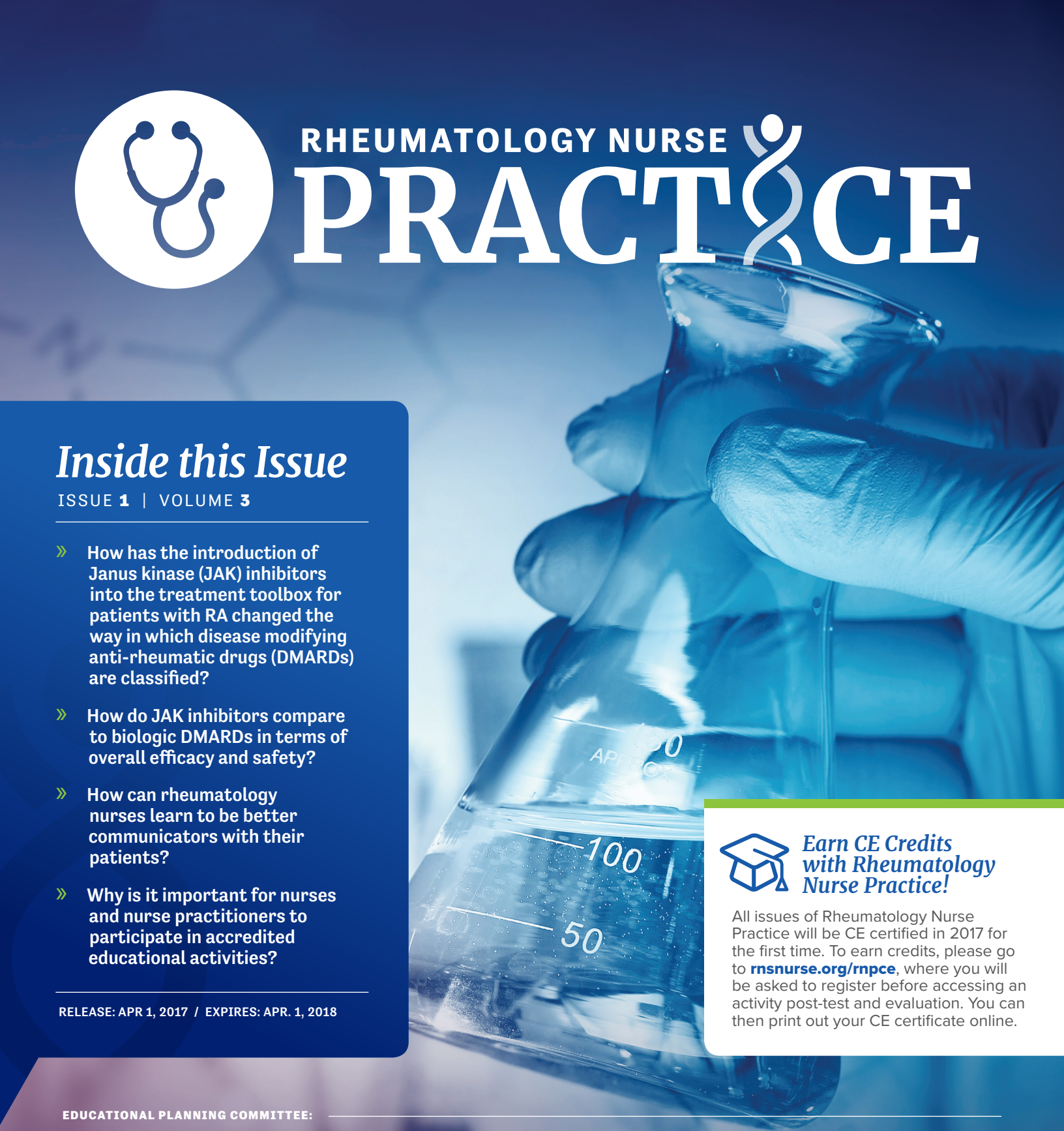
RHEUMATOLOGY NURSE PRACTICE



Inside this Issue

ISSUE 1 | VOLUME 3

- How has the introduction of Janus kinase (JAK) inhibitors into the treatment toolbox for patients with RA changed the way in which disease modifying anti-rheumatic drugs (DMARDs) are classified?
- How do JAK inhibitors compare to biologic DMARDs in terms of overall efficacy and safety?
- How can rheumatology nurses learn to be better communicators with their patients?
- Why is it important for nurses and nurse practitioners to participate in accredited educational activities?

RELEASE: APR 1, 2017 / EXPIRES: APR. 1, 2018

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EDUCATIONAL PLANNING COMMITTEE:

Sheree C. Carter, PhD, RN, RN-BC
BOARD CERTIFIED IN RHEUMATOLOGY NURSING
Assistant Professor
The University of Alabama
Capstone College of Nursing
Tuscaloosa, Alabama

Iris Zink, MSN, NP, RN-BC
BOARD CERTIFIED IN RHEUMATOLOGY NURSING
Nurse Practitioner
Lansing Rheumatology
Lansing, Michigan

Elizabeth Kirchner, CNP, RN-BC
BOARD CERTIFIED IN RHEUMATOLOGY NURSING
Nurse Practitioner
Cleveland Clinic
Cleveland, Ohio

Jacqueline Fritz, RN, MSN, CNS, RN-BC
BOARD CERTIFIED IN RHEUMATOLOGY NURSING
Critical Care and Rheumatology Specialist
Medical Advancement Center
Cypress, California

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Learning Objectives

1. *Identify key features that differentiate biologic DMARDs from small molecule kinase inhibitors*
2. *Explain the advantages and disadvantages of the broad anti-Janus kinase (JAK) activity of currently approved and investigative JAK inhibitors in the treatment of rheumatoid arthritis (RA)*
3. *Assess the clinical applicability of common safety issues that have been identified among approved and investigational JAK inhibitors*
4. *Develop strategies to overcome common medication adherence obstacles in patients with RA*

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Sheree Carter, PhD, RN, RN-BC, is the nurse planner for this activity.

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

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Scott Kober, MBA, President, 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.

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This newsletter was reviewed by **Linda Grinnell-Merrick, MS, NP-BC**. Ms. Grinnell-Merrick has disclosed the following relevant financial relationships specific to the subject matter of the content included in this educational activity: Pfizer, GlaxoSmithKline, Horizon/A; Janssen/C, SB; AbbVie, Celgene/SB.

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How Drugs Work:

The Differences Between Novel Small Molecules and Biologics in the Treatment of Rheumatoid Arthritis

The management of rheumatoid arthritis (RA) has undergone a dramatic evolution over the past 30 years (Figure 1). Prior to 1988, steroids and non-steroidal antiinflammatory drugs (NSAIDs) were the only options for improving symptoms and controlling RA pain. Although steroids and NSAIDs provided symptomatic relief, these agents did nothing to slow the progression of this debilitating joint disease. With the discovery that methotrexate (MTX)—a chemotherapeutic agent—was effective in RA, patients finally had an option for delaying disease progression. Other related chemical compounds also showed activity in RA and joined the class known as conventional disease-modifying antirheumatic drugs (DMARDs).[1]

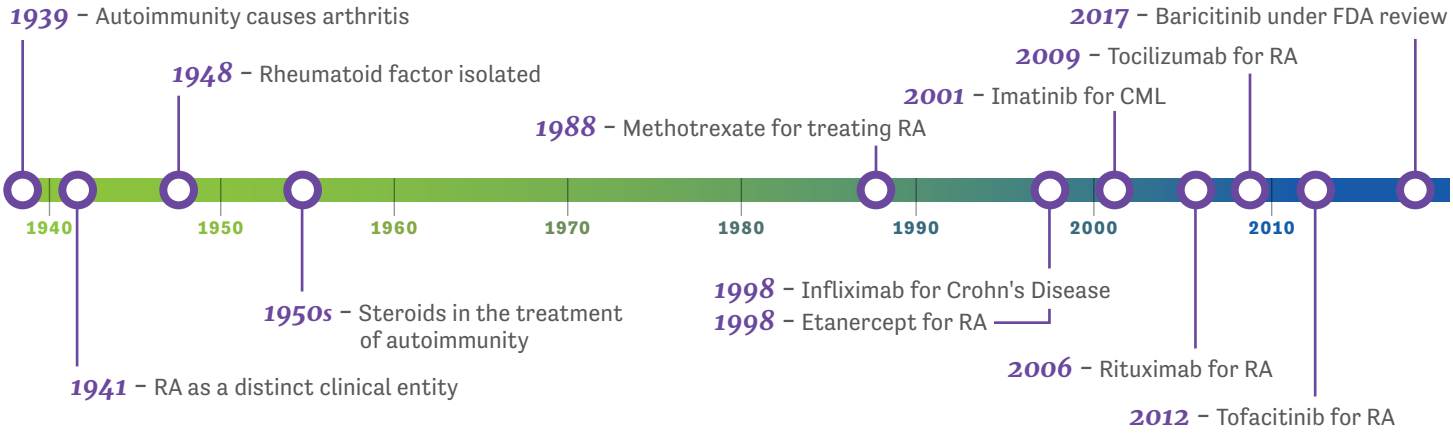
The development of biologic DMARDs in the late 1990s was the next major milestone in the treatment of RA. Unlike conventional DMARDs, biologics were developed with the goal of altering the inflammatory processes underlying RA. As knowledge about the various cytokines and immune system cells involved in RA grew, biologic agents targeting tumor necrosis factor (TNF), interleukin (IL)-6, and T cell and B cell function were developed.[1]

