# Five Balances in the Management of Rheumatoid Arthritis

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## Abstract

Rheumatoid arthritis (RA) is the most common chronic autoimmune joint disease. The etiology of RA is complex, and then it is impossible to cure completely today and it should be individualized treatment. Immune system is complex. Existing statistical techniques based on reductionism cannot discover many relevant disease risk factors and complex interaction relationship. The disease network model based on complex network is important for the analysis and treatment of RA disease. In this Review, we have found five important layers of RA complex network and presented five balances regulating strategy in the management of RA. We have followed up one RA patient (wife of the author) for one year using this strategy, and the management effect is good. This Review argues RA is self-limiting to some extent, and good management with five balances regulating strategy would have positive significance, among which the balance between neuroendocrine system and immune system is the most important. During the day, glucocorticoid plays an important role in controlling inflammation, and human growth hormone plays an important role in eliminating inflammation during the slow-wave sleep at night. Five balances core concepts can shed light on the management of other causes of arthritis.

## Keywords

Rheumatoid Arthritis, Autoimmune Diseases, Complex Network, Balance, Network Medicine

## 1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disorder characterized by chronic synovial inflammation [1] [2]. RA occurs when autoimmune response leads to tissue damage. Tissue damage in RA is mostly caused by type III hypersensitivi-

ty, with the participation of antibodies, complement, antigen-antibody complex, macrophages, T cells and B cells. Small joints of the hands and feet are more frequently affected. However, this varies with each individual. The main characteristics of RA are stiffness and swelling of the joints as a result of inflammation of the synovium. RA primarily involves the joints, but should be considered a syndrome that includes extraarticular manifestations [3]. RA has a significant negative impact on the ability to perform daily activities, including work and household tasks, and health related quality of life [4].

RA is more common between the ages of 35 and 50 years, with females being more often affected than males (2.5:1) roughly [3]. Guidelines issued by an international task force of rheumatologists suggest that the primary target of RA treatment be clinical remission, defined as the absence of signs and symptoms of significant inflammatory disease. Methods for early diagnosis and effective treatment are needed, as RA presents with a very narrow therapeutic window for remission. It has to be effectively managed within 3 - 6 months after the onset of the disease [1].

But, the exact cause of RA is not clear. The epidemiological of RA shows that RA disease is associated with degradation of thymus. RA usually occurs after about 15 years of thymus degradation. Both genetic and environmental factors have been identified to play a role in disease initiation and progression. Chronic inflammation caused by stressor is important factor. Stressors can be classified into physical and psychological, factors which cause stressor also greatly influence the treatment and rehabilitation of RA patient [2] [5] [6].

In future, research on personalised estimates of risk will be important. The ultimate goal should be to provide personalised estimates of harm for each drug [7] [8] [9] [10]. Due to the complexity of RA and the increasing treatment arsenal, it can be difficult for rheumatologists to provide optimal RA care in all patients [11]. Therapy needs to be balanced against patient factors and treatment-related risks [3] [12].

Because of the large impact of RA on health status and healthcare expenditures, there is a growing interest in self-management for RA patients. Self-management refers to the individual's ability to manage the symptoms, treatment, physical and psychological consequences and lifestyle changes. Thus, self-management encompasses a variety of activities like making lifestyle changes to promote health, such as exercising. However, mastering balance in these various self-management activities can be a complex task for patients [13].

It is assumed that all chronic diseases are localized expressions of general imbalance and that treatment of chronic disease starts with regulating a patient's psychological and physical conditions rather than with focusing on the diseases themselves [2] [6].

The primary aims of this Review are: RA is a heterogeneous disease with a complex and yet not fully understood pathophysiology. It seems that using five balance regulating strategies could assist rheumatologists in achieving low dis-

ease activity or remission in the majority of their patients, ensuring better clinical outcomes, and promoting better work productivity, less comorbidity.

## 2. Methods

We searched Web Science and MEDLINE using the key terms "rheumatoid arthritis" in conjunction with "diagnosis", "pathogenesis", "treatment" and "physical activity". We confined our Review to publications in English reporting studies performed in humans older than 18 years of age.

