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# Introductory Chapter: Rheumatoid Arthritis - Overview of Current Facts and Strategies

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## 1. Introduction

Rheumatoid arthritis (RA) is a chronic multi-system inflammatory autoimmune disease of indefinite etiology. The disease primarily affects synovial joints eventually progressing to ongoing inflammation, destruction of both cartilaginous and bony elements of the joint, with resultant pain and disability. The disease additionally displays a spectrum of extra-articular multisystem manifestations [1]. The worldwide prevalence of RA remains underestimated, data gathered from Western regions illustrated prevalence between 0.5 and 1% in white individuals, with prevalence rates ranging between 0.6 and 0.9% in the studied black individuals. The female to male ratio in rheumatoid arthritis is 2:1 to 3:1. A high concordance rate is observed in monozygotic twins 12–15% compared to 2–3% in dizygotic twins [2–4].

Theories behind the evolution of autoimmunity in rheumatoid arthritis are clearly multifactorial. The inflammatory process usually develops in a predisposed individual who is probably exposed to a provocative trigger of autoimmunity via epigenetic modifications. A number of risk factors comprising genetic as well non genetic elements provide the hostile environment for the change towards autoimmunity. Evidences revealed a significant impact of familial genetic risk factors featuring  $\geq 50\%$  of the total risk of developing seropositive RA, with highest incidence rates among first-degree relatives. Among the most influential non genetic risk factors there comes smoking. Smoking provides a stimulus to epigenetic transformation, particularly in individuals with high-risk RA-susceptibility alleles.



**Figure 1.**  
*Etio-pathogenic factors and disease evolution in rheumatoid arthritis.*

Environmental risk factors also include; particulate exposure, periodontal disease, bronchiectasis, diet, obesity and the oral contraceptive impact, respiratory, oral, intestinal and genital tract mucosal sites [1, 5], **Figure 1**.

## 2. Role players in the initiation and propagation of autoimmunity in rheumatoid arthritis

a. **Neo-epitopes generation:** genetic and environmental factors operate to ultimately result in the inflammatory and destructive synovial response. Stressors including cigarette smoke can act on cells in mucosal sites and promote post-translational conversion of the amino acid arginine to citrulline in a range of proteins, including intracellular proteins (such as histones) and matrix proteins (for example, fibronectin, collagen, fibrinogen, enolase and vimentin) via induction of peptidyl arginine deaminases in a process called citrullination (also known as deimination) rendering them antigenic [6–8].

Citrullination may also be induced by the oral microbiota: *P. gingivalis*, common in periodontal disease which expresses peptidyl arginine deaminases and can induce citrullination. *A. actinomycetemcomitans*, also producing a toxin that increases calcium influx into neutrophils, can lead to citrullination of peptides and has been recently implicated in RA etiology. Post-translational modifications (citrullination, carbamylation, and acetylation) are potentially capable of generating neo-epitopes (neo-peptide antigens). Animal and human data about autoimmunity in rheumatoid arthritis suggest a model in which multiple environmental influences mucosal immune function promoting epigenetic transformations with trafficking of pro-inflammatory PAMPs making use of the enhanced mucosal permeability. Hence, the initial shift towards autoimmunity may present at mucosal sites as reported in previous researches with sputum samples positive for ACPA-IgA and IgG [9, 10].

b. **Major histocompatibility complex binding and peptide presentation:** specific class II human leukocyte antigen (*HLA*; also known as major histocompatibility complex—MHC) loci, which encode MHC molecules *HLA-DRB1\*01* and *HLA-DRB1\*04* display a very strong association with RA. The altered peptides bind to MHC protein heterodimers on antigen presenting cells, especially those containing the shared epitope [a specific amino acid motif QKRAA commonly encoded by some alleles of the HLA-antigen D-related (DR) locus significantly associated with the risk of developing RA]. Being bound to MHC complex the antigenic epitope gets presented by the antigen-presenting cells (dendritic cells and macrophages) to the antigen-specific T lymphocyte receptor to stimulate T lymphocyte activation and differentiation. Over 100 non-HLA genetic risk factors (loci) including polymorphisms of PTPN22, TRAF1-C5, STAT4, TNFAIP3, and PADI4 have been associated with an increased risk of developing RA [11, 12].

