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Canadian Rheumatology Association Recommendations for the Pharmacological Management of Rheumatoid Arthritis with Traditional and Biologic Disease-modifying Antirheumatic Drugs: Part II Safety

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Canadian Rheumatology Association Recommendations for the Pharmacological Management of Rheumatoid Arthritis with Traditional and Biologic Disease-modifying Antirheumatic Drugs: Part II Safety

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ABSTRACT. ***Objective.*** The Canadian Rheumatology Association (CRA) has developed recommendations for the pharmacological management of rheumatoid arthritis (RA) with traditional and biologic disease-modifying antirheumatic drugs (DMARD) in 2 parts. Part II, focusing on specific safety aspects of treatment with traditional and biologic DMARD in patients with RA, is reported here.

Methods. Key questions were identified *a priori* based on results of a national needs-assessment survey. A systematic review of all clinical practice guidelines and consensus statements regarding treatment with traditional and biologic DMARD in patients with RA published between January 2000 and June 2010 was performed in Medline, Embase, and CINAHL databases, and was supplemented with a "grey literature" search including relevant public health guidelines. Systematic reviews of postmarketing surveillance and RA registry studies were performed to update included guideline literature reviews as appropriate. Guideline quality was independently assessed by 2 reviewers. Guideline characteristics, recommendations, and supporting evidence from observational studies and randomized trials were synthesized into evidence tables. The working group voted on recommendations using a modified Delphi technique.

Results. Thirteen recommendations addressing perioperative care, screening for latent tuberculosis infection prior to the initiation of biologic DMARD, optimal vaccination practices, and treatment of RA patients with active or a history of malignancy were developed for rheumatologists, other primary prescribers of RA drug therapies, and RA patients.

Conclusion. These recommendations were developed based on a synthesis of international RA and public health guidelines, supporting evidence, and expert consensus in the context of the Canadian health system. They are intended to help promote best practices and improve healthcare delivery for persons with RA. (First Release June 15 2012; J Rheumatol 2012;39:1583–602; doi:10.3899/jrheum.120165)

Key Indexing Terms:
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QUALITY OF HEALTHCARE

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including industry funding, consultancies, commercial interests, and direct involvement in any guidelines included in the systematic review for the last 3 years are shown in the Appendix of Part I of the CRA Recommendations [First Release Sept 15, 2011; J Rheumatol 2012;39:xxxx].

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Recommendations provided here are intended to be read in conjunction with the Canadian Rheumatology Association Recommendations for the Pharmacological Management of Rheumatoid Arthritis. These recommendations address specific safety questions that were identified *a priori* and are not intended to cover all safety aspects concerning treatment with traditional and biologic disease modifying antirheumatic drugs (DMARD).

Traditional and biologic DMARD have greatly enhanced the care of persons with rheumatoid arthritis (RA); however, potential risks associated with their use need be considered. The Canadian Rheumatology Association (CRA) has developed recommendations for the pharmacological management of RA with traditional and biologic DMARD in 2 parts. Part I described the development process of CRA recommendations in detail and included 5 overarching RA care principles along with 26 treatment recommendations[1]. Part II, reported here, focuses on specific safety aspects of treatment with traditional and biologic DMARD in patients with RA.

A pre-guideline national needs assessment survey of Canadian rheumatologists performed by the CRA[2] identified the following prominent safety concerns related to the use of traditional and biologic DMARD: (1) perioperative care; (2) screening for latent tuberculosis infection (LTBI) prior to the initiation of biologic therapy; (3) optimal vaccination practices; and (4) appropriate treatment strategies for RA patients with active malignancy or a history of malignancy. The objective was to develop recommendations addressing these specific safety aspects of treatment with traditional and biologic DMARD, based on a synthesis of international RA and public health guidelines, supporting evidence from randomized and observational studies, and expert consensus of the national working group, taking into consideration the Canadian healthcare context.

Target patient population. The target population is adult patients (age ≥ 18 years) with RA according to current[3] or prior classification criteria[4] and patients with early inflammatory arthritis suspected to have RA by a trained healthcare professional. These recommendations may also be relevant to patients with other rheumatologic/nonrheumatologic conditions in which the same drug therapies are being used, although differences in patient populations should be evaluated.

Target users. These recommendations are intended for rheumatologists or other primary prescribers of RA medications who are treating patients with RA in community and academic practice settings and RA patient consumers. Recommendations may also be of interest to provincial and federal RA stakeholders and decision-makers.

What is covered. Specific key questions addressed here are presented in Table 1.

What is not covered. Cardiovascular risk assessment, pregnancy/lactation, and other perioperative issues including glucocorticoid management and management of cervical spine disease are important safety concerns relevant to the treatment of RA, but were beyond the scope of these recommendations. Specific safety information for each agent is not reviewed in detail here; rather, up-to-date advisories, warnings, and recalls can be obtained through the Health Canada MedEffect Homepage [http://www.healthcanada.gc.ca/medeffect), and can be received as e-mail alerts via the US Food and Drug Administration MedWatch Safety Alerts for Human Medical Products [http://www.fda.gov/Safety/MedWatch/Safety Information/SafetyAlertsforHumanMedicalProducts/default.htm]. Complete drug product monographs are available through the Health Canada Drug Product Database [http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php]. CRA treatment recommendations for RA are published separately[1].

Applicability/dissemination strategies. These recommendations were endorsed by the CRA in January 2012 for a period of 2 years and will be reviewed after the 2-year period to determine if they remain current in the face of emerging evidence. For information on updates visit the CRA website [www.rheum.ca].

MATERIALS AND METHODS

Detailed methodology for the development of these recommendations following a systematic framework for guideline adaptation[5] [available at:

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Table 1. Key questions regarding safety of pharmacological management of rheumatoid arthritis (RA) with traditional and biologic disease-modifying antirheumatic drugs (DMARD).

Perioperative Care
1. Should treatment with methotrexate be suspended prior to surgery?
2. Should treatment with biologic DMARD be suspended prior to surgery?
Latent Tuberculosis Infection (LTBI)
3. For which biologic DMARD therapies is screening for LTBI recommended?
4. What is the role of interferon-gamma release assays (IGRA) in the diagnosis of LTBI in patients with RA?
5. Which patients with RA should be considered for treatment with tuberculosis prophylaxis?
6. When can treatment with biologic DMARD be started in RA patients receiving tuberculosis prophylaxis?
Vaccination
7. Which vaccines are indicated in patients with RA?
8. If indicated, when should *inactive vaccines* be administered in patients with RA treated with traditional and/or biologic DMARD?
9. If indicated, when should *live vaccines* be administered in patients with RA treated with traditional and/or biologic DMARD?
Malignancy
10. Should treatment with traditional and/or biologic DMARD be modified in patients with *active malignancy*?
11. Should treatment with traditional and/or biologic DMARD be modified in patients with *a history of lymphoma*?
12. Should treatment with traditional and/or biologic DMARD be modified in patients with *a history of nonmelanoma skin cancer*?
13. Should treatment with traditional and/or biologic DMARD be modified in patients with *a history of solid tumor*?

http://www.adapte.org] is described in detail in Part I of the CRA recommendations[1].

In brief, a Canadian multidisciplinary guideline working group was assembled on behalf of the CRA, consisting of RA clinical experts, researchers, patient consumers, and a family physician (listed as coauthors). Additional expertise was sought in the development of recommendations regarding screening for latent tuberculosis infection (LTBI) and vaccination, as well as for malignancy, through consultation with external clinical content experts in infectious diseases (M.A. Gardam) and malignancy (J. Askling).

Defining the scope. Key safety questions were identified *a priori* based on results of a national needs assessment survey[2].

Search strategy. A systematic review of all clinical practice guidelines and consensus statements regarding treatment with traditional and biologic DMARD in patients with RA published between January 2000 and June 2010 was performed in Medline, Embase, and CINAHL databases, and the "grey literature" (e.g., guideline clearinghouses, rheumatology association websites, etc.) according to published guidance[6]. In addition, relevant Canadian and international public health and safety/surveillance guidelines and advisories were reviewed. A supplementary systematic review of postmarketing surveillance/RA registry studies on the risk of malignancy in RA patients published from January 2008 to June 2010 was performed in Medline, Embase, and CINAHL databases in order to incorporate the most recent published evidence in this area (for search details visit the CRA website [www.rheum.ca]; the online appendix available from http://rheum.ca/images/documents/supporting_information_Rheumatology.pdf.

Appraisal of guideline quality. Guideline quality was assessed using a validated questionnaire, the Appraisal of Guidelines Research and Evaluation (AGREE) instrument, which provides a guideline rating of recommend (R), recommend with provisos (R*), or would not recommend (WNR)[7].

Grading evidence. Systems for assigning levels of evidence differed across guidelines and were translated to a single simplified grading system[8] from the Scottish Intercollegiate Guideline Network (SIGN) (Table 2).

Evidence synthesis. Information on guideline characteristics, recommendations, AGREE quality scores, and supporting evidence from randomized controlled trials (RCT) and observational studies was abstracted and synthesized into evidence tables for each key question.

