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The Journal of the Canadian Rheumatology Association



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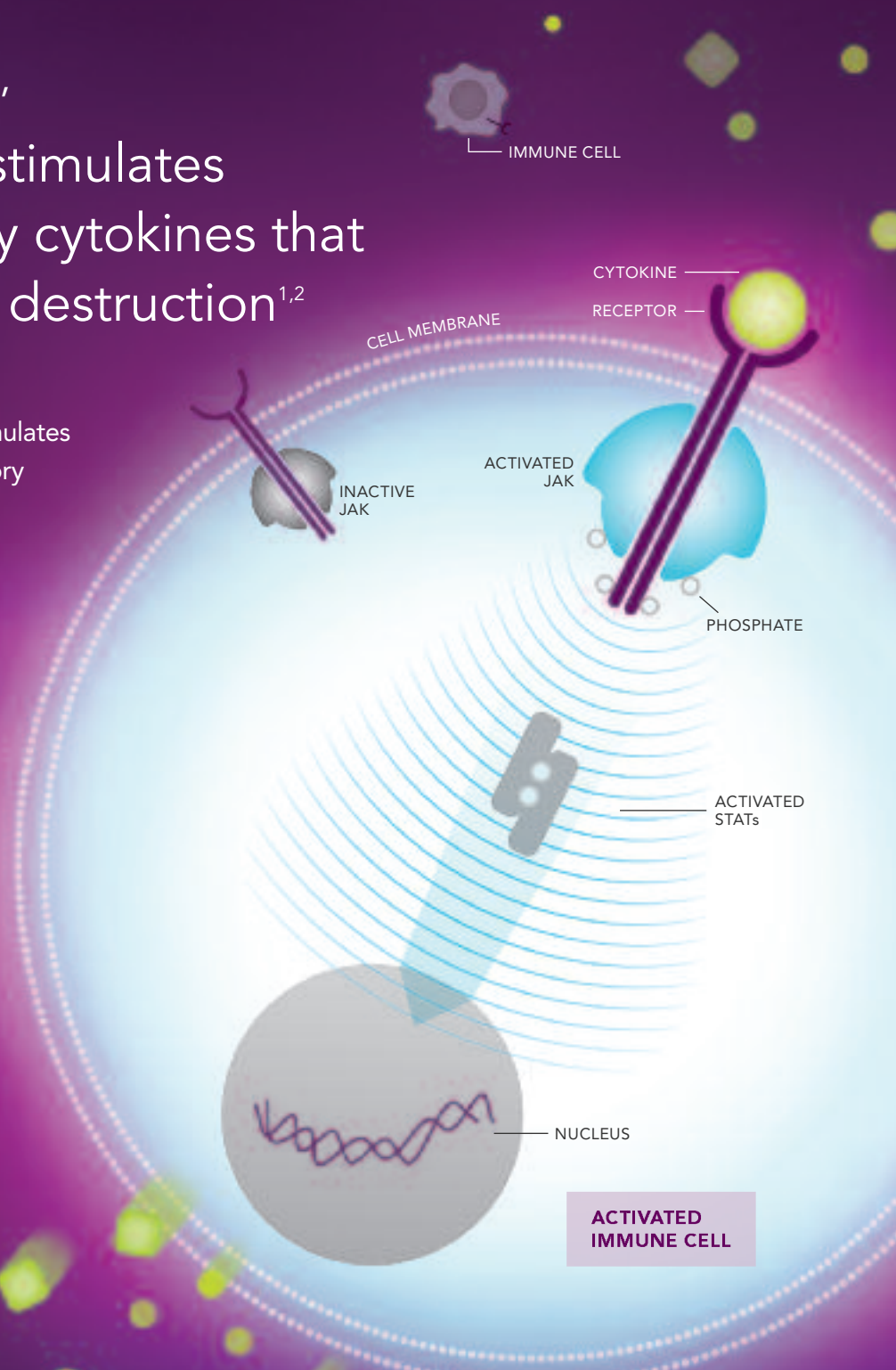
In rheumatoid arthritis,

JAK signalling stimulates pro-inflammatory cytokines that perpetuate joint destruction^{1,2}

Janus kinase (JAK) signalling stimulates the production of pro-inflammatory proteins (e.g., cytokines and chemokines), which contributes to the persistent inflammation and joint destruction found in rheumatoid arthritis (RA).³⁻⁵

JAK pathways can provide a different and intracellular approach to understanding RA.⁶

JAK
PATHWAYS
IN ACTION



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The Six Million Dollar Rheumatologist

By Philip A. Baer, MDCM, FRCPC, FACR

"For five seasons between 1974 and 1978, actor Lee Majors played Col. Steve Austin, on the mega-popular television show The Six Million Dollar Man. Barely surviving a near fatal crash, Austin was equipped with a bionic arm, two bionic legs and a bionic eye, making him 'better, stronger, faster,' and all for the price of..." well, you can guess.

"I've had recent knee surgery. Both knees are kind of down to the bone and [I have] a little bit of back problems. It's from almost 48 years of stunt work. I did 90 per cent of all my stuff."

- "Lee Majors dishes on Six Million Dollar Man role", CBC Interview, 2011.

Eventually everybody will be a potential rheumatology patient, even the fabled Six Million Dollar Man, now 74 years old. My long-distance diagnosis is spinal and peripheral osteoarthritis (OA). A wide variety of therapies are available, usually administered in multimodal fashion, from the generic acetaminophen to the more expensive viscosupplements, and the ultimate undertaking, joint replacement surgery. Moving from the individual patient to a national perspective, the cost of total hip and knee replacements increased in Canada by \$100 million over the 2010-12 timeframe, according to Canadian Institute for Health Information (CIHI) data.

In September 2013, the Society of Actuaries and the Canadian Institute of Actuaries (CIA) released a report entitled *Sustainability of the Canadian Health Care System*; "the findings indicate that, without significant government intervention, the Canadian health care system in its current form is not sustainable."

That started me thinking about my own economic role as a typical rheumatology clinician. Am I a six million dollar rheumatologist? After 27 years in practice, I have certainly had six million dollars in gross revenue pass through my hands. Regrettably, the stickiness of that bundle of dollars has been rather low when judged by my latest bank account statement. I do have the satisfaction of contributing to Canada's economy over the last quarter century, including funding my share of Senate spending, perpetually dry-docked submarines, and failed Ontario initiatives in e-Health, green energy, and power plant construction, among others. On the other hand, I feel happy about the money I have generated for employee salaries, local

business service providers, and worthwhile infrastructure and social services funded by my tax dollars.

Could I be a six million dollar rheumatologist in another context? Well, CIHI and the CIA indicate that Canadian spending on drugs accounts for 16% of health expenditures, versus only 14% for physician services. We all know that biologic therapies are a driver of drug costs in rheumatology. At \$20,000 per patient per year for biologic therapy, if I have 100 patients on biologics, I am generating two million dollars a year in direct costs. I could be a six million dollar rheumatologist every three years! With rheumatologists in my local area retiring, and preferentially transferring patients who are on biologics to me for ongoing care, biologic spending dispensed under my signature can only increase. No doubt some of our colleagues with bigger practices could be six million dollar a year rheumatologists already.

Of course, I am also ignoring the offsetting financial benefits of treatments which reach the target of remission or low disease activity, facilitated in many patients by biologic therapies: maintenance of work productivity, and reduction in other direct and indirect costs (short- and long-term disability, joint replacement surgery, etc.). Perhaps I should get a credit of a million dollars a year against my practice's drug costs to be fair. Lee Majors was married for nine years to Farrah Fawcett. After they split, Fawcett said, "If he's the six million dollar man, I'm the ten billion dollar woman." Will there be a ten billion dollar rheumatologist? I hope not.

Philip A. Baer, MDCM, FRCPC, FACR

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AWARDS, APPOINTMENTS, ACCOLADES



Dr. Cheryl Barnabe was the first recipient of the CRA (CIORA)-TAS Clinician Investigator Award in 2013. This award supports further investigation in inflammatory arthritis (IA) aligned with the research pillars of the CIORA grant program. Dr. Barnabe's research program, called "Arthritis Care for Indigenous Populations," uses multiple research methodologies to describe disparities in morbidity, identify treatment gaps creating these disparities, and develop interventions to enhance access to relevant and effective healthcare services, encompassing therapeutics, primary care, specialist, and multidisciplinary health services, for indigenous people in Canada.

Dr. Barnabe is an Assistant Professor in the Department of Medicine and the Department of Community Health Sciences at the University of Calgary, as well as a Scientist with the Arthritis Research Centre of Canada (ARC), and a Faculty Member in the McCaig Bone and Joint Health Institute and the Institute of Public Health.



Dr. Julie Barsalou received the Earl J. Brewer Research Award in 2013 for her abstract entitled "The Effect of Maternal Antimalarial Intake during Pregnancy on the Risk of Neonatal Lupus" that she presented at the American College of Rheumatology (ACR) Annual Meeting in San Diego.

The Earl J. Brewer Research Award, from the American Academy of Pediatrics' Section on Rheumatology, is presented annually to a fellow who is training at an accredited training program in the US or Canada who has distinguished themselves in an area of clinical research. Dr. Julie Barsalou is completing a lupus fellowship at the Hospital for Sick Children of Toronto under the supervision of Dr. Earl Silverman and Dr. Deborah Levy. She will be joining the Pediatric Rheumatology, Immunology, and Allergy division at CHU Sainte-Justine in Montreal as a pediatric rheumatologist.



Dr. Nigil Haroon is the 2013 recipient of the Spondylitis Association Bruckel Award, administered by the Spondylitis Association of America (SAA), and named after the co-founder of the association, Jane Bruckel. The award was established in 2011 to identify young investigators who are likely to drive the field of spondyloarthritis forward. In 2013 SAA selected Dr. Nigil Haroon for this award recognizing his contributions to the care and understanding of patients with spondyloarthritis.

Dr. Haroon is a clinician scientist at the University Health Network and an Assistant Professor of Medicine and Rheumatology at the University of Toronto. He is the co-director of the spondylitis clinic at the Toronto Western Hospital and chairs the Wait-Time Initiative of the CRA. Dr. Haroon recently published the first study that showed that TNF inhibitors are potentially disease-modifying drugs in ankylosing spondylitis (AS). His research focuses on disease pathogenesis and progression, and he indicates that "there has been significant progress in our understanding of the pathogenesis of AS, thanks to modern high-throughput techniques. We endeavour through our laboratory research program to gain a better understanding of the role of novel genes in AS pathogenesis and treatment responses."



Dr. Peter Tugwell was one of 25 appointments to the rank of Officer of the Order of Canada, the second-highest ranking conferred by our country. The Officer appointment "recognizes a lifetime of achievement and merit of a high degree, especially in service to Canada or to humanity at large."

Dr. Tugwell is a Canada Research Chair, Professor of Medicine and Epidemiology and Community Medicine, as well as Director of the Centre for Global Health at the University of Ottawa. He is the founding Coordinating Editor of the Cochrane Musculoskeletal Review Group, former Division Head of Rheumatology at McMaster University and still has a rheumatology practice at the University of Ottawa. He is co-Editor-in-Chief of the Journal of Clinical Epidemiology. He is Convenor of the Campbell and Cochrane Equity Methods Group, Co-Chair of the Campbell International Development Review Group, a former member of the Cochrane Steering Group, and a founding member of Cochrane, having co-chaired the very first Oxford meeting.

