Chapter 1

Current Understanding of the Pathogenesis of Rheumatoid Arthritis, Unmet Needs in Treatment, Ongoing Research and the Future

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Current Understanding of the Pathogenesis of Rheumatoid Arthritis

Rheumatoid arthritis is a systemic autoimmune inflammatory disorder affecting the peripheral joints. The exact pathogenesis of rheumatoid arthritis remains is unclear although strong evidence suggests the involvement of cytokines are important in disease progression since cytokines play a fundamental role in various inflammatory processes, articular destruction, and rheumatoid arthritis -associated comorbidities [1-3].

Fibroblast-like synoviocytes (FLS) play a pivotal role in the pathogenesis of rheumatoid arthritis through aggressive proliferation and invasion, and certain proinflammatory cytokines may affect synoviocyte proliferation. To evaluate whether interleukin-21 (IL-21) could promote proliferation and proinflammatory cytokine production by rheumatoid arthrtis-FLS, immunohistochemistry and immunoblotting were performed by these authors to observe the expression of IL-21 receptor (IL-21R) in synovial tissues and FLS from rheumatoid arthritis and osteoarthritis patients. The MTS assay was used to analyze rheumatoid arthritis-FLS proliferation. The concentrations of IL-6 and tumor necrosis factor-α (TNF-α) in culture supernatants were determined by enzyme-linked immunosorbent assay (ELISA). The signaling pathways triggered by IL-21 were characterized by immunoblotting. IL-21R was upregulated in the synovial tissues and FLS of rheumatoid arthritis patients as compared with osteoarthritis patients. IL-21 stimulated rheumatoid arthritis-FLS proliferation

and promoted the production of TNF-α and IL-6, and blockade of IL-21/IL-21R pathway with IL-21 rheumatoid arthritis Fc attenuated IL-21-induced proliferation and secretion of TNF-α and IL-6. IL-21 induced activation of the ERK1/2, PI3K/AKT and STAT3 pathways, and blockade of these pathways attenuated IL-21-induced proliferation and secretion of TNF-α and IL-6. These results suggested that IL-21 could promote rheumatoid arthritis-FLS proliferation and production of proinflammatory cytokines and, therapeutic strategies targeting IL-21 might be effective for the treatment of rheumatoid arthritis [4].

Recent studies have shown that IL-37 is a key cytokine in regulating inflammatory response, mainly by inhibiting the expression, production, and function of proinflammatory cytokines. IL-37, formerly named IL-1F7, shares similar structural pattern to the IL-1 family. IL-37 is widely expressed in several types of cells, organs, and tissues, including monocytes, plasma cells, dendritic cells, the testis, thymus, and uterus. IL-37 is believed to play potential roles in autoimmune diseases by suppressing immune responses and inflammation. Immunohistochemistry staining on the synovial tissue from individuals with active RA demonstrated the presence of large amounts of IL-37 in the diseased synovial lining [5].

Zhao and others stated the plasma level of the anti-inflammatory cytokine IL-37 was decreased in drug responders after DMARD treatment in rheumatoid arthritis and was positively correlated with pro-inflammatory cytokines (IL-17A, TNF-α) and disease activity (CRP, DAS28) in rheumatoid arthritis patients Thus, IL-37 expression in rheumatoid arthritis and during DMARD treatment appears to be controlled by the level of pro-inflammatory cytokines. This results in a strong correlation between plasma levels of IL-37 and disease activity in rheumatoid arthritis patients [6].