## 3. Results

RA is still considered a chronic, incurable disease [14] [15] [16]. Immune system is complex. Existing statistical techniques based on reductionism cannot discover many relevant disease risk factors and complex interaction relationship. The disease network model based on complex network is important for the analysis and treatment of RA disease [17]. In this Review, we have found five important layers of RA complex network and presented five balances regulating strategy in the management of RA. This strategy would have positive significance (Figure 1).

### 3.1. Balance between Neuroendocrine System and Immune System

RA is more prevalent among women. Sex hormones were thought to play a role in the pathogenesis and also in the improvement of RA during pregnancy, due to their effects on the immune system [18].

RA could be induced or aggravated by many factors, among which mental factors play a large part in terms of its development, aggravation and recurrence. Mental factors include negative emotions such as tension, anxiety, fear, anger, depression, worry, grief, etc.; stressful events such as family disputes, death of family members, job changes, impending tests, etc.; or over-fatigue or sleep disorders [2].

In RA therapy, anti-inflammatory drugs are often used to control the effects of inflammation. Glucocorticoid is one of these powerful drugs.

Accordingly, the neuronal function could be related to the processes involved in the course of RA and associated with fatigue and depression. Neuroendocrine hormones triggered during stress response may lead to immune dysregulation or altered or amplified cytokine production thus resulting in an increase in disease activity. Various types of transmitter substances in the neuroendocrine-immune network include human growth hormone, growth hormone releasing hormone, somatostatin, epinephrine, norepinephrine, acetylcholine, serotonin, substance P, vasoactive intestinal peptide, glucagon, insulin, cytokines, and growth factors [19]. The stress response and induction of a dysregulation in the cytokine balance can trigger the hypothalamic-pituitary-adrenal axis and sympathetic nervous system.

In conclusion, neuroendocrine-immune network is a general system. During the day, glucocorticoid plays an important role in controlling inflammation, and
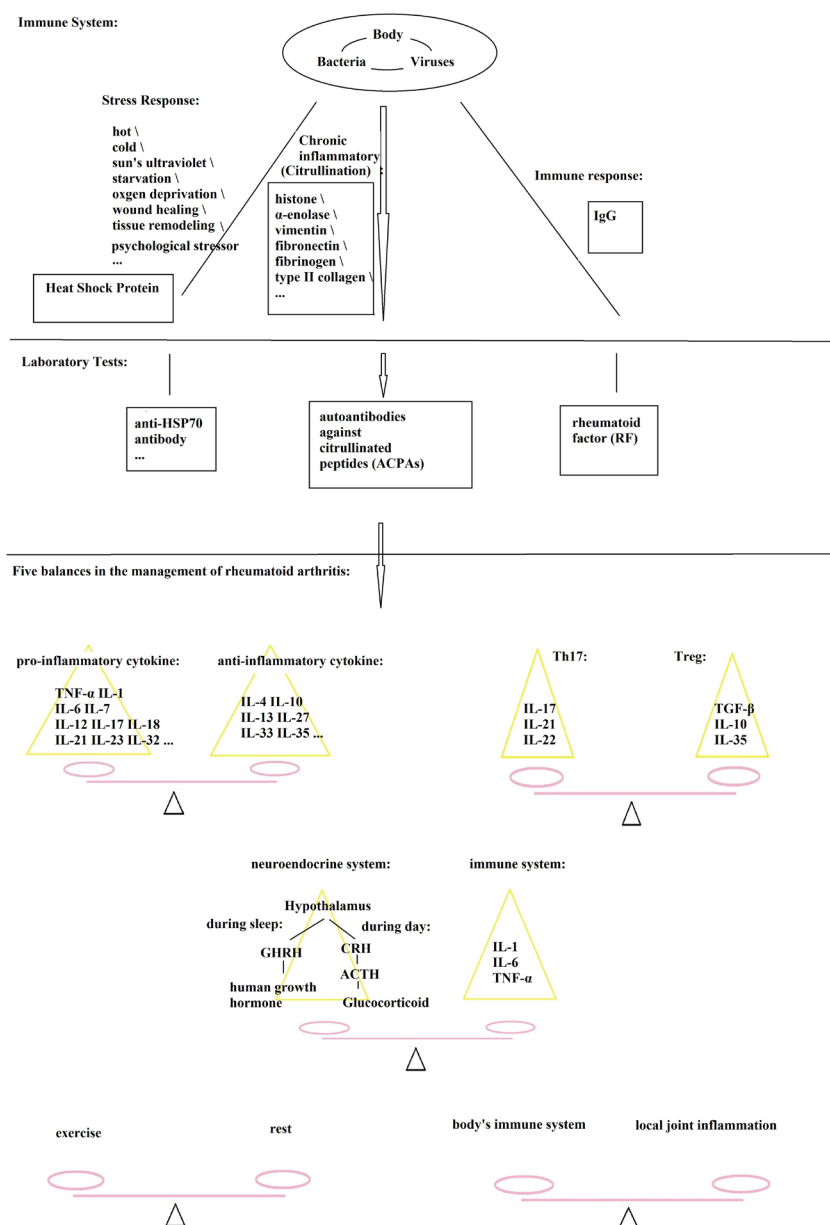
**Figure 1.** Five balances in the management of rheumatoid arthritis.