The next major leap in RA drug development was spurred on by the success of blocking intracellular tyrosine kinases in patients with cancer. In 2001, imatinib, a potent anti-leukemia agent, became the first small molecule tyrosine kinase inhibitor (TKI) to be approved by the U.S. Food & Drug Administration (FDA) for any indication. Other TKIs soon followed for the treatment of solid tumors, and clinical experience began to grow with this new class of agents highlighting a unique mechanism of action. At the same time, researchers were discovering more about the role of tyrosine kinase signaling in the development and progression of autoimmune diseases. In

ACTIVITY SUMMARY

In this issue of Rheumatology Nurse Practice, we will explore the major differences between biologic DMARDs and novel small molecules in the treatment of RA, and the implications of these differences on disease management. Although small molecules targeting other pathways are currently under development, this newsletter focuses specifically on the JAK family of tyrosine kinases.

Figure 1
Evolution of RA Classification and Management[1]



CML, chronic myelogenous leukemia.

2012, tofacitinib, a Janus kinase (JAK) inhibitor, became the first small molecule kinase inhibitor to be approved for RA.

Mechanisms of Action: How Do These Agents Work?

The key features that differentiate biologic DMARDs and small molecule kinase inhibitors are summarized in Table 1. Technically, MTX and other conventional DMARDs, as well as most other drugs with chemical rather than biologic origins, meet the criteria for small molecule therapeutics. However, the newer, more complex small molecules under development in RA are designed to inhibit intracellular signaling processes involved in disease pathophysiology and are emerging as a distinct class. To differentiate these agents from simpler small molecules, these new agents are called targeted synthetic DMARDs (tsDMARDs).[2]

Biologics

Biologic DMARDs are large, complex proteins (>1 kilodalton in size) that have been engineered to target a specific mediator of the inflammatory cascade, such as tumor necrosis factor (TNF).[1] Because of their size, biologic agents cannot penetrate cells. Instead, these agents act as antibodies, or exert antibody-like functions, to block extracellular targets such as the following:

- Cell-surface receptors, such as the IL-1 receptor or T cell and B cell receptors
- Circulating cytokines (TNF, IL-6) that bind to cell-surface receptors and activate intracellular responses

Biologics are highly selective for their targets, and as a result, have narrow and predictable clinical consequences. Anti-TNF agents only disrupt the physiologic effects of TNF, which are generally confined to systemic inflammation.[1] The off-target effects of anti-TNF agents are also related to controlling systemic inflammation, such as improvements in atherosclerosis (see more in the *Cardiovascular Effects* section).[3]

Small Molecule JAK Inhibitors

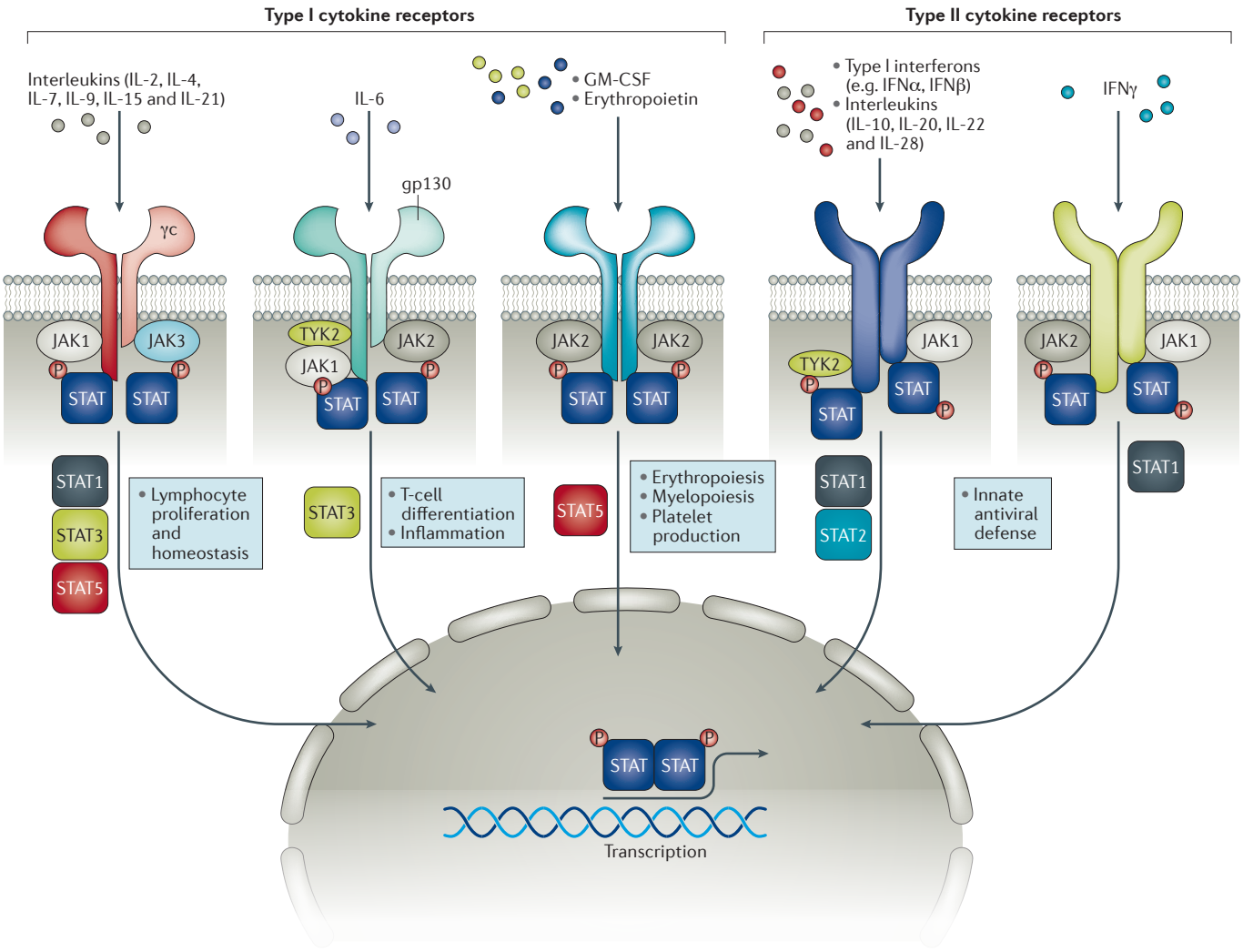
The small size of tofacitinib and other JAK inhibitors (<700 daltons in size) enables these medications to be given orally, to penetrate cells, and to alter intracellular signaling. Proinflammatory cytokines and immune system cells rely on the intracellular JAK signaling pathway to coordinate the inflammatory response. The JAK family consists of 4 proteins: JAK1, JAK2, JAK3, and

Table 1

Key Features of Biologics and Small Molecules[1]

	Biologics	Small Molecules
Chemical composition	Protein	Organic small molecule
Molecular weight	>1 kDa	<700 Da
Administration	Parenteral	Oral
Target	Extracellular	Intracellular
Mechanism of action	Blocking, depletion	Enzyme inhibition
Specificity	High	Low/variable
Stability	Protease and heat-sensitive	Mostly stable
In vivo half-life	Longer	Shorter
Degradation	Catabolism	Metabolism
Manufacturing costs	High	Low/variable
Generic agents	Biosimilars	Identical chemical copies

kDa, kilodalton; Da, dalton



GM-CSF, granulocyte/macrophage-colony stimulating factor

tyrosine kinase 2 (TYK2). The JAK proteins work together to transmit intracellular signals involved in cell growth, survival, and differentiation. Through their effects on intracellular signaling, JAKs also influence the function of immune and hematopoietic cells.[4] However, a single JAK protein cannot carry any signals on its own; it must pair with another member of the JAK family. JAKs can group together as pairs of identical proteins (JAK2/JAK2), or as a mixed set (JAK1/JAK3). These pairs of JAK proteins mediate the signals of dozens of cytokines, chemokines, and growth factors that have been implicated in the pathophysiology of RA (Figure 2).[1, 4]

Several small-molecule inhibitors are being developed with varying degrees of specificity for the different JAK proteins. As an example, an agent that blocks the activity of JAK1 inhibits the effects of cytokines that transmit signals through any of the JAK1-containing pairs: JAK1/JAK1, JAK1/JAK2, JAK1/JAK3, and JAK1/TYK3. Tofacitinib has broad activity against JAK1 and JAK3, and, to a lesser extent, JAK2. As a result, tofacitinib inhibits most of the known mediators of the autoimmune inflammatory response that rely on JAK-mediated signaling.

