Review Article

Recent Advances in Rheumatology

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Current scientific information in Autoimmune rheumatic diseases (AIRD) revolutionised the outlook in dealing with the different diseases, Moving from the concept of NETosis through interferon based pathogenic modification gives a new horizon to have a deep insight into the rheumatological disorders. We have newer classification criterias of different diseases being identified with an objective to pick up the disease very early so that we can start treatment and better outcome may be predicted, In therapeutic armamentarium the availability of oral small molecule along with different biosimilars has made the outcome of different disease a dramatic positive turn. The improvement of quality of life adding to the upliftment of functional classes of different AIRD . In addition the artificial intelligence with the use of machine learning is coming in an exciting way which would really change the dimension of assessing and managing the different AIRDs.

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"Medical science has made such tremendous progress that there is hardly a healthy human left"

— Aldous Huxley

The field of Rheumatology and Clinical Immunology is an amusing paradox. The origin of musculo-skeletal conditions can be traced as far back as the origin of the modern man, with evidence of gout having existed in Egyptians around 2640 BC, and skeletal evidence of Ankylosing Spondylitis unearthed by archaeologists, dating back to 1500 BC. Yet the real advent of modern Rheumatology, as we know it now, is a relatively recent phenomenon, mainly accelerated in the last few decades, since the introduction of Glucocorticoids in the 1950s. Even leading medical organisations in Rheumatology were established only recently as far as the history of modern medicine goes, with the American College of Rheumatology being established as late as 1988.

As modern medicine and its changing trends highlight a global shift in interest in auto-immunity and the various pathways leading to rheumatic disease, newer targets for diagnosis and therapy are being thoroughly examined, with newer molecules for targeted treatment, and the incorporation of machine learning and Artificial Intelligence in healthcare.

Basic and Translational Sciences :

At the core of any scientific research lies the glaring question: "Why?" Molecular research addresses this directly, constantly trying to unveil novel pathways leading to various diseases that may further an understanding of them and shed light on ways to prevent or halt pathogenetic processes in the same.

Editor's Comment :

- **The concept of treat to target (T2T) in autoimmune rheumatic disease (AIRD) is gaining importance in current scientific literature.**
- **This is extrapolated from the recent advances in translational science by identification of enhanced NET osis with their impaired clearance triggering immune dysregulation Possible targets to inhibit NET osis with identification newer molecules with exciting results are being published in literature in RA, SLE, AAV, APS.**
- **Different potential biomarkers are also evolving as newer diagnostic and prognostic supportive tools in different AIRD.**
- **In the therapeutic domain the oral small molecules and biosimilars have revolutionised therapeutic outcomes of different AIRD.**
- **We are moving into the world of artificial intelligence (AI) through which we would utilise the focussed machine learning evidence in our future practise balancing the science and art of medicine.**

NETs cast wider than expected :

The role of neutrophils in autoimmune/ autoinflammatory conditions has been examined with a fine-toothed comb in the past few years, with the release of neutrophilic granules and NETosis (Neutrophilic Extracellular Trap formation) being highlighted as a key pathway involved in disease pathogenesis.

Enhanced NET formation and their impaired

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clearance trigger immune dysregulation and tissue damage, a phenomenon already established in autoimmune disease[1]. Three pathways of NET formation are known[2] – Suicidal or lytic NETs (infective/ antigenic stimuli leading to activation of neutrophil receptors and ROS mediated cell and nuclear membrane lysis); Vital NETosis (complement mediated, without cell lysis); and mitochondrial (mitochondrial DNA released, involving C5a complement component and Lipopolysaccharides as triggers). Patients with some autoimmune diseases have a distinct population of neutrophils called low-density granulocytes (LDGs), which are more prone to release NETs.

Such NETosis has been profiled in ANCA-associated vasculitides, especially leading to increased thrombosis, a mechanism similar to that noted in Antiphospholipid Antibody Syndrome. SLE patients have enhanced NETosis as well[3], and dysregulated NET formation leading to increased PAD4 mediated generation of citrullinated proteins and thus a potential pathogenic pathway leading to Rheumatoid Arthritis was extensively studied in 2019[4].

Possible targets to inhibit NETosis are being studied at present, like Calcineurin inhibitors (Calcium mobilisation is essential for NETosis), metformin (reduces the NET-IFNa pathway), and TAK-242[5] (a TLR4 inhibitor) – but substantial trials are needed before further comments can be made. Overall, our knowledge of the genetic undercurrent determining NETosis and its implications have farther effects that initially imagined, and this is a fertile land for further research at present.

Systemic Sclerosis – the race for biomarkers :

Systemic Sclerosis and its well-established features of autoimmunity, inflammation, vasculopathy and the final frontier of fibrosis have paved their way to a new interest in molecular studies. Skin biopsy specimens have been evaluated for gene signatures using microarrays that have led to sub-classifying Scleroderma into 4 distinct genotypic subsets: proliferative, inflammatory, normal-like and limited[6]. This has also revealed gene clustering, with certain genes being upregulated more in one subset as opposed to another.