human growth hormone plays an important role in eliminating inflammation during the slow-wave sleep at night. Mental factors can lead to the onset, recurrence or aggravation of RA through neuroendocrine and immune function disorders. Conversely, positive mental psychological activity could prevent or alleviate the state of RA [2] [5] [6].

## 3.2. Balance between Pro-Inflammatory Cytokine and Anti-Inflammatory Cytokine

Cytokines carry out many crucial biological processes like cell growth, proliferation, differentiation, inflammation, tissue repair and regulation of the immune response [20] [21]. It is well known that they play an important role in the pa-

thogenesis of RA and are responsible for inflammation and joint destruction that occur during arthritis [22]. There occurs an imbalance between the pro- and anti-inflammatory cytokine activities which leads to multisystem immune complications [20].

The inflammatory milieu in the synovial compartment is regulated by a complex cytokine network. It is believed that B cells, T cells and over-production of various pro-inflammatory cytokines and de-regulation of anti-inflammatory cytokines regulate the pathophysiology of RA. Clinical interventions clearly demonstrate that of these components, tumour necrosis factor (TNF), interleukin 6 (IL-6), and probably granulocyte-monocyte colony stimulating factor are essential to the process. Cytokines lead to the induction or aggravation of the inflammatory response by activating endothelial cells and attracting immune cells to accumulate within the synovial compartment [3].

Although immune system which is regulated by cytokine network is complex, many of cytokines such as TNF-$\alpha$ IL-6 IL-17 have been tested as therapeutic targets with notable success in RA and subsequently other inflammatory diseases, whereas targeting of other cytokines rendered low or no therapeutic success [3].

In conclusion, it is important to recovery balance of cytokine network and to improve immune function [23].

### 3.3. Balance between Th17 and Treg

Recently, RA is described as an autoimmune disease mediated by T cells, especially effector The T helper 17 cells (Th17 cells) [24]. The protective role of T regulatory cells (Treg cells) and the pro-inflammatory role of Th17 (by secreting IL-17) have been elucidated and emphasized in the pathogenesis of RA. In patients with active RA increased Th17 levels and decreased Treg levels were found. Th17 and Treg cells (Th17/Treg balance) have a fundamental role in determining the outcome of RA.

Th17 cells play an important role in maintaining mucosal barriers and contributing to pathogen clearance at mucosal surfaces. In the case of autoimmune disorders, Th17 cell over activation can cause an inappropriate amount of inflammation. Treg cells are considered to have a protective role against bacterial and fungal infections and also in suppression of autoimmune response. They express forkhead box P3 (FoxP3), CD4, CD25 and produce TGF-$\beta$ and IL-10. Treg cells do not promote immune function, but act to decrease it instead. Treg cells actively suppress activation of the immune system and prevent pathological self-reactivity. The critical role Treg cells play within the immune system is evidenced by the severe autoimmune syndrome (IPEX syndrome) that results from a genetic deficiency in Treg cells. Despite their low numbers during an infection, Treg cells are believed to play an important role in the self-limitation of the immune system, they have been shown to prevent the development of various autoimmune diseases.

In 1989, Strachan proposed his *Hygiene Hypothesis Theory*: the reduction of exposure to common pathogens such as helminthes increased the prevalence of

allergic and autoimmune diseases in areas where sanitary conditions improved [25].

