RHEUMATOLOGY NURSE PRACTICE NEWSLETTER

Inside this Issue

ISSUE 2 | VOLUME 1

EDUCATIONAL PLANNING COMMITTEE:

Sheree C. Carter, PhD, RN
Assistant Professor
The University of Alabama
Capstone College of Nursing
Tuscaloosa, Alabama

Iris Zink, MSN, NP
Nurse Practitioner
Beals Institute
Lansing, Michigan

Elizabeth Kirchner, CNP
Nurse Practitioner
Cleveland Clinic
Cleveland, Ohio

Jacqueline Fritz, RN, MSN, CNS
Critical Care and Rheumatology Specialist
Medical Advancement Center
Cypress, California

RNS RHEUMATOLOGY NURSES SOCIETY™

RNSnurse.org

Learning Objectives

1. *Describe the function of key cell types such as B and T cells, monocytes, and osteoclasts in the development and progression of RA*
2. *Describe the function of key cytokines such as tumor necrosis factor and interleukin-6 in the development and progression of RA*
3. *Identify at least three systemic manifestations of RA*
4. *Explain the possible role of biomarkers and biosimilars in the future of care for patients with RA*

Disclosure

It is the policy of the Rheumatology Nurses Society (RNS) that the education presented within RNS-provided activities be unbiased and based upon scientific evidence. To help participants make judgments about the presence of bias, RNS provides information that planners, teachers, authors, developers, and activity managers have disclosed about financial relationships they have with commercial entities that produce or market products or services related to the content of this educational activity. And relation relationships that an individual may have with commercial entities have been disclosed and reviewed, and any potential conflicts have been resolved.

Relationships are abbreviated as follows:
E, Educational planning committee; **G**, Grant/research support recipient; **A**, Advisor/review panel member; **C**, Consultant; **S**, Stock shareholder; **SB**, Speaker bureau; **PE**, Promotional event talks; **H**, Honoraria; **O**, Other.

Sheree Carter, PhD, RN, has disclosed the following relevant financial relationships specific to the subject matter of the content included in this educational activity: Celgene, Antares, Amgen/A.

Jacqueline Fritz, RN, MSN, CNS, has disclosed the following relevant financial relationships specific to the subject matter of the content included in this educational activity: GlaxoSmithKline/A, Celgene, AbbVie/SB.

Elizabeth Kirchner, CNP, has disclosed the following relevant financial relationships specific to the subject matter of the content included in this educational activity: Iroko, Amgen/A, Crescendo Biosciences/SB.

Iris Zink, MSN, NP, has disclosed the following relevant financial relationships specific to the subject matter of the content included in this educational activity: AbbVie/A,SB; Celgene/A; Antares/C: Bristol Myers-Squibb/SB.

RHEUMATOLOGY NURSE PRACTICE NEWSLETTER

Target Audience

The intended audience for this activity includes rheumatology nurses, rheumatology advanced practice nurses, and infusion nurses.

Content Direction

Scott Kober, MBA, Principal, MedCaseWriter, has disclosed that he does not have any relevant financial relationships specific to the subject matter of the content of the activity.

Content Freelancer

Anne Jacobson, MPH, CHCP, Medical Writer, has disclosed that she does not have any relevant financial relationships specific to the subject matter of the content of the activity.

Content Peer Reviewer

This newsletter was reviewed by **Deanna Owens, MSN, RN.** Ms. Owens has disclosed the following relevant financial relationships specific to the subject matter of the content included in this educational activity: Celgene/A, SB; Antares/C; Janssen, AbbVie/SB.

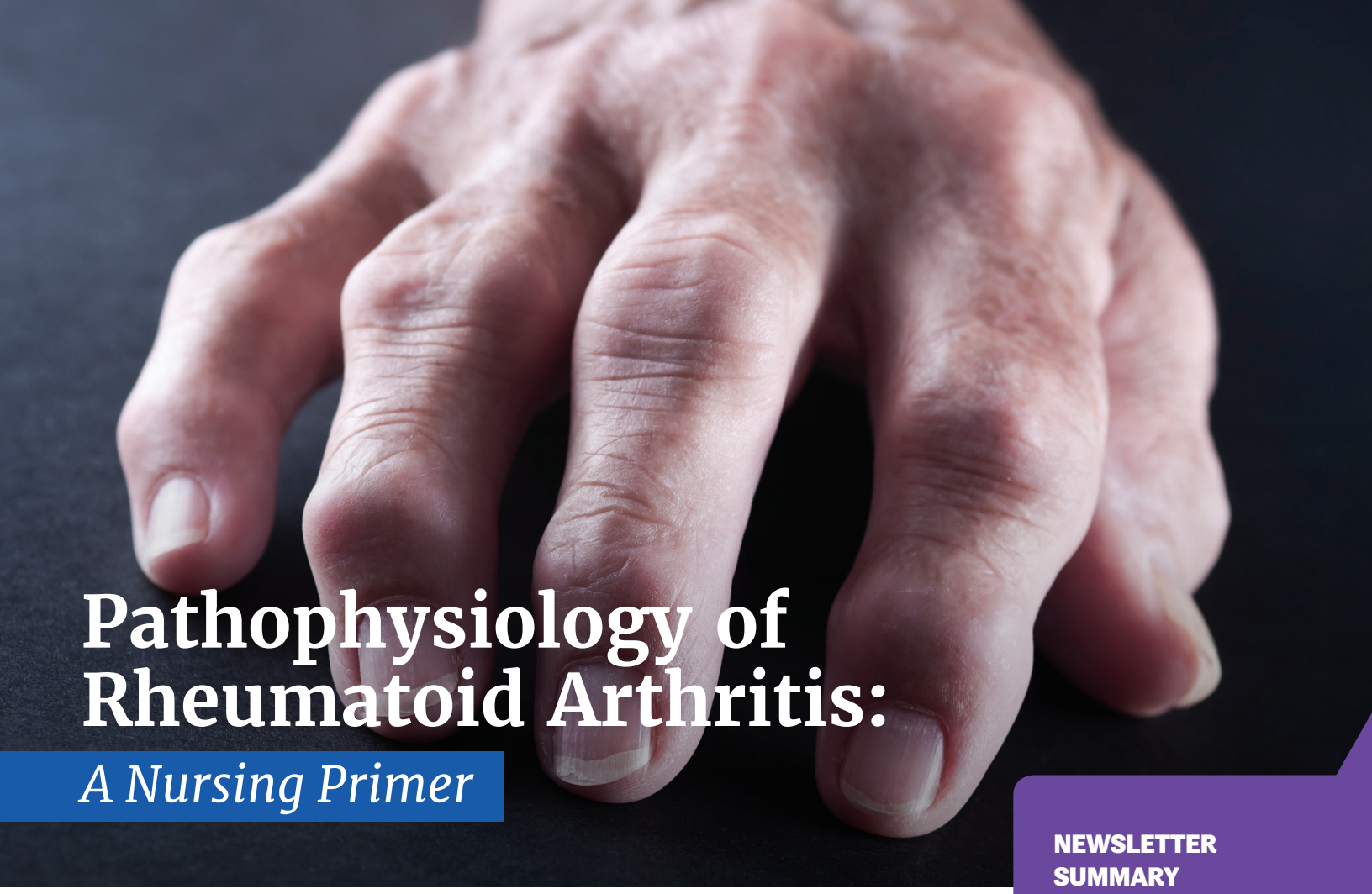
Production Management

Kevin D. Lyons, Executive Director of the Rheumatology Nurses Society and Cheif Executive Officer of Lyons Den Solutions, LLC. has disclosed that he does not have any relevant financial relationships specific to the subject matter of the content of the activity.

Product Disclosure

This educational activity includes discussion of published and/or investigational uses of agents that are not indicated by the U.S. Food and Drug Administration. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

The educational content of this activity has been peer reviewed and validated to ensure that it is a fair and balanced representation of the topic, based on the best available evidence.



Pathophysiology of Rheumatoid Arthritis:

A Nursing Primer

NEWSLETTER SUMMARY

In this issue of Rheumatology Nurse Practice, we explore the underlying autoimmune processes that drive RA and how these mechanisms can influence treatment decisions.

Rheumatoid arthritis (RA) is a chronic condition that can have a significant impact on joint health and function, but it is technically not just a joint disease. The pathophysiology of RA is better described as a sustained immune response directed against the 'self' that causes chronic inflammation throughout the body, and especially the joints. Recognizing RA as an autoimmune disease has important consequences for every stage of disease management.

The Immune System: An Overview

The immune system is a complex system of specialized organs, tissues, and cells that work together to protect the body from harm. Each day, the immune system is bombarded with potentially harmful exposures. While a normally functioning immune system is able to keep environmental, physical, infectious, and other stressors at bay, any malfunction can lead to serious conditions such as bacterial sepsis, cancer, and autoimmune disease.[1]

The following section provides a brief review of the normal immune response, including the roles of different immune system cells and signaling molecules involved in innate and adaptive immunity. Understanding how the key immune system players normally function can be helpful in recognizing what goes wrong in patients with RA.