Development of recommendations. Consistent with our methodological framework for the development of the CRA recommendation through guideline adaptation, we evaluated recommendations made by other countries for implementation in Canada using published guidance[5]. We emphasized recently published recommendations from countries with similar epidemiology to Canada (e.g., similar background incidence/prevalence rates for infections, malignancy, etc.) that were deemed to be of high methodological quality and provided citable evidence. Recommendations were reworded according to published criteria for improving implementation of guidelines[9]. The full working group voted on recommendations using a modified Delphi consensus technique, where each working group member registered a vote from 0, strongly disagree, to 10, strongly agree, and disagreements were resolved through discussion and multiple rounds of voting accordingly. Extended review was performed by the full CRA executive committee.

No representatives of pharmaceutical companies were involved in any phase of guideline development.

RESULTS

Recommendations

A summary of CRA recommendations is presented in Table 3.

I. Perioperative Care — *Understanding potential perioperative risks in patients with RA*

Patients with RA are commonly treated with immunosuppressive medications including corticosteroids, methotrexate (MTX), and/or biologic DMARD, which may increase their risk of perioperative infections or affect wound healing. Stopping therapy, however, may result in a flare and impede recovery from surgery[10,11,12]. The balance of these risks needs to be considered when deciding if treatment should be suspended in the perioperative period, and if so, when therapy should be withheld and restarted.

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Table 2. Custom system for assigning level of evidence and strength of recommendation[8]. From Bykerk, et al. J Rheumatol 2012; 39:xxxx; with permission.

Level of Evidence		Strength of Recommendation	
I	Metaanalyses, systematic reviews of RCT, or individual RCT	A	Strong recommendation: • Direct level I evidence
II	Metaanalysis, systemic reviews of observational studies (cohort/case control studies), or individual observational studies OR RCT subgroup/post hoc analyses	B	Moderate recommendation: • Direct level II evidence or extrapolated level I evidence
III	Nonanalytic studies, e.g., case reports, case series	C	Weak recommendation: • Direct level III evidence or extrapolated level II evidence
IV	Expert opinion	D	Consensus recommendation:
NR	Recommendations are not linked to evidence		• Expert opinion based on very limited evidence

RCT: randomized controlled trial; NR: not reported.

Table 3. Canadian Rheumatology Association (CRA) recommendations addressing specific safety aspects of treatment with traditional and biologic (DMARD) in patients with rheumatoid arthritis (RA).

Recommendations	Level	Strength
Perioperative care		
1. Methotrexate can be safely continued in the perioperative period for RA patients undergoing elective orthopedic surgery.	I	A
2. Biologics should be held prior to surgical procedures. The timing for withholding therapy should be based on the individual patient, the nature of the surgery, and the pharmacokinetic properties of the agent (see Table 4). Biologic DMARD may be restarted postoperatively if there is no evidence of infection and wound healing is satisfactory.	II, IV	C
Latent tuberculosis infection (LTBI)		
3. Screening for latent tuberculosis infection (LTBI) is recommended prior to starting anti-tumor necrosis factor (anti-TNF) therapy (II), abatacept (ABAT) and tocilizumab (TCZ) (IV). Screening should consist of a history including an assessment of LTBI epidemiologic risk factors, physical examination, tuberculin skin test (TBST) and chest radiograph in high-risk groups (II). Physicians should exercise clinical judgement as to the need to repeat screening in patients who tested negative in prior screening and have new epidemiologic risk factors (IV).	II, IV	B
4. Interferon-gamma release assays (IGRA) may be an option to identify false-positive TBST in patients who have received the Bacille Calmette-Guérin (BCG) vaccine and have no epidemiologic risk factors.	IV	D
5. Any RA patient with LTBI should be considered for prophylactic therapy.	II	B
6. Biologic agents may be started 1-2 months after the initiation of LTBI prophylaxis.	II, IV	B
Vaccination		
7. Vaccination for influenza and pneumococcus is recommended for patients with RA before or during treatment with traditional and biologic DMARD (II). Hepatitis B vaccine should be considered in high-risk groups (IV). Zoster vaccine should be considered in high-risk groups (IV). Zoster vaccine should be considered in RA patients age 60 years or older (IV).	II, IV	B
8. Inactivated vaccines should ideally be administered prior to starting treatment with methotrexate and/or biologic DMARD as these medications may attenuate the immune response.	I, II	B
9. Live vaccines should be administered at least 2 weeks and ideally 4 weeks prior to starting treatment with biologic DMARD. In patients currently receiving biologic therapy, treatment with the biologic should be suspended and the vaccine administered after an appropriate interval based on the pharmacokinetic properties of the agent (see Table 4). Herpes zoster vaccine may be given to patients receiving methotrexate (≤ 25 mg/week) and/or low-dose corticosteroids (< 20 mg per day).	IV	D
Malignancy		
10. In general, in RA patients with active malignancy, treatment with traditional and biologic DMARD should be delayed/withheld while patients are receiving chemotherapy or radiotherapy. Treatment decisions should be made on a case-by-case basis in conjunction with a cancer specialist and the patient.	IV	D
11. In RA patients with a history of lymphoma, hydroxychloroquine, sulfasalazine, and rituximab may be used. Treatment with anti-TNF therapy is not recommended. Treatment with other traditional and biologic DMARD should be used with caution.	II, IV	C
12. In RA patients with a history of nonmelanoma skin cancer, traditional DMARD may be used. Treatment with biologic DMARD should be used with caution.	II, IV	C
13. In RA patients with a history of solid malignancy, traditional DMARD may be used. Treatment with biologic DMARD should be used with caution.	II, IV	C

Recommendation 1:
MTX can be safely continued in the perioperative period for RA patients undergoing elective orthopedic surgery. (Level I; Strength A)

Summary of guidelines. The search identified 3 clinical practice guidelines and 1 consensus statement that addressed perioperative use of MTX in patients with RA (AGREE rating: Recommend (R) = 2, Recommend with provisos (R*) = 2).

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Three guidelines recommended that MTX can be safely continued during elective orthopedic surgery[13,14,15] and one guideline recommended a 1-week interruption of treatment before and after surgery[16].

Recommendation/supporting evidence adapted from: Visser 2009[15] (R*), British Society for Rheumatology (BSR) 2009[14] (R), BSR 2008[13] (R).

Summary of evidence linked to recommendation. Visser 2009[15], BSR 2009[14], and BSR 2008[13] referred to evidence from RCT and observational studies that examined outcomes in RA patients who stopped versus those who continued MTX prior to elective orthopedic surgery. The largest RCT of RA patients undergoing elective orthopedic surgery[17] showed a lower rate of postoperative complications including infection in patients who continued MTX perioperatively [i.e., 2/88 (2%)] compared to those who discontinued MTX [11/72 (15%)] and fewer flares 6 weeks after surgery [0/88 (0%) vs 6/72 (8%)]. Consistent results were also reported in a smaller RCT of 64 RA patients[18] and in a retrospective cohort study of 122 RA patients[19]. Only 2 small cohort studies (N = 32 and 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[20,21].

Evidence to recommendation. The guideline panel agreed there was sufficient evidence from randomized trials to support the use of MTX in the perioperative period in patients undergoing elective orthopedic procedures. Decisions regarding other types of surgery should be made on a case-by-case basis after considering the nature of the surgical procedure, patient-related factors (e.g., comorbid conditions), and the need to maintain perioperative disease control.

Barriers to implementation. None.

Recommendation 2:

Biologic DMARD should be held prior to surgical procedures. The timing for withholding biologic DMARD should be based on the individual patient, the nature of the surgery, and the pharmacokinetic properties of the agent (Table 4). Biologic DMARD may be restarted postoperatively if there is no evidence of infection and wound healing is satisfactory. (Level II (anti-tumor necrosis factor; anti-TNF), IV; Strength C)

Summary of guidelines. The search identified 12 clinical practice guidelines and 1 consensus statement that addressed perioperative management in RA patients treated with biologic DMARD (AGREE rating: Recommend (R) = 2, Recommend with provisos (R*) = 11). All guidelines recommended holding biologic DMARD prior to surgery[22,23,24,25,26,27,28,29,30,31,32] except 2009 BSR guidelines[14], which suggest that biologic DMARD could be continued in most cases of elective orthopedic surgery.

Timing for withholding therapy before surgery. Recommendations for withholding biologic DMARD before surgery varied from 1 week to 2 months for anti-tumor necrosis factor (anti-TNF) therapy, abatacept (ABAT), and tocilizumab (TCZ)[22,23,25,26,27,28,31]. Only 1 guideline commented on rituximab (RTX) and suggested that RTX should be held 6 months prior to surgery, and can be held even longer, until the peripheral B cell count is normal, in situations where disease activity is well controlled[29]. Six guidelines suggested that the timing for withholding therapy should be based on the pharmacokinetic properties of the agent used[27,28,30,31,32,33]. One guideline recommended withholding biologic DMARD for 3–5 half-lives[30], while another[33] distinguished between different surgical scenarios, i.e., holding anti-TNF agents for 2 half-lives when surgery is performed in a "sterile environment" (e.g., cataract) and 5 half-lives for surgeries performed in a "septic environment" (e.g., colon) or in "septic risk situations" (e.g., joint prosthesis).

