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Casey Seifert

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The Acutely Ill Patient on Biologics; What Primary Care Should Know

Casey Seifert

University of North Dakota

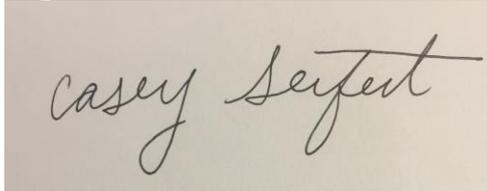
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Date: 3/12/2018

### Abstract

The following case study shows a 59-year-old man on biologic therapy who visited his primary care provider for an upper respiratory illness. He was treated with symptomatic management with very close follow up by his primary care provider. Recommendations for the primary care provider on the treatment of the acutely ill patient on biologic therapy are outlined as they related to the case. Biologic therapy is used to treat inflammatory conditions thought to be caused by inappropriate immune response. When on biologic therapy, however, a patient may have a decreased immune system to combat infectious agents. Articles related to increased risk of infections, guidelines for withholding biologics during active infection, and immunization considerations were reviewed. It was found that the decrease in immune activity caused by biologic therapy puts patients at increased risk for infection. Biologic treatment should be withheld during active infection, and patients on biologic therapy require close monitoring for worsening of acute respiratory symptoms. Specific vaccination recommendations were found, with live vaccinations being contraindicated during active treatment with biologics.

*Keywords:* biologic therapy, immune response, vaccination

### The Acutely Ill Patient on Biologics; What Primary Care Should Know

Biologic response modifiers, or biologics, are a class of prescription medications that target immune system proteins to block the inflammatory response. Biologics are classified by the type of protein that they inhibit; tumor necrosis factor, B cells, T cells, or interleukins (Bombardier, 2012). These inflammatory blockers are useful in the treatment of many autoimmune and inflammatory conditions such as rheumatoid arthritis, psoriasis, Crohn's disease, irritable bowel syndrome, and juvenile arthritis. Often, biologics are not first line treatment options, but instead are reserved for use when other treatments have failed and are generally only prescribed by specialists (Saag et al., 2008). Although primary care providers may not be prescribing biologics to their patients, it is important to understand their immune-suppressing effects so that safe and effective treatment plans can be made in the primary care setting.

The primary care provider may see patients who are currently on biologic therapies prescribed by a specialist for unrelated complaints. The following case will highlight such an instance where a patient is seeking primary care for an upper respiratory illness while on a biologic for rheumatoid arthritis. The case and following discussion of literature will demonstrate factors that the primary provider should consider in the treatment of the acutely ill patient that is on a biologic.

#### **Case Report**

A 59-year-old Caucasian man presented to clinic with a five-day history of fever, chills, body aches, cough, and rhinorrhea. These symptoms had a very sudden onset, stating that he went to work in the morning feeling fine, and then had to leave work early due to sudden fatigue. Aches were described as generalized muscle aching and weakness, cough was non-productive and not worse during the night or when recumbent. He did not have any associated shortness of

breath or chest pains. Rhinorrhea was described as “clear and dripping”. He had tried over the counter cough drops and non-steroidal anti-inflammatory medications for pain relief and fever reduction with some improvement in symptoms. He had multiple sick contacts in his office at work who exhibited the same symptoms. He had received the annual flu vaccination, but not the pneumococcal vaccination, and had no recent travel history.

Pertinent medical history would include diagnosis of rheumatoid arthritis for which he was managed by a Rheumatologist and was taking adalimumab subcutaneous injections and methotrexate. Also, he carries a diagnosis of essential hypertension for which he was taking an angiotensin converting enzyme inhibitor. He is a non-smoker with no known allergies, and lives in a house with his wife.

On physical exam vitals were noted as a blood pressures of 142/90, respiratory rate of 30, heart rate of 90, oxygen saturation level of 98%, and oral temperature of 102.4 degrees Fahrenheit. Generally, he did not appear in acute distress and was well groomed. Much of the exam was unremarkable, with lung sounds clear bilaterally without crackles or wheezes, heart with normal rate and rhythm, and negative for any joint swelling or tenderness. Only pertinent positives found were on the ear, nose, and throat exam was clear rhinorrhea from bilateral nares.

Based on physical exam and history of presenting illness it was concluded that this patient likely had a viral upper respiratory illness. Differential diagnoses would include acute bronchitis, pneumonia, influenza, or acute coryza. Given the unremarkable physical examination and five-day duration of symptoms a viral cause was thought to be most likely. No further lab work or diagnostics were performed, and symptomatic care was recommended. Testing for influenza was considered but deferred as the patient was past the recommended three-day

window for antiviral medication administration, therefore the treatment plan would not deviate from symptomatic care with a positive result of an influenza test.

Symptomatic care education was provided and included the use of over the counter non-steroidal anti-inflammatory agents and acetaminophen for fever reduction, over the counter cough suppressant at bedtime, and increase in fluid intake. Given the patient's current use of the biologic therapies adalimumab and methotrexate he was instructed to return to clinic if symptoms did not improve in two to three days as he is at increased risk for developing infections due to his drug-induced immunocompromised state. If symptoms persisted further, workup would be indicated to rule out a bacterial infection. During the closure of the visit the patient questioned if he should continue to take his adalimumab while he is not feeling well. He was advised to reach out to his Rheumatologist for guidance.

