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# RHEUMATOLOGY NURSE NEWSLETTER

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*Practical information and tools you can apply to your everyday practice!*

### LEARNING OBJECTIVES

Upon completion of this activity, participants will be able to do the following:

- Describe the mechanisms of action of the infusible and injectable biologics that have been approved by the US Food and Drug Administration for the treatment of rheumatoid arthritis (RA)
- List the primary pros and cons of infusion therapy for the treatment of RA
- Identify common adverse events faced by patients who receive infusible biologics for RA ■

### STATEMENT OF EDUCATIONAL NEED

Infusion and injection-site reactions are among the most common side effects associated with biologic treatment of RA. As nurses are often responsible for counseling patients regarding potential

medication-related side effects and treating any side effects that do arise, it is imperative that they understand screening techniques, premedication protocols, and the most common side effects associated with individual biologics.

This activity is designed for rheumatology nurses, rheumatology advanced practice nurses, and infusion nurses. ■

### INTRODUCTION

*Rheumatology Nurse* is a CE-certified newsletter series designed for nurses who manage patients with RA *by* nurses who understand firsthand the complexities and challenges of managing patients with RA.

Each newsletter contains practical information and tools you can apply to your everyday practice! ■

# Faculty Disclosure Statement

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

**Kori Anne Dewing, MN, ARNP**, has disclosed the following relevant financial relationships that have occurred within the past 12 months: Pfizer Inc, Genentech, Inc., Biogen Idec Inc./SB; Wyeth, Amgen Inc./A.

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Off-label and/or investigational use of the following products will be discussed within the literature of this enduring activity: tocilizumab, certolizumab pegol, golimumab, ocrelizumab, and ofatumumab. ■

*The staff of the Institute for Continuing Healthcare Education involved in the development of this educational activity has no relevant financial relationships to disclose.*

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Jackie Dawson, MSN, RN, is the nurse planner for this activity. ■

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## MANAGEMENT OF INFUSION-BASED BIOLOGIC THERAPY IN RA

### Introduction

Newer therapies designed to block the biologic effects of inflammatory cytokines, such as tumor necrosis factor (TNF), are now part of the mainstream clinical management of rheumatoid arthritis (RA). Biologic therapy options in RA include antibodies that block TNF (infliximab and adalimumab), IL-1 (anakinra), and CD20 (rituximab), as well as soluble TNF receptors (etanercept) and fusion proteins that inhibit T-cell activation (abatacept). These biologics may be more effective than traditional agents because they modify the underlying inflammatory process in addition to alleviating symptoms. In addition, early incorporation of biologics may lead to earlier functional improvement, less radiographic damage, and greater reductions in disease activity.<sup>1</sup>

Biologics are administered via either subcutaneous injection or intravenous (IV) infusion. Successful use of biologics requires extensive patient education and, during infusions themselves, direct administration and monitoring by the rheumatology or infusion nursing staff.



## ROLE OF NURSES IN

# Infusion Therapy

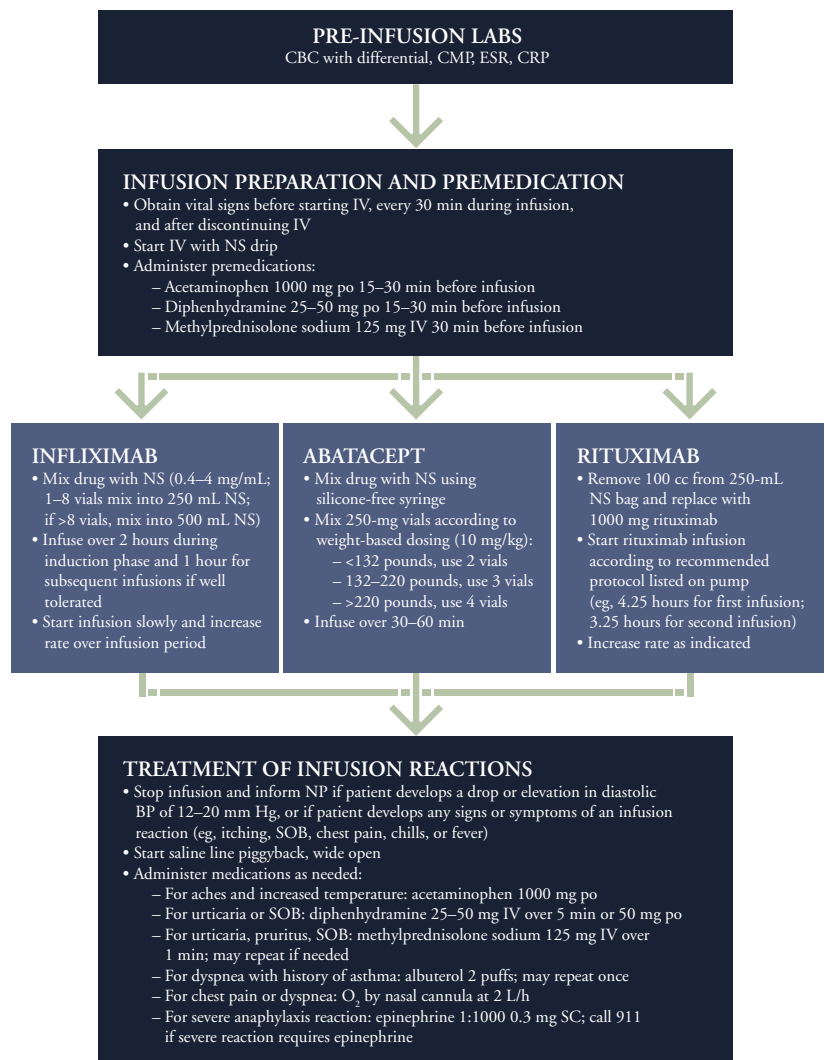
Infusion-based biologics have expanded the role of nurses in RA management. Patient education and advocacy have become primary responsibilities of RA nurses involved in the administration of infusible biologics. Today's well-informed patients are able to participate in their own care, determine whether adequate responses are being achieved, and alert the nurse or ordering provider when any concerns arise. Also, as the liaison between patient and ordering provider, infusion nurses often manage the RA treatment plan and ensure the appropriate delivery of care.<sup>2</sup> Indeed, it is often the special relationship of trust that develops over time between patient and nurse that allows for high-level education tailored to specific needs of an individual patient.

