Drug Therapy

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13. Biologic drugs

New opportunities for treating JIA have been introduced in the last few years with substances known as biologic agents. Physicians use this term for drugs produced through biological engineering, which, unlike methotrexate or leflunomide, are primarily directed against specific molecules (tumour necrosis factor or TNF, interleukin 1 or 6, T cell receptor antagonist) in the inflammatory pathway. Biologic agents have been shown to block the inflammatory process that is typical of JIA. There are now several biologic agents specifically approved for use in JIA.

Biologic agents are all very expensive. Biosimilars have been developed for several of these treatments, so that after the expiry of the patent, similar drugs with a lower cost might become available.

In general, biologic agents are all associated with an increased risk of infection. Hence, it is important to be fully informed and aware of preventative measures, such as vaccinations (live-attenuated vaccines are only recommended before starting the treatment, while killed vaccinations could be given during treatment). Screening for latent tuberculosis (tuberculosis skin test or PPD) is mandatory in patients for whom biologic treatment is considered. In general, whenever an infection occurs, the therapy with a biologic agent should be at least temporarily discontinued. However, discontinuation should be always discussed with the treating physician on a case-by-case basis.

For the possible association with tumours, see the section on anti-TNF below.

There is only limited information on the use of biologic drugs during pregnancy but in general it is recommended to stop the use of the drugs; again, a case-by-case assessment is recommended.

Risks associated with the use of other biologics may be similar to those discussed for anti-TNF treatments; however, the number of patients treated is smaller and the follow-up is shorter. Some complications observed on treatment, such as the occurrence in some patients of macrophage activation syndrome, seem to be more likely related to the underlying disease (systemic JIA for macrophage activation syndrome) than to the treatment itself. Painful injections leading to treatment discontinuation is mainly seen with anakinra. Anaphylactic reactions are mainly observed with intravenous treatments.

13.1 Anti–TNF agents

Anti-TNF drugs selectively block TNF, an essential mediator of the inflammatory process. They are used alone or in association with methotrexate and are effective in most patients. Their effect is quite rapid and their safety has been shown to be good at least for a few years of treatment (see the safety section, below); however, longer follow-ups are needed to establish potential long-term side effects.
Biologic agents for JIA, including several types of TNF blockers, are the most widely used and they differ largely in terms of the method and frequency of administration. Etanercept is administered subcutaneously once or twice per week, adalimumab subcutaneously every 2 weeks and infliximab with intravenous monthly infusions. Others are still under investigation (e.g. golimumab and certolizumab pegol).
In general, anti-TNF are employed for most JIA categories with the exception of systemic JIA, in which case other biologics are normally used, such as anti IL-1 (anakinra and canakinumab) and anti IL-6 (tocilizumab). Persistent oligoarthritis is normally not treated with biologic agents. As is the case for all second level drugs, biologic agents must be administered under strict medical control.
All drugs have a potent anti-inflammatory effect that persists as long as they are administered. Side effects are mainly represented by a greater susceptibility to infections, especially reactivation of latent tuberculosis. Evidence of serious infectious should lead to discontinuation of the drug. In some rare instances, treatment has been associated with the development of autoimmune diseases other than arthritis. There is no evidence that treatment may cause a higher incidence of cancer in children.
Several years ago, the Food and Drug Administration issued a warning

about the possible increase of tumours (especially lymphomas) associated with longer use of these drugs. There is no scientific evidence that this risk is real, although it has also been suggested that the autoimmune disease itself is associated with a small increase in the rate of malignancy (as occurs in adults). It is important that doctors discuss with the families the risk and benefit profile associated with the use of these drugs.
Since experience with TNF-inhibitors is recent, very long-term safety data are still lacking. The next section describes the anti-TNF that are currently available.

13.1.1 Etanercept

Description: Etanercept is a human monoclonal antibody which works by TNF receptor blockade, meaning that the drug interferes with the link between TNF and its receptor on the cells of inflammation thereby blocking or decreasing the inflammation process that forms the basis of juvenile idiopathic arthritis.

Dosage/modes of administration: Etanercept is administered by subcutaneous injection, either weekly (0.8 mg/kg - maximum 50 mg - /week) or twice a week (0.4 mg/kg - maximum 25 mg - 2 times per week); patients, as well as family members, can be taught to self-administer their injections.

Side effects: Local reactions (red spot, itching, swelling) at the injection site may occur but are usually of short duration and mild intensity.

Main paediatric rheumatic diseases indications: Juvenile idiopathic arthritis with polyarticular course in children who have not responded to other drugs such as methotrexate. It has been used (with no clear evidence to date) to treat JIA-associated uveitis when methotrexate and topical steroid treatment are insufficient.

13.1.2 Infliximab

Description: Infliximab is a chimeric (part of the drug is derived from mouse protein) monoclonal antibody. Monoclonal antibodies link to TNF, thereby blocking or decreasing the inflammation process that is the basis of juvenile idiopathic arthritis.

Dosage/modes of administration: Infliximab is administered

intravenously in a hospital setting, after a more frequent induction regime it is usually every 8 weeks (6 mg/kg at each infusion) in association with methotrexate to decrease its side effects.

Side effects: During the infusion, allergic reactions may occur, ranging from mild reactions (shortness of breath, red skin rash, itching) that are easily treated, to serious allergic reactions with hypotension (lowering of the blood pressure) and risk of shock. These allergic reactions occur more often after the first infusions and are due to an immunization against a portion of the molecule, which is of mouse origin. If an allergic reaction occurs, use of the drug is stopped. The use of a lower dosage (3 mg/kg/infusion), although effective, can be associated with a higher frequency of serious adverse events.