For JAK inhibitors, having broad anti-JAK activity brings advantages and disadvantages. On the plus side, blocking multiple JAK family members provides wide protection against proinflammatory cytokines. However, blocking so many intracellular signaling pathways contributes to an increased risk of off-target side effects. As mentioned previously, the JAK family mediates the differentiation of hematopoietic cells. By disrupting the function of these pathways, tofacitinib induces changes in neutrophil counts, lymphocyte counts, and hemoglobin levels in patients with RA (see *Hematologic Changes* in the next section).[5]

Figure 2
Overview of JAK-STAT signaling processes[49]

Treatment Efficacy in RA

Biologic DMARDs

In general, all biologic DMARDs show similar efficacy in patients with RA.[6-8] The only exception is anakinra, which is less effective than other biologics.[9,10] Studies comparing the efficacy of RA medications often describe responses as American College of Rheumatology (ACR) 20, ACR50, and ACR70 responses, indicating an improvement of at least 20%, 50%, and 70%, respectively, relative to baseline disease activity. For patients who are starting treatment for RA, approximately 56-67% can expect to achieve an ACR50 response with a biologic DMARD plus MTX, compared with 41% who start treatment with MTX alone.[6] For patients with an inadequate response to single-agent MTX, the likelihood of achieving an ACR50 response by adding a biologic DMARD ranges from 50% to 56%.[9] Given comparable efficacy, the choice of biologic often depends on factors such as side effect profile, convenience (route and frequency of administration), cost, and access (insurance coverage).[6-8]

Despite the effectiveness of biologic DMARDs, a substantial minority of patients with RA—approximately 30-35%—will fail to achieve an adequate response to biologic therapy. Others will fail to maintain long-term control of RA disease activity, or experience unacceptable side effects associated with anti-TNF therapy, a non-TNF biologic, or concomitant MTX.[11]

Small Molecule JAK Inhibitors

The small molecule JAK inhibitors control RA disease activity through novel mechanisms of action, with different clinical effects compared with conventional and biologic DMARDs. Therefore, it is important to consider the safety and efficacy of these agents in detail.

Tofacitinib

In 2012, tofacitinib became the first small-molecule kinase inhibitor to be approved by the FDA for the treatment of RA. Tofacitinib is indicated for adults with moderate-to-severe RA who have had an inadequate response to, or are intolerant of, MTX. Tofacitinib may be given at a dose of 5 mg twice daily alone or in combination with MTX. An extended-release, once-daily formulation of tofacitinib 11 mg is also available.[12]

Tofacitinib was approved by the FDA based on the results of multiple trials of patients with previously treated RA, including the phase 3 ORAL Solo and ORAL Standard studies.[13,14] The ORAL Solo study included 611 patients with active RA who failed prior treatment with at least 1 other RA medication, including conventional DMARDs or biologic agents.[13] Patients were randomly assigned to 1 of 4 treatment groups:

- Tofacitinib 5 mg twice daily for 6 months
- Tofacitinib 10 mg twice daily for 6 months
- Placebo for 3 months followed by tofacitinib 5 mg twice daily for 3 months
- Placebo for 3 months followed by tofacitinib 10 mg twice daily for 3 months

Patients were assessed at 3 and 6 months to determine whether they met the criteria for ACR20, ACR50, and ACR70 responses. After 3 months, patients treated with both doses of tofacitinib were significantly more likely than those in the

Table 2

Responses to Tofacitinib or Placebo After 3 Months in Patients Who Failed Prior RA Treatment[13]

Response at 3 Months	Tofacitinib 5 mg BID (n = 243)	Tofacitinib 10 mg BID (n = 245)	Placebo (n = 122)	*P* Value*
ACR20 response	59.8%	65.7%	26.7%	< 0.001
ACR50 response	31.1%	36.8%	12.5%	< 0.001
ACR70 response	15.4%	20.3%	5.8%	< 0.01

**P value for both comparisons: tofacitinib 5 mg BID versus placebo and tofacitinib 10 mg versus placebo.*
ACR, American College of Rheumatology.

Response	Tofacitinib 5 mg (n = 204)	Tofacitinib 10 mg (n = 201)	Adalimumab 40 mg (n = 204)	Placebo (n = 108)	*P* Value*
ACR20 response at 6 months	51.5%	52.6%	47.2%	28.3%	<0.001
Change in HAQ-DI score from baseline at 3 months	-0.55	-0.61	-0.49	-0.24	≤0.05
Clinical remission (DAS28-ESR < 2.6) at 6 months	6.2%	12.5%	6.7%	1.1%	≤0.001

**P value for all comparisons of active treatment (tofacitinib or adalimumab) versus placebo. ACR, American College of Rheumatology; DAS28-ESR, Disease Activity Score for 28-joint counts and erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index.*

Table 3
Responses to Tofacitinib or Adalimumab in Patients with Active RA on Background Methotrexate[14]

placebo arms to achieve ACR20/50/70 responses (Table 2). After 6 months, the patients who started with placebo and switched to tofacitinib achieved responses that were comparable to those in patients who were treated with tofacitinib in the first 3 months of the study.

Patients treated with tofacitinib also had greater improvements in physical functioning, as measured by Health Assessment Questionnaire–Disability Index (HAQ–DI). Despite these benefits, however, there were no differences between tofacitinib and placebo in the proportion of patients who achieved clinical remission, as measured by the Disease Activity Score for 28–joint counts and erythrocyte sedimentation rate (DAS28–ESR). These findings underscore the challenges of achieving clinical remission (DAS28–ESR <2.6) in patients who have failed prior standard therapy for RA.

The ORAL Standard trial evaluated treatment with tofacitinib or adalimumab added to MTX in patients with an inadequate response to MTX.[14] In the trial, 717 patients with active RA despite treatment MTX were randomly assigned to 1 of 5 treatment groups for 12 months:

- Tofacitinib 5 mg twice daily
- Tofacitinib 10 mg twice daily
- Adalimumab 40 mg by SC injection once every 2 weeks
- Placebo for 3 or 6 months followed by tofacitinib 5 mg twice daily
- Placebo for 3 or 6 months followed by tofacitinib 10 twice daily

Results showed that tofacitinib and adalimumab were superior to placebo in patients on background MTX therapy (Table 3). After 6 months, a similar proportion of patients in the tofacitinib and adalimumab groups achieved an ACR20 response: 52% in the tofacitinib 5 mg group, 53% in the tofacitinib 10 mg group, and 47% in the adalimumab group. By comparison, only 28% of patients in the placebo groups met the ACR20 response criteria. Patients treated with tofacitinib or adalimumab were also significantly more likely than those receiving placebo to experience improved HAQ–DI scores or achieve clinical remission. The trial was not designed to compare the efficacy of tofacitinib and adalimumab.

The potential therapeutic benefits of tofacitinib have been explored in other subgroups of patients with RA. The ORAL Start trial examined the role of tofacitinib as an alternative to MTX as initial RA treatment.[15] In the trial, 958 patients with previously untreated RA were randomly assigned to tofacitinib 5 mg once daily, tofacitinib 10 mg once daily, or MTX titrated to a dose of 20 mg over 8 weeks. After 6 months of first–line treatment, 25.5% and 37.7% of patients treated with tofacitinib 5 mg and 10 mg, respectively, achieved ACR70 responses. By comparison, 12.0% of patients treated with MTX achieved an ACR70 response. Treatment with tofacitinib also resulted in a greater reduction in the progression of structural joint damage compared with MTX. In a follow-up analysis of the ORAL Start study, the greater clinical, functional, and radiologic benefits of single–agent tofacitinib relative to MTX monotherapy persisted throughout 2 years of treatment.[16]

Baricitinib

Baricitinib is an oral kinase inhibitor with potent JAK1/JAK2 activity, moderate activity against TK2, and negligible activity against JAK3.[4] The FDA is currently reviewing baricitinib, and a decision regarding its approval for use in the treatment of RA is expected by April 2017.[17]

The phase 3 RA–BEACON trial compared baricitinib and placebo in 527 patients with moderately to severely active RA who did not respond to biologic

DMARDs or experienced intolerable side effects on biologics.[18] At the time of entering the study, patients had been previously treated with 1 (42%), 2 (30%), or ≥3 (27%) biologic DMARDs. This includes approximately 38% of patients who had a history of treatment with 1 or more non-TNF biologic DMARDs (eg, abatacept, tocilizumab, rituximab, or anakinra). Patients were randomly assigned to start once-daily treatment with baricitinib 2 mg (n=174), baricitinib 4 mg (n=177), or placebo (n=176).