During the infusion of biologics in patients with RA, nurses are responsible for several components of patient care, including the following<sup>3</sup>:

- Patient screening
- Drawing preinfusion labs
- Mixing infusion agents
- Monitoring patient vital signs
- Screening for signs and symptoms of infusion reactions
- Managing any infusion-related adverse events (including administering rescue medications)
- Planning for future infusions

Key steps in this process are illustrated in Figure 1. ■

**FIGURE 1**  
*Sample Institutional Protocol for Infusion Therapy*



## PATIENT SCREENING

Patient screening is a key preliminary step to the initiation of treatment with an infusible biologic. In particular, screening allows nurses to identify any potential contraindications to infusion therapy, such as current infections or previous reaction to IV therapy. Elements of screening and their potential implications are listed in Table 1.<sup>3</sup>



**TABLE 1**  
*Pretreatment Screening for Infusible Biologics*

Screening Variable	Implications for Biologic Treatment
Known allergies, including allergies to foods, medications, latex, and murine or other proteins	Patients with previous or current allergies may have an elevated risk of allergic drug reactions
Heart failure	The use of TNF inhibitors is not recommended in patients with severe congestive heart failure
Disorders or events tied to the immune system, such as cancer, infections, or recent or upcoming vaccinations	TNF inhibitors suppress elements of innate and acquired immunity, and increase the vulnerability of patients with immune system challenges. No live-virus vaccines should be given to this subset of patients
Vaccination with attenuated live-virus products	Live vaccines should not be given to patients undergoing treatment with all biologics
Previous reactions to monoclonal antibodies, including abatacept, infliximab, rituximab, alemtuzumab, or trastuzumab	Patients with a history of infusion reactions have an elevated risk of future reactions
Recent or upcoming elective surgery	Biologic therapies may increase the risk of postoperative infection
Pregnancy, nursing, or childbearing age	The effects of biologics on fertility, fetal growth, and milk production are not well defined
Residence or frequent travel outside the United States	Treatment requires routine visits to a doctor's office or infusion center, as well as access to infusible biologics
History of tuberculosis or histoplasmosis	Treatment with biologics may elevate the risk of reactivating these infections
COPD	Abatacept should be used with caution in patients with COPD
Diabetes	GDH pyrroloquinoline quinone-based glucose monitoring systems may react with maltose present in abatacept, resulting in falsely elevated blood glucose readings

COPD=chronic obstructive pulmonary disease, GDH=glucose dehydrogenase, TNF=tumor necrosis factor.

## PREMEDICATION

Given the prevalence of infusion reactions, premedication with agents that can prevent or minimize infusion-related adverse events is an integral step of biologic administration. According to the protocol of individual institutions, premedications may include oral acetaminophen and diphenhydramine 15 to 30 minutes before the infusion or a nonsedating antihistamine taken at least an hour before the infusion, along with IV methylprednisolone 30 minutes before the infusion.

As an analgesic and antipyretic, **acetaminophen** relieves mild-to-moderate pain and reduces fever. **Diphenhydramine** is an antihistamine that blocks the H1 histamine receptor, resulting in a range of effects, including relief of hives (urticaria), itching, and other allergic symptoms, as well as relaxation of smooth muscle contraction. **Methylprednisolone sodium** is a corticosteroid used to relieve inflammation, including swelling, heat, redness, and pain. Methylprednisolone is frequently used during infusion reactions that are acute and result in symptoms such as throat swelling and angioedema.

In addition to standard premedications, some centers may use other agents in appropriate patients. For example, the sedative **alprazolam** is an antianxiety medication with smooth muscle relaxation properties.<sup>4</sup> **Famotidine**, an H2-receptor antagonist, has been shown to be particularly effective in preventing allergic reactions secondary to medication administration.<sup>5</sup>

Side effects associated with agents used for premedication pose an interesting clinical challenge. For example, when

premedication with diphenhydramine is used, patients should be alerted to the potential need for someone to drive them home due to drowsiness. In addition, the side effects of some premedications may mimic those of biologic-related infusion reactions (see Infliximab section later in this article).<sup>6</sup> Antihistamines, for instance, may cause dry mouth, sedation, flushing, hypotension, and headache. A metallic or sour taste is often associated with the use of methylprednisolone or corticosteroids. ■

## MANAGING INFUSION REACTIONS

Infusion reactions may occur at any time during an infusion or from several hours to days after the procedure. Therefore, screening for an infusion reaction should begin with documentation of the presence of, or lack of, problems with any previous

infusions. It is also important to have baseline vital signs from which to compare later on if the patient develops any unusual symptoms. While clinic or center protocols on the frequency of vital sign checks may vary, a minimum standard is at baseline, at intervals of 15 to 30 minutes during infusion, and after the infusion is complete before releasing the patient.

Infusion reactions may include the development of urticaria, pruritus, headache, fever, chills, or sudden back pain. Cardiopulmonary reactions, such as chest pain, dyspnea, arrhythmia, hypotension, or hypertension, may also signal an infusion reaction.<sup>5,7</sup> Patients may often sense the impending onset of these symptoms before they become clinically evident. With experience, infusion nurses often learn to read patients' body language and their facial expressions, allowing them to sense

an impending reaction and therefore intervene quickly before the patient panics or becomes overly concerned. Accordingly, it is important for nurses to educate patients about the signs and symptoms of infusion reactions and to encourage them to report any of these sensations as soon as they develop.<sup>3</sup>

To facilitate routine monitoring and standardized treatment of infusion-related adverse events, each institution should develop a protocol for the management of infusion reactions. Having a protocol in place also gives autonomy to the infusion nurse, demonstrates value in his or her judgment, and improves overall patient care. Some centers may choose to classify reactions as either mild or severe and manage reactions according to these classifications.