The parasites related to protective effects of the aggressiveness of the disease in patients with RA, already described in the literature, are Schistosoma mansoni, Schistosoma japonicum, Ascaris suum, Heligmosomoides polygyrus bakeriand Hymenolepsis diminuta, Leishmania and Malaria. Such pathogens inhibit the secretion of Th17 cytokines, induce the appearance of tolerant dendritic cells and promote the proliferation of Treg cells [24] [25].

In conclusion, intestinal immunity is a part of systemic immunity. In childhood, developing immune system must receive stimuli (from infectious agents, symbiotic bacteria, or parasites) to adequately develop Treg cells. In adulthood, eating food include probiotics would be useful.

### 3.4. Balance between Exercise and Rest

RA is autoimmune disorder by immune complex precipitation. Taking adequate rest would be useful to the recovery of RA, but long-time rest would aggravate complex precipitation.

The available data suggest that physical activity (PA) is beneficial and should be encouraged in patients with RA [26]. Moderate exercise training is associated with improvement of expression of CD28 on Th cells and Th1/Th2 balances. Exercise also improves metabolism and helps to clear the immune complex. Therefore, exercise training could be helpful for a decrease in the risk of infections and in the progression of RA.

PA may diminish disease activity, improve bone mineral density, slow radiographic disease progression at the small joints, and slow the development of atherosclerosis. Engaging in PA also enhances self-esteem and decreases both fatigue and pain perception [27]. Regular exercise is recommended as both safe and useful to maintain muscles strength and overall physical function. PA is also beneficial for patients with RA complaining of fatigue [28].

But, over exercise would be harmful. In RA, fatigue is reported in over 80% of RA patients. Fatigue is severer for patients with moderate to severe disease activity, compared with those with low disease activity. Then fatigue could induce sleep disorder. It is reported only 18.5% of RA patients had sleep of good quality.

In RA complex feedback loops involving cytokines, such as IL-1 and TNF-$\alpha$ produced in response to inflammatory, appear to play a role in the regulation of non-rapid eye movement (REM) sleep. Thus the inflammatory may result in changes to the sleep cycle, including an increase in slow-wave sleep relative to REM sleep. Most of RA patients do not have a good sleep quality. Several studies have found sleep fragmentation, low sleep efficiency, frequent awakenings and poor sleep quality in this group of patients [29]. Sleep is often considered a state of the brain that improves immune function. Sleep disorders could be detrimental to the metabolism and immune regulatory functions of the human body. High-quality and deep sleep can promote the secretion of growth hormone, affect the activity of thymus and other immune organs, and restore the immune

balance [5] [30] [31].

In conclusion, the clearance of immune complexes is limited by the total amount of phagocytes and the capacity of metabolism, exercise intensity would be increased gradually. Research has shown that aerobic exercise can improve PA in RA, while PA decreases chronic inflammation and reduces pain, all without adversely affecting disease activity.

### 3.5. Balance between Body's Immune System and Local Joint Inflammation

RA is the local expression of the general imbalance of the human body. Once the abnormal immune response has become established (which may take several years before any symptoms occur), plasma cells derived from B lymphocytes produce RF and ACPA in large quantities. Once the inflammatory reaction is established, the synovium thickens, the cartilage and the underlying bone begin to disintegrate and evidence of joint destruction accrues.

Typically in RA progression, the process of disease attack is often from small joints to large joints. Small joints of the hands and feet are most commonly involved (proximal interphalangeal joints, and metacarpophalangeal or metatarsophalangeal), followed by wrists and ankles, elbows, knees and shoulders, but almost any joint can be affected.

It is reported that 36 of 256 RA patients (14.1%) had self-limiting arthritis [32]. Within the process of improvement, the recovery process is often from large to small joints [1] [32] [33].

In recovery process, massage and exercise can induce diffusion of the immune complex, then increased antigen would cause the secondary immunity.

Meanwhile, we must pay attention to the same shape trauma which can cause secondary response to the whole body just like Koebner response or the isomorphic response which were found in Psoriasis, Juvenile idiopathic arthritis, vascular inflammatory.

In conclusion, within the improvement of RA, we must pay attention to over-massage and over-exercise which can cause the secondary immunity. In addition, we must pay attention to local trauma which can cause Koebner response or the isomorphic response.