After 3 months, patients treated with baricitinib were significantly more likely than patients in the placebo group to achieve clinically meaningful responses (Table 4). The benefits of baricitinib treatment were larger with the 4-mg dose than the 2-mg dose. More than half of patients in the 4-mg group achieved an ACR20 response and experienced a meaningful improvement in physical functioning (≥0.3 improvement in baseline HAQ-DI score). Furthermore, 31% reached the threshold for low RA disease activity, and 1 in 6 patients achieved clinical remission.

The benefits of baricitinib were seen in all subgroups of patients with RA, irrespective of the number of previous lines of anti-TNF and/or non-TNF biologic therapy. Therefore, baricitinib appears to be an effective option for controlling disease activity in patients with highly-refractory RA.

The phase 3 RA-BEAM trial was a head-to-head comparison of baricitinib vs. adalimumab in patients who had an inadequate response to MTX.[19] In the trial, 1,305 patients were randomly assigned to baricitinib 4 mg once daily, adalimumab 40 mg every 2 weeks, or placebo added to background MTX. Baricitinib demonstrated superiority to adalimumab, as measured by ACR20 response and DAS28-CRP, as early as 12 weeks after starting treatment (Table 5). A follow-up analysis of the RA-BEAM trial showed that patients can be switched from adalimumab to baricitinib without the need for a washout period. In the trial, 51 patients who failed to achieve or maintain an ACR20 response after at least 16 weeks of treatment with adalimumab were switched to baricitinib. After switching to baricitinib, 67% achieved an ACR20 response within 12 weeks, with no increase in the risk of adverse effects.[20]

Additional clinical trials have examined the role of baricitinib given earlier in the RA treatment continuum. In the phase 3 RA-BUILD study, baricitinib improved RA disease control compared with placebo in patients who failed conventional DMARDs such as MTX but had not yet initiated biologic DMARD therapy.[21] In another phase 3 trial, baricitinib alone or in combination with MTX provided better control of RA disease activity than MTX monotherapy as initial treatment for patients with active RA.[22]

Other Novel Small Molecules

Several other JAK inhibitors are currently being studied in patients with RA and other autoimmune diseases.[4] Filgotinib is the first selective JAK1 inhibitor developed for the treatment of RA. In the recent phase 2 DARWIN 1 and DARWIN 2 trials, filgotinib demonstrated efficacy as a single agent and in combination with MTX in patients with active RA.[23,24] ABT-494 is another investigational, oral, selective JAK1 inhibitor. In the phase 2 BALANCE I and BALANCE II studies, ABT-494 showed promising activity in patients

Table 4

Responses to Baricitinib in Patients with an Inadequate Response to Biologic Therapy[18]

Response at 3 Months	Baricitinib 4 mg (n = 177)	Placebo (n = 176)	*P* Value*
ACR20	55%	27%	<0.001
HAQ-DI score improvement of ≥0.3	54%	35%	≤0.001
Low disease activity (DAS28-CRP ≤3.2)	31%	9%	≤0.001
Clinical remission (DAS28-CRP <2.6)	16%	4%	≤0.001

ACR, American College of Rheumatology; DAS28-CRP, Disease Activity Score for 28-joint counts and C-reactive protein; HAQ-DI, Health Assessment Questionnaire-Disability Index

	Baricitinib (n = 487)	Adalimumab (n = 330)	Placebo (n = 488)	*P* Value*
RESPONSES AT 12 WEEKS				
ACR20	70%	61%	40%	≤0.001 baricitinib vs placebo; ≤0.5 baricitinib vs adalimumab
Low disease activity (DAS28-CRP ≤3.2)	44%	35%	14%	≤0.001 baricitinib vs placebo; ≤0.01 baricitinib vs adalimumab
Clinical remission (DAS28-CRP <2.6)	24%	19%	4%	≤0.001 baricitinib vs placebo
RESPONSES AT 24 WEEKS				
ACR20	74%	66%	37%	≤0.001 baricitinib vs placebo; ≤0.5 baricitinib vs adalimumab
Low disease activity (DAS28-CRP ≤3.2)	52%	48%	19%	≤0.001 baricitinib vs placebo
Clinical remission (DAS28-CRP <2.6)	35%	32%	8%	≤0.001 baricitinib vs placebo

ACR, American College of Rheumatology; DAS28-CRP, Disease Activity Score for 28-joint counts and C-reactive protein.

Table 5
Responses to Baricitinib or Adalimumab in Patients with an Inadequate Response to Methotrexate[19]

with moderate-to-severe RA and an inadequate response to MTX or anti-TNF therapy.[25,26] Both filgotinib and ABT-494 are currently undergoing further evaluation in phase 3 studies in patients with RA. Peficitinib (a JAK1/JAK3 inhibitor) and decernotinib (a JAK3 inhibitor) are also under development.

Biologics and Small Molecules: Safety Considerations

Biologic DMARDs and JAK inhibitors share many of the same precautions that apply to immunosuppressive agents. These include screening patients for latent tuberculosis, making sure patients are up to date on routine vaccines, and having patients avoid live vaccines once they have started treatment. In addition, laboratory monitoring for liver function, kidney function, and hematologic abnormalities is recommended during treatment. The potential for drug-drug interactions should be assessed and managed. For example, a dose reduction of tofacitinib to 5 mg once daily is recommended for patients taking CYP3A4/CYP2C19 inhibitors due to the risk of increased drug exposure.[27]

Given that JAK inhibitors are a relatively new class of medications for patients with RA, it is important to review some of the safety issues in more detail.

Serious Infections

Biologic DMARDs increase the risk of serious infection by suppressing key mediators of normal immune system function.[28] Serious infections are generally described as infections that require hospitalization and/or parenteral antibiotics to manage.[29] The risk of serious infection is approximately 2% for patients taking traditional DMARDs, or 20 serious infections per 1,000 patients treated. Compared with traditional DMARDs, biologics increase the risk of serious infection by about 30%, although the risk is dose-dependent. In absolute numbers, standard-dose biologic agents result in 6 additional cases of serious infection per 1,000 patients per year, relative to traditional DMARDs. With high-dose biologics, the risk increases to 17 additional cases of serious infection per 1,000 patients per year, on top of what would be expected with traditional DMARDs. Combination biologic regimens pose the highest risk: 55 additional serious infections per 1,000 patients per year compared with traditional DMARDs.

Novel small molecules also increase the risk of infection by altering cytokine signaling related to lymphocyte function. The rates of serious infection among patients treated with tofacitinib are within the range of those observed with biologic DMARDs.[29] In one recent meta-analysis, the risk

of serious infection ranged from 3% to 5.5% across the different biologic DMARDs, including anti-TNF agents, abatacept, rituximab, and tocilizumab. In the same study, the risk of serious infection was 3% for tofacitinib. The risk of serious infection did not differ significantly between tofacitinib 5 mg and 10 mg doses.[29]

Hematologic Changes

Treatment with tofacitinib is associated with changes in hematologic parameters, including neutrophil levels, lymphocyte counts, and hemoglobin levels. A recent long-term safety analysis focused on the hematologic effects of tofacitinib in patients with RA (n=9,129) who were treated with tofacitinib, adalimumab, MTX, or placebo and observed for up to 7 years.[5]

NEUTROPHIL COUNTS

Neutrophil counts tended to decrease in the early months of tofacitinib treatment and then stabilized over time. After 24 months, the mean changes in absolute neutrophil count (ANC) were $-1.09 \times 10^3/mm^3$ and $-1.49 \times 10^3/mm^3$ among patients treated with tofacitinib 5 mg and 10 mg, respectively. No patients developed clinically meaningful neutropenia (ANC $<0.5 \times 10^3/mm^3$). The magnitude of ANC change among tofacitinib-treated patients was comparable to that observed in other treatment groups. The mean changes in ANC were $-0.35 \times 10^3/mm^3$ at 6 months for patients treated with placebo; $-1.23 \times 10^3/mm^3$ at 12 months for patients treated with adalimumab; and $-1.22 \times 10^3/mm^3$ at 24 months for patients treated with MTX.[5]

