Biologic response modifiers to decrease inflammation: Focus on infection risks

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Biologic response modifiers are a novel class of drugs used by subspecialists to treat immune-mediated conditions such as juvenile idiopathic arthritis and inflammatory bowel disease. Also known as 'cytokine inhibitors', they are proteins whose purpose is to block the action of cytokines involved in inflammation. The desired therapeutic effect is to reduce or control inflammation. Tumour necrosis factor- α (TNF- α) inhibitors are the prototypes, but newer agents in this class target other cytokines such as interleukin(IL)-6, IL-12, and IL-23, or the proteins that target cytokine receptors on lymphocytes. They typically act by inhibiting the normal inflammatory processes involved in the immune response, particularly for macrophages. These agents are often used in combination with other immunosuppressive drugs such as methotrexate or steroids. The immune-modulating effects can persist days to weeks after discontinuation. Evidence indicates that patients treated with biologic response modifiers are at higher risk of tuberculosis infection and may be at higher risk of fungal or other infections with intracellular pathogens. This practice point offers guidelines on the preventive strategies that should be used in patients who will be or who are taking these immune-modifying agents.

Key Words: *Immune modulators; Infection; Juvenile idiopathic arthritis; Macrophages; TNF- α ; Tuberculosis*

The purpose of the present practice point is to describe the significant risks of infection associated with using medications that modify immune responses. These agents are also known commonly as biologic response modifiers (BRM) or proinflammatory cytokine inhibitors, such as tumour necrosis factor- α (TNF- α) inhibitors. The prescription of BRM and monitoring while on therapy should be the purview of specialists (eg, a paediatric rheumatologist, gastroenterologist or dermatologist) who are familiar with their indications and risks in children and adolescents. This document is intended for primary care practitioners and paediatricians, and will address only the increased risk of selected infections while taking these agents and provide guidance on some risk-reduction strategies. The present practice point will not address systemic or topical anti-inflammatory agents such as steroids or tacrolimus, nor will it address the potential association of malignancy with BRM therapy.

Cytokines such as TNF- α are part of the family of proteins that modulate the inflammatory process and are produced by cells involved in inflammation, most notably monocytes, macrophages and T lymphocytes. Some cytokines enhance inflammation (proinflammatory cytokines) while others may suppress inflammation.

Les modificateurs de la réponse biologique pour réduire l'inflammation : pleins feux sur les risques d'infection

Les modificateurs de la réponse biologique sont une nouvelle catégorie de médicaments qu'utilisent les surspécialistes pour traiter des maladies d'origine immunologique comme l'arthrite juvénile idiopathique et les maladies inflammatoires de l'intestin. Également connus sous le nom d'« inhibiteurs de la cytokine », ce sont des protéines qui visent à bloquer l'action des cytokines qui participent à l'inflammation. L'effet thérapeutique souhaité consiste à réduire ou à contrôler l'inflammation. Les inhibiteurs du facteur de nécrose tumorale α (TNF- α) en sont les prototypes, mais les agents les plus récents de cette catégorie ciblent d'autres cytokines, tels que l'interleukine (IL)-6, l'IL-12 et l'IL-23 ou les protéines qui ciblent les récepteurs de la cytokine sur les lymphocytes. D'ordinaire, ils agissent en inhibant les processus inflammatoires normaux qui participent à la réaction immunitaire, notamment les macrophages. Ces agents sont souvent utilisés en association avec d'autres immunosuppresseurs, tels que le méthotrexate ou les stéroïdes. Les effets de modulation immunologique peuvent persister de quelques jours à quelques semaines après l'arrêt du traitement. Selon les données probantes, les patients traités au moyen de modificateurs de la réponse biologique sont plus vulnérables à l'infection tuberculeuse et peut-être aux infections fongiques ou à d'autres infections contenant des pathogènes intracellulaires. Le présent point de pratique contient des lignes directrices sur les stratégies préventives qui devraient être utilisées auprès des patients qui prennent ou prendront ces agents.

In some disease states that are immune-modulated or auto-immune in nature (eg, juvenile idiopathic arthritis [JIA] or inflammatory bowel disease) many of these proinflammatory cytokines are inexplicably increased or 'up regulated', thereby contributing to inflammation, and ultimately, tissue destruction. Over the past 10 years, inhibitors of the proinflammatory cytokines were developed to diminish this 'excess inflammation' with the aim of preventing long-term organ or tissue damage in these diseases (1).