Timing for withholding therapy after surgery. Eight guidelines recommended that biologics may be restarted postoperatively if there is no evidence of infection and wound healing is satisfactory[22,23,25,26,27,28,30,31,33]. A Spanish guideline[32] suggested waiting 10–14 days and a Japanese TCZ guideline[24] recommended holding TCZ for at least 2 weeks. French TCZ guidelines[27] emphasized postoperative monitoring for patients receiving TCZ, as these patients may have no fever or elevation of C-reactive protein.

Recommendation/supporting evidence adapted from: American

Table 4. Mean half-lives of biologic agents licensed for use in Canada (June 2011). Retrieved from Health Canada Drug Product Database: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php.

	Mean Half-life, days	2 Half-lives, days	5 Half-lives, days
Etanercept (ETN)	4.3	8.6	21.5
Adalimumab (ADA)	14	28	70
Infliximab (IFX)	8–10	16–20	40–50
Golimumab (GOL)	12	24	60
Certolizumab (CTZ)	14	28	70
Rituximab (RTX)	21	42	105
Abatacept (ABAT)	13	26	65
Tocilizumab (TCZ)	13	26	65

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College of Rheumatology (ACR) 2008[31] (R), Spanish Society of Rheumatology (SER) 2010[32] (R*).

Summary of evidence linked to recommendation. Both ACR 2008[31] and Spanish 2010[32] guidelines referred to the same 3 cohort studies that examined risks for postoperative infections in RA patients treated with anti-TNF. The largest was a retrospective cohort study of 768 RA patients that underwent 1219 elective orthopedic procedures and reported a nonsignificant increased odds of surgical site infections in patients who continued anti-TNF therapy (OR 1.5, 95% CI 0.43–5.2)[34]. In that study, surgical site infections were observed in 41/1023 (4%) patients that did not use anti-TNF, 6/104 (5.8%) patients that stopped anti-TNF (4 half-lives), and 8/92 (8.7%) patients that continued anti-TNF. A retrospective cohort study of 91 RA patients that underwent orthopedic surgery[35] reported a higher incidence of perioperative infections in patients treated with anti-TNF therapy relative to patients who were not treated with anti-TNF (OR 5.3, 95% CI 1.1–24.9). A small prospective cohort of 31 RA patients that underwent orthopedic surgery did not report a significant increase in postoperative infections or healing complications associated with anti-TNF therapy[36].

Evidence to recommendation. Although data examining perioperative infections associated with the use of biologic therapies are mostly retrospective and limited to treatment with anti-TNF agents, the guideline panel agreed that caution dictates that biologics should be temporarily interrupted for most surgical procedures in view of the potential increased risk of infection. The timeline for withholding therapy should depend on the clinical scenario considering the type of surgery (e.g., sterile, septic), patient factors (e.g., comorbidities, history of infection), and the pharmacokinetic properties of the agent (Table 4).

Barriers to implementation. None.

II. Latent Tuberculosis Infection (LTBI) — *Understanding potential risks for TB reactivation in patients with RA*

TNF-α plays a central role in the host defense from tuberculosis (TB) in the formation of granulomas and containment of disease[37]. Keane, *et al*[38] were the first to show an increase in reactivation of LTBI when they reported 70 cases of TB associated with infliximab (IFX), of which 57% of cases were extrapulmonary (not involving the lungs) and nearly 25% were disseminated (spread to multiple areas of the body). Other population registries have reported elevated rates of TB in RA patients treated with anti-TNF relative to RA patients not treated with anti-TNF therapy and the general population, respectively[39,40,41,42,43,44,45,46,47,48]. Some reports have suggested that risks for TB reactivation may vary across anti-TNF agents, with higher risks reported in RA patients treated with the monoclonal antibodies IFX and ADA relative to those treated with the soluble TNF-receptor antagonist etanercept (ETN)[42,46]. Multiple biologic agents with different mechanisms of action are now available for the treatment of RA. A network metaanalysis of RCT and open-label extension studies of all 9 biologics currently licensed for use in Canada reported an increased short-term risk of TB reactivation in RA patients treated with biologics relative to RA patients not treated with biologics[49].

In Canada, screening for LTBI is indicated for persons receiving immunosuppressant medications, such as anti-TNF and other biologic DMARD[50].

Important considerations about screening for LTBI in patients with RA. When making a diagnosis of LTBI, it is important to consider both the patient's background risk of TB infection based on an assessment of epidemiologic risk factors (Table 5) and results of diagnostic tests. There is currently no "gold standard" for the diagnosis of LTBI, which poses a challenge when assessing the validity of diagnostic tests. A 1-step tuberculin skin test (TBST) performed according to the Mantoux method is widely used in Canada [for more information on performing TBST, and for specific indications for 2-step testing, see Public Health Agency of Canada 2007 Canadian Tuberculosis Standards: http://www.phac-aspc.gc.ca/tbpc-latb/pubs/tbstand07-eng.php]. Current Canadian Tuberculosis Standards[50] provide different thresholds for interpreting TBST results based on the presence of LTBI risk factors. In general, a TBST should be considered positive if the induration is ≥ 5 mm. TBST, however, have important limitations, including the potential for false-positive results in persons exposed to nontuberculosis mycobacterial infection or those with a history of Bacille Calmette-Guérin (BCG) vaccination [for information on worldwide BCG vaccination practices see the BCG World Atlas: http://www.bcgatlas.org], and the potential for false-negative results in RA patients receiving immunosuppressants or with comorbidities causing immunosuppression (e.g., cancer chemotherapy) or due to cutaneous anergy[51].

Interferon-γ (IFN-γ) release assays (IGRA) are more recent alternatives to TBST. IGRA are T cell-based *in vitro* assays that measure IFN-γ production following exposure to mycobacterial antigens. In healthy populations with low risk of LTBI, IGRA were reported to have similar sensitivity and improved specificity relative to TBST in persons with a history of BCG

Table 5. Risk factors for latent tuberculosis infection (LTBI). Adapted from the Public Health Agency of Canada (PHAC) 2008 Tuberculosis Fact Sheet: http://www.phac-aspc.gc.ca/tbpc-latb/fa-fi/tb can-eng.php.

- Close contact with individuals known or suspected to have TB (e.g., family members or people sharing living spaces)
- History of active TB or radiograph suggestive of past TB that was not adequately treated
- Living in (and/or travelling to) communities with high rates of latent or active TB
- Low-income populations (e.g., urban homeless)
- Residents of longterm care and correctional facilities
- Occupational exposure to high-risk groups (e.g., healthcare workers)

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vaccine[51]. IGRA, however, may have reduced sensitivities in persons who do not have an intact immune system[51], are more costly, and are not widely accessible in Canada.

A Web-based tool to help interpret a TBST or IGRA detailed in Menzies, *et al*[52] is available [http://www.tstin3d.com/en/calc.html].

The decision to initiate TB prophylactic therapy prior to starting biologic DMARD should be guided by an assessment of epidemiologic risk factors and LTBI screening test results. Given the relatively low TB incidence in Canada, RA patients without the presence of any LTBI epidemiologic risk factors (Table 5) will have a higher likelihood of a false-positive screening result, which may result in unnecessary exposure to prophylactic therapy carrying certain risks. Consultation with an infectious disease specialist should be sought as appropriate.

Recommendation 3:
Screening for LTBI is recommended prior to starting anti-TNF therapy (Level II), abatacept (ABAT) and tocilizumab (TCZ) (Level IV). Screening should consist of a history including an assessment of LTBI epidemiologic risk factors, physical examination, TBST, and a chest radiograph in high-risk groups (Level II). Physicians should exercise clinical judgment as to the need to repeat screening in patients who tested negative in prior screening and have new epidemiologic risk factors (Level IV). (Level II, IV; Strength B)

Summary of guidelines. The search identified 15 clinical practice guidelines and 6 consensus statements that addressed which patients to screen for LTBI (AGREE rating: Recommend (R) = 2, Recommend with provisos (R*) = 18, Would not recommend (WNR) = 1). All guidelines with recommendations for anti-TNF therapy recommended screening for LTBI prior to initiation of anti-TNF therapy[16,22,23,25,26,30,33,53,54,55,56,57,58,59]. Seven guidelines commented on screening prior to ABAT[22,28,30,31,32,55,57] and 7 prior to TCZ[22,24,27,30,32,55,57], and all recommended LTBI screening, although 5 guidelines highlighted that the magnitude of risk is unknown[22,24,27,30,55]. Eight guidelines commented on screening prior to RTX[22,29,30,31,32,55,57,60]. Four recommended screening[22,31,32,57] and 4 recommended that systematic screening was not necessary[22,30,55,60], although 2 stated that most patients treated with RTX will have been previously screened[55,60]. All guidelines recommended a TBST and 3 added that an IGRA is an acceptable alternative[22,27,30]. All guidelines recommended a chest radiograph, except for 2008 ACR guidelines, which suggested a chest radiograph only if there were epidemiologic risk factors[31]. All guidelines but one[56] emphasized that an assessment of epidemiologic risk factors and/or a physical examination should also be performed.

Recommendation/supporting evidence adapted from: European League Against Rheumatism (EULAR) 2010[61] (R), Canadian Tuberculosis Standards 2007[50], and British Thoracic Society 2005[62].

