RESPIRATORY INVOLVEMENT IN RHEUMATOID ARTHRITIS PHYSIOLOGIC ABNORMALITIES AND DETERMINANTS OF RADIOGRAPHIC

BY

DR. ASMAHAN MOHAMED ISMAIL

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ABSTRAK

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Latar Belakang

Kesan penyakit rheumatoid arthritis ke atas sistem pernafasan boleh dilihat dalam beberapa bentuk termasuk kesan ke atas selaput pleura, nodul paru-paru, interstitial pulmonary fibrosis, and obliterative bronchiolitis.

Ellman dalam tahun 1947 telah menunjukkan terdapatnya kesan pada kedua-dua lobar paru-paru dalam pesakit rheumatoid arthritis dan lebih banyak kes dikesan selepas itu. Selain daripada kesan di atas, penyakit yang lebih teruk yang mengakibatkan kerosakan pada fungsi paru-paru boleh terjadi di dalam pesakit RA walaupun X-ray dada menunjukkan paru-paru dalam keadaan normal.

Dalam tahun 1994, M. Linstow dan rakan penyelidik telah juga menunjukkan pesakit dengan penyakit RA mempunyai fungsi paru-paru yang abnormal.

Objektif

Tujuan utama penyelidikan ini adalah untuk mengkaji prevalen dan kesan penyakit RA ke atas paru-paru mereka. Kesan ini dikaji dengan menggunakan spirometri untuk melihat fungsi paru-paru di dalam pesakit RA manakala kajian kesan penyakit ke atas paru-paru dilihat dengan menjalankan ujian radiografi. Objektif selanjutnya adalah untuk melihat kesan aktiviti penyakit ke atas paru-paru.

Metodologi

Penyelidikan telah dijalankan diantara bulan November 2000 hingga Oktober 2001. Pesakit rheumatoid arthritis yang menghadiri Klinik Rheumatoid dan dimasukkan ke dalam wad, Hospital Universiti Sains Malaysia yang telah memenuhi kriteria kemasukan dan penyisihan dikenal pasti. Semua pesakit mestilah disahkan diagnosis rheumatoid arthritis menggunakan kriteria dari American Rheumatic Association. Apabila telah dikenal pasti, penerangan ringkas mengenai penyelidikan diberi. Pemeriksaan asas termasuklah ujian penuh sistem darah termasuk kadar sedimentasi sel darah merah, ujian fungsi renal dan hati. Kesan ke atas sistem immunologi diselidik dengan mengambil penyiasatan faktor rheumatoid, factor anti-nuklear, kadar sistem komplemen dan protein

reaktif-C. Penyiasatan spirometri akan dijalankan kepada semua pesakit dan bacaan yang tertinggi akan diambil untuk keputusan akhir. Kesemua pesakit juga dikehendaki menjalani pemeriksaan radiografi paru-paru dan simptom penyakit paru-paru contohnya batuk berpanjangan dan kesesakan nafas ditanya. Pesakit juga akan diperiksa kewujudan krepitasi pada bahagian bawah paru-paru secara klinikal.

Keputusan

Keputusan menunjukkan terdapat perbezaan yang signifikan di antara purata FVC, FEV_1 dan FEV_1/FVC dalam pesakit rheumatoid arthritis dibandingkan dengan nilai jangkaan yang diselaraskan mengikut nilai normal di dalam populasi.

Jenis fungsi respiratori yang paling kerap ditemui dalam pesakit rheumatoid arthritis ialah jenis restriktif di mana FVC% adalah kurang dari 80%.

Ujian radiograf paru-paru mengesan 12 filem radiograf yang abnormal dalam pesakit RA dan daripada jumlah tersebut, 50% mempunyai fungsi paru-paru yang normal. Radiograf paru-paru abnormal yang paling kerap dijumpai adalah 'peribronchial thickening and/or pleural thickening' dan 'interstitial lung disease'.

