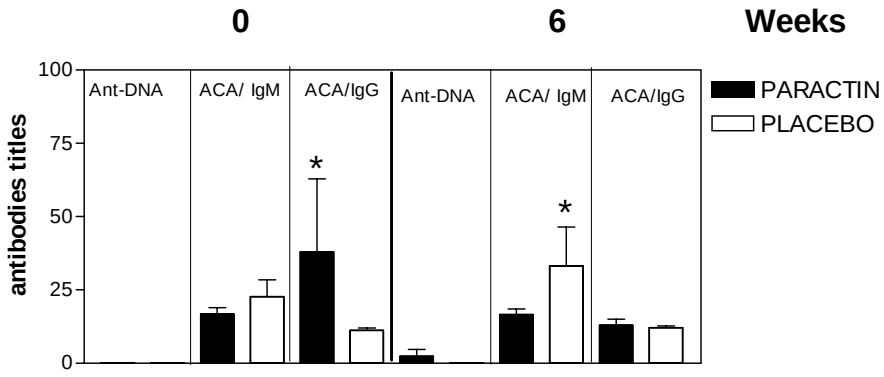
14 patients diagnosed with rheumatoid arthritis were recruited in this double blind, placebo controlled research. Patients were given either 200mg of ParActin® or NSAIDs (placebo) once daily for 6 weeks.

Autoantibodies Titers

Abnormal Immunoglobulin G (IgG) antibodies are produced by the lymphocytes in the synovial membranes. They act as antigens. Other IgG and IgM antibodies react with these abnormal antigens to produce immune complexes. The reactive IgM is called the Rheumatoid Factor (RF).

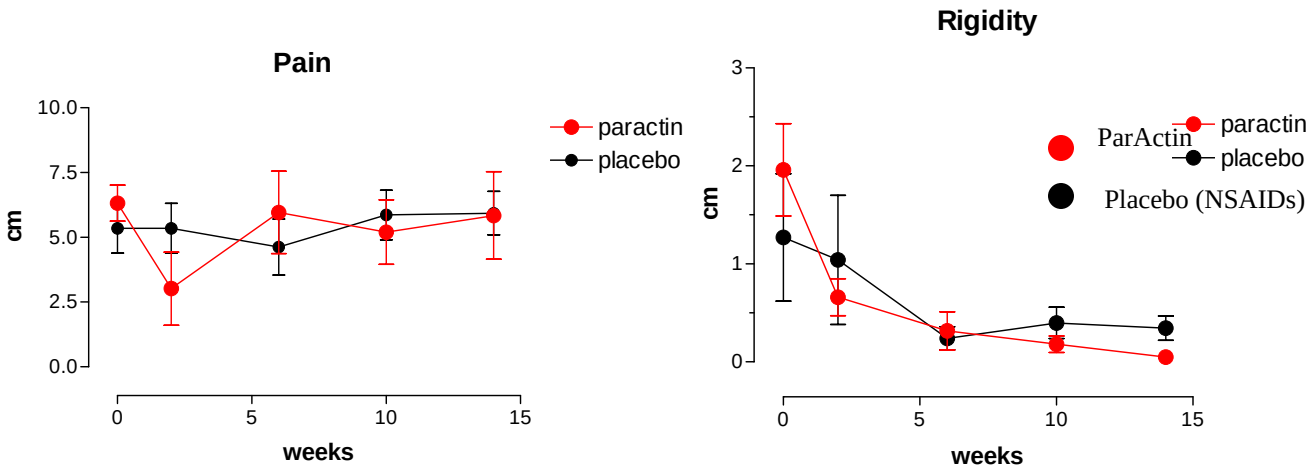
Measurement of IgG, IgM and IgA anti-cardiolipin autoantibodies (aCL) by EIA is the standard procedure for the detection of antiphospholipid antibodies (aPL) in patients with rheumatoid arthritis. High levels of anti-cardiolipin antibodies occur in thrombosis, fetal loss, thrombocytopenia and several other disorders. IgG and IgA class anti-cardiolipin antibodies (ACA) appear to be more closely associated with anti-phospholipid syndrome and low levels of IgM antibodies can be identified in other autoimmune diseases such as rheumatoid arthritis and lupus. Patients with rheumatoid arthritis do not develop Anti-DNA antibodies.





At the end of the 6 weeks trial, both groups are showing no change in IgA and IgM, and significant reduction in the IgG level.

At the end of the 6 weeks trial, both groups are showing no change in anti-DNA antibodies. This result is expected as the presence or absence of anti-DNA antibodies does not affect rheumatoid arthritis. There are significant reductions in both classes of IgM and IgG anti-cardiolipin antibodies in the ParActin® group, which correlate with a decrease in the RA activity. The placebo group that is taking NSAIDs is showing increase in IgM ACA titers and no change in IgG ACA titers.



Effect of ParActin® on clinical symptoms. Bar represents the mean±SEM of paractin (n=5) and placebo (n=9). *p<0.05 compared with ParActin group.

As observed in the above figure, a significant decrease of pain compared to the NSAIDs placebo group is observed up to 2 weeks of ParActin® treatment, after which the analgesic effect decreases to overlap the NSAIDs placebo group at week 5, with no change thereafter. The rigidity chart shows that both ParActin® and NSAIDs placebo groups significantly decrease the intensity of rigidity test with ParActin® group decreasing more than the placebo throughout the 15 weeks treatment period. These findings indicate that ParActin® maybe as effective as traditional NSAIDs in reducing pain and improving rigidity in patients with early stage rheumatoid arthritis.

Conclusion

Our previous research has shown ParActin® to naturally activate PPAR gamma, thereby inhibit NF kappa B, and reduce pro-inflammatory cytokines such as Interleukin 2, Interferon gamma, TNF α, and COX 2. The anti-inflammatory effect of ParActin® has significant effect on auto-immune inflammatory serological markers, specifically in normalizing the hematocrit, hemoglobin, C - reactive protein. ParActin® is also effective in reducing the IgG ACA titers, which correlates well with a decrease of rheumatoid arthritis clinical activity. We conclude that ParActin® is useful for reducing clinical symptoms for patients with early stage rheumatoid arthritis.