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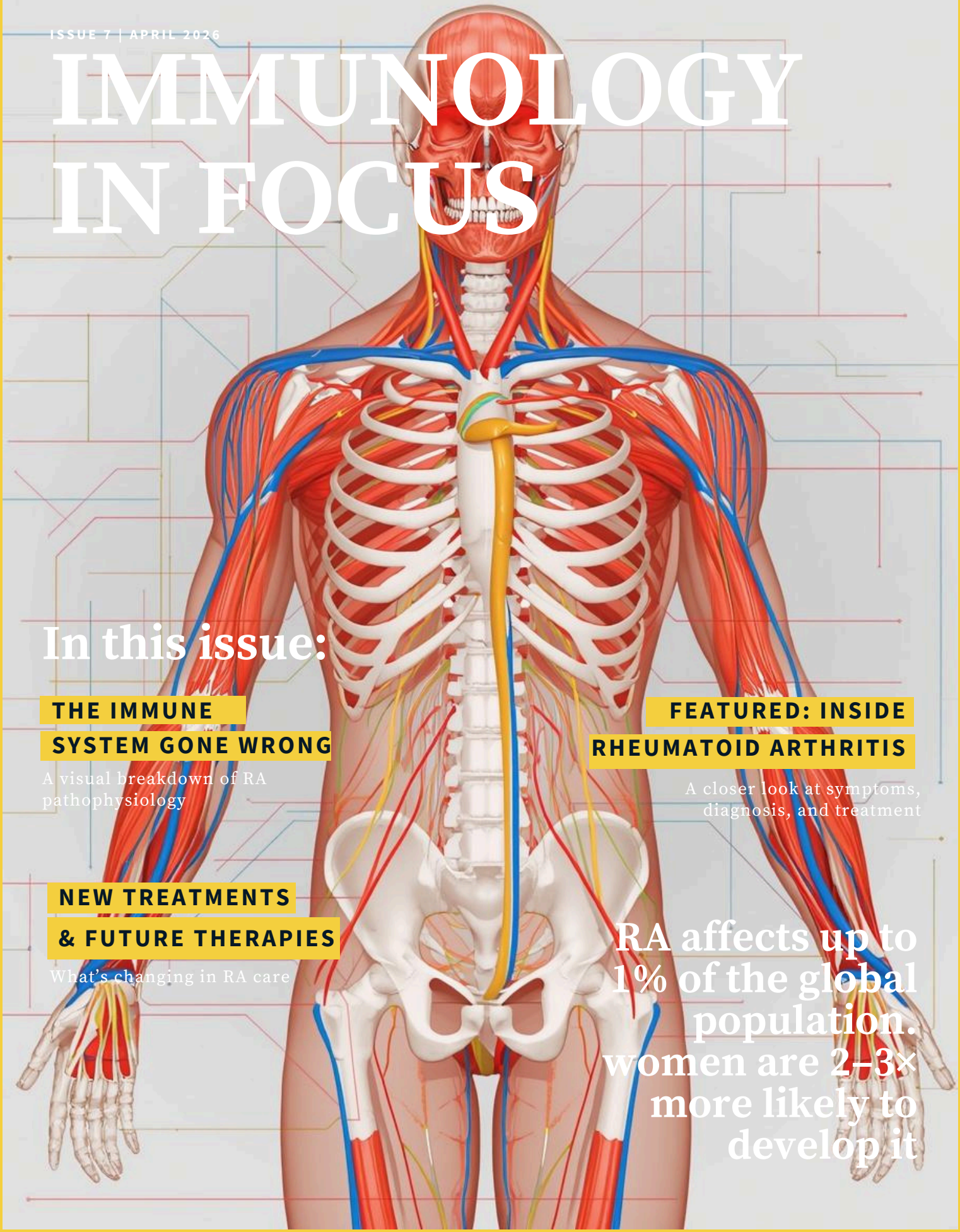
IMMUNOLOGY IN FOCUS



In this issue:

THE IMMUNE SYSTEM GONE WRONG

A visual breakdown of RA pathophysiology

FEATURED: INSIDE RHEUMATOID ARTHRITIS

A closer look at symptoms, diagnosis, and treatment

NEW TREATMENTS & FUTURE THERAPIES

What's changing in RA care

RA affects up to 1% of the global population. women are 2–3× more likely to develop it

WHAT IS RHEUMATOID ARTHRITIS?