### **Literature Review**

Patients on biologic therapy with acute illness, such as the individual in the above case, require special considerations when being treated in primary care. The use of a biologic suppresses the natural immune response, and therefore puts a patient at increased risk for development of infection and reduces the ability of the body to combat the infection effectively (Le Saux, 2012). The patient also may require closer follow-up and careful consideration of opportunistic infection as opposed to general community acquired bacteria (Bryant & Baddley, 2016). It also may be necessary to discontinue use of the biologic while an active infection is occurring (Saag et al., 2008). Additionally, the primary care provider must consider the immune-suppressing effects of biologics when recommending and giving vaccinations.

Biologic use suppresses the natural immune response by inhibiting tumor necrosis factor and the T-cell mediated responses that are responsible for the inflammatory cascade that kills or

preserves dormancy of pathogens (Le Saux, 2012). This is helpful to reduce the inflammatory effects of some diseases, but it is non-specific, meaning all inflammatory responses are reduced, including the response to an external pathogen that may cause illness. Those on biologics have an increased risk of developing infections, with infections of the upper respiratory tract being the most common (Menter et al., 2008).

Individuals on biologics are also at increased risk for more serious opportunistic infections such as mycobacteria infection, tuberculosis, herpes zoster, pneumocystis, and histoplasmosis (Bryant & Baddley, 2016). Based on a Cochrane review of current literature related to adverse effects of biologic therapy, the actual risk of developing a serious infection or reactivating latent tuberculosis while on biologic therapy is relatively low. The review included 160 randomized control trials which included almost 50,000 total participants, and included studies that examined the effects of biologics on the risks of developing serious infections, tuberculosis reactivation, and development of lymphomas and other malignancies. Overall, the review found that biologics were associated with statistically significant risk increase for development of serious infections and reactivation of latent tuberculosis. Serious infection risk, however, was overall relatively low, but did show that 35 biologic-treated individuals out of 1000 experienced a serious infection compared to 26 out of 1000 individuals on the placebo. Tuberculosis infections were also relatively uncommon, with 20 biologic-treated individuals out of 10,000 developing or reactivating tuberculosis compared to 4 out of 10,000 in the placebo group (Singh et al., 2011).

Although the increased risk of opportunistic infection is relatively low, it would be prudent for the primary care provider to include such conditions in the differential diagnosis for the patient presenting with acute illness, particularly a respiratory illness. For example, in a

community-acquired pneumonia the typical host with a normal immune system likely would have a *Pneumococcus* infection, whereas the immunocompromised host may have a more atypical cause such as *Aspergillus* or mycobacterium. In this instance, the patient may require different, and perhaps more intensive antibiotic treatment and input from a specialist (Rali, Veer, Gupta, Singh, & Bhanot, 2016).

Much of the literature focused on serious complications and infections related to biologic use. In the literature review, there were no pertinent articles found related to common infections seen in primary care and the use of biologics, or for common infections in the immunocompromised host. Several general treatment recommendations, however, were found that indicate that immunocompromised patients should be monitored more carefully for infection due to their increase susceptibility and decreased ability to fight infections. Kopylov and Afif (2014) recommend identifying and treating infections early in the infectious process in the individual on biologic therapy, and that the infection treatment takes precedent over the biologic therapy continuation. This sentiment is echoed by Pagalilauan and Limaye (2013) in that primary care providers need to be increasingly aware of the immunosuppressed patient and that they may be co-managing with a specialist, as the use of immune-suppressant therapy increases. Often the immunocompromised patient will seek out primary care for common complaints such as fever, new onset of cough, and gastrointestinal disturbances, which have the possibility of developing into a serious infection. Additionally, the signs of infection may be more subtle with immunosuppression, so the threshold for use of diagnostic labs, imaging, and treatment may be lower for this type of patient (Pagalilauan & Limaye, 2013).

Influenza is a common cause of infection in the immunosuppressed individual, and like the patient outlined in the case study above, can cause upper respiratory symptoms. In the

individual using a biologic, which suppresses the immune response, there may be an increased risk of secondary complications related to the viral influenza infection, such as viral or bacterial pneumonia (Weigt, Gregson, Deng, Lynch, & Belpe- Rio, 2011). This may prompt the primary care provider to follow up with the patient closely to ensure that the viral influenza does not cause a secondary infection, which would need to be treated promptly. The case study above outlines the close follow-up the primary provider suggested, with a return visit necessary if no improvement in two days.

The patient in this case also had a very prudent question regarding when he should hold his biologic medications. As biologics reduce the immune response, they may allow for infectious processes to continue and grow within the body. The decision to hold or stop biologic therapy generally would be overseen by the specialist prescribing the medication as they have more knowledge of the patient's therapy and plan of care in relation to the biologic (Saag et al., 2008). The primary care provider, however, should be aware of the general guidelines for indications to hold or discontinue a biologic in the setting of an acute illness.

