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Is There a Need for New Drugs to Manage Rheumatoid Arthritis?

A chronic progressive autoimmune condition, **Rheumatoid arthritis** (RA) can be debilitating and disabling. It affects multiple organs and tissues and can cause long-term pain, discomfort, unpredictable flares, and loss of joint function. Commonly presenting as an inflammatory erosive symmetrical polyarthritis, it usually affects the proximal small synovial joints of hands and feet. Left untreated, it can destroy the articular cartilage and juxta-articular bone, leading to chronic pain, progressive joint destruction and deformity, loss of function, disability and excess mortality. Insufficiently treated RA leads to irreversible joint damage in ~80% of patients, and maximum destruction occurs in the first two years of the disease. Impaired physical functioning has a significant impact on the quality of life. Disability impacts ~30-40% of RA patients and ~30% patients stop working prematurely.[1-5]

Multiple oral as well as injectable treatment options such as corticosteroids, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), targeted synthetic DMARDs (tsDMARDs) and biologic DMARDs (bDMARDs) are currently available for the management of RA.

Methotrexate (MTX), a csDMARD, forms the backbone of RA treatment and ~25-40% of patients achieve significant improvement with this monotherapy. For patients who do not respond to/tolerate MTX, other csDMARDs such as Hydroxychloroquine (HCQ), Sulfasalazine (SSZ), or Leflunomide (LEF) may be considered. For patients not responding to these 1L agents, a combination of a csDMARD with 2L agents such as a bDMARD (TNF inhibitor – Etanercept, Infliximab, Adalimumab, Golimumab, Certolizumab; IL-6 receptor antagonist – Tociluzumab, Sarilumab; CD80/86 costimulation modulator –

Efficacy of DMARDs for the Management of RA[1]

Therapy	Mechanism of Action	Efficacy (ACR 70 Response Rate)
csDMARDs		
Methotrexate	Unknown	20-40%
Sulfasalazine	Unknown	8%
Leflunomide	Pyrimidine Synthesis Inhibition	10%
Hydroxychloroquine	Unknown	Unavailable
tsDMARDs		
Tofacitinib	JAK Inhibition	20% (MTX IRs) 14% (TNF Inhibitor IRs)
Baricitinib		24% (MTX IRs) 17% (TNF Inhibitor IRs)
bDMARDs		
Etanercept	TNF Inhibition	20% (MTX IRs) 12% (TNF Inhibitor IRs)
Infliximab		
Adalimumab		
Golimumab		
Certolizumab		
Tocilizumab	IL-6 Receptor Antagonism	22% (MTX IRs) 12% (TNF Inhibitor IRs)
Sarilumab		
Abatacept	CD80/86 Co-stimulation Modulation	22% (MTX IRs) 10% (TNF Inhibitor IRs)
Rituximab	CD20 Antagonism	22% (MTX IRs) 12% (TNF Inhibitor IRs)

csDMARD: Conventional Synthetic DMARD; tsDMARD: Targeted Synthetic DMARD; bDMARD: Biologic DMARD; IR: Inadequate Responder; ACR: American College of Rheumatology

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Abatacept; IL-1 receptor antagonist – Anakinra), or a csDMARD with a tsDMARD (JAK inhibitor – Tofacitinib) may be considered. The combination of MTX with a bDMARD or a tsDMARD has transformed the treatment of RA over the last two decades, and provides remission or low disease activity (LDA) in ~50% of patients. Rituximab, a CD20 antibody, and baricitinib (JAK inhibitor) are 3L treatment options for TNF inhibitor refractory patients.[1,3]

Evolution of treatment paradigm and gaps in management

EULAR and ACR recommend early initiation (within three months of disease onset) of "treat-to-target" approach to induce remission (defined as no disease activity) and low disease activity (LDA), assessed by clinical disease activity index (CDAI). Along with the availability of tsDMARDs and bDMARDs, with their superior efficacy and faster onset of action, the EULAR and ACR recommendations have revolutionized the management of RA.[1,2,3,7,8]

Early diagnosis and treatment may prevent or limit progression of joint damage in ~90% of patients with early RA. It is possible to gain remission or LDA in ~50% of patients but disease flares are common and durable remission is elusive.[1,3,9] New therapies with mechanisms of action similar to therapies already approved for RA are not expected to provide any additional benefit in terms of efficacy and safety beyond the current benchmarks. Novel MoAs are needed to bring a fresh perspective to the treatment approach.