UNDERSTANDING RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic autoimmune disease that mainly affects the musculoskeletal system.[1] In RA, the immune system mistakenly targets the body's own tissues, mainly attacking the synovial lining of joints.[1] This leads to persistent inflammation, causing pain, swelling, and stiffness that can progressively damage joints over time if left untreated.[2]

RA most commonly affects small joints in a symmetrical pattern, such as the hands and wrists. This makes daily tasks such as writing or gripping objects increasingly difficult.[3] One of the hallmark clinical features of RA is prolonged morning stiffness, often lasting more than one hour.[4] As the disease progresses, inflammation within the joint promotes the formation of abnormal tissue known as pannus, which gradually erodes cartilage and bone, ultimately leading to deformities and loss of joint function.[5]

RA is often confused with osteoarthritis due to similar symptoms and both being joint diseases. However, these diseases have different etiologies.[6] Unlike osteoarthritis, which is caused by simple wear and tear, RA is driven by immune system dysfunction, making it different from more common joint diseases such as osteoarthritis.[6]

RA AT A GLANCE

- Affects about **0.5–1%** of the population worldwide.[1]
- Women are affected about **2–3 times more** often than men.[1]
- Common symptoms include joint pain, swelling, fatigue, and morning stiffness lasting **more than 1 hour**.[2 8]

WHY DOES IT MATTER?

In RA, inflammation is not just a local response, as it becomes systemic, meaning it can affect multiple organs and systems throughout the body.[7] Patients often experience symptoms beyond joint pain, including fatigue, low-grade fever, and weight loss, reflecting widespread immune activation.[3] Additionally, RA can affect multiple organ systems, increasing the risk of cardiovascular disease, lung involvement, and other extra-articular manifestations.[4]

Understanding RA as an autoimmune and systemic disease, not just a "wear and tear" joint condition, is important for appreciating both its complexity and its clinical significance.

QUIZ: DIAGNOSE THE PATIENT!

Instructions:

Each patient presents with joint symptoms. Based on the symptoms presented in each case, decide whether the condition is **Rheumatoid Arthritis (RA)** or **Osteoarthritis (OA)**. Flip the page to check your answers!

Cases:

1. **A 45-year-old woman presents with:**
- Symmetrical swelling in **both hands**
- Morning stiffness lasting **>1 hour**
- Fatigue

2. **A 70-year-old man presents with:**
- Knee pain that worsens with activity
- **Minimal** morning stiffness
- No systemic symptoms

3. **A 52-year-old patient presents with:**
- Warm, swollen finger joints
- **Positive anti-CCP** antibodies
- Symptoms affecting **both sides** of the body

4. **A 65-year-old patient presents with:**
- Hip and knee pain
- **Stiffness improves** with movement
- X-ray shows cartilage degeneration

5. **A 48-year-old woman presents with:**
- Joint pain, fatigue, and low-grade fever
- Stiffness lasting **over an hour**
- Swelling in **both wrists**

Answers:

1. RA
2. OA
3. RA
4. OA
5. RA

ETIOLOGY: WHAT CAUSES RHEUMATOID ARTHRITIS?

As mentioned, RA does not come from a single cause, but from a combination of genetic predisposition and environmental exposures. Understanding the causes and etiology is critical for identifying vulnerable populations and appreciating how RA develops. There are many factors that plays into RA, such as:

1. **Genetic Predisposition**

One of the main genetic associations in RA is the **HLA-DR4 allele**. This allele plays a major part in the histocompatibility complex (MHC) class II region.[9] When there is a genetic variation to this allele (HLA-DRB1 alleles), it can influence how the immune system presents antigens, increasing the likelihood of an autoimmune response, leading to a higher risk of developing the disease.[9]

1. **Environmental Triggers**

When environmental factors are added on top of genetic risk, they exacerbate the risk of developing RA. **Smoking** has been shown to increase the risk of RA in individuals with **HLA-DRB1 alleles**[10], and is also associated with developing more severe disease progression. It has been found that smoking is also associated with the formation of **anti-citrullinated protein antibodies (ACPA)**, triggering RA-specific immune reactions.[11]

3. **Hormonal causes**

Hormonal influences also play a role, as RA is significantly more prevalent in women than in men.[1] This suggests that sex hormones, particularly estrogen, may influence immune system activity due to their ability to modulate the immune response using androgen and estrogen receptors.[12] [13] However, the underlying mechanisms behind this imbalance of gender prevalence in RA are still not clear.