84.6% pesakit yang mempunyai radigraf paru-paru yang normal mempunyai ujian fungsi paru-paru jenis restriktif. Di dalam kajian ini di dapati tidak ada perkaitan di antara tanda-tanda penyakit dan aktiviti penyakit dengan fungsi paru-paru.

Kesimpulan

Fungsi fisiologi sistem paru-paru ke atas pesakit rheumatoid arthritis adalah abnormal walaupun mereka tidak mempunyai simptom atau tanda-tanda penyakit. Kebanyakan pesakit mempunyai kesan restriktif ke atas sistem paru-paru mereka. Pengesanan kesan ini adalah lebih baik menggunakan spirometri dibandingkan dengan radiografi paru-paru. Fungsi paru-paru ini tidak dipengaruhi oleh tanda-tanda penyakit, kesan ke atas radiografi paru-paru dan aktiviti penyakit rheumatoid arthritis.

ABSTRACT

RESPIRATORY INVOLVEMENT IN RHEUMATOID ARTHRITIS – PHYSIOLOGIC ABNORMALITIES AND DETERMINANTS OF RADIOGRAPHIC

Background

Pulmonary disease in rheumatoid arthritis (RA) may take many forms including pleural lesions, lung nodules, interstitial pulmonary fibrosis, and obliterative bronchiolitis. In 1947, Ellman first described diffuse bilateral interstitial changes in the lungs of a patient with rheumatoid arthritis and many similar cases have been reported throughout the world. In addition to the distinct lung disorders mentioned above, low grade disease of the respiratory tract, and even considerable impairment of respiratory function, may occur in rheumatoid arthritis in spite of radiologically normal lungs. M. Linstow and colleagues in 1994 have showed that patients suffering from RA have prominent functional pulmonary abnormality.

Objective

The aim of this study is to evaluate prevalence and characteristic of respiratory involvement in patients with rheumatoid arthritis. The characteristic will be determined by doing a lung function test in all patient confirmed to have rheumatoid arthritis while evaluation of the radiographic changes is done with a chest radiograph. The second objective is to assess the relationship between disease activity and lung involvement.

Subjects and methods

The study was carried out during a period between November 2000 to October 2001. The patients were recruited from Rheumatology Clinic and medical wards, Hospital Universiti Sains Malaysia who fulfilled inclusion and exclusion criteria. All patients should satisfy the American Rheumatic Association criteria for Rheumatoid Arthritis. Once patients were identified, a brief explanation of the study was made. Baseline investigations includes full blood count, erythrocyte sedimentation rate, renal and liver function test. The immunological system is evaluated by doing a rheumatoid factor, complement level and C-reactive protein. Lung function test were performed for all patients and highest reading was taken as the final result. A chest radiograph was done on all patients included in this study. They were

also asked for associated respiratory symptoms of chronic cough, shortness of breath and assessed of presence of basal crepitations clinically.

Results

There were significant different in the mean FVC, FEV_1 and FEV_1/FVC of patients with RA as compared to normal population. The most common types of respiratory function abnormality in patients with RA was restrictive type where the FVC% was less than 80%.

Assessment of chest radiograph revealed twelve abnormalities in the chest x-ray of RA patients and out of this , 50% of the lung function test is normal. The most common abnormalities detected is peribronchial and/or pleural thickening and interstitial lung disease.

While 84.6% of patients with normal chest x-ray had restrictive type of abnormality on their lung function test. There were no relationship between the sign and disease activity with lung function test.

Conclusion

The physiological function of the respiratory system in rheumatoid arthritis patients are abnormal eventhough they remain asymptomatic.

The most common abnormalities in rheumatoid lung disease by doing the lung function test is the restrictive type. Lung function test predicts lung abnormalities better than assessment of chest radiography. The lung function is not affected by sign, chest radiographic finding and activity of disease. However there is suggestion that the longer the disease, the more likely to have abnormal and more severe impairment of the lung function test.

