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Transition de la pédiatrie à l'âge adulte

Iatrogenic effects of immune suppressants in the pediatric age

Iatrogénie des immunosuppresseurs chez l'enfant

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Objectives

- To describe toxicity of corticosteroids, specifically in the pediatric age.
- To describe toxicity of biologics in pediatrics, in particular with regard to infections and neoplasms.
- To describe the problems related to vaccinations in pediatric rheumatology, both for immunogenicity and for side effects.

1. Introduction

The drugs used to treat autoimmune diseases suppress the inflammatory and immune response through different mechanisms. Several immunosuppressants have been demonstrated to be effective in children in placebo-controlled clinical trials leading to official approval, although immunosuppressive agents are often used off-label given the evidence reported by observational or uncontrolled published studies.

Different immunosuppressants are used in pediatrics: antiproliferative/antimetabolic agents (methotrexate, leflunomide, azathioprine, mycophenolate mofetil, cyclophosphamide), calcineurin inhibitors (cyclosporine, tacrolimus), hydroxychloroquine, colchicine and biologic agents. The principal immunosuppressive agents employed in childhood with their mechanism of action and possible side effects are listed in Table 1.

2. Corticosteroids

The first treatments employed in transplantation and in various autoimmune diseases, alone or with other immunosuppressive agents, were corticosteroids. These drugs negatively affect both innate and adaptive responses by down regulating the transcription of pro-inflammatory genes, reducing the expression of adhesion molecules and lowering reactive oxygen species generation.

Although highly effective, safety profile of corticosteroids remains the major concern especially when used at high doses and/or for long periods. Side effects include hyperglycemia, weight gain, sodium retention and hypertension, skin alterations, myositis, gastritis, behavioral changes and mood disorders (irritability, agitation, anxiety, insomnia and depression), ocular toxicity (cataract and retinopathy) and susceptibility to infections.

A specific concern of pediatric