Main paediatric rheumatic diseases indications: Infliximab is not approved for juvenile idiopathic arthritis and is used off-label for JIA and uveitis (i.e. there is no indication on the drug label for the use in juvenile idiopathic arthritis).

13.1.3 Adalimumab

Description: Adalimumab is a human monoclonal antibody. It is effective by linking to TNF and preventing its effects. It thereby blocks or decreases the inflammation process that forms the basis of juvenile idiopathic arthritis.

Dosage/modes of administration: It is administered by a subcutaneous injection every 2 weeks (24 mg/square meter per injection up to a maximum of 40 mg per injection), usually in association with methotrexate.

Side effects: Local reactions (red spot, itching, swelling) at injection site may occur but are usually of short duration and mild intensity.

Main paediatric rheumatic diseases indications: Juvenile idiopathic arthritis with polyarticular course in children who have not responded to other drugs such as methotrexate. It has been used (with no clear evidence to date) to treat JIA-associated uveitis when methotrexate and topical steroid treatment are insufficient.

13.2 Other biologic agents

13.2.1 Abatacept

Description: Abatacept is a drug with a different mechanism of action directed against a molecule (CTL4Ig) important for the activation of white blood cells called T lymphocytes. Currently, it can be used to treat children with polyarthritis who do not respond to methotrexate or other biologic agents.

Dosage/modes of administration: Abatacept is administered intravenously, in a hospital setting, monthly (6 mg/kg at each infusion) and in association with methotrexate to decrease its side effects. Subcutaneous abatacept is being studied for the same indication.

Side effects: No major side effects have been observed to date.

Main paediatric rheumatic diseases indications: Juvenile idiopathic arthritis with polyarticular course in children who have not responded to other drugs such as methotrexate or anti-TNF drugs.

13.2.2 Anakinra

Description: Anakinra is the recombinant version of a natural molecule (IL-1 receptor antagonist) that interferes with the action of IL-1 to inhibit the inflammation process, in particular in systemic juvenile idiopathic arthritis and autoinflammatory syndromes such as cryopirin-associated periodic syndromes (CAPS).

Dosage/modes of administration: Anakinra is administered subcutaneously every day (usually 1 to 2 mg/kg, up to 5 mg/kg in some low-weight children with a severe phenotype, rarely more than 100 mg per day at each daily injection).

Side effects: Local reactions (red spot, itching, swelling) at the injection site may occur but are usually of short duration and mild intensity. Severe adverse events on treatment are rare; they include some severe infections, some cases of hepatitis and, in systemic JIA patients, some cases of macrophage activation syndrome.

Main paediatric rheumatic diseases indications: The drug is indicated in patients with cryopirin-associated periodic syndromes (CAPS) after the age of 2. It is often used off-label (i.e. there is no indication for the treatment) in systemic juvenile idiopathic arthritis patients who are dependent on corticosteroids and in some other autoinflammatory diseases.

13.2.3 Canakinumab

Description: Canakinumab is a second generation monoclonal antibody specific for a molecule called interleukin 1 (IL1) and therefore inhibits the inflammation process, in particular in systemic juvenile idiopathic arthritis and autoinflammatory syndromes, such as cryopirin-associated periodic syndromes (CAPS).

Dosage/modes of administration: Canakinumab is administered subcutaneously every month (4 mg/kg at each injection) in systemic juvenile idiopathic arthritis.

Side effects: Local reactions (red spot, itching, swelling) at the injection site may occur but are usually of short duration and mild intensity.

Main paediatric rheumatic diseases indications: The drug has recently received approval for use in systemic juvenile idiopathic arthritis patients who are corticosteroid-dependent and in children with cryopirin-associated periodic syndromes (CAPS).

13.2.4 Tocilizumab

Description: Tocilizumab is a monoclonal antibody specific for the receptor of a molecule called interleukin 6 (IL6); it inhibits the inflammation process, in particular in systemic juvenile idiopathic arthritis.

Dosage/modes of administration: Tocilizumab is administered intravenously in a hospital setting. In systemic JIA, tocilizumab is administered every 15 days (8 mg/kg in children weighing more than 30 kg or 12 mg/kg in children weighing less than 30 kg) and usually in association with methotrexate or corticosteroids. In non-systemic JIA with a polyarticular course, tocilizumab is administered every 4 weeks (8 mg/kg in children weighing more than 30 kg or 10 mg/kg in children weighing less than 30 kg).

Side effects: General allergic reactions may occur. Other severe adverse events on treatment are rare; they include some severe infections, some cases of hepatitis and, in systemic JIA patients, some cases of macrophage activation syndrome. Abnormalities in liver enzymes (transaminase) and reduction of white blood cells such as platelets and neutrophils, as well as changes in lipid levels are sometimes observed.

Main paediatric rheumatic diseases indications: The drug has recently received approval for use in systemic juvenile idiopathic

arthritis patients who are corticosteroid-dependent and also in juvenile idiopathic arthritis with polyarticular course in children who have not responded to other drugs such as methotrexate.

13.3 Other biologic agents available or under study

There are other biologics such as rilonacept (anti IL-1 for subcutaneous administration), rituximab (anti-CD20 for intravenous infusions), tofacitinib (JAK-3 inhibitor as a pill) and others which are being used in the treatment of some adult rheumatic diseases and only experimentally in children. Studies to evaluate their efficacy and safety profile are underway or will begin in the next few years. At present, very limited information on their use in children is available.