CHAPTER 1

INTRODUCTION

1.1. Physiologic Abnormalities

Physiologic abnormalities are common in rheumatoid arthritis (RA). Abnormalities suggestive of interstitial lung disease (ILD) are reported in 22%-40% of patients (Hakala M. 1988, Anaya J-M et al 1995). The changes most commonly seen in association with ILD parellel those of any fibrosing lung disease include reduction in lung volumes, pulmonary compliance and abnormalities in diffusing capacity for carbon monoxide (DLCO). Many RA patients with normal chest radiographs may be found to have abnormalities in pulmonary functions. Physiologic testing also often shows evidence of obstruction to airflow, which may reflects other pulmonary manifestation of RA including bronchiectasis, bronchiolitis obliterans, chronic airway obstruction, or cricoarytenoid arthritis (King TE 1998, Lake FR et al 1996, Shannon TM et al 1992)

The goal of physiology is to explain the physical and chemical factors that are responsible for the origin, development, and progression of the disease. The diagnosis and treatment of most respiratory disorders have come to depend heavily on an understanding of the basic physiological principles of respiration and gas exchange (Rhoades and Pflanzer 1996).

1.1.1. Factors Affecting Physiologic Abnormalities

Diseases that alter pulmonary function tests can be divided into obstructive and restrictive disorders. With an obstructive disorders, expiratory flows are obstructed, and with restrictive disorder, lung inflation is restricted. Obstructive diseases include bronchial asthma and chronic obstructive airway disease (COAD) while restrictive diseases include interstitial lung disease in connective tissue diseases, chest wall and pleural derangements and neuromuscular diseases.

1.1.2. Methods Used to Assess Physiologic Abnormalities

A simple method for studying pulmonary function is to record the volume movement of air in and out of the lungs, a process called spirometry. One of the most useful test is to assess the overall ability to move air in and out of the lungs (ventilation) is called forced vital capacity (FVC). This is the maximum amount of air that can be breath forcefully and rapidly exhaled after a deep breath. From FVC, another important determinant that can be obtained is the forced expired volume exhaled in one second. This volume is termed forced expiratory volume (FEV_1) has the least variability of the measurements obtained from a forced expiratory manoeuvre and is considered one of the most reliable measurement.

Another useful way of expressing FEV_1 is as percentage of FVC (i.e. FEV_1/FVC x 100), which corrects for the differences in lung size. Normally FEV_1 is 80% or more of the FVC (i.e, 80% of an individual's forced vital capacity can be exhaled in the first second)

In obstructive lung disorders, FVC and FEV_1 are both reduced with a prominent reduction in FEV_1 and the ratio of FEV_1/FVC is reduced

drastically below normal (<80%). In restrictive type, both FVC and FEV_1 are reduced making the ratio of FEV_1/FVC is normal or slightly higher (Rhoades and Pflanzer 1996)

The typical findings of RA associated lung disease include reduced lung volumes and diminished diffusion capacity and hypoxemia, a findings characteristic of restrictive lung disease. Kenneth et al in 1996 have found at least 32.4% abnormal findings was identified by pulmonary function test as restrictive type in 336 patients with rheumatoid arthritis and known lung disease. These abnormal findings include FVC < 80% of predicted in 42 patients and evidence of radiographic infiltrates in 40 patients (Kenneth et al 1996).

Other study done by Perez T et al found 18% of 50 studied patients with RA had an obstructive type of lung function abnormality.

1.2. Radiographic Abnormalities

Pulmonary disease in rheumatoid arthritis may take many forms, including pleural lesions, lung nodules, and interstitial lung disease. Rheumatoid arthritis interstitial lung disease (RA-ILD) is particularly debilitating, with

reported prevalence ranging from <2% to >40% and a survival rate as low as 39% (Hakala M 1988 , Anaya J-M et al 1995). The most common manifestations are pleural abnormalities and ILD. In ILD, the most common finding is that of bilateral interstitial abnormalities that are asymmetric (Remy-Jardin et al 1994, Roschman RA et al 1987). Fibrosing alveolitis may be apparent on the chest radiograph in approximately 5% of patient. It usually produces basal reticular nodular shadowing, but may progress to a coarser and more widespread lung field involvement and honeycombing may appear (Locke GB 1963). As fibrosis advances, there is a tendency for severe volume loss. Disease progression results in a more reticular nodular pattern (David Sutton).