4. **Infections**

Additional risk factors include environmental exposures, such as infections. Infections may promote the formation of immune complexes, which can stimulate the production of **rheumatoid factor (RF)**, an autoantibody directed against immunoglobulin G that contributes to RA pathogenesis.[3] The bacterium *Porphyromonas gingivalis* in periodontal diseases was shown to express enzyme PADI4, which promotes citrullination of host proteins, a key step in the generation of anti-CCP antibodies, promoting PA pathogenesis.[14] Emerging evidence also highlights the role of the gut microbiome in shaping immune responses, with specific bacterial profiles associated with the development of autoantibody-positive RA.[3] [15] While infections have been proposed as potential triggers, no single pathogen has been definitively identified, highlighting the multifactorial nature of RA.

PATHOPHYSIOLOGY: HOW DOES RA DEVELOP?

The pathophysiology of rheumatoid arthritis comprises many complex interconnections between genetic susceptibility, environmental triggers, and immune system dysregulation. At its core, RA represents a failure of immune tolerance, where the body's defense system begins to target its own joint tissues.[5]

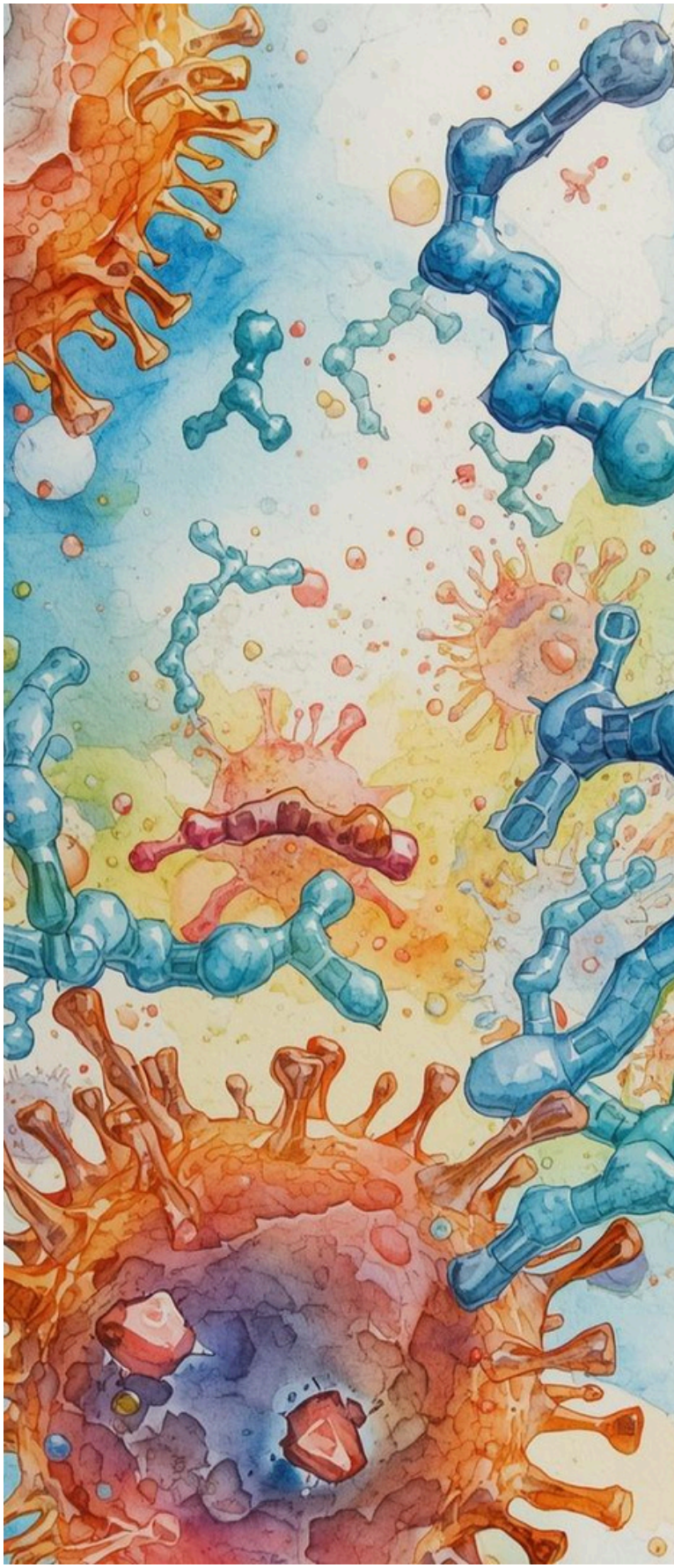
The disease process begins when immune cells such as T cells and B cells are activated and infiltrate the synovial membrane, the thin layer of tissue lining the joints.[3] These immune cells release a cascade of **pro-inflammatory cytokines**, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 (IL-1), which amplify and sustain inflammation.[4] This inflammatory environment transforms the normally delicate synovial membrane into a thickened, aggressive tissue known as pannus.[4]