LYMPHOCYTE COUNTS

Lymphocyte counts showed an initial small increase in the first 3 months of treatment with tofacitnib, followed by gradual reductions for up to 48 months. At 24 months, the mean changes in lymphocyte counts relative to baseline were $-0.24 \times 10^3/mm^3$ for patients treated with tofacitinib 5 mg and $-0.36 \times 10^3/mm^3$ for patients treated with tofacitinib 10 mg. By comparison, lymphocyte counts were unchanged in the placebo group at 6 months, increased by $0.35 \times 10^3/mm^3$ by 12 months in the adalimumab group, and decreased by $-0.20 \times 10^3/mm^3$ by month 24 in the MTX group. Across all time points, <1% of tofacitinib-treated patients experienced clinically meaningful lymphopenia (ANC $<0.5 \times 10^3/mm^3$).[5]

HEMOGLOBIN LEVELS

Hemoglobin levels increased in the early months of tofacitinib treatment, but also stabilized over time. At 24 months, the mean hemoglobin levels in the tofacitinib 5-mg and 10-mg groups increased by 0.47 g/dL and 0.28 g/dL, respectively. Elevated hemoglobin levels correlated with beneficial changes in inflammatory markers, including ESR and CRP. Anemia was rare, with fewer than 1% of patients experiencing a clinically meaningful decrease in hemoglobin (≥3 g/dL decrease from baseline or a hemoglobin level of ≤7 g/dL). By comparison, 1.1% of patients treated with MTX developed clinically meaningful anemia. Among tofacitinib-treated patients, changes in hemoglobin levels did not result in fatigue or altered vitality scores.[5]

Cardiovascular Effects

Compared with the general population, patients with RA face a 1.5-fold higher risk of cardiovascular (CV) morbidity and mortality.[30] The increased risk is due to a higher prevalence of traditional CV risk factors (eg, smoking), as well as risk factors associated with RA itself (eg, chronic inflammation).[31] Given the importance of CV risk management in patients with RA, it is critical to understand the interplay between RA medications and CV risk.

The beneficial CV effects of anti-TNF agents are well documented. In patients with RA, anti-TNF therapy is associated with a 54% reduction in the pooled risk of all CV events, a 31% reduction in stroke and other cerebrovascular events, and a 19% reduction in myocardial infarction (MI).[3] Non-TNF biologic agents also appear to improve CV risk profiles in patients with RA.[32]

JAK inhibition appears to alter lipid metabolism, but with no evidence of long-term CV toxicity. One recent long-term safety analysis focused on the CV effects of tofacitinib across multiple phase 2 and 3 studies (N = 9,098).[33] Lipid levels increased within the first 1-3 months of tofacitinib treatment and stabilized thereafter. The magnitude of increase across several lipid measures—including low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol, and triglyceride levels—was greater for tofacitinib-treated patients than for patients in placebo, adalimumab, and MTX groups included within the analysis.

However, among patients treated with tofacitinib, the increases in lipid levels did not translate into an increased risk of major adverse CV events (MACE). In studies with up to 24 months of follow-up, the MACE incidence was 58 events per 100 patient-years in tofacitinib-treated patients, and 99 events per 100 person-years in patients who received placebo. The overall MACE rate, as well as the individual rates of MI, heart failure, and cerebrovascular events, did not increase in tofacitinib-treated patients with up to 60 months of follow-up.[33]

Safety in Special Patient Populations

Another difference between biologic DMARDs and small molecule kinase inhibitors involves the suitability of these therapeutic classes in patients with renal or hepatic impairment.[1] Approximately 25% of patients with RA have some degree of renal insufficiency, defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 and/or the presence of proteinuria.[34] In general, biologics are safe and effective at standard doses in RA patients with renal insufficiency or severe renal disease, including those on dialysis.[1,35,36] In contrast, the safety of novel small molecules is less well characterized in patients with renal dysfunction.[1] The dose of tofacitinib should be reduced to 5 mg once daily in patients with moderate or severe renal impairment.[27]

Abnormal liver function is not a contraindication to biologic therapy with anti-TNF agents or rituximab.[1] However, treatment with tocilizumab—the biologic DMARD that targets the IL-6 receptor—increases liver enzymes in up to 50% of RA patients.[37] For patients who develop elevated liver enzymes, step-wise tocilizumab dose modifications are recommended based on the severity of these abnormalities.[37] Precautions are also in place for small molecule therapy based on liver function. Tofacitinib should be used at a reduced dose of 5 mg once daily in patients with moderate hepatic impairment and is contraindicated in those with severe hepatic impairment.[27]

Safety of Investigational JAK Inhibitors

Investigational small molecules will undergo a formal safety review as part of the FDA approval process. In the RA-BEACON trial of baricitinib, laboratory abnormalities affecting neutrophil counts, creatinine levels, and lipid levels were mostly minor and did not lead any patients to withdraw from the study.[18] The rates of serious infection were similar (2-3%) in the placebo, baricitinib 2 mg, and baricitinib 4 mg groups at 3 months and 6 months.[18] Similarly, in the RA-BEAM trial, the rates of serious infection in RA patients on background MTX were 1.0%, 0.6%, and 1.4% in the baricitinib, adalimumab, and placebo groups, respectively.[20] The safety profiles of filgotinib and ABT-494 appear to be consistent with other small molecule kinase inhibitors in patients with RA.[23-26]

Biologics and Small Molecules: Considerations for Adherence

Poor adherence to recommended therapy is major obstacle to effective RA management. According to the World Health Organization, improving medication adherence in patients with chronic medications would have an even greater effect on clinical outcomes than improving drug efficacy.[38] Across all chronic diseases, only about 50% of patients consistently take their medications as prescribed.[38] Estimates of adherence to conventional and biologic DMARDs vary from 30% to 80%, depending on the definitions of adherence and the methods of assessment.[39]

Multiple factors contribute to poor adherence, including socioeconomic factors (age, gender, education, social support), health system factors (insurance coverage, patient/provider relationship), RA-related factors (disease severity, comorbid depression), and patient-related factors (self-efficacy, knowledge and beliefs about treatment).[39] To the extent that aspects of the medications themselves may influence adherence, it is important to differentiate among oral, injectable, and intravenous RA therapies.

General Adherence Trends in RA

One recent study highlighted the widespread challenge of poor adherence in routine RA practice. The study included 329 RA patients who were starting biologic DMARD therapy with adalimumab. Of these, 41% reported low to moderate adherence at least once during the first 18 months of treatment.[40] Medication adherence was measured at 6, 12, and 18 months using the Compliance Questionnaire for Rheumatology (CQR), a 19-item self-reported questionnaire with total scores ranging from 0 (no adherence) to 100 (highest possible adherence). A total CQR score <75 indicated compromised adherence to treatment. Overall, 23% of patients reported consistently low to moderate adherence (CQR <65) to their biologic DMARD at each study time point.

Poor adherence to biologic therapy adversely affects disease control and response to treatment. The Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate (BRAGGSS) evaluated the importance of strict adherence to anti-TNF therapy in 392 patients with RA who were starting biologic treatment.[41] Most patients were prescribed subcutaneous etanercept (42.9%) or adalimumab (47.1%), while others were prescribed certolizumab (9.7%) or golimumab (0.3%). Within 6 months of starting therapy, 27% of patients reported that they were not taking their biologic on the day they agreed upon with their rheumatology provider. There were no differences in adherence rates among the anti-TNF agents. Compared with adherent patients, non-adherent patients were less likely to meet the European League Against Rheumatism (EULAR) criteria of a "good response" to biologic therapy at 6 months (53% vs 39%; P=0.015). Non-adherent patients also

had significantly smaller reductions in ESR and smaller changes in their DAS28 score, indicating higher disease activity.

Another obstacle to effective biologic DMARD treatment involves the concept of 'primary nonadherence,' which describes situations wherein patients are reluctant to start new medications. One recent study examined fill rates among 373 patients with RA who were prescribed their first injectable biologic DMARD (an anti-TNF agent in 89% of cases).[42] More than half of patients (54%) did not fill their biologic at a pharmacy or have the biologic administered within 30 days of the initial prescription, and 39% had not filled their prescription within 180 days. Patients who filled their biologic DMARD prescriptions within 30 days were more likely to be younger, female, have worse RA disease severity, have higher pain scores, and were more likely to have filled prior prescriptions for any medications.

Regardless of the RA medication selected, patients require appropriate education and support to ensure that they begin treatment as prescribed.