1.2.1. Methods Used to Determine Radiographic Abnormalities

Depending on the diagnostic modality used to detect disease, prevalence rates of ILD in RA are reported with wide variance. Radiographically, the changes seen with ILD and RA are indistinguishable from those seen with idiopathic pulmonary fibrosis or ILD associated with other connective tissue diseases (Lynn T. Tanoue 1998).

The plain chest radiograph is an insensitive means of identifying ILD, yielding a prevalence rate of 2%-6%. High Resolution CT Scanning (HRCT) is more sensitive method of detecting interstitial changes in fibrosing lung disease (Hansell DM et al 1991). The prevalence of pulmonary interstitial changes in RA identified by HRCT is reported from 10% - 47%.

1.3. Rheumatoid Arthritis

Rheumatoid arthritis affects about 1% of the population worldwide. The natural history of the disease is characterized by the infiltration of immunocompetent cells into the synovial fluid and tissue, and stimulation and proliferation of synovial fibroblast (Edward D. Harris, JR.1990). Epidemiologic studies have shown that 30% of patients developed pathological joint erosions within the first year and 70% within 2 years (Joachim R. Kalden 2001, Van der Hiejde DM 1995). Based on the epidemiologic data, RA can no longer be considered a benign disease that only affects joint function, since statistical analyses have shown increased mortality compared to general population (Mitchell DM et al 1986, Scott DL et al 1987).

Rheumatoid arthritis is usually an aggressive disease that needs to be treated forcefully if subsequent deformity and disability are to be reduced. The long term outcomes in RA include not only joint destruction, work and functional disability, psychological dysfunction, and treatment related side effects as well as associated co-morbid illnesses. Any of these can potentially compromise the quality of life and life expectancy (Peter Brooks, 1998).

1.3.1. Defination

Rheumatoid arthritis is a systemic disease characterized by subacute or chronic non-suppurative inflammatory arthritis that affects mainly peripheral joints, usually in a symmetric manner. It characteristically follows a prolonged course of exacerbation and remission (Gary W.Hunninghake, Anthony S.Fauci 1979).

1.3.2. Pathogenesis

The cause of rheumatoid arthritis is unknown. Indeed, it is possible that many different arthritogenic stimuli activate the immune response in the

immunogenetically susceptible host. The presentation of a relevant antigen to an immunogenetically susceptible host is believed to trigger rheumatoid arthritis.

The pathogenesis of RA will be divided into 5 stages (Edward D.Harris 1990):-

i.   Stage 1

Antigen- presenting cells (APC) such as macrophages of dendritic cells in the synovial membrane are the first to be involved in the human immune response. These APC ingest, process, and present foreign proteins antigens to T-lymphocytes, which initiate a cellular immune response and stimulate the differentiation of B-lymphocytes into plasma cells that secrete antibody. The patient will probably has no symptom during this stage.

ii.   Stage 2

T-lymphocytes and antigen initially activate B-lymphocytes in the synovial membrane. The B-cells then proliferate, and some differentiate into antibody-secreting cells. These steps are mediated by cytokines, particularly interleukin-2. The production of antibodies within an expanding scaffold of new blood vessels and synovial-cell proliferation lead to process called

angiogenesis (Koch AE et al 1986). The development of an extensive network of new blood vessels in the synovial membrane is essential to the evolution of rheumatoid arthritis. During this stage, the patient will complaint of malaise, mild joint stiffness and swelling without abnormality detected radiologically.

iii.   Stage 3

Accumulation of neutrophils in the synovial fluid acts as the chemoattractants within the joint space. Once within the joint fluid, neutrophils probably are rapidly activated by the phagocytosis of cellular debris and aggregates of immune complexes. The activation of neutrophils results in degranulation, with the release of proteinases (Hibbs MS et al 1984) and the production of additional chemotactic stimuli, such as leukotrienes B4, reactive oxidants and products of arachidonic acid metabolism (Ehmgreen J.et al 1987).