The pannus plays a central role in joint destruction, as it invades surrounding cartilage and bone, releasing enzymes that degrade structural components and promote erosion.[4] Over time, this leads to irreversible joint damage, deformities, and reduced mobility.[4]

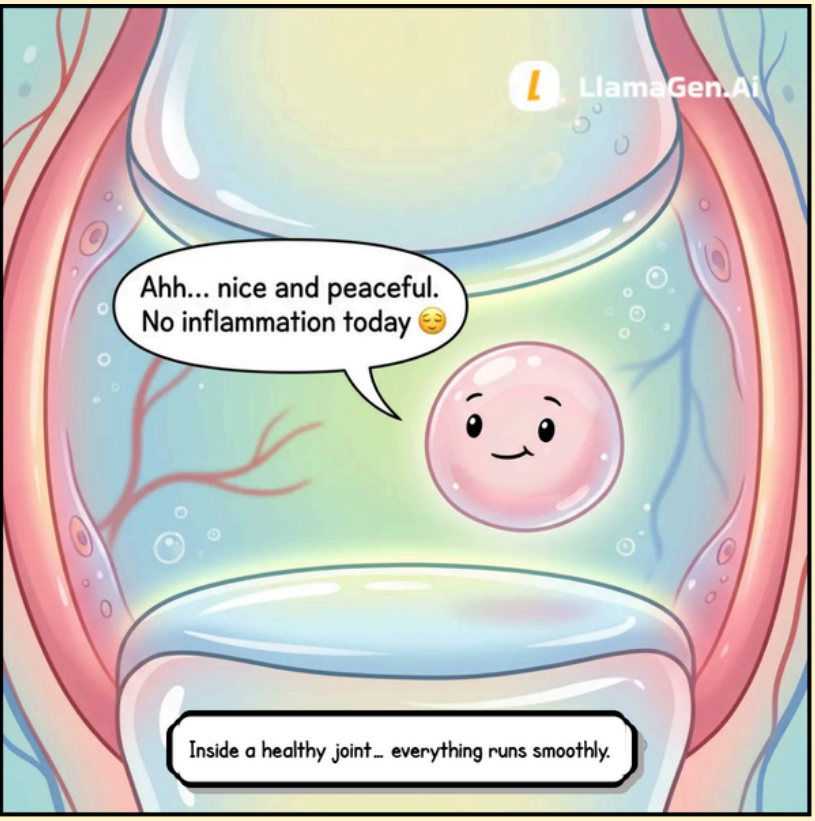
A defining feature of RA is the presence of autoantibodies, particularly **rheumatoid factor (RF)** and **anti-cyclic citrullinated peptide (anti-CCP) antibodies**.[3] Anti-CCP antibodies are especially important, as they are highly specific for RA and can often be detected before clinical symptoms appear.[3] These antibodies form immune complexes that further stimulate inflammation and contribute to tissue damage.[3]