Summary of evidence linked to recommendation. EULAR 2010 guidelines[61] did not make specific recommendations for LTBI screening, but performed a systematic review of observational studies that evaluated TB risk associated with anti-TNF therapy to inform their treatment recommendations[63]. In studies that included patients treated with ETN, IFX, or ADA, the risk of TB reactivation in persons treated with anti-TNF therapy relative to RA patients not receiving anti-TNF therapy ranged from 4 (95% CI 1.3–12) for a Swedish biologics registry[39] to 5.8 (95% CI 2.5–15.4) for a Spanish biologics registry[43]. Two observational studies suggested that ETN is associated with a lower risk of TB reactivation relative to ADA and IFX[42,46]. Risk ratios for RA patients treated with IFX compared to RA patients not treated with biologic DMARD ranged from 4 in a US study based on Food and Drug Administration reporting[38] to 19.9 in a Spanish cohort[44]. In Spain, a reduced risk of TB reactivation was associated with compliance with screening recommendations[43]. Trials for ABAT and TCZ required screening for TB prior to entry, so the risk of reactivation associated with these agents is unknown. French guidelines, however, reported 6 cases of TB in both ABAT and TCZ clinical trial programs[27,28]. French RTX guidelines reported no increased risk of TB in patients with lymphoma treated with RTX[29].

The Canadian Tuberculosis Standards[50] provided evidence from observational studies showing that epidemiologic risk factors, specific chest radiograph abnormalities, and positive TBST are associated with increased risk of TB reactivation. The British Thoracic Society guidelines[62] suggested that TBST responses may be attenuated, based on results from a cohort of patients with established RA from Peru, in which 87% of patients were taking glucocorticoids. The Canadian Tuberculosis Standards 2007 cited observational studies that suggested that ≥ 15 mg prednisone daily can suppress a TBST[50].

Evidence to recommendation. The panel based this recommendation on data showing an increased risk of TB reactivation associated with anti-TNF therapy and an unknown risk with ABAT and TCZ. Universal screening prior to RTX was not felt to be necessary based on the experience in patients with lymphoma. In addition, it was also noted that most RA patients treated with RTX would previously have been screened. The panel recommended that a TBST should ideally be performed when patients are not receiving immunosuppressants, particularly not when receiving glucocorticoids at doses ≥ 15 mg prednisone/day, and that TBST results should be interpreted according to the Canadian Tuberculosis Standards[50]. In general, a TBST should be considered positive if the induration is ≥ 5 mm. A 10-mm cutoff may be considered to reduce false-positives in patients with no epidemiologic risk factors, but this decision should be individualized to the patient. A chest radiograph may not be necessary in all patients, although physicians should consider that chest radiographs might show evidence of previous TB infection in

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someone with a negative TBST. In addition, patients may also have recent chest radiographs that were performed as part of the RA baseline assessment or for other purposes that can help inform decision-making. In patients with a negative baseline screen who travel to endemic areas and/or have other new epidemiologic risk factors, rescreening can be considered.

Barriers to implementation. None.

Recommendation 4:
IGRA may be an option to identify false-positive TBST in patients who have received the BCG vaccine and have no epidemiologic risk factors. (Level IV; Strength D)

Summary of guidelines. The search identified 5 clinical practice guidelines and 1 consensus statement that addressed the role of IGRA (AGREE rating: Recommend (R) = 1, Recommend with provisos (R*) = 5). Three guidelines recommended that IGRA could be considered as an alternative to TBST[22,24,27], and 3 suggested that they may have a role, but their role is currently unclear[30,31,55]. Three guidelines suggested that they might have a role in patients who have received prior BCG vaccine[30,31,55], with one guideline adding that they may also have a role in patients receiving immunosuppressants or in patients who have had prior non-TB mycobacterial infection[22]. Two guidelines cautioned that false-negatives may occur with both IGRA and TBST[22,55].

Recommendation/supporting evidence adapted from: Canadian Tuberculosis Standards 2007[50] and US Centers for Disease Control (CDC) 2010[64].

Summary of evidence linked to recommendation. the CDC 2010 guidelines[64] and Canadian Tuberculosis Standards 2007[50] reviewed diagnostic studies showing that IGRA have similar sensitivity and improved specificity relative to TBST. The Canadian Tuberculosis Standards 2007 reported that in patients who received the BCG vaccine after the age of 12 months, TBST had lower specificity, but still performed well[50]. Both TBST and IGRA results were relatively unchanged in patients who received BCG vaccine prior to 12 months of age.

Evidence to recommendation. The panel acknowledged that data on longterm outcomes in patients with positive IGRA are lacking, that IGRA are not widely accessible, and that IGRA are more costly than TBST. The panel highlighted, however, that in particular situations an IGRA might be helpful, such as in identifying false-positive TBST in patients vaccinated with BCG, and have no epidemiologic risk factors, particularly if the vaccination occurred after 12 months of age. In patients with epidemiologic risk factors, the results of an IGRA should not be used to change the therapeutic decision in patients who screen positive with a TBST.

Barriers to implementation. Increased cost of IGRA and limited availability across Canada.

Recommendation 5:
Any RA patient with LTBI should be considered for TB prophylactic therapy. (Level II; Strength B)

Summary of guidelines. The search identified 8 clinical practice guidelines and 3 consensus statements that commented on which RA patients should be considered for LTBI prophylaxis (AGREE rating: Recommend (R) = 1, Recommend with provisos (R*) = 10). Three guidelines recommended treatment for any patient with LTBI, without further specification[26,27,33]. Five guidelines recommended treatment for any patient with epidemiological risk factors, a positive TBST, or chest radiograph findings of prior TB[31,32,54,57,58], and one guideline recommended treatment with a positive TBST or chest radiograph only[24]. Two guidelines recommended that the treatment decision should balance the risk of TB reactivation with the risks associated with prophylactic treatment[22,23]. An Australian guideline provided a risk assessment algorithm that incorporated historical features, TBST or IGRA, and chest radiograph findings[22].

Recommendation/supporting evidence adapted from: EULAR 2010 (R)[61], Canadian Tuberculosis Standards 2007[50], and British Thoracic Society 2005[62].

Summary of evidence linked to recommendation. The evidence for this recommendation draws on the discussion in Recommendation 3. Compliance with screening recommendations that included initiation of prophylactic therapy has been associated with a reduced incidence of TB reactivation in a country with a relatively high TB prevalence (Spain)[43]. Evidence on the effectiveness of screening in countries with a low TB prevalence is lacking. In Canada, 9 months of prophylactic therapy with isoniazid (INH) is currently indicated as first-line therapy for persons who screen positive for LTBI[50]. The British Thoracic Society, however, highlighted that prophylactic therapy with INH is associated with low, but not insignificant risks of hepatotoxicity[62]. The risk of hepatotoxicity has been reported to be lower with rifampin[65], although rifampin is considered second-line therapy, based on less longterm experience.

Evidence to recommendation. The guideline panel agreed that, in general, all patients who screen positive for LTBI should be offered prophylactic therapy. Treatment decisions should, however, incorporate a patient's individual risk of TB reactivation and the risk of toxicity with prophylactic therapy, particularly in patients at low risk for TB. Patients should be monitored for hepatoxicity and consultation with an infectious disease specialist should be sought as appropriate.

Barriers to implementation. Timely access to infectious disease specialists.

Recommendation 6:
Biologic agents may be started 1–2 months after the initiation of LTBI prophylaxis. (Level II, IV; Strength B)

Summary of guidelines. The search identified 8 clinical prac-

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tice guidelines and 2 consensus statements that addressed when to start biologic therapy after initiation of TB prophylaxis (AGREE rating: Recommend (R) = 1, Recommend with provisos (R*) = 9). Four recommended waiting at least 3 weeks[24,27,28,33] and 3 recommended waiting at least 1 month after initiating prophylactic therapy prior to starting biologics[22,23,26]. Two additional guidelines did not make a recommendation, but commented that observational evidence supported the use of biologic agents after 1 month[31,55]. Only one guideline suggested that biologic therapy may be started concurrently, but did not formalize this as a recommendation[16]. These recommendations were made in reference to anti-TNF therapy, except for one guideline for ABAT[28] and 2 guidelines for TCZ[24,27].

Recommendation/supporting evidence adapted from: Furst 2010 (R*)[55].

Summary of evidence linked to recommendation. Furst 2010[55] reviewed observational evidence from Spain, which showed that RA patients who screened positive for LTBI and were treated with anti-TNF therapy following 1 month of TB prophylaxis had a significantly reduced risk of TB reactivation.

Evidence to recommendation. The guideline panel recognized that the timeline for starting a biologic after initiating treatment with TB prophylaxis would depend on patient-related factors including the patient's individual risk of TB reactivation and their need for biologic therapy to attain/maintain disease control. In general, waiting 1–2 months was considered appropriate, as the majority of side effects from INH will occur in the first 2 months of therapy. If this delay is too long, biologic therapy may be started earlier in a shared decision between patient and physician after an informed discussion of benefits and risks.

Barriers to implementation. None.

III. Vaccination — *Understanding issues surrounding vaccination practices in patients with RA*

Patients with RA are at increased risk for developing vaccine-preventable infections associated with significant morbidity and mortality[66,67]. There are likely several factors contributing to this increased risk, including immune system dysfunction, comorbidities, and/or use of immunosuppressant therapies used to treat RA[68]. Immunocompromised individuals who are underimmunized are vulnerable to serious infections and even death; however, healthcare providers should also consider that inappropriate administration of live vaccines can lead to serious adverse events in the immunocompromised host[69].

