BMH MEDICAL JOURNAL

BMH Med. J. 2017;4(2):47-54 **Review Article**

Newer Diagnostic And Therapeutic Modalities For Autoimmune Rheumatic Diseases

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Keywords: auto immune rheumatic diseases, diagnosis, treatment

There is refinement of classification criteria for various rheumatic diseases like Rheumatoid arthritis (RA) Systemic Lupus Erythematosus (SLE), vasculitis, Sjogren's syndrome etc. in the last few years which help the clinician in establishing early diagnosis and therapy. In case of uncertainties in the diagnosis, clinicians need to carefully interpret the result of autoantibody tests in the background of the clinical context [1]. A growing number of autoantibodies have specificity for particular clinical phenotypes. They can also offer prognostic information and sometimes diagnostic certainty. Early use of Disease Modifying Anti Rheumatic drugs (DMARDs) and biological agents to attain no or low disease activity measured by primary complex indices markedly changed the outcome in most of the autoimmune rheumatic diseases.

Diagnosis

Many patients with autoimmune rheumatic diseases like RA, SLE or progressive systemic sclerosis (PSS), the autoantibodies precede the clinical symptoms by many years. Patients with RA might have detectable Anti Citrullinated Peptide (antiCCP) many years before the onset of arthritis [2]. In SLE, ANA or anti dsDNA may be accumulated in the patients serum, months or years before the clinical onset of the disease [2,3]. Patients with Raynaud's phenomenon and positive anti-topoisomerase I antibody are more likely to progress to systemic sclerosis than those without this autoantibody. In myositis patients, those with myositis specific antibodies like anti Jo-1 can develop finer lung fibrosis, mechanics hands, non erosive polyarthritis and Raynaud's phenomenon collectively called *antisynthetase syndrome*. The recent advances in the understanding of the immunopathogenic mechanisms of systemic autoimmune diseases and the clinical relevance of the autoantibodies helped a lot in the early diagnosis and proper management [4] (See **Table 1**).

Management

Significant advances has been made in our understanding of autoimmune rheumatic diseases and its management in the past decade. The limit of what conventional drugs like NSAIDs, steroids and DMARDs can achieve has probably been reached. Improved understanding of the pathogenesis of these diseases with the introduction of more targeted treatments is beginning to show encouraging

signs of improvement in the outlook of these patients [5].

Table 1: Clinical Relevance Of Autoantibodies

Antibody	*Antibody Prevalence (%)*	*Major Clinical Features*
SLE		
1. dsDNA	70-80	Renal/Skin disease
2. Smith (Sm)	10-30	Renal disease
3. Nucleosome	60-90	Renal/Skin disease
4. U1RNP	15-20	Raynaud's syndrome, puffy fingers Myositis hypergamma globulinemia
5. α Actinin	20	Renal disease
6. C_1q	40-50	Active disease, renal involvement
SLE / Sjogren syndrome		
1. Ro/SSA	30-40	Kidney disease, skin disease (photosensitivity, cong. heart block, neonatal lupus)
2. La/SSB	15-20	Heart block, SICCA symptoms Subacute cutaneous lupus
Inflammatory Myositis		
Jo-1	20-30	Anti synthetase syndrome
Mi-2	8-12	Dermatomyositis/Polymyositis
TRIM 33	10-30 (Dermatomyositis)	Malignancy
U1RNP	8-15	Mixed connective tissue disease
Progressive systemic sclerosis		
Centromere	15-40	Limited scleroderma, pulmonary hypertension
Scl-70	10-40	Diffuse cutaneous scleroderma, ILD
RNA polymerase III	5-25	Renal crisis, pulmonary hypertension

Rheumatoid arthritis

The approach to treatment of RA has been 3 major advances in the last 15 years that has changed the outcome of the disease. They are:

1. Early intervention with DMARDs and low dose steroid bridging
2. Treat to target or tight control strategy
3. Use of biological response modifiers and Targeted synthetic DMARDs

Early intervention: Early use of DMARDs preferably methotrexate with low dose steroids for 12-24 weeks, started within 3-6 months of onset of RA has achieved marked clinical benefits. Combination of synthetic DMARDs with low dose steroids are widely useful in patients with poor prognostic factors like early erosion, strongly positive rheumatoid factor or anti CCP or high disease activity [6].