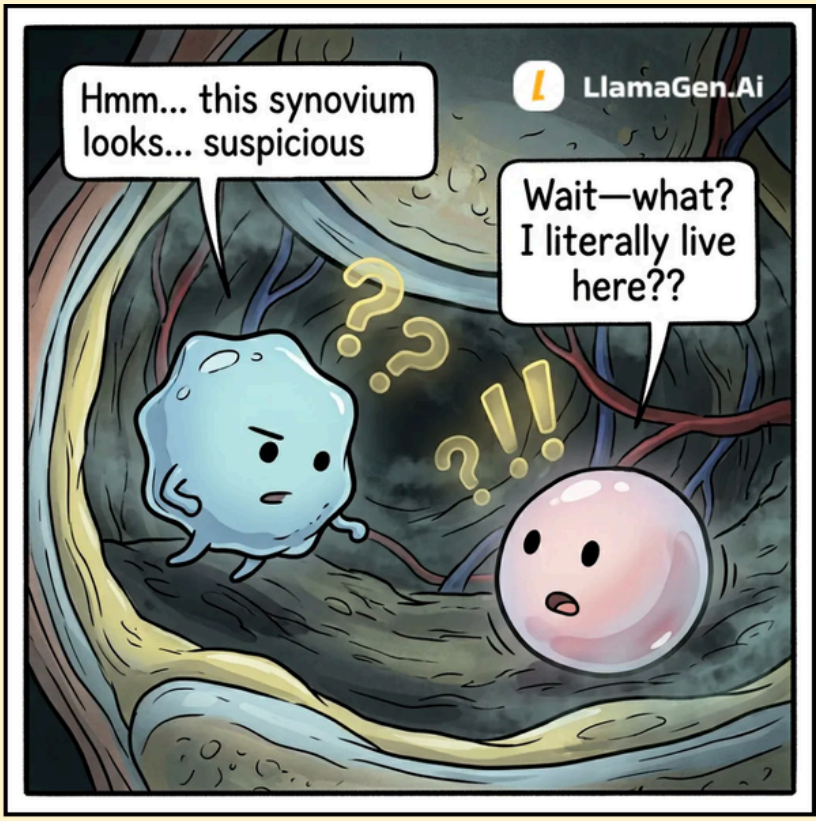
Since RA involves systemic inflammation, the same inflammatory mediators circulating in the bloodstream can affect other organs, explaining the increased risk of cardiovascular disease, lung involvement, and systemic complications.[4] This highlights the systemic nature of RA and further reinforces why it must be treated as more than a localized joint condition.

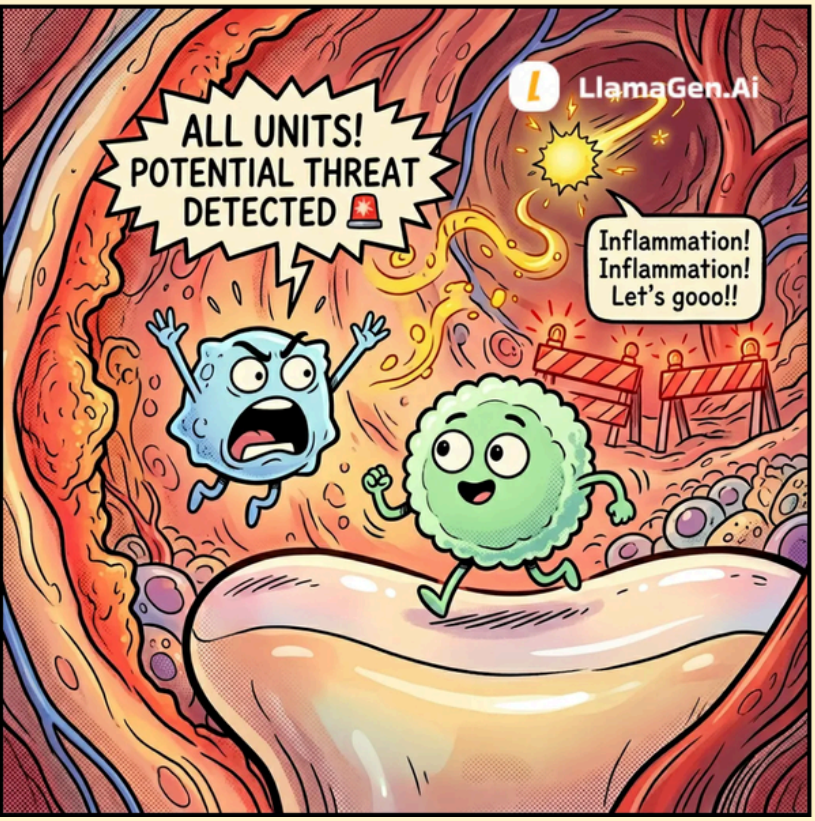
Overall, RA can be understood as a self-perpetuating inflammatory cycle. This is why most modern therapies aim to break this cycle, particularly drug therapies that target key cytokines such as TNF-α.[3]