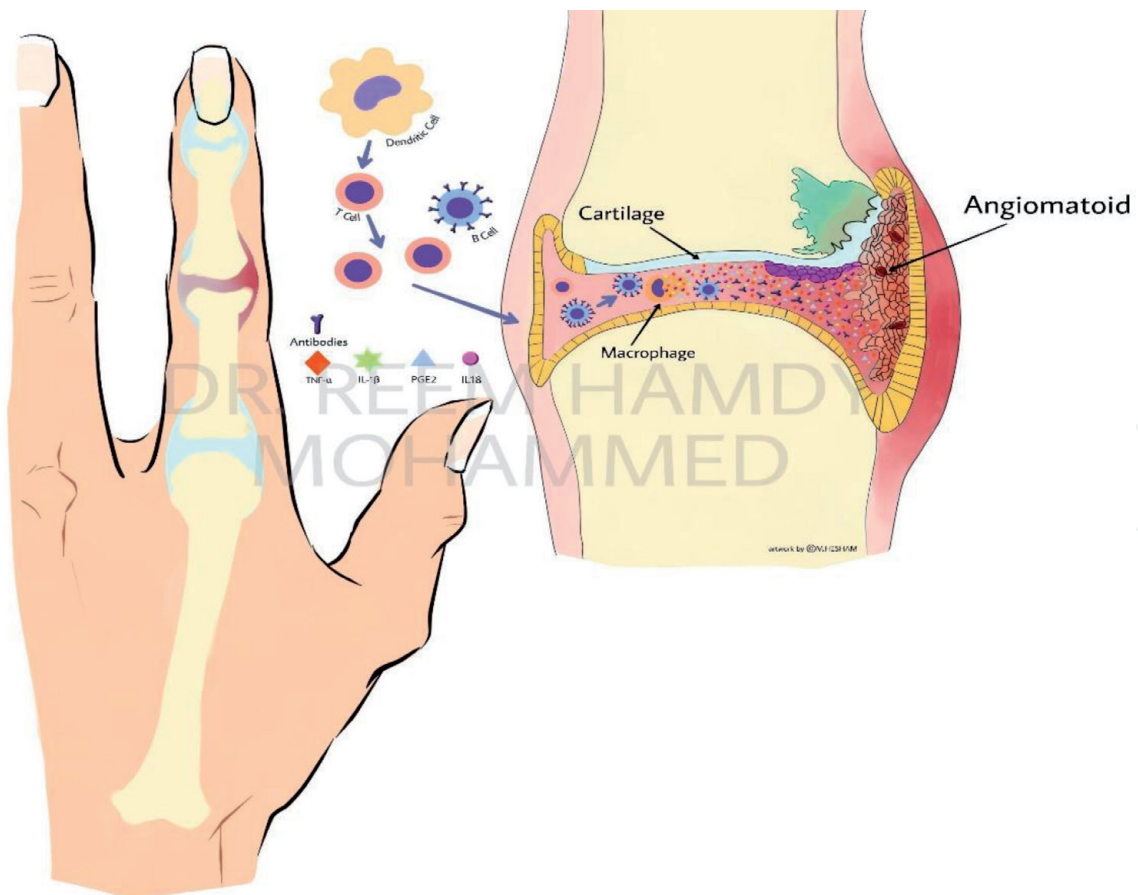
c. **The adaptive immune system:** the activated T lymphocyte stimulates the release of pro-inflammatory cytokines including RANKL, TNF- $\alpha$ , GM-CSF, IL-2, IL-17 and IFN- $\gamma$ . The antigen-stimulated T lymphocyte then promotes B cell priming via T-B cell receptor signaling pathways then stimulate specific antibody responses by the stimulated B lymphocytes against the

neo-epitopes (neo-antigens) promoting a self-directed immune response. In addition to autoantibody production the activated B lymphocytes releases IL-6 [13, 14].