Treat to target or tight control strategy: Targeting no or low disease activity by regular monitoring using primary composite measures of disease activity and adhering to a predefined treatment strategy when compared with unstructured treatment conveys better outcome [9]. In the past, this was not possible primarily because of the complexity of measures assessing disease activity in RA and insufficient knowledge of optimal treatment strategies. Disease activity score 28 (DAS 28), simplified disease activity index (SDAI), clinical disease activity index (CDAI), routine assessment

of patient index data (RAPID3) (see **Table 2** and **3**) are all validated and similarly functioning measures now used in every day case allowing physicians to treat-to-target [5].

Table 2: Measures included in composite score commonly used in RA

	DAS 28	SDAI	CDAI	RAPID 3
Swollen joint	+	+	+	
Tender joint	+	+	+	
Physicians global assessment		+	+	
Patients global assessment	+	+	+	+
Functional score pain				+
ESR / CRP	+	+		

Table 3: Activity level cut off for composite indices

Activity level	DAS28(0-10)	SDAI(0-86)	CDAI(0-76)	Rapid 3 (0-30)
High	>5.1	>26	>22	>12
Moderate	3.2-5.1	11-26	10.1-22	6.1-12
Low	2.6-3.2	3.3-11	2.9-10	3.1-6
Remission / Near remission	<2.6	<3.3	<2.8	≤ 3

Biological Response Modifiers (BRMs): Despite aggressive treatment strategies and early use of synthetic DMARDS treatment, failures are not uncommon in RA. A significant minority of patients (15-20%) fails to achieve satisfactory disease control. Hence better therapeutic agents are needed for these patients. Laboratory research in the understanding of immunopathogenesis especially the cytokine milieu and their network in RA contributed heavily towards the development of biological agents (Biological response modifiers -BRMs). Biological agents are molecules produced by biotechnology, used to neutralize or nullify action of any physiological molecule or cellular receptors. In refractory RA and other autoimmune rheumatic diseases BRMs against cytokines like TNF alpha, interleukins as well as anti B cell agents like Rituximab or costimulation blockers of T cells like abatacept are found to be very useful [7,8].

Biological Response Modifiers used in Rheumatic Disease

1) **Cytokine targeting Biologics**
   - (a) Anti Tumor Necrosis Factor α agents : Infliximab, Etanercept
     Adalimumab, Golimumab
     Pegylated certolizumab
   - (b) Anti Interleukin (IL1) agents
     IL1 antagonists: Anakinra, Rilonacept, Canakinumab
   - (c) IL6 antagonists : Tocilizumab
   - (d) Anti-IL-17 agents –Sekukinumab
   - (e) IL 12and 23antagonist -Ustekinumab

2) **Cell targeting biologics**
   - (a) Anti B cell agents : Rituximab
   - (b) Costimulation blockers
     Inhibitor of T cell activation: Abatacept
     Inhibitor of B Lymphocyte stimulator - Belimumab
   - (c) Anti osteoclast agents (Anti RANK Ligand drugs)
     Denosumab

Targeted synthetic DMARDs: Many new small molecules with specific actions are developed in the last few years. Tofacitinib acts by inhibiting the JAK (Janus Kinase enzyme) which is modulating the signal transduction and cell activation by IL-6, GMCSF and interferons [10]. This drug is found to be beneficial in RA as monotherapy and in combination with Methotrexate in a dose of 5mg twice daily orally. It is available in United States and India, but not yet in Europe. The newer derivative Baricitinib is also under trial. Iguratimod, a novel DMARD, acts by inhibiting the NF-κB and blocking the production of immunoglobulins and various inflammatory cytokines (IL-1, IL-6 and TNF); is used in Japan is found to be useful in RA [11]. Its efficacy and tolerability are comparable to sulphasalazine and Methotrexate. In combination with Methotrexate, it has synergistic actions and does not significantly increase adverse events. A newer derivative of D-Pencillamine named Bucillamine is also approved for use in RA in many countries in Asia pacific region.

