

Improvement in Safety Monitoring of Biologic Response Modifiers After the Implementation of Clinical Care Guidelines by a Specialty Pharmacy Service in an Academic Health System

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ABSTRACT

BACKGROUND: Tumor necrosis factor (TNF)-alpha inhibitors and other biologic response modifiers (BRMs) are frequently used to treat a variety of inflammatory diseases. Use of these agents may increase risk of serious infections, malignancies, and other complications such as worsening symptoms of heart failure or demyelinating disease. Because of these risks, a baseline assessment and routine monitoring have been recommended, but standardized guidelines for monitoring have yet to be established.

OBJECTIVE: To measure the compliance with the recommended safety monitoring in the Clinical Care Guidelines for BRMs at the University of Illinois Hospitals and Health Sciences System (UI Health).

METHODS: The Clinical Care Guidelines for BRMs was developed by a committee of pharmacists, nurses, and physicians based on an assessment of published literature and medication labeling. The guidelines included recommendations for safety monitoring prior to BRM therapy, such as the tuberculosis (TB) test, Hepatitis B surface Antigen (HBsAg) test, liver function test (LFT), complete blood count (CBC), up-to-date vaccinations, risk assessment for cancer, pregnancy testing, monitoring for contraindications with concomitant medications, concomitant disease state risk assessment, and patient education. The guidelines were introduced to UI Health in February 2012 by a systemwide email and by in-services given by the health system's Specialty Pharmacy Service. In-services were given in the clinics known to generate large numbers of BRM orders (e.g., gastroenterology and rheumatology) and at the outpatient center for infused therapies. The purpose of the in-services was to introduce providers to the guidelines and encourage their compliance. To ensure that guideline requirements were met when BRMs were ordered, a process was established to identify BRM orders, assess the orders for compliance with 4 of the safety monitoring tests from the guidelines (TB, HBsAg, LFT, and CBC), and make interventions. When necessary, Specialty Pharmacy Services coordinated with the pharmacists and other providers in the clinic to order lab tests and ensure they were completed prior to the start of therapy. Feedback was provided during the study to proactively improve compliance with the guidelines. After completion of the study, a report containing outpatient prescription orders for BRMs (abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab, and tocilizumab) from August 2011 through July 2012 was generated from the electronic medical record. Retrospective analyses of completion of safety monitoring were conducted for patients administered BRM treatment. Completion rates were compared before and after implementation of guidelines in February 2012. Completion was considered to have occurred when all 4 safety monitoring tests had been conducted—TB (unless known to be positive from a previous test), HBsAg, LFT, and CBC. Completion data from August 2011 through January 2012 were before the guidelines were implemented, and data from February 2012 through July 2012 were after the guidelines. Chi square analyses were performed on completion frequencies in the patients before and after the guidelines were implemented.

RESULTS: Of the 320 unique patient BRM orders evaluated in this study, 195 (61%) were generated in the Rheumatology clinic, 99 (31%) in the Gastroenterology clinic, 21 (6.5%) in the Dermatology clinic, and 5 (1.5%) in the Transplant clinic. Before the guidelines were implemented, 54 (31%) of 173 patient orders complied with the safety monitoring by having all 4 clinical tests performed at the appropriate time points. After guideline implementation, 88 (60%) of 147 patient orders were compliant and had all 4 clinical tests conducted, which represents a statistically significant improvement in the rate of compliance (Pearson chi square = 26.43, degrees of freedom (df) = 1, $P < 0.0001$). This significant improvement in compliance rates after guideline implementation was observed in both the new patient group and the patients with continuing prescription orders/treatment changes. There was also an improvement in patients whose prescriptions were dispensed by UI Health and to a lesser degree those whose prescriptions were dispensed by an outside pharmacy. When the new patient group was analyzed separately ($n = 92$), 50 patients were treated before the guidelines were implemented, and 42 patients were treated after the guidelines were implemented. Compliance rates with safety monitoring in these 2 groups were 52% pre-implementation and 83% post-implementation, which represented a statistically significant improvement in compliance (Pearson chi square = 10.03, $df = 1$, $P = 0.0015$). Similar results were observed in the second patient subgroup with continuing prescription orders/treatment change ($n = 228$). A total of 123 patients were treated before the guidelines were implemented, and 105 were treated after the guidelines were implemented. Compliance rates were 23% pre-implementation compared with 50% post-implementation, which represented a statistically significant improvement in compliance (Pearson chi square = 18.99, $df = 1$, $P < 0.0001$).

CONCLUSION: Given the widespread and long-term use of BRMs, safety monitoring and management should be an important part of a comprehensive medication management program for their use. A coordinated effort may have a significant impact on compliance with safety monitoring guidelines.

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What is already known about this subject

- Anti-tumor necrosis factor (TNF)-alpha agents, along with other biologic response modifying (BRM) drugs such as T-cell co-stimulation blockers, interleukin-6 receptor antagonists, and B-lymphocyte stimulators, are used in the treatment of many inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. TNF-alpha specifically is a key therapeutic target, and many TNF-alpha inhibitors are currently approved for use and are prescribed by specialty clinics such as rheumatology, dermatology, and gastroenterology, with an increasing frequency and for longer duration of use.

What is already known about this subject (continued)

- Due to their immune suppressive properties, anti-TNF-alpha agents have been implicated in increasing the risk of certain types of malignancies, infections, and other complications that have resulted in boxed warnings. Serious warnings include the potential for reactivation of tuberculosis (TB) or hepatitis B and risk of liver injury and lymphoma.
- There are safety recommendations in the literature for screening and monitoring with the use of these medications, including testing for TB and hepatitis B prior to initiation as well as periodic complete blood count (CBC) and liver function test (LFT) monitoring.

What this study adds

- To the authors' knowledge, this is the first study that measured compliance with safety guidelines for BRMs. This study then looked at pre- and post-implementation compliance rates to see if a specialty pharmacy service had an impact on the health system's adherence to the guidelines.
- The data from this retrospective study indicated that the rate of compliance with safety monitoring was improved in the entire patient sample after guidelines were implemented but were most strikingly improved in the new patients. This study indicated that safety monitoring improved dramatically when Specialty Pharmacy Services took a proactive role in managing compliance with standard guidelines.
- Although the effect on outcomes is a subject of further research, this study improved the likelihood of safe use of BRMs at a health system.

Tumor necrosis factor (TNF)-alpha is an integral pro-inflammatory cytokine that is responsible for modulating intracellular pathogens and granuloma formation.^{1,2} TNF-alpha is predominantly produced by macrophages and promotes the release of other inflammatory cytokines. TNF-alpha is critical in immune defense against infections and contributes to the development of certain cancers.^{2,3} Because of the role of TNF-alpha in inflammation, it has been identified as a key therapeutic target for treating inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis, and inflammatory bowel disease.³ Multiple TNF-alpha agents, such as adalimumab (Humira, Abbott), etanercept (Enbrel, Amgen), infliximab (Remicade, Janssen), certolizumab (Cimzia, UCB), and golimumab (Simponi, Janssen), have been approved by the U.S. Food and Drug Administration (FDA) to manage and treat several immunological conditions.⁴⁻⁸

The use of anti-TNF-alpha agents increases the risk of serious infections, including reactivation of tuberculosis (TB) and viral hepatitis B, requiring black box warnings because of significant increased risk of morbidity and mortality.^{4,9-12} TNF-alpha is vital for granuloma formation, and anti-TNF-alpha agents can reactivate latent TB, a granulomatous disease.¹³ The mechanism by which viral hepatitis B is reactivated with anti-TNF-alpha agents is not well understood. Abnormal liver function can also occur during treatment and may result in cholestatic disease and hepatitis. Most studies recommend discontinuing treatment if alanine aminotransferases exceeds 5 times the upper limit of normal or if jaundice develops.^{11,14} Inhibition of TNF-alpha is suspected to increase the risk of malignancy, specifically lymphoma, although several meta-analyses and systemic reviews have failed to find consistent evidence supporting this conclusion.^{3,9,15,16} Furthermore, new onset or worsening symptoms of congestive heart failure (CHF) have been reported as well as a decline in control of demyelinating diseases such as multiple sclerosis (MS).^{4,6,10,12} Although not designated as a black box warning, the presence of conditions such as CHF or MS should prompt an evaluation of risk of use versus possible benefits, and anti-TNF-alpha agents should be used with caution.