Immune System Cells

Multiple cell types are involved in coordinating an immune response (Table 1). In a well-functioning immune system, millions of cells work together to orchestrate the nonspecific innate immune response and highly targeted adaptive immune response.[1]

Innate Immune Response

Cells of the innate immune system coordinate the initial nonspecific response

Cell Type	Description	Think of it as...
B cell	• Specialized white blood cell central to the humoral immune response and adaptive immune system • Produces antibodies against soluble antigens	The air traffic controller who takes in information and disseminates it to a number of different sources
Dendritic cell	• A type of antigen-presenting cell that captures, processes, and presents antigens to T cells • Also presents appropriate costimulation molecules to induce a T cell response	The switchboard operator who fields incoming calls and relays the most urgent messages to the authorities
Fibroblast	• Connective tissue cell that produces and maintains the extracellular matrix	The flooring contractor who provides a strong foundation and subfloor
Monocyte	• Type of white blood cell typically involved in infection response • Differentiates into macrophages in the presence of damaged tissue	The superhero who gets ready to change shape in the face of danger
Macrophage	• A specialized monocyte that removes dead cell material via phagocytosis	The trash collector who cleans up all types of debris
Neutrophil	• Specialized cell of the innate immune system that ingests and destroys pathogens • Partly responsible for inflammatory tissue damage	A steamroller that indiscriminately crushes everything in its path
Osteoblast	• Type of bone cell that creates new bone tissue	The construction crew that builds new structures
Osteoclast	• Type of bone cell that resorbs bone tissue • Implicated in joint damage in RA patients	The demolition crew that knocks down old structures
T cell	• Specialized white blood cell central to the cell-mediated immune response • Helper T cells (CD4+ T cells) stimulate the secretion of proinflammatory cytokines (IL-1, IL-6, TNF-α), production of MMPs, and production of osteoclasts	The firefighter who reacts immediately to any threat with broad, nonspecific life-saving skills

CTLA4 = cytotoxic T-lymphocyte antigen 4; IL-1 = interleukin-1; IL-6 = interleukin-6; MMP = matrix metalloproteinases; TNF = tumor necrosis factor

Table 1
Cell Types Involved in RA Development[1]

to perceived threats such as infection and injury.[2] Normally, the innate immune response begins when macrophages encounter a non-self pathogen. Activated macrophages release inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin (IL)-6 to attract other immune system cells to the burgeoning battle site. The rapid influx of cell types includes neutrophils, which engulf and destroy foreign microorganisms, and monocytes, which differentiate into macrophages and replenish the supply of cytokine-producing first responders. The frenzied activity of the innate immune response can cause inflammation, pain, redness, and swelling. Inflammatory cytokines dilate the blood vessels to increase local blood flow and permeability, which manifests as swelling and heat. The rapid migration of immune system cells and their destructive local activity also accounts for the pain.

Once the foreign organism is cleared, immune system cells release anti-inflammatory cytokines to terminate the local inflammatory response. In patients with RA, however, cells of the innate immune system misread self-antigens as a threat that is never neutralized. Thus, the innate immune response is persistently activated, with macrophages continually expressing TNF, IL-6, and other inflammatory cytokines.[2]

Adaptive Immune Response

The adaptive immune system provides a more versatile and specialized form of defense that provides increased protection from a second attack of the same pathogen. During the innate immune response, local inflammation increases the flow of lymph from the site of infection into lymphoid tissue. Immature dendritic cells that have ingested a sample of the pathogen within the infected tissue travel within the lymph to the nearest lymph node,

where they arrive as mature antigen-presenting cells.[3] This activates the lymphocytes of the adaptive immune system, including T and B cells, to hunt for and destroy any cells that display the threatening antigen. In patients with RA, this results in the production of antibodies against self-antigens, or autoantibodies.

The interactions between immune system cells can be dysfunctional in multiple ways that lead to RA. Some patients with RA have a highly reactive innate immune response, whereas dysfunctional adaptive immunity is the dominant mechanism driving RA in others.[4] For additional details on the activity of various immune system cells involved in RA, refer to the *Core Curriculum for Rheumatology Nursing* available for purchase on the Rheumatology Nurses Society website.

Cytokines and Immune System Function

Immune system cells communicate using an elaborate language of chemical signals.[5] Cytokines are specialized proteins that act as local messengers to coordinate the innate and adaptive immune responses. At the tissue level, the balance of proinflammatory and antiinflammatory cytokines influences the degree of inflammation and potential for tissue injury.

TNF and IL-6 are the major cytokines involved in the development of RA, although other cytokines and signaling molecules can amplify the inflammatory response (Table 2).[5]

Table 2
Cytokines and Other Molecules Involved in RA Development[1]

Proinflammatory cytokines	Description	Think of it as...
IL-1	• Stimulates the release of MMP from fibroblasts and chondrocytes	Music that can be felt through the floor
IL-6	• Activates T cells, induces the acute-phase response, and stimulates the proliferation of synovial fibroblasts • Produced by T cells, monocytes, macrophages, and synovial fibroblasts	Music played over the loudspeaker
TNF	• Promotes the initiation and progression of inflammation • Produced primarily by monocytes and macrophages, but also by B cells, T cells, and fibroblasts	The DJ who plays his own music and regulates the timing, speed, and flow of music played by others
Anti-inflammatory cytokines	**Description**	**Think of it as...**
IL-4	• Inhibits the production of IL-1, IL-6, IL-8, and TNF • Decreases inflammation and inhibits cartilage damage	Soothing music that relays calming signals
IL-10	• Inhibits the production of IL-1 and TNF • Reverses cartilage degradation	A mute button that inhibits the music of pro-inflammatory cytokines
Other molecules	**Description**	**Think of it as...**
CTLA4	• An antigen found on the surface of T cells • T-cell activation requires a "costimulatory" signal, which occurs when the T-cell receptor (TCR) binds with another surface antigen, CD28	The ignition on the fire truck, without which firefighters cannot respond to threats
JAK	• A family of intracellular enzymes that process cytokine signals through the JAK-STAT signaling pathway	A cable car that provides the only access down highly desirable roads
MMP	• A family of enzymes capable of degrading extracellular matrix proteins • Implicated in synovial inflammation	Termites that can degrade the subfloor
RANKL	• Promotes osteoclast differentiation and joint cartilage invasion	The chief of the demolition crew who directs the wrecking ball toward particular structures

CTLA4 = cytotoxic T-lymphocyte antigen 4; JAK = Janus kinase; IL-1 = interleukin-1; IL-4 = interleukin-4; IL-6 = interleukin-6; IL-10 = interleukin-10; MMP = matrix metalloproteinases; RANKL = receptor activator of nuclear factor kappa-B ligand; TNF = tumor necrosis factor

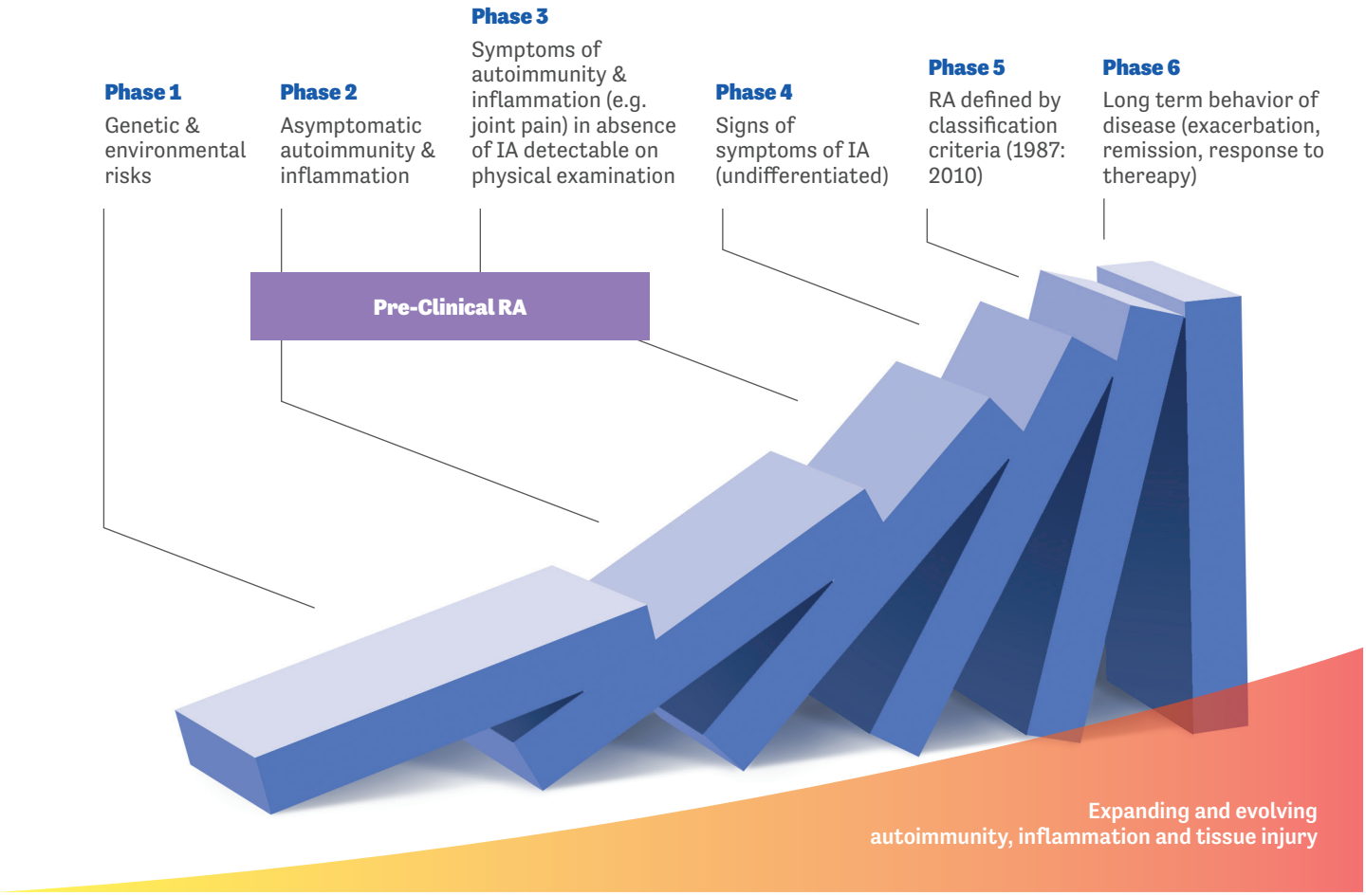


Figure 1
Phases of Development of RA[6]

Immune System Dysfunction in RA

The development of RA typically progresses through multiple phases of immune system dysfunction, inflammation, and tissue injury (Figure 1). It begins with a mix of genetic and environmental risk factors that increase the patient's susceptibility to autoimmunity (Phase 1). Once the autoimmune response is triggered, patients enter a period of asymptomatic inflammation (Phase 2). During this period, autoantibodies and cytokines are beginning to alter the composition of synovial fluid and set the stage for tissue damage. However, changes remain subtle enough to go unnoticed by patients and clinicians. Near the end of the pre-clinical period, the earliest symptoms of inflammation are starting to manifest (Phase 3). Patients may begin to feel some joint discomfort, although clinical signs such as synovitis are not yet detectable on physical examination.