**TABLE 2**  
*Medications Used in the Management of Infusion Reactions*

Medication	Common Infusion Reaction Indications	Recommended Dose and Rate of Administration	Potential Medication Side Effects	Notes/Precautions
Acetaminophen	<ul style="list-style-type: none"> <li>• Body aches</li> <li>• Fever</li> </ul>	<ul style="list-style-type: none"> <li>• 1000 mg po</li> </ul>	<ul style="list-style-type: none"> <li>• Allergic reaction (rare)</li> </ul>	<ul style="list-style-type: none"> <li>• None</li> </ul>
Diphenhydramine	<ul style="list-style-type: none"> <li>• Urticaria</li> <li>• Shortness of breath</li> </ul>	<ul style="list-style-type: none"> <li>• Usual dose is 10–50 mg - 25 mg over 1 minute</li> <li>- Flush with 20 mL NS</li> <li>• Up to 100 mg may be given; maximum dose is 400 mg/24 h</li> </ul>	<ul style="list-style-type: none"> <li>• Drowsiness</li> <li>• Dizziness</li> <li>• Sinus tachycardia, palpitations, cardiac arrhythmias</li> <li>• Rash and/or urticaria</li> </ul>	<ul style="list-style-type: none"> <li>• Incompatible with methylprednisolone sodium when used in the same syringe</li> </ul>
Methylprednisolone sodium	<ul style="list-style-type: none"> <li>• Urticaria</li> <li>• Pruritus</li> <li>• Shortness of breath</li> </ul>	<ul style="list-style-type: none"> <li>• 250–500 mg for acute reaction</li> <li>- Each 500-mL fraction can be given over 2–5 minutes or by infusion over 10–20 minutes</li> <li>• Do not exceed 1.5 g/24 h</li> </ul>	<ul style="list-style-type: none"> <li>• Sinus bradycardia</li> </ul>	<ul style="list-style-type: none"> <li>• Do not use in patients allergic to sulfites</li> <li>• Incompatible with diphenhydramine when used in the same syringe</li> </ul>
Albuterol	<ul style="list-style-type: none"> <li>• Dyspnea, especially in patients with a history of asthma</li> </ul>	<ul style="list-style-type: none"> <li>• 1–2 puffs every 4–6 hours as needed for shortness of breath</li> <li>• Take deep breath while depressing inhaler</li> <li>• Hold breath for 10 seconds</li> </ul>	<ul style="list-style-type: none"> <li>• Heart palpitations</li> <li>• Tachycardia</li> <li>• Hypertension</li> <li>• Tremor</li> <li>• Nervousness</li> <li>• Dizziness</li> <li>• Heart burn</li> <li>• Throat irritation</li> </ul>	<ul style="list-style-type: none"> <li>• None</li> </ul>
Epinephrine hydrochloride	<ul style="list-style-type: none"> <li>• Severe anaphylactic reaction</li> </ul>	<ul style="list-style-type: none"> <li>• 0.2–0.5 mg of 1:10,000 solution</li> <li>• 1 mg over 1 minute or longer</li> <li>• Flush with 20 mL NS</li> <li>• In cardiac arrest, 1 mg of 1:10,000 solution IV; may repeat every 3–5 minutes</li> </ul>	<ul style="list-style-type: none"> <li>• Hypertension</li> <li>• Sinus tachycardia</li> <li>• Hypotension</li> <li>• Local tissue ischemia</li> <li>• Chest pain</li> </ul>	<ul style="list-style-type: none"> <li>• Available prediluted 0.1 mg/mL (1:10,000 solution) in 3- or 10-mL syringes</li> <li>• Dilute 1:1000 to 1:10,000 by adding 10 mL NS to 1 mg (or 1 mL of 1:1000 solution)</li> </ul>
Oxygen	<ul style="list-style-type: none"> <li>• Chest pain</li> <li>• Dyspnea</li> </ul>	<ul style="list-style-type: none"> <li>• 2 L/h by nasal cannula</li> </ul>	<ul style="list-style-type: none"> <li>• None</li> </ul>	<ul style="list-style-type: none"> <li>• None</li> </ul>

Mild reactions might include pruritus without rash, throat irritation, fever, or chills. Management strategies depend on the specific infusion agent, but potential steps include slowing the infusion rate while continuing to monitor symptoms. If symptoms persist, the infusion may be stopped until symptoms disappear and then restarted at a lower rate. Agents such as antihistamines or acetaminophen may also be given.

In the event of a severe reaction, the infusible medication should be stopped until the patient can be evaluated and treated. Severe reactions are very rare but may include the development of hypotension, bronchospasm, or signs of anaphylactic shock. If these symptoms arise, the protocol might call for stopping the biologic infusion, opening a saline infusion line, and/or alerting the clinician. Where appropriate, steroids, epinephrine, bronchodilators, or other interventions may be initiated.<sup>2,3</sup> Agents commonly used in the management of infusion-related adverse events are summarized in Table 2. ■

## PLANNING FOR FUTURE INFUSIONS

In most instances, an infusion reaction to a specific medication need not preclude the use of that medication in the future, although the severity of the infusion reaction will often dictate the need for future prophylaxis. For example, standard premedications (antihistamines, corticosteroids, and/or acetaminophen) are especially important before subsequent infusions for patients who have experienced mild infusion reactions. By contrast, the addition of more aggressive premedications, such as oral corticosteroids the night before and morning of the next infusion, may be appropriate for patients who have experienced moderate-to-severe infusion reactions.<sup>3</sup> In addition, it is important for the infusion nurse to alert the provider to any moderate-to-severe reaction, as that may indicate a change in therapy. ■

Agent	Mechanism of Action	Primary Indications	IV Dose	Common Side Effects
Abatacept	Inhibits T-cell activation by binding to specific receptors on APCs, blocking the interaction between APCs and T cells	Treatment of moderate-to-severe RA in adults and juvenile idiopathic arthritis	Dose according to body weight: • <60 kg: 500 mg • 60–100 kg: 750 mg • >100 kg: 1000 mg Repeat dose 2 and 4 weeks after initial dose, then repeat every 4 weeks	Headache, upper respiratory tract infection, nasopharyngitis, nausea
Rituximab	Monoclonal antibody that binds to the CD20 antigen on B lymphocytes and activates complement-dependent cytotoxicity	Moderate-to-severe RA in combination with MTX after inadequate response to one or more anti-TNFs	1000 mg on day 1 and 15 in combination with MTX	Hypertension, nausea, upper respiratory tract infection, arthralgia
Infliximab	Chimeric monoclonal antibody that binds to TNF- $\alpha$ and antagonizes endogenous activity that can prevent disease and allow diseased joint healing	Improves signs and symptoms of ankylosing spondylitis, Crohn's disease, psoriatic arthritis, RA, ulcerative colitis	Starting dose of 3 mg/kg at weeks 0, 2, and 6, then 3–10 mg/kg every 8 weeks; always used in combination with MTX	Antinuclear antibodies, upper respiratory tract infection, headache, nausea

APC=antigen presenting cell, MTX=methotrexate, TNF=tumor necrosis factor.