**d. In situ activation of stromal cells:** fibroblast-like synoviocytes FLS, antigen presenting cells and macrophages within the synovial joints gets similarly and synchronously stimulated to release a cascade of pro-inflammatory mediators promoting arthritis with cartilage and bone damage.

FLS masters the intra-articular production of prodigious amounts of MMPs and small-molecule mediators such as MMPs, prostaglandins, leukotrienes, and RANKL. They additionally express IL-6 receptors and specific patterns of microRNAs that could contribute to their activated phenotype. FLS exhibit an invasive phenotype that is responsible for cartilage damage and can potentially migrate from joint to joint to propagate disease. The macrophages like synoviocytes participate actively via local release of TNF- $\alpha$ , IL-1, IL-6, IL-8 and chemokines (CCL19, CCL21) [15–17].

**e. Ectopic germinal centers:** the adaptive immune cells infiltrate the synovial sublining with almost half of the sublining cells CD4+ memory T cells that can either diffusely infiltrate the tissue or, in 15–20% of patients, form ectopic germinal centers in which mature B cells proliferate, differentiate and produce antibodies (rheumatoid factor RF and anti-citrullinated C peptide ACCP) [18, 19].



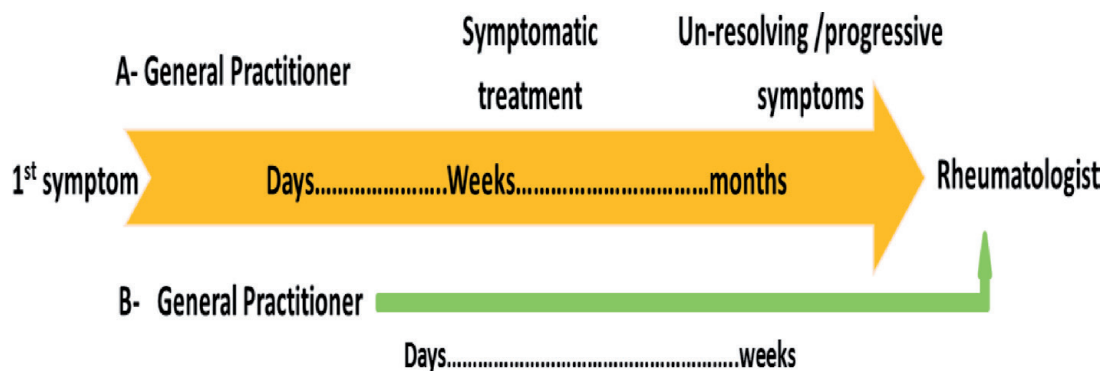
**Figure 2.** Proximal interphalangeal joint with macrophages, dendritic cell, T cell, B cells infiltrates with hypertrophied synovium, intra-synovial angioma and pannus formation. “By Dr. Maya H Ibrahim” the original image provider.

The development of manifest disease in rheumatoid susceptible patients usually requires a second hit driven by cross-reactivity, or molecular mimicry to pathogen-specific antigens, in the settings of an inevitable lag of pathogen-immune complex clearance (**Figure 2**).

### 3. Diagnosis of rheumatoid arthritis

The diagnosis of rheumatoid arthritis requires the integration of proper history taking, careful clinical examination and investigations. Patients might face a period of delay in establishing their diagnosis from weeks to months due to incomplete or intermittent symptoms, defective/unaccomplished clinical/radiographic and laboratory assessments particularly with early disease [20].

### 4. Patients' journey to diagnosis



Standard of care in rheumatoid arthritis aims at the following [21]:

- Establishing early diagnosis of RA.
- Identifying arthritis in need of treatment.
- Designing the ideal way to successfully initiate synthetic non biologic DMARDS.
- Providing low remission rates with standard DMARDS.
- Identifying other potential therapeutic targets in aggressive disease.
- Ensuring availability and safety of biologic DMARDS.
- Providing standardized measures for patient assessment, follow-up and treatment modulation.