Benefits of IV Therapy in Patients with Poor Adherence

For patients in whom poor adherence is a concern, IV therapy may be preferable to injectable or oral medications. Although few head-to-head comparisons of medication adherence are available in RA patients, there are lessons to be learned from other chronic diseases. In a study of patients taking bisphosphonate therapy, patients demonstrated poorer adherence to once weekly oral treatment compared with IV medications given every 3 months or once per year.[43] Some patients who take oral MTX may develop bothersome gastrointestinal side effects that interfere with adherence. For these patients, parenteral MTX may be more tolerable.[44]

Challenges with Subcutaneous Therapy

Injectable medications can provide greater convenience than IV therapy for some RA patients, but they are not necessarily an appropriate option for all patients who need a biologic DMARDs. Fear of needles negatively affects adherence in patients who are prescribed self-injected RA medications. In one study of 310 patients with RA, 45% reported some degree of "needle phobia" that would potentially deter them from using injectable biologics.[45]

Poorly managed injection-site reactions (ISRs) may negatively affect patient satisfaction and contribute to poor medication adherence among patients who self-inject biologic DMARDs. The Rheumatoid Arthritis: Patient Insights, Strategies + Expectations (RAISE) study evaluated ISRs in 239 patients who self-inject with etanercept (51%) or adalimumab (49%).[46] Most patients (94%) reported some degree of discomfort when injecting biologic DMARDs, and 23% report needlestick pain and burning with every injection. The burning sensation lasted for a mean of 1.4 hours. One-third of patients (34%) described the sensation as moderately or very bothersome, and 1 in 8 patients (13%) had considered skipping their injections because of ISRs.

Furthermore, rheumatologists appear to underestimate the frequency and severity of ISRs in patients with RA. The RAISE study also evaluated perceptions about ISRs among 47 rheumatologists who managed patients taking subcutaneous (SC) anti-TNF therapy. The rheumatologists estimated that <20% of RA patients experienced ISRs, and when ISRs occurred, the symptoms were probably not bothersome. Poorly managed ISRs may negatively affect patient satisfaction and contribute to poor medication adherence among patients who self-inject biologic DMARDs.

Patient Preferences and Route of Administration

For many patients with RA, the route of administration ranks highly among considerations for therapy.[47] In one survey of medication preferences among 380 patients with RA, respondents ranked the attributes of treatment in the following order of importance:

- Route of administration
- Frequency of administration
- Likelihood of serious adverse events
- Monthly out-of-pocket cost
- Medication burden (i.e., need to take with another medication)
- Reduction in joint pain and swelling
- Improvement in daily activity

Another study examined treatment preferences among 500 patients treated with anti-TNF therapy administered by SC injection (60%) or IV administration (40%).[48] In general, patients tended to prefer the administration route they were currently using: 90% of patients in the SC group preferred self-injection, and 72% of patients in the IV group preferred IV administration. However, fewer than half of patients in either group reported ever discussing options with their rheumatology providers regarding alternative anti-TNF agents, routes of administration, or locations for treatment

(eg, home vs. clinic). Furthermore, despite generally being satisfied with treatment efficacy, 46% of IV biologic users expressed interest in options for receiving their anti-TNF therapy at home. Given the growing number of treatment choices available to RA patients, it is increasingly important to discuss the full range of options for oral, SC, and IV administration.

The availability of new oral medications represents a major milestone for RA patients. Among routes of administration, 56% of patients reported in one study a preference for oral therapy over treatment administered by SC injection or IV infusion.[47] Another study examined medication preferences in 1,588 patients with active RA who were receiving oral (43%) or injectable DMARDs (54%).[2] Patients rated 'oral administration' as the most important and desirable feature of RA medication. The ability to avoid concomitant treatment with MTX was also highly valued.

Summary

Nearly 2 decades after the introduction of biologic DMARDs, an increasing number of patients have started an anti-TNF agent or non-TNF biologic to control their RA. JAK inhibition offers an alternate mechanism of action for controlling RA disease activity in patients who have failed multiple prior lines of therapy. Tofacitinib, now an established therapy for patients with refractory RA, may be moving toward earlier use in the natural history of RA. In the future, baricitinib and other investigational JAK inhibitors may provide additional options for patients who require alternatives to biologic DMARDs.

Although oral therapy is not the optimal choice for all patients, the ability to manage RA with a once-daily or twice-daily pill has important implications for patient satisfaction, medication adherence, and, ultimately, the success of treatment. In the next issue of *Rheumatology Nurse Practice*, we will explore the increasingly complexity of RA treatment algorithms, including strategies for selecting biologic DMARDs or JAK inhibition in appropriate patients.

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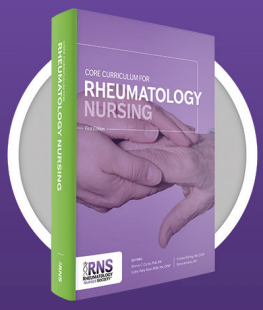

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Don't Make Your Patient Visits Feel Like a Horror Movie

by Elizabeth Kirchner, CNP, RN-BC

AUTHOR PROFILE:

Elizabeth Kirchner, CNP, RN-BC

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

The scariest movie I ever saw was called "The Ring." I'm not exactly sure what it was about, because I "watched" it while hiding under my jacket in the movie theater. Something about a cursed girl who lived on an island off Seattle, and she inadvertently made horses commit mass suicide, plus she also hurt a lot of people with her Jedi Mind Tricks, and her curse lived on through haunted videotapes. I think. There was maybe also something about a well, but that part was *way too scary* to even peek at.

Anyway, the point is that the only thing I remember clearly from the film (which, I'm told, is excellent. Love love love Naomi Watts!) is that at the end of the movie, the heroine realizes that at the root of all this evil is the fact that the cursed girl (Samara) just wanted to be heard. Perhaps killing people via haunted videotapes might be an overreaction, even if you feel like no one is listening to you, but if you have ever been ignored over and over again, you might have an inkling of what Samara was going through.

Extreme Japanese-horror-movie-remake examples aside, being listened to—being *heard*—is a universal need. When we are being listened to, it means that a connection has been made, that we matter, that our existence matters, and that we're not alone. The privilege of listening is an awesome gift.

Confession time: I was not always a good listener. I think I may have been born a not-good-listener. There was that incident when Ms. Rosengarten (third-grade teacher) called my mother in tears because "Betsy just won't stop talking." I just chatted my way right through elementary school and junior high, leaving a trail of crying teachers in my wake.

As we all know, our mouths and ears cannot really be functional at the same time. So all that talking meant not much listening.

I don't think I really started learning how to listen until I was in college when the typical freshman adjustment period was accompanied by some fairly crippling social anxiety. Luckily for me, a professor noticed my panic in small class seminars and gave me some of the best advice I ever received: "If you don't know what to say," he told me, "ask people about themselves." So I did. And since I had nothing else to do but pay attention, I got a lot of practice listening. After several years of listening, I feel like I got to be pretty good at it.

For some (unlike me), being a good listener comes naturally, but if it doesn't, it's not really a tough skill to master. Most, if not all, nursing programs actually teach therapeutic listening skills, but just in case you don't feel like going back to nursing school, here are a few real-world tips that may help you be a better listener with your patients:

1. Start every visit with open-ended, low-pressure questions. "How are you?" is a good one. "Did you have a good holiday?", "How was the wedding?" or any appropriate topic you remember from the patient's last visit can also work. We're going for something personal but not expressly geared towards illness.

2. Look at the patient. Not at the computer. Not at the chart. And certainly not at your watch or the clock on the wall. Just put your hands in your lap, smile, and look at the person who is talking to you.

3. Wait for the patient to finish speaking. Then wait another few seconds. Your patient may be so surprised that someone is actually listening that it takes them a moment to go on, but once they realize you aren't going to move on and jump in, they may get past a generic answer ("Fine") and tell you something meaningful ("My daughter came to visit and I haven't seen her for 3 years!")

4. Listening is not the same as waiting for your turn to speak. When a patient is talking to you, giving them your complete attention is a must.

5. Periodically during a visit, and especially at the end, ask the patient "Is there anything else you want to tell me?" You may be surprised what they have been holding back.

So for those of you who are already gifted listeners, thank you and carry on. But if you are someone who often finds yourself distracted during patient visits or talking more than you listen, don't worry, there's a good listener inside of you just waiting to come out.

And for those of you who are intrigued by my first paragraph and are thinking it would be really fun to rent "The Ring" this weekend (and you value sleeping without nightmares), listen to me very, very carefully: Don't.