# Infusion-Based RA Therapies

*The infusible biologics each have unique mechanisms of action, indications, and dosing and administration requirements. In addition, the risks and patterns of infusion-related adverse events vary among infliximab, abatacept, and rituximab. To appropriately manage these risks, rheumatology nurses should be aware of the properties of each drug and counsel patients accordingly regarding what they can expect during treatment (Table 3).*



## INFLIXIMAB

Infliximab is currently the only Food and Drug Administration (FDA)-approved TNF-inhibitor administered by IV infusion. In combination with methotrexate (MTX), infliximab is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active RA.<sup>8</sup>

The recommended dose of infliximab is 3 mg/kg, administered intravenously over 2 hours at weeks 0, 2, and 6, followed by every 8 weeks thereafter. For patients who experience an incomplete initial response to this regimen, additional drug can be given by increasing the dose, the frequency of administration, or both. Infliximab may be given at a maximum dose of 10 mg/kg and as often as every 4 weeks. Infliximab should be administered in combination with MTX to minimize the production of human antichimeric antibodies, which may result in the loss of therapeutic benefit. Patients

who are positive for antibodies to infliximab are approximately 2- to 3-fold more likely to have an infusion reaction than those who are negative.<sup>8</sup>

Infusion reactions are the most common adverse effect associated with infliximab therapy.<sup>7</sup> Although individual trials report varying rates of infusion reactions to infliximab, the overall rate of reaction is estimated to be approximately 20%. For 3% of patients, infusion reactions are severe enough to require discontinuation of infliximab treatment.<sup>8</sup> Patients who have had a break in treatment may be at higher risk of experiencing an infusion reaction; consideration should be given to using premedication in these patients.

The majority of infusion reactions are characterized by nonspecific symptoms such as pruritus, headache, nausea, fever, chills, dizziness, and chest or back pain.<sup>7,8</sup> Less common reactions may include hypotension, bronchospasms, wheezing, and urticaria. Patients often exhibit more than one symptom of infusion reactions, and these symptoms are often managed by more than one intervention.<sup>9</sup>

Several trials have examined the characteristics of infliximab-related infusion reactions. One prospective open-label study monitored 113 patients who received infliximab infusions over a mean period of 60 weeks. Infusion reactions were observed during 104 (8.8%) of the 1183 infusions delivered during the treatment period. Although only a small percentage of infusions resulted in a reaction, 60 of the 113 patients (53%) experienced at least one reaction over the course of treatment.<sup>7</sup> Most reactions were mild, and all resolved within 30 minutes of the discontinuation of treatment. The rare serious reactions, characterized by chest tightness, shortness of breath, and flushing, resolved within minutes of administering IV diphenhydramine and/or methylprednisolone sodium succinate.<sup>7</sup>

Findings from this trial suggest that the risk of infusion reactions to infliximab therapy is influenced by timing but not

dose. Infusion reactions occurred most frequently during infusion 3 at week 6 (23% of infusion reactions), followed by infusion 4 at week 14 (19%). Taken together, reactions occurring during the week 6 and week 14 infusions accounted for 42% of all infusion reactions.<sup>7</sup> In addition, the frequency of infusion reactions was similar among patients who were treated with the 3-mg/kg dose (8.0%) and the 5-mg/kg dose (10.3%), suggesting that infusion reactions are not dose related.<sup>7</sup>

A second trial explored potential risk factors for infusion reactions, such as baseline antinuclear antibody (ANA) status and use of MTX, among infliximab recipients. Of 213 patients in the trial with RA, 21% developed infusion reactions. The odds ratio for experiencing infusion reactions was 2.1 for the presence of ANAs at baseline; 3.1 for administration of infliximab without MTX; 3.6 for administration of infliximab as monotherapy; and 4.6 for both the presence of ANAs at baseline and the use of infliximab without MTX.<sup>10</sup> Other predictors of infusion reactions included lower age at disease onset ( $P=0.012$ ) and longer disease duration ( $P=0.036$ ). By comparison, age, sex, C-reactive protein level, erythrocyte sedimentation rate, Health Assessment Questionnaire, and Disease Activity Score-28 at baseline were not associated with an increased prevalence of infusion reactions among RA patients treated with infliximab.<sup>10</sup> ■

## PREMEDICATION

Evidence from clinical trials of infliximab premedication is complicated. Some studies have suggested that premedication, which is given with the intent of lowering infusion-reaction risk, may instead have the opposite effect. Indeed, in some studies, infusion reactions were more common among patients who received prophylactic antihistamine pretreatment than among those who received no prophylaxis.

In one trial, pretreatment with diphenhydramine was administered to patients in 2 clinical circumstances:

1. To all patients before infusions 3 and 4, due to the higher risk of reactions during these infusions
2. To any patient with a history of infusion reactions regardless of the infusion number

Infusion reactions were observed in 13.2% of pretreated patients, compared with 7.5% of patients who were not pretreated ( $P<0.05$ ).<sup>7</sup> This trial illustrated the difficulty of attributing excess infusion reactions to the infusion medication, the infusion number, the infusion patient, or the premedication itself. By definition, pretreatment was provided only during higher-risk infusions or to higher-risk patients. Moreover, the bulk of reactions among pretreated patients included pruritus, flushing, hypotension, and headache, which, as the study authors noted, are all known side effects of antihistamines.<sup>7</sup>

In a phase 4 trial examining the utility of betamethasone vs placebo pretreatment in patients with RA, infusion reactions developed in <5% of 840 infliximab infusions delivered to 355 patients. However, more patients in the corticosteroid pretreatment group (16.8%) than in the placebo pretreatment group (10.2%) developed reactions during infliximab infusion. According to the study authors, the increased risk associated with betamethasone pretreatment was most likely due to infusion reactions caused by the pretreatment itself. On the basis of these findings, the authors recommended against the use of betamethasone as a systemic pretreatment before infusions with infliximab.<sup>6</sup>

Beyond premedication, concurrent therapy may also influence the risk of infusion reactions. To characterize the features of immediate-type infusion reactions, investigators evaluated data from 639 patients who were treated with infliximab

at a large university hospital during a 5-year period. In this group of patients, approximately half ( $n=323$ ) were taking daily oral low-dose glucocorticoids at baseline (median dose, 5 mg/day). Those taking low-dose glucocorticoids had a lower risk of infusion reaction (4.6%) compared with those who were not on daily steroid therapy (8.6%;  $P=0.057$ ), suggesting that daily low-dose oral prednisolone may provide protection from infliximab infusion reactions.<sup>9</sup>

Nurses must also remain mindful of the black box warning for rituximab, which notes an increased risk of infection (bacterial sepsis, tuberculosis, invasive fungal and other opportunistic infections) in all patients and hepatosplenic T-cell lymphoma in patients with Crohn's disease. ■

### ABATACEPT

Abatacept, an inhibitor of T-cell activation, is indicated for the treatment of moderately to severely active RA in adults. It is supplied in 250-mg vials, and weight-based dosing is used to approximate an overall dose of 10 mg/kg (2 vials for patients <60 kg [ $<132$  pounds]; 3 vials for patients 60–100 kg [132–220 pounds]; and 4 vials for patients >100 kg [ $>220$  pounds]). Abatacept is administered as a 30-minute IV infusion at weeks 0, 2, and 4, and every 4 weeks thereafter.<sup>11</sup> Abatacept does not require premedication, but institutions may include premedication in their administration protocols.