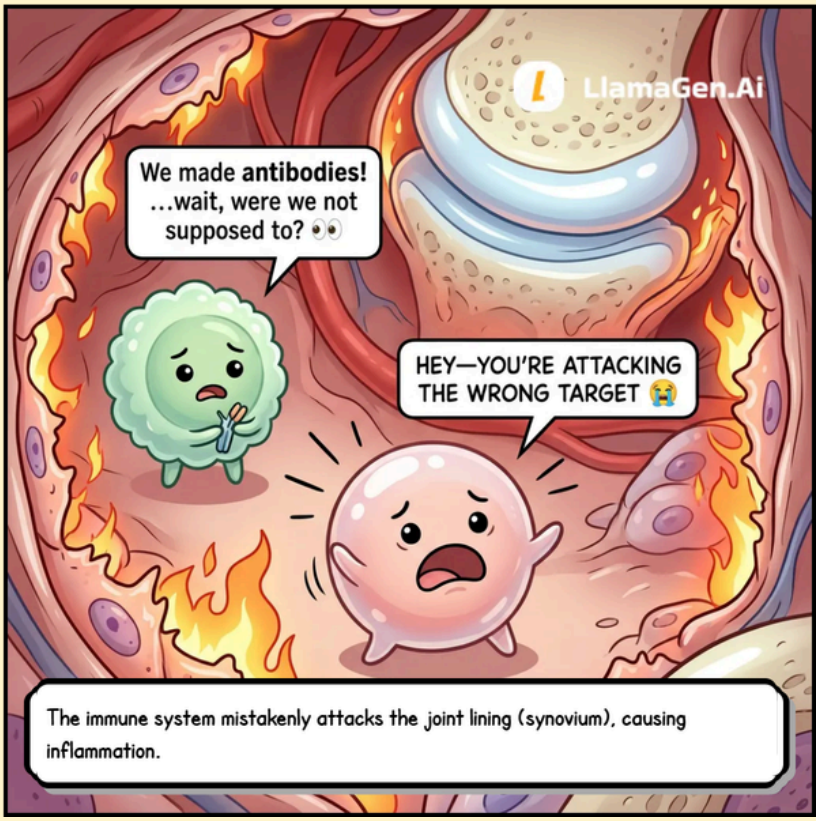


THE IMMUNE SYSTEM GONE WRONG: AN RA COMIC









SIGNS & SYMPTOMS: RECOGNIZING RA EARLY

CATCHING SIGNS EARLY

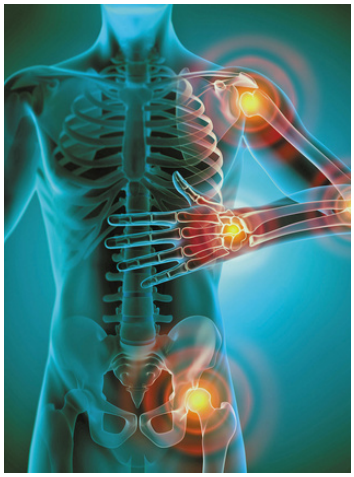
Rheumatoid arthritis presents with a combination of joint-specific and systemic symptoms, reflecting its nature as both a musculoskeletal and immune-mediated disease. Noticing these features early is essential, as prompt treatment can significantly alter disease progression. Here are some of the main signs to look out for:

1. Joint Pain, Swelling, and Stiffness

The most prominent symptoms of RA involve inflammation of the **synovial joints**.[2]

Prolonged morning stiffness is a hallmark symptom of RA. This typically lasts more than one hour, which improves with movement rather than rest.[1] This is a key difference from osteoarthritis, where stiffness is usually brief and worsens with activity.