Tuberculosis Prophylaxis and Biologics Treatment for Rheumatoid Arthritis

By Nicholas M. Baniak, BSc; Vernon M. Hoepfner, MD, FRCPC; and
Wojciech P. Olszynski, MD, PhD, FRCPC, CCD

Tuberculosis (TB) infection is a prevalent, mostly latent, disease. Being treated with anti-tumor necrosis factor (TNF) inhibitors, a form of biologic therapy used for the treatment of rheumatoid arthritis (RA), is believed to increase the risk of reactivation. Accordingly, RA patients are recommended to go through screening for latent TB prior to initiating biologic therapy. If RA patients are found to have latent TB, it is recommended they initiate TB prophylaxis prior to beginning TNF inhibitor therapy. In the present study, a group of patients positive for latent TB were not provided prophylaxis before commencing TNF inhibitor therapy and were subsequently closely monitored for the development of overt TB symptoms. Of the 213 patients examined, 52% were male and 48% female, with 71% being over the age of 50. Furthermore, 95% of patients had been receiving treatment for longer than one year, with the longest being treated for 10 years. None of the patients showed evidence of active TB while on biologic therapy.

Introduction

A third of the world's population is infected with TB,^{1,2} including 4% of the United States population.³ In Canada, certain ethnicities possess higher levels of latent TB infection, such as foreign-born and First-Nations populations. There is an increased risk of TB associated with the use of TNF inhibitors, therapies commonly used for the management of autoimmune disorders, such as RA.³ In a study of over 112,000 Canadian patients with RA, the rate of TB in patients not treated with TNF inhibitors was 2.2/1000 patients, compared to 2.6/1000 patients in those treated with TNF inhibitor therapy.^{4,5}

Mycobacteria are facultative intracellular pathogens.^{1,6} When inhaled, TB bacilli are taken in by alveolar macrophages and encapsulating granulomas are subsequently developed in an attempt to limit the spread of the infectious bacteria.^{1,6} Since the patient is not able to completely eliminate the pathogens, the resulting granulomas are the characteristic feature of latent pulmonary TB (LTBI).⁷ Most immune-competent hosts have a sufficiently strong immune response to TB bacteria, limiting these pathogens to the lungs and associated lymph nodes.^{7,8} The histiocytic transformation and formation of granulomas represents residual infection.⁶ Disease reactivation occurs

when latent bacteria from pre-existing granulomas are reactivated into an active, virulent state; reactivation is most common when the host immune response weakens or is suppressed.⁷ Suppression of immune response is a well-known side effect of TNF inhibitor therapy.

The interaction between activated macrophages and interferon-gamma (IFN- γ)-secreting lymphocytes is vital to controlling the infection. TNF α , which is released by activated immune cells, also plays an important role in both granuloma formation and maintenance through its effects on expression of adhesion molecules and chemokines.⁹⁻¹⁴ Therefore, TNF inhibitor treatment may cause the granuloma to fail, allowing TB release and reactivation.¹¹ In a TNF-deficient mouse model, rapid TB infection and subsequent death is observed.^{7,15}

TB screening is recommended for the identification of latent TB infection in patients considering initiating TNF inhibitor therapy for RA,¹⁶ as surveys have shown that the incidence of TB is increased following the initiation of TNF inhibitor therapy.¹¹ Therefore, it is imperative that LTBI is identified and treated prior to initiating TNF inhibitor therapy to minimize the risk of reactivation.¹⁷

The 2012 American College of Rheumatology (ACR) treatment recommendations for those with latent TB (pos-

itive TST [tuberculin skin test] and negative chest X-ray [CXR]) are to take prophylactic medication before initiating any biologic medicine, such as a TNF inhibitor.¹⁴ The treatment for LTBI is isoniazid (INH) 5 mg/kg (up to 300 mg) once daily or 15 mg/kg (up to 900 mg) twice weekly¹⁸ for nine months.^{1,19-21} However, as with any medication, the risk of side effects when taking the TB prophylaxis, especially hepatotoxicity, must be weighed against the benefit of preventing reactivation of TB.²²⁻²⁴

In Saskatoon, Canada, RA patients with a positive TB skin test, but no other overt signs of TB, are initiated on TNF inhibitor therapy (after failing disease modifying anti-rheumatic drugs [DMARDs]) without prophylaxis and are monitored closely at the Saskatoon TB clinic. Patients with positive TSTs were compared to patients on TNF inhibitors with a negative TST to see if reactivation rates of TB differed between the two groups. The literature has shown no consistent pattern of serious TB infection risk associated with the use of TNF inhibitors.²⁵ In this study, it was hypothesized that the patients who were TST positive were not at any increased risk of TB reactivation by taking TNF inhibitors.

The objective of this study was to determine if patients who test positive for TB have a significantly different risk of reactivation when not provided prophylaxis as compared to those who are prophylactically treated.

Materials and Methods

The cohort for this investigation consisted of all patients receiving biologic therapy at the office of a private urban rheumatology clinic and from the Royal University Hospital (RUH) in Saskatoon, Canada. Patient medical charts (n = 213) were reviewed from 2002-2012 for the following variables: age, gender, type of biologic therapy, types of DMARDs (particularly prednisone), and signs of active TB.

Patients were divided into two groups: those with either a positive TST (> 5 mm) or those with a negative TST (≤ 5 mm).

Of the patients with a positive TST, 26 had RA, eight had ankylosing spondylitis (AS), and five had psoriatic arthritis (PsA). Of the patients with a negative TST, 127 had RA, 29 had AS, 16 had PsA, and two had inflammatory bowel disease (IBD) arthropathy.

Total time that patients were receiving biologics was measured in months and patient years due to the unequal time in follow up in the different patients. There was no minimum amount of time that a patient had to be receiving biologics to be included, with the minimum time being three weeks for one patient. However, only two patients were receiving biologics for less than one year. No patient received TB prophylaxis.

Results

No evidence of TB reactivation occurred in either patient group. All of the patients included in this survey had moderate to severe RA as evidenced by having symptoms despite multiple types of DMARD treatments, and had thus been administered TNF inhibitor therapy. There were 39 patients with a positive TST currently receiving a TNF inhibitor and 174 patients with a negative TST receiving a TNF inhibitor. The majority of patients in both groups were over the age of 50 and were concurrently administered DMARDs (Table 1). Despite TNF inhibitor therapy, none of the patients showed evidence of active TB in follow up.

All but two of the positive TST patients received TNF inhibitors for at least 12 months, with the two receiving therapy for 6.9 and 0.7 months (Table 2). At each time interval, the total number of patients that made that length of time was tabulated. The numbers steadily decreased; none of the patients were treated with biologics for more than 120 months (Figure 1). In total, the positive TST patients accumulated 146 patient years of TNF inhibitor therapy and the negative TST patients 746 patient years.

Patients were treated with a range of TNF inhibitors; it was common for the patients to have been administered

Table 1

TNF Inhibitor-treated RA Patient Characteristics for Those with a Positive TST versus Those with a Negative TST

Characteristic	Positive TST*	Negative TST**
Age over 50 years	76.9%	70.0%
Male : female	22 male : 17 female	88 male : 86 female
Patients on DMARDs	77.8%	74.7%
Number of patients with TB	0%	0%

* Based on 39 patients; ** Based on 174 patients.

more than one form of TNF inhibitor therapy over the course of their treatment (Table 3). A total of 74% of positive TST patients and 59% of negative TST patients were receiving infliximab at some point in time, which was the most commonly-used TNF inhibitor. Of the remaining agents, the most common to least commonly administered were adalimumab, abatacept, rituximab, tocilizumab,

etanercept, and golimumab. None of the TST-positive patients had taken golimumab.

Of the 39 patients with a positive TST, 17 (44%) had a history of prednisone use, while 59 of the 174 patients (34%) with a negative TST had a history of prednisone use.

Discussion

Despite using TNF inhibitors without TB prophylaxis in a population considered at risk for TB reactivation, that being patients with a positive TST, no cases of reactivation were observed. Investigations have reported that the majority of LTBI reactivations due to TNF inhibitor administration occur in the early phase of treatment,^{4,11,26-28} with the median time of reactivation between 12-17 weeks.^{4,11} In this chart review, all but two of the patients received TNF inhibitors for more than 12 months. Furthermore, all of the patients were monitored closely at the Saskatoon TB clinic for two years after initiating TNF inhibitor therapy. If TB were to occur, the reactivations would have been most likely within that two-year window.^{11,26}

The level of increased risk of TB reactivation among the different biologics has been reported to differ. In one study, incident rates of TB reactivation were found to be highest with infliximab (1.5/1000 patient years), followed

Table 2

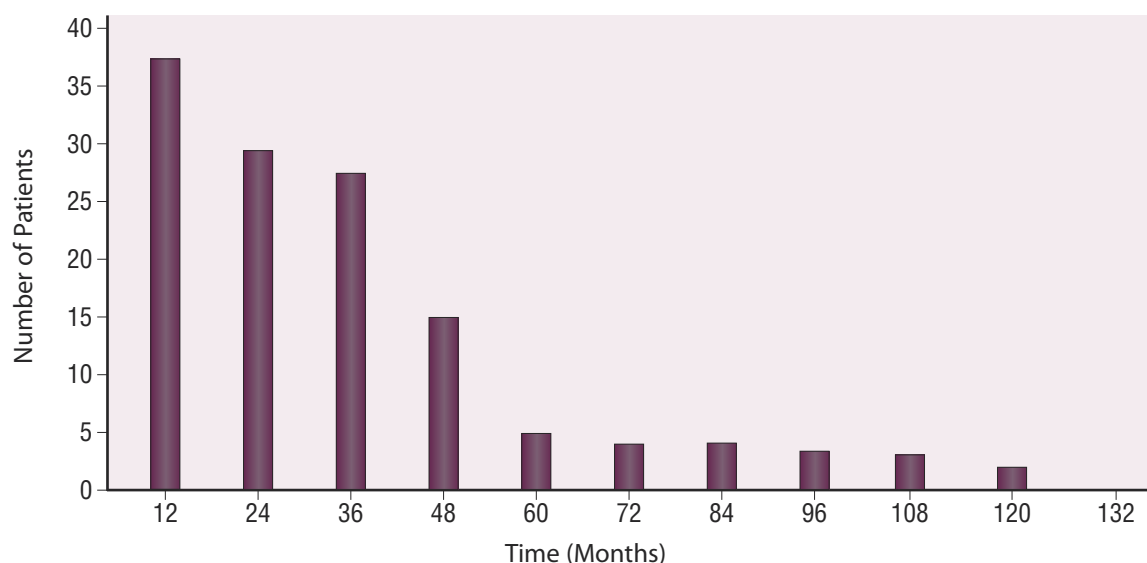
Minimum Length of Time Patients with a Positive TST Have Received TNF Inhibitors*

Time on TNF Inhibitor	Number of Patients
12	37
24	29
36	26
48	15
60	5
72	4
84	4
96	3
108	3
120	1
132	0

* Total patient-years was 146.2.

Figure 1.

Patients with a Positive TST Receiving TNF Inhibitors: Minimum Length of Time



Legend: At each time interval, the total number of patients that made that length of time was tabulated. Therefore, the numbers steadily decrease until none of the patients are on biologics for more than 120 months.

by adalimumab (0.9/1000 patient years), and then etanercept (0.5/1000 patient years).¹⁷ Other reports also placed infliximab as the most at risk for causing TB reactivation, followed by adalimumab, then etanercept.²⁶ Some studies have found a three- to four-fold higher risk when on infliximab or adalimumab as compared to etanercept;²⁷⁻²⁹ while other investigations have claimed there to be no difference between infliximab, adalimumab, and etanercept with respect to TB reactivation.²⁵

There has been no consistent pattern of serious TB infection risk associated with the use of TNF inhibitors.²⁵ Adalimumab was launched after the risk of TB had emerged and screening initiated, which may account for some of the over-reported rates of TB in patients on adalimumab, as a consequence of increased vigilance.²⁵ The mechanism of action of rituximab is not a concern for TB reactivation as while receiving TNF inhibitors.³⁰ In fact, there are no reported cases to date with patients being treated with rituximab,³⁰ nor have increased rate of TB been shown with tocilizumab.²⁸ However, since none of the patients developed active TB in our study, there does not appear to be an increased risk with any of the medications used.