The recently adopted American College of Rheumatology/European League Against Rheumatism ACR/EULAR classification criteria were established in 2010 with the aim to identify patients with early inflammatory arthritis that is mostly due to rheumatoid arthritis. They have been proposed by the faculty as classification rather than diagnostic criteria to facilitate stratifying patients with similar characteristics for clinical research studies particularly clinical trials with intent to

treat. The development of diagnostic criteria for RA as other autoimmune disorders is still challenged by inter/intra-individual variability and chances of misdiagnosis. However, the current criteria might be used to inform diagnostic decision making in clinical practice [22].

## 5. ACR/EULAR 2010 classification criteria for rheumatoid arthritis

The classification criteria proposed by the American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) included clinical and serological variables that can be applied only to individuals with  $\geq 1$  swollen joint [22].

### 5.1 Joint involvement and distribution: 0–5 points

Any swollen or tender joint (excluding the distal interphalangeal joints of hands and feet, the first metatarsophalangeal joints and the first carpometacarpal joints) on clinical examination; additional evidence from MRI or ultrasonography may be used to identify additional joints.

1 large joint (shoulder, elbow, hip, knee or ankle): 0 points

2–10 large joints: 1 point

1–3 small joints (the metacarpophalangeal joint, the proximal interphalangeal joint, the second to fifth metatarsophalangeal joints, the interphalangeal joint of the thumb and the wrist): 2 points

4–10 small joints: 3 points

>10 joints (of which  $\geq 1$  is a small joint): 5 points

Additional small joints include the temporomandibular joint, sternoclavicular joint, acromio-clavicular joint and others, as reasonably expected in RA.

### 5.2 Symptom duration: 0–1 points

This variable refers to the patient's self-report on the maximum duration of signs and symptoms of any joint that is clinically involved at the time of assessment.

<6 weeks: 0 points

$\geq 6$  weeks: 1 point.

### 5.3 Serology (according to respective laboratory standards): 0–3 points

Negative for RF (equal or less than upper limit of normal) and negative for ACPA: 0 points

Low-positive for RF (>1–3 times upper limit of normal) or low-positive for ACPA: 2 points

High-positive for RF (>3 times upper limit of normal) or high-positive for ACPA: 3 points.

### 5.4 Acute-phase reactants (according to local laboratory standards): 0–1 points

Normal CRP (C-reactive protein) and ESR (erythrocyte sedimentation rate) levels: 0 points

Abnormal CRP levels or abnormal ESR: 1 point

A score of  $\geq 6$  points is required for classification as definite rheumatoid arthritis (RA).

## 6. Disease activity scoring in rheumatoid arthritis

Scoring system	Formula	Disease activity states			
		Remission	Low disease activity	Moderate disease activity	High disease activity
SDAI	SJC28 + TJC28 + PGA + EGA + CRP	≤3.3	>3.3–11	>11–26	>26
CDAI	SJC28 + TJC28 + PGA + EGA	≤2.8	>2.8–10	>10–22	>22
DAS	Complex formula including the Ritchie index, SJC44, ESR and GH	≤1.6	>1.6–2.4	>2.4–3.7	>3.7
DAS28	Complex formula including the TJC28, SJC28, ESR (or CRP) and GH	≤2.6	>2.6–3.2	>3.2–5.1	>5.1

*CDAI, Clinical Disease Activity Index; CRP, C-reactive protein (in SDAI in mg per dl); DAS, Disease Activity Score; DAS28, DAS using 28-joint counts; EGA, Evaluator Global Assessment (on a 0–10 cm scale); ESR, erythrocyte sedimentation rate; GH, global health (that is, patient global assessment); PGA, patient global assessment (on a 0–10 cm scale); RA, rheumatoid arthritis; SDAI, Simplified Disease Activity Index; SJC, swollen joint count (the number indicates the number of joints taken into account); TJC, tender joint count (the number indicates the number of joints taken into account) [23–25].*

## 7. Different definitions of remission

### 7.1 American Rheumatism Association

Five or more must be fulfilled for at least two consecutive months—morning stiffness not exceeding 15 minutes—no fatigue—no joint pain (by history)—no joint tenderness or pain on motion—no soft tissue swelling in joints or tendon sheaths—ESR (W) < 30 mm/h (f); <20 mm/h (m) [26].