Learning to Meet Our Patients Where They Are

by Iris Zink, MSN, NP, RN-BC

AUTHOR PROFILE:

Iris Zink, MSN, NP, RN-BC

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

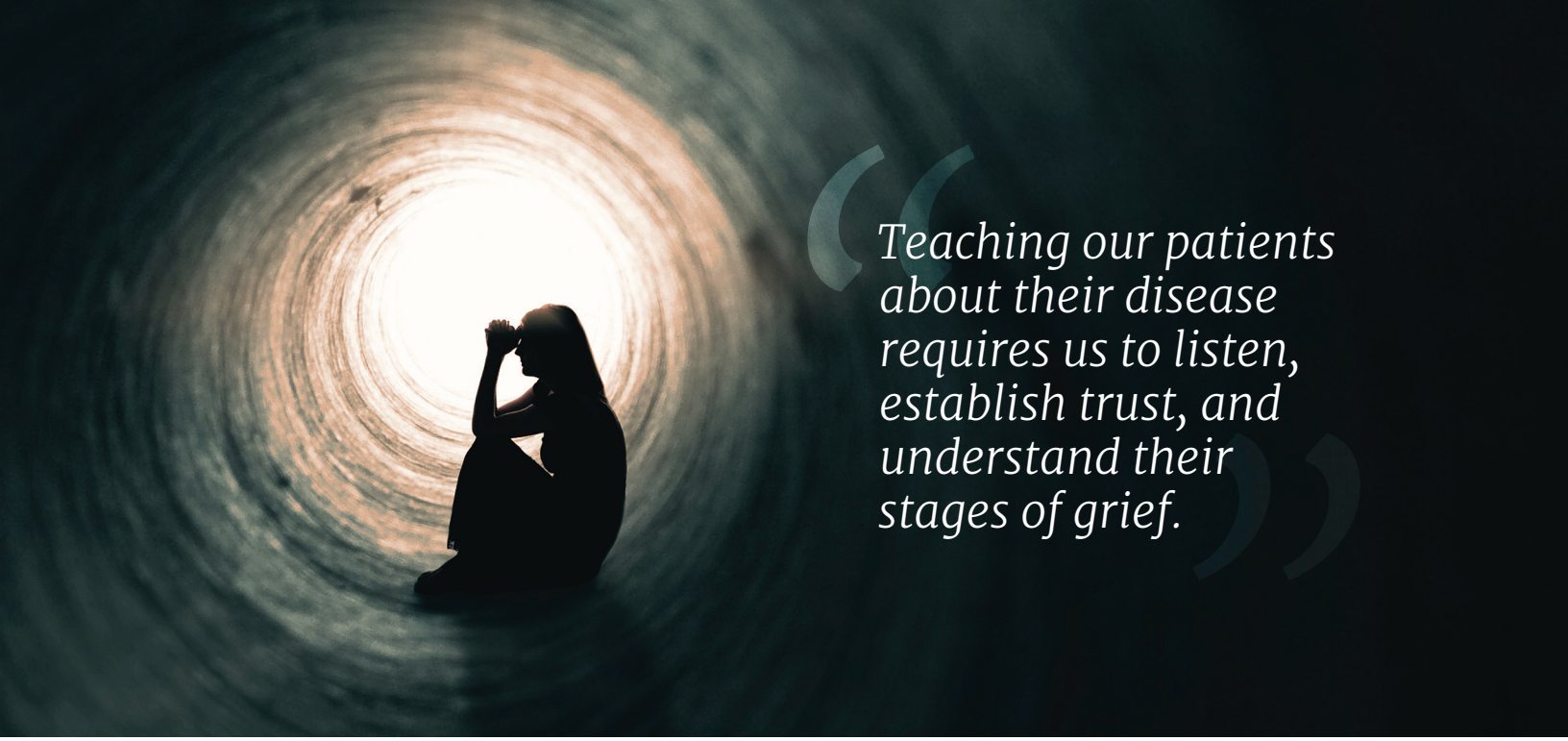
Being diagnosed with a chronic condition such as rheumatoid arthritis (RA) is typically a life-altering event for our patients and always involves a difficult and often emotional conversation. It is important to always recognize the sensitive and fragile nature of our patients when they receive a diagnosis from their provider and to be mindful of the medical terminology we are using. What seems to be obvious to us may not always be clear to our patients. Issues such as comprehension problems or language barriers can often make difficult discussions even more complicated.

Cindy was a recent new patient of mine who came to me after issues with insurance and transportation forced her to change rheumatology providers. A 40-year-old Hispanic woman, Cindy had been taking etanercept for what she told me was diagnosed as "psoriatic arthritis." She had stopped the medication approximately 6 months ago due to hearing loss. This was not a medication-related side effect I was familiar with, so I started by going through additional probing questions with Cindy to try to dig further into the root of her problems.

As Cindy's hearing was spotty, we communicated by writing notes on paper. Nonetheless, the answer to her issues still remained murky, so I ordered a full panel of labs. The result confirmed what I was suspecting—she had RA, not psoriatic arthritis (PsA), and the inflammation—and not etanercept—was the driver of the hearing loss.

Armed with a full battery of information, I was excited to be able to share my findings with Cindy at her appointment the next week and get her on the right track to controlling her disease. Alas, Cindy was a no-show at her scheduled appointment. I called her mother (the emergency contact in her records) and then eventually drove to Cindy's house for an in-home visit. Driving to see one of our patients in their own home is certainly a time-consuming process, but I have learned that making that sacrifice and seeing what is truly going on with a patient in their own setting is the best way to see the impact their disease is having on their life.

So here we were—myself and my nursing student—watching Cindy slowly walk down the stairs of her house with her mother's assistance. The four of us sat down at the kitchen table and started to devise our plan. It was clear that Cindy had given up hope that she would ever feel better or hear clearly again, so our first challenge was to convince her that RA was our enemy and not the medications she had been previously prescribed. To try to "win" an immediate gain, I put Cindy



on prednisone 20 mg daily so that she would be able to ambulate more easily and dress herself in the morning. I used drawings and illustrations to explain to her how we would need to target specific cytokines to impact her disease.

Cindy's previous rheumatologist had cycled her through two TNF inhibitors without success (the incorrect diagnosis of PsA didn't help). While she remained on daily methotrexate, her disease was a long way from remission. I initially introduced rituximab as an option, hoping that it could both help reduce the inflammation that had caused her hearing loss and halt the damage that her RA was causing to her overall health.

Cindy had several questions for me, which she wrote down and I responded to. I made sure not to rush through anything and to try to answer things as thoroughly as I was able. Her family was extremely surprised and grateful that I had gone to the trouble of visiting Cindy at home and took care to make sure she was comfortable working with me to help manage her disease. A religious family, they kept telling me that I "was a blessing." I told them that I would pray for Cindy and continue to work with her until we got her disease under control. Two cycles of rituximab later, Cindy can now navigate stairs on her own, we are titrating down her use of prednisone, and she's awaiting a cochlear implant evaluation to help her hearing.

Teaching our patients about their disease requires us to listen, establish trust, and understand their stages of grief. In her landmark 1969 book, *On Death and Dying*, Elisabeth Kübler-Ross laid out the five stages of grief based upon her personal divorce.[1] They are anger, denial, acceptance, bargaining, and depression. It is common that our patients will cycle through these emotions—not necessarily in linear order—and it's up to us to be aware of those patients who may be grieving over their diagnosis and its impact on their quality of life. Cindy, for instance, had clearly reached the "depression" stage. It was only by stepping beyond my usual patient boundaries and visiting Cindy in her home that she was able to break through and learn that her disease, and not her medication, was the enemy.

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Getting at That "One Thing" That Makes a Difference

by Jacqueline Fritz, RN, MSN, CNS, RN-BC

AUTHOR PROFILE:

Jacqueline Fritz, RN, MSN, CNS, RN-BC

Jacqueline Fritz, RN, MSN, CNS, RN-BC, is Owner and Coordinator of Education at the Medical Advancement Center in Cypress, CA. Her primary responsibility is working as an advanced practice nurse for a large rheumatology practice where she is involved in patient visits, research programs, and infusion center coordination. In addition, she enjoys speaking, teaching, and learning about immunology.

We all have patients who are hard to connect with, stubborn beyond belief despite what we think is clear evidence that refutes their deep-seated obstinence. How often do we hear, "The side effects are too great. I'd rather suffer in pain than take this new medication that puts me at risk of cancer or dying from infection."

Figuring out the right approach for our most stubborn patients is a challenge. I often find myself falling into the role of an analytical communicator,[1] providing my patients with reams of information and data to try and convince them that treating the cause of their disease is the only way to prevent their immune system from taking them hostage.

For some patients, a more effective technique is serving as the "relator" where I primarily focus on being supportive of them no matter what they may want to believe in and demonstrating that I care about them as individuals.[1]

Different communication styles work for different patients, and I often find myself having to quickly size up a patient when I first meet them to determine what technique they are most likely to respond to. A good example came about with Barbara, a new patient I met in the hallway 2 months ago after her recent diagnosis of rheumatoid arthritis (RA).

No matter how much evidence I provided to the contrary, Barbara was adamant that any biologic therapy would shut down part of her immune system or cause cancer, and she refused to try one. Unfortunately, her liver was already rebelling against the high daily dose of ibuprofen and hydrocodone she was taking, and her inflammation was out of control. Barbara had recently gone through the heartbreaking process of having her wedding ring cut off due to her deformities, and she was having increasing difficulty getting through each day without having to make major concessions. She could no longer dress herself, button her clothes, or care for her grandchildren on her own.