As mentioned, the preferred regimen for treating LTBI is nine months of INH daily.^{1,19,21,22} The efficacy of INH has been reported as 60% for six months of daily INH (> 80% completion),^{31,32} and 90% for nine months of daily INH.³³ The completion rate is, however, very low, with one study showing persistence as low as 39%,³⁴ and other reports claiming rates between 50 and 60 %.^{35,36}

There are considerable risks associated with TB prophylaxis. The most serious side effect of INH is toxic

hepatitis.²³ Hepatic adverse effects from INH range from a mild increases in aminotransferases (10%-20%) to overt hepatitis, which is rare.²⁴ Risk factors include age over 35 years, being female, baseline elevation of aspartate aminotransferase (AST), and the concurrent use of alcohol.^{26,29,37} With over one million patients treated with INH since 1991, the incidence of INH-associated liver injury has been estimated at 1/1000 patients,¹⁹ hospitalization rates have been reported at 0.1 to 0.2/1000, and mortality rates of 0.0 to 0.3/1000.^{6,20,37} In public health clinic studies, the incidence of INH hepatotoxicity has varied between 0.1%²⁴ and 4%.³⁸ The differences is perhaps due to age of the population or definition of hepatotoxicity in these studies.³⁹ Another study found a rate of 5.63 hepatotoxic events per 1,000 patients, with higher rates associated with patients over the age of 50.³⁹ It should be noted that in this database study, only 41% of patients were to found to have completed three months of INH therapy, and only 22% six months of therapy.³⁹ The toxicity may have been higher in some instances if the compliance had been higher.³⁹ In one trial, 53% of the 255 patients that completed the nine months of INH therapy reported some symptoms during the treatment.² In the same trial, hepatotoxicity accounted for 40% of those patients permanently discontinued from the treatment.²

There are competing risks when considering treatment: TNF inhibitors and the reactivation of TB versus INH toxicity and compliance. If the annual risk of TB is greater than the risk of drug induced hepatitis, then prophylaxis should be received.²² Conversely, if the risk of hepatitis is greater, then patients should not receive prophylaxis, but rather be monitored closely, having any symptoms that develop investigated quickly and diagnosed early.²² When risk outweighs benefit, patients with an abnormal chest X-ray consistent with past TB (or prior extra pulmonary TB that has been adequately treated in the past) can begin TNF inhibitor treatment while being monitored clinically every three months.²² If no adequate treatment was received, then the risk-benefit analysis favors chemotherapy.²²

To illustrate the point, consider treatment for an average RA patient in Saskatchewan. The incidence of TB in Canada is 5.1/100,000, while in Saskatchewan it is somewhat higher at 6.2 /100,000.³¹ Specific incidences of TB in Saskatchewan are less than 1/100,000 for Caucasians, 43/100,000 for status First Nations, 23/100,000 for Metis, and 17/100,000 for foreign-born Canadians.³¹ The progression from latent infection to active TB has a

Table 3

Breakdown of TNF-inhibitor Usage in the Two Patient Groups*

TNF Inhibitor	Positive TST**	Negative TST***
Infliximab	74.1%	58.6%
Adalimumab	33.3%	26.4%
Abatacept	29.6%	17.8%
Rituximab	7.4%	8.6%
Tocilizumab	11.1%	9.8%
Etanercept	3.7%	23.6%
Golimumab	0%	6.9%

*The percentages are based on patients receiving medication for any period of time. ** Based on 39 patients.

*** Based on 174 patients.

universal estimate of a 10% incidence with a positive TST.³¹ In Saskatchewan, the rates are 0.8% and 6.9% for White-European and Status First Nation individuals, respectively.³¹ In order to make a risk calculation, the annual risk of TB should be multiplied by five (due to the increased risk caused by TNF inhibitor therapy) to account for TNF inhibitor medications,²² which would be divided by the risk of INH hepatitis.³¹ A ratio of less than one indicates observation is best, while a ratio of more than one would indicate that prophylaxis is preferred.³¹ The incidence would be determined by reviewing local epidemiology for the patient group and the toxicity as 278/100,000 people.³¹ For example, a Caucasian in Saskatchewan would have a risk of $([1/100,000] \times 5) / ([278/100,000])$, which would be 0.02, strongly favoring observation.³¹ Even for a Status First Nation patient, the ratio would be 0.8 $([43 \text{ cases}/100,000 \text{ people}] \times 5) / ([278 \text{ cases}/100,000 \text{ people}])$.³⁰

In this study, 76.2% of the RA patients treated with TNF inhibitors with a positive TST were over the age of 50 years, they would have been at a higher risk of toxicity. The risk-benefit ratio was less than one for all of the patients as well. Therefore, all of the patients theoretically would be safer not receiving prophylaxis.

In addition to being safer for the patient, not having to give prophylaxis would be beneficial for the health care system in terms of cost. In a study using financial information from Montreal, Canada, the estimated cost of treating one patient with nine months of INH was \$1,073 if no symptoms developed, and \$1,131 if symptoms developed but therapy was still completed.² Costs were attributable to routine visits, therapeutic agents, pharmacy charges, routine testing, and unscheduled visits. The costs of evaluation and management of specific adverse events varied from \$668 to \$1,249, depending on the severity of the adverse event.² Although medication is inexpensive for LTBI, the total costs are high because close monitoring is imperative due to the risk of drug-induced hepatitis.²

The exact risk of morbidity of TB associated with corticosteroid therapy is unknown, but therapy with them is a well-known risk factor for TB.⁴⁰ Reactivation of TB after patients were administered corticosteroids has been documented.⁴¹⁻⁴³ Corticosteroids have an immunosuppressive effect, which can promote TB reactivation, therefore, careful observation of patients taking steroids is required.^{42,44} However, there has also been no relationship found between total dose or duration and risk.⁴²

One of the limitations of this study was the small number of patients (39) with a positive TST, making it impossible to compare results with previous studies. With an expected risk of TB in TST-positive patients on TNF inhibitors of 2.6/1,000, the study would need about 400 patients to show one case of TB. There are not enough people in Saskatchewan to provide sufficient numbers. As far as we know, Saskatchewan is the only place providing biologics to TST-positive patients without receiving TB prophylaxis prior to therapy. Consequently, all the patients must come from Saskatchewan, making it very difficult to attain sufficient numbers of patients.

Although the numbers of patients in this study are not sufficient to compare the levels of risks with other studies, it shows that none of the RA patients on TNF inhibitors had reactivation of their TB.

Conclusion & Summary

In this investigation we demonstrated that RA patients on TNF inhibitors who did not receive prophylaxis are not at risk for TB reactivation. Although we could not fully answer the objective question of whether patients are at increased risk by not being on prophylaxis, the study acts as a probing study into the possibility of treating RA with biologics in patients with latent TB without the need for TB prophylaxis. Between 400 and 5,000 patients would be needed to objectively determine that there is no increased risk, but it is at least suggested. More investigations are needed, along with more follow up to provide more data.

We would like to acknowledge K. Shawn Davison for his contributions to editing.

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Vaccination in Juvenile Rheumatic Diseases

By Suzanne E. Ramsey, MD, FRCPC

A three-year-old presents with juvenile idiopathic arthritis (JIA). A 14-year-old with systemic lupus erythematosus (SLE) on prednisone has functional asplenia. A 17-month-old patient has received intravenous immunoglobulin (IVIG) for Kawasaki disease. A 10-year-old with juvenile dermatomyositis has just discontinued IVIG and methotrexate (MTX). What vaccine issues must be addressed in these patients?

With many new immunosuppressive therapies and evolving provincial immunization schedules¹⁻⁴ we review our guidelines annually with our vaccinology colleagues and make reference to international guidelines.⁵ Routine inactivated vaccines should be brought up-to-date. Live virus vaccines are generally considered contraindicated in immunosuppressed children and should be given before escalating treatment or when there is a gap in immunosuppression. High dose steroids (prednisone 10 mg/d-20mg/d or 0.2 mg/kg/d for more than two weeks), disease modifying anti-rheumatic drugs (DMARDs), and biologics may reduce vaccine response, as may active inflammatory disease. Systemic corticosteroids are one of the greatest risk factors for infection in rheumatology patients;⁶ DMARDs and biologics impact infection risk variably and require further study.

Viral Vaccines

Vaccination to ensure two doses of the measles, mumps, rubella, and varicella (MMRV) vaccine should be considered early in a child's life. MMRV can be given as early as 12 months and repeated within three months.¹ This vaccine may be safe in JIA patients on low dose MTX (< 10 mg/m²) but its safety has not been established during more intensive therapies.⁷ Limited data exist on varicella zoster virus (VZV) vaccine safety in rheumatology patients. Extrapolation from children with hematologic malignancy is difficult given that rheumatologic immunosuppression

is typically chronic. Indeterminate VZV or negative hepatitis B serology in previously vaccinated patients may improve with an additional booster.^{2,3} Secondary prophylaxis for VZV may be necessary. Rheumatology patients may benefit from personal and household annual influenza vaccines. Cold-adapted live flu vaccine (nasal mist) is more effective than injected inactivated vaccine; however,

there is no safety data in immunocompromised children. Vaccination of siblings should be safe unless the patient is considered profoundly immunosuppressed, in which case live vaccines should be avoided for household contacts.²

Live vaccines are delayed in children treated with IVIG, as it typically contains inactivating levels of MMR and VZV antibody. Specifically, MMRV vaccines for Kawasaki Disease patients must be delayed for 11 months after treatment with high dose IVIG (2 gm/kg). Lower doses of IVIG and other blood products require a lesser delay.¹ Plans for international travel should trigger consultation with a Public Health or a Travel Medicine consultant, as travel vaccines such as yellow fever and oral typhoid are contraindicated in immunosuppressed patients.¹

Bacterial Vaccines

Gram-positive infections may add to morbidity and mortality. Unvaccinated children should receive



Dr. Ramsey is a well-respected clinician-educator in the field of pediatric rheumatologic diseases.

pneumococcal vaccines, although the ideal timing in the disease course is unclear. Guidelines for previously unvaccinated immunocompromised children are pneumococcal conjugate vaccine (PCV) (*e.g.*, Pnevna 13) followed no sooner than eight weeks by pneumococcal polysaccharide vaccine (PPSV) (*e.g.*, Pneumovax 23).¹ Patients with surgical or autoimmune splenectomy require special consideration and pneumococcal, hemophilus influenza, and meningococcal vaccine are all recommended prior to planned splenectomy followed by pneumococcal antibiotic prophylaxis.⁸

Further Considerations

Following the cessation of immunosuppression, a protocol should be established for each child. While a remote risk of disease flare or adverse event may exist with vaccination, risk-benefit ratios typically strongly favour immunization. It is generally accepted, however, that a vaccine should be avoided if it has precipitated a disease flare or with highly active disease.²

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A Call To Action For Adult Vaccination: Immunocompromised Patients At Increased Risk

By Carolyn Whiskin, RPh, BScPhm, NCMP; Derek Haaland, MD, MSc, FRCPC; William Bensen, MD, FRCPC; and Vivien Brown, MDCM, CCFP, FCFP, NCMP

The Issue

Pediatric vaccination in Canada experiences high levels of adherence due to well-established protocols, public health support, and school-based programs. The same cannot be said for adult immunization. There is no established “check point” for adults regarding updating their vaccines and, according to the 2006 Canadian Immunization Survey, most adult Canadians are under-immunized for all vaccines. It has been suggested that a good time for this preventative health care discussion may occur at age 50 when adult screening tests for bowel and breast cancers, amongst others, begin.