Important considerations regarding vaccination practices in patients with RA

Physicians and patients with RA should monitor and ensure that all vaccines indicated for the adult general population are monitored and kept up to date [described in detail in the 2006 Canadian Immunization Guide available from the Public Health Agency of Canada Immunization and Vaccine website: http://www.phac-aspc.gc.ca/publicat/cig-gci/]. In patients initiating longterm treatment with immunosuppressive therapies for their RA, particular attention should be paid to the status of childhood, annual influenza, and pneumococcal vaccines.

Vaccines can either be live attenuated or inactivated (Table 6). Live attenuated vaccines contain whole, living bacteria or viruses, which induce immunity by actively replicating within the host. Patients receiving immunosuppressive therapy may be at increased risk for disseminated infection if live attenuated vaccines are given. Inactivated vaccines contain killed bacteria or viruses. These vaccines may induce broad immunity because multiple antigens are present and pose no increased risk to immunocompromised persons. However, because the response may be weaker than that induced by live organisms, multiple doses are usually needed[70].

Wherever feasible, persons with RA should be immunized at times when a maximum immune response can be anticipated (i.e., before initiating immunosuppressive therapy)[70]. Many patients, however, may require vaccines while receiving treatment with immunosuppressive medications. Healthcare providers should weigh the potential for a reduced vaccine-related immune response against the potential for disease flare that may result from withholding immunosuppressive medication to administer the vaccine.

A summary of vaccine recommendations is presented in Table 7.

Recommendation 7:
Vaccination for influenza and pneumococcus is recommended for patients with RA before or during treatment with traditional and biologic DMARD (Level II). Hepatitis B vaccine should be considered in high-risk groups (Level IV). Zoster vaccine should be considered in RA patients age 60 years or older (Level IV). (Level II, IV, Strength B)

Summary of RA guidelines. The search identified 13 clinical practice guidelines and 1 consensus statement that addressed vaccine indications (AGREE rating: Recommend (R) = 3, Recommend with provisos (R*) = 11). The EULAR 2011 vaccination guidelines[71] recommend that vaccination status should be assessed during the initial investigation of patients with RA, and 4 French biologic guidelines[27,28,29,33] recommended that clinicians should ensure that all indicated vaccines are up-to-date in patients with RA before starting biologic agents. Twelve guidelines recommended influenza and pneumococcal vaccine for all patients with RA[23,27,28,29,31,32,33,54,58,71,72], and one guideline recommended these vaccines only for patients over age 65 years[24]. Five guidelines recommended immunization against hepatitis B if risk factors are present[31,32,58,60,61] and one guideline suggested that zoster vaccine could be considered in all patients with RA[71].

Recommendation/supporting evidence adapted from: EULAR 2011[71] (R)*) and the Canadian Immunization Guide 2006[70].

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Table 6. Classification of common live attenuated and inactivated/killed vaccines. From the Public Health Agency of Canada (PHAC) Canadian Immunization Guide: http://www.phac-aspc.gc.ca/publicat/cig-gci/p01-eng.php and from Rahier, et al[66].

Live Attenuated Vaccines	Inactivated/killed Vaccines
Bacillus Calmette-Guerin (BCG)	Diphtheria
Influenza, nasal	Hemophilus influenza type B (protein conjugate)
Measles/mumps/rubella (MMR)	Hepatitis A
Polio, oral	Hepatitis B
Smallpox	Human papilloma virus (HPV)
Varicella/herpes zoster	Inactivated poliomyelitis (IPV)
Yellow fever	Influenza, intramuscular
	Meningococcal
	Pertussis
	Pneumococcal (23-valent polysaccharide)
	Pneumococcal (7-valent protein conjugate)
	Rabies
	Tetanus typhoid, intramuscular

Tetanus and diphtheria toxoids adsorbed combined with component pertussis (Tdap); tetanus and diphtheria (Td) and component pertussis vaccine combined with diphtheria and tetanus toxoids adsorbed (DTaP) are combined inactivated vaccines.

Table 7. Summary of CRA recommendations for vaccination in patients with rheumatoid arthritis (RA) (Recommendations 7–9).

	Inactivated/Killed Vaccines			Live Attenuated Vaccines	
	Influenza (annual)	Pneumococcal (booster after 3-5 yrs)	Hepatitis B	Herpes Zoster	Other
Methotrexate*	✓	✓	✓†	✓††	Caution
Leflunomide	✓	✓	✓†	✓††	Caution
Sulfasalazine	✓	✓	✓†	✓††	Caution
All biologics	✓	✓	✓†	Avoid	Avoid

✓ Recommended; ideally administer prior to initiating therapy. † Recommended in high-risk groups including residents, travelers or close contact with individuals from hepatitis B endemic areas, illicit drug users, persons engaging in risky sexual behaviors/history of sexually transmitted infection, men who have sex with men, chronic liver disease, occupational exposures, frequent blood transfusions. †† Recommended in RA patients > 60 years old. * Methotrexate ≤ 25 mg per week.

Summary of evidence linked to recommendation. Evidence for the recommendation was based on results of a recent systematic review undertaken to inform EULAR 2011 recommendations for patients with autoimmune inflammatory rheumatic diseases[67].

Influenza — One observational study showed a reduction in infection at 1 year in 34 patients with RA who received influenza vaccine compared to 20 patients who did not [acute bronchitis, 7 (22.6%) vs 1 (4.3%), respectively; viral respiratory infections, 19 (61.3%) vs 2 (8.7%)][73]. Two other observational studies also found a reduction in hospital admissions and mortality from influenza and pneumonia in elderly patients with rheumatic diseases who received the influenza vaccine[74,75].

Pneumococcus — Pneumococcal infection is one of the main causative pathogens for pulmonary infections, and RA patients have been reported to be at increased risk for pulmonary infections and death from pulmonary infections in observational studies[67].

Herpes zoster — An increased risk of herpes zoster has been reported in RA patients compared to healthy population controls from 2 administrative databases (adjusted hazard rate ratios 1.7 and 1.9, respectively)[67]. In addition, treatment with glucocorticoids, azathioprine, leflunomide, and anti-TNF was associated with increased risks of herpes zoster[67].

Human papilloma virus (HPV) — The risk of HPV in patients with RA is unknown, although there is observational evidence that patients with systemic lupus erythematosus have a higher rate of HPV infection, particularly high-risk (oncogenic) HPV subtypes. The systematic review[67] supported the safety of HPV vaccination in patients with autoimmune inflammatory rheumatic diseases, although data on adverse events were often based on small samples.

Evidence to recommendation. In general the panel emphasized that patients should be encouraged to monitor and keep up-to-date with all vaccinations indicated for the adult Canadian general population. Influenza (annual) and pneumococcal vaccine (with booster every 3–5 years) were recom-

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mended for all patients with RA based on an increased risk of infection and evidence supporting efficacy and safety of these vaccines in RA patient populations. The risk of hepatitis B in patients with RA is unknown, although vaccination against hepatitis B was recommended in high-risk groups, consistent with recommendations for the Canadian general population. Zoster vaccine was recommended for RA patients age 60 years and over based on an increased risk of infection in RA patients and efficacy of this vaccine in reducing the infection risk in the general population. The efficacy and safety of the HPV vaccine has not been evaluated in RA, although the Canadian National Advisory Committee on Immunization recommends vaccination against HPV in women aged 14 to 26 years in the general population[76].

Barriers to implementation. None.

Recommendation 8:
Inactivated vaccines should ideally be administered prior to starting treatment with MTX and/or biologic DMARD as these medications may attenuate the immune response. (Level I, II; Strength B)

Summary of guidelines. The search identified 8 clinical practice guidelines and 1 consensus statement that addressed administration of inactivated vaccines in RA (AGREE rating: Recommend (R) = 1, Recommend with provisos (R*) = 8). All 9 guidelines recommended that it is preferable to administer inactivated vaccines prior to starting immunosuppressive therapy, 7 of which added that, if necessary, inactivated vaccines may be given during immunosuppressive treatment, including treatment with biologics[22,27,28,29,33,55,71]. The EULAR 2011 vaccination guidelines also noted that, ideally, vaccination should be considered when the disease is stable[71]. Two French guidelines recommended waiting at least 2 weeks before treatment with ABAT[28] or TCZ[27]. Five guidelines included recommendations for RTX[29,55,58,71,72] and all strongly suggested that vaccinations should be administered before initiating RTX, with 2 suggesting an interval of 4 weeks between vaccine administration and initiation of RTX therapy[29,72].

Recommendation/supporting evidence adapted from: EULAR 2011[71] (R*) and Canadian Immunization Guide 2006[70].