There will be a balance of the above effect and prevent the unwanted adherence of neutrophils at the non-inflammatory sites. The inhibitor of interactions that is Interleukin-8, is produced by endothelial cells and fibroblast (Gimbrone MA Jr et al 1989). The synovial cell proliferation

occurs without polarization or invasion of cartilage. The patient will present with joint pain and swelling, and morning stiffness. The radiographic changes in this stage is soft tissue swelling.

iv.   Stage 4

The irreversible destruction of cartilage occurs in stage 4 of the disease. It begins when proliferating synovial membrane becomes organized in an invasive front that invades cartilage, tendons, and subchondral bone and lead to destruction.

The principles proteinases released by rheumatoid synovial cells, collagenase and stromelysin, are capable of destroying almost all the matrix proteins present in articular cartilage and bone.

There will be more pronounced swelling of the joints and morning stiffness will be present. At this stage, the MRI reveals proliferation pannus with radiographic evidence of periarticular osteopaenia.

v.   Stage 5

By the time rheumatoid arthritis reached stage 5, irreversible destruction of cartilage is well underway, and attempts to protect joints from progressive

destruction are futile. There will be erosion of subchondral bone, invasion of cartilage by pannus, chondrocyte proliferation and stretching of the ligaments around the joints.

The patient will have joint swelling and pain plus loss of function and early deformity. Clinically, there will be instability of the joints, flexion contractures, decreased range of motion with extra-articular complications.

The precise pathogenic mechanism whereby lung lesions arise in rheumatoid arthritis remains unclear and there is little relevant information on the interstitial lung disease of RA. There is some direct evidence for the local production of TNF-alpha. Alveolar macrophages isolated from broncho-alveolar lavage (BAL) of RA patients with and without interstitial lung disease produced significantly increased amount of TNF-alpha compared to normal controls (Gosset P, Perez T, Lassalle P et al 1991). There was no difference noted in IL-1 levels. Additionally, alveolar macrophages from patients treated with disease-modifying agents (DMARDs) or corticosteroids produced significantly less TNF-alpha.

Fibrosis is usually associated with increased synthesis and turnover of collagen. Neutrophils collagenase levels were increased in those RA patients

with evidence of interstitial lung disease compared to other RA patients (Gilligan DM et al 1990, Weilland JE et al 1987). One study demonstrated that 11 of the 14 RA patients with established interstitial lung disease had increased neutrophils, collagenase, and Type III procollagen peptide levels in the lavage fluid (Gilligan DM et all 1990). Lavage cells (probably macrophages) released increased levels of neutrophils chemotactic activity (presumably IL-8) which probably was responsible for the directed migration of neutrophils to the inflammatory site (Garcia JG 1987, James HL et al 1999).

1.3.3. Diagnosis of Rheumatoid Arthritis

The first criteria for the classification of rheumatoid arthritis were published in 1958. These were used heavily for 30 years and were revised in 1988. The revised criteria were formulated from a computerized analysis of 262 contemporary, consecutively studied patient with RA and 262 control subjects with rheumatic disease other than RA (Arnett FC, Edworthy SM, Bloch DA, et al 1988).

It is important to note that the criteria were designed principally for disease classification for epidemiologic purposes, not for diagnosis in individual

cases. Most rheumatologist believed that the diagnosis of rheumatoid arthritis must be made on clinical grounds in individual patients. Nonetheless, the following criteria are useful as guidelines for making the diagnosis:-

a. Morning stiffness in and around joints lasting at least one hour before maximal improvement is noted.

b. Swelling of the soft tissue (arthritis) observed by physician around three or more joints. At least 3 joint areas have soft tissue swelling or joint effusions, not just bony overgrowth. The 14 possible joint areas involved are right or left proximal interphalangeal, metacarpophalangeal, wrist, elbow, knee, ankle and metatarsophalangeal joints.

c. Swelling (arthritis) of the proximal interphalangeal, metacarpophalangeal or wrist joints.

d. Symmetric arthritis, simultaneous involvement of the same joint areas on both side of the body.

e. Subcutaneous nodule over bony prominences, extensor surfaces, or juxtaarticular region observed by a physician.

f. A positive test for Rheumatoid Factor.

g. Radiographic evidence of erosions, periarticular osteopenia, or both in the joints of the hand, wrist, or both.