This is not yet the current standard practice in Canada; as such, when patients require treatments which may suppress their immune system, specialists prescribing these therapies cannot assume that their patient's vaccinations have been updated. At the time of treatment initiation, the question becomes: “Who is responsible for ensuring vaccinations are given?” While the family physician has traditionally been responsible for advising on the use and administration of vaccines, specialists initiating treatment that will suppress the immune system have a level of responsibility to discuss and ensure their patients are vaccinated before treat-

ment initiation. At the CRA ASM in 2013, rheumatologists were surveyed regarding vaccinations. Results indicated that, although a discussion regarding vaccination was considered important by the majority of those surveyed, it was not part of regular practice. Reasons for not discussing vaccination included the amount of other necessary information to be discussed regarding diagnosis and treatment options, the patient being overwhelmed with information, and lack of time and nursing support. While it is important to note that adult vaccination may not have the same impact in preventing disease as it does in children, it has significant impact on attenuating disease in adults, decreasing morbidity and mortality rates. Our current statistics are dramatic as the death rate from vaccine preventable disease is 100-fold increased in adults compared to children.

What is the Current Status In An At-risk Population?

A retrospective population-based cohort of rheumatoid arthritis (RA) patients aged 66 years and older was assembled using Ontario health administrative data from April 1, 1992 to March 1, 2010. All patients were required to have had at least one exposure to a disease-modifying antirheumatic drug (DMARD), biologic agent, or oral glucocorticoid at the time of cohort entry. Infection rates were found to be higher in this population compared to the general population, with the highest incidence of infection seen for bacterial pneumonia, herpes zoster, and skin or soft tissue infections. When vaccinations are not given prior to administration of immunosuppressant agents, the already vulnerable patient is left unprotected. The consequence of acquiring pneumonia or shingles is beyond the burden of the infection itself, as patients are required to withhold their primary treatment until the infection clears. This has the potential to cause a relapse of the condition being treated; in the case of biologic treatment, missed doses can increase immunogenicity and result in a decrease in treatment effectiveness and increased adverse effects. Patients described loss of remission and increased disease burden of the initial chronic disease long after the secondary illness resolved. In a biologic clinic in Hamilton, Ontario, six cases of shingles were diagnosed within a one-month period, all resulting in withholding treatment. The resultant post-herpetic neuralgia along with arthritic flares were impactful for these patients. Not one of the six cases had received a zoster vaccination

and none reported their physician discussing vaccination before treatment initiation.

Invasive pneumococcal disease (IPD) due to streptococcus pneumonia has the highest incidence rate in the young and those over 50 years of age; risk of death due to IPD also increases with age. The incidence of shingles within a patient's lifetime is 30%, which also increases with age. Of greatest concern is the percentage of patients with post-herpetic neuralgia lasting greater than one year; rates have been shown to rise from 15% to 40% going from age 50 to older than age 70. The question is not only "What is the cost of vaccination?", but also, "What is the cost of not being vaccinated?"

A Call To Action

The CRA has published guidelines regarding appropriate use of vaccines prior to and during DMARD/biologic therapy. In 2013 the National Advisory Committee on Immunization (NACI) guidelines were updated with regards to immunocompromised patients. However, guidelines must be implemented to be effective. At The Charlton Centre for Specialized Treatment in Hamilton, Ontario, a protocol has been developed based on these guidelines. The protocol was launched in April 2013 by protocol authors Carolyn Whiskin and Dr. Jay Keystone. Since that time, referring physicians to the clinic have all received paper and electronic versions of the protocol (see Appendix 1). The Clinic's director of pharmacy programs, Carolyn Whiskin, subsequently visited each referring physician to discuss implementation of the protocol into their practice. Some rheumatologists have incorporated the protocol recommendations into their referral note to the Primary Health Care Provider along with providing a copy for the patient to share on their next visit to their family doctor. Other specialists have included vaccine discussion as part of a checklist for new patients entering their practice and built it into their electronic medical records. Some rheumatologists have taken the initiative to prescribe the vaccines not covered under government funding (*e.g.*, the conjugated pneumococcal vaccine [PPV13] and the herpes zoster vaccine), as these are both highly recommended for patients who will be receiving biologic DMARDS. Ideally, the discussion regarding vaccination needs to happen at the time of diagnosis, rather than waiting until biologic treatment is prescribed. At the Charlton Clinic, patients are screened when a prescription for biologic treatment is received. If



Vaccine Protocol For Patients Receiving Immunosuppressant Therapy

Vaccines administered *prior* to the initiation of immunosuppressant therapy (including DMARDs) reduce the risk of infection in patients with inflammatory arthritis (RA, PsA, AS), crohn's/ulcerative colitis, psoriasis and all other autoimmune diseases. To offer maximum protection and prevent interruption of treatment, *all* vaccines should ideally be administered 4 weeks (2 weeks minimum) prior to the initiation of treatment.

For patients *already* receiving immunosuppressant treatment, vaccination with inactivated vaccines is recommended **even though the benefit may be reduced**.

Live vaccines are not recommended during active treatment and **should be administered 4 weeks prior to treatment or 3 months after the discontinuation of therapy** (see Special Considerations: Live Vaccines).

Recommended Protocol Prior to Starting Immunosuppressive Therapy

Vaccine	Notes
Pneumococcal **Conjugate vaccine *Polysaccharide vaccine	<p>Prenar 13 (conjugate vaccine) should always be given first followed by Pneumovax (polysaccharide vaccine) at least 8 weeks later to cover remaining serotypes. Prenar 13 does not require a booster.</p> <p><u>NOTE:</u> If Pneumovax has been given previously, administer Prenar 13 at least 1 year later. A second dose of Pneumovax is recommended 5 years after the first dose</p>
**Herpes zoster (shingles)	<p>Approved for those over 50 especially for high risk patients. Higher risk of shingles has been noted in patients with autoimmune diseases.</p> <p>As a live vaccine, herpes zoster (Zostavax) is administered 4 weeks prior to administering immunosuppressant therapy, or 3 months after discontinuation.</p> <p>Herpes zoster vaccine may be administered to individuals on anti-TNF biologics on a case by case basis after review with an expert in immunodeficiency (NACI recommendation B, fair.)</p>
* Influenza	Annual immunization recommended.

Vaccinations to be considered for all adults regardless of immunosuppressant therapy

In addition to the vaccines listed below, all practitioners must ensure all adults have had their primary childhood vaccinations. (ie. MMR). In some at risk patients a booster of Meningococcal vaccine is suggested (students and military living in residential accommodations and African travel).

Vaccine	Notes
*Hepatitis A and B	Suggested for high risk patients due to occupation, travel, liver disease, sexual behaviour, illicit drug use or blood transfusions.
* Tetanus/Diphtheria/Pertussis (Tdap)	Suggested as a one- time booster in place of a Td dose.
* Tetanus/Diphtheria (Td)	Given every 10 years to all adults.

* These vaccinations may be funded by the Ontario government based on medical condition, illicit drug use or sexual behaviour

** These vaccinations are not funded by the Ontario government for adults. Private insurers may cover this expense.



Special Considerations: Live Vaccines

- Live vaccines include
MMR, varicella, herpes zoster, **FluMist** (nasal influenza vaccine), yellow fever and oral typhoid, BCG and rotavirus
 - Live Vaccine Administration - There are no contraindications to giving multiple vaccines at the same clinic visit. Two or more live virus vaccines may be given at the same visit, or if this is not possible, separated by a period of at least 4 weeks.
 - Live vaccines are **not recommended** in combination with the following medications except as noted below with the herpes zoster (shingles) vaccine:
Azathioprine, cyclosporine, cyclophosphamide, leflunomide, mercaptopurine, methotrexate and all biologic DMARDs
 - Corticosteroid therapy is **not a contraindication** to administering a live vaccine when steroid therapy is short-term (i.e., less than 14 days) ; or a low-to-moderate dose (less than 20 mg of prednisone or equivalent per day for an adult) ; or long-term, alternate-day treatment with short-acting preparations; or maintenance physiologic replacement therapy; or administered topically, inhaled, or locally injected (e.g., joint injection).
- NOTE:** Herpes zoster (shingles vaccine) may be administered to individuals on anti-TNF biologics on a case by case basis (see chart on previous page) and given with the following medications provided that the drug doses are less than:
- Methotrexate 0.4mg/kg/week
 - Azathioprine 3mg/kg/day
 - 6-Mercaptopurine 1.5mg/kg/day
- Live vaccines can be given in combination with:
Gold preparations, hydroxychloroquine and sulfasalazine

This immunization protocol was developed by Carolyn Whiskin, RPh, BScPhm, NCMP in consultation with Dr Jay Keystone, MD, MSc (CTM), FRCPC for the Charlton Centre for Specialized Treatments. This project was supported by educational grants from Pfizer Canada and Merck & Co., Inc. If you are interested in utilizing this document for your own clinic, please contact the Centre at 905-526-7306 or JFriedrich@charltoncentre.com.
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this discussion has been missed, a window of opportunity exists during the time that reimbursement is being coordinated for vaccinations to be updated. A cover letter to accompany the vaccine protocol can be sent to the patient's family physician at the request of the specialist prescribing immunosuppressant therapy and the patient.

While uptake of the protocol at some rheumatologists' offices has been slow to be implemented, others have gone from no vaccination discussion to 100% of patients receiving information and following up with their family physician. The herpes zoster vaccine is not a covered benefit in any province; PPV13, although a benefit for children, has limited coverage across Canada for at risk patients. It is important to note that provincial regulations are under regular revision. As there is a cost associated with some vaccines, the decision to pursue vaccination is still patient based, with only 30% of private insurers covering the expense.

Infectious disease prevention through the vaccination of immunosuppressed patients makes sense biologically, given that any relative risk reduction will have the biggest pay-off in a group with high baseline risk. That said, infection risk and vaccine responses in a given individual are multifactorial, with both disease-related and medication-related factors playing a role. In fact, in terms of infection risk, there is evidence that active disease may play a bigger role in immunocompromised patients than disease-modifying treatment itself. Thus, rheumatoid disease control via immunosuppression, somewhat paradoxically, may well be the single most important factor in infection reduction.

Coordinated multicentre efforts will be required to delineate the clinical effects of vaccination in our immunosuppressed population. Studies on immunogenicity of vaccines in such patients will be relevant, but even more important will be the long-term clinical follow up of large numbers of patients to track infection incidence.

The time has come to take action. The role of rheumatologists is expanding and the use of immunosuppressive medication requires not only a fully informed patient, but also a fully vaccinated patient to reduce inherent, preventable risk. As we have national guidelines from NACI and the CRA, it is becoming increasingly clear that the standard of care in Canada includes aggressive prevention of infections in immunosuppressed patients.

Our role is to advocate, facilitate, and ultimately vaccinate our population if we are to achieve the outcomes of disease modification that we seek in our at-risk, adult population.

Suggested Readings

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Robert Inman Lectureship

By Claire Bombardier, MD, FRCPC

In November of 2013, we celebrated the 10th anniversary of the Robert Inman Lectureship. This visiting professorship was established by Dr. Claire Bombardier, current Rheumatology Division Director at the University of Toronto. Dr. Inman served as Division Director from 1991-2003 and this visiting professorship was created to honour his contribution to our University program, pay homage to his commitment to rheumatology, and feature his area of research: spondyloarthropathies.

Dr. Inman, originally from Toronto, completed his undergraduate degree at Yale University and his medical degree at McMaster University. He did his training in internal medicine at Vanderbilt University and his fellowship in rheumatology at Cornell University, based at the Hospital for Special Surgery in New York City. He worked as a research fellow at the Hammersmith Hospital in London before returning to a faculty position as Assistant Professor of Medicine at Cornell University. In 1983 he returned to Toronto. Presently, Dr. Inman is a Professor in the Departments of Medicine and Immunology and attending physician at Toronto Western Hospital.