### 7.2 DAS/DAS 28 threshold for remission

For the DAS: Ritchie joint index and 44 swollen joint count with either ESR or CRP versions, remission: <1.6

For the DAS28: 28 tender and swollen joint count with either ESR or CRP versions, remission: <2.6 [27].

### 7.3 SDAI/CDAI remission

$$\text{SDAI} = (28\text{TJC}) + (28\text{SJC}) + \text{MDGA} + \text{PtGA} + \text{CRP}^*$$

$$\text{CDAI} = (28\text{TJC}) + (28\text{SJC}) + \text{MDGA} + \text{PtGA}^*$$

$$\text{SDAI remission} \leq 3.3^{**} \times \text{CDAI remission} \leq 2.8^{**} \text{ [28, 29].}$$

### 7.4 Boolean definitions

Depend on meeting a (low) level in each of a series of separate disease activity measures Boolean-based definition at any time point, a patient must satisfy all of the following—Tender Joint Count ≤1—Swollen Joint Count ≤1—CRP ≤1 mg/dL—Patient Global Assessment ≤1 (on a 0–10 scale) [30].

### 7.5 ACR-EULAR 2011 definition of remission

- For clinical trials: Boolean—SJC, TJS, PtGA, CRP all ≤1 or index-based—SDAI ≤3.3 [30]

- For clinical practice: Boolean—SJC, TJC, PtGA all  $\leq 1$  or index-based—CDAI  $\leq 2.8$

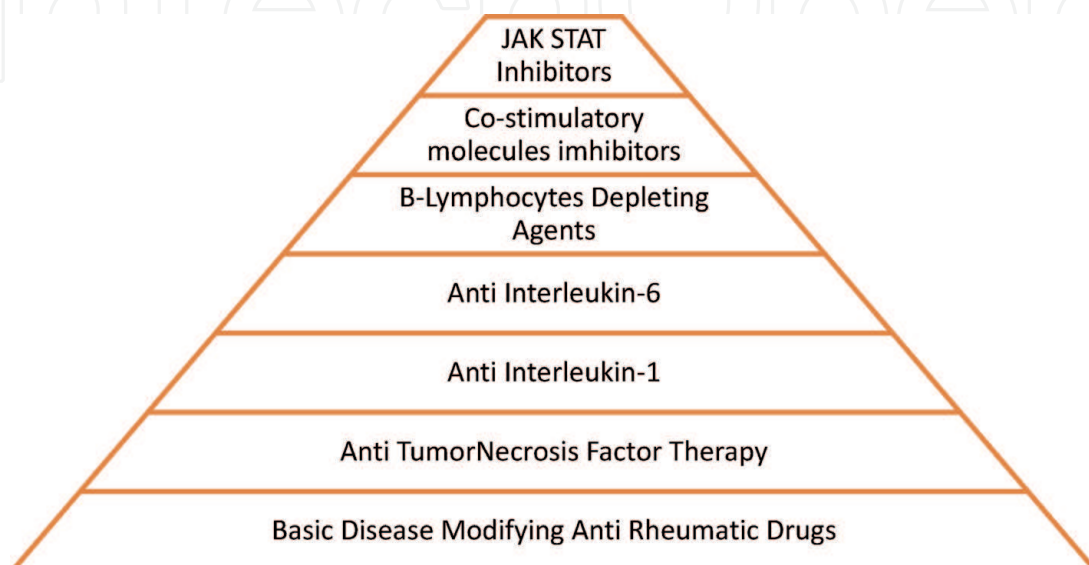
Factors that contribute to poor prognosis in rheumatoid arthritis include the following [25]:

- Persistently moderate or high disease activity despite conventional synthetic DMARD (csDMARD) therapy according to composite measures including joint counts.
- High acute phase reactant levels.
- High swollen joint count.
- Presence of RF and/or ACPA, especially at high levels.
- Presence of early erosions.
- Failure of two or more csDMARDs.