To make a diagnosis of rheumatoid arthritis, at least the first four symptoms must have been present for six or more weeks.

For classification purposes, a patient shall be said to have rheumatoid arthritis if she/he has satisfied at least 4 out of these 7 criteria above. Patients with 2 clinical diagnoses are not excluded.

These new criteria demonstrate 91 to 94 percent sensitivity and 89 percent specificity for the diagnoses of rheumatoid arthritis (Arnett FC et al 1988).

1.3.4. Management of Rheumatoid Arthritis

The goal of therapy of rheumatoid arthritis are to relief pain, reduction of inflammation, protection of articular structures, maintenance of function and control of systemic involvement. None of the therapeutic interventions is curative, and therefore all must be viewed as palliative, aimed at relieving the signs and symptoms of the disease (Fauci et all 1998).

Management of patients with RA involves an interdisciplinary approach. The value of informing patients and their families about the nature of rheumatoid arthritis, its tendency to have remission followed by flares of activity, its potential effects on the activities of daily living and energy levels are very important and should be reinforced constantly (Lorig KR, Lubek D, et al 1985).

Adequate rest matched with non-weight bearing exercises to maintain or increase muscle tone without exacerbating joint inflammation is also important aspect of the therapeutic regimen. The inflamed joint is particularly vulnerable to the effects of motion. In joint with effusions, exercise may lead to the development of intraarticular pressures sufficient to shut down synovial blood flow, resulting in ischaemia and tissue damage from oxygen metabolites during reperfusion after the motion-induced hypoxia (Merry P, Winyard PG, et al 1989).

Modification in diet may be helpful if the patient can tolerate it. There is evidence that substituting omega-3 fatty acids such as eicosapentaenoic acid found in certain fish oils or plants for dietary omega-6 essential fatty acids found in meat (Pike MC 1989, Harrison's Textbook 1998).Omega-3 fatty

acids may decrease the production of leucotriene B4, Interleukin-1 beta, Interleukin-1 alpha, and tumor necrosis factor by stimulated peripheral blood mononuclear cells (Sperling RI et al 1987, Endress S et al 1989). Clinical improvement was noted in groups of patients with rheumatoid arthritis who were treated with supplemental icosapentaenoic acid and docosahexanoic acid (Kremer JM, Jubiz W, et al 1987).

Medical management of rheumatoid arthritis includes non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids and disease modifying anti rheumatic drugs (DMARDs). Historically, DMARDs were viewed as toxic drugs and to be introduced if absolutely necessary. The alternative name for it was second line therapy, implying that other therapies such as analgesic and NSAIDs had to have failed in controlling patient's symptoms before DMARDs were justified (Emery P, Conaghan P, Quinn M 2001). Now early used of anti rheumatic drugs reduces long term disability in RA. Early treatment of rheumatoid arthritis, using a 'sawtooth' approach to management results in a remission rate of about 30% which is substantially higher than traditional pyramid treatment (Fries JF 1990, Mottonen T, Paimela L, et al 1996). With the 'sawtooth' approach, combinations of anti rheumatic drugs are used from initial diagnoses, the patient is reviewed at

frequent intervals, and treatment goals are established in terms of a reduction on the disease activity. If no appreciable reduction in disease activity is noted, corticosteroids or other anti rheumatic drugs are added.

A. Non steroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs has the capacity to block the activity of cyclo-oxygenase enzyme and therefore the production of prostaglandin, prostacyclin and thromboxanes. This is important to exert action as an analgesic, anti-inflammatory and antipyretic properties. However the used of NSAIDs has fallen worldwide due to their toxic side effects particularly gastric irritation (Peter Brooks 1998).