In the next phase, patients begin to show signs and symptoms of inflammation, but the symptoms are not yet severe enough to meet the diagnostic criteria for RA (Phase 4). As the underlying disease continues to progress without intervention, patients' signs and symptoms meet the diagnostic criteria for RA (Phase 5). Whether the final phase of RA (Phase 6) is characterized by effective disease control and clinical remission, or by progressive joint damage and functional impairment, depends on how effectively the underlying disease process is managed.

The phases in this model act as a line of dominos, falling toward clinically active RA. Most of the dominos have fallen by the time RA is diagnosed (Phase 5), leaving only one left standing (Phase 6). With current diagnostic and treatment tools, the only opportunity to improve outcomes in RA is to keep that last domino upright. In the future, providers may find earlier opportunities for intervention. Detecting and treating patients at the phase of subclinical RA (Phases 3 or 4) could prevent the onset of clinical symptoms. Eventually, clinicians may be able to prevent the initial autoimmune trigger from firing in patients with background risk factors for RA, thereby preventing the first domino from ever falling.

Genetic and Environmental Risk Factors

Although the exact cause is unknown, RA appears to arise from a mix of genetic risk factors, environmental exposures, and chance. Studies in twins suggest that 53% to 65% of the risk of developing RA is attributable to genetic susceptibility. Much of the inherited risk of RA has

been identified in patients who harbor a specific genetic profile called the human leukocyte antigen (HLA)-DRB1 'shared epitope' (SE) allele.[7] Certain gene-environment interactions can affect the magnitude of genetic risk factors.[8] For instance, smoking only modestly increases RA risk in patients who do not harbor any HLA-DRB1 SE alleles. By comparison, smoking increases the risk of RA by 6.5-fold and 21-fold, respectively, in patients with 1 or 2 copies of the HLA-DRB1 SE allele.[9]

Multiple other environmental risk factors have been studied as potential triggers for RA, including infectious agents such as Epstein-Barr virus, cytomegalovirus, and *Escherichia coli*. Given that RA disproportionately affects women, the potential influence of hormone exposure on RA development is also an area of research interest.[7]

Autoimmunity in RA

Autoantibodies are a hallmark feature of RA that signal more severe disease and an active underlying autoimmune process. Autoantibodies are produced by the adaptive immune system, with the involvement of both B and T cells.[4] The activation of the autoimmune response is an early event that occurs years before clinical manifestations become apparent. In a retrospective study of blood donors who went on to develop RA, autoantibodies were detectable in the blood a median of 4.5 years before the onset of RA symptoms.[10]

Some models of autoimmune disease suggest a multi-step pathway that involves: 1) an initial trigger that activates general autoimmunity, and 2) a second trigger that directs the autoimmunity toward a specific disease pathology such as RA. Under different circumstances, the same initial autoimmune response may result in different autoimmune diseases such as systemic lupus erythematosus (SLE) or type 1 diabetes.[4]

Rheumatoid factor (RF) was the first autoantibody identified in patients with RA. Up to 80% of patients

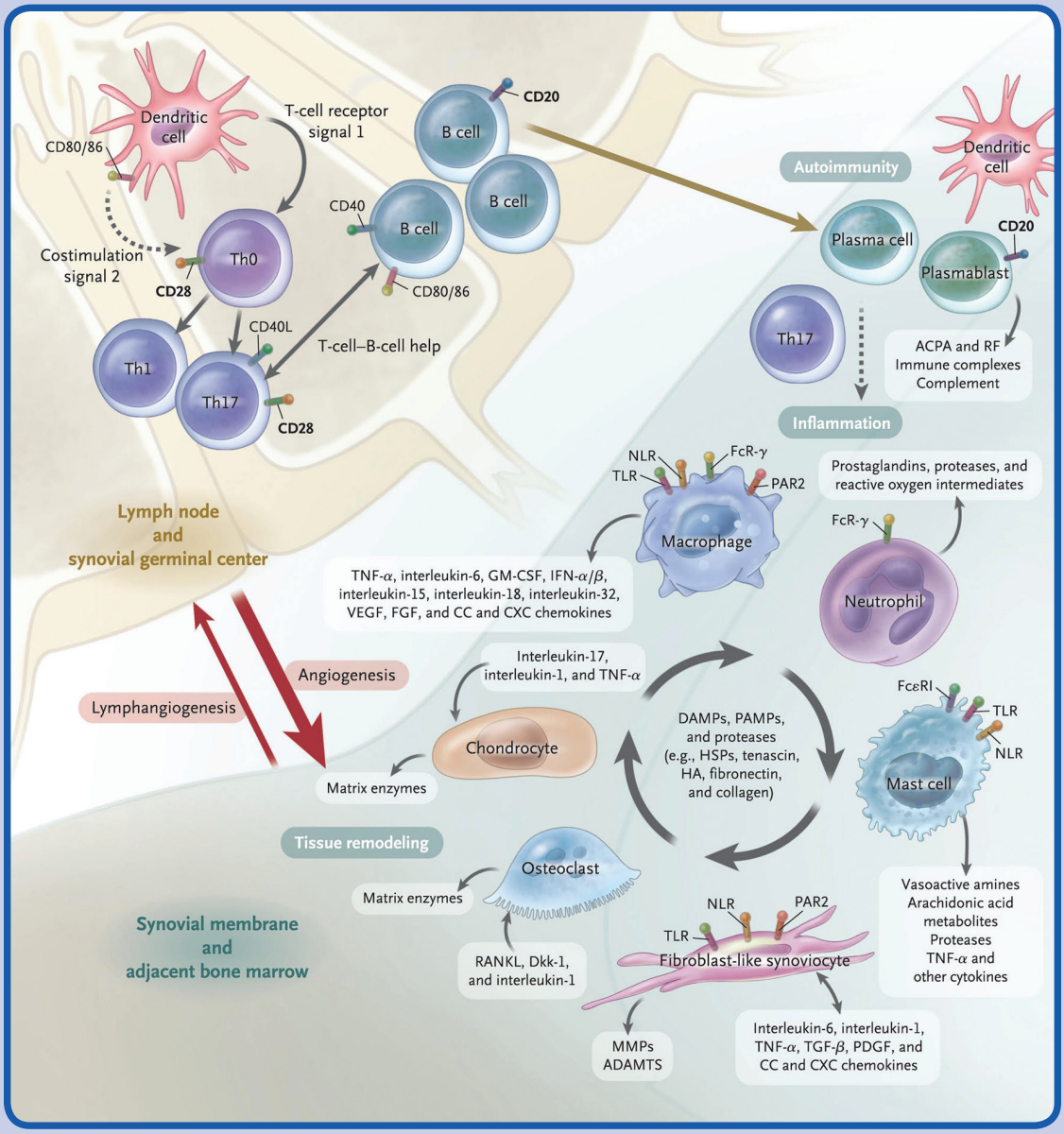


Figure 2 **Adaptive and Innate Immune Processes within the Joint in Rheumatoid Arthritis**

The costimulation-dependent interactions among dendritic cells, T cells, and B cells are shown as occurring primarily in the lymph node; these events generate an autoimmune response to citrulline-containing self-proteins. In the synovial membrane and adjacent bone marrow, adaptive and innate immune pathways integrate to promote tissue remodeling and damage. Positive feedback loops mediated by the interactions shown among leukocytes, synovial fibroblasts, chondrocytes, and osteoclasts, together with the molecular products of damage, drive the chronic phase in the pathogenesis of rheumatoid arthritis.

Reference Note:

1. Carter SC, Patty-Resk C, Ruffing V, Hicks D, eds. Core Curriculum for Rheumatology Nursing. First Ed. Rheumatology Nurses Society;2015.

