Biologic Agents in the Treatment of Childhood-Onset Rheumatic Disease

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Over the last 20 years, newly developed biologic therapeutic agents have revolutionized treatment and outcomes in rheumatology and several other areas of medicine. In the best of circumstances, biologic agents can maximize both effectiveness and safety through highly specific inhibition of targeted molecules and cell types. Several effective biologics have been developed and approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of adult rheumatic conditions, such as rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and systemic lupus erythematosus (SLE).

Biologic agents are rarely specifically developed for or initially tested in childhood-onset rheumatic diseases. Nevertheless, many biologic agents have demonstrated remarkable effectiveness in children with rheumatic diseases in placebo-controlled clinical trials leading to FDA and EMA approvals, as well as in observational studies and uncontrolled published reports leading to significant "off-label" use.

Biologic therapeutic agents have led to improvements in both short-term and long-term outcomes in children with rheumatic disease. In long-term studies of patients with juvenile idiopathic arthritis (JIA) prior to the biologic era of treatment, functional limitation and radiologic evidence of joint damage were quite common, and a significant number of patients had active disease many years after diagnosis.[1-4] The implementation of biologic therapies for use in children has allowed for frequent achievement of minimal disease activity[5] and presumably, although less studied, improvement in long-term functional outcomes. In addition, biologic agents are given parenterally (subcutaneous or intravenous) and are typically administered every 1-4 weeks, which may result in a lower proportion of missed medication doses compared with medications administered orally once or twice daily.

Biologic therapeutics generally refer to agents that were created from a living organism and have a specific protein or gene target. When defined broadly, biologics have been used for decades; indeed, insulin, which is produced from living organisms and has a specific target, has been used for almost 100 years to treat diabetes. The era of biologics in pediatric rheumatology began in 1999 with the FDA approval of etanercept for polyarticular JIA. Since that time, the use of biologics has increased dramatically and is anticipated to continue increasing for the foreseeable future.

In this review, we present general considerations about treatment with biologics, details on commonly used biologic in pediatric rheumatology, including the mechanism of action, FDA- and EMA-approved indications, off-label uses, available safety information, and potential future uses.

CBC	Complete blood count
EMA	European Medicines Agency
FDA	US Food and Drug Administration
IL	Interleukin
JIA	Juvenile idiopathic arthritis
LFT	Liver function testing
MAS	Macrophage activation syndrome
SLE	Systemic lupus erythematosus
SQ	Subcutaneous
TB	Tuberculosis
TNF	Tumor necrosis factor
TNFi	TNF inhibitors

General Considerations

General Indications

In JIA, initiation of biologic agents is usually recommended after treatment with at least 1 nonbiologic disease-modifying antirheumatic drug (eg, methotrexate) has failed to control the disease after an adequate trial (typically 3-6 months). A biologic agent may be part of the initial treatment regimen if there is a higher risk of poor outcomes (eg, rheumatoid factor-positive polyarthritis or systemic JIA) or if nonbiologic disease-modifying antirheumatic drugs have been proven to be ineffective (eg, for the treatment of sacroiliitis). The American College of Rheumatology has published recommendations on the use of biologics in JIA.[6,7]

There is no standard duration of therapy for biologic agents. Generally, patients should achieve and maintain a state of minimal disease activity for an extended period of time (typically >6 months, sometime much longer) before consideration of discontinuation. Attempts to discontinue biologic agents are frequently unsuccessful, although many patients may be able to discontinue therapy for months or even years before needing to reinitiate therapy.

Risk of Serious Infection

All currently available biologic agents in rheumatology have the potential to decrease the immune system ability to respond adequately to infection. Unsurprisingly, serious infections are the most commonly occurring serious adverse event that may be attributable to biologics. When evaluating the risk of infection associated with biologics, it is important to consider the inherent or background risk of infection associated with

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the underlying rheumatologic condition, as well as the risk associated with alternative, equally effective therapies. Unfortunately, these risks are often not well characterized.[8]

Published studies have shown that the rates of serious infections (typically defined as those requiring hospitalization or intravenous antimicrobials) associated with the biologics approved for JIA are generally similar.[9] Any differences in reported infection rates are more likely attributable to differences in the underlying patient populations using the agents (eg, children with refractory disease) instead of the agents themselves. Most published comparative studies have reported a risk of serious infection associated with biologics that varies from no increased risk to approximately a doubling of the risk compared with methotrexate, the most commonly prescribed nonbiologic drug.[9-12]