In the major efficacy trials of abatacept, infusion reactions occurred in approximately 9% of abatacept recipients, compared with 6% of patients receiving placebo.<sup>11</sup> Dizziness, headache, and hypertension were the most common infusion reactions reported.

In the ASSURE (Abatacept Study of Safety in Use With Other RA Therapies) trial, which was designed specifically to examine the safety of abatacept, infusion reactions occurred more commonly in the arm

receiving abatacept in addition to a second biologic agent than placebo.<sup>12</sup> ASSURE enrolled 1231 patients with active RA who completed 1 year of abatacept treatment added to a background of treatment with at least one traditional nonbiologic and/or biologic disease-modifying antirheumatic drug (DMARD).<sup>12</sup> The safety analysis defined acute infusion-related events as those that started within 1 hour of the infusion; peri-infusional events were defined as any event that occurred within 24 hours of the start of infusion. According to these definitions, there was a nonsignificant trend toward higher event rates in the abatacept group compared with placebo for both acute reactions (10.0% vs 7.1%) and peri-infusional reactions (24.3% vs 20.3%). However, these reactions led to discontinuation of treatment in only 0.6% of patients receiving abatacept and 0.2% receiving placebo.<sup>12</sup> ■

### RITUXIMAB

Rituximab is a chimeric monoclonal antibody that selectively depletes CD20+ B cells and activates complement-dependent cytotoxicity. It was approved in March 2006 for the treatment of moderately to severely active RA in patients on concomitant MTX who have failed therapy with at least one TNF inhibitor. Rituximab improves symptoms and slows the progression of structural damage in patients with RA, even for those patients who have not responded to previous nonbiologic and biologic therapies.<sup>13</sup>

Roughly one-third (32%) of patients develop infusion reactions within 24 hours of initial treatment with rituximab. The majority of these reactions are mild to moderate in severity and do not require cessation of therapy. The risk of an infusion reaction drops to 11% with the second infusion. Concomitant administration of IV steroids lessens the risk of infusion reactions and is therefore recommended for all rituximab infusions. In a 2007 consensus statement on the use of rituximab in patients with RA, 100 mg methylprednisolone was suggested for

premedication before the first rituximab infusion. Antihistamine premedication was also recommended.<sup>14</sup> This recommendation applies to re-treatment courses as well.

Infusion reactions during treatment with rituximab are usually mild to moderate and may manifest as hypertension, nausea, rash, fever, pruritus, and urticaria. Reactions can be successfully managed with acetaminophen, antihistamines, bronchodilators, and/or glucocorticoids, and seldom lead to withdrawal of treatment. Severe reactions are rare in patients with RA but are more commonly seen in patients with non-Hodgkin lymphoma. Accordingly, a black box warning is included on rituximab labeling that indicates a danger of fatal infusion reactions, tumor lysis syndrome, severe mucocutaneous reactions, and progressive multifocal leukoencephalopathy resulting in death.<sup>13,14</sup> ■

## *Injectable* **BIOLOGICS**

*Three biologics are currently available for self-administration via subcutaneous injection—etanercept, adalimumab, and anakinra (Table 4). For each of these, injection-site reactions (ISRs) are a common adverse event associated with therapy. However, ISRs tend to be mild, resolve with no or minimal treatment, and rarely interfere with future therapy.*

### *Etanercept*

Etanercept is a synthetic, fully human, soluble TNF receptor that binds to circulating TNF, thereby preventing the activation of TNF receptors on the surface



of target cells. It is indicated for reducing signs and symptoms of RA, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA. The recommended dose of etanercept is 50 mg per week, which can be delivered using an autoinjector or a single-use prefilled syringe. Etanercept can be used alone or in combination with MTX.<sup>1</sup> A black box warning was added in March 2008 noting a risk of serious infection (bacterial sepsis and tuberculosis) during and after treatment with etanercept.

Etanercept-related ISRs have been reported in up to 42% of patients. In a randomized trial of etanercept combined with MTX vs MTX alone in 89 patients with persistent RA despite previous use of MTX, ISRs were the only adverse events that occurred more frequently in the etanercept-plus-MTX group (42% vs 7%;  $P < 0.001$ ). In these patients, all ISRs were mild, characterized by erythema with or without itching, pain, or swelling. Most resolved without treatment within a median of 3 days of the injection, and no ISR necessitated discontinuation of etanercept treatment.

Importantly, the development of ISRs did not adversely affect the clinical benefits of etanercept. Among etanercept recipients, a similar proportion of patients who did (72%) and did not (71%) develop ISRs met the American College of Rheumatology 20 criteria by the end of the 24-week trial.<sup>2</sup>

ISRs associated with etanercept therapy are characterized by 2 distinctive features:

1. They tend to diminish in frequency over time
2. They may develop at previous injection sites (a phenomenon called *recall ISR*)

The likelihood of developing ISRs during treatment with etanercept does not appear to be substantially influenced by dose. In one randomized trial, 234 patients received twice-weekly subcutaneous injections of etanercept 10 mg, etanercept 25 mg, or placebo for 6 months. ISRs developed in 49% of the 25-mg etanercept group and 43% of the 10-mg etanercept group compared with 13% of the placebo group ( $P < 0.001$  for both groups). ISRs developed most frequently within the first month of therapy and tapered in occurrence over subsequent months.<sup>3</sup> ■

### Adalimumab

Adalimumab, a recombinant human IgG1 monoclonal antibody against TNF, is indicated for the treatment of moderately to severely active RA in adult patients who have had an inadequate response to one or more DMARDs. This TNF inhibitor is self-administered with a subcutaneous injection at a dose of 40 mg every 2 weeks.<sup>4</sup> A black box warning notes a risk of tuberculosis in patients receiving adalimumab.