Summary of evidence linked to recommendation. MTX/DMARD — Studies identified by a systematic review undertaken to inform EULAR 2011 vaccination guidelines[67] showed that patients treated with MTX had similar responses to the influenza vaccine relative to non-RA controls, although 2 studies showed a reduced response to pneumococcal vaccine[77,78]. Seroprotection was observed in 68% of DMARD-treated patients following hepatitis B immunization[79]. Biologics — RCT and controlled studies showed comparable levels of seroprotection to influenza vaccine in RA patients treated and not treated with anti-TNF therapy, although 2 studies reported a modestly impaired response in anti-TNF users, which did not result in a lower rate of seroprotection[77,78]. One controlled study described a reduced immune response to treatment with anti-TNF plus MTX after influenza immunization[78]. Two controlled studies showed a reduced response to pneumococcal vaccine in patients who were treated with anti-TNF agents[80,81], and 2 showed reduced responses in patients treated with anti-TNF plus MTX[77,78]. In these 2 latter studies, patients who were treated with MTX alone also had lower immune responses. Results from 3 studies on the efficacy and safety of immunization in RTX-treated patients showed reduced responses to influenza[82,83] and pneumococcal vaccines[84].

Evidence to recommendation. The panel recommended administering inactivated vaccines prior to starting immunosuppressive therapy to maximize the immune response, especially in patients treated with B cell-depleting agents (RTX). The Canadian Immunization Guide[70] recommended that inactive vaccines ideally be administered 14 days before initiating immunosuppressive therapy. This may, however, not be feasible in all patients. Inactivated vaccines may be given to patients treated with MTX and/or biologic DMARD but the potential for an attenuated response should be communicated to the patient.

Barriers to implementation. None.

Recommendation 9:
Live vaccines should be administered at least 2 weeks and ideally 4 weeks before starting treatment with biologic DMARD. In patients currently receiving biologic therapy, treatment with the biologic should be suspended and the vaccine administered after an appropriate interval based on the pharmacokinetic properties of the agent (Table 4). Herpes zoster vaccine may be given to patients receiving MTX (≤ 25 mg/week) and/or low-dose corticosteroids (< 20 mg/day). (Level IV; Strength D)

Summary of guidelines. The search identified 11 clinical practice guidelines and 2 consensus statements that addressed administration of live vaccines in RA patients (AGREE rating: Recommend (R) = 1, Recommend with provisos (R*) = 12). All emphasized that live attenuated vaccines were not recommended in patients treated with biologic DMARD[22,23,25,26,27,28,29,31,32,33,55,58,71]. The recommended minimum interval to wait after administering a live vaccine prior to starting a biologic agent varied. Three guidelines recommended waiting 4 weeks for any live vaccine prior to starting anti-TNF therapy[23,25,58]. Two guideline groups made specific recommendations for yellow fever vaccine, one recommended a 3-week interval prior to starting ABAT or TCZ[33], and one recommended a 2-week (ideally 4-week) interval before starting either ABAT or TCZ[27,28] and 4 weeks before starting the first RTX infusion[29].

In patients currently receiving biologic therapy, the recommended interval for withholding biologics varied across the different agents. One guideline group recommended waiting 5

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half-lives for patients receiving anti-TNF agents[33], ABAT[28], and TCZ[27] and 1 year after the last dose of RTX, adding that 6 months could be adequate[29]. Three guidelines recommended waiting 6 months after the last IFX infusion and 2–3 weeks after the last ETN dose[23,25,58], and one suggested that live vaccines could be administered within 3 months of ABAT therapy[55]. The Canadian Immunization Guide[70] advised that live attenuated vaccines should be avoided in patients who are immunocompromised unless data are available to support their use or the risk of natural infection is higher than the vaccination risk.

Recommendation/supporting evidence adapted from: EULAR 2011[71] (R*), US Centers for Disease Control and Prevention (CDC 2011)[69], and the Canadian Immunization Guide 2006[70].

Summary of evidence linked to recommendation. CDC 2011 guidelines[69] provided reports of severe complications following vaccination with live attenuated vaccines in immunocompromised patients, although such events have not been reported specifically in patients with RA. The Canadian Immunization Guide[70] and the Advisory Committee on Immunization Practices (ACIP)[69] stated that herpes zoster vaccine may be administered to patients treated with short-term corticosteroid therapy (< 14 days) or low to moderate doses (< 20 mg/day) and in patients treated with topical, inhaled, and locally injected steroids (intraarticular, bursal, or tendon injection) unless there is clinical or laboratory evidence of immunosuppression. The ACIP also added that herpes zoster vaccine may be given to RA patients treated with low-dose MTX (≤ 0.4 mg/kg/week) or AZA (≤ 3.0 mg/kg/day). These recommendations were based on expert opinion.

Evidence to recommendation. The guideline panel agreed that live vaccines should generally be avoided in patients with RA during treatment with biologic DMARD, based on the potential increased risk for infection combined with the paucity of research studies. A 2-week (ideally 4-week) interval between administration of the live vaccine and starting the first dose of biologic therapy was considered reasonable and was in line with recommendations from the Canadian Immunization Guide[70]. For RA patients already treated with biologics, the panel recommended that the timing for withholding/restarting therapy should be based on the pharmacokinetic properties of the agent used (Table 4), consistent with the Canadian Immunization Guide. There may, however, be rare circumstances where more timely administration of live vaccines in patients currently receiving biologic therapy may be considered (e.g., outbreak). The decision to administer or withhold a particular live vaccine should be judged on a case-by-case basis balancing the potential risk of developing infection from the agent for which vaccine protection is being sought against the risk of infection from the vaccine. Consultation with an infectious disease specialist should be sought as appropriate.

Barriers to implementation. Timely access to infectious disease specialists.

IV. Malignancy — *Understanding potential risks for malignancy in patients with RA*

Patients with RA have been shown to have an overall slightly increased risk of malignancy relative to the general population, although notably, risks for site-specific cancers have been shown to vary, with increased risks reported for lung cancer and malignant lymphomas and decreased risks reported for breast and colorectal cancers[85]. An increased inflammatory burden in patients with RA is thought to contribute to increased lymphoma risks and local inflammatory responses are hypothesized to play a role in certain cancers[86,87]. Higher disease activity in RA has been associated with greater risks of lymphoma[87]. Cytokine pathways including TNF and nuclear factor-κB are also important in tumor surveillance, and blocking these pathways can theoretically increase cancer risk[86]. Whether treatment with biologic DMARD and other immunosuppressant therapies used in RA increases overall and/or site-specific risks for malignancy remains an active area of investigation.

Treatment with anti-TNF therapy was associated with increased short-term risks of malignancy in pooled analyses of early clinical trials of IFX and ADA[88] and ETN[89], although doses of anti-TNF in these trials were often higher than recommended in clinical practice and very few events were observed in the control group. A recent pooled analysis of 74 RCT of ETN, IFX, and ADA that included patients with RA receiving recommended doses of anti-TNF and blinded adjudication of cancer events did not report a significant increase in the short-term risk of malignancy [excluding nonmelanoma skin cancer (NMSC)][90]. Consistent results were also reported in a recent metaanalysis of RA registries/prospective observational studies focusing on treatment with anti-TNF (ETN, IFX, and ADA)[91]. Two studies included in this review examined risks for recurrent malignancy in RA patients with a history of malignancy, and found no increased risk of malignancy in patients treated with anti-TNF therapy relative to patients treated with traditional DMARD, although numbers were too small to allow a definite conclusion[92,93]. Increased risks of malignancy (excluding NMSC) have also not been reported in RCT/open-label extension studies of ABAT, RTX, and TCZ[27,94,95], although data from population registries with longer followup are currently unavailable.

Understanding limitations in evidence regarding risk of malignancy in patients with RA

Randomized controlled trials, while being the "gold standard" for evaluating drug efficacy, have inherent limitations when studying safety outcomes[86,96,97]. RCT generally lack adequate sample sizes and followup to detect rare adverse events, particularly certain malignancies with longer latencies. Further, RCT of biologic DMARD typically exclude patients with a history of malignancy diagnosed within 5 years and patients with comorbidities who may be at higher risk of malignancy. Such strict eligibility criteria can affect back-

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ground risks for malignancy and limit generalizability to RA patients seen in routine practice.

Observational studies including product surveillance systems, administrative databases, and clinical disease/drug registries can be useful tools for evaluating drug safety. We included recently published observational studies (last 3 years) in a supplemental systematic search to help inform recommendations for malignancy. Observational studies provide real-world data that may be more generalizable to patients seen in routine practice and longer followup periods, providing improved ascertainment of rare events. These studies, however, may be vulnerable to types of selection bias, such as negative channeling bias, where individuals at the lowest risk for developing malignancy may have a higher probability of being treated with biologic therapy and/or other imbalances between exposed and unexposed groups. In addition, sample size constraints and duration of followup can also affect precision of risk estimates from these studies[86,96,97].

Direct evidence examining the risk of incident cancers and/or relapse in patients who have a history of malignancy is sparse given current warnings/contraindications concerning the use of biologic therapies in patients with RA. Few studies report site-specific risks for malignancy and estimates of both overall and site-specific risks of malignancies associated with biologic therapies other than ETN, IFX, and ADA (e.g., CTZ, golimumab, ABAT, TCZ) are limited. Therefore, indirect evidence evaluating risks for malignancy in RA patients with no history of malignancy treated with anti-TNF (ETN, IFX, and ADA) was predominantly used to inform recommendations for malignancy.