I tried explaining to Barbara that the risks of large cell tumors are no more significant in patients with RA than the general population (the incidence of lymphoproliferative malignancies is slightly higher). Patients with RA have less than a 1% standardized incidence ratio increase in the prevalence of breast and colon cancer compared to the general population.[2] Nonetheless, Barbara wouldn't budge, so I decided to try another approach.

Last year, I had the pleasure of joining a pain specialist, Ellyn Schreiner, MPH, RN-BC, CHPN, on one of the live broadcasts that are part of the *Rheumatology Nurse Practice* education. During our conversation, one thing in particular that Ellyn mentioned really hit home. "Ask your patient," she said, "what the most important thing they miss that would like to be able to do again." I tried that with Barbara and she instantly perked up. "It would be great if I could play with my grandchildren!"

That was the opening to a level-headed discussion that I needed, and I quickly moved on to other quality-of-life issues that Barbara was struggling with. "Wouldn't it be worth trying something to help you feel better?" I asked. There were many options that might help reduce her inflammation and allow her to live with less pain, I explained, and the risks

associated with these options were very mild. I reminded Barbara that inflammation doesn't just affect the joints but also has a detrimental effect on the lungs, blood vessels that surround the heart, and really the whole body. She looked at me in shock, clearly never remembering hearing about this. "Really?" she said. "They do?"

Barbara soon after agreed to try her first biologic therapy, motivated by the goal of playing once again with her grandchildren. Happily, after 3 infusions of golimumab monotherapy (we could not use methotrexate due to her elevated liver function tests), Barbara is responding well. Her tender joint count has decreased from 18 to 4 and her swollen joints from 12 to 2. Her latest liver function test was normal.

Our conversations have now shifted from the need to try a biologic therapy to the need to stay on one. I find myself regularly reminding Barbara that she should call if there is any significant change in her health and that she needs to keep me abreast of any medical procedures she has scheduled (I can't tell you know many times patients forget to tell me about getting an abscessed tooth removed or have impending surgery scheduled).

At our most recent visit, Barbara hugged me and told me how happy she was that she was able to take her grandchildren to the park and play with them for an hour. It's only by listening to my colleague, Ellyn, and continuing to educate myself that I was able to break through to Barbara and get her on the right path. It was a good reminder that "one size does not fit all" when talking to our patients and that we always need to gently probe to find that pivot point that resonates and helps us to overcome their defenses.

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Why CE Accreditation Matters to Nurses

by Sheree C. Carter, PhD, RN, RN-BC

AUTHOR PROFILE:

Sheree C. Carter, PhD, RN, RN-BC

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

This issue of *Rheumatology Nurse Practice* (RNP) is the first of several coming out this year that will offer continuing education (CE) credit hours for nurses. Your initial reaction may involve nothing more than an "OK, so what?" shrug of the shoulders. Rest assured, the lengthy journey that has allowed the Rheumatology Nurses Society (RNS) to attach CE credit hours to this education was undertaken with a clear purpose to bring more value and sophistication to our audience of nursing professionals.

From its inception, we have gone to great lengths to bring you the highest caliber *enduring* education through RNP. The term *enduring* describes any "non-live" CE activity that endures (sustains content without notable changes) over time. Enduring activities may include online and recorded-live events, courses, e-books, and self-learning web materials, as well as print materials such as RNP, which is offered both in hard copy and online format. Just like the milk carton in your refrigerator, though, enduring activities have an expiration date. Generally, the opportunity to earn CE credit for participating in a specific enduring activity is up to two years following the date of its original release.

State requirements vary regarding the number of credit hours that both RNs and LPN/VNs must earn through participation in and completion of CE-certified activities for renewal of licensure. See NURSE.com (http://ce.nurse.com/RStateReqmnt.aspx) to look up the requirements of each state, the District of Columbia, Guam, Puerto Rico and the U.S. Virgin Islands. Please note that this site contains advertisements for various sites that can help fulfill CE requirements; we do not endorse any of those sites through our referral here.

Why so many differences from state to state regarding licensure renewal requirements? The story goes back more than 100 years, when state governments first enacted laws designed to protect the public's health and welfare by overseeing and ensuring the safe practice of nursing. All states and territories have enacted a nurse practice act (NPA), a law enacted by the state's legislature that establishes a State Board of Nursing with the authority to develop administrative rules or regulations to clarify the law. NPA laws typically include language related to discipline of the profession, scope of practice, and standards for education pre-and post-licensure.[1] Because NPAs are overseen by state-controlled boards and are not tied to national standards, there are significant variations from state to state.

Requirements for initial and continuing nursing licensure are complex. It is easier to think of each state as a separate country rather than a united republic. Some states, such as Connecticut, do not require CE's for RNs or LPN/VNs for general licensure. Other states, such as Virginia, have a much more complex system (up to eight different options) to satisfy CE requirements. For those states that require CE, the necessary number of required hours varies. Some states require nurses to obtain a certain number of CE credits annually while others require more credits over a 2- or 3-year period.

Washington, for example, is one of the states with the most stringent CE requirements. Every 3 years, both RNs and LPN/VNs are

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required to complete 531 hours of active nursing practice as well as 45 hours of CE-certified education. Even U.S. territories such as Puerto Rico have systems in place to ensure that nurses appropriately keep up with the profession, requiring 3 hours of infection control education specific to HIV, hepatitis, or tuberculosis. The Puerto Rico nursing board also caps the number of hours that RNs and LPN/VNs can earn through enduring education (20 of the 30 required hours for each licensing period for RNs, 15 of 21 required hours for LPN/VNs). Those of you who are travel nurses, or work in multiple states and carry multiple licenses, understand all too well the trials of meeting various state requirements and paying their associated fees.

In the last decade, nursing has poised itself to accept greater autonomy and responsibility in the care of our patients, impacting patient outcomes, health disparities, and access to care. There are scores of specialty practice nursing entities and numerous levels of advanced practice nursing degrees available, as well as massive specialty organizations offering credentials in specialty practice. Each one of these typically requires nurses to complete periodic CE credit hours, which may include CEs in pharmacology, HIV/AIDS, infection control, pain management, identifying and reporting child abuse, and other topics. The newly available RN-BC rheumatology nursing certification by portfolio offered by the American Nurses Credentialing Center requires a minimum of 10 hours of annual rheumatology/rheumatology nursing CE each year as part of an individual's requirement to maintain certification.

There are numerous paths nurses may take to obtain useful continuing education; however, not all paths are created equal or contain the required rigor required for acceptance as a CE activity. Hence the need for highly respected organizations to train, oversee, and maintain high standards through accredited providers. Along with American Nurses Credentialing Center (ANCC) CEs, most RNs are able to count the medical profession's American Medical Association Physician's Recognition Award Category 1™ (AMA PRA Category 1) credits on equal basis—1 hour of CME credit = 1 hour CE.

There is some cross acceptance of CEs and an increasing push for medical education providers to obtain Joint Accreditation from three bodies in one application—from the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the ANCC.

In late 2016, RNS completed the rigorous process that allows us to provide CE credits for education of appropriate rigor. You are reading our first independently accredited piece right now. To prepare RNS for this milestone, we have in place a Lead Nurse Planner, Nurse Planners, and other support staff within our Provider Unit to ensure that we strictly adhere to the ANCC's accreditation standards and guidelines when offering credit hours for educational activities.

There are instructions within this issue pointing you to the web portal you will need to visit to acquire CE credits. Within that portal, you will find a post-test that you will need to pass to ensure that you read and absorbed this education, as well as a short activity evaluation. We certainly encourage even those nurses who are not required to complete annual CE hours to go onto the portal to test your knowledge and competence regarding the topics covered within this issue of RNP.

One last topic we will cover here concerns medical assistants. Medical assistants who are certified through the American Association of Medical Assistants (AAMA) are allowed a certain number of CEs to be "outside of" AAMA-provided CEs. There are restrictions, just as with RN and LPN licensure renewals, requiring responsibility for each individual to check with their organizations for these allowances. This particular publication is rated with a higher (more comprehensive) rating of 3.7 on a scale of measurement consisting of the following rubric; Very easy = 1; Somewhat easy = 2; Moderate = 3; Difficult = 4; Very difficult = 5. The difficulty of material is dependent on the target audience.

Nursing careers take widely divergent paths and require differing levels of education, all leading to a special set of skills, knowledge and practice. It is incumbent upon the RNS to provide quality CE activities meeting the gaps identified for the rheumatology nurse to provide safe and competent care to the public. We welcome your ideas and input regarding your personal professional gaps and needs. Lastly, we hope we are able to provide quality resources both for you and other members of your healthcare team. If your organization is able to accept our CEs, rest assured we maintain and are evaluated by the highest standards.

Reference

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Sarasota, FL 34243
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Commercial Support

Supported by educational grants from Pfizer and Lilly.

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