Lee and others examined the effect of interleukin-17 (IL-17) on the expression of Toll-like receptors (TLRs) in fibroblast-like synoviocytes (FLS) from patients with rheumatoid arthritis and osteoarthritis and investigated the region downstream of IL-17 for TLR expression and the downstream signals responsible for the effect of IL-17 in TLR expression. Levels of IL-17 protein in the serum and synovial fluid of rheumatoid and osteoarthritis patients The IL-17 mRNA expression in synovial fluid monocytes was higher in rheumatoid than in osteoarthritis patients. Immunohistochemical staining showed greater expression of IL-17, TLR2, TLR3 and TLR4 in synovial samples from rheumatoid arthritis compared with osteoarthritis patients. Interleukin-17 increased the expression of TLR2, TLR3 and TLR4 in RA FLS; IL-23 augmented the IL-17-induced expression of TLR2, TLR3 and TLR4 in RA FLS. Blocking STAT3 with S3I-201 reduced IL-17-induced TLR3 expression in RA FLS. Their results suggested that IL-17 is a major cytokine in pathogenesis of rheumatoid arthritis. The IL-17 influences the innate immune system

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by increasing the synovial expression of TLR2, TLR3 and TLR4. They concluded control TLR3 expression via the STAT3 pathway in rheumatoid arthritis FLS [7].

It has been known that the occurrence of rheumatoid arthritis was closely correlated with DNA hypo¬methylation in CD4+ T cells, in which DNA methyltransferase plays a certain role. This study investigated the effect of miR-126 on CD4+ T cell subgroup in rheumatoid arthritis patients and the alternation of DNA hypomethylation, in an attempt to provide new sights into the pathogenesis and treatment of rheumatoid arthritis. CD4+ T cells separated from rheumatoid arthritis patients were transfected with miRNA (miR)-126 expression vector or miR-126 inhibitor expression vector. The expression levels of CD11a, CD70 and DNMT1 mRNA were examined by real-time PCR. Protein levels of CD11a and CD70 were tested by flow cytometry while DNMT1 protein level was quantified by Western blotting. DNA was modified by sodium bisulfite and was sequenced for the methylation status of promoters of CD11a and CD70 genes. Both mRNA and protein expressions of CD11a and CD70 genes in CD4+ T cells were elevated by miR-126 transfection, along with decreased DNMT1 protein level but not mRNA level. The methylation degree of promoters of both CD11a and CD70 genes were significantly depressed after miR-126 transfection. The transfection by miR-126 inhibitor effectively reversed such effects. In rheumatoid arthritis patients, elevated miR-126 may promote the expression of CD11a and CD70 via the induction of hypomethylation of gene promoters by depressing DNMTI1 protein levels [8].

Biomarkers are defined as anatomical, physiological, biochemical, molecular parameters or imaging features that can be used to refine diagnosis, measure the progress of diseases, or predict and monitor the effects of treatment. They can also be associated with the severity of specific disease states [9]. Typical biological biomarkers could encompass genetic markers, products of gene expression, autoantibodies, cytokine/growth factors, acute phase reactants, tissue abnormalities visualized by immunohistochemistry in synovial biopsy, a product of tissue degradation, or a cell subset that can be phenotyped and enumerated. Sources of these biomarkers could be the serum/plasma, urine, synovial fluid, tissue biopsy, or cells from blood, fluid, lymph node, or tissue. In contrast, a clinical biomarker would constitute a physical variable (sign or symptom), a clinical judgment, or an outcome measurement that emerges as a sequel of the underlying disease process. In rheumatology, this variable may be not only joint counts, global assessment, pain score, duration of morning stiffness, and other clinical variables but also composite indices or functional, radiographic scores [9].

Rheumatoid arthritis is a complex disease that develops as a series of events often referred to as disease continuum and would benefit from novel biomarker development for diagnosis where new biomarkers are still needed.

Burska and others reviewed the current knowledge's relation to cytokine used as a biomarker in rheumatoid arthritis However, given the complexity and heterogeneous nature of rheumatoid arthritis the authors stated it is unlikely that a single cytokine may provide sufficient discrimination.Therefore, multiple biomarker signatures may represent more realistic approach for the future of personalized medicine in rheumatoid arthritis [9].