Due to the severity of identified risks associated with anti-TNF-alpha agents, several tests are recommended before and during treatment. A test for TB is required prior to initiating treatment and annually thereafter. TB testing may include a tuberculin skin test (TST), QuantiFERON-TB Gold blood test, and/or chest x-ray to rule out infection. Treatment of the infection is indicated after a positive result from a TB test is discovered.¹¹ Hepatitis B viral status should be assessed prior to initiation of treatment and monitored or possibly treated in patients who are hepatitis B positive.^{11,13,17,18} Liver function tests (LFT) and complete blood counts (CBC) are recommended prior to initiation and every 3 months or as frequently as the prescriber deems necessary during the course of therapy. This monitoring is performed to assess for opportunistic infections, malignancies, and liver abnormalities.^{18,19} The appropriate frequency and duration of LFT and CBC monitoring for patients on long-term treatment are unclear. It is also recommended that all patients started on anti-TNF-alpha agents are up to date on routine vaccinations prior to treatment initiation, with live vaccines administered no less than 4 weeks prior to initiation.²⁰⁻²² Along with T-cell co-stimulation blockers, interleukin-6-receptor antagonists, and B-lymphocyte stimulators, anti-TNF-alpha agents are categorized as biologic response modifiers (BRMs).²³⁻²⁵ Other BRMs share similar recommendations for screening and ongoing monitoring. Of the BRMs prescribed at the institution featured in this study, 93% were categorized as anti-TNF-alpha agents and, so, are the focus of this study.

Development of Clinical Care Guidelines for BRMs

This study was conducted at the University of Illinois Hospitals and Health Sciences System (UI Health), located in Chicago. UI Health includes a 495-bed hospital, an outpatient facility, specialty clinics, and seven health science colleges, including the University of Illinois at Chicago College of Pharmacy. UI Health serves a diverse population, predominantly African American (50.7%) and Hispanic (11.6%), with an outpatient insurance coverage of 42.6% government payer and 49.1% private insurance. Specialty Pharmacy Services, a division of the Ambulatory Care Pharmacy Department, was established in 2012 to provide coordinated, comprehensive care to patients treated with specialty pharmaceuticals or biologics, such as anti-TNF-alpha agents. The Specialty Pharmacy Services team consists of an assistant director, a clinical staff pharmacist, a clinical liaison pharmacist, a prior authorization technician, a pharmacy clerkship student, and several independent study pharmacy students. Some of the service's responsibilities include investigation of pharmacy coverage benefits, patient education on specialty medications, in-clinic training on self-injectable medications, coordinating start of therapy with the prescribing physician, refill management, and safety monitoring.

The Clinical Care Guidelines for BRMs was developed by a committee of pharmacists, nurses, and physicians at UI Health, based on an assessment of published literature and medication labeling.^{4-8,11,14,17,18,20-27} The guidelines were introduced to the health system in February 2012. The goal of the guidelines was to reinforce safety monitoring recommendations by assisting providers with clinical decisions for specific BRMs by implementing standardized monitoring and screening criteria. The guidelines provided recommendations for initiation of therapy and continuing therapy. In these guidelines, recommendations for safety monitoring prior to BRM therapy included infection risk assessment, TB tests, Hepatitis B surface Antigen (HBsAg) test, LFT, CBC, up-to-date vaccinations, risk assessment for cancer, pregnancy testing, monitoring for contraindications with concomitant medications, concomitant disease state risk assessment, and patient education. A detailed checklist for anti-TNF-alpha agents is shown in Figure 1, and the complete text of the BRM Clinical Care Guidelines is in the Appendix.

Study Objective

The objective of this study was to measure the compliance with the recommended safety monitoring in the Clinical Care Guidelines for BRMs at UI Health. A retrospective cohort of patients who were prescribed BRMs before and after implementation of the guidelines were studied by measuring the completion rates of safety monitoring.

Methods

Implementation of Clinical Care Guidelines

The Clinical Care Guidelines for BRMs was introduced to the health system via a systemwide email and in-services in the clinics known to generate large numbers of BRM orders, particularly gastroenterology, rheumatology, and the outpatient center for infused therapies. To ensure that guideline requirements were met when BRMs were ordered, the process outlined in the following paragraph was established to identify BRM orders, assess the orders for compliance with guidelines, and make interventions to ensure compliance when necessary. This process was performed by independent study pharmacy students under the supervision of the clinical staff pharmacist for Specialty Pharmacy Services, who also had a hybrid role providing clinical pharmacy services in the Gastroenterology clinic and had close relationships with prescribers and patients. All orders for BRMs were evaluated regardless of the origin of the prescription. Of the 320 unique patient BRM orders evaluated in this study, 195 (61%) were generated in the Rheumatology clinic, 99 (31%) in the Gastroenterology clinic, 21 (6.5%) in the Dermatology clinic, and 5 (1.5%) in the Transplant clinic. At the time of this study, only the Gastroenterology clinic and the Transplant clinic had a clinical pharmacist assigned to the service. The most common diagnoses from the electronic medical record (EMR) were rheumatoid arthritis (116, 36%); Crohn's disease (75, 23%); ankylosing spondylitis (27, 8%); ulcerative colitis (24, 8%); psoriasis (20, 6%); psoriatic arthritis (19, 6%); and sarcoidosis (17, 5%). Other diagnoses mentioned less than 2% of the time were juvenile idiopathic arthritis, Behcet's disease, adult onset Stills disease, uveitis, granulomatous disease, mixed connective tissue disease, Pityriasis Rubra Pilaris, and post-transplant immunosuppression.

The Specialty Pharmacy Service identified all new BRM orders using 1 of the following approaches: (a) referral to the clinical staff pharmacist, (b) referral to the prior authorization technician for evaluation of insurance benefits, or (c) bi-weekly review of new and continuing BRM orders downloaded from the EMR. The process for assessing the BRM order for compliance with the guidelines was the same regardless of the method used to identify the order. First, utilizing the BRM Pre-Order Checklist, individual risk assessments (infection, hepatotoxicity, cancer, concomitant disease state, concomitant medications, and pregnancy) were evaluated, and the EMR was reviewed for compliance with the laboratory test requirements. If the EMR did not show complete compliance with all 4 laboratory tests (TB, HBsAg, LFT, and CBC) prior to the start of therapy or if other safety issues were identified, Specialty Pharmacy Services alerted the prescriber (usually an attending physician, resident, or fellow) by way of an internal message through the EMR or via telephone. The clinical pharmacist assigned to the specialty clinic was notified as well, and the communications were documented in the EMR. Feedback

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FIGURE 1 Anti-TNF-Alpha Agents Pre-Order Checklist