### 4. Discussion

Rheumatic disease is common in China [34]. We have followed up Mrs Wu (wife of the author) for three years who is located in Jiangsu province of China. She was 45 years old in 2013. In July 2013 due to concerning about her child's college entrance examination, Wu underwent pressure and her hands and feet got pain. Two years later she recovered gradually without taking any drugs.

In May 2015, because of her new job stress, she had got a three-month history of fatigue, tension and insomnia, then her hand and feet got pain again, followed by wrists and ankles, elbows, knees and shoulders [35]. In October 2015, she

went to hospital for unbearable pain. The laboratory analyses provided the following results.

Her RF was 281 U/ml, ACPAs was 369.8 U/ml, erythrocyte sedimentation rate (ESR) was 69 mm/h and C-reactive protein was 95.24 mg/l. According to the classification criteria, jointly published by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), Wu's total score was 10 [36] [37] [38] [39].

After diagnosis we have kept using five balances regulating strategy for one year. From January 2016, she had taken the following medications: diclofenac sodium enteric-coated sustained capsules (COX-2 inhibitors), at 19 pm 100 mg per day, which peak hour is 3 hours and half-life is 7 hours. Then her morning stiffness significantly reduced. But the treatment effect was influenced by the level of work fatigue from time to time. Subsequently she began to terminate employment on April 2016. 6 months later she achieved full remission, her pain reduced to small finger joints, and she could take regular and moderate exercise every day.

The management insights presented in this Review and Wu's case experience constitute the basis for self-management strategies of rheumatoid arthritis [12] [36]:

**About Balance between neuroendocrine system and immune system:**

Maintaining peace of mind

Stopping work when necessary

More sleep

Not taking sleeping pills

Less sex life

Moderate outdoor activities under the sunshine

**About Balance between pro-inflammatory cytokine and anti-inflammatory cytokine:**

Preventing infection

Not living in polluted environment

Eating nutritious food

Keeping body warm

**About Balance between Th17 and Treg:**

Eating protein rich foods

Eating food which is easy to digest

Eating food which consists of probiotics

Eating food which is not allergic

Not eating greasy food

No abuse of antibiotics

**About Balance between exercise and rest:**

More rest with lying down

In high disease activity state or moderate disease activity state, having more rest, but also paying attention to exercise joints

In low disease activity or remission state, doing more exercise gradually

In remission state doing more aerobic exercise

**About Balance between body's immune system and local joint inflammation:**

Protecting joints from trauma

In High disease activity state or moderate disease activity state no massage

In Low disease activity or remission state tender massage

In High disease activity state or moderate disease activity state not taking bath

In Low disease activity or remission state taking tender bath

Drinking plenty of water

When sleep more turning over

Sleeping on a hard bed

## 5. Summary

RA is a chronic inflammatory autoimmune disease, which can cause cartilage and bone damage as well as disability. Early diagnosis and good management are keys to optimal therapeutic success. We have used five balances regulating strategy to follow up the patient with RA, among which the balance between neuroendocrine system and immune system is the most important. It seems that using this strategy could assist rheumatologists in achieving low disease activity or remission in the majority of their patients.

This Review argues that RA is self-limiting to some extent, but the duration of disease will leave sequela with different degrees of joint deformation. Therefore, it is necessary to use this strategy in the RA management early. During the day, glucocorticoid plays an important role in controlling of inflammation, and human growth hormone plays an important role in eliminating inflammation during the slow-wave sleep at night. Finally, RA and psoriatic arthritis are two of the most prevalent inflammatory rheumatic musculoskeletal diseases. Five balances are also important to other causes of arthritis, such as psoriatic arthritis, reactive arthritis, osteoarthritis, infectious arthritis.

RA disease network model based on complex network is important for the analysis and treatment of disease. But at the present stage the research of complex network theory is not clear enough to describe the relationship between structure and function of complex system [40] [41]. Through reviewing literature, this Review has found five important layers of RA complex network. At next step we hope more researchers to participate in "Network Medicine" study to accumulate more cases, constantly improve the RA network model and analyze parameters characteristic and interaction relationship of RA network model. Only common characteristics network model based on the more RA patients improved in the future, could RA be individualized treated.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

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