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Remission of Rheumatoid Arthritis with Millennium Therapy

In the last two decade a revolutionary change happened in the treatment of rheumatoid arthritis or autoimmune inflammation. The treatment technique, called the millennium therapy, combines several immunosuppressants given serially by intravenous infusion or oral route.

However, combination therapy is only given to rheumatoid arthritis patients with positive rheumatoid factor. Treatment should be given in early stage or at acute relapse of rheumatoid arthritis. This new technique can help in preventing joint erosion and damage, physical inability, and early death in rheumatoid arthritis patient at early stage.

John Darmawan MD PhD, WHO Expert on Rheumatic Disease disclosed this while visiting Seroja Rheumatic Center in Semarang, early May.

This new treatment method provides satisfactory result in patients with disease duration less than 5-7 months, he explained. It is mainly for patients with first grade joint erosion. Patient may achieve drug-free remission sustained for a lifetime if early relapse is treated immediately. Drug-free remission may be achieved using drug combination readily available in Indonesia.

For patients with second grade erosion and disease duration of more than 7 months, remission with therapy may be achieved. This remission may also be sustained for a lifetime with minimum dose (maintenance dose) of 1-2 immunosuppressants. By maintaining remission with therapy, the progress of autoimmune inflammation process is halted. This means that no new joint erosion or diminishing of the halted erosion.

RHEUMATOID arthritis is a chronic and progressive disease, which is likely to cause joint damage and disabilities. Around 99-100% of rheumatoid arthritis patients with positive rheumatoid factor will develop erosion and joint damage with physical disabilities and sometimes early death.

This fact, according to Prof. Pincus (1988), a rheumatologist from the US who was quoted by John Darmawan, shows that treatment methods that have been used for the past half century failed to stop disease progression.

Rheumatoid arthritis does not only involve joint, but also the whole body. General symptoms of rheumatoid arthritis with positive rheumatoid factor include generalized pain, loss of appetite, weight loss, mild fever, fatigue (physical and mental), and anemia. Patients always feel tired and have morning stiffness on waking up. Fatigue and stiffness could last the whole day.

John Darmawan explained that uncontrolled seropositive rheumatoid arthritis would cause joint damage in 99% patients after 25 years. At later stage of rheumatoid arthritis, complications in the skin, blood vessels (vasculitis), bone marrow (causing anemia), eye damage, lungs and pleura (shortness of breath), heart, muscle, intestines, nerves and other body part could arise. In some patients, rheumatoid nodules at the elbow could be found.

Risk of early death in seropositive rheumatoid arthritis patients is 6 times higher compared to seronegative rheumatoid arthritis patients (without rheumatoid factor) and healthy population. "If early stage seropositive rheumatoid arthritis is treated with the state-of-the-art treatment before joint erosion, remission without therapy may be achieved in the long term. It may be maintained for a lifetime by eradication of early relapses," said Darmawan.

The new therapy needs a sophisticated equipment to detect early erosion after a disease duration of one month. Joint erosion and bone damage may be detected with MRI (Magnetic Resonance Imaging), DEXA (Densitometer), and Sonography (Ultrasonography) within one month of disease appearance. While conventional X-ray could only show joint erosion after a disease duration of more than 3 months.

According to Darmawan, seropositive rheumatoid arthritis patients should be treated with a stronger medication (immunosuppressants) at early stage before the appearance of permanent damage. Administration of this drug should be regularly monitored for adverse effect and accompanied by regular blood and urine tests. This drug could cause some adverse effects, e.g. moon face (facial edema), renal dysfunction, anemia and gastric hypersensitivity.

Dose of autoimmune suppressant is far smaller than the dose of chemotherapeutics. In small doses and short duration of use, immunosuppressants rarely cause adverse effects. If there is adverse effect, usually it is mild and easy to control. However, monitoring for adverse effect should always be conducted.

Updated therapy for seropositive rheumatoid arthritis patients is started with an infusion of a combination of cyclophosphamide, methylprednisolone and methotrexate. This is accompanied by taking a combination of cyclosporine, leflunomide and mycophenolate mofetil orally. Depending on the severity of the disease, the combination of infusion and oral drug could be a combination of only 2-3 immunosuppressants. This combination therapy is only given to rheumatoid arthritis patients with seropositive rheumatoid factor. Treatment should be done in early stage of the disease or in acute relapse of rheumatoid arthritis.

Each immunosuppressant has different mechanism in causing drug adverse effect. The autoimmune inflammation suppression effect of the drug is collective. According to publication in the USA and Darmawan's experience, small dose rarely caused adverse effects, especially when given by infusion. Cyclophosphamide and methylprednisolone given by infusion only rarely caused mild adverse effect compared if given orally.

After remission, infusion should gradually be stopped, while oral therapy is continued while monitoring the 1-hour erythrocyte sedimentation rate and level (dilution) of CRP (C-Reactive Protein). If erythrocyte sedimentation rate is less than 20mm/1 hour and CRP level becomes negative, oral drug could be stopped one by one.

Erythrocyte sedimentation rate and CRP level are good parameters, taking into consideration increased erythrocyte sedimentation rate caused by menstruation, pregnancy, infection, low Hb and increased CRP level caused by infection. By maintaining CRP level within normal limits, the rheumatoid arthritis process could be stopped.

According to John Darmawan, when immunosuppressants are taken orally, monitoring for drug adverse effect should be conducted every 1-3 months by blood and urine testing. General practitioner and family physician could administer oral combination of immunosuppressants under the guidance of a rheumatologist or internist – rheumatologist. In the meantime, infusion with combination of immunosuppressants is best left to the internist - rheumatologist or rheumatologist.

In the first two years of free-drug remission, patient is advised not to conduct any physical work (routine overloading) and avoid severe mental and physical stress. This is to prevent relapse of seropositive rheumatoid arthritis. Physical and mental trauma could trigger the relapse of seropositive and seronegative rheumatoid arthritis.

Recently in the western countries, a molecular biology recombinant drug with generic name *etanercept* has been used by injection 3 times daily. The parenteral preparation is named *infliximab*. Combination of etanercept or infliximab with methotrexate in rheumatoid arthritis patients helps to achieve remission and could be maintained in the long term. Both drugs have been used for 6 years in the USA.

“So, with this new treatment method, rheumatoid arthritis patients should not experience joint erosion and damage anymore.” said Darmawan who also coordinated rheumatic disease research in developing countries all around the world.

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