Check box if risk assessment and education are completed

- Infection Risk Assessment
 - No clinical signs of active infection such as fever, cough, flu-like symptoms
 - Caution in history of chronic, recurrent, serious, or opportunistic infection, or with underlying predisposing condition
 - White blood cell count and/or absolute neutrophil count not significantly reduced (within 1 mo prior to initiation and repeated q3mo during maintenance)
 - Negative test for tuberculosis (TB) infection (QuantiFERON-TB Gold or PPD, repeated annually) or clear history of being adequately treated if test for TB is positive. Refer to Pulmonary or ID if TB test is positive and not treated
 - Negative hepatitis B surface antigen (HBsAg). If HBsAg or hepatitis B core antibody positive, refer to Hepatology
 - Vaccinations up-to-date (esp. children) including pneumococcal, influenza, hepatitis B.^a No live vaccines within 4 wk
- Hepatotoxicity Risk Assessment
 - Liver transaminases $\leq 5\times$ upper limit of normal (within 1 mo prior to initiation and repeated q3mo during maintenance)
- Cancer Risk Assessment (lymphomas, breast, colorectal, melanoma, nonmelanoma skin cancers)
 - No history or clinical signs for malignancy
 - Caution (although not absolutely contraindicated) in high risk patients such as:
 - Male patients, esp. adolescent or young adults, with Crohn's disease or ulcerative colitis receiving azathioprine or 6-mercaptopurine treatment (lymphoma risk)
 - Moderate to severe COPD and heavy smoking history (lung, head/neck cancer risk)
 - ≤ 18 yo (lymphoma and other cancers risk)
 - Patients with psoriasis who have had prior prolonged phototherapy treatment (nonmelanoma skin cancer risk)
- Concomitant Disease State Risk Assessment
 - Negative for demyelinating disease (multiple sclerosis, Guillain-Barre syndrome, optic neuritis, transverse myelitis) or seizure disorder
 - No signs of moderate or severe congestive heart failure (New York Heart Association class III or IV)
 - No history of lupus-like syndrome (negative ANA and anti-dsDNA autoantibodies, if suspected)
 - Negative for significant thrombocytopenia
- Concomitant Medication Contraindications
 - NOT taking anakinra (Kineret), abatacept (Orencia), tocilizumab (Actemra), rituximab (Rituxan) or another anti-TNF agent
- Pregnancy Assessment
 - If clinically pregnant or pregnancy test positive, the risks versus benefits of treatment were discussed with the patient and decision to proceed with treatment documented in the medical record
- Patient Education
 - Risk Evaluation and Mitigation Strategy (REMS) Medication Guide reviewed with patient
 - Patient instructed to seek medical care when clinical signs of infection occur (fever, cough, flu-like symptoms)
 - Patient instructed about proper food and water hygiene. To avoid *Listeria and Salmonella*, avoid raw eggs, unpasteurized milk products (soft cheeses should be verified), hot dogs or deli meats (unless reheated until steaming hot), and uncooked meat/fish, and cook food to proper temperatures. To avoid *Legionella*, avoid potentially contaminated water and unclean hot tubs
 - Patient informed about the risk of live vaccines (e.g., measles/mumps/rubella, herpes zoster, oral polio vaccine, intranasal influenza, varicella, oral typhoid)
 - Patient instructed to communicate plans of travel to areas of endemic tuberculosis (outside the United States) or endemic mycoses (Ohio or Mississippi River valleys)
 - Patient instructed on administration (if applicable)

^aRecommendations for hepatitis B vaccination: end-stage renal disease, HIV, chronic liver disease, intravenous drug abuse, > 1 sex partner in the previous 6 months, men who have sex with men, persons seeking evaluation or treatment for a sexually transmitted disease, health care personnel, etc. (Centers for Disease Control and Prevention. Recommended adult immunization schedule—United States, 2011. MMWR 2011²¹).

COPD=chronic obstructive pulmonary disease; ID=infectious disease; mo=month; PPD=purified protein derivative; q3mo=every 3 months; TNF=tumor necrosis factor; wk=weeks; yo=years old.

during the study was provided on a patient-by-patient basis to proactively improve compliance with the guidelines. Specialty Pharmacy Services would then contact patients on behalf of the prescriber and coordinate with the clinical pharmacist or other providers to order the required labs and assist with any follow-up needed.

In conjunction with the evaluation of safety monitoring, the Specialty Pharmacy Service completed an insurance benefits review for patients starting on treatment with a BRM. If a prior

authorization was required, it was submitted to the insurance company. Prior authorization requests were approved 96% of the time, with the only reason for denial being non-FDA approved indications, such as sarcoidosis. Once the prior authorization was approved and the patient was ready to initiate therapy, an appointment was made with the patient for education and training (for self-injectable BRMs) or for the infusion or injection (for clinic-administered BRMs). The pharmacist or the nurse in the Infusion Center were responsible for

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FIGURE 2 Sample Compliance Notification Letter

Dear Dr. (insert name)

After a recent review of (patient name, birth date) it has come to our attention that your patient may be due for one of the following tests as outlined in the clinical care guidelines for Anti-TNF medications adopted by (health care provider) in (date). This is based on the information currently available in PowerChart.

Labs that are due:

LFT – Last tested on (insert date)

Needs to be completed within one month prior to treatment then every three months.

CBC – Last tested on (insert date)

Needs to be completed within one month prior to treatment then every three months.

For more details regarding these guidelines please visit: (insert link to guidelines)

Also if the prescription has been suspended, discontinued, or the patient is no longer on treatment, please update the patient's medication profile to the correct status. This will ensure a decrease in the amount of unnecessary notifications sent out.

For your reference the following labs are up to date with the current guidelines:

Tuberculosis Test (TST or quantiFERON) – Last tested on (insert date)

Needs to be completed prior to starting treatment and then annually.

Hepatitis B Test (HBsAg) – (insert date)

Needs to be documented or completed prior to starting treatment.

Thank You,

Specialty Pharmacy Services
(phone number)

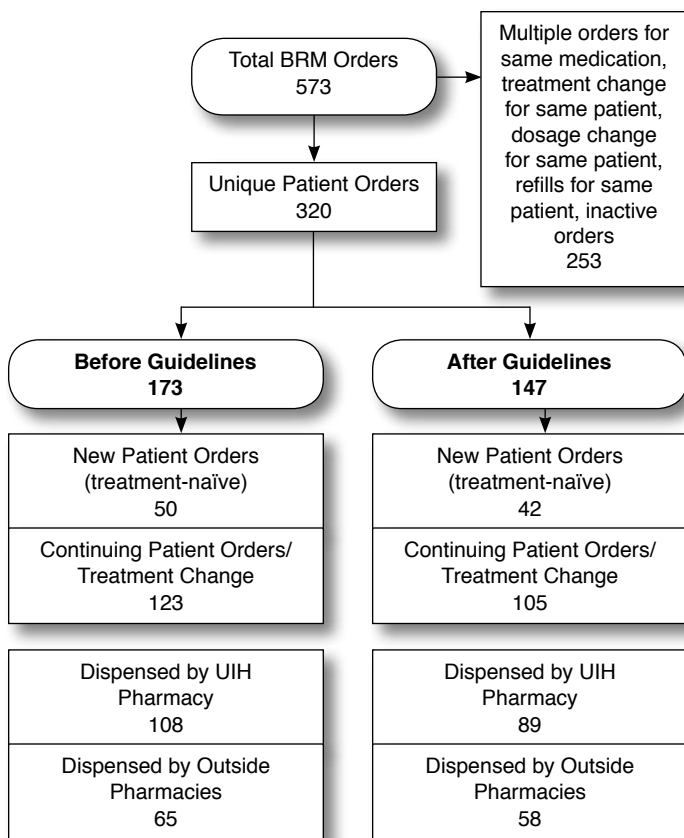
verifying compliance with the guidelines before any medication was dispensed or administered to the patient by the health system. If compliance was not complete, the prescriber could authorize dispensing or administration if it was deemed that the benefit of the medication outweighed the safety risk represented by noncompliance with the guidelines. This occurred for missing LFTs or CBCs, if the patient could not or refused to return to the lab for the tests, or if the tests were done outside the health system and documentation was not provided. Treatment was not initiated in new patients if they did not have a TB test because of the black box warning in product labeling. For prescriptions dispensed by a pharmacy outside the health system, compliance with the guidelines was verified

prior to referring the prescription to the designated pharmacy. Overall, this process improved the likelihood that BRMs were prescribed in accordance with safety measures prior to start of therapy.