Given the limited research evidence, recommendations for malignancy are generally grouped as follows: (1) medications that are an option (evidence that there is either no increased risk or no theoretical increased risk); (2) medications that should be used with caution due to unknown risks; and (3) medications that should be used with caution as at least some evidence of increased risks have been presented. Since risks related to treatment decisions in patients with RA and cancer are both individual patient- and cancer-dependent, treatment decisions for RA patients with malignancy (active or past) should be made on a case-by-case basis in conjunction with a cancer specialist and the patient. The need to control RA disease activity should be balanced against the risk of cancer progression or recurrence, considering the individual type and prognostic features of the malignancy.

A summary of malignancy recommendations is presented in Table 8.

Recommendation 10:
In general, in RA patients with active malignancy, treatment with traditional and biologic DMARD should be delayed/withheld while patients are receiving chemotherapy or radiotherapy. Treatment decisions should be made on a case-by-case basis in conjunction with a cancer specialist and the patient. (Level IV; Strength D)

Summary of guidelines. The search identified 7 clinical practice guidelines that commented on the use of DMARD in patients with active or a recent history of malignancy (AGREE rating: Recommend with provisos (R*) = 7). One guideline addressed treatment with traditional DMARD and recommended that in patients who develop a tumor, all DMARD should be discontinued except antimalarials, gold salts, and sulfasalazine (SSZ)[16]. The remaining guidelines addressed treatment with anti-TNF therapy[22,33,54], ABAT[28], RTX[29], or TCZ[27], and all recommended against the use of biologic therapy in patients with active malignancy.

Recommendation/supporting evidence adapted from: Not applicable. Consensus recommendation.

Summary of evidence linked to recommendation. No evidence was identified that addressed the use of traditional or biologic DMARD in RA patients with active malignancy.

Evidence to recommendation. The panel acknowledged that there may be situations in which RA drug therapy may be necessary in patients with active malignancies; however, in these select cases treatment decisions should be a shared decision between the rheumatologist, the oncologist, and the patient. In general, the panel considered that therapies used to treat RA including MTX and/or biologics may increase the risk of infection in an already immunocompromised host receiving systemic treatment for active malignancy, as well as the potential for drug interactions that are not yet elucidated. Finally, the panel also considered that systemic therapies administered to treat active malignancies may help achieve/maintain RA disease control, obviating the need for DMARD therapy.

Barriers to implementation. Timely access to an oncologist.

Recommendation 11:
In RA patients with a history of lymphoma, hydroxychloroquine, sulfasalazine, and rituximab may be used. Treatment with anti-TNF therapy is not recommended. Treatment with other traditional and biologic DMARD should be used with caution. (Level II, IV; Strength C)

Summary of guidelines. The search identified 10 clinical practice guidelines and 2 consensus statements that addressed the use of traditional and biologic DMARD in patients with a history of hematologic malignancies (AGREE rating: Recommend (R) = 1, Recommend with provisos (R*) = 11). One guideline commented on traditional DMARD and stated that both leflunomide (LEF) and MTX are contraindicated if lymphoproliferative disease has been diagnosed and/or treated within the last 5 years[31]. Nine guidelines commented on anti-TNF therapy and all recommended against the use of anti-TNF therapy in patients with a recent history of lymphoma[16,22,23,25,26,31,33,54,55]. Two guidelines recommended that anti-TNF therapy should not be used (or is not preferred)

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Table 8. Summary of CRA recommendations regarding treatment with traditional and biologic disease-modifying antirheumatic drugs (DMARD) in rheumatoid arthritis (RA) patients with malignancy (Recommendations 10–13).

	Option	Use with Caution (risk unknown/ no evidence)	Use with Caution (some evidence of increased risk)
Active malignancy, receiving cancer chemotherapy/radiation.	*	*	*
History of malignancy			
Lymphoma	Sulfasalazine, hydroxychloroquine, rituximab	Abatacept, tocilizumab	Methotrexate, anti-TNF
Nonmelanoma skin cancer	Methotrexate, leflunomide, sulfasalazine, hydroxychloroquine	Abatacept, rituximab, tocilizumab	Anti-TNF
Solid tumor	Methotrexate, leflunomide, sulfasalazine, hydroxychloroquine	Abatacept, rituximab, tocilizumab	Anti-TNF (melanoma)

* Treatment decisions should be made on a case-by-case basis in conjunction with a cancer specialist and the patient. Anti-TNF: anti-tumor necrosis factor.

in patients with any history of lymphoma[16,33]. Two guidelines considered anti-TNF therapy contraindicated in patients diagnosed with lymphoproliferative disorders diagnosed within 5 years[31,54], with one also considering these agents relatively contraindicated after 5 years[54]. Three guidelines recommended that anti-TNF therapy is not contraindicated in patients with a history of malignancy with no recurrence after > 10 years[23,25,26]. Two additional guidelines did not provide a specific recommendation, but stated that evidence for an increased risk of lymphoma with anti-TNF therapy is conflicting[22,55]. Three guidelines commented on ABAT[22,28,55] and one guideline recommended against using ABAT in patients who have had a history of lymphoma within the last 5 years[28]. Two guidelines commented on RTX[22,29]; one guideline stated that RTX may be used in patients with a history of B cell lymphoma[29] and the other suggested that RTX may be used in patients with a history of cancer that has been treated and considered cured[22]. Both guidelines highlighted that, to date, no increased risks for lymphoma have been observed in patients treated with RTX. Three guidelines commented on TCZ[22,27,55]; one guideline recommended that, in the absence of data, TCZ should not be used in patients with a history of hematological cancer in the past 5 years, although in patients with a history of lymphoma who have failed other therapies (including RTX), TCZ may be considered after discussion with the hematologist[27].

Recommendation/supporting evidence adapted from: Not applicable. Consensus recommendation.

Summary of evidence linked to recommendation. MTX/DMARD — one nested case-control study examined the risk of incident lymphoma (not recurrence) in RA patients treated with MTX compared to RA patients treated with other DMARD and reported a small but not statistically significant increased risk associated with MTX (RR 1.23, 95% CI 0.97–1.57)[99]. In that study, no increased risk of lymphoma was associated with use of LEF, SSZ, antimalarials, or gold. Four studies examined risks of lymphoproliferative disease in patients with RA treated with MTX and/or other DMARD relative to the general population and all showed an increased risk [non-Hodgkin's lymphoma: standardized incidence ratio (SIR) = 5.1, 95% CI 2.2–10[100], SIR = 5.4, 95% CI 1.1–15.7[101]; any lymphoproliferative disease: SIR = 3.8, 95% CI 2.2–6.2[102]; lymphoma: SIR = 1.7, 95% CI 0.9–3.2[103]].

Biologics — A Cochrane network metaanalysis of randomized trials examining the safety of biologic therapy (excluding TCZ) did not observe an increased risk of lymphoma associated with any biologic therapy (OR 0.53, 95% CI 0.17–1.66), although data were limited to very few events[49]. Similarly, 4 observational studies compared the risk of lymphoma in RA patients treated with anti-TNF therapy relative to RA patients who were biologic-naive; none showed an increased risk associated with anti-TNF therapy, although small numbers of malignancies and lack of precision around study estimates precluded definitive conclusions (RR 1.4, 95% CI 0.8–2.1[104]; HR 1.1, 95% CI 0.5–2.4[105]; OR 1.0, 95% CI 0.6–1.8[106]; and HR 5.0, 95% CI 0.9–27.9[107]. Eight studies reported an increased risk of lymphoma in RA patients treated with anti-TNF compared to the general population[103,104,106,107,108,109,110,111], among which one study reported a higher risk associated with ADA or IFX relative to ETN (ADA: OR 4.7, 95% CI 1.3–17.7; IFX: OR 4.1, 95% CI 1.4–12.5)[109]. In an RCT open-label extension study, no increased risk of lymphoma was observed in RA patients treated with ABAT relative to RA patients treated with traditional DMARD[95].

Evidence to recommendation. The panel recommended that hydroxychloroquine and SSZ may be used based on expert opinion, and RTX based on experience of its use as a treatment for B cell lymphoma. Caution should be used with MTX and other DMARD, based on the increased risk of lymphoma in RA patients taking MTX compared to the general population and case reports of reversible lymphoma in patients exposed to MTX. No study, however, has shown an increased risk of lymphoma in RA patients treated with MTX relative to RA patients not taking MTX. Anti-TNF therapy was not recommended based on an increased risk of lymphoma in RA patients relative to the general population, although the panel

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recognized that a conclusive increased risk of lymphoma in patients treated with anti-TNF therapy relative to patients who were biologic-naive has not been shown. For ABAT and TCZ there was insufficient evidence to evaluate the risk.

Barriers to implementation. None.

Recommendation 12:
In RA patients with a history of a nonmelanoma skin cancer, traditional DMARD therapy may be used (IV). Other RA drug therapies should be used with caution (anti-TNF II, other biologics IV). (Level II, IV; Strength C)

Summary of guidelines. The search identified 5 clinical practice guidelines and 1 consensus statement that addressed the use of traditional and biologic DMARD in patients with a history of nonmelanoma skin cancer (NMSC) (AGREE rating: Recommend with provisos (R*) = 6). No guideline provided a recommendation for traditional DMARD. Four guidelines addressed anti-TNF therapy[22,33,54,55]; 2 did not provide a specific recommendation but stated that the data for an increased risk with anti-TNF therapy is conflicting[22,55]; 2 guidelines, both by French guideline development groups, recommended that patients with recent basal cell carcinoma[33] or patients with locally aggressive skin tumors treated by complete excision[54] are still eligible for treatment with anti-TNF therapy. The French guideline group also extended this recommendation for ABAT[28] and TCZ[27]. No specific recommendations were made for RTX.