What are BRM that alter the immune response?

BRM are either antibodies to proinflammatory cytokines or proteins that target the cytokine receptors, but their common net effect is a proinflammatory cytokine 'inhibitor' effect, thus modifying the immune response. The majority of currently approved agents are specific to one cytokine or protein, such as TNF- α inhibitors. Newer drugs in this class target other proinflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-12 and IL-23, or the proteins that target cytokine receptors on lymphocytes. The agents listed in Table 1 are current and include some of the more common agents presently used in paediatrics. A comprehensive list of BRM and detailed description of their mechanisms of action are beyond the scope of this practice point.

TABLE 1
Biologic response modifiers (alphabetical order by generic name) approved in Canada*

Generic name	Trade name	Mechanism of action	Description	Route	Half-life
Abatacept	Orencia [†]	Binds to CD80 and CD86 on antigen-presenting cells, and therefore blocks production of TNF- α , IL-2 and interferon- γ	Selective costimulation modulator protein fused to human IgG	Intravenous	8 to 25 days
Adalimumab	Humira [‡]	TNF antagonist	Humanized IgG1 monoclonal antibody	Subcutaneous	10 to 20 days
Anakinra	Kineret [§]	Binds to IL-1 α receptor	Human monoclonal antibody against IL-1	Subcutaneous	4 h to 6 h
Canakinumab	Illaris [¶]	Binds to IL-1 β receptor and prevents interaction of cell surface receptors	Monoclonal antibody against IL-1 β	Subcutaneous	26 days
Certolizumab	Cimzia ^{**}	TNF antagonist	Humanized PEGylated Fab' of a TNF- α monoclonal antibody	Subcutaneous	14 days
Etanercept	Enbrel ^{††}	TNF antagonist	Soluble p75 TNF- α receptor fusion protein construct that binds to and inactivates TNF- α	Subcutaneous	70 h to 132 h
Golimumab	Simponi ^{‡‡}	TNF antagonist	IgG1k with human variable regions	Subcutaneous	7 to 20 days
Infliximab	Remicade ^{‡‡}	TNF antagonist	Humanized IgG1k with murine variable regions	Intravenous	9.5 days
Natalizumab	Tysabri ^{§§}	Blocks integrin association with vascular receptors limiting adhesion and transmigration of leukocytes	Monoclonal antibody against the alpha-4 subunit of integrin molecules	Intravenous	3 to 17 days
Riloncept	Arcalyst ^{¶¶}	Binds to IL-1 α and β and prevents interaction of cell surface receptors	IL-1 receptor fusion protein	Subcutaneous	8.6 days
Tocilizumab	Actemra ^{***}	IL-6 receptor antagonist	Humanized monoclonal antibody	Intravenous	Variable 3 to 10 days
Ustekinumab	Stelara ^{‡‡}	IL-12 and IL-23 antagonist	Humanized monoclonal antibody	Subcutaneous	20 to 24 days

*List is complete at July 1, 2011 but not all are approved for use in children. [†]Bristol-Myers Squibb, USA; [‡]Abbott Laboratories, USA; [§]Biovitrum, Sweden; [¶]Novartis, Switzerland; ^{**}UBC Inc, Belgium; ^{††}Immunex Corporation, USA; ^{‡‡}Janssen Biotech, Inc, USA; ^{§§}Elan Pharmaceuticals, Inc, Ireland; ^{¶¶}Regeneron Pharmaceuticals, Inc, USA; ^{***}Roche, Switzerland. IgG Immunoglobulin G; IL Interleukin; TNF Tumour necrosis factor

BRM therapy is administered either intravenously or subcutaneously weekly, every two weeks, monthly or bimonthly depending on the disease that is being treated and the half-life of the drug. Most of these drugs are given in combination with other immunosuppressive drugs, such as methotrexate, to optimize the anti-inflammatory effect.

How do BRM increase the risk of infection?