The American College of Rheumatology issues guidelines for treatment with biologics, and Saag et al. (2008) stated that biologic therapy should not be initiated, used, or resumed while an active bacterial infection is present that requires the use of antibiotics. It also should not be used during active tuberculosis infection, herpes zoster infection, or in the presence of non-healing infected skin ulcers. This guideline also suggested that biologics should not be used during a severe upper respiratory infection that is viral or bacterial, but the parameters for what constitutes a severe infection are not outlined. Specific classes of biologics (anti-tumor necrosis factor agents, T lymphocyte blockers, and rituximab) do provide specific parameters for holding

therapy during a presumable viral upper respiratory infection when the fever is greater than 101 degrees Fahrenheit (Saag et al., 2008).

The biologic should continue to be withheld during the full course of antibiotics and until full recovery has been achieved. Additionally, if a patient continues to be susceptible to multiple infections or is infected with an opportunistic pathogen the biologic therapy should be completely discontinued and not re-started (Menter et al., 2008). This was reiterated in the American College of Rheumatology 2015 guideline that indicated that biologic treatment benefits should outweigh the risk of infection, and should be discontinued in the setting of severe or recurrent infections (Singh et al., 2016).

In order to prevent infections from developing in the individual on biologic therapy the primary care provider should ensure that all recommended vaccinations are current. This may prevent some illnesses from developing or reduce the severity of symptoms experienced by the patient (Weigt, Gregson, Deng, Lynch, & Belpé- Rio, 2011). Prior to starting biologic therapy, it is recommended that the patient be given any vaccinations that they would be routinely due for based on the United States Center for Disease Control guidelines, as well as screening for tuberculosis to ensure that the patient does not have latent or unknown tuberculosis that could potentially be re-activated once the immune system is suppressed (Bombardier, 2012).

The American College of Rheumatology recommends that prior to initiating biologic therapy a patient should receive the killed recombinant pneumococcal vaccination, influenza vaccination, hepatitis B vaccination series, the human papillomavirus vaccination, and the live attenuated herpes zoster vaccination (Singh et al., 2016). The Canadian Rheumatology Association has similar recommendations for administration of vaccinations and provides guidelines for timing of each vaccination. Live vaccinations should be administered at least two

to four weeks prior in initiating biologic therapy, and inactive killed vaccinations can be given any time prior to initiation of treatment (Bombardier, 2012).

Vaccination is important for the patient on biologic therapy as it can prevent contraction of disease, and decrease the severity of symptoms experienced. Observational studies have found that individuals with rheumatoid arthritis who take medications like biologics or other immune suppressing therapies have fewer symptoms and complications with influenza if vaccinated. A study comparing vaccinated versus unvaccinated individuals with rheumatoid arthritis found that the unvaccinated group had a higher incidence of acute bronchitis and viral respiratory infections over a year-long period (Stojanovich, 2006). Two additional observational studies found decrease in hospital admissions and mortality from influenza and pneumonia in older adults with rheumatoid arthritis who received the influenza vaccination (Bombardier, 2012).

Once a patient is on biologic therapy it is not recommended that live vaccinations be administered. The use of live vaccinations while on biologic therapy is contraindicated as the patient's immune system is decreased and introducing a live form of a virus or bacteria may cause actual disseminated infection. Common live vaccinations include the measles, mumps, rubella, nasal influenza mist, varicella, and herpes zoster vaccinations (Bombardier, 2012). Inactive vaccinations can be given while a patient is on biologic therapy, but the immune response may not be as active, and reduced antibody production may occur. The influenza intramuscular vaccine and the pneumococcus vaccination are both inactive vaccinations and are recommended to be given routinely to individuals while on biologic treatment (Bombardier, 2012).

Based on the recommendations outline above, it would be advisable for the patient in this case study to hold his biologic therapy during his acute upper respiratory illness. He was

experiencing fevers consistently over the threshold of 101 degrees Fahrenheit, and therefore would be classified as having a severe viral infection in the context of using a tumor necrosis factor inhibitor. It also would be important for the primary care provider to consider alternatives to the common causes of infection, as those on biologics may be at risk for opportunistic infections. The primary care provider needs to closely monitor the patient's condition for progression to a more acute bacterial or viral pneumonia, with close follow-up and low threshold for obtaining further laboratory work and imaging to ensure there is no advancement of the infection. The patient had obtained his annual influenza vaccination, so if he did have influenza the severity of his symptoms would likely be decreased. The patient would, however, be a candidate for a pneumococcal vaccination, and should receive this once his illness subsides to prevent the development of future pneumonia due to his immunocompromised state.

#### **Learning Points**

- **The patient on biologic therapy has a reduced immune response, and is therefore at increased risk for common and opportunistic infections (Le Saux, 2012).**
- **Biologic therapy should be withheld while a patient has an active severe infection or while on antibiotic treatment (Saag et al., 2008).**
- **Live vaccinations should be given prior to initiating biologic therapy, and should not be given while on biologic therapy (Bombardier, 2012).**
- **Killed vaccinations can be given while on biologic therapy, and the influenza and pneumococcal vaccinations are highly recommended to reduce incidence and severity of potential upper respiratory illness (Bombardier, 2012).**

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