Up to 20% of patients receiving adalimumab injections develop ISRs vs 14% of placebo recipients enrolled in adalimumab trials. Most adalimumab-related ISRs are mild and do not require drug discontinuation.<sup>4</sup>

In ARMADA (Anti-Tumor Necrosis Factor Research Study Program of the Monoclonal Antibody Adalimumab [D2E7] in Rheumatoid Arthritis), 15.3% of the patients in the adalimumab group and 3.2% in the placebo group developed ISRs. In these patients, ISRs were mostly mild or moderate and manifested as pain, erythema, localized rash, and hemorrhage at the injection site.<sup>5</sup>

ISRs occurred at a similar rate during the STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis) trial. In STAR, 636 adult patients with RA were randomly assigned to treatment with adalimumab 40 mg subcutaneously every 2 weeks or placebo while continuing standard antirheumatic therapy. During the trial, 19.5% of patients in the adalimumab group and 11.6% of patients in the placebo group reported ISRs, which were defined as erythema and/or itching, hemorrhage, pain, or swelling. Of these, injection-site pain was the most common symptom in both the adalimumab (11.3%) and placebo (10.7%) groups.<sup>6</sup> ■

### Anakinra

Anakinra is a humanized recombinant IL-1 receptor antagonist that blocks the activity of IL-1 in synovial joints. This

self-injectable biologic is indicated for slowing the progression of structural damage in adult patients with moderately to severely active RA who have failed one or more DMARDs. Anakinra is administered once daily via a 100-mg subcutaneous injection and can be used alone or in combination with DMARDs other than TNF inhibitors.<sup>7</sup>

The majority of patients—up to 80%—develop ISRs over the course of treatment with anakinra. ISRs are typically mild and may include redness, swelling, and pain that lasts for up to 28 days. Patients who are going to develop ISRs usually develop them early in treatment; ISRs rarely occur after the first month of therapy in patients who have not previously developed them.<sup>7</sup> ■

**TABLE 4**  
*Subcutaneous Injectable Biologic Response Modifiers*

Agent	Mechanism of Action	Primary Indications	Dose	Common Side Effects
Etanercept	Recombinant monoclonal antibody that binds to TNF receptors and blocks inflammatory and immune responses	Improves signs and symptoms of RA with or without MTX, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis, and juvenile idiopathic arthritis	50 mg once weekly or 25 mg twice weekly	Injection-site reaction, infection, autoantibodies, headache, nausea
Adalimumab	Recombinant monoclonal antibody that binds to TNF- $\alpha$ , which in turn antagonizes pathologic pain and joint destruction	Treatment of moderate-to-severe RA after lack of response to one or more DMARDs	40 mg every other week; if not taking MTX, may increase to up to 40 mg weekly	Headache, rash, injection-site reaction, upper respiratory tract infection
Anakinra	Binds to the IL-1 receptor and reduces degradation of cartilage and bone resorption	Improves signs and symptoms of ankylosing spondylitis, Crohn's disease, psoriatic arthritis, RA, ulcerative colitis	100 mg once daily	Headache, injection-site reaction, infection, nausea, diarrhea, WBCs decreased

DMARD=disease-modifying antirheumatic drug, IL=interleukin, MTX=methotrexate, TNF=tumor necrosis factor, WBC=white blood cell.

**TABLE 5**  
*Investigational Biologic Response Modifiers*

	Drug Class	Mechanism of Action	Route of Administration
Tocilizumab	Interleukin modulator	IL-6 inhibitor	IV
Certolizumab pegol	Monoclonal antibody	TNF inhibitor	SC
Golimumab	Monoclonal antibody (fully human)	TNF inhibitor	SC/IV
Ocrelizumab	Monoclonal antibody	CD20 inhibitor	IV
Ofatumumab	Monoclonal antibody (fully human)	CD20 inhibitor	IV

IL-6=interleukin-6, IV=intravenous, SC=subcutaneous, TNF=tumor necrosis factor.

## CONCLUSION

With the increasing use of infusion-based therapies, rheumatology nurses play a critical role in ensuring the safe administration of biologics and eliciting maximum responses to RA therapy. In addition to participating in treatment planning, nurses screen patients, prepare and start infusions, monitor clinical stability, and manage infusion-related adverse events.<sup>2</sup>

Nurses also play an important role in patient education. Patients value and trust the information provided to them by nurses and other healthcare professionals. Therefore, it is extremely important for nurses to remain up-to-date on current information and apply appropriate educational principles to all infusion patients. Patients must realize that RA is a permanent chronic disease and that the best outcomes result from suppression of inflammation, which results from ongoing treatment and evaluation. Patients need to be reminded to stay on their medication even when they feel better.

For patients with RA, biologic agents slow joint destruction, improve physical functioning, and relieve the signs and symptoms of this potentially debilitating disease. When patients understand that infusion-related adverse events are typically infrequent, mild, and easily managed without disruption of therapy, they often desire to continue treatment in order to gain the benefits of biologics.<sup>3</sup> Delivered by a rheumatology nurse, patient education is essential for maximizing patient compliance and improving clinical outcomes.

Several new biologic therapies are in late-stage development for the treatment of RA, including agents that are administered via subcutaneous injection or IV infusion (Table 5). As new biologics become available for clinical use, the rheumatology nurse will continue to play a prominent role in the safe and effective care of patients with RA. ■

# Prevention & Management of ISRs

ISRs are a nearly inescapable part of long-term therapy with subcutaneous biologics.<sup>8</sup> However, proper injection technique can curb their frequency, and vigilant screening can facilitate their treatment.<sup>9</sup> Once again, the role of the rheumatology nurse—as the teacher of self-injection hygiene, post-injection ISR screening, and self-care of ISRs—is critical to the success of subcutaneous biologic therapy.