Organ or organ system	Description	Contributing factors / potential treatment targets
Blood vessels	Atherogenesis, stroke, vasculitis (inflammation of the blood vessels)	IL-6, TNF
Bone	Fractures, low bone mineral density, osteoporosis	TNF, RANKL
Cardiovascular system	Myocardial infarction, pericarditis (inflammation of the sac surrounding the heart)	IL-6, TNF
Central nervous system	Cognitive impairment, depression, fatigue, myelopathy (degeneration of the spinal cord), neuropathy	IL-1, IL-6, TNF
Eye	Episcleritis (inflammation of the episcleral tissue within the eye), keratoconjunctivitis sicca (dry eyes), retinal vasculitis (inflammation of the retinal vessels), scleritis (inflammation of the white of the eye), secondary Sjögren's syndrome	Inflammatory response
Kidney	Glomerulonephritis (inflammation of the glomerulus and other compartments of the kidney)	IL-6, TNF
Liver	Acute phase response, altered lipid metabolism, iron redistribution	IL-6
Lung	Bronchiolitis obliterans organizing pneumonia (a type of non-infectious pneumonia), pleuritis (inflammation of the lining of the lungs), pulmonary fibrosis (scarring of the lungs)	Antirheumatic medication, inflammatory response
Mouth	Periodontitis (inflammation of the gums and bones that support the teeth), secondary Sjögren's syndrome, xerostomia (dry mouth)	Inflammatory response
Muscle	Insulin resistance, muscle loss	IL-1, TNF
Spleen	Felty's syndrome (combination of RA, enlarged spleen, and neutropenia)	Inflammatory response
Other	Amyloidosis (accumulation of amyloid protein in the tissues and organs), subcutaneous rheumatoid nodules, other rheumatoid nodules	Antirheumatic medication, inflammatory response, rheumatoid factor

IL-1 = interleukin-1; IL-6 = interleukin-6; IL-10 = interleukin-10; RANKL = receptor activator of nuclear factor kappa-B ligand; TNF = tumor necrosis factor.

Table 3
Systemic Manifestations of Rheumatoid Arthritis[5]

with RA will test positive for RF in the blood and synovial fluid. Anti-citrullinated peptide antibodies (anti-CCPs) are also present in RA and other rheumatic diseases. Although RF and anti-CCP are not specific to RA, there is a strong mechanistic link between these autoantibodies and the inflammatory pathways that are active in RA. RF and anti-CCP are independently associated with joint damage in RA, and the prognosis is particularly severe when both autoantibodies are present. Several other autoantibodies have been detected in RA, including antibodies against carbamylated proteins (anti-CarP), nuclear antigens (e.g., anti-RA33), and collagen.[4] This underscores the broad nature of autoimmunity in patients with RA.

Chronic Inflammation in RA

The chronic inflammation, swelling, and joint pain in patients with RA are the byproducts of a dysfunctional immune system (Figure 2). As the pathophysiology of RA progresses, patients experience a massive infiltration of macrophages, neutrophils, and monocytes into the synovial fluid, where these immune system cells release TNF, IL-6, and other proinflammatory cytokines. In addition, activated antigen-presenting cells trigger T and B cells to mount an adaptive immune response at the site of joint inflammation.[7]

Joint Destruction

A high propensity for joint damage is the major feature that distinguishes RA from other inflammatory joint diseases. Accordingly, the next phase of RA progression involves the cytokine-directed destruction of cartilage and bone.[4]

The synovial membrane is rich with cells that normally maintain a healthy joint architecture, including chondrocytes, osteoclasts, and osteoblasts. In RA, macrophages and other immune cells have infiltrated the joint and filled the synovial fluid with proinflammatory cytokines and other signaling molecules. The synovial membrane

attaches directly to both cartilage and bone, making these structures vulnerable to damaging signals.[4]

Cartilage damage occurs when cytokines and metalloproteinases activate chondrocytes to degrade the cartilage matrix. Likewise, proinflammatory cytokines promote the differentiation and activation of osteoclasts, which degrade bone.[4,7]

Systemic Effects of Chronic Inflammation

Although joint destruction is a hallmark feature of RA, the joints are not the only targets of chronic inflammation and tissue damage. Patients with RA are vulnerable to systemic complications that arise from the same underlying inflammatory process (Table 3).[5]

Patients with extraarticular manifestations of RA appear to have worse outcomes than patients whose symptoms are confined to their joints.[5] In particular, cardiovascular disease (CVD) is a major cause of morbidity and mortality in RA.[11] As a risk factor, RA is on par with type 2 diabetes in elevating the lifetime risk of CVD.[12] Compared with individuals without RA, patients with RA are 2.4-times more likely to develop any type of CVD and 3.6-times more likely to develop heart failure.[13]

Considerations for RA Management

Long-term RA management involves a series of choices about the timing of starting and switching therapy, the role of biomarkers, and management of poor clinical response and drug holidays. Soon, the availability of biosimilar agents may spur new questions. It is important to consider how the underlying pathophysiology of RA influences current and future management decisions.

Biologic Therapy

Although nonspecific antiinflammatory therapy such as corticosteroids can control RA symptoms, these agents do not address the underlying autoimmunity.[14] Biologic therapies block the interactions between cytokines and immune system cells responsible for the chronic inflammation and structural damage of RA (Table 4).[14]

Current biologic therapy in patients who do not respond to an initial disease modifying anti-rheumatic drug (DMARD) often begins with an anti-TNF agent given in combination with methotrexate (MTX).[15] TNF inhibitors and MTX are routinely given together to take best advantage of their complementary mechanisms of action.[16] Anti-TNF agents show potent activity against myeloid cells (e.g., monocytes and dendritic cells), whereas MTX primarily inhibits lymphocytes.[16] When used in combination, TNF-targeted therapies and MTX provide broad coverage against both myeloid and lymphoid cell types.[16] By comparison, tocilizumab acts against a broader range of immune system cells, and provides effective suppression of lymphoid and myeloid cell types when used as single-agent therapy.[16]

To date, no single RA therapy has been shown to provide long-term control of disease activity in the majority of patients.[14] The wide variations in treatment response reflect the heterogeneity of RA and the diversity of the underlying disease processes.[14]

Table 4
Biologic Therapies Used in RA Management[1]

Drug	Target	Mechanism of Action
Infliximab	TNF	Anti-TNF monoclonal antibody
Adalimumab	TNF	Anti-TNF monoclonal antibody
Golimumab	TNF	Anti-TNF monoclonal antibody
Certolizumab pegol	TNF	Pegylated anti-TNF monoclonal antibody
Etanercept	TNF	Fusion protein of IgG combined with the TNF receptor
Anakinra	IL-1	Soluble IL-1 receptor antagonist
Rituximab	B cells	Anti-CD20 monoclonal antibody
Abatacept	T cells	Fusion protein of IgG combined with the CTLA-4 receptor
Tocilizumab	IL-6	Anti-IL-6 receptor monoclonal antibody
Tofacitinib	JAK	Small molecule inhibitor of the JAK3 enzyme

JAK = Janus kinase; IL-1 = interleukin-1; IL-6 = interleukin-6; TNF = tumor necrosis factor

Several investigational agents are also under development for the treatment of RA. These include new agents directed toward familiar cytokines (e.g., IL-6, IL-17, JAK) as well as novel targets such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and receptor activator of nuclear factor kappa-B ligand (RANKL).[17]

Biomarkers

In current practice, RA patients start one therapeutic option and wait approximately 3 months before determining whether that treatment is working.[15] If the response is inadequate after 3 months, clinicians adjust treatment or switch to another regimen for another 3-month trial.[15] Meanwhile, the patient's underlying RA may progress.

One of the next frontiers in RA management involves being able to select the treatment that best matches the unique features of each patient's immune dysfunction.[14]

One of the next frontiers in RA management involves being able to select the treatment that best matches the unique features of each patient's immune dysfunction.[14] Given the central role of B cells in producing autoantibodies, logic follows that patients with high RF and/or anti-CCP titres should be particularly responsive to B cell-targeted therapy. This theory has been borne out in clinical trials, where rituximab—a B cell inhibitor—is slightly more effective in patients who test positive for autoantibodies than in seronegative patients.[18,19] Yet at present, the ability to pinpoint the best first choice therapy for every patient with RA remains out of reach.

Moving forward, biomarkers may be getting patients one step closer to the goal of individualized therapy. The multi-biomarker disease activity (MBDA) score is a measure of RA disease activity based on 12 serum biomarkers.[20] The individual biomarkers included in the MBDA assay represent the spectrum of pathologic mechanisms underlying RA disease activity, including cytokine signaling, synovial invasion, cartilage and tissue remodeling, and immune response. Furthermore, the MBDA biomarkers correspond with the specific signs and symptoms of RA captured by the DAS28-CRP score, including tender joints, swollen joints, the patient global assessment, and CRP.[20]

Compared with other measures of disease activity, the MBDA score is the only marker that differentiates between high and low risk of radiographic progression in patients with early RA who have not started DMARD therapy. In the future, the MBDA score may be further developed as a tool to understand which patients are more likely to benefit from intensive therapy due to high-risk features such as an increased risk for radiographic progression.[21] To date, however, limitations in reimbursement coverage for the MBDA score assay have created a barrier to widespread use in clinical practice.[22]

Multiple novel biomarkers are currently being developed to predict response to RA therapy. One investigational biomarker test measures serum interferon (IFN) levels to determine whether patients should be treated with anti-TNF therapy or another type of medication.[23] In a study of patients with RA and no prior exposure to TNF-targeted therapy, a higher pretreatment IFN-beta/IFN-alpha ratio (>1.3) significantly predicted a lack of response to TNF inhibitors at 12 to 14 weeks.[23] In these patients, RA therapies that work through a non-TNF mechanism of action may be a more effective choice.