Normally, TNF- α or other proinflammatory cytokines generate an inflammatory response to pathogens. This effect is particularly evident for the T cell-mediated immune responses that are essential for the destruction of cells harbouring intracellular pathogens, for the formation of the granulomas and for ensuring an adequate cell-mediated immune response. Effectively maintaining this inflammatory response ensures that pathogens within cells are killed or remain dormant – an immune response that prevents new pathogens from propagating. However, if the inflammatory response is inhibited (eg, in the setting of BRM) this process is impaired and inflammatory responses are blunted. The inhibition of this immune response potentially permits reactivation of infections that have been controlled previously and/or leads to an inadequate immune response to new pathogens requiring cell-mediated immunity.

What infections are increased in this clinical setting?

There is substantial evidence that using BRM (eg, anti-TNF- α therapy) increases the risk of tuberculosis and fungal infections regardless of the underlying medical condition, even when compared with standard immunosuppressive therapy (2-4). The risk may be lower in patients with early rheumatoid arthritis who have not received previous treatment with disease-modifying drugs or methotrexate (5). Data are less clear as to whether the risk of infections from bacteria and viruses increases with the use of anti-TNF- α therapy, when compared with the risk in patients who receive standard therapy with corticosteroids, methotrexate, azathioprine, cyclophosphamide and others (6-9). The risk of reactivating tuberculosis with other BRM therapy has not been as well studied, but is likely to be similar to the risk posed by anti-TNF- α therapy.

Increased incidence and severity of infections caused by other mycobacteria (ie, leprosy and non-tuberculous mycobacteria) have also been reported with using BRM, as have infections with molds or endemic fungi such as *Histoplasma capsulatum*, *Blastomyces dermatidis* or *Coccidioides immitis*, and intracellular bacteria such as *Listeria monocytogenes*. Reactivation of *Strongyloides* should also be considered in patients from endemic areas.

There are case reports of adults reactivating chronic viral infections such as herpes simplex, varicella-zoster, and hepatitis B while on anti-TNF- α therapy (3,7). The role of BRM therapy in potentially reactivating Epstein-Barr virus infections, with attendant potential for developing lymphoma, is unclear; however, case reports have been published.

The risk of infection appears to be related to the length of therapy. Owing to the long half-life of some drugs (ranging from three to 24 days), the increased risk of infection may persist for weeks and possibly months after discontinuing the drug.

In the populations studied thus far, there does not appear to be a significant increased risk of infections with more common bacterial pathogens, such as *S. pneumoniae*. Although there are no published studies involving children, there does not appear to be an increased risk of bacterial infections in the postoperative period in adults receiving BRM. The long-term effects of BRM on the developing fetal immune system when used in pregnancy are unknown. There is also little or no evidence thus far of increased risk of infections in the children of women who received BRM during pregnancy or lactation.

PREVENTING INFECTIONS

Tuberculosis

Before initiating BRM therapy, all asymptomatic patients should be evaluated for latent tuberculosis infection (LTBI). A detailed epidemiological history with particular focus on exposures to *Mycobacterium tuberculosis* is important. A tuberculin skin test (TST) and a chest radiograph should be performed (Table 2). The cut-off of 5 mm of induration should be used as a positive result for a TST. Blood-based assays for TB (interferon- γ release assays)

TABLE 2
Recommendations for patient work-up before initiation of biologic response modifier (BRM) therapy

Tuberculin skin test and/or blood-based assay for tuberculosis (the latter if 5 or more years of age)
Chest radiograph
Document vaccination status and verify that all recommended inactivated vaccines for age are up-to-date, including yearly injectable influenza vaccine
Document vaccination status and, if required, administer all live virus vaccines a minimum four weeks before initiation of BRM therapy unless contraindicated. For a list of contraindications please consult <i>The Canadian Immunization Guide</i> < http://www.phac-aspc.gc.ca/publicat/cig-gci/p03-07-eng.php >
Counsel household members regarding risk of disease and ensure vaccination for prevention of exposure to varicella and influenza and other transmissible infections
Depending on risk of past exposure, consider serology for <i>Histoplasma</i> , <i>Toxoplasma</i> and other intracellular pathogens
Consider serology for hepatitis B, varicella-zoster and Epstein-Barr virus
Counselling with respect to: <ul style="list-style-type: none"> • food safety <http://www.cps.ca/english/statements/ID/FoodborneInfections.htm> • maintenance of dental hygiene • exposure to heavy concentrations of garden soil, pets and other animals • high-risk activities (eg, excavation sites or spelunking and <i>Histoplasma capsulatum</i>) • travel to areas endemic for pathogenic fungi (eg, southwestern United States and <i>Coccidioides</i> species), or to areas where tuberculosis is endemic.

could also be used, because there is evidence they are more sensitive than the TST in patients who are immunosuppressed. If clinical suspicion for LTBI is high, some experts recommend empirical therapy for LTBI, typically with nine months of isoniazid treatment. Treatment with BRM should be postponed until at least one month of prophylaxis has been completed.