In a systematic review of safety data from 18 clinical trials, ISRs were much more common among patients treated with anakinra (67.2%) than among those receiving adalimumab (17.5%) or etanercept (22.4%).<sup>8</sup> Regardless of the biologic administered, however, several general techniques can help to minimize the occurrence and/or severity of ISRs.<sup>10</sup> Therefore, patients should understand and implement the following strategies:

- Allow medicine to warm to room temperature before injection
- Remove air bubbles from the syringe before injection
- Apply topical alcohol to the injection area before injection
- Allow the topical alcohol to dry before injecting
- Relax muscles in the injection area
- Break through the skin quickly
- Do not change the direction of the needle as it enters or leaves the injection site
- Do not reuse disposable needles
- Do not use medications, including prefilled syringes and self-injectors, that have expired
- Rotate injection sites on the body from one injection to the next
- Choose injection sites that are known to be less painful than others, including the front of the thighs, the outer upper arms, and the abdomen at least 2 inches away from the navel
- Avoid administering a new injection at the site of an active ISR

Most ISRs resolve without treatment within several days post-injection. ISRs that cause discomfort may be treated with cold compresses, topical corticosteroids, oral antihistamines, or acetaminophen. Interrupting or discontinuing treatment because of ISRs is rarely necessary.<sup>10</sup> ■

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# CASE STUDY

*Charles R. is a 54-year-old man who presents after 6 months of worsening joint pain, primarily in his hands and feet.*

Despite treatment with over-the-counter NSAIDs recommended by his primary care physician, Charles is having difficulty with the physical demands of his job in an electronics warehouse. Upon evaluation with a 28 joint-count exam, Charles has 22 tender and 10 swollen joints. Results of an x-ray are negative for erosion.

Charles' laboratory results indicate the following:

- CBC: Mild anemia (HCT=31%)
- CMP: Normal chemistry
- CRP: 2.3 mL/dL (normal=0–0.5 mL/dL)
- ESR: 52 mm/h (normal <20 mm/h)
- RF: 120 IU/mL (normal <20 IU/mL)
- Anti-CCP antibodies: 2100 EU (strongly positive)

After being diagnosed with RA, Charles begins treatment with methotrexate (15 mg/d) and prednisone (10 mg/d). Additionally, the rheumatology nurse writes a note to Charles' supervisor recommending that he be placed on light duty.

One month later, Charles self-reports a 50% improvement in symptoms. However, results of his 28 joint-count exam are unchanged, and his laboratory

results show persistent elevation of inflammatory markers. According to his treatment plan, Charles plans to taper off of prednisone during the next 2 months.

When he returns to the office after this tapering-off period, Charles reports deteriorating symptoms, telling the nurse, "I feel worse now than when I first came here." Upon examination, 26 of 28 joints are tender, and 20 of 28 are swollen. The rheumatologist prescribes treatment with etanercept, a TNF inhibitor. Although Charles initially expresses anxiety about self-administering treatment, he is much more relaxed after successfully giving himself the first injection during his office visit.

Four weeks after his initial injection, Charles calls the nurse and expresses concern that he is developing an allergy to etanercept. He is particularly concerned that he may have to stop treatment "just when it was starting to work."

When prompted about specific signs and symptoms, Charles explains that he has developed an area of redness and swelling approximately 4 inches wide that spans the entire injection site. The area is warm and itchy but not painful, and he has no systemic symptoms such as angioedema or throat irritation. ■

**QUESTIONS:** While providing injection teaching, what information, if any, would you tell Charles regarding possible injection-site reactions? How would you deliver any necessary education? What might you suspect is causing the reaction? What specific guidance would you provide for Charles to alleviate his symptoms related to the injection-site reaction?

**Kori Dewing:** The most common side effect associated with injectable anti-TNF agents is an injection-site reaction. In clinical trials of etanercept, injection-site reactions occurred in 37% of patients.<sup>1</sup> Most injection-site reactions occur shortly after a patient has started therapy and dissipate over time. Patients should be instructed, however, to inform their provider if skin reactions become more frequent or serious.

Common injection-site reactions include redness and tenderness at the point of injection. There may also be warmth, swelling, or itching. These symptoms typically improve and disappear within a few days of the injection.

Nurses should be aware that an injection-site reaction **is not** the same as a true allergic reaction, which can cause a rash throughout the body, swelling of the lips or tongue, and/or difficulty breathing. Although injection-site reactions are common, only rarely do they require a change in therapy. Because patients always have questions after learning how to give a self-injection, I encourage them to sign up for patient-support programs provided by pharmaceutical companies so that they have access to a knowledgeable nurse by phone any time or day of the week.

Because most minor injection-site reactions lessen in severity and usually disappear over time, I would encourage Charles to continue with his current treatment regimen. That said, there are little tricks I would review with Charles that may help reduce pain and potential local reactions. For starters, I would tell him that medication should be warmed to room temperature before administration. While the medication is warming, I would suggest icing the injection site to help reduce the pain of the injection. If Charles is using a prefilled syringe, it may help to inject the medication slowly. Sometimes, pretreatment with acetaminophen or an antihistamine may also be useful. ■

1. Enbrel [package insert]. Thousand Oaks, CA: Amgen and Wyeth Pharmaceuticals; 2006.

Name \_\_\_\_\_

## LEARNING ASSESSMENT

# Request for Credit & Evaluation Form

### *Activity Instructions & Criteria for Success*

Complimentary CE credit is offered to all activity participants. To successfully complete this activity and obtain a Statement of Credit, the learner is required to read the entire newsletter, complete the learning assessment, and complete the activity evaluation form. Once your documentation has been completed, **please submit your forms via fax to 215-592-9085**. Learners are required to correctly answer 80% of the post-test questions. Statements of Credit will be forwarded via regular mail within 4 to 6 weeks. All forms must be received by June 30, 2010 to be eligible for continuing-education credit.