Recommendation/supporting evidence adapted from: Not applicable. Consensus recommendation.

Summary of evidence linked to recommendation. There was no evidence identified that evaluated the risk of NMSC with DMARD use, or the risk of recurrent NMSC in patients with a history of NMSC for any therapy. There was conflicting evidence for an increased risk of NMSC associated with anti-TNF therapy. Wolfe, *et al* reported an increased risk of basal-cell carcinoma (BCC) or squamous cell carcinoma (SCC) in RA patients treated with anti-TNF compared to RA patients not receiving anti-TNF therapy (OR 1.5, 95% CI 1.2–1.8)[111]. A Swedish cohort reported no increased risks of skin cancer (including SCC) in RA patients treated with anti-TNF therapy relative to RA patients who were biologic-naive[112]. One study found an increased risk of BCC and SCC in RA patients receiving anti-TNF therapy compared to the general population[113]. Another Swedish study found an increased risk of SCC in RA patients compared to the general population for an inpatient RA cohort (SIR 3.6, 95% CI 1.8–6.5), but not in an early RA cohort (SIR 0.7, 95% CI 0.2–1.6)[114]. A recent individual patient-level metanalysis of all RCT of ETN, ADA, and IFX reported an increased short-term risk of NMSC associated with anti-TNF therapy (RR 2.02, 95% CI 1.11–3.95)[90]. A recent metaanalysis of observational studies also reported an increased risk of NMSC associated with anti-TNF therapy (pooled RR 1.45, 95% CI 1.15–1.76)[91]. Data for ABAT and TCZ based on post-hoc analyses from RCT and open-label extension studies did not show an increase in NMSC[27,28]. No evidence was available for RTX.

Evidence to recommendation. The recommendation for NMSC refers to BCC and locally advanced SCC treated curatively by excision. The guideline panel agreed that treatment with traditional DMARD was an option in patients with a history of NMSC. Evidence supporting an increase risk of NMSC associated with anti-TNF therapy suggests particular caution and closer surveillance in these patients. Evidence of an increased risk of NMSC is lacking for other biologics and similar caution is warranted. Decisions should be made on a case-by-case basis after discussion with the patient and skin cancer specialists considering the patient's risk/benefit profile. In patients with a history of NMSC treated with biologic therapy, sun protection and routine skin surveillance is recommended.

Barriers to implementation. None.

Recommendation 13:
In RA patients with a history of solid malignancy, traditional DMARD may be used (Level II, IV). Treatment with biologic DMARD should be used with caution (anti-TNF, Level II; other biologics Level IV). (Level II, IV; Strength C)

Summary of guidelines. The search identified 8 clinical practice guidelines and 2 consensus statements that addressed the use of DMARD in patients with prior solid malignancy (AGREE rating: Recommend with provisos (R*) = 10). No guidelines provided a recommendation for traditional DMARD. Seven guidelines commented on anti-TNF therapy; 2 recommended that anti-TNF may be considered in patients with a history of solid malignancy that has been treated and cured after 5 years, in consultation with an oncologist[16,33], with one adding that particular attention should be paid in patients with malignancies with a high risk for metastasis (e.g., breast)[33]. Three guidelines advised that anti-TNF therapy is not contraindicated in patients with a history of solid tumor more than 10 years previously who are free of recurrence[23,25,26]. Two additional guidelines did not provide a specific recommendation, but offered that evidence for an increased risk of solid tumors with anti-TNF therapy is conflicting[22,55]. Three guidelines commented on ABAT[22,28,55]; one recommended against using ABAT in patients who have a history of solid tumor treated and considered cured within the last 5 years[28] and the other 2 guidelines did not provide a recommendation. Three guidelines commented on RTX[22,29,55] and all highlighted that to date there have not been reports of increased risks for solid tumors in patients treated with RTX. One guideline suggested that it was reasonable to consider treatment with RTX in RA patients with a history of solid malignancy that is considered cured[22]; another suggested that

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RTX may be used in patients with a history of solid malignancy that was treated and considered cured more than 1 year earlier, but to use caution in cases with a high risk of metastasis (e.g., breast)[33]. Three guidelines commented on TCZ[22,27,55]; one recommended that in the absence of data, prudence dictates that TCZ not be used in patients with a history of solid cancer in the past 5 years[27] and 2 did not provide a specific recommendation, but stated that no increased risk of solid tumors have been observed in RA patients treated with TCZ compared to RA patients treated with DMARD[22,55].

Recommendation/supporting evidence adapted from: Not applicable. Consensus recommendation.

Summary of evidence linked to recommendation. MTX/DMARD — Treatment with specific traditional DMARD was not associated with statistically significant increased risks of lung cancer in a nested case-control study within an administrative claims database[115]. Two studies reported an increased risk of lung cancer in RA patients treated with MTX relative to the general population (SIR 2.9, 95% CI 1.6–4.8[100]; and SIR 3.5, 95% CI 1.4–7.1[101]), one of which also reported an increased risk of melanoma (SIR 3.0, 95% CI 1.2–6.2[100]).

Biologics — RA patients treated with anti-TNF were not at increased risk for solid tumors relative to RA patients treated with traditional DMARD in 4 studies[105,111,112,115], although one study found an increased risk of melanoma associated with IFX (OR 2.6, 95% CI 1.0–6.7) and ETN (OR 2.4, 95% CI 1.0–5.8)[111]. Treatment with anti-TNF therapy was not associated with an increased risk for solid tumors relative to the general population in 3 studies[107,110,114], although in an analysis of specific types of solid malignancies, one study reported an increased risk of lung cancer[114] and a separate study reported a nonsignificant trend toward an increased risk for smoking-related cancers (SIR 2.2, 95% CI 0.7–5.1[107]). An increased risk of smoking-related cancers[107,114] and a decreased risk of breast cancer[111,114] have also been reported in RA patients not on anti-TNF therapy relative to the general population. ABAT was not associated with an increased risk of solid tumors relative to RA patients receiving traditional DMARD or the general population in an open-label extension study[95].

Evidence to recommendation. The recommendation refers to patients with a history of any solid tumour, including melanoma, but excluding NMSC. The panel recommended that DMARD may be used, based on expert opinion. Longstanding experience with MTX in real-world patients and very little evidence of an increased risk of malignancy suggests that it is likely safe, particularly given the history of its use in oncologic conditions. Biologic therapy should be used with caution based on limited evidence and a theoretical increased risk. For anti-TNF therapy, particular caution is warranted in patients with a history of melanoma, as one study found an association with anti-TNF exposure. For ABAT, RTX, and TCZ there was insufficient evidence to evaluate the risk. Ideally, a longer cancer-free followup prior to initiating biologic therapy is preferred, especially for cancers with a high risk of recurrence. Decisions should be individualized considering the type of cancer and the need to control RA disease activity, and should be made in conjunction with the treating oncologist wherever possible.

Barriers to implementation. None.

DISCUSSION

Thirteen recommendations were developed addressing specific safety aspects of treatment with traditional and biologic DMARD, including: (1) perioperative management, (2) screening for LTBI and indications for initiating TB prophylaxis, (3) optimal vaccination practices, and (4) management of patients with malignancy (active and past). These recommendations were based on a synthesis of international RA guidelines, public health guidelines/advisories, supporting evidence from observational studies and RCT, and expert consensus of a Canadian national working group, in the context of the Canadian healthcare system. Consultation with external clinical content experts in infectious disease and malignancy was sought to ensure that the most relevant literature and current practice views were appropriately represented. The safety topics addressed here were identified directly from a large sample of Canadian rheumatology health professionals[2] and we anticipate that these recommendations will help support clinical decision-making and enhance the care of patients with RA. We emphasize that these recommendations should be used with the clinical judgment of the treating physician acting according to unique clinical circumstance. Consultation with specialists (e.g., infectious disease, oncology) should be sought as appropriate. Recommendations presented here will be subject to update and change as new data emerge.

Specific data limitations have been discussed in each section. In general, future research that would contribute to a better understanding regarding the safe utilization of RA drug therapies include: (1) RCT and/or controlled prospective studies examining the risk of perioperative infections in patients treated with biologics, particularly newer biologics (ABAT, RTX, TCZ) and specific attention to schedules for withdrawing/reinstituting therapy; (2) improved surveillance/reporting of TB reactivation in patients treated with ABAT and TCZ; (3) prospective studies examining longterm risks of TB reactivation in individuals with positive IGRA; (4) quasiexperimental studies examining the effectiveness of vaccination on reducing vaccine-preventable infections in RA populations; (5) improved surveillance/reporting of risks for malignancy in patients with a history of malignancy treated with MTX and biologic therapies; and (6) large multisite/multinational RA registry studies evaluating longterm site-specific cancer risks for individual biologic agents that may theoretically have differential risks and effects on cancer prognosis.

Conclusion. Thirteen recommendations were developed by a

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Canadian national multidisciplinary working group as a knowledge tool to help support clinical decision-making regarding specific safety aspects surrounding treatment with traditional and biologic DMARD in RA, with special consideration of the Canadian healthcare system.

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