RA most commonly affects joints in a **symmetrical pattern**, particularly the metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints, and wrists.[1] This distribution is highly characteristic and often used clinically to differentiate RA from other joint disorders.[1]



2. Systemic Symptoms

Beyond joint symptoms, RA is also associated with **systemic inflammation**, which can lead to fatigue, low-grade fever, and weight loss.[3]

These symptoms are driven by circulating inflammatory mediators and may precede joint manifestations in some patients.[1]

3. Disease Progression and Functional Impact

If untreated, chronic inflammation leads to progressive joint damage, including cartilage degradation and bone erosion.[1] Over time, this can result in joint deformities, reduced range of motion, and loss of function.[3]

These structural changes significantly impact daily activities such as writing, gripping objects, and walking.[3]

DIAGNOSIS JOURNEY: FROM SYMPTOMS TO CONFIRMATION

Diagnosing rheumatoid arthritis requires a multidimensional approach, as no single test can definitively confirm the disease. Instead, clinicians rely on a combination of clinical findings, laboratory markers, and imaging studies.

1

Clinical Evaluation

The diagnostic process begins with identifying key clinical features, including symmetrical joint involvement, persistent symptoms (>6 weeks), and morning stiffness.[1]

2

Laboratory Testing

Blood tests checking for:

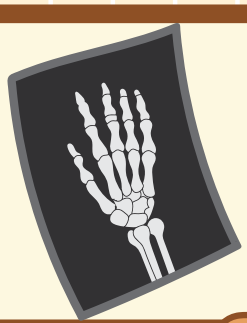
- **Rheumatoid Factor (RF):** Present in many RA patients, but not specific[15]
- **Anti-Cyclic Citrullinated Peptide (Anti-CCP) Antibodies:** Highly specific for RA and strongly predictive of disease progression[3]
- **Inflammatory Markers:** Elevated ESR and CRP indicate active inflammation[1]

3

Imaging Techniques

Imaging is used to assess joint damage and detect early disease:

- **X-rays:** Show joint space narrowing and bone erosion[1]
- **MRI and Ultrasound:** Detect early synovitis and inflammation before structural damage occurs[1]



4

ACR/EULAR Classification Criteria

This scoring system helps **standardize diagnosis** and guide early treatment decisions by accounting for criteria such as the number of joints involved, serology (RF, anti-CCP), inflammatory markers, and symptom duration.[17]

TREATMENTS: MANAGING AND CONTROLLING RA

Although rheumatoid arthritis (RA) currently has no cure, significant advances in treatment have made it possible to effectively control symptoms, slow disease progression, and preserve joint function. Modern management strategies focus not only on relieving pain and inflammation, but also on targeting the underlying immune dysregulation that drives the disease. There are **3 main types** of treatments being used currently:

1. **First-Line Drug Therapies**

Initial treatment is often aimed at providing rapid relief from pain and inflammation, particularly during acute flare-ups. **Nonsteroidal anti-inflammatory drugs (NSAIDs**) are commonly used to reduce joint pain and swelling by inhibiting inflammatory pathways.[19] However, while effective for symptom relief, NSAIDs do not alter the underlying disease process or prevent long-term joint damage.[19]

Corticosteroids are another key component of early management, as they act quickly to suppress inflammation by modulating immune activity.[20] These agents are often used as short-term "bridging therapies" while more definitive treatments are initiated, helping to control symptoms during the early stages of disease management.[20]

3. **Disease-Modifying Anti-Rheumatic Drugs (DMARDs)**

Unlike first-line therapies, disease-modifying anti-rheumatic drugs (DMARDs) directly target the immune mechanisms responsible for RA and are considered the cornerstone of treatment.[21] **Methotrexate** is usually the first-line DMARD and works by inhibiting immune cell proliferation and reducing inflammatory signaling, thereby slowing disease progression.[21]

For patients with more severe or treatment-resistant disease, **biologic DMARDs** may be introduced. These therapies are designed to target specific components of the immune system, such as tumor necrosis factor (TNF) or interleukin-6 (IL-6), both of which play crucial roles in promoting inflammation.[21] By selectively blocking these pathways, biologics can significantly reduce disease activity and prevent joint damage.[21]

More recently, targeted synthetic DMARDs (tDMARDs), such as **Janus kinase (JAK) inhibitors**, have emerged as an additional therapeutic option. These small-molecule drugs interfere with intracellular signaling pathways involved in immune activation, offering another layer of precision in RA treatment.[22]