It is now understood that the cyclo-oxygenase enzyme system that produces prostaglandin consists of at least 2 basic isoforms, the cyclo-oxygenase 1 and cyclo-oxygenase 2 (Bahkle YS et al 1996).

The cyclo-oxygenase 1 performs 'housekeeping' duties, maintaining a normal gastrointestinal mucosa and renal blood flow while cyclo-oxygenase 2 is the inducible form seen in inflammation site, the brain and the colon cancer cells.

Newer drugs is the specific cyclo-oxygenase 2(COX-2) inhibitors such as rofecoxib and celecoxib (Emery P, et al 2001). The rationale for the development of these newer drugs is to prevent inhibition of all type of prostaglandin particularly in the gastric mucosa which acts as gastric mucosa protective effects. The effectiveness and low incidence of gastrointestinal or renal side effects of such drugs as meloxicam have been shown in clinical trials (Mueller C et al 1996, Ford Hutchinson A 1997).

B. Glucocorticoid

Mechanism of glucocorticoid action in affective symptomatic therapy for RA are still poorly understood, and there has been only limited success in the search for effective but less toxic steroid preparations (Sam Panthakalam 2001). Low dose of less than 7.5 mg/daily prednisolone has been advocated as useful additive therapy to control symptoms (Fauci et al 1998).

Meta-analysis of short term low dose prednisolone (<15 mg/daily) versus placebo and NSAIDs in rheumatoid arthritis has shown that prednisolone in low doses may be used intermittently in patients with RA, particularly if the disease cannot be controlled by other means (Peter C Gotzsche, Helle Krogh Johansen 1998).

C. Disease Modifying Anti Rheumatic Drugs (DMARDs)

Long term data support the view that anti rheumatic drugs reduce long term disability in rheumatoid arthritis. In a study nearly 3000 patients with rheumatoid arthritis followed up for an average of 9 years, consistent use of DMARDs (hydroxychloroquine, sulphasalazine, auronofin, intramuscular gold, D-penicillamine, methotrexate and azathioprine) were associated with better long term disability index determined by the Health Assessment Questionnaire, and this effect occurred over all periods of disease duration (Fries JF, William CA, et al 1996).

NSAIDs and prednisolone failed to show this reduction in disability. These data suggest that consistent use of anti rheumatic drugs may reduce long term disability by up to 30%.

Another study has shown that if patients whose rheumatoid arthritis is well controlled by disease modifying agents are given placebo instead of their anti rheumatic drugs, flare up of the disease occurs in a considerable number (Wolde ST, Breedveld FC, et al 1996).

Several other randomized, non-placebo controlled clinical trial in early RA have compared the effects of various therapeutic combinations with

conventional monotherapeutic strategies. These combined therapeutic regimens have generally included methotrexate (MTX), sulphasalazine, and hydroxychloroquine . Combination of MTX and sulphasalazine have been shown to be better than MTX alone (Haagsma CJ et al 1994, Boers M et al 1997, Dougados M et al 1999).

Cyclosporin A provides additional benefit in patients who do not respond adequately to MTX (Tugwell P, Pincus T, et al 1995), and weekly MTX, sulphasalazine, and hydroxychloroquine are better than MTX or MTX plus sulphasalazine over a two year period without an increased in toxicity (O'Dell JR, Haire CE et al 1996).

In a recent study, a combination of prednisolone (60 mg daily tapering to 7.5 mg daily at six weeks intervals), sulphasalazine (2 grams daily), and MTX (7.5 mg weekly) was shown to be better than sulphasalazine alone over 56 weeks in early RA (Boers M et al 1997). Use of prednisolone in combination is increasing after reports that it reduces erosion rates in RA (Kirwan JR 1995).

One of the major limitation of DMARDs is that their association with considerable toxicity, and therefore careful patient monitoring is necessary. Another problem with DMARDs is that discontinuing treatment is patients

who are in remission can lead to recurrence of synovitis (i.e., a flare). This observation was supported by a randomized, double blind, placebo controlled, multicenter study, which evaluated the effect of terminating second line therapy in 285 patients with a favorable response to treatment (ten Wolde S, Breedveld FC, et al 1996).