After the initiation of BRM therapy, the guidelines required quarterly CBCs and LFTs as well as annual TB tests. For continuing patients with treatment changes, a TB test was not repeated for a patient who was previously deemed TB-positive. Instead, a chest x-ray was performed to confirm absence of disease. These patients were considered compliant with the TB test for purposes of this study. In order to assess guideline compliance with subsequent prescription refills, the pharmacist monitored each refill dispensed by the health

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FIGURE 3 Data Collection Flow Chart



BRM=biologic response modifier; UIH=University of Illinois Hospitals and Health Sciences System.

system's pharmacy. If any lab tests were required at the time of a refill, the patient and prescriber were notified, and the tests were ordered. A template letter (see Figure 2) included space for the prescriber's name, patient name, patient date of birth, date the labs were completed, which labs were due, and an electronic link to the Clinical Care Guidelines. The intent of the notification letter was to create a standardized process to remind the prescriber of needed labs for continued use of the BRM. While 197 (62%) of the prescriptions for BRMs were filled at UI Health, compliance with guidelines was assessed for all orders regardless of the dispensing pharmacy. It was not possible to reliably monitor ongoing (refill) guideline compliance for prescriptions dispensed by pharmacies outside the health system, since the service had little influence on dispensing and refill coordination with no access to those records.

Data Collection

A report containing outpatient prescription orders for BRMs (abatacept, adalimumab, certolizumab, etanercept, golimumab,

infliximab, and tocilizumab) from August 2011 through June 2012 was generated from the EMR. The data contained in the report reflected 6 months of orders before implementation of the guidelines, followed by 6 months of orders after guideline implementation (including 1 month during which guidelines were introduced to the health system). Duplicate orders (more than 1 order for the same medication) or orders discontinued or inactivated prior to start of therapy were deleted from the dataset. Some patients contributed more than 1 BRM episode of use to the analysis due to dose change, medication change, or renewal; therefore, the dataset was restricted to the first episode of use per patient. The resulting list was validated by cross-referencing medication records and physician notes in the EMR to ensure that only active (dispensed by any pharmacy or clinic-administered) orders were in the dataset. Each active order was categorized as a new start (treatment-naïve patients) or continuing order/treatment change (renewal or change in BRM; see Figure 3).

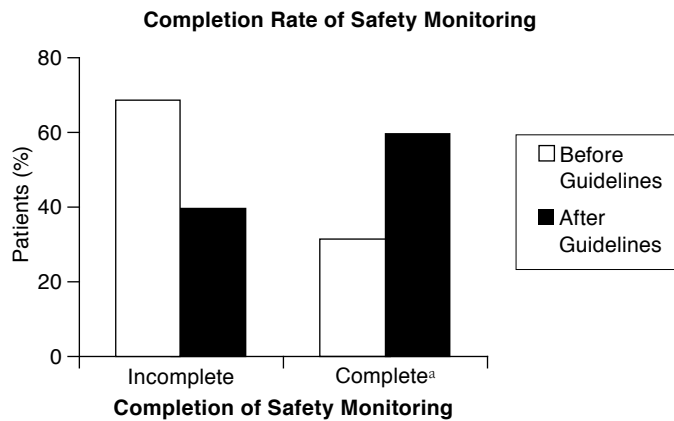
Once active orders were isolated, the medical record for each patient was reviewed to determine compliance with all 4 laboratory tests (TB, HBsAg, LFT, and CBC) required by the guidelines. The medication order date was compared with the date for each individual laboratory test. Orders classified as a new start were considered completely compliant if the TB test was completed within 1 year of the order date; if the HBsAg was completed any time before the order date; and if the LFT and the CBC were completed within 1 month of the order date. Orders classified as a continuation or treatment change were considered completely compliant if the TB test was completed within 1 year of the current order date; if the HBsAg was completed at any time; and if the LFT and the CBC were completed within 3 months of the current order date. For patients who had a positive TB test upon initiation of BRM therapy, repeat TB tests were not necessary with continuation or treatment change orders because any repeat test would likely be positive. Therefore, an order classified as a continuation or treatment change was considered compliant for TB even if no test was done within a year of the current order date if the initial TB test was positive, and the patient was evaluated and treated by the Infectious Disease Service. Compliance was measured as a composite rate that represented compliance with all 4 tests, since the guidelines adopted by the health system mandated all 4 lab tests. If there was clinical justification for noncompliance, such as with the CBC or the LFT, treatment was still initiated, but the patient was deemed noncompliant for purposes of this study.

Statistical Analyses

Retrospective analyses of completion of safety monitoring were conducted for patients administered BRM treatment. Completion rates were compared before and after implementation of guidelines in February 2012. Completion was considered to have occurred when all 4 safety monitoring tests

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FIGURE 4 Compliance with Safety Monitoring During BRM Treatment Before and After Guidelines



	Overall Completion of Safety Monitoring		
	Incomplete	Complete	Total
Pre-Feb 2012	119 (69%)	54 (31%)	173
Post-Feb 2012	59 (40%)	88 (60%)	147
Total	178	142	320

^aShows significantly increased rate of compliance in the group of patients treated after the guidelines ($P < 0.001$).

had been conducted—TB (unless known to be positive from a previous test), HBsAg, LFT, and CBC. Completion data from August 2011 to January 2012 were results before the guidelines were implemented, and data from February 2012 to July 2012 were results after the guidelines. Chi square analyses were performed on completion frequencies in the patients before and after guidelines were implemented, using IBM SPSS v. 19 (SPSS Inc., Chicago, IL) software.

Results

Percentage of compliance with the guidelines was determined for each lab test (TB, HBsAg, LFT, and CBC) in both the new order group and the group containing continuing orders and treatment changes. An improvement was seen in compliance with safety monitoring in patients treated during the 6-month period post-implementation of the guidelines, compared with compliance in the patient group treated during the 6-month period before guideline implementation (Figure 4). A total of 573 orders were initially examined, and it was determined that 320 were for unique patients. Before the guidelines were implemented, there were 173 patient orders, and 31% ($n = 54$) of patient orders complied with the safety monitoring by having all 4 clinical tests performed at the appropriate time points. After guideline implementation, there were 147 patient orders, and 60% ($n = 88$) of the patients were compliant and had all

TABLE 1 New Versus Continuing Patients

New Patients	Incomplete	%	Complete	%	Total
Pre-Feb 2012	24	48	26	52	50
Post-Feb 2012	7	17	35	83 ^a	42
Total	31		61		92
Continuing/Treatment Change					
Pre-Feb 2012	95	77	28	23	123
Post-Feb 2012	52	50	53	50 ^b	105
Total	147		81		228

^aPearson chi-square = 10.03, degrees of freedom = 1, $P = 0.0015$.

^bPearson chi-square = 18.99, degrees of freedom = 1, $P = < 0.0001$.

TABLE 2 Dispensing Locations

Dispensed by UI Health	Incomplete	%	Complete	%	Total
Pre-Feb 2012	76	70	32	30	108
Post-Feb 2012	34	38	55	62	89
Total	110		87		197
Dispensed by Outside Pharmacies					
Pre-Feb 2012	43	66	22	34	65
Post-Feb 2012	25	43	33	57	58
Total	68		55		123

UI Health = University of Illinois Hospitals and Health Sciences System.

4 clinical tests conducted, which represents a statistically significant improvement in the rate of compliance (Pearson chi square = 26.43, degrees of freedom (df) = 1, $P < 0.0001$).