Internationally, Dr. Inman has held numerous leadership positions within the American College of Rheumatology (ACR), including President of the Northeast Region and membership on the Board of Directors. He is past-Chair of the Medical and Scientific Advisory Board of the Spondylitis Association of America (SAA).

He continues to be a leader in ankylosing spondylitis (AS), serving as a member of the Steering Committee of the International Ankylosing Spondylitis Genetics Consortium and as a member of the Executive Committee of the Spondyloarthritis Research Consortium of Canada (SPARCC). Locally, he is Director of the Arthritis Center of Excellence at The University Health Network, a multidisciplinary research program incorporating basic and clinical investigators.



Dr. Inman has been the recipient of numerous research awards, including the Distinguished Investigator Award from the CRA and the Jonas Salk Award from the March of Dimes. Nationally, he was selected to deliver the Dunlop-Dottridge Lecture at the 1998 annual meeting of the CRA, along with receiving awards for the Woodbury Lectureship at Dalhousie University, the Ogryzlo Lectureship at the University of Manitoba, and the Little Lectureship at the University of Toronto.

Each year speakers are chosen who can emulate this type of dedication, teaching, and research in spondyloarthropathies. This event is well-attended and the reputation of the Robert Inman Lectureship continues to grow as it becomes a prestigious part of the University of Toronto citywide rheumatology rounds.

Robert Inman Lecturers

Year	Lecturer
2013 (November)	James T. Rosenbaum, Professor of Inflammatory Diseases, Professor of Ophthalmology, Medicine and Cell Biology, Oregon Health & Science University, Portland, Oregon
2013 (January)	Paul Bowness, Professor of Medicine, Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences University of Oxford, United Kingdom
2012	Muhammad Asim Khan, Professor of Medicine, Case Western Reserve University School of Medicine Cleveland, Ohio
2011	Deferred
2010	Matthew Brown, Professor of Immunogenetics, University of Queensland Diamantina Institute, Brisbane, Australia
2009	Robert Colbert, Chief, Pediatric Translational Research Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, Maryland
2008	John D. Reveille, Professor of Medicine and Director, Division of Rheumatology and Clinical Immunogenetics, The University of Texas Medical School at Houston, Texas
2007	Joachim Sieper, Professor of Medicine, Department of Rheumatology, Charites, Campus Benjamin Franklin & German Rheumatology Research Center, Berlin, Germany
2006	Desiree van der Heijde, Professor of Rheumatology, University Hospital Maastricht, The Netherlands
2005	Peggy Crow, Professor of Medicine, Weill Medical College of Cornell University-NYH-HSS Senior Scientist, Research Division, Hospital for Special Surgery, New York
2004 (Inaugural)	Jurgen Braun, Rheumazentrum-Ruhrgebiet, Herne and Ruhr-Universitat Bochum, Germany

*Claire Bombardier, MD, FRCPC
Professor of Medicine and Pfizer Research Chair in
Rheumatology, University of Toronto
Director, Division of Rheumatology, University of Toronto
Senior Scientist, Institute for Work & Health and Toronto
General Research Institute, University Health Network
Canada Research Chair in Knowledge Transfer for
Musculoskeletal Care
Co-scientific Director, Canadian Arthritis Network
Toronto, Ontario*

News of Newfoundland & Labrador

By Paul Dancey, MD, FRCPC

My last regional update for the *CRAJ* was almost 10 years ago. I was still in the early stages of working at the Janeway Children's Hospital and Memorial University as a pediatric rheumatologist. I can recall leaving the hospital every day with a stack of charts to review in the evening in preparation for the next clinic. With current privacy laws I would probably be arrested before reaching my car if I tried to do that again. While it is interesting to meet new patients, I have also come to appreciate getting to know patients over the longer term. While that stops at age 18 (not really long term!), patients still drop in to let me know how they are doing. I received my first consult request recently for the child of a former patient. Yet another mark in the passage of time.

In the last update I was hoping that a subspecialty nurse would be added to the team. For the last several years, Betty Sheppard has taken on this role dividing her time between rheumatology and gastroenterology. Her presence has made a huge difference to improving patient care. The diagnosis and treatment plan is relatively straightforward, compared to figuring out how to start methotrexate or biologic injections for a patient living in rural parts of Newfoundland or isolated areas of Labrador. Betty seems to have a direct line to everyone and can get things done quickly.

The number of patients coming through the adult rheumatology program continues to be almost overwhelming for the small but outstanding group of rheumatologists in the province. Dr. Nayef Al-Ghanin came aboard in August of last year, joining Dr. Sean Hamilton, Dr. Proton Rahman, Dr. Majed Khraishi, and Dr. Ramin Yazdani. Given their research and teaching responsibilities their numbers fall well short of the seven full time equivalent rheumatologists needed to serve the province. Despite the challenges there has been a significant improvement in access to rheumatology care with the assistance of a team of allied health professionals. A rheumatology nurse practitioner helps triage standardized referral forms, and can direct patients into a rheumatology health program that includes



Our new medical school building in lovely St. John's.

the services of a physiotherapist, occupational therapist, pharmacy, as well as the rheumatologist. Patients with inflammatory disease thus have early access to an effective multidisciplinary team.

Newfoundland and Labrador is on the eastern edge of the country and the leading edge of research and technology development. Dr. Khraishi and software engineers at Newfoundland and Labrador Research Technologies (www.nlrt.ca) have developed several apps for both screening and monitoring arthritic disease; these are available on iTunes. Genetic research is one of our strengths, which will be further facilitated with the opening of a new genetic research facility at Memorial University. The medical school class size has now expanded from approximately 60 to 80 students. The new medical school building opening later this year will provide state of the art classroom technologies and an advanced patient simulator.

So despite the rumors of fog, the sun is always shining out this way. Come and visit and you might just choose to stay.

*Paul Dancey, MD, FRCPC
Associate Professor of Medicine,
Pediatric Rheumatologist,
Janeway Children's Hospital and Rehabilitation Centre
St. John's, Newfoundland*

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The product monograph is also available by calling 1-800-387-8781.

Reference: SIMPONI® I.V. Product Monograph, Janssen Inc., November 28, 2013.

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RA Guidelines: Practice Patterns of Rheumatologists in Canada Compared to CRA Recommendations for RA (Part IV)

By Sankalp V. Bhavsar, MD, FRCPC; on behalf of Carter Thorne, MD, FRCPC, FACP; Claire Bombardier, MD, FRCPC; Vivian P. Bykerk, MD, FRCPC; Glen S. Hazlewood, MD, FRCPC; Pooneh Akhavan, MD, FRCPC; Orit Schieir, MSc; and Sanjay Dixit, MD, FRCPC

In this instalment, we present the results of survey questions pertaining to treatment with biologic disease-modifying antirheumatic drugs (DMARDs) and perioperative care.

1. Which of the following statements regarding anti-tumor necrosis factor (TNF) therapy in rheumatoid arthritis (RA) is false?

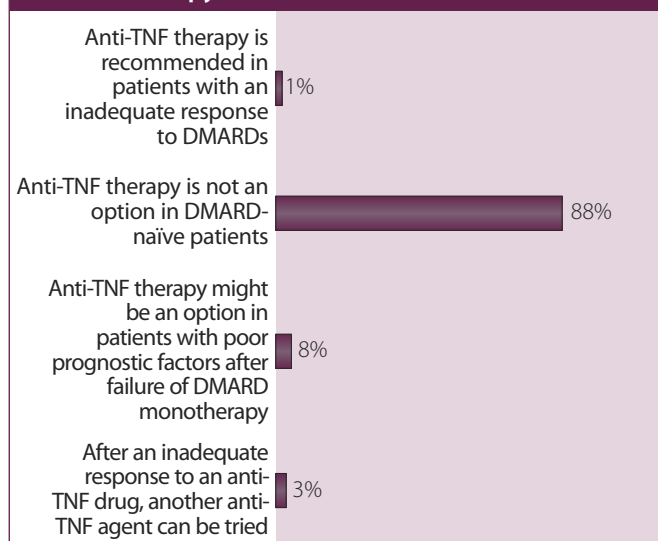
Answer: Anti-TNF therapy is not an option in DMARD-naïve patients.

Recommendation/supporting evidence: European League Against Rheumatism (EULAR) 2010,¹ Canadian Agency for Drugs and Technologies in Health (CADTH) 2010,² EULAR 2013.³

Systematic reviews performed by EULAR¹ and CADTH² considered all anti-TNF agents (adalimumab [ADA],

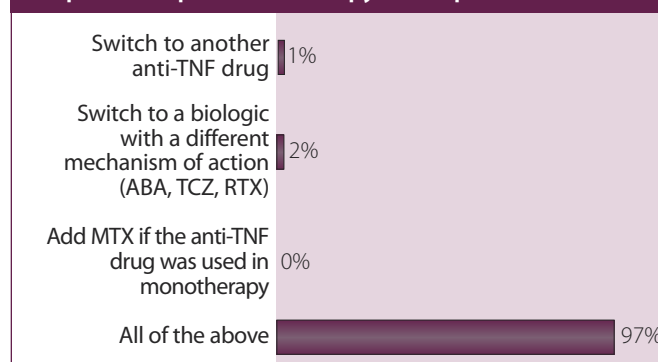
certolizumab [CTZ], etanercept [ETN], infliximab [IFX], and golimumab [GOL]) and trials in both DMARD-inadequate responders and methotrexate (MTX)-naïve patients. There is direct randomized controlled trial (RCT) evidence of efficacy for all anti-TNF therapies in patients who have had an inadequate response to MTX. For IFX, ETN, ADA, and GOL, there is also RCT evidence for efficacy in patients who are MTX-naïve. Some patients in these trials were also DMARD-naïve and all patients had early RA with high baseline disease activity. There were no head-to-head trials comparing anti-TNF agents. Although the 2013 update of the EULAR recommendations³ has abandoned the former recommendation that DMARD-naïve patients with poor prognostic markers might be considered for combination therapy of MTX plus a biologic, the exceptional use of a biologic agent in such patients is not precluded.

Table 1. Which of the following statements regarding anti-TNF therapy in rheumatoid arthritis is false?



2. A patient with RA has had an inadequate response with an anti-TNF agent. Which of the following are possible options for therapy in this patient?

Table 2. A patient with RA has had an inadequate response with an anti-TNF agent. Which of the following are possible options for therapy in this patient?



Answer: All of the above.

Recommendation/supporting evidence: EULAR 2010,¹ CADTH 2010,² EULAR 2013.³

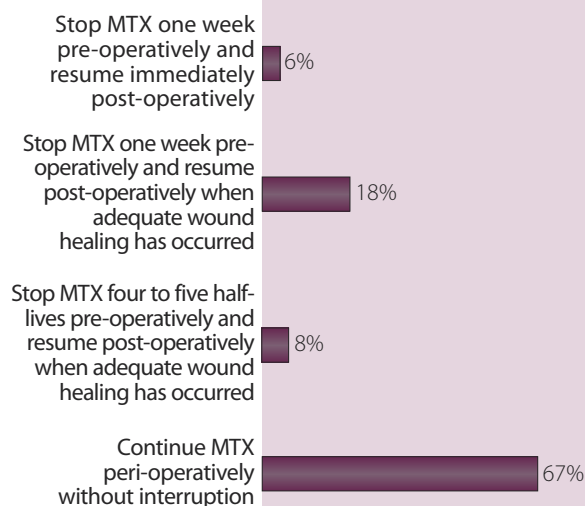
A systematic review of RCTs used to inform the EULAR 2010 guidelines¹ provided evidence supporting the efficacy of rituximab (RTX), abatacept (ABA), tocilizumab (TCZ), and GOL in patients who have failed one anti-TNF agent. CADTH² referred to a health technology assessment performed by the National Institute of Clinical Excellence (NICE) on options for treatment with biologic agents after failure of an anti-TNF; the conclusion was that switching to another anti-TNF may have some benefit based on observational studies. There is also RCT evidence for dose escalation of biologics. We found contradictory evidence for IFX (two trials showing benefit and one showing no benefit) and found evidence against dose escalation of ETN. There was no evidence provided to support dose/interval adjustment of ADA. Current evidence does not suggest a specific agent to be preferable to another TNF inhibitor when there is active disease, despite initial treatment with a TNF inhibitor.