Researchers have analyzed the synovial tissue of RA patients to identify genes that are differentially expressed between responders and non-responders to TNF inhibition. In particular, synovial fluid expression of the PIK3CD protein significantly corresponded with response to anti-TNF therapy.[24] Another emerging biomarker of drug response in RA is a protein called a disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS5), which is normally suppressed by IL-6. Higher baseline levels of ADAMTS5 significantly predict better response to treatment with tocilizumab.[25]

Antidrug Antibodies

Patients with RA live in a state of heightened immune reactivity, which drives the chronic inflammatory response and can trigger the development of autoantibodies such as RF and anti-CCP. The same hyperreactivity can also trigger the production of antibodies against any new perceived threats, including biologic therapy. Antidrug antibodies (ADAbs) can bind and neutralize biological agents, dramatically reducing the concentration of active, unbound drug molecules in the blood.[26]

The development of ADAbs is now recognized as one of the leading limitations of biologic therapy in RA.[27] Patients who test positive for ADAbs have lower serum drug levels ($P<0.001$) and lower rates of treatment response ($P<0.001$) than patients who do not develop ADAbs.[28] The development of ADAbs can reduce the likelihood of clinical response by up to 97%. Patients who test positive for ADAbs are also more likely to develop side effects such as injection-site reactions and are more likely to discontinue their biologic therapy.[27]

After an inadequate response to	Consider switching to:
A single TNF inhibitor	• A non-TNF biologic ± MTX • An alternate TNF inhibitor ± MTX
Multiple TNF inhibitors	• A non-TNF biologic ± MTX • Tofacitinib ± MTX
A single non-TNF biologic agent	• An alternate non-TNF biologic agent ± MTX
A TNF inhibitor and a non-TNF biologic	• An alternate TNF biologic ± MTX • Tofacitinib ± MTX
Multiple non-TNF biologic agents	• Tofacitinib ± MTX • A TNF inhibitor ± MTX

Table 5
Current Strategies for Switching RA Therapy[34]

The different molecular structures of biologic agents influence the likelihood of developing ADAbs, which may be an important factor in treatment selection for some patients. In general, monoclonal antibodies (e.g., adalimumab and infliximab) are more immunogenic, or more likely to produce an immune response, than fusion proteins (e.g., etanercept). Approximately one-third of patients treated with adalimumab will test positive for ADAbs, compared with 0% to 11.5% of patients treated with etanercept.[26,28] Additional factors such as disease duration and concomitant immunosuppressive therapy can also influence the risk of ADAb development. In one study, patients who received lower median doses of concomitant MTX therapy (15 mg/wk vs. 20 mg/wk) and had longer disease duration (14 years vs. 7.7 years) were more likely to test positive for ADAbs after 3 months of anti-TNF therapy.[29]

Monitoring for serum drug levels and ADAbs is an investigational strategy for identifying early signs of poor response to biologic therapy and determining the next best steps for treatment.[30] In one recent study, a positive test for ADAbs 3 months after starting anti-TNF therapy significantly predicted a poor treatment response at 12 months.[29] Another study examined the potential value of testing serum drug levels at the first sign of inadequate response to infliximab, adalimumab, etanercept, or rituximab. Patients with undetectable drug levels were significantly less likely than those with detectable levels to demonstrate a good clinical response at the next evaluation.[31] These findings support the use of ADAb testing to identify patients who are likely to benefit from switching to an alternate biologic agent with a different mechanism of action and/or less immunogenic potential.[31] Multiple commercial assays are currently available to detect ADAbs in patients undergoing treatment with anti-TNF therapy.[32] It is important for nurses to recognize that the validity of testing for ADAbs remains somewhat controversial and that few practices have currently adopted the testing. Future ACR guidelines may clarify the role of ADAb testing in the management of patients with inadequate responses to biologic therapy.

Switching RA Therapy

Up to 50% of patients who start treatment with a TNF inhibitor will discontinue treatment due to inadequate response or side effects.[33] In 2015, the ACR is expected to publish updated recommendations for RA management that include guidance on switching therapies, but with considerable flexibility for individualizing therapy (Table 5).[34] One common strategy is to switch to an alternate anti-TNF agent.[35] While this approach works in some cases, a second TNF inhibitor is often less effective than the first, leading to high discontinuation rates.[33]

In a study of Medicare recipients with RA who started treatment with anti-TNF therapy (N=26,738), 6.5% required a switch to a second biologic agent within 12 months. Of these patients, 42% switched to a second TNF inhibitor, while 58% switched to a non-TNF biologic agent. Patients who switched between TNF-targeted agents were more than twice as likely to fail second-line treatment as those who switched from an anti-TNF agent to a non-TNF biologic (18.8% vs. 7.3%).[36]

Drug Holidays

One emerging strategy in RA management involves tapering or discontinuing biologic therapy in patients who meet strict criteria for clinical remission. The goals of pursuing drug-free remission are to minimize the long-term costs and side effects of indefinite treatment. These potential benefits must be balanced against the risks of worsening clinical, radiographic, and functional outcomes. With careful monitoring, select patients with RA are able to maintain a drug-free remission after discontinuing biologic therapy.[37]

For many patients with RA, however, drug holidays are unplanned. Patients can miss scheduled doses due to treatment costs, changes in health insurance coverage, poor adherence, and other barriers. In a recent RA registry study, 15% of patients who were prescribed MTX reported missing 1 or more MTX doses within the past 4 weeks.[38]

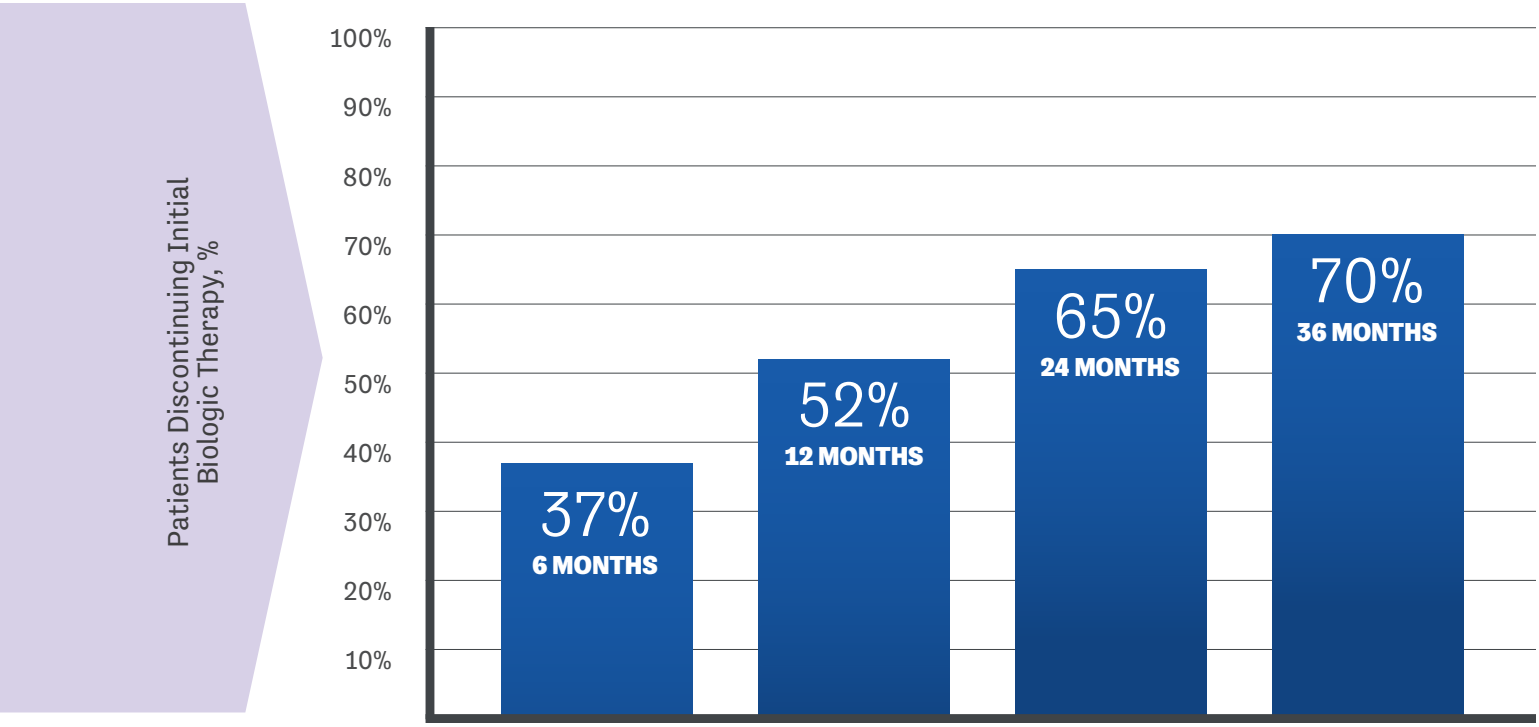


Figure 3
Frequency of Discontinuation of First-Line Biologic Therapy in Real-World Practice[39]

Discontinuation rates for biologic therapy are even higher. A study of pharmacy records from patients within a Canadian clinic examined discontinuation patterns among RA patients (N=623) with at least 1 prescription for a biologic agent, including abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab, and anakinra. Within the first 6 months of treatment, more than one-third of patients had discontinued their first biologic agent (Figure 3). By 36 months, 70% of patients stopped taking their first biologic treatment. In many cases, socioeconomic factors correlated with treatment disruption. Patients who worked only part-time were significantly more likely to stop taking their first biologic agent than patients who were employed fulltime. In addition, patients with annual incomes below $20,000 (in Canadian dollars) were more than twice as likely as those with incomes between $80,000 and $100,000 to discontinue biologic therapy.[39]

What are the consequences of treatment discontinuation on the immune system? One study of patients who interrupted their anti-TNF therapy for a short period due to planned surgery provided a unique opportunity to examine the effects of discontinuing effective therapy.[40] Patients who interrupted their RA treatment, even by skipping just 1 scheduled dose, were significantly more likely to experience a short-term disease flare than patients who did not discontinue treatment (P=0.02). There were no differences in surgical complications such as infection between those who did and did not discontinue anti-TNF therapy.