Gaps that emerging therapies need to address for meaningful differentiation

- **Therapies for the management of pre-RA phase:**
  - ➤ At-risk pre-RA individuals will develop RA when multiple criteria are met. Diagnosing at-risk pre-RA patients is challenging as:[10,11]
    - ✓ No biomarkers/lab tests can identify pre-RA patients who will certainly develop RA in the future.
    - ✓ Only one-third of individuals in the pre-RA phase are likely to develop RA over time. Of the remaining, half of the patients are likely to go into remission while in the remaining patients it would persist as undifferentiated arthritis.
    - ✓ Large scale screening and follow-up of at-risk population (genetic and environmental factors, autoantibody-positivity, symptoms without clinical arthritis) may not result in optimal utilization of healthcare resources.
  - ➤ However, treating individuals with early disease may be less challenging.[12,13]
    - ✓ Increasing evidence suggests that the first few months after symptom onset represents a pathologically distinct phase of the disease and may offer an opportunity to permanently switch off the disease process.
    - ✓ Resolution of early inflammation is through ordered production of anti-inflammatory mediators such as lipid-derived lipoxins, protectins, and resolvins. These chemical mediators act as agonists for anti-inflammatory and pro-resolving mechanisms that help in restoration of homeostasis.
      - – These mediators are likely to help in the development of resolution-targeted therapies to control unwanted side-effects of aberrant inflammation early in the disease process.
      - – Chronic inflammation in established disease is associated with disordered resolution, fibroblast activation and hyperplasia. This persistent inflammatory infiltrate may be less amenable to resolution with therapies.
- **Personalized therapies:** Identification and treatment of pre-RA patients with highly personalized therapies could revolutionize the treatment paradigm of RA. Therapies targeting individual patient segments could be the way forward.
- **Therapies that provide durable remission** and allow tapering/withdrawal of toxic immunosuppressants and therapies that can quickly subdue flares without intensification of toxic therapies.
- **Therapies to limit the impact of comorbidities:** RA is associated with several comorbidities including cardiovascular disease, infections, malignancies, depression, osteoporosis, GI ulcers, asthma and COPD. However, mortality in RA is mainly attributed to CV disease, infections and malignancies.
  - ➤ Future RA therapies that limit CV disease and infections could improve long-term outcomes of RA patients. However, there is no pipeline activity targeting comorbidities in RA.
- **Therapies for patients with inadequate response or intolerance to bDMARDs and tsDMARDs:** Immunogenicity and secondary drug failure can be difficult to manage and therapies are needed to help in management of patients with such challenging issues.
- **Development of preventive strategies such as vaccines** for the population at risk of progression to RA.

Treatment paradigms are well recognized for RA, with availability of multiple mechanisms to target different disease pathways. As the understanding of RA pathophysiology improves, new mechanism and targets are being discovered for drug development and this could lead to improved outcomes in terms of better efficacy as well as preservation of joint anatomy and functionality.

Recent evaluation of the RA pipeline reveals about 80 assets in clinical development with 1 asset in pre-registration, 7 assets in Phase III, 40 assets in Phase II, and 32 assets in Phase I. Several novel therapies in the RA pipeline include BTK inhibitors, IRAK4 inhibitors, Syk Tyrosine Kinase inhibitors, BAFF antagonist, CSF antagonists, and dual inhibitors such as IL-17 + TNF inhibitor, BTK + JAK inhibitor, and BAFF + APRIL inhibitor. Regulatory T cell (Treg) based immunotherapy, a highly personalized therapeutic approach in very early stage of development, may have the ability to slow down or stop the clinical progression of RA.

Therapies with higher efficacy and a durable remission are likely to fill some of the gaps in the current standard of care. Future therapies that target pre-RA phase or CV comorbidities in RA could change the treatment paradigm to significantly reduce the disease burden of this debilitating and crippling disease.

Conclusion

Systemic autoimmunity may be present for years before subclinical synovitis and RA. There is a need to understand the differences in the cytokines, chemokines and immune cell alterations between pre-RA patients and patients with recently diagnosed RA for targeted drug development to prevent RA. Disease and patient heterogeneity makes treatment challenging and durable remission is usually not achieved.

Early diagnosis and treatment of RA is the best way to improve patient outcomes and achieve drug-free remission. Identifying and treating “at-risk” patients in the pre-RA phase could prevent RA and decrease the overall burden of disease.

Therapies directed towards management of non-responders/partial responders could improve the chances of sustained remission. Additional novel therapies targeted at specific unmet needs and patient segments will help in improving long-term disease outcomes and quality of life of RA patients. Personalized therapies such as Treg immunotherapy may be the first step in that direction. Resolution-targeted therapies acting via stimulation of anti-inflammatory mediators such as lipoxins, protectins and resolvins could target early disease in the future.

Thus, novel agents and treatment approaches are needed to manage a multifactorial disease such as RA to bridge the gap between the treatment goals and aspirations of patients and treating physicians. Better understanding of RA pathophysiology and relevant genetic/serum biomarkers will underline future drug development efforts.

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