This improvement in compliance rates after guideline implementation was observed in the new patient group and in the patients with continuing prescription orders or treatment changes (Table 1). When the new patient group was analyzed separately ($n = 92$), 50 patients were treated before the guidelines were implemented, and 42 patients were treated after the guidelines were implemented. Compliance rates with safety monitoring in these 2 groups were 52% and 83%, respectively, which represented a statistically significant improvement in compliance (Pearson chi square = 10.03, $df = 1$, $P = 0.0015$). Similar results were observed in the second patient subgroup with renewed prescription orders or changes in treatment. Of the patients treated before guidelines were implemented ($n = 123$), 23% were compliant with safety monitoring compared with 50% ($n = 105$) after guidelines were implemented, which represented a statistically significant improvement in compliance (Pearson chi square = 18.99, $df = 1$, $P < 0.0001$).

For patients who received their prescriptions from UI Health ($n = 197$), 108 patients were treated before guidelines were implemented, and 89 were treated after the guidelines were implemented (Table 2). Compliance rates with safety monitoring in these 2 groups increased from 30% to 62%. A smaller but relatively comparable increase was achieved for

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patients who received their prescriptions from outside pharmacies (n=123), with 65 patients treated before guidelines were implemented, and 58 patients treated after the guidelines were implemented. Compliance rates in these 2 groups increased from 34% to 57%.

Discussion

The data from this retrospective study indicated that the rate of compliance with safety monitoring was improved after guidelines were implemented. Compliance was most strikingly improved in the new patients. This study indicated that safety monitoring improved dramatically when Specialty Pharmacy Services took a proactive role in managing compliance with standard guidelines. Prior to implementation of the Clinical Care Guidelines for BRMs in February 2012, a complete risk assessment was not consistently performed by providers in the health system. Similar findings were found in a survey of rheumatologists in the United States by Cush and Yazici (2005), who showed that rheumatologists relied primarily on clinical assessments (history, physical examination; 92%), hepatic enzymes (69%), and CBC (77%) when initiating treatment with a BRM.²⁸ Although specific laboratory monitoring is not currently mandated, the authors recommended that a CBC and LFT be performed every 3 months for the first 12 months for patients already started on anti-TNF-alpha agents. UI Health guidelines were implemented to provide a checklist to ensure that necessary monitoring is performed as a routine standard of care when an order for a BRM is initiated. As BRMs are more widely prescribed and their long-term use becomes more common, safety monitoring should become a standard of practice. This study represented UI Health's effort to develop and implement safety guidelines. The Clinical Care Guidelines was an interpretation of published literature and was current at the time of its release.

To our knowledge, this is the first study that measured compliance with safety guidelines for BRMs. The safety risks associated with BRMs have been widely described in the literature and recommendations have been made for assessing and monitoring safe use of these agents.^{17,29,30} It is widely believed that the introduction of BRMs has significantly improved patient outcomes for a variety of indicated diseases; however, the safety concerns require careful screening of candidates, especially in patients at risk for adverse events, for example, patients with certain comorbidities or patients receiving an immunomodulator along with BRMs.²⁹ Some have called for systems to monitor the safety and effectiveness of BRMs in everyday practice.³⁰ Implementation of safety guidelines for BRMs at UI Health was one such approach for monitoring safety. This approach was comprehensive and proactive and resulted in a significant increase in compliance with guidelines. What is not yet known is the relationship of guideline compliance to patient outcomes, and if improving the safe use of these biologics would result in other benefits, such as improved adherence to medication

therapy. Previous studies reported on adherence with BRMs and the impact of various disease state management programs on BRM medication persistency and adherence.³¹⁻³⁴ One study found that specialty pharmacies reported greater refill adherence for adalimumab than retail pharmacies.³³ This was due in part to proactive refill management performed by the specialty pharmacies, such as reminder mailings, telephone calls, or emails prior to the time that a refill is needed. In a study of a rheumatoid arthritis disease therapy management program at a specialty pharmacy, patients who participated in the program had significantly greater adherence to their injectable medications compared with retail pharmacy patients.³² Safety monitoring is an element of treatment that should be considered for any comprehensive program for BRM management. For example, it could be easily integrated with a proactive refill management program. Compliance with safety guidelines requires patients to be actively involved in their care and requires coordination between all members of the health care team. It is possible that getting patients more involved in their care and the safe use of their medications may result in better adherence and improved outcomes. The nature of the relationship needs to be studied, along with an assessment of which elements of a program have the greatest potential impact on outcomes. We propose that safety monitoring and management be a core element of any patient-centered program for BRMs.

In this study, we used the location of our Specialty Pharmacy Service within the health system to access the EMR and make interventions to ensure safety at the start of therapy. This direct access offered the opportunity to monitor and address safety concerns in a way that was not possible in a retail or traditional specialty pharmacy. This study generated questions that should be explored. Appropriateness of the guidelines as written was questioned. Monitoring safety parameters is labor intensive, and some of the tests, such as the TB test, may be more clinically important than others, such as quarterly CBCs or LFTs. There is a need for input from thought leaders on the nature, frequency, and duration of assessments with the possible development of standardized and widely accepted guidelines for safety monitoring. Further research is needed to determine the clinical relevance of the guidelines and the relationship between improved safety monitoring and clinical, economic, or humanistic outcomes. One hypothesis is that improved safety monitoring will lead to improved clinical outcomes, fewer adverse events, and lower total costs of care due to reduced utilization of health care services and more judicious use of BRMs. An additional hypothesis is that improved safety monitoring and the coordinated care offered by the health system leads to better patient satisfaction with the provided health care. These are all questions that merit further research for this class of medications.

Improvement in Safety Monitoring of Biologic Response Modifiers After the Implementation of Clinical Care Guidelines by a Specialty Pharmacy Service in an Academic Health System

There were challenges associated with implementing the Clinical Care Guidelines at UI Health. A major challenge was the lack of payment for this labor-intensive service. The analytics, monitoring, and follow-up required numerous people, including pharmacists, technicians, and pharmacy students in Specialty Pharmacy Services. For this service to be viable, justification for payment should be made and a payment source should be identified. Different models may be explored, for example, a pay-for-performance model based on the ability of the service to prevent adverse events and to save money by ensuring appropriate use. There were also challenges implementing the guidelines and the monitoring service. For example, many different prescribers were involved in ordering BRMs. It was a challenge to effectively communicate the guidelines to all providers, making frequent in-services necessary. Additionally, BRM orders originated from a variety of clinics, and referrals to Specialty Pharmacy Services were not made consistently from all of the clinics. A biweekly download of all BRM orders from the EMR provided a safety net so that orders could be reviewed on a timely basis. Not all prescription orders were dispensed by the health system pharmacy; therefore, it was difficult to monitor guidelines throughout the refill process for these orders. This may have resulted in a fragmentation of care when compared with patients who received all of their care from UI Health, including prescriptions, and who received the full potential benefit of safety monitoring. Better coordination with pharmacies outside the health system, assuming they embrace the guidelines, would allow for the same standard of care for all patients. Finally, it was a challenge to ensure complete compliance with the guidelines because not all providers agreed that the 4 lab tests should be mandatory. It was widely accepted that the TB test and the HBsAg were required prior to the start of new treatment; however, some providers considered the CBC and the LFT as recommended but not mandatory. The health system intends to review the results of this study and consider whether the guidelines should be revised.