Rheumatoid arthritis is a chronic rheumatic condition hallmarked by joint inflammation and destruction by self-reactive immune responses. Clinical management of rheumatoid arthritis patients is often hampered by its heterogeneous nature in both clinical presentation and outcome, thereby highlighting the need for new predictive biomarkers. Several studies have recently revealed a role for type I IFNs (interferons), mainly IFNα, in the pathogenesis of a subset of rheumatoid arthritis patients. Genetic variants associated with the type I IFN pathway have been linked with rheumatoid arthritis development, as well as with clinical features. Moreover, a role for IFNα as a trigger for rheumatoid arthritis development has also been described. A type I IFN signature has been associated with the early diagnosis of rheumatoid arthritis and clinical outcome prediction in patients undergoing biological drug treatment, two challenging issues for decision-making in the clinical setting. Moreover, these cytokines have been related to endothelial damage and vascular repair failure in different autoimmune disorders.

These authors stated, together with chronic inflammation and disease features, they could probably account for the increased cardiovascular disease morbidity and mortality of these patients. The main aim of the present review was to provide recent evidence supporting a role for type I IFNs in the immunopathology of rheumatoid arthritis as well as to analyse their possible role as biomarkers for disease management [10].

Zivojinovic and others evaluated the effect of a tumor necrosis factor-α (TNF-α) inhibitor (etanercept) on innate inflammatory and Th17 cytokines in patients with rheumatoid arthritis. Serum levels of interleukin 6 (IL-6), TNF-α, IL-32, IL-23, IL-17A, IL-21, and IL-22 were measured in patients with rheumatoid arthritis and 25 healthy controls. Serum IL-6 levels were positively correlated with levels of the erythrocyte sedimentation rate and C-reactive protein, and 28-joint Disease Activity Score at baseline. Serum IL-21 levels were positively correlated with levels of rheumatoid factor), antimutated citrullinated vimentin antibodies at baseline and after 24 weeks of treatment with etanercept.The authors stated multiple inflammatory pathways contribute to persistent chronic inflammation in rheumatoid arthritis. In contrast to nonresponders, etanercept therapy modulated serum cytokine levels and caused a marked decrease of IL-6 levels in responders. IL-21 might be involved in the regulation of autoantibody production in rheumatoid arthritis[11].

In patients with rheumatoid arthritis for whom rituxi-

mab therapy failed despite adequate B cell depletion, IL-6-directed therapy might be a more logical and effective treatment choice than T cell costimulation blockade. Further controlled studies investigating other possible mechanisms are needed to validate these initial findings [12].

Rheumatoid Arthritis Classification Criteria

Previously, Rheumatoid Arthritis (RA) was defined by the presence of four of seven criteria set by the American College of Rheumatology (ACR). In 2010, the ACR collaborated with the European League Against Rheumatism (EULAR) and developed a new classification criteria which focuses on patients with synovitis for less than 6 weeks of whom symptoms are not better explained by another diagnosis. The new criteria set is thought to be more sensitive in identifying patients in the early stages of RA prior to developing erosive disease. Therefore allowing for the early initiation of DMARD therapy. Scoring is based on 4 categories: 0-5 points for number and site of involved joints, 0-3 points for serologic abnormality, 0-1 points for elevated acute phase response and 0-1 points for the duration of symptoms. A total score of 6 or more increases the possibility of RA [13].

Current Treatment Options

Presently, treatment options for RA include glucocorticoids (systemic or intraarticular), conventional synthetic

disease Modifying anti-rheumatic drugs (csDMARDS) and biologics (bDMARDs). Methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ) and leflunomide (LEF) are considered csDMARDS. Biologics include tumor necrosis factor inhibitors like infliximab, adalimumab, etanercept, certolizumab, and golimumab. New biologics include abatacept, rituximab and tocilizumab [14].

Based on current ACR/EULAR recommendations, treatment of mild active disease begins with HCQ or SSZ. MTX can be added after three to six months in cases of no response. In patients resistant to this triple therapy after three to six months, MTX can be combined with a TNF inhibitor or new biologic such as abatacept.

The initial treatment of newly diagnosed moderate RA usually begins with MTX and the addition of NSAIDS or glucocorticoids for symptom relief until MTX takes effect. For patients who MTX is not an option due to contraindication such as pregnancy, alcoholism, liver disease, severe renal impairment with GFR <30, physicians can choose another csDMARD or bDMARD monotherapy. Disease activity should be reevaluated every 3-6 months. If a patient fails to respond to maximum dosing of MTX, the addition of other csDMARDs are considered. Patients who have not responded to two csDMARDS are usually eligible for a biologic plus MTX. Despite being more expensive, biologics have some advantages over the csDMARDs, such as chance of tapering and discontinuation

in patients with remission [14].