4. **Lifestyle and Supportive Management**

In addition to pharmacological treatment, non-drug approaches also play a crucial role in improving long-term outcomes and quality of life.[1] Physical therapy and regular exercise help maintain joint mobility, reduce stiffness, and strengthen muscles, which can relieve strain on affected joints.[1] These strategies are not substitutes for medical treatment but serve as important complementary approaches that support overall disease management.[2]

FUTURE RESEARCH & FINDINGS: THE NEXT STEPS IN RHEUMATOID ARTHRITIS

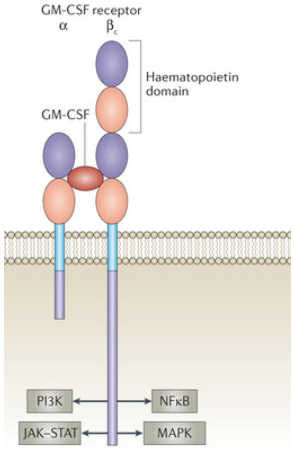
THE NEXT FRONTIER IN RA

Although current therapies have improved outcomes in rheumatoid arthritis (RA), not all patients respond the same to the treatments we use today. As a result, research is shifting toward more precise, targeted, and preventative approaches that aim to transform RA care.[23]

Precision Medicine: Personalized Treatment Strategies

RA is a very heterogeneous disease, meaning patients have distinct molecular and immune profiles. This is why precision medicine uses biomarkers such as anti-CCP antibodies, gene expression patterns, and cytokine profiles to predict disease progression and guide treatment selection for each patient.[23]

Recent technological advances in multi-omics technologies (genomics, proteomics, transcriptomics) have enabled the identification of synovial and blood-based signatures that correlate with treatment response.[23] This could allow clinicians to select the most effective therapy earlier, reducing reliance on the current trial-and-error approach.[23]



GM-CSF receptor structure[28]

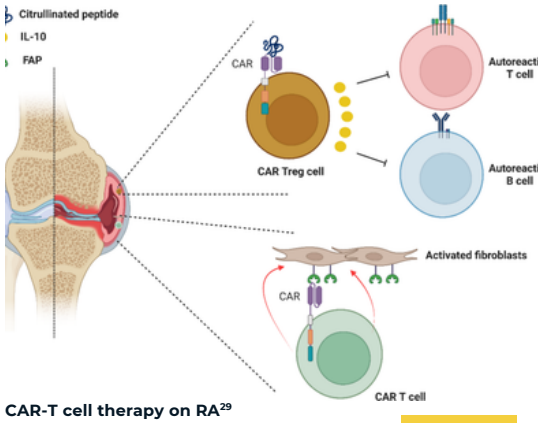
New Biologics: Expanding Therapeutic Targets

While early biologics focused on TNF inhibition, newer therapies target additional inflammatory pathways, including IL-7 and GM-CSF, which play key roles in sustaining joint inflammation.[24]

These therapies are important for patients who do not respond to traditional treatments. Research into the synovial microenvironment has also revealed that every patient has different dominating immune cell populations, supporting the need for more mechanism-specific biologics.[24]

Immunotherapy Advances: Reprogramming Immunity

Emerging therapies aim not just to suppress inflammation, but to modify the immune system itself. One promising approach is cell-based immunotherapy, including CAR-T cell strategies that target autoreactive B cells responsible for producing pathogenic autoantibodies.[25]



CAR-T cell therapy on RA[29]

Researchers are also looking into therapies that enhance regulatory T-cell (Treg) function to restore immune tolerance and prevent autoimmune attack, representing a shift toward long-term immune rebalancing rather than temporary suppression.[26]

Looking Ahead: Can Rheumatoid Arthritis Be Prevented?

One of the most exciting developments in RA research is the possibility of preventing RA before the symptoms appear. RA is now known to begin during a preclinical phase, where individuals may have autoantibodies such as anti-CCP but no visible joint damage yet.[27]

Recent clinical trials have investigated abatacept, a drug that inhibits T-cell activation, in individuals at high risk of developing RA. In a randomized controlled trial, abatacept significantly reduced inflammation and delayed progression to clinically apparent RA, with only 8% of treated individuals developing RA compared to 35% in the placebo group.27 These effects persisted even after treatment stopped, suggesting that early intervention may have lasting disease-modifying effects.[27]

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Team #49