## 8. The treat-to-target in rheumatoid arthritis

The treatment paradigm in rheumatoid arthritis has experienced a dramatic shift in the latest two decades. Recently, the strategy changed from a treat to relief to a treat to target. The current approaches in RA are concerned with early aggressive intervention with one or more conventional or traditional synthetic DMARDs (cs/tsDMARDs) and/or biologic DMARDs (bDMARDs) either as mono or combination therapy, in addition to symptomatic anti-inflammatory therapy (NSAIDs, low-dose prednisone). This tight control policy aims to; normalize, sustain or maximize physical functionality via retardation or arrest of joint damage. The treat-to-target is the currently established management approach in the international recommendations provided by ACR, EULAR and the Asia Pacific League of Associations for Rheumatology [31, 32], **Figure 3**.

Recent update on the guidelines of management of rheumatoid arthritis as provided by the EULAR European League Against Rheumatism in 2019 announcing the following overarching principles [33]:



**Figure 3.**  
*Identified synthetic and biologic disease modifying anti-rheumatic drugs in rheumatoid arthritis.*



- Treatment of patients with RA should target the best care and must be based on a shared decision between the RA patient and the rheumatologist.
- Disease activity, structural damage, patient safety, and other comorbidities, including the risk for thromboembolism must be considered when prescribing treatment.
- Rheumatologists are responsible for the primary care of the patient as they possess the optimal depth and breadth of experience regarding the use of all types of DMARDs, including efficacy, outcomes, risk assessment and knowledge of comorbidities.
- The heterogeneous nature of rheumatoid arthritis mandates patients' access to effective disease modifying anti-rheumatic drugs with successful multiple mechanisms of action.
- RA incurs high individual, medical and societal costs, should be considered while prescribing therapy by the rheumatologist.

### **8.1 EULAR 2019 recommendations**

In 2019 the EULAR taskforce stated a number of updated recommendations emphasizing the strategy to start DMARDs therapy as soon as the diagnosis of RA is made. These recommendations included [33]:

- Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient. Adopted definitions for disease activity states assessment and therapy include: (a) remission ACR-EULAR remission definition—Boolean or index based, (b) low disease activity state according to any of the validated composite disease activity measures that include joint counts moderate and high disease activity, and (c) respective disease activity state according to any of the validated composite disease activity measures that include joint counts.
- Monitoring should be frequent in active disease (every 1–3 months); if there is no improvement by at most 3 months after the start of treatment or the target has not been reached by 6 months, therapy should be adjusted.
- Methotrexate MTX should be part of the first treatment strategy—the anchor drug.
- In patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy.
- Short-term glucocorticoids should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible.
- If the treatment target is not achieved with the first csDMARD strategy, in the absence of poor prognostic factors, other csDMARDs should be considered.
- If the treatment target is not achieved with the first csDMARD strategy, when and poor prognostic factors are present, a bDMARD or a tsDMARD should be added.
- Biologic DMARDs and traditional synthetic DMARDs (tsDMARDs) should be combined with a csDMARD; in patients who cannot use csDMARDs as

comedication, IL-6 pathway inhibitors and tsDMARDs may have some advantages compared with other bDMARDs.

- If a bDMARDs or tsDMARDs has failed, treatment with another bDMARD† or a tsDMARD‡ should be considered; if one TNF inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF inhibitor.
- If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering bDMARDs or tsDMARDs, especially if this treatment is combined with a csDMARD.
- If a patient is in persistent remission, tapering the csDMARD could be considered.

## 9. Summary

- Establish early diagnosis of rheumatoid arthritis.
- Identify patients with arthritis in need for treatment.
- Arrange for evidence-based management.
- Apply aggressive measures to target disease.
- Apply standardized measures for assessment of disease activity, functional assessment, patient and physician global assessment.
- Tailoring of therapy with potential consideration of patient safety, comorbidities and costs.

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