### *Activity Post-Test Questions: (Please circle the letter that matches the correct response to each question below)*

1. Which of the following is not considered to be a possible advantage of early administration of a biologic in the treatment of RA?
  - a. Less radiographic damage
  - b. Fewer side effects
  - c. Earlier functional improvement
  - d. Greater reductions in disease activity
2. What specific advice should be given to patients being premedicated with diphenhydramine?
  - a. Do not eat within 12 hours of your infusion
  - b. Bring an extra layer of clothing for warmth after your infusion
  - c. Drink at least 2 glasses of water the morning of your infusion
  - d. Make sure someone is available to drive you home after your infusion
3. Which of the following statements is true regarding methylprednisolone sodium?
  - a. It is frequently used during infusion reactions that are acute and result in symptoms such as throat swelling and angioedema
  - b. It reduces mild-to-moderate pain and reduces fever
  - c. It is an antianxiety medication with smooth muscle relaxation properties
  - d. Its use may cause dry mouth, sedation, flushing, hypotension, and headache
4. Which of the following FDA-approved infusible biologics are TNF inhibitors?
  - a. Infliximab and rituximab
  - b. Rituximab and abatacept
  - c. Infliximab only
  - d. Infliximab and abatacept
5. Which of the following steps may be taken in patients who have an incomplete initial response to infliximab?
  - a. Increase the frequency of administration
  - b. Increase the dose
  - c. Both A and B
  - d. Neither A nor B
6. A 48-year-old patient is about to receive his first infusion of rituximab. Which would be the most appropriate premedication to give him before his infusion?
  - a. Acetaminophen
  - b. Diphenhydramine
  - c. Methylprednisolone
  - d. Betamethasone
7. According to published literature, injection-site reactions are most common with the use of which of the following subcutaneous biologics?
  - a. Anakinra
  - b. Etanercept
  - c. Adalimumab
  - d. The prevalence of injection-site reactions is similar for all 3 of these subcutaneous biologic response modifiers
8. Patients who have an injection-site reaction to one medication should always be immediately switched to a different medication.
  - a. True
  - b. False
9. How frequently do anaphylactic reactions occur during biologic infusions?
  - a. >5% of the time
  - b. 3%–4% of the time
  - c. 1%–2% of the time
  - d. <1% of the time
10. A 37-year-old patient with RA complains of aches and has a temperature of 103 degrees 15 minutes after the start of his first infusion of abatacept. Which medication would be most appropriate to administer to ameliorate his symptoms?
  - a. Acetaminophen
  - b. Diphenhydramine
  - c. Albuterol
  - d. Epinephrine

The learning objectives designed for this activity (listed below), can help me strive toward:

1=Significant improvement, 2=Moderate improvement, 3=Reinforcement of my current practices, 4=Learning objective was not met in this activity	Significant Improvement	Moderate Improvement	Reinforcement	Not Met
1. Describe the mechanisms of action of the infusible and injectable biologics that have been approved by the US Food and Drug Administration for the treatment of RA	1	2	3	4
2. List the primary pros and cons of infusion therapy for the treatment of RA	1	2	3	4
3. Identify common adverse events faced by patients who receive infusible biologics for RA	1	2	3	4

Please indicate the extent of your agreement with the following statements:	Strongly Disagree		Not Sure		Strongly Agree	
	1	2	3	4	5	6
1. The information presented in this newsletter was pertinent to my professional needs	1	2	3	4	5	6
2. The information presented was current	1	2	3	4	5	6
3. The information was presented in a fair and balanced manner, and examined with scientific rigor	1	2	3	4	5	6
4. The newsletter was well organized	1	2	3	4	5	6
5. The content of this newsletter contributes valuable information that will assist me in improving patient outcomes	1	2	3	4	5	6
6. Based on my experience, I would recommend future newsletters to my colleagues	1	2	3	4	5	6
7. Were you able to locate information about faculty disclosure at the beginning of the newsletter?	Yes			No		
8. Did you perceive any bias or commercial influence in the newsletter? If "YES," please describe further: _____	Yes			No		
9. As a result of reading this newsletter, I intend to assist in implementing change at my facility. If "YES," please explain: _____	Yes			No		

10. The following is the primary barrier to implementing change at my facility:
- a. Lack of knowledge regarding evidence-based strategies
  - b. Misperceptions of or negative attitudes about research and evidence-based care
  - c. Demanding patient workloads
  - d. Fears about practicing differently from peers
11. Based upon the information presented in this educational activity, which of the following statements best reflects your understanding of RA?
- a. I have learned everything I need to learn about RA
  - b. I would like to learn more about RA

Please check all that apply:

I am a/an  RN  NP  CNS  CRNA  CNM  RA Nurse  Infusion Nurse  Other \_\_\_\_\_

Name \_\_\_\_\_

Address \_\_\_\_\_ City, State, ZIP \_\_\_\_\_

E-mail \_\_\_\_\_

To help us better plan for education in this area, and to invite you to participate in future educational development, we may contact you for your expertise, a possible future faculty invitation, or for further outcomes reports. If we MAY NOT contact you, please check here: \_\_\_\_\_

I certify that I have participated in the above-named continuing-education activity.

Signature \_\_\_\_\_ Date \_\_\_\_\_

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KORI ANNE DEWING



**1.** *Why did you initially choose to specialize in RA?*

It was serendipitous. My mother was diagnosed with RA when I was young, and I grew up in a household affected by this disease. During nursing training, I was drawn toward patient education. When I graduated, a colleague steered me toward a job opening at our clinic, and the rest is history! Working in rheumatology allows me to focus on my patient education skills, helping people with RA take better care of themselves.

**2.** *Where have you improved most professionally as it relates to patient care since you began your nursing career?*

My first degree was in biology. Back then, 15 to 20 years ago, not a single class of mine covered the immune system. Since then, with the HIV/AIDS crisis and drug-resistant superbugs, there is much more research and understanding of the immune system. In rheumatology, there has been an explosion of new therapies targeting specific aspects of the immune system. As a result, my understanding of the complexity of immunology has increased.

**3.** *Besides a regular paycheck, what keeps you motivated as a nursing professional?*

The relationships I build with my patients and the "thank yous" I receive.

**4.** *What do you enjoy most about your job?*

My job is intellectually challenging as well as emotionally rewarding.

**5.** *What is the biggest frustration about your job?*

Social inequalities. I get very frustrated when patients have insufficient insurance coverage and cannot afford medications they need to help halt progression of disease.

**6.** *Can you recall a particularly rewarding patient interaction that occurred in the last 12 months?*

Just last month, I had a new RA patient referred to our clinic after he had been suffering for several months and was no longer able to work. He was tired, withdrawn, and had significant trouble moving about. I remember how his eyes lit up when I told him I expected him to be able to feel much better and return to work soon. At our next visit, I hardly recognized him! He was smiling and had returned to work as I predicted.

**7.** *What makes you hopeful about significant improvements to the overall treatment of patients with RA in the next 5 years?*

There have been significant improvements in the treatment of RA with the identification and subsequent targeting of specific inflammatory cytokines and mediators.

**8.** *Why would you tell a graduating nursing student to consider specializing in caring for rheumatology patients?*

There is a huge need for nurses to join the rheumatology specialty. It is projected that there will be a rheumatologist shortage in the next 10 years. Nurses can make a huge difference in the lives of patients with RA.

**9.** *In what area do you find that the majority of new nursing graduates specifically need to develop their skills?*

I think it is difficult for all nurses to articulate difficult scientific concepts in a language that patients can understand and appreciate. This helps patients understand how medications work and the risks associated with treatment.

**10.** *What is the single biggest thing you wish the general public understood about your job?*

There is still a lot of misconception by the general public and even physicians about the training and role of a nurse practitioner in rheumatology.

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