3. A patient with RA is maintained on MTX 20 mg PO weekly.

She is scheduled for a total knee replacement. Regarding perioperative management of MTX, you would suggest?

Answer: Continue MTX perioperatively without interruption. Recommendation/supporting evidence: Visser 2009,⁴ British Society for Rheumatology (BSR) 2009,⁵ BSR 2008.⁶

Table 3. A patient with RA is maintained on MTX 20 mg PO weekly. She is scheduled for a total knee replacement. Regarding peri-operative management of MTX, you would suggest:



The BSR^{5,6} and Visser et al⁴ referred to evidence from RCT and observational studies that examined outcomes in RA patients who stopped treatment versus those who continued MTX prior to elective orthopedic surgery. The largest RCT of RA patients undergoing elective orthopedic surgery showed a lower rate of postoperative complications, including infection in patients who continued MTX perioperatively (2/88 [2%]) compared to those who discontinued MTX (11/72 [15%]), and fewer RA flares six weeks after surgery (0/88 [0%] vs. 6/72 [8%]). Consistent results were also reported in a smaller RCT of 64 RA patients and in a retrospective cohort study of 122 RA patients. Only two small cohort studies (n = 32 and n = 38, respectively) have reported an increased risk of local infections in RA patients who continued compared to those who discontinued MTX prior to orthopedic surgery.

For further information on these recommendations and the supporting evidence of these results, please consult the CRA RA Guidelines document, available at www.rheum.ca/en/publications/cra_ra_guidelines.

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Orit Schieir, MSc; and

Sanjay Dixit, MD, FRCPC

ACR in San Diego: Imprinting New Memories Over Old Ones

By Philip A. Baer, MDCM, FRCPC, FACR

My first American College of Rheumatology (ACR) conference in San Diego was unforgettable. The year was 2005 and it was probably the last conference I attended without bringing my own laptop. Internet cafes were still in vogue in the exhibit area. I booked at the last minute and ended up at a cheap non-ACR hotel under renovation, which was serviceable; I did not spend much time there. The convention centre was a nice walk away through the Gaslamp Quarter. There were also enough ACR-sanctioned hotels around that I could catch the conference shuttle (impossible now without paying an added fee, but things were looser back then).

I attended a preconference Advisory Board from which I only recall one thing: Do not try to blank out an LCD projector by putting a piece of paper in front of the lens! Fortunately, the hosts put out the resulting fire at the “wisps of smoke” stage.

I had an evening flight booked home on the last day of the conference. I remember standing in bright sunshine outside the convention centre and finding a cab. By the time I arrived at the airport, thick fog had descended. My flight was repeatedly delayed and then cancelled as the plane never made it to San Diego. Not good when I had an office booked the next day and a continuing medical education (CME) presentation to deliver that evening. I called my wife with the bad news, and she contacted my secretary to deal with the patients.

Fortunately, I had company. I met up with Dr. Jan Schulz, a rheumatology colleague I knew from my training in Montreal. He was stranded too, and neither one of us had a hotel room. We joined forces and returned to my cheap hotel hoping for a room, as all the airport vicinity hotels were fully booked. It turned out they only had one room left, with a queen bed. We ended up spending the night sleeping fitfully in it, before returning to the



airport and testing our luck. I ended up on a flight to Houston and then Toronto. A taxi from the airport dropped me at my presentation venue, minutes before the talk was to start. My wife met me there with my laptop, much to the relief of the organizing representative. No one complained too much that I delivered my presentation wearing a neon-green T-shirt I had been given at one of the ACR exhibit booths: it was the only clean shirt I had left!

Fast forward to 2013. The CRA Annual Scientific Meeting (ASM) in February meant I spent Valentine's Day without my wife in Ottawa, and the ACR in October meant I was celebrating my birthday on Canada Night with many of my colleagues, but with my wife back home again. Fortunately, my son Jeffrey decided to take advantage of the hotel room I had already booked, and the need to use his vacation days before the end of the year, to join me in San Diego.

Consequently, I have much better memories this time. A nicer hotel, a spacious convention centre, a conference replete with cutting-edge basic and clinical science presentations and excellent reviews of rheumatology and non-rheumatology topics of interest to rheumatologists, Thieves Markets, workshops, and Meet-the-Professor sessions all helped. The latter two series had strong Canadian content, with featured speakers including Dr. Janet Pope, Dr. Robert Inman, Dr. Ed Keystone, Dr. Walter Maksymowych and Dr. Baer (not this Baer—I know I have nothing to teach other rheumatologists—that was Dr. Alan Baer, an American expert on Sjogren's. Canadians were also well-represented as faculty at the numerous pre-meeting courses, including Dr. Vivian Bykerk, Dr. Hani El-Gabalawy, and Dr. Mary-Ann Fitzcharles. There really is something for everyone.

I presented two posters, featuring Canadian registry data, including one which was selected for a Guided Poster Tour. I had the run of the conference the rest of the

time, once all of our CRA and CRAJ meetings were completed. One particular highlight was the opening lecture presented by Dr. Craig Venter, the geneticist who won the race to sequence the human genome. He is a fascinating character, and I highly suggest reading his autobiography, *A Life Decoded: My Genome: My Life*. Another interesting session modelled on the CRA was The Great Debate: Biologics or Triple Therapy for the Treatment of Rheumatoid Arthritis? with Dr. James O'Dell and Dr. Ron van Vollenhoven as combatants. I think I know whom Dr. Vandana Ahluwalia and Dr. Keystone, the Canadian co-authors of the RACAT study on this topic recently published in the *New England Journal of Medicine (NEJM)*,¹ were cheering for.

The host city provided great weather and many sites to see, including the famous San Diego Zoo, the USS Midway, Balboa Park, the Embarcadero, and a heritage Old Town district. Excellent food, from Mexican to BBQ and everything in between, was also readily accessible. No fog this time, though Air Canada advanced our return flight home by five hours, forcing me to miss the last morning of the meeting (I forgive them as they did upgrade me to business class three times in the last two months, twice gratis).

I look forward to seeing many of you at ACR 2014 in Boston.

Reference

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Philip A. Baer, MDCM, FRCPC, FACR
Editor-in-chief, CRAJ
Scarborough, Ontario



Reunited in 2013: Dr. Baer and Dr. Schulz.

Don't Go It Alone!

Arthritis Cross-disciplinary Research Leads to Development of a Peer-to-Peer Mentoring Program

Dr. Mary Bell, from Sunnybrook Health Sciences Centre, investigated the impact of a peer support program on people living with early inflammatory arthritis (EIA). Her unique research team included two patients, also known as "consumers": Dawn

Richards, PhD, from the Canadian Arthritis Network's Consumer Advisory Council, and Jennifer Boyle, PhD. The intervention model they developed resulted in improvements for mentees in overall impact of arthritis on life, coping efficacy, and social support.

A subsequent pilot randomized control trial (RCT), supported with a grant from the Canadian Initiative for Outcomes in Rheumatology Care (CIORA), showed that early peer support improved perceived social support but had little effect on other outcomes.

However, Dr. Bell and Dr. Jennifer Stinson at the Hospital for Sick Children have recently been awarded a Canadian Institute for Health Research (CIHR) grant to develop an online version of peer-to-peer mentoring for adolescents and the research team is now seeking funding to do a larger RCT. Research thus far has been made possible in part through funding from the Canadian Arthritis Network (CAN) and the Canadian Institutes of Health Research (CIHR).

For more information about the research, contact Mary Bell at mary.bell@sunnybrook.ca.



Update on Immunization in Patients with Autoimmune Rheumatic Diseases

By Shelly McNeil, MD, FRCPC; and Diva Miri, MD

Mrs. M is a 56-year-old woman with longstanding rheumatoid arthritis (RA) for which she has been maintained on methotrexate (MTX) for many years. Because of ongoing disease activity and functional limitation, hydroxychloroquine was added three months ago. Despite this, she has had ongoing disease activity and a decision has been made to initiate therapy with infliximab. Prior to starting this agent, you wish to review her immunization history and ensure that she has been brought up to date on all recommended vaccinations.

Patients with chronic inflammatory rheumatic or autoimmune conditions are known to be at approximately two-fold greater risk of severe infections than healthy adults. While the mechanism of increased risk is not entirely understood, it is likely to be multifactorial and involve aberrations in immune system function, prevalent underlying comorbidity, and the immunosuppressive properties of many of the therapeutic agents used to manage disease. Immunization therefore represents an important and sometimes overlooked element of the care of these patients.

Several principals guide the immunization of immunocompromised patients due to disease or therapy. Patients with underlying autoimmune rheumatic diseases (RD) and those undergoing treatment with immunosuppressive medications should receive all routinely recommended inactivated adult vaccines (Table 1). In general, patients receiving immunosuppressive doses of medications should not receive live attenuated vaccines because of the risk of disseminated disease caused by the vaccine strains; the decision to withhold live vaccines should be made after careful assessment of the risk:benefit of a particular live vaccine in an individual patient given the patient's underlying diagnosis and degree of immunosuppression. Many patients with chronic inflammatory conditions are cared for by both primary-care and specialty physicians, so it is critical that rheumatologists actively review immunization histories at each visit and seize opportunities to provide all recommended vaccines, or provide clear guidance to primary-care physicians about which vaccines should be

provided or avoided. Because the immune response to some vaccines may be suboptimal in this population, protection should be optimized by providing recommended vaccines as early in the disease course as possible and, ideally, before initiation of immunosuppressive medications. Protection should also be optimized by ensuring that all household and other close contacts of these patients have received all recommended vaccines.

Further history from Mrs. M reveals that she has received all recommended childhood vaccines, but has never received any vaccines as an adult. She works as a librarian, has three adult children and one infant grandchild. She is married and monogamous. Aside from her RA, she is well and takes no medications other than her MTX and hydroxychloroquine.

Like all adults, Mrs. M should receive a single dose of tetanus-diphtheria-acellular pertussis (Tdap) vaccine. While serious disease due to pertussis typically occurs in young infants, approximately 20% of all cough illness in adults lasting longer than 10 days is due to pertussis. The incidence of pertussis is increasing in adolescents and adults since the advent of routine pertussis immunization in childhood. Administration of Tdap is of particular importance in Mrs. M because of her risk of transmitting pertussis to her infant grandchild, who would be at high risk of severe disease. Following a single dose of Tdap, Mrs. M should continue to receive a booster dose of tetanus-diphtheria toxoid (Td) every 10 years.

Annual influenza immunization is recommended in patients immunocompromised due to disease or therapy. Only trivalent inactivated influenza vaccine (TIV) should be used in this population. Live attenuated influenza vaccine (LAIV) should not be used, but is safe in household contacts of immunocompromised patients. Although influenza vaccine effectiveness may be lower than in healthy adults, limited studies suggest that the majority of immunocompromised adults will mount a protective humoral antibody response to TIV. Delivery of TIV into the dermis of the skin has the potential to enhance the immune response to influenza vaccine by exposing the vaccine antigen to antigen-presenting dendritic cells present in high concentrations in the dermis. Amongst adults aged 60 years and older, intradermal TIV has been shown to elicit immune responses that are superior to conventional intramuscular TIV. Based upon improved immunogenicity in the elderly, it is reasonable to consider the use of intradermal TIV in younger immunocompromised patients to optimize protection. A high-dose TIV vaccine containing four times the influenza antigen present in conventional TIV products has been shown to elicit higher immune responses in elderly adults and in patients with human immunodeficiency virus. When this vaccine becomes available in Canada in the near future, it will offer an alternative with improved immunogenicity and potentially improved effectiveness in immunocompromised adults. Studies of the immunogenicity and efficacy of adjuvanted TIV, intradermal TIV, quadrivalent and high-dose TIV are urgently needed to inform decisions about the preferred influenza vaccination strategy in this high-risk population.