Patients with a clinical picture suggestive of either pulmonary or extrapulmonary tuberculosis should be promptly investigated in collaboration with infectious disease specialists.

Other infections

Currently, a high index of clinical suspicion is required to diagnose infectious diseases early and initiate appropriate diagnostic and treatment strategies. Similar infection control precautions apply to patients receiving BRM compared with patients who are not receiving these agents, and are based on infecting organisms and syndromic presentation.

To decrease the risk of infections with *L. monocytogenes*, *Toxoplasma gondii*, and other pathogens associated with undercooked meat or eggs, patients should avoid eating undercooked or delicatessen meats, raw eggs or unpasteurized milk products, including soft cheeses (10). Avoiding direct contact with soil or kitty litter (for *T. gondii*), kittens (for *Bartonella*), pet reptiles (for *Salmonella*), other pet bites or scratches (for *Pasteurella*), construction sites, farmyard barns and cave exploration (for high concentration of fungal spores) may also decrease the risk of these infections (Table 2).

Vaccine considerations

If possible, all routine immunizations should be up-to-date before starting BRM. For inactivated vaccines (eg, diphtheria, pertussis, tetanus, polio [DpTP] vaccine, meningococcal and pneumococcal conjugate vaccines) immunizations should be administered 14 or more days before starting BRM to improve the immune response. If the patient is on high-dose steroids, the interval between immunization and start of BRM should be one month. Annual injectable (inactivated) influenza vaccines are recommended for patients. The serological response to inactivated vaccines, such as injectable influenza vaccine, has been studied in adults undergoing BRM therapy. Such patients develop an adequate (though diminished) immune response compared with adults not receiving BRM therapy.

Children ≤ 59 months of age should complete their primary series of pneumococcal conjugate vaccine (11) before initiating BRM, if practical. Assuming they are a minimum of 24 months of

age, a dose of pneumococcal polysaccharide vaccine can be considered at least eight weeks after the last dose of pneumococcal conjugate vaccine. In children >59 months of age who have not completed their conjugated pneumococcal vaccine series previously, a dose of pneumococcal polysaccharide vaccine or a dose of conjugate pneumococcal vaccine, followed a minimum eight weeks later by the polysaccharide vaccine, can be considered.

Live virus vaccines are generally contraindicated for immunocompromised patients. Their history of disease or immunization against varicella, measles, mumps and rubella should be documented. Testing for antibody to these viruses should be performed if documentation is lacking. If evidence of immunity is lacking and there are no contraindications to live vaccines (such as high-dose steroids or other immunosuppressive therapy) live virus vaccines (measles, mumps, rubella [MMR] and varicella vaccines) should be given four weeks or more before starting BRM therapy (11). The safety of live virus vaccines (eg, live, attenuated influenza and rotavirus vaccines) while a child is receiving BRM therapy has not been specifically evaluated.

Skin testing for tuberculosis can be performed on the same day as MMR immunization. Otherwise, testing should be delayed four to six weeks after immunization with MMR, because this vaccine can temporarily suppress reactivity of TST.

Knowing the vaccination history of household members is especially important in this setting to prevent transmission of a vaccine-preventable illness. Household members who are varicella non-immune should receive varicella vaccine if there are no contraindications. Although the risk of transmitting a vaccine-type virus is minimal, keeping any lesions at the vaccine site covered until they are healed is recommended. Making sure that all household members have received the seasonal influenza vaccine is strongly recommended.

CONCLUSION

Increasingly, BRM are being developed to treat diseases that have an autoimmune component (eg, JIA, inflammatory bowel disease, psoriasis). Other uses include periodic fever syndromes with an auto-inflammatory pathogenesis. Screening for tuberculosis, immunization and preventive counselling for infection risks will continue to be essential strategies for managing children and adolescents who are receiving these medications. In addition, a heightened awareness of the potential for other infections in this population is an essential component of ongoing co-managed primary care.

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