Systemic lupus erythematosus

The improved understanding about the pathogenesis, more judicious use of pharmacological agents which are potentially toxic, invention of newer therapeutic agents like mycofenolate and belimumab, early detection and prompt treatment of infection and renal replacement therapies result in considerable improvement in the prognosis of SLE [12,13]. In 1956 the four year survival with SLE was 50%, but in 2013 the 15 year survival is 85%. It is found that mycofenolate in comparison with cyclophosphamide is an equally useful induction agent in lupus nephritis but is much less toxic. It is also more beneficial than azathioprine for maintenance treatment. Many studies showed equivalent efficacy of low dose intravenous cyclophosphamide (six fortnightly pulses of 500mg) compared to NIH protocol 750mg/m2/monthly IV for 6 months followed by quarterly infusion for 2 years [14].

Increased recognition of multifaced role of B cells in SLE led to the development of novel drugs notably Rituximab and Belimumab. In SLE, B cells produce autoautobodies, causes activation of T cells, cytokine secretion and modulation of dendritic cells. They also act independently as antigen presenting cells. CD20 is a beta lymphocyte specific antigen that is expressed by pre beta cells and mature B cells. Rituximab is a chimeric monoclonal IgG1 antibody to CD20. Administration of Rituximab causes beta cell depletion lasting for 6-12 months. Rituximab has been mainly used in refractory lupus nephritis, when conventional drugs have failed. In addition to RA and SLE, Rituximab is used in refractory ANCA associated vasculitis like Wegeners granulomatosis, Type II mixed cryoglobulinemia and dermatomyositis. 2 doses of 1000mg is usually given at 15 day interval as slow IV infusion.

B cells rely on several different cytokines for its proliferation, activation and maturation. B lymphocyte stimulator (BlyS) also known as B cells activating factor (BAFF), a cytokine of TNF family is a notable example. Belimumab is a monoclonal human antibody that inactivates BlyS, causing inhibition of B cell maturation. The drug is appropriate for use in antibody positive active SLE patients who are receiving standard treatment. The drug is found to have a steroid sparing effect. It also reduces constitutional symptoms like fatigue, skin and joint disease. It is not approved for the use in major organ lupus like nephritis or CNS involvement [13].

B cell modulating treatment inhibiting costimulatory molecules like Epratuzumab (antiCD22 monoclonal antibody) is under clinical trial. Atacicept is a drug which inhibits interaction between BLys and a proliferation inducing ligand (APRIL) with their receptors. It suppresses the differentiation and survival of B cells and could be an emerging therapeutic agent in the treatment of lupus [15].

Although pathogenic autoantibodies in SLE are derived from B cells, evidence suggests that T cell dysfunction exist in SLE. The main target of T cell directed treatment has been the inhibition of costimulation of T cells. Abatacept is a fusion protein consisting of T lymphocyte associated antigen-4 (CTLA-4) and modified Fc portion of human immunoglobulin. CTLA4 competes with CD28 for binding to CD80/86; thus abatacept down regulates T cell activation. Initial clinical trials

with abatacept and low dose cyclophosphamide followed by maintenance treatment with azathioprine is promising.

Interleukin 6 inhibition with Tocilizumab, a monoclonal antibody that inhibit IL6 receptors showed improvement in mild to moderate lupus [16]. Anti TNF agents are well known to cause lupus and may cause flare up of disease, hence generally not recommended in SLE.

Autologous stem cell transplantation has been used as a therapeutic strategy in SLE and other autoimmune rheumatic diseases in patients who are refractory to conventional treatment. The reported overall survival is 81% with 18% mortality recorded at 2 years. Despite high morbidity and mortality, the ability to achieve a sustained disease free state in patients with poor prognosis supports the application of autologous stem cell transplantation in patients with refractory lupus [17].