Limitations

Several important limitations of this study should be noted. The EMR did not always have complete documentation of lab tests, especially if those tests were performed outside the health system. There was a method to scan outside lab results to the UI Health EMR; however, they were not always accurate and updated at the time of the study. If completion of the required labs could not be confirmed, the record was deemed noncompliant and may have resulted in the over-reporting of the non-compliance rate. Some BRM orders may have been excluded from this study if electronic prescribing was not utilized, which resulted in the prescription order not being captured by the EMR. For example, if a prescription was faxed directly to a specialty pharmacy or verbally ordered by telephone, and the electronic documentation of the order was inadvertently omitted, the result would be no record of it in the EMR. Therefore, these orders were not available for compliance

monitoring unless a referral was made to Specialty Pharmacy Services for a review of benefits. Additionally, due to lack of access to outside pharmacy records for ongoing monitoring and refill management, only new start orders could be reliably assessed for compliance if the prescription was filled by a pharmacy outside the health system.

Conclusion

Despite the limitations, this study has important implications for patients, providers, health care systems, managed care organizations, and researchers. Given the widespread and long-term use of BRMs, safety monitoring and management should be an important part of a comprehensive medication management program for BRMs. A coordinated effort can have a significant impact on compliance with safety monitoring guidelines. Research should be conducted to determine the relationship between compliance to safety guidelines and outcomes. Direct access to the EMR, prescribers, and patients facilitates a coordinated approach to ensure safe use of medications. Overall, this study increased the probability that interventions would be made to ensure safe use of BRMs at UI Health.

Authors

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DISCLOSURES

This study was conceived and designed by Stubbings, Hanson, Khamo, Gannon, and Orr. Gannon and Khamo collected the data. Sodhi interpreted the data with assistance from Stubbings. All authors contributed to the writing and revision of the manuscript.

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APPENDIX Biologic Response Modifiers Screening and Monitoring Criteria

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**BIOLOGIC RESPONSE MODIFIERS:
SCREENING AND MONITORING CRITERIA**
February 2012

Key Content Expert: John Garofalo, PharmD

These systematically developed statements have been created to assist the practitioner in the formulation of health care decisions in specific clinical circumstances. They are not to be construed as an inflexible set of correct procedures or protocols.

In each clinical circumstance the exercise of individual judgment is essential.

Guidelines are based upon statistical averages and opinions of practicing clinicians. Variation from these guidelines does not constitute improper care or improper professional judgment. Evaluation of these variations requires detailed analysis of the facts and circumstances surrounding the individual patient's care.

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APPROVAL DATE: February 3, 2012

**SUBJECT: BIOLOGIC RESPONSE MODIFIERS: SCREENING AND MONITORING
CRITERIA**

OBJECTIVE

To establish a uniform policy to screen patients for contraindications to initiating biologic response modifier (BRM) therapy and establish requirements for on-going monitoring for patients receiving a BRM.

DEFINITIONS

BRMs include the following classes of drugs:

- TNF inhibitor: certolizumab (Cimzia®), adalimumab (Humira®), etanercept (Enbrel®), infliximab (Remicade®), golimumab (Simponi®).
- T-Cell co-stimulation blocker: abatacept (Orencia®)
- Interleukin-6 receptor antagonist: tocilizumab (Actemra®)
- Monoclonal Antibody: belimumab (Benlysta®)

POSITION STATEMENTS

- BRMs are indicated for certain chronic medical conditions and have several severe and potentially fatal adverse effects.
- It is important that patients are screened for contraindications prior to the initiation of therapy and monitored closely throughout their treatment course.

PROCEDURE

1. Prior to the initiation of a BRM, the prescriber or designee will complete the corresponding pre-order risk assessment checklist (addenda A-D).
2. The prescriber or designee will document the completion of the checklist using the corresponding note template for that drug or drug class.
3. The checklist is to be completed at least annually.
4. If the medication is filled at a UIC pharmacy, the pharmacist will verify completion of the checklist prior to dispensing the medication.
5. The Infliximab (Remicade®) Communication Form will be completed by the prescriber or designee and sent to UIC Oncology Pharmacy prior to each infliximab infusion (addendum E).

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6. The Infliximab (Remicade®) Infusion Checklist (addendum F) will be completed by the infusion nurse prior to each infliximab infusion and sent to the UIC Oncology Pharmacy.
7. *Dosing and infusion rate information can be found in the Ambulatory Care Infusion Guide.*

Addenda

- Addendum A: Abatacept (Orencia®) Pre-Order Checklist
- Addendum B: Anti-TNF Agent Pre-Order Checklist
- Addendum C: Belimumab (Benlysta®) Pre-Order Checklist
- Addendum D: Tocilizumab (Actemra®) Pre-Order Checklist
- Addendum E: Infliximab (Remicade®) Communication Form
- Addendum F: Infliximab (Remicade®) Infusion Checklist

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Addendum A:

Abatacept (Orencia®) Pre-Order Checklist
(to be completed by Prescriber on an annual basis)

Date and time: _____ (or place encounter sticker here)

Patient Name and second identifier: _____

Check Box if Risk Assessment and Education completed

- Infection Risk Assessment
 - No clinical signs of active infection such as fever, cough, flu-like symptoms
 - Caution in history of chronic, recurrent, serious, or opportunistic infection, or with underlying predisposing condition
 - Negative test for tuberculosis (TB) infection (QuantiFERON®-TB Gold or PPD, repeated annually) or clear history of being adequately treated if test for TB is positive. Refer to Pulmonary or ID if TB test is positive and not treated
 - Negative hepatitis B surface antigen (HBsAg). If HBsAg or hepatitis B core antibody positive, refer to Hepatology
 - Vaccinations up-to-date (esp. children) including pneumococcal, influenza, hepatitis B.* No live vaccines within 4 wk
- Cancer Risk Assessment (lung, lymphoma)
 - No history or clinical signs for malignancy
- Concomitant Disease State Risk Assessment
 - Caution in adults with COPD
- Concomitant Medications
 - NOT taking anakinra (Kineret®), tocilizumab (Actemra®), rituximab (Rituxan®), or an anti-TNF agent (infliximab [Remicade®], etanercept [Enbrel®], adalimumab [Humira®], certolizumab pegol [Cimzia®], golimumab [Simponi®])
- Pregnancy Assessment
 - If clinically pregnant or pregnancy test positive, the risks versus benefits of treatment were discussed with the patient and decision to proceed with treatment documented in the medical record
- Patient Education
 - Patient instructed to seek medical care when clinical signs of infection occur (fever, cough, flu-like symptoms)
 - Patient instructed about proper food and water hygiene. To avoid *Listeria* and *Salmonella*, avoid raw eggs, unpasteurized milk products (soft cheeses should be verified), hot dogs or deli meats (unless reheated until steaming hot), and uncooked meat/fish, and cook food to proper temperatures. To avoid *Legionella*, avoid potentially contaminated water and unclean hot tubs
 - Patient informed about the risk of live vaccines (e.g., measles/mumps/rubella, herpes zoster, oral polio vaccine, intranasal influenza, varicella, oral typhoid)
 - Patient instructed to communicate plans of travel to areas of endemic tuberculosis (outside the U.S.) or endemic mycoses (Ohio or Mississippi River valleys)
 - Patient instructed on administration (if applicable)

*Recommendations for hepatitis B vaccination: end-stage renal disease, HIV, chronic liver disease, intravenous drug abuse, > 1 sex partner in the previous 6 months, men who have sex with men, persons seeking evaluation or treatment for a sexually transmitted disease, health care personnel, etc. (Centers for Disease Control and Prevention. Recommended adult immunization schedule—United States, 2011. MMWR 2011;60(4))

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Addendum B:

Anti-TNF Agent Pre-Order Checklist (infliximab (Remicade®), etanercept (Enbrel®),
adalimumab (Humira®), certolizumab pegol (Cimzia®), golimumab (Simponi®)
(to be completed by Prescriber on an annual basis)

Date and time: _____ (or place encounter sticker here)