Biosimilars

Biosimilars represent another emerging opportunity to target key mediators of immune system dysfunction in patients with RA. Also called "follow-on biologics," biosimilars are defined as biological products that are highly similar to an already approved agent, with no meaningful differences in efficacy, safety, or potency.[41] The U.S. Food & Drug Administration (FDA) approved the first biosimilar agent in March 2015, a biosimilar to filgrastim, a granulocyte colony-stimulating factor (G-CSF) used to prevent infection in patients undergoing various cancer treatments and in patients with severe chronic neutropenia.[42]

Multiple recent studies have demonstrated comparable safety and efficacy between biosimilars and their reference biologics in RA, including biosimilars to infliximab (CT-P13; BOW015), etanercept (HD203), adalimumab (ABP 501), and rituximab (CT-P10).[43-47] Some of these biosimilar agents are already being used to treat patients with RA in Europe, Asia, and other regions.[48] The FDA has established an abbreviated pathway for biosimilar agents to gain approval in the United States.[41]

With the expectation that biosimilars will soon be available to treat RA in the United States, the ACR recently published a position statement on the use of biosimilars in rheumatology.[41] The ACR recommends a range of precautions to ensure the safe and effective use of these new agents in clinical practice:

- Patients who are stable on biologic therapy should not be switched automatically to a biosimilar agent as a cost-saving measure without prior consent of the prescribing clinician
- Clinicians should have the ability to specify "dispense as written" on all prescription medications

- Biosimilars should have names that are distinct from the reference medications to avoid confusion and facilitate easy reporting of postmarking safety data
- Safety data for each biosimilar should be collected and analyzed separately (i.e., not pooled with other biosimilars) to ensure that unique safety risks are identified

Any differences in the manufacturing processes between biosimilars and reference agents can influence the safety and efficacy of treatment.[41] The ACR position statement includes a cautionary tale from Europe, where a biosimilar form of erythropoietin increased the risk of a potentially fatal adverse event—pure red cell aplasia—by 95%.[41,49] The safety problem was traced to a change in the manufacturing process that altered the molecular structure of the biosimilar, increasing the likelihood that patients produced antibodies against erythropoietin.[41,49] This experience underscores the importance of fully understanding the potential interactions—both beneficial and harmful—between biosimilars and the immune system.[41]

Future Perspectives

Understanding the pathophysiology of RA provides a strong foundation for addressing common clinical issues in RA management. For example, with the knowledge that RA is truly a systemic disease, providers may be in a better position to recognize and manage conditions such as CVD in patients with RA. With the discovery that up to one-third of patients treated with anti-TNF therapy will develop ADAbs, clinicians can now test for ADAbs as a possible explanation for poor response to biologic therapy. New studies demonstrate that non-TNF autoimmune pathways may be important treatment targets in patients who fail their first anti-TNF therapy. In the future, treatment tools such as new biomarkers and biosimilars may provide additional options for targeting the autoimmune response in patients with RA.

References

1. Carter SC, Patty-Resk C, Ruffing V, Hicks D, eds. Core Curriculum for Rheumatology Nursing. First Ed. Rheumatology Nurses Society;2015.
2. Gierut A, Perlman H, Pope RM. Innate immunity and rheumatoid arthritis. *Rheum Dis Clin North Am*. 2010;36:271-s96.
3. Janeway CA Jr, Travers P, Walport M, et al, eds. Immunobiology: The Immune System in Health and Disease. 5th edition. New York: Garland Science; 2001.
4. Smolen JS, Redlich K. Rheumatoid arthritis. In: The Autoimmune Diseases. Fifth Edition. Rose N, Mackay I, Eds. Elsevier, Inc; 2014.
5. Gibofsky A. Overview of epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis. *Am J Manag Care*. 2012;18:S295-302.
6. Deane K. Can rheumatoid arthritis be prevented? *Best Pract Res Clin Rheumatol*. 2013;27:467-485.
7. Gibofsky A. Epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis: a synopsis. *Am J Manag Care*. 2014;20:S128-135.
8. Sparks JA, Costenbader KH. Genetics, environment, and gene-environment interactions in the development of systemic rheumatic diseases. *Rheum Dis Clin North Am*. 2014;40:637-657.
9. Klareskog L, Stolt P, Lundberg K, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. *Arthritis Rheum*. 2006;54:38-46.
10. Nielen MM, van Schaardenburg D, Reesink H, et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. *Arthritis Rheum*. 2004;50:380-386.
11. Scarno A, Perrotta FM, Cardini F, et al. Beyond the joint: Subclinical atherosclerosis in rheumatoid arthritis. *World J Orthop*. 2014;5:328-335.
12. van Halm VP, Peters MJ, Voskuyl AE, et al. Rheumatoid arthritis versus diabetes as a risk factor for cardiovascular disease: a cross-sectional study, the CARRE Investigation. *Ann Rheum Dis*. 2009;68:1395-1400.
13. Ong KL, Wu BJ, Cheung BM, Barter PJ, Rye KA. Arthritis: its prevalence, risk factors, and association with cardiovascular diseases in the United States, 1999 to 2008. *Ann Epidemiol*. 2013;23:80-86.
14. Saxena A, Raychaudhuri SK, Raychaudhuri SP. Rheumatoid arthritis: disease pathophysiology. In: Inflammation, Advancing Age and Nutrition. Elsevier, Inc. 2014.
15. Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2012;64:625-639.
16. Witte T. Methotrexate as combination partner of TNF inhibitors and tocilizumab. What is reasonable from an immunological viewpoint? *Clin Rheumatol*. 2015;34:629-634.
17. Koenders MI, van den Berg WB. Novel therapeutic targets in rheumatoid arthritis. *Trends Pharmacol Sci*. 2015;36:189-195.
18. Chatzidionysiou K, Lie E, Nasonov E, et al. Highest clinical effectiveness of rituximab in autoantibody-positive patients with rheumatoid arthritis and in those for whom no more than one previous TNF antagonist has failed: pooled data from 10 European registries. *Ann Rheum Dis*. 2011;70:1575-1580.
19. Wendler J, Burmester GR, Sörensen H, et al. Rituximab in patients with rheumatoid arthritis in routine practice (GERINIS): six-year results from a prospective, multicentre, non-interventional study in 2,484 patients. *Arthritis Res Ther*. 2014;16:R80.
20. Curtis JR, van der Helm-van Mil AH, Knevel R, et al. Validation of a novel multibiomarker test to assess rheumatoid arthritis disease activity. *Arthritis Care Res*. 2012;64:1794-1803.
21. Hambardzumyan K, Bolce R, Saevarsdottir S, et al. Pretreatment multi-biomarker disease activity score and radiographic progression in early RA: results from the SWEFOT trial. *Ann Rheum Dis*. 2014. [Epub ahead of print].
22. Myriad Genetics. Myriad Genetics reports fiscal second-quarter financial results. February 3, 2015. http://investor.myriad.com/releasedetail.cfm?ReleaseID=894449.

References (cont.)

23. Vashisht P, Dorschner JM, Jensen MA, et al. Baseline serum interferon beta/alpha ratio predicts response to tumor necrosis factor alpha inhibition in rheumatoid arthritis. Presented at the 2014 American College of Rheumatology Annual Meeting. November 14-19, 2014; Boston, MA. Abstract 2927.

24. Julia A, Avila G, Celis R, et al. PIK3CD overexpression in the synovial membrane of rheumatoid arthritis patients is associated with response to anti-TNF therapy. Presented at the 2013 American College of Rheumatology Annual Meeting. October 26-31, 2013; San Diego, CA. Abstract 1903.

25. Tsuzaka K, Takao M, Nishida J. ADAMTS5 is a biomarker for the efficacy prediction of tocilizumab in rheumatoid arthritis. Presented at the 2014 American College of Rheumatology Annual Meeting. November 14-19, 2014; Boston, MA. Abstract 2263.

26. Benucci M, Li Gobbi F, Meacci F, et al. Antidrug antibodies against TNF-blocking agents: correlations between disease activity, hypersensitivity reactions, and different classes of immunoglobulins. *Biologics*. 2015;9:7-12.

27. Maneiro JR, Salgado E, Gomez-Reino JJ. Immunogenicity of monoclonal antibodies against tumor necrosis factor used in chronic immune-mediated Inflammatory conditions: systematic review and meta-analysis. *JAMA Intern Med*. 2013;173:1416-1428.

28. Chen DY, Chen YM, Tsai WC, et al. Significant associations of antidrug antibody levels with serum drug trough levels and therapeutic response of adalimumab and etanercept treatment in rheumatoid arthritis. *Ann Rheum Dis*. 2015;74:e16.

29. Jani M, Chinoy H, Warren RB, et al. Clinical utility of random anti-TNF drug level testing and measurement of anti-drug antibodies on long-term treatment response in rheumatoid arthritis. Presented at the 2014 American College of Rheumatology Annual Meeting. November 14-19, 2014; Boston, MA. Abstract 2924.

30. Rosas J, Llinares-Tello F, de la Torre I, et al. Clinical relevance of monitoring serum levels of adalimumab in patients with rheumatoid arthritis in daily practice. *Clin Exp Rheumatol*. 2014;32:942-948.

31. Mazilu D, Opriş D, Gainaru C, et al. Monitoring drug and antidrug levels: a rational approach in rheumatoid arthritis patients treated with biologic agents who experience inadequate response while being on a stable biologic treatment. *Biomed Res Int*. 2014;2014:702701.