Spondyloarthritis (SpA)

Response to therapy with synthetic DMARDs like sulphasalazine and methotrexate in SpA like ankylosing spondylitis was quite unsatisfactory as these drugs are not very effective in axial disease [18,19]. Thalidomide and Biphosphonates like Palindronate has been used with limited benefits. Dramatic improvement has been noticed with the use of anti TNF agents in early ankylosing spondylitis, psoriatic arthritis and other types of SpA [20]. Infliximab, Etanercept and Adalimumab demonstrated effectiveness in these conditions. There is rapid resolution of sacroiliitis and spondylitis. As anti TNF therapy is highly effective for axial, peripheral and entheseal disease, these agents should be used in all patients refractory to NSAIDs and conventional synthetic DMARDs like sulphasalazine or methotrexate. In Psoriatic arthritis and SpA, anti IL17 agents like Secukinumab [21,22] is giving promising results. Sekukinumab is already available in India. A phosphodiesterase-4 inhibitor Apremilast and IL 12 / 23 antagonists like Ustekinumab are also found to be useful in psoriatic arthritis

Table 4: Anti TNF agents

Name	Infliximab	Etanercept	Adalimumab	Golimumab	Certolizumab
Structure	Mouse-Human Chimeric monoclonal antibody against TNFα	TNFα receptor Fc region dimeric fusion protein	Fully humanized monoclonal antibody against TNFα	Fully humanized monoclonal antibody against TNFα	PE gylated Fc free, fab fragment of monoclonal antibody against TNFα
Dose & route of administration	3-5mg/kg slow IV every two weeks for 3 doses then once monthly	25mg twice weekly Subcutaneously	40mg every two weeks Subcutaneously	50mg monthly Subcutaneously	400mg monthly Subcutaneously
Indications	RA Ankylosing spondylitis Psoriatic arthritis Inflammatory bowel diseases	RA Ankylosing spondylitis Psoriatic arthritis Juvenile idiopathic arthritis	RA, Psoriatic arthritis	RA	RA

Table 5: Anti Interleukin Agents

Name	Anakinra	Rilonacept	Canakinumab
Structure	IL-1 receptor antagonist	Dimeric fusion Protein directed against IL1	Fully humanized monoclonal antibody directed at IL1β
Dose & route of administration	100mg daily subcutaneous	80-120mg weekly subcutaneously	150mg subcutaneously
Indications	RA (Less effective than TNF agents), Juvenile Idiopathic arthritis(JIA), Adult onset Still's disease	Cryopyrin associated periodic syndrome (CAPS), Muckle wells syndrome, Refractory gout	Refractory gout

Osteoporosis

Biological agents like Teriparatide and Denosumab open new avenues in the management of refractory osteoporosis. An array of pharmacological agents like biphosphonates, Raloxifene, Salmon calcitonin and Strontium in addition to calcium and Vitamin D supplementation are already available for therapy of osteoporosis.

1-34 Teriparatide produced using recombinant DNA technology retains all biological activity of intact PTH peptide and is recommended for treatment of severe osteoporosis in men and women at a dose of 20 mcg/day subcutaneously.

Denosumab is a human monoclonal antibody against RANK [23]. Osteoblasts express RANKL (Receptor Activator of Nuclear factor Kappa B Ligand) a member of TNF superfamily of ligands and receptors. Osteoclast precursors express RANK. Denosumab reduces bone resorption by inhibiting formation, function and survival of osteoclasts. It is given at a dose of 60mg subcutaneously every 6 months.

Biosimilars

Biosimilars are bio therapeutic products which are similar in terms of quality, safety and efficacy to an already available biological disease modifying drug [24]. Several pharmaceutical companies in the developing nations like India developed biosimilar versions of originator (reference) product. The biosimilars or "follow on biologics" are new biopharmaceutical products and not the generic versions of innovator biopharmaceuticals. The active ingredient in the biosimilar are not identical to the innovator (reference) product. The properties of biopharmaceutical products dependent on the manufacturing process, protein source of extraction, purification process etc. resulting in heterogeneity of the resulting follow on biological agent.

In India, biosimilars of Etanercept, Infliximab, Adalimumab and Rituximab are available. They are actually intended copies of the originator. These agents are markedly cheap in comparison to the originators and are broadening the access of these drugs to more needy patients in developing countries. Because there is limited clinical database at approval of these biosimilars, switching or substitution between innovator product and biosimilar should be viewed actually as a change in pharmacotherapy. The efficacy and safety of these drugs are very similar though the experience is limited. The immunogenicity of biosimilars is another concern which requires further studies.

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