Patient Name and second identifier: _____

Check Box if Risk Assessment and Education completed

- Infection Risk Assessment
 - No clinical signs of active infection such as fever, cough, flu-like symptoms
 - Caution in history of chronic, recurrent, serious, or opportunistic infection, or with underlying predisposing condition
 - White blood cell count and/or absolute neutrophil count not significantly reduced (within 1 mo prior to initiation and repeated q3mo during maintenance)
 - Negative test for tuberculosis (TB) infection (QuantiFERON®-TB Gold or PPD, repeated annually) or clear history of being adequately treated if test for TB is positive. Refer to Pulmonary or ID if TB test is positive and not treated
 - Negative hepatitis B surface antigen (HBsAg). If HBsAg or hepatitis B core antibody positive, refer to Hepatology
 - Vaccinations up-to-date (esp. children) including pneumococcal, influenza, hepatitis B.* No live vaccines within 4 wk
- Hepatotoxicity Risk Assessment
 - Liver transaminases $\leq 5 \times$ upper limit of normal (within 1 mo prior to initiation and repeated q3mo during maintenance)
- Cancer Risk Assessment (lymphomas, breast, colorectal, melanoma, nonmelanoma skin cancers)
 - No history or clinical signs for malignancy
 - Caution (although not absolutely contraindicated) in high risk patients such as
 - Male patients, esp. adolescent or young adults, with Crohn's disease or ulcerative colitis receiving azathioprine or 6-mercaptopurine treatment (lymphoma risk)
 - Moderate to severe COPD and heavy smoking history (lung, head/neck cancer risk)
 - ≤ 18 yo (lymphoma and other cancers risk)
 - Patients with psoriasis who have had prior prolonged phototherapy treatment (nonmelanoma skin cancer risk)
- Concomitant Disease State Risk Assessment
 - Negative for demyelinating disease (multiple sclerosis, Guillain-Barre syndrome, optic neuritis, transverse myelitis) or seizure disorder
 - No signs of moderate or severe congestive heart failure (New York Heart Association class III or IV)
 - No history of lupus-like syndrome (negative ANA and anti-dsDNA autoantibodies, if suspected)
 - Negative for significant thrombocytopenia
- Concomitant Medication Contraindications
 - NOT taking anakinra (Kineret®), abatacept (Orencia®), tocilizumab (Actemra®), rituximab (Rituxan®) or another anti-TNF agent
- Pregnancy Assessment
 - If clinically pregnant or pregnancy test positive, the risks versus benefits of treatment were discussed with the patient and decision to proceed with treatment documented in the medical record
- Patient Education
 - Risk Evaluation and Mitigation Strategy (REMS) Medication Guide reviewed with patient
 - Patient instructed to seek medical care when clinical signs of infection occur (fever, cough, flu-like symptoms)
 - Patient instructed about proper food and water hygiene. To avoid *Listeria* and *Salmonella*, avoid raw eggs, unpasteurized milk products (soft cheeses should be verified), hot dogs or deli meats (unless reheated until steaming hot), and uncooked meat/fish, and cook food to proper temperatures. To avoid *Legionella*, avoid potentially contaminated water and unclean hot tubs
 - Patient informed about the risk of live vaccines (e.g., measles/mumps/rubella, herpes zoster, oral polio vaccine, intranasal influenza, varicella, oral typhoid)
 - Patient instructed to communicate plans of travel to areas of endemic tuberculosis (outside the U.S.) or endemic mycoses (Ohio or Mississippi River valleys)
 - Patient instructed on administration (if applicable)

*Recommendations for hepatitis B vaccination: end-stage renal disease, HIV, chronic liver disease, intravenous drug abuse, > 1 sex partner in the previous 6 months, men who have sex with men, persons seeking evaluation or treatment for a sexually transmitted disease, health care personnel, etc. (Centers for Disease Control and Prevention. Recommended adult immunization schedule—United States, 2011. MMWR 2011;60(4))

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Addendum C

Belimumab (Benlysta®) Pre-Order Checklist
(to be completed by Prescriber on an annual basis)

Date and time: _____ (or place encounter sticker here)

Patient Name and second identifier: _____

Check Box if Risk Assessment and Education completed

- Infection Risk Assessment
 - No clinical signs of active infection such as fever, cough, flu-like symptoms
 - Caution in history of chronic, recurrent, serious, or opportunistic infection, or with underlying predisposing condition
 - Negative test for tuberculosis (TB) infection (QuantiFERON®-TB Gold or PPD, repeated annually) or clear history of being adequately treated if test for TB is positive. Refer to Pulmonary or ID if TB test is positive and not treated
 - Negative hepatitis B surface antigen (HBsAg). If HBsAg or hepatitis B core antibody positive, refer to Hepatology
 - Vaccinations up-to-date (esp. children), incl. pneumococcal, influenza, Td/Tdap, hepatitis B.* No live vaccines ≤ 4 wk
- Cancer Risk Assessment (including non-melanoma skin cancer)
 - No history or clinical signs for malignancy
- Concomitant Disease State Risk Assessment
 - Caution in history of depression or other psychiatric illness
- Pregnancy Assessment
 - If clinically pregnant or pregnancy test positive, the risks versus benefits of treatment were discussed with the patient and decision to proceed with treatment documented in the medical record
- Patient Education
 - Risk Evaluation and Mitigation Strategy (REMS) Medication Guide reviewed with patient
 - Patient instructed to seek medical care when clinical signs of infection occur (fever, cough, flu-like symptoms)
 - Patient instructed about proper food and water hygiene. To avoid *Listeria* and *Salmonella*, avoid raw eggs, unpasteurized milk products (soft cheeses should be verified), hot dogs or deli meats (unless reheated until steaming hot), and uncooked meat/fish, and cook food to proper temperatures. To avoid *Legionella*, avoid potentially contaminated water and unclean hot tubs
 - Patient informed about the risk of live vaccines (e.g., measles/mumps/rubella, herpes zoster, oral polio vaccine, intranasal influenza, varicella, oral typhoid)
 - Patient instructed to communicate plans of travel to areas of endemic tuberculosis (outside the U.S.) or endemic mycoses (Ohio or Mississippi River valleys)

*Recommendations for hepatitis B vaccination: end-stage renal disease, HIV, chronic liver disease, intravenous drug abuse, > 1 sex partner in the previous 6 months, men who have sex with men, persons seeking evaluation or treatment for a sexually transmitted disease, health care personnel, etc. (Centers for Disease Control and Prevention. Recommended adult immunization schedule—United States, 2011. MMWR 2011;60(4))

Improvement in Safety Monitoring of Biologic Response Modifiers After the Implementation of Clinical Care Guidelines by a Specialty Pharmacy Service in an Academic Health System

APPENDIX Biologic Response Modifiers Screening and Monitoring Criteria (continued)

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University of Illinois Medical Center
Chicago, Illinois

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UNIVERSITY OF ILLINOIS MEDICAL CENTER AT CHICAGO
CENTER CARE GUIDELINES

Addendum D

Tocilizumab (Actemra®) Pre-Order Checklist
(to be completed by Prescriber on an annual basis)

Date and time: _____ (or place encounter sticker here)