There is also an increased risk of opportunistic infections with biologic agents, but the risk in children appears to be very small. By far, the most common opportunistic infection is herpes zoster (varicella reactivation).[9,13] For many biologics, including tumor necrosis factor (TNF) inhibitors (TNFi), interleukin (IL)-1 inhibitors, tocilizumab, and abatacept, it is recommended that patients be screened for latent tuberculosis (TB) before initiating therapy because biologic therapy can result in reactivation of latent TB. If testing for TB is positive, appropriate therapy should be initiated before initiating biologic therapy.

Other Adverse Effects

The biologic agents used in rheumatology generally do not produce minor, nonspecific adverse effects that are common to many other classes of medications, such as headache or nausea. This is likely because of their highly specific molecular targets. Adverse effects that are specific to particular biologic agents are presented below.

Because biologics are large proteins, they must be administered parenterally. Those administered by intravenous infusion may produce infusion reactions, but this is not common. Those administered by subcutaneous injection may produce injection site reactions, but, with the exception of anakinra, this is also not common. Injection site reactions may benefit from topical glucocorticoids or antihistamines. Injection site pain may be decreased by topical application of ice before and after the injection, allowing the syringe warm to room temperature before injection, injecting the medication slowly, and rotating injection sites.

Biologic agents are not known to cause any decrease in linear growth. In fact, by decreasing systemic inflammation and systemic glucocorticoid burden, some biologic agents have been shown to restore height velocity that was lost because of disease.[14] TNFi have been associated with undesired weight gain in some studies of adults. A study of children did not confirm this finding,[15] but weight gain as an uncommon idiosyncratic reaction is possible.

Because the immune system conducts tumor surveillance, there is concern about a possible increase in malignancy with biologic agents. This concern is discussed in detail in the TNFi section below. There are no published data about the risk of malignancy associated with other biologic agents in children because they are much less frequently used, but data from adults is reassuring.[16]

Immunizations

There are important considerations regarding immunizations for any patient receiving treatment with a biologic. Ideally, all age-appropriate immunizations should be given at least 4 weeks before initiating therapy, as immunosuppression can dampen immunogenicity,[17] as well as theoretically lead to uncontrolled viral replication in the case of live vaccines. However, a 4 week or longer delay in initiating therapy is not always practical given the frequent desire to start biologic therapy expeditiously. The Infectious Diseases Society of America has published guidelines regarding vaccination of the immunocompromised host,[18] which state that patients currently receiving immunosuppression should not receive live virus vaccines (eg, measles-mumps-rubella, varicella, live-attenuated influenza, rotavirus, yellow fever), but should receive annual influenza vaccines and pneumococcal conjugate and pneumococcal polysaccharide vaccines, if not previously given.

Cost

Biologic agents are considerably more expensive than their nonbiologic predecessors. Although these higher costs may, in part, be justified by the costs associated with their development and complex manufacturing processes, access to the biologic agents is often constrained by limited healthcare resources. "Biosimilar" agents that are akin to, but distinct from, generic versions of nonbiologic medications are now becoming commercially available.[19] It remains to be seen how the availability of biosimilars will affect the cost of biologic therapies in pediatric rheumatology.

Specific Biologic Agents

The **Table** lists each of the biologic agents according to their mechanism of action and includes administration information and their indications and off-label uses.

TNFi

TNFi were among the first biologics successfully developed for the treatment of rheumatic diseases and remain the most frequently prescribed, especially for JIA.[20]

TNFi work by binding TNF alpha, a key proinflammatory cytokine. There are currently 5 commercially available TNFi. Etanercept is a TNF receptor fusion protein, infliximab, adalimumab, and golimumab are monoclonal antibodies against TNF, and certolizumab is a PEGylated monoclonal antibody against TNF. To date, only etanercept and adalimumab have received FDA approval for pediatric rheumatology indications, but the other TNFi are occasional prescribed in clinical practice.

Etanercept was approved by the FDA in 1999 for the treatment of polyarticular (≥5 affected joints) JIA based upon demonstrated efficacy in a randomized, placebo-controlled clinical

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