This research then led to the burning question researched in all diseases of a chronic nature: Can this help in identifying newer biomarkers of disease? Analysis of skin samples from diffuse cutaneous SSc patients, revealed a four-gene biomarker panel consisting of THBS1, COMP, SIGLEC1 and IFI44, the expression of which are regulated by TGFß and IFN?, and they correlated moderately well with the mRSS[7]. Amidst the search for newer biomarkers, the utility of quantification of Endothelial cell-derived extracellular vesicles[8] (EVs) from the body fluids of SSc patients has been a recent topic of interest wherein both positive and negative correlations with cutaneous and internal organ involvement have been found. The content of these EVs are now targets of research to derive any connection between their levels and the amount of disease activity.

Driving damage in RA: synovial fibroblasts :

RA, being the prototypical disease for rheumatologists worldwide, is the gift that keeps giving. 2019 has driven further research in the field of synovial tissue architecture driving joint damage. Synovial fibroblasts cultured from RA joints have shown increased expression of FAPa (a dipeptidyl peptidase) and THY1 (Thymus cell antigen 1). Mass cytometry showed that FAPa+THY1- effector fibroblasts in the synovial lining have been associated with increased bone and cartilage destruction, with very little inflammation; while FAPa+THY1+ fibroblasts in sub-synovial layer caused more severe inflammation with very little damage to the joint or cartilage. Now it remains to be seen if such distinct fibroblast signatures can lead to more targeted therapeutic strategies.

Cytokine Cross-talk: IL 16 :

Comprehensive quantitative proteomics analysis of synovial tissue in Rheumatoid Arthritis patients revealed that serum IL-16 levels correlated positively with MMP-3 levels, and this was also the biomarker that decreased in serum following therapy with conventional or biologic DMARDs[9]. IL-16 is a serum biomarker that has also shown correlation with disease severity in primary knee Osteoarthritis, and further claims to fame for this cytokine may well be on their way.

Clinical Criteria Updates :

As a decade ends and another begins, this relatively nascent specialisation of Rheumatology has grown in leaps and bounds, and as expected, academic circles mandate the revision of existing set classification or diagnostic criteria in light of new evidence.

Systemic Lupus Erythematosus :

The American College of Rheumatology and European League Against Rheumatism (ACR/EULAR) have recommended the use of a revised and updated 2019 classification criteria for SLE, which includes ANA positivity at a tire of at least 1:80 as an entry criterion required to classify a patient as having Lupus. Further criteria have been divided into clinical and

Entry criterion
Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

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If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria
Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight	Immunology domains and criteria	Weight
Constitutional		***Antiphospholipid antibodies***	
Fever	2	Anti-cardiolipin antibodies OR	
Hematologic		Anti-β2GP1 antibodies OR	
Leukopenia	3	Lupus anticoagulant	2
Thrombocytopenia	4	***Complement proteins***	
Autoimmune hemolysis	4	Low C3 OR low C4	3
Neuropsychiatric		Low C3 AND low C4	4
Delirium	2	***SLE-specific antibodies***	
Psychosis	3	Anti-dsDNA antibody* OR	
Seizure	5	Anti-Smith antibody	6
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria >0.5g/24h	4		
Renal biopsy Class II or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

Fig 1 — New 2019 SLE EULAR/ACR classification criteria

immunological domains and criteria, with weightage being distributed among the parameters. Proliferative lupus nephritis proven on biopsy holds the maximum weightage, and a total score of 10 or more weightage points are needed to classify a patient as a case of Lupus[10]. This has demonstrated a sensitivity and specificity of 96.1% and 93.4% (Fig 1).

IgG4-Related Disease :

IgG4-related disease and its propensity to form fibroinflammatory, tumefactive lesions in virtually any organ in the body, also had its classification criteria updated and somewhat complicated. A 3-step process was validated by an international multispeciality groups of physicians: "First, it must be demonstrated that a potential IgG4-RD case has involvement of at least one of 11 possible organs in a manner consistent with IgG4-RD. Second, exclusion criteria consisting of a total of 32 clinical, serological, radiological and pathological items must be applied; the presence of any of these criteria eliminates the patient from IgG4-RD classification. Third, eight weighted inclusion criteria domains, addressing clinical findings, serological results, radiological assessments and pathological interpretations, are applied[11]."

Therapeutics :

Moving towards Small Molecules in Rheumatic Diseases

The advent of biologics and small oral molecules has recently changed the existing scenario of pharmacologic treatment of rheumatic diseases. These drugs have innovative mechanisms of action, that target specific parts of the pathogenetic pathways in various diseases. Conventional biologic DMARDs have paved their way to newer biological like Sarilumab (IL-6 antagonist) for Rheumatoid Arthritis, biosimilars (Fig 2), and more recently, the oral small molecules that have brought a "pill in the pocket" alternative to regular injections for disease control. There are many more undergoing trials and in the pipeline for release in the near future (Fig 3), although their safety and efficacy studies need further investigation. JAK-inhibitors like Tofacitinib, Upadacitinib and Baricitinib are upcoming areas of prime interest for rheumatologists worldwide.