Unmet Needs

Despite recent advancements in controlling the symptoms and disease progression of Rheumatoid Arthritis (RA) in afflicted patient, many obstacles are still present and require further investigation. In an ideal situation all patients would have their disease diagnosed early prior to bone, cartilage, and soft tissue damage. Each and every patient would also achieve remission, without the need for multiple drugs therapies. These patients would no longer be longer being reliant on medications they may not be able to afford, and or tolerate. Additionally, biomarkers would be available to help curtail the time it took to find a treatment plan specifically for that patient, all the while shortening the time it took to achieve remission. No longer would they be labelled as non-responders, or treatment-resistant, but would rather be able to regain full functionality in their daily living activities. Furthermore, the side-effect profiles of most of these agents used in treatment of RA remains a safety concern. It is these statements above for which we refer to as unmet needs in patients with RA.

Since the advent of disease modifying antirheumatic drugs (DMARDs) many patients suffering from RA have achieved remission, and effective management in relation to their symptomology. As a result of this Methotrexate (MTX) became one of the gold standards in RA treatment, but not without complete success. MTX monotherapy, while able to show rapid improvement in symptoms, only 40% of patients were able to show a 50% improvement in the American College of Rheumatology criteria for improvement (ACR50), and only 20% will be able to achieve ACR70 [15]. From here researchers were able to develop agents which specifically targeted and neutralized pro-inflammatory cytokines. The most popular and prevalent of these being anti-tumor necrosis factor (Anti-TNF), such as Etanercept, Infliximab, and Adalimumab. However; while remarkable in helping some patients achieve remission, it remains that up to 30% of patients with RA will show inadequate response to their first biologic therapy [16]. In addition for patients who had failure of at least one Anti-TNF, the response rate of biological agents is only about 20-40% after adjustment for the placebo response [17].

As many refractory patients remain, many still have active disease and progressive advancement in disability and are are forced to have treatments switched constantly. For this reason it may be useful to have predictive biomarkers and clinical characteristics in place for which an individual patient can have a specific treatment identified and tailored for them. One method of achieving this has been in using repeated disease activity assessments. Monthly assessment of disease activity for patients with moderate to high disease activity, and every 3-6 months for patients with sustained low disease activity or remission is currently recommended. [18]. These scores while

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useful in monitoring disease activity and response to treatment, are limited in assessing disease prognosis, and the need for identifying patients who would benefit most from early aggressive intervention is still currently not available. For this reason advances in identifying specific serum biomarkers has been undertaken. More classically Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have shown correlations with disease activity, but they are not specific for RA and may be affected by a variety of external factors. It has thus been speculated that in such a complex disease a multi-biomarker disease activity (MBDA) score may be necessary to measure true disease activity. These scores are calculated based on serum concentration of multiple biomarkers which represents the many different pathways involved in the pathophysiology of RA, and while still in the initial stages of validation and development, may ultimately result in the ability to provide tighter disease control [19].

As with most treatments available for alleviation of disease, DMARDs and Biological agents have their own dangerous side-effect profiles. These may include risk of serious infection, Tuberculosis reactivation, malignancy, immune reactions, and cardiovascular risks. One meta-analysis of 160 randomized clinical trials and 46 extension studies, conveyed that biologics as a group in the standard-dose model were significantly associated with an increased risk of serious infection compared with control treatment (odds ratio 1.37, 95% confidence interval [CI]

1.04- 1.82) [20]. Anti-TNF therapy also showed association with increased risk of latent tuberculosis reactivation thus leading to the standardized practice of screening patients prior to initiation, which has substantially reduced the risk of reactivation [21]. The risk of lung cancer and lymphoma malignancy in RA patients while already elevated prior to treatment may even be higher in patients treated with infliximab as demonstrated by meta-analysis. Although, as suggested by a number of observational registries Anti-TNF agents are not all associated with increased malignancy risk [22].