Recommendations for the prevention of pneumococcal disease in immunocompromised adults have recently changed in Canada (Table 1). Invasive pneumococcal disease is an important cause of morbidity and mortality in immunocompromised adults, those 65 years and older and adults of all ages with medical comorbidities. There are currently two vaccines available for the prevention of pneumococcal disease in adults. The immunogenicity of 23-valent pneumococcal polysaccharide vaccine (PPV-23) has been evaluated in patients with chronic rheumatic or autoimmune diseases with mixed results. In general, patients with systemic lupus erythematosus (SLE), RA, and those on disease-modifying antirheumatic drugs (DMARDs), including monotherapy with MTX, tend to mount protective immune responses less frequently than

healthy adults to some vaccine strains. Some data suggest the duration of antibody protection may also be reduced. A 13-valent conjugated pneumococcal vaccine (PCV-13) has recently been authorized for use in adults in Canada and is now recommended by the National Advisory Committee on Immunization (NACI), for all immunocompromised adults. While no studies of vaccine effectiveness of PCV-13 have been done, PCV-7, the 7-valent pneumococcal conjugate vaccine used prior to PCV-13 has been shown to prevent invasive pneumococcal disease in HIV-infected adults; PPV-23 was not effective in such patients. Studies of the immunogenicity of PCV-13 in immunocompromised adults have shown mixed results but, in general, PCV-13 appears to be more immunogenic in patients who have undergone hematopoietic stem cell transplant and those with HIV infection; the data is less convincing in patients with solid organ transplant. There have been no studies of immunogenicity or effectiveness of PCV-13 in patients with autoimmune RDs. Given the importance of invasive pneumococcal disease as a cause of morbidity and mortality in immunocompromised adults, the suboptimal effectiveness of PPV-23, and the potential immunologic advantages of PCV-13, NACI now recommends that all immunocompromised patients receive both PCV-13 and PPV-23 to provide optimal humoral immunity against the 13 pneumococcal strains in PCV-13, and to broaden coverage against the additional pneumococcal strains in PPV-23. Because the immune response to PCV-13 is impaired in patients who have recently received PPV-23, the timing of administration of these vaccines is very important. Patients who have not received PPV-23 should receive a dose of PCV-13 followed eight weeks later by a dose of PPV-23; a single booster dose of PPV-23 five years later completes the series. Patients who have had PPV-23 in the past should receive a dose of PCV-13 at least one year after the dose of PPV-23; a single booster dose of PPV-23 should be given at least eight weeks after the PCV-13 and five years after PPV-23 to complete the series.

Mrs. M should receive a dose of PCV-13 now followed by PPV-23 in eight weeks and a booster in five years. PCV-13 and PPV-23 can be co-administered with influenza vaccine for convenience.

Shingles, caused by reactivation of latent varicella zoster virus from the spinal and cranial sensory ganglia, is characterized typically by unilateral pain and vesicular

Table 1

Routinely Recommended Adult Immunizations

Inactivated Vaccines	Indication	Further Doses
Diphtheria/Tetanus (Td)	All adults	Every 10 years
Acellular pertussis (Tdap)	All adults	
Influenza*	Adults ≥ 65 years, high-risk [†]	Yearly
PPV-23	Adults ≥ 65 years, high-risk [†]	Booster dose at 5 years ^{††}
PCV-13	Immunocompromised adults	PPV-23 after 2 months, then 5 years later ^{††}
Human papillomavirus (HPV)	Males and females 9 years -26 years	3 doses
Quadrivalent conjugate meningococcal	2 years – 55 years, high risk	8 weeks, every 5 years
Live Attenuated Vaccines		
Measles/Mumps	Adults born 1970 or later	High risk (HCW, military, students)
Rubella	Susceptible adults	
Varicella zoster	Susceptible adults	8 weeks
Herpes zoster	Adults ≥ 60 years (consider ≥ 50 years)	

*Refers to TIV vaccines given intramuscularly or intradermally. LAIV should not be used in immunocompromised patients.

[†]High-risk conditions include cardiac or pulmonary disorders (including asthma), diabetes mellitus and other metabolic diseases, cancer, immune compromising conditions (due to disease and/or therapy), renal disease, anemia or hemoglobinopathy, conditions that compromise the management of respiratory secretions, morbid obesity (Body Mass Index [BMI] ≥ 40), and pregnancy; residents of chronic care facilities or nursing homes and household contacts of patients with high risk conditions should also be vaccinated.

^{††}Includes high-risk conditions listed for influenza in addition to functional or anatomic hyposplenism, sickle cell disease, cochlear implant, cerebrospinal fluid leak, chronic liver disease, alcoholism, illicit drug use, smoking, and homelessness.

^{†††}Single booster dose after five years recommended in those with functional or anatomic asplenia, sickle cell disease, hepatic cirrhosis, chronic renal failure or nephrotic syndrome, HIV, and immunosuppression due to disease or therapy.

^{††††}Immunocompromised adults who have never received pneumococcal vaccine before should receive PCV-13 followed eight weeks later by PPV-23 and a single booster dose of PPV-23 five years later; those who have received PPV-23 in the past should receive one dose of PCV-13 at least one year after PPV-23; a single booster dose of PPV-23 should be given a minimum of eight weeks after PCV-13 and five years after PPV-23.

rash in a dermatomal distribution. Approximately one in three adults will develop shingles in their lifetime; rates of shingles in immunocompromised adults are two- to five-fold higher than in the general population. Patients with RA have a rate of shingles of 13-14 cases per 1,000 person-years compared to 1.5-4 cases per 1,000 person-years in healthy adults. Additionally, persons with immunocompromise are much more likely to experience complications of shingles, including the risk of disseminated disease and much higher rates of post-herpetic neuralgia, a chronic, debilitating neuropathic pain syndrome. Thus, prevention of shingles is a high-priority area of vaccine research and development.

At present, there is only one licensed shingles vaccine, a live-attenuated herpes zoster vaccine which, in clinical trials, has been shown to prevent approximately half of all shingles cases and two-thirds of cases of post-herpetic neuralgia in healthy adults aged 60 years and older and to have slightly better efficacy in adults 50 to 59 years old.

The herpes zoster vaccine is currently recommended for all Canadian adults aged 60 years and older and may be considered in those aged 50 years and older who desire protection from shingles, or who are anticipating immunosuppression which would put them at increased risk of disease. In general, live-attenuated shingles vaccine is contraindicated in the immunocompromised. Chronic inflammatory, RD and autoimmune diseases are not, in themselves, a contraindication to this vaccine; however, many of the medications used to treat these conditions are sufficiently immunosuppressive to warrant caution, and there is little data to guide decision-making with some routinely used DMARDs. Given the disproportionate burden of shingles in the immunocompromised population, careful risk:benefit assessment should be undertaken in patients receiving or intending to start DMARDs. When possible, herpes zoster vaccine should be administered prior to initiation of immunosuppressive therapy to optimize immunogenicity and safety. Ideally, the vaccine

should be administered two to four weeks prior to initiation of therapy. In patients already on immunosuppressive agents that contraindicate this vaccine, consideration should be given to withholding the immunosuppressive to provide opportunity to administer needed vaccines. The period between holding an agent and giving a live-attenuated vaccine must be determined based on the pharmacologic properties of the agent, but should generally not be less than one month.

The herpes zoster vaccine can safely be administered to patients on low-dose steroids (< 20mg/d of prednisone or its equivalent), MTX (2 0.4mg/kg/week), azathioprine (\leq 3.0mg/kg/d) and 6-mercaptopurine (\leq 1.5mg/kg/d). There is a limited but growing body of evidence that the vaccines may be safe and effective in patients on anti-tumor necrosis factor (TNF) biologic agents. In a study assessing safety of the herpes zoster vaccine in almost 45,000 patients with a wide array of RDs using linked datasets in the US, 47 patients who had received anti-TNF agents within 30 days before or after receipt of the vaccine were identified. None of them experienced serious adverse events and none developed shingles within 42 days of vaccination. In a similar study examining risk of zoster in almost 464,000 patients with underlying autoimmune disorders, 663 patients receiving anti-TNF agents at the time of vaccination were identified. Again, none experienced a serious adverse event and none developed zoster. In fact, the hazard ratio for herpes zoster associated with vaccination was 0.61 (95% CI 0.52, 0.71), suggesting a protective effect of vaccination even in patients receiving anti-TNF agents. Based on this data, the NACI now recommends that the herpes zoster vaccines may be administered to patients on anti-TNF biologics on a case by case basis after review with an expert in immunodeficiency. There is insufficient data to support this approach in patients on non-anti-TNF biologics or a combination of anti-TNF biologics and other immunosuppressive DMARDs.

New heat-inactivated and subunit herpes zoster vaccines are currently in Phase 2 and 3 clinical trials and may fill an important clinical gap in preventing shingles among the growing population of immunocompromised persons.

Given Mrs. M's age and anticipated need for anti-TNF therapy, she should be offered live attenuated shingles vaccine at least two weeks, but ideally four weeks prior

to starting infliximab. Mrs. M should be vaccinated even if she does not recall having chickenpox as a child as the vast majority of Canadian adults have been exposed to varicella zoster virus. No serologic testing is required before or after vaccination. Given the increased risk of recurrent zoster in immunocompromised adults, Mrs. M should be offered herpes zoster vaccine even if she has had a prior episode of shingles. In that setting, administration of the vaccine should be delayed at least one year following resolution of shingles, as it is likely that vaccine will not offer benefit over naturally augmented cell-mediated immunity in the year following a shingles episode. Live attenuated shingles vaccine can be administered on the same day as influenza vaccine, PPV-23, and PCV-13.

Suggested Readings

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Rheumatoid Arthritis and Herpes Zoster

By Gordon Dow, MD, FRCPC

A 63-year old woman presented with a 12-year history of poorly controlled seropositive rheumatoid arthritis (RA) treated with oral methotrexate (MTX) 20 mg weekly and prednisone 7.5 mg-10 mg per day. While preparing to initiate anti-tumor necrosis factor (TNF) therapy, she developed exquisite pain over her left forehead. Analgesic therapy prescribed at a walk-in clinic was ineffective, and four days after onset of pain she developed erythema and multiple vesicles over the left side of the nose and left forehead. Twenty-four hours after onset of this rash, she presented to her rheumatologist for her next scheduled appointment.

At least 90% of adults in Canada have had previous infection with varicella-zoster virus (VZV) acquired in childhood, and are at increased risk for herpes zoster (HZ) reactivation from latent reservoirs in cranial and dorsal root sensory ganglia. Adults have a 20%-30% lifetime risk of developing HZ, with an incidence of approximately 130,000 cases in Canada each year.¹ Risk increases with older age, local trauma, psychological stress, immunosuppressive conditions, and immunosuppressing medications. HZ is a significant concern for patients with RA and their caregivers because of the profound disability induced by both acute neuritis and postherpetic neuralgia (PHN). PHN is the most notorious adverse consequence associated with HZ. It is usually defined as the persistence of pain more than four weeks after rash disappearance, but this definition is arbitrary and varies between studies. PHN is uncommon in persons younger than 60, and is not increased in the immunocompromised host. The incidence of PHN may be lower in persons receiving anti-TNF therapy.²

Are Patients with RA at Increased Risk for HZ?

