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Drug Therapy

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13. Biologic drugs

New treatment options have been introduced in the last few years with the development of 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). Biologic agents have been identified as important means of blocking the inflammatory process that is typical of JIA. There are now several biologic agents almost all specifically approved for use in JIA.

Biologic agents are all very expensive. Biosimilars have been developed for several of these drugs, 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 insist on patient/parent information and prophylactic measures, such as vaccinations (knowing that live-attenuated vaccines are only recommended before starting the treatment, while other vaccinations could be performed during treatment). Screening for tuberculosis (tuberculosis skin test or PPD) is also 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, as they are newer drugs, 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. TNF blockers are the most widely used biologic agents in JIA. There are several types, 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 agents 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 immuosuppressive drugs, biologic agents must be administered under strict medical supervision.
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 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, real long-term safety data are still lacking. The next section describes the anti-TNF agents that are currently available.

13.1.1 Etanercept

Description: Etanercept is a TNF receptor blocker, meaning that the drug prevents the link between TNF and its receptor on the inflammatory cells, thereby blocking or decreasing the inflammation process that is 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 administer the 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, 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 a sensitisation to 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, is usually associated with a higher frequency of adverse events.

Main paediatric rheumatic diseases indications: Infliximab is not approved for juvenile idiopathic arthritis and is used off-label (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. Monoclonal antibodies link to TNF, thereby blocking or decreasing the inflammation process that is 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 off-label (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) 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. 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 on the drug label for the use) 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 the 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 14 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 systemic juvenile idiopathic arthritis. 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 (transaminases) and reduction of 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 tablet) 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.