Patient Name and second identifier: _____

Check Box if Risk Assessment and Education completed

- Infection Risk Assessment
 - No clinical signs of active infection such as fever, cough, flu-like symptoms
 - Caution in history of chronic, recurrent, serious, or opportunistic infection, or with underlying predisposing condition
 - Absolute neutrophil count (ANC) $\geq 2000/\text{mm}^3$ at baseline or $> 1000/\text{mm}^3$ during maintenance (within 1 mo prior to initiation and repeated q4-8wk* during maintenance)
 - Negative test for tuberculosis (TB) infection (QuantiFERON®-TB Gold or PPD, repeated annually) or clear history of being adequately treated if test for TB is positive. Refer to Pulmonary or ID if TB test is positive and not treated
 - Negative hepatitis B surface antigen (HBsAg). If HBsAg or hepatitis B core antibody positive, refer to Hepatology
 - Vaccinations up-to-date (esp. children) including pneumococcal, influenza, hepatitis B.** No live vaccines within 4 wk
- Hepatotoxicity Risk Assessment
 - ALT or AST $\leq 1.5 \times$ upper limit of normal (ULN) at baseline or $\leq 3 \times$ ULN during maintenance (within 1 mo prior to initiation and repeated q4-8wk* during maintenance)
 - If ALT or AST persistently elevated to $> 1-3 \times$ ULN, dose has been lowered to 4 mg/kg (if applicable)
- Cancer Risk Assessment
 - No history or clinical signs for malignancy
- Concomitant Disease State Risk Assessment
 - Platelet count $\geq 100,000/\text{mm}^3$ at baseline or during maintenance (within 1 mo prior to initiation and repeated q4-8wk* during maintenance)
 - Caution in patients at high risk of gastrointestinal perforation (i.e. diverticulitis, gastric or duodenal ulcer, taking concomitant NSAIDs, corticosteroids, or methotrexate)
 - Lipids parameters monitored at 4-8 wk then q24wk and abnormalities treated if applicable
 - Negative for demyelinating disease (multiple sclerosis, chronic inflammatory demyelinating polyneuropathy)
- Concomitant Medications
 - NOT taking anakinra (Kineret®), abatacept (Orencia®), rituximab (Rituxan®), or an anti-TNF agent (infliximab [Remicade®], etanercept [Enbrel®], adalimumab [Humira®], certolizumab pegol [Cimzia®], golimumab [Simponi®])
 - Caution used in co-administration of medications metabolized via CYP450, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 (e.g. warfarin, most statins, cyclosporine, oral contraceptives, omeprazole, etc.)
- Pregnancy Assessment
 - If clinically pregnant or pregnancy test positive, the risks versus benefits of treatment were discussed with the patient and decision to proceed with treatment documented in the medical record
- Dosage Assessment
 - Dose does not exceed 800 mg in adults
- Patient Education
 - Risk Evaluation and Mitigation Strategy (REMS) Medication Guide reviewed with patient
 - Patient instructed to seek medical care when clinical signs of infection occur (fever, cough, flu-like symptoms)
 - Patient instructed about proper food and water hygiene. To avoid *Listeria* and *Salmonella*, avoid raw eggs, unpasteurized milk products (soft cheeses should be verified), hot dogs or deli meats (unless reheated until steaming hot), and uncooked meat/fish, and cook food to proper temperatures. To avoid *Legionella*, avoid potentially contaminated water and unclean hot tubs
 - Patient informed about the risk of live vaccines (e.g., measles/mumps/rubella, herpes zoster, oral polio vaccine, intranasal influenza, varicella, oral typhoid)
 - Patient instructed to communicate plans of travel to areas of endemic tuberculosis (outside the U.S.) or endemic mycoses (Ohio or Mississippi River valleys)

*every 2-4 weeks for patients with systemic juvenile idiopathic arthritis

**Recommendations for hepatitis B vaccination: end-stage renal disease, HIV, chronic liver disease, intravenous drug abuse, > 1 sex partner in the previous 6 months, men who have sex with men, persons seeking evaluation or treatment for a sexually transmitted disease, health care personnel, etc. (Centers for Disease Control and Prevention. Recommended adult immunization schedule—United States, 2011. MMWR 2011;60(4))

Improvement in Safety Monitoring of Biologic Response Modifiers After the Implementation of Clinical Care Guidelines by a Specialty Pharmacy Service in an Academic Health System

APPENDIX Biologic Response Modifiers Screening and Monitoring Criteria (continued)

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**UNIVERSITY OF ILLINOIS MEDICAL CENTER AT CHICAGO
CENTER CARE GUIDELINES**

Addendum E

UIMC Infiximab (Remicade®) Treatment Communication Form

Date and time: _____ (or place encounter sticker here)

Patient Name and second identifier: _____

The information on this page does not constitute an order, but is for the communication of the intention to treat a patient with infiximab.

This document is to be completed before a patient is scheduled for infusion. In addition, no infusions will be prepared until this document is completed, signed and forwarded to the UIC Oncology Pharmacy.

Infiximab:

Initial:

- 5mg/kg _____ mg IV at week 0, 2, 6 (infuse over NOT less than 2 hours); Number of doses: _____
- 3mg/kg _____ mg IV at week 0, 2, 6 (infuse over NOT less than 2 hours); Number of doses: _____
- _____ mg/kg _____ mg IV q _____ week (infuse over NOT less than 2 hours); Number of doses: _____

Maintenance:

- 5mg/kg _____ mg IV every 8 weeks (infuse over NOT less than 2 hours); Number of doses: _____
- 3mg/kg _____ mg IV every 8 weeks (infuse over NOT less than 2 hours); Number of doses: _____
- _____ mg/kg _____ mg IV q _____ week (infuse over NOT less than 2 hours); Number of doses: _____

Prescriber's name (Please Print) _____ Contact Phone/Pager # _____

Prescriber's signature _____ Date and Time: _____

Name of person scheduling patient (Please Print) _____

Contact Phone/Pager # _____

Pharmacy reviewer's name (Please Print) _____

Date and Time: _____

**UIC Oncology Pharmacy
Ext 6-6985, FAX 6-1363, tube 810**

Improvement in Safety Monitoring of Biologic Response Modifiers After the Implementation of
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APPENDIX Biologic Response Modifiers Screening and Monitoring Criteria *(continued)*

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**UNIVERSITY OF ILLINOIS MEDICAL CENTER AT CHICAGO
CENTER CARE GUIDELINES**

Addendum F

Infliximab (Remicade®) Infusion Checklist

(to be completed by Nurse administering medication prior to each infusion)

Date and time: _____ (or place encounter sticker here)

Patient Name and second identifier: _____

Clinical Assessment

- **Patient may not receive infusion for any abnormal or missing findings as surveyed below until test completed or addressed. Contact prescriber with information.**
 - Test for tuberculosis (TB) infection (e.g. QuantiFERON®- TB Gold, PPD) negative or clear history of being adequately treated if test for TB positive (prior to initiation and annually)
Yes ___ No ___ Not available ___
 - HBs-Antigen negative (prior to initiation) Yes ___ No ___ Not available ___
- **Prescriber must authorize continuation of treatment if any of the below finding is abnormal or not available and must document receipt of this information and the decision to continue with treatment in the eMR.**
 - Patient reports fever, cough, signs/symptoms of respiratory infection, arthralgias, myalgias?
Yes ___ No ___
 - Patient has an abnormal temperature, pulse rate, respiration rate, or blood pressure?
Yes ___ No ___
 - Patient has traveled to areas of endemic tuberculosis or endemic mycoses such as Ohio or Mississippi River valleys or outside the United States? Yes ___ No ___
 - Liver transaminases abnormal (prior to initiation and Q 3 months)
Yes ___ No ___ Not available ___
 - WBC count abnormal (prior to initiation and Q 3 months)
Yes ___ No ___ Not available ___

Prescriber contacted: _____

Date and Time: _____

Pharmacy Information

Date of last dose: _____ Today is dose # _____ of _____ ordered

Weight based dosing and frequency: _____

Original Pt Wt _____ kg /Current Pt Wt _____ kg (if > 10% difference in weight, contact prescriber)

- IV access established: Yes ___ No ___
- Patient received pre-medication: Yes ___ No ___
- Remicade Medication Guide given to patient (available from pharmacy): Yes ___ No ___
- Pharmacy may prepare infliximab as ordered: Yes ___ No ___

RN's Signature _____ Contact Phone/Pager # _____

Please fill out the above information and send to Oncology Pharmacy (Tube # 810)