D. Immunosuppressive Agent

The immunosuppressive drugs azathioprine and cyclophosphamide have been shown to be effective and exert therapeutic effects similar to those of the DMARDs. These agents cause variety of side effects and therefore these drugs have been reserved for patients who have clearly failed therapy with DMARDs (Fauci et al 1998).

E. Tumor Necrosis Factor- targeted therapy (Infliximab and Etanercept)

Since TNF plays a pivotal role in the host's immune system, a new era in the treatment of RA focused on 2 different approaches to decreases the activity of tumor necrosis factor (TNF). The acton of TNF are mediated by its binding to 2 different receptors (p55 and p75) on a group of cells that includes neutrophils, vascular endothelial cells, and fibroblast. These receptor are also found in soluable form in the serum and synovial fluid and

may act to regulate TNF (O'Dell R 1999). Two different approaches are available to decrease TNF activity: treatment with anti-TNF-alpha antibodies (Infliximab) and administration of soluable TNF receptors (Etanercept). Both of these approaches have produced substantial improvement in patients with RA (Kavanaugh AF 1998).

Weinblatt and collegues report significant improvement when etanercept was added to therapy with MTX for patients with RA. Seventy one percent of the patients given etanercept plus MTX had a twenty percent improvement in measures of disease activity as compared to twenty seven percent in placebo group (Weinblatt ME et al 1999).The place of these new TNF-blocking agents has yet to be clarified due to long term consequences and effectiveness of these agents are not yet fully understood.

F. Stem Cell Transplantation

Stem cell transplantation might offer the ability to give much higher doses of chemotherapy with the change of possibly ablating the autoimmune disease completely. However, as mortality from autologous stem cell rescue is around 1 %, this treatment can now be considered for patients with severe progressive connective tissue disease (Peter Brooks 1998).

1.3.5. Respiratory Involvement In Rheumatoid Arthritis

Rheumatoid arthritis is a disease that primarily affects the joint, but it also involves other organs and tissues, including the lungs and pleura. Pleuropulmonary disease is more common in patient with RA who have severe chronic articular disease, high titers of rheumatoid factor, subcutaneous nodules, and other systemic manifestation such as cutaneous vasculitis.

The pleuropulmonary manifestation include pleurisy, pulmonary nodules, ILD, bronchiolitis obliterans and pulmonary hypertension. Pleural involvement by the rheumatoid process is the most common thoracic complication of RA and accounts for attack of pleurisy with and without effusion. Interstitial pneumonitis and pleural disease may precede articular manifestations (Swhwarz MI , 1993).

The intrapulmonary rheumatoid or necrobiotic nodule, which is pathologically identical to subcutaneous nodule in rheumatoid arthritis, is more common in men than in women. The lung nodules may wax and wane with the appearance of subcutaneous nodules and the activity of RA. In other

instances, they may completely dissapear or may continue to increase in size and numbers for years (Gary W.H.,1979).

Although many of the patients with RA and ILD may be asymptomatic, they typically present with dyspneoa and a non productive cough. Other symptoms such as fever, pleuritic chest pain, and haemoptysis are distinctly less common, unless there are co-existing rheumatoid nodule or pleural disease. Clubbing may be present in fifty to seventy five percent of these patients, and crepitations are usually audible especially over the lower lung fields (Gary W.H.,1979).

Chronic airway obstruction is a common finding in RA. In a study by Geddes et al of 100 patients with RA and normal chest radiographs and 84 control subjects matched for age, sex, and smoking habits, indices of air flow obstruction (FEV1, FEV1/FVC) were significantly lower in patients with RA (Geddes et al, 1979). In a more recent study of another series of 100 patients with RA, the prevalence of airway obstruction (FEV1, FEV/FVC, FEF 25-75 or FEF 25-75/FVC) in 81 non-smoking patients was 16% (Vergnenegre A. et al, 1997). This was significantly higher than a comparison groups of patients with non-RA joint disease matched for age and sex.