Antifibrotics in Scleroderma :

In light of recent advances in the understanding of the pathogenesis of fibrosis in Scleroderma, many agents are being tried in trials to discover their efficacy as anti-fibrotic agents, as currently there are no known effective measures to reverse or halt fibrosis on this

S.no	Biosimilar	Active moiety	Originator	Approved indication	Launch date in India
1	Etacept	Etanercept	Enbrel	As, RA, PsA, Ps, JIA	Apr 2013
2	Intacept	Etanercept	Enbrel	As, RA, PsA, Ps, JIA	Mar 2015
3	Infimab	Infliximab	Remicade	AS, IBD,RA PsA,Ps	Sep 2014
4	Exemptia	Adalimumab	Humira	AS,IBD, RA, PsA, Ps	Dec 2014
5	Reditux RA	Rituximab	Mabthera	Leukemia, lymphoma, RA	Apr 2007

Fig 2: Some Biosimilars in use in India

Drug	Disease	Mechanism of action	Trial phase	Name of trial
Filgotinib	PsA	JAK1 inhibition	Phase 2	Equator
	RA		Phase 3	Finch 2
	SpA		Phase 2	Tortuga
Upadacitinib	RA	JAK1 inhibition	Phase 3	Select-next
	SpA		Phase 2	Select Axis 1
Guselkumab	PsA	IL23p19 inhibition	Phase 2	NCT 02319759
Bimekizumab	PsA	IL17 A-F inhibition	Phase 3	NCT02963506NCT03355573
	SpA		Phase2	NCT02430909
	RA		Phase 2	
BCD-085	PsA	IL 17 inhibition	Phase 3	PATERA
Brodalumab (siliq)	PsA	IL 17 inhibition	Phase 3	
Clazakizumab	PsA	IL 6 inhibition	Phase 2	
AMG 592	RA	LT regulation	Phase 2	
Sarilumab	PsA	IL6 inhibition	Phase 2	
Mavrilimumab	RA	GM-CSF pathway inhibition	Phase 2	
GSK3196165	RA	Anti-GM-CSF	Phase 2	
Namilumab	RA	Anti-GM-CSF	Phase 2	
MORAb-022	RA	Anti-GM-CSF	Phase 1	
DEN-181 1	RA	LT regulation	Phase 1	
Dercernotinib	RA	JAK3 inhibition	Phase2/3	
Peficitinib	RA	JAK 1–3 inhibition	Phase 3	RAJ3-RAJ4

Fig 3 — Biologicals and small molecules under development in rheumatic diseases

DRUG	TARGET	OUTCOME OF TRIAL
Fresolimumab	TGF-β	Phase 2, improvement in mRSS and gene biomarker in skin
Abituzumab	αv integrin	Phase 2, enrolling
SAR100842	LPA1 receptor	Phase 2, trend toward improvement in mRSS
Tocilizumab	IL-6 receptor	Phase 2, trend toward improvement in mRSS 48 weeks; possibly slower decline in FVC
Pirfenidone	Fibroblast proliferation	Phase 2, acceptable safety profile
Nintedanib	Inhibits multiple receptor tyrosine kinases and non-receptor tyrosine kinases	Phase 3, enrolling
Abatacept	Fusion protein to CTLA-4	Phase 2, enrolling
Rilonacept	IL-1	Phase 2, enrolling

disease. The list of agents and their targets have been illustrated in Fig 4, although it remains to be seen what efficacy and safety data is finally churned out at the end of these trials.

Machine Learning/AI :

Machine learning (ML) is a subset of artificial intelligence finding increasing applications in Rheumatology, with growing datasets providing a basis for application of machine learning via deep learning, supervised/unsupervised learning and reinforcement learning[12]. Automated image recognition is already in use, and newer programmes in ML, especially using Supervised Learning, are being developed to individualise disease prediction models. Algorithms can now aid in e-diagnosis, disease course and patterns of disease, treatment related modifiable factors and the risk or benefit of an intervention as previously studied in national cohorts.

Hence, in the future, shared decision-making will include the patient's opinion, the rheumatologist's evidence-based experience, as well as algorithms drawn up by machine-learned evidence.

In conclusion, one may cite a hundred or so ongoing trials or review analyses in the field of rheumatology, and yet the core components of individualised decision-making and a few already well-established treatment protocols are the pillars continuing to support clinical judgement. A new era beckons, where further research in targeted therapy and artificial intelligence may help us take better decisions, thus bringing down the time to diagnosis and better patient outcomes.

Limitation :

Even with all these developments we could not translate significantly the clinical achievement in our daily clinical practise . We would need more evidence based scientific information in future for translating bench to bedside practise.

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