Several recent population-based studies³⁻⁸ of patients with RA have documented a crude incidence of HZ of approximately 10/1,000 patient years. This is twice the risk documented in the non-RA population after adjusting for age.⁴ This increased risk is not merely due to immunosuppressive disease-modifying antirheumatic drug (DMARD) therapy. An incidence of 8.0 per 1,000 patient-years in RA patients on minimal therapy was documented, in contrast

to occurrences of 11.2 and 10.6 per 1,000 patient-years for patients treated for moderate and severe disease, respectively.⁶ The risk of HZ in the general population ranges from three to four per 1,000 patient-years.^{4,9} This data would suggest that the immune dysregulation of RA itself is associated with an increased risk of HZ.

Which Immunosuppressive Medications Increase Patient Risk for HZ?

Steroid therapy is unequivocally associated with HZ reactivation, and its impact is dose-dependent. The impact of DMARD therapy is less clear, partly due to the confounding influence of concurrent steroid use in large cohort studies. A nested case control study⁴ found that oral steroids had the highest adjusted odds ratio (2.51), while the odds ratio for biologic DMARDs was similar to traditional DMARDs (1.54 vs. 1.37). The risk for HZ was similar regardless if steroid was used alone or combined with DMARD therapy. Significant increased HZ risk has been documented with cyclophosphamide, azathioprine, prednisone, leflunomide, and COX-2 selective non-steroidal anti-inflammatory drugs (NSAIDs), but not with MTX or biologic DMARDs.³

It is currently unclear whether biologic DMARD therapy increases the risk of HZ versus traditional DMARDs (Table 1). Only one study⁸ showed an increased risk with anti-TNF therapy when drugs in this class are evaluated in combination. This study⁸ had significant methodologic flaws, including use of patient self-report for case finding, and use of hospital-based clinics for the

Table 1

Biologic DMARDs vs. Non-biologic DMARDs: Increased Risk in HZ?³⁻⁸

Author	Design	# in RA Cohort	HZ Incidence Rate per 1,000 Patient-years	HZ risk for Biologic DMARD (group analysis) vs. Non-biologic DMARD	HZ Risk with Steroid	Subgroup Analysis
Wolfe, 2006 ³	Prospective cohort survey	10,614	13.2	No increase	Increase	↓ Risk with adalimumab
Smitten, 2007 ⁴	Claims database, nested case control	122,272	9.8	No increase	Increase	Not studied
Strangfeld, 2009 ⁵	Biologic registry, prospective	5,040	8.3	No increase	Increase	↓ Risk etanercept
McDonald, 2009 ⁶	Claims database, retrospective	20,357	10.0	No increase	Increase	↓ Risk etanercept and adalimumab
Winthrop, 2013 ⁷	Claims database, retrospective	36,212	12.2	No increase	Increase	Similar risk between anti-TNFs
Galloway, 2013 ⁸	Biologic registry, prospective	15,554	14.2	Increased	Not reported	↑ Risk with infliximab

biologic DMARD cohort versus community-based clinics for the control population. Subgroup analyses in several studies have shown an increased risk for specific biologic DMARDs, particularly infliximab, as evinced in Table 1. The weight of evidence currently indicates that HZ risk is similar between biologic and traditional DMARDs, and the more menacing culprit is corticosteroid therapy.

Should Patients with RA Be Vaccinated Against HZ?

The effectiveness of HZ vaccination in the patient with RA is unknown, given that immunocompromised persons were excluded from the two largest registration trials^{10,11} for this vaccine. In these two trials,^{10,11} vaccination decreased HZ risk in healthy adults aged older than 60 by 51% (3.3% vs. 1.6%),¹⁰ and by 70% (0.88% vs. 0.27%) in adults aged 50 to 59.¹¹ The Shingles Prevention Study (SPS)¹⁰ found the vaccine was well-tolerated, with mild inoculation-site side effects in 48% of vaccine recipients, versus 16% in the placebo group.

The SPS¹⁰ also documented a 67% reduction in PHN (0.1 vs. 0.4%). Based on this study,¹⁰ the number needed to vaccinate to prevent one case of shingles over three years was 59, and to prevent one case of PHN was 364. Longer-term follow-up of a patient subgroup from the SPS has shown that statistical significance for protection was lost by the third year post-vaccination for PHN and the sixth year post-vaccination for HZ.¹²

A recent retrospective cohort study¹³ examined 463,541 Medicare beneficiaries with immune-mediated disease. It documented a 40% decrease in HZ (HR 0.61; 95% CI 0.52-0.71) over two years, suggesting efficacy in the immunocompromised population.

Other impediments to vaccination include its cost (approximately \$200), recent vaccine shortages, modest efficacy, and requirement for frozen storage and transport. Given that the risk of HZ is two-to-three-fold higher in the RA population, carries significant risk of disability, and appears to be vaccine responsive, persons with RA age 50 or older can be offered vaccination after discussing the pros and cons above.

Should Patients Who Have Had a Previous Episode of HZ Be Vaccinated?

HZ vaccine trials enrolled patients regardless of prior HZ episodes. One recent study¹⁴ demonstrated that there is no added benefit to HZ vaccination in persons with documented HZ in the previous two years, suggesting that natural infection boosts cell-mediated immunity to VZV.

When Should Patients With RA Be Vaccinated Against HZ?

Ideally, patients with RA should be offered HZ vaccine more than two weeks prior to initiating immunosuppressive therapy. Live vaccines have traditionally been prohibited in

patients receiving DMARD therapy or if receiving prednisone in doses greater or equal to 20 mg per day. Recent data has documented that vaccine risk with traditional DMARDs is low and vaccination in this subgroup is now permissible.¹⁵

A study¹³ identified 633 patients who received HZ vaccination while receiving biologic therapy, with no evidence of HZ or varicella in the ensuing 42 days. This finding provides only preliminary reassurance, however, given that claims databases are insensitive to vaccine complications. We have documented one patient with localized vaccine-induced HZ while on infliximab therapy (material submitted for publication). VZV-associated retinal necrosis has been described in two immunocompromised patients after receiving HZ vaccination.¹⁶ HZ vaccination cannot be presently recommended while patients are receiving biologic DMARD therapy. Holding this therapy for three half-lives would seem prudent based on current data, with resumption of biologic DMARD therapy two weeks post-vaccination.

Return to Our Clinical Case

Early treatment of HZ speeds healing and decreases the severity of acute neuritis but may have minimal impact on the risk of PHN. The greatest clinical benefit is derived if treatment is initiated within 72 hours after the onset of rash, especially in patients older than age 50, who are prone to more prolonged pain. Early initiation of therapy is even more important in the immunocompromised patient or any patient with HZ ophthalmicus given their increased risk of complications. Antiviral therapy should be given to these patients even if they present after 72 hours.

The immunocompromised host with disseminated zoster or patient with sight-threatening disease should be hospitalized to receive intravenous acyclovir at a dose of 10 mg/kg three-times daily for seven days. Topical corticosteroid drops and ophthalmology assessment is required for patients with HZ ophthalmicus. For patients who do not have HZ ophthalmicus or other complications, we recommend valacyclovir 1,000 mg three-times daily or famciclovir 500 mg three-times daily for seven days. These medications are preferable to oral acyclovir, given its poor bioavailability and more frequent dosing requirement.

The best treatment for acute neuritis is rapid initiation of antiviral therapy and low dose amitriptyline (25 mg per day). There is no benefit to use of adjunctive corticosteroids or gabapentin.

Our patient made a complete recovery after being given valacyclovir 1,000 mg TID, amitriptyline 25 mg QHS, and topical ophthalmic steroid under the guidance of an ophthalmologist.

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Top Ten Things Rheumatologists Should (And Might Not) Know About Tuberculosis

By Michael Gardam, MD, CM, MSc, FRCPC; and Kamran Khan, MD, MPH, FRCPC

In our tuberculosis (TB) clinic we see large numbers of patients referred by rheumatologists. These referrals are mostly for those being considered for immunosuppression with anti-tumour necrosis factor (TNF) alpha inhibitor therapy or other agents. To a lesser extent, we see patients with active TB involving bones and joints. The following is a list of the top ten issues we feel important to share with our rheumatology colleagues that have been gleaned from our experience over the past decade.

1. Tuberculin Skin Test

The Tuberculin Skin Test (TST) is a highly sensitive test in immunocompetent individuals and is our preferred test for the diagnosis of latent TB infection in such patients. However, it must be planted, read, and recorded correctly as false positive and negative results can have serious consequences. A threshold of ≥ 5 mm induration is considered positive for latent TB infection among patients being considered for, or taking anti-TNF alpha inhibitors. In RA patients taking traditional non-steroidal disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, the threshold is 10 mm.

2. Interferon Gamma Release Assays

TST specificity can be reduced in individuals who have received Bacillus Calmette–Guérin (BCG) vaccination, especially if received after five years of age. Interferon Gamma Release Assays (IGRAs) may be used for such individuals, as they are more specific than the TST.

3. Positive TSTs

BCG vaccination within the first year of life is generally not responsible for positive TSTs in adulthood. Given that the vast majority of countries give this vaccine just after birth, prior vaccination only occasionally enters into our interpretation of a positive TST.

4. Test Sensitivity

Sensitivity of the TST is reduced in immunocompromised individuals. The T-SPOT.TB (IGRA) test is more sensitive than the TST but may not be available in many areas. Like the TST, sensitivity of the QuantiFERON Gold (IGRA) test is suboptimal in immunosuppressed patients.

5. Latent TB Infection

There is no gold standard test to diagnose latent TB infection. Discordant results between the TST and IGRAs must be interpreted in the context of epidemiological and clinical risk-factors for TB.

6. Risk Factors

The 5 mm TST cutoff to diagnose latent TB infection in patients being considered for anti-TNF alpha therapy may be problematic: many patients being tested will have no TB risk factors, but nonetheless may be required to be tested prior to receiving anti-TNF alpha therapy. Testing patients with no risk factors is generally discouraged because the positive predictive value is extremely low (*i.e.*, the vast majority of positive TSTs would not represent latent TB infection). A recent decision analysis supports this approach, although we recognize that there are medical-legal issues that drive testing in this population.

7. Corticosteroids

Corticosteroids also pose an increased risk of TB reactivation. A dose equivalent to 15 mg of prednisone for more than one month should be considered a risk for TB reactivation. Where possible, such patients should be tested for latent TB infection before starting immunosuppressive therapy.

8. Initiating Treatment for Latent TB Infection

Isoniazid (5mg/kg up to a maximum of 300 mg per day) for nine months or rifampin (10mg/kg up to a maximum of

600 mg per day) for four months are appropriate treatments for latent TB infection. Both require regular monitoring of liver function tests, especially in patients who are concurrently receiving hepatotoxic medications. It is critically important to first rule out active TB before initiating treatment for latent TB infection.

9. Therapeutic Concerns

As a potent inducer of cytochrome P450, rifampin therapy will significantly increase corticosteroid metabolism and could induce an Addisonian crisis in some patients on long-term corticosteroids.

10. Accurate Diagnosis

Consider TB as a cause of chronic progressive monoarticular arthritis in the appropriate setting (e.g., in a foreign-born patient from a TB-endemic country). Sending fluid and/or tissue for mycobacterial culture can be very helpful to establish the diagnosis.

Suggested Readings

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- inflammatory bowel disease
- severe liver impairment or active liver disease
- severe renal impairment or deteriorating renal disease
- known hyperkalemia
- patients <18 years of age

SERIOUS WARNINGS AND PRECAUTIONS:

- **Risk of CV adverse events:** ischemic heart disease, cerebrovascular disease, congestive heart failure (NYHA II-IV)
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 - NSAIDs can promote sodium retention which can increase blood pressure and/or exacerbate congestive heart failure
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- Not recommended for use with other NSAIDs (except low-dose ASA)
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Reference: 1. IMS data, October 2012-March 2013. NSAID Market, monthly data, prescriptions.



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