Optimization of Current Treatment Regimen Ongoing Research

This is an exciting time for RA research. The development of biologics has opened an area of research studying potentially new biologics and reevaluating current treatment options. There are numerous ongoing studies on side effects, dosing, comparative efficacy, timing and possibility of tapering [23]. These studies help to optimize already established available treatments. For instance, a new study confirms that subcutaneous methotrexate should be routinely used or contemplates in patients with severe RA prior to starting biologic therapy [23]. Another interesting study, CAPRA-2, suggests the use of delayed-release prednisone may be more successful at reducing fatigue (compared to DMARD treatment alone) and improving morning stiffness (compared to DMARD plus immediate

release prednisone) [24-25].

New Biologics

There are several new biologics in development. For example, Decernotnib, a second generation JAK inhibitor specifically targeting JAK3, shows promising results in phase IIb studies when administered with MTX in patients who were not responsive to MTX alone. Side effects include transaminitis, neutropenia and dyslipidemia [26-27].

Additionally, Sarilumab, an anti-IL-6R mAb, showed efficacy when combined with MTX in patients who did not respond to MTX alone in Phase III trials [28]. Similarly, Sirukumab, a human anti-IL-6 mAb, showed efficacy when combined with MTX in patients who did not respond to MTX alone in Phase II trials [29].

Treatment Alternatives

As the side effects of synthetic drugs are common and usually unavoidable, new experiments search for naturally derived therapeutic medications such as bovine lactoferrin, which has anti-inflammatory properties [29]. Based on many randomized clinical trials, another potential naturally derived medication is human chorionic gonadotropin (HCG). As a physiological hormone, it increases IL-10 and IL-27 levels and reduces IL-17 [30-31].

Two other alternative treatments currently under investigation are simvastatin and hesperidin which shows improvement of biomarkers such as Matrix metalloprotienease-3 (MMP-3), cartilage oligomeric matrix protein (COMP) [32].

Cost-Effectiveness of Treatment

Biologics are expensive and timing of initiation is debatable. Additionally, there are several biologics available with comparable efficacy. Therefore, many studies are looking at the cost-effectiveness of biologics and its impact on productivity. Interim results from the PRIZE study, found an association of increased productivity in early RA patients who responded to etanercept/MTX combined treatment [33]. Another study using data from the CREATE registry compared cost-effectiveness of infliximab, etanercept and adalimumab. Cost-effectiveness was calculated based on total mean cost of treatment divided by percentage of patients who reached remission within two years. Adalimumab was found to be the most cost-effective of the three [34].

Future Direction

Activity and Severity Assessment

At present, the disease activity score 28 (DAS 28) is used to assess disease activity and severity in daily practice. One area which deserves more attention is finding biomarkers that can help in more accurate determination of disease activity and severity. There is ongoing research

for the last 10 years about proteomics, genomic, and metabolic technologies use in this field [35].

Personalization

Response to current RA treatment is variable. It is not fully understood why some patients are nonresponsive. Variations are seen with weight, smoking status, co-administration with other drugs, and serotype [36]. As discussed previously, the pathogenesis of RA is complex. Further research is needed to develop biomarkers that can predict treatment response and allow for personalization of treatment regimens [37].

Studies to uncover the cause of RA have recently ended up scrutinizing the importance of pro-inflammatory cytokine such as tumor necrosis factor α (TNF-α) and interleukin (IL)-6 in the pathogenesis of RA. TNF-α inhibitors are increasingly used to treat RA patients who are non-responsive to conventional anti-arthritis drugs. Agents targeting IL-6 such as tocilizumab (TCZ) attracted significant attention as a promising agent in RA treatment. The mechanism of anti-IL-6 in the treatment of RA, provide the key efficacy and safety data from clinical trials of approved anti-IL-6, TCZ, as well as six candidate IL-6 blockers including sarilumab, ALX-0061, sirukumab, MEDI5117, clazakizumab, and olokizumab, and their future perspectives in the treatment of RA [38].

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