32. van Schouwenburg PA, Rispens T, Wolbink GJ. Immunogenicity of anti-TNF biologic therapies for rheumatoid arthritis. *Nat Rev Rheumatol*. 2013;9:164-172.

33. Chatzidionysiou K, Askling J, Eriksson J, et al. Effectiveness of TNF inhibitor switch in RA: results from the national Swedish register. *Ann Rheum Dis*. 2015;74:890-896.

34. Singh JA. New ACR recommendations for the management of rheumatoid arthritis. Presented at the 2014 American College of Rheumatology Annual Meeting. November 14-19, 2014; Boston, MA.

35. Emery P, Gottenberg JE, Rubbert-Roth A, et al. Rituximab versus an alternative TNF inhibitor in patients with rheumatoid arthritis who failed to respond to a single previous TNF inhibitor: SWITCH-RA, a global, observational, comparative effectiveness study. *Ann Rheum Dis*. 2014. [Epub ahead of print].

36. Rosenblatt L, Lobo F, Cockrum P, et al. Biologic switching rates among patients with rheumatoid arthritis. *Ann Rheum Dis*. 2013;72:A561.

37. Tanaka Y, Hirata S. Intensive intervention can lead to a treatment holiday from biological DMARDs in patients with rheumatoid arthritis. *Drugs*. 2014;74:2129-2139.

38. Curtis JR, Bharat A, Chen L, et al. Physician awareness of suboptimal patient adherence to MTX: results from a large U.S. rheumatoid arthritis registry. Presented at the 2014 American College of Rheumatology Annual Meeting. November 14-19, 2014; Boston, MA. Abstract 2367.

39. Choquette L, Laliberte MC, Desjardins O. Biologic discontinuation in rheumatoid arthritis: experience from a Canadian clinic. Presented at the 2014 American College of Rheumatology Annual Meeting. November 14-19, 2014; Boston, MA. Abstract 499.

40. Wendling D, Balblanc JC, Brousse A, et al. Surgery in patients receiving anti-tumour necrosis factor alpha treatment in rheumatoid arthritis: an observational study on 50 surgical procedures. *Ann Rheum Dis*. 2005;64:1378-1379.

41. American College of Rheumatology Position Statement. Biosimilars. February 2015. http://www.rheumatology.org/Practice/Clinical/Position/Biosimilars_02_2015/.pdf.

42. Food & Drug Administration. FDA approves first biosimilar product Zarxio. March 6, 2015. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436648.htm.

43. Yoo DH, Prodanovic N, Jaworski J, et al. Efficacy and safety of CT-P13 (infliximab biosimilar) over two years in patients with rheumatoid arthritis: comparison between continued CT-P13 and switching from infliximab to CT-P13. Presented at the 2014 American College of Rheumatology Annual Meeting. November 14-19, 2014; Boston, MA. Abstract L1.

44. Yoo DH, Park W, Jeka S, et al. A randomized, controlled, multicenter, 2-arm, parallel-group, double-blind study to demonstrate the equivalence of CT-P10 to innovator rituximab with respect to pharmacokinetic profile in patients with rheumatoid arthritis. Presented at the 2013 American College of Rheumatology Annual Meeting. October 26-31, 2013; San Diego, CA. Abstract 1736.

45. Kay J, Wyand M, Chandrashekara S, et al. BOW015, a biosimilar infliximab, in patients with active rheumatoid arthritis on stable methotrexate doses: 54-week results of a randomized, double-blind, active comparator study. Presented at the 2014 American College of Rheumatology Annual Meeting. November 14-19, 2014; Boston, MA. Abstract L20.

46. Bae SC, Kim J, Choe JY, et al. A randomized, double-blind, phase 3 equivalence trial comparing the etanercept biosimilar, HD203, with etanercept (Enbrel®), in combination with methotrexate (MTX) in patients with rheumatoid arthritis (RA). Presented at the 2014 American College of Rheumatology Annual Meeting. November 14-19, 2014; Boston, MA. Abstract 2825.

47. PR Newswire. Amgen announces positive top-line results from phase 3 study evaluating the efficacy and safety of biosimilar candidate ABP 501 compared with adalimumab in patients with moderate-to-severe rheumatoid arthritis [press release]. February 3, 2015.

48. Yoo DH. The rise of biosimilars: potential benefits and drawbacks in rheumatoid arthritis. *Expert Rev Clin Immunol*. 2014;10:981-983.

49. McKoy JM, Stonecash RE, Cournoyer D, et al. Epoetin-associated pure red cell aplasia: past, present, and future considerations. *Transfusion*. 2008;48(8):1754-1762.

How I Learned About *the Immune System*

by Elizabeth Kirchner, CNP

AUTHOR PROFILE:

Elizabeth Kirchner, CNP

Elizabeth Kirchner, CNP, is a nurse practictioner at the Cleveland Clinic in Cleveland, Ohio, and the Education and Curriculum Chair of the Rheumatology Nurses Society.

Picture this: A 43-year-old nurse practitioner (that's me) on the floor of her 8-year-old daughter's ~~Disaster Area~~ bedroom, drawing different colored blobs with pointy things sticking out of them and rectangular-shaped objects floating towards them.

A few triangles are trying to get involved but there isn't much space left on the poster board. The letters "C" and "B" and "A" and the numbers "4" and "3" figure prominently in the project. Arrows point one way, then another, up, down, diagonally. Things are connected by lines, but after several minutes, it's impossible to tell which lines are connected to which objects.

When I am done, I have clearly failed to figure out the complement system, although I have created a pretty good facsimile of a blindfolded 3-year-old's efforts to copy a Jackson Pollack painting.

I'm stumped.

Diagramming worked great for understanding the Kreb's Cycle when I was in nursing school. I read, reread, and then re-reread the chapters on the complement system in 3 different basic immunology textbooks. I Googled it. I Wikied it. I watched a podcast given by a lovely immunologist in California whose name I can't remember. But I just can't seem to get the big picture.

My advice to anyone having trouble with basic immunology is to first look at the big picture...

OK, I get that there are three ways to activate the complement system. I get that antigens and antibodies are involved. I'm trying to memorize all these pathways and numbers and enzymes, and then it hits me: Mrs. MacDonald's 9th grade American Experience class!

When we were learning about the design and architecture of Washington DC, Mrs. MacDonald taught us what is possibly the most useful 3-word phrase in the English language: "Form Follows Function." When I started thinking about the complement system backwards, it suddenly all made sense.

The point of the complement system—its function—is to blow stuff up that doesn't belong there. What do you need to blow stuff up? Bombs. What are the equivalent of bombs in the immune system? Membrane Attack Complexes. What do you need A LOT OF to build a MAC? C3b. What is the point of the 3 pathways of activation? To build C3b.

Realizing that rote memorization is not the secret to understanding the immune system has helped me tremendously. So my advice to anyone having trouble with basic immunology is to first look at the big picture, figure out what the desired end result is (the function), and then work backwards from there (to understand the form). If you're like me, you will save yourself a lot of frustration. Not to mention a lot of art supplies.

How I Learned About *the Immune System*

by Iris Zink, MSN, NP

AUTHOR PROFILE:

Iris Zink, MSN, NP

Iris Zink, MSN, NP, is a nurse practitioner at the Beals Institute in Lansing, Michigan, and the President-Elect of the Rheumatology Nurses Society.

When I first started as a rheumatology nurse, I got my hands on anything I could to help me learn about things that would help me to better serve my patients. Books, journal articles, you name it and I devoured it. Some things were easier to learn than others, and the immune system was definitely not one of them! But by breaking the immune system down into small pieces and relating the actions of the various components into tangible analogies, I found I was able to retain and then relate important concepts to my patients.

There are handy tables within this issue of *Rheumatology Nurse Practice* that offer some advice on how to think about and explain many of the major players in the immune systems, but I have some additional tricks that worked for me.

We all know that everyone has **white blood cells (WBCs)**. In normal immune systems, there is a feedback loop that tells the WBCs when to react and then when to turn off the reaction. In individuals with an autoimmune disorder, this feedback loop is broken.

Our WBCs can be further divided into **T cells** and **B cells**, which can both be further broken down as well. Patients with RA do not possess the shutoff button to turn down T cell activity. **Regulatory T cells** (the fireman and police) are there to direct traffic into and out of the joint space, but in patients with RA, they are on an extended coffee break, allowing way too many inflammatory proteins into the joint space.

Memory T cells are supposed to differentiate the good guys from the bad guys (pathogens), but they get lazy in patients with autoimmune disease and allow bad guys in to attack the body's tissues. In normal immune systems, **cytoclastic T cells** act like garbage collectors by removing damaged or destroyed cells. In patients with RA, these cells are also dysfunctional and allow the joint space to get swollen and boggy with cellular activity. This increased cellular debris then starts to wear away at the cartilage within the joint space, create boney erosions and leading to a thickening of the wall or lining of the joint space.

Helper T cells are the paramedics of the immune system, the first responders to an immune "alarm." Once in the joint space, these new-on-the-job helper T-cells secrete pro-inflammatory mediators called cytokines to fill the joint space.

A **cytokine** is a hormone-like protein that is constantly in communication with other hormone-like proteins. When I think about cytokines, I think of my teenage daughters. They are social media experts, using Facebook/Instagram/Snapchat to bring other cytokines such as various interleukins and tumor necrosis factor into the drama of joint destruction.

Our WBC's also can differentiate into B cells, which act in a similar fashion as T cells by identifying foreign invaders and proteins, and protecting the body from pathogens.

Of course, there are other players that impact the performance of the immune system, such as macrophages, and there are further mental tricks you can develop to help you remember how all of these systems function and work together. What worked for me may not work for you, but everyone should have their own way to remember and convey important information to our patients in a manner they understand.

How I Learned About *Biologic Therapies*

by Jacqueline Fritz, RN, MSN, CNS

Learning the science of rheumatology is, for me, an ongoing project. The immune cascade is amazing and yet daunting to comprehend. The exciting part is that science has not only found DNA markers to help make a diagnosis, but each year, more medications to put RA into remission. When I joined my current rheumatology practice, there were 3 drugs in the biologic family and now there are 13.

Learning is constantly ongoing in rheumatology, and it is our duty to stay on top of trends and new findings...

At my first rheumatology conference, I spent much of my time reading about the various biologic therapies on my pocket reference (sadly, this was before the days of the iPhone). I learned what the suffix "mab" meant. I learned that the term monoclonal antibody signified a laboratory-produced substance that locates and binds to a specific cytokine such as tumor necrosis factor. I learned that the term "chimeric" referred to the mouse protein present in infliximab and etanercept. Not long after I returned, a patient who was taking infliximab earnestly asked me if the drug would make her want to eat more cheese!

Initially I strived to remember which drug had the "emab" (hamster) vs. the "zumab" (humanized) protein, but I quickly realized that drug classification, function, and side effects were much more important than the genesis of the protein used to manufacture each drug.

Breaking down the medications and explaining their actions and side effects to our patients can be a daunting task. I always find that I struggle getting my patients to understand that RA is a disease that affects not just the bones, but every organ and vessel in the body. Patients are often so focused on potentially serious but unlikely side effects of treatment such as lymphoma, progressive multifocal leukoencephalopathy, or chronic lymphocytic leukemia that they don't focus enough on the importance of mitigating inflammation to improve their quality of life and reduce the possibility of crippling pain and deformity.

With the advertising on television, once the diagnosis of RA is made, I often get patients who request "the drug that (golfer) Phil Mickelson uses" or "you know, the lady on the horse with daisies!" It's important for us to explain to those patients that we'll start with less invasive therapies such as methotrexate and steroids that might well control their disease before potentially ramping up to those drugs they have heard about on TV.

An unrelated but short piece of advice—warn your patients frequently that no biologic can be combined with another biologic and that they MUST have labs as ordered, be cautious with any potential infection, and hold any rheumatologic drug during illness for 2 weeks before and after surgery. I have learned you can never remind your patients about this too much.

Learning is constantly ongoing in rheumatology, and it is our duty to stay on top of trends and new findings to better serve our patients. Resources such as those provided by RNS are one way to stay abreast of the field and become a lifelong learner.

AUTHOR PROFILE:

Jacqueline Fritz, RN, MSN, CNS

Jacqueline Fritz, RN, MSN, CNS, is owner and Coordinator of Education at the Medical Advancement Center in Cypress, CA, where she teaches RN/BSN programs at various facilities. She is also a Critical Care Clinical Nurse Consultant to many acute care facilities in the California area, such as Cigna, Arcadia Methodist, and Doctor's Hospital of Lakewood.

My Most Memorable Patient

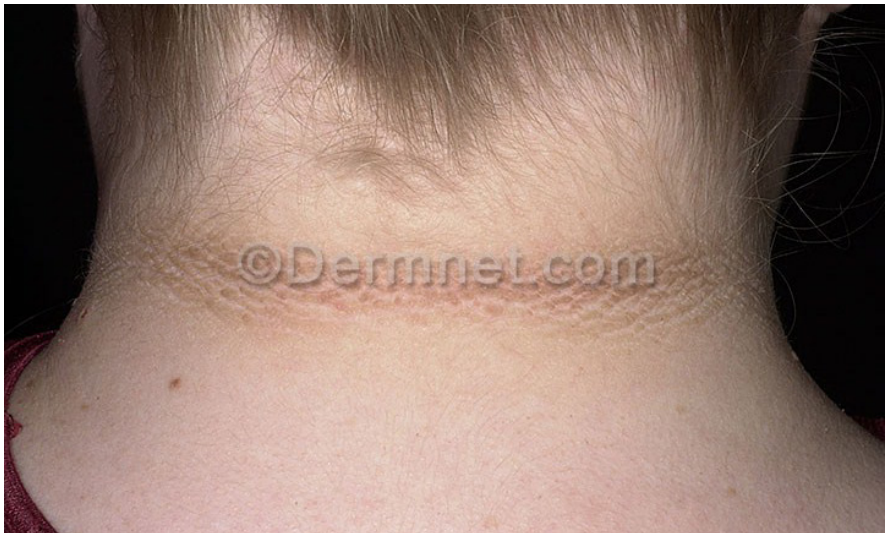
by Sheree Carter, PhD, RN

Several years ago, I was involved in an early trial of adalimumab in pediatric patients with juvenile inflammatory arthritis (JIA). One precocious 12-year-old girl enrolled in the trial, who I will call Lucy, was the only child of parents in their late 50s. The endomorph gene was obvious in this family. Consequently, it was difficult to obtain an accurate joint count in Lucy, largely because of her little fingers and joints that were well protected by fat stores.

Over the years, Lucy had learned to "work her disease," becoming adept in using her disease for secondary gains and parental attention. Just my looking at her often elicited a whimper, sending mom and dad running to her side before I even touched Lucy.

Six weeks into the trial, it was evident that Lucy was not receiving the study medication. During the weeks before the trial was unblinded and patients were allowed to switch over to adalimumab, I came to know Lucy and her parents quite well.

Lucy had used her disease as a free pass to get out of many classes at school, especially physical education (PE). That is where she told me she felt the most inadequate. Her classmates would often bully her because of her size and inability to perform even the seemingly smallest of physical activities. While she longed to jump on the trampoline in the gym, she was unable to climb up onto the mat.



Acanthosis nigricans

The worst part of Lucy's day came when she had to change into her gym clothes. As Lucy began to talk to me, I noticed for the first time that she always wore clothing that covered her neck and her underarms. When she got changed for PE, however, her uniform did not cover up her neck region. Showing her neck to me, she spoke in a soft, timid tone with tears in her eyes.

"My neck always looks dirty. The kids say I am nasty and I don't bathe. They don't want to be around a pig pen. Then they start making pig noises at me."

I could tell Lucy was deeply hurt, and many of her avoidance strategies were used as defense mechanisms to protect her feelings. Upon examination, we discovered that Lucy had a condition called acanthosis nigricans (see image) that causes a brownish, poorly-defined hyperpigmentation of the skin and body folds. Lucy's condition was manifest on the posterior lateral folds of her neck, armpits, and around her navel.

To make matters worse, Lucy's parents told me about their daily routine after picking up Lucy from school. It involved going to McDonald's and getting her favorite treat—a large chocolate shake and a large order of fries—as a snack.

And so, while we waited for the open label portion of the trial to open, I started working on incorporating some changes into Lucy's lifestyle that would make a difference regardless of her drug regimen.

I started by researching acanthosis nigricans to see if there were some way to lessen its effects. I settled on a complementary alternative treatment that involved three parts baking soda mixed with one part water to form a thick paste. I advised Lucy to gently scrub the paste over the areas of her neck that were discolored and let it dry for 15 minutes before washing it off. This became part of her daily bedtime routine. After a few weeks, what was once a dark brown patch across Lucy's neck was now reduced to a pencil thin line. At her next visit, she bounced in the office singing, "I am not a pig pen."

The next step was to get Lucy to engage in some physical activity. Greedily, I wanted an activity that both Lucy and her parents could enjoy together, but they threw up barriers at everything I suggested. We finally settled on Lucy trying out a mini-trampoline that one of our fellows donated. Lucy's father built a walker-like contraption for support so that Lucy could bounce to her heart's desire. Lucy loved it, bouncing for hours while watching TV.

The next obstacle was the daily McDonald's run. I was unable to convince the family to cut their visit out entirely, but they agreed to limit it to only once a week. It was at least a start.

After 6 weeks of these changes in her routine, we finally reached the open label phase of the trial, and Lucy was put onto adalimumab. Within a few weeks' time, she became a different person. She began losing weight, engaging in more physical activities, and developing friendships at school. Seeing these positive changes encouraged Lucy's parents to try even harder. They all agreed to cut out the McDonald's run entirely, and mom and dad even began taking short walks around the neighborhood as soon as they dropped Lucy off at school.

Being a nurse involved in clinical research isn't all about the success or failure of a new drug on a horrible disease such as JIA, but about the luxury of time that you get to spend with patients and their families. Moreover, it is about what you can learn when patients and their families invite you into the inner circle and the little differences that we can make to positively influence our patients' lives

AUTHOR PROFILE:
Sheree C. Carter, PhD, RN

Sheree C. Carter, PhD, RN, is an Assistant Professor at The University of Alabama Capstone College of Nursing, Tuscaloosa, Alabama, and President of the Rheumatology Nurses Society.

RHEUMATOLOGY NURSES SOCIETY™

2131 Woodruff Road Suite 2100#200
Greenville, SC 29607
Toll Free: (800) 380-7081

RNSnurse.org

Commercial Support

Supported by an educational grant from Pfizer.

General Disclosure & Copyright Statement

The opinions expressed in this publication are those of the participating faculty and not those of the Rheumatology Nurses Society, Pfizer, or any manufacturers of products mentioned herein.

This information is provided for general medical education purposes only and is not meant to substitute for the independent medical judgment of a healthcare professional regarding diagnostic and treatment options of a specific patient's medical condition. In no event will the Institute be responsible for any decision made or action taken based upon the information provided in this activity. Participants are encouraged to consult the package insert for all products for updated information and changes regarding indications, dosages, and contraindications. This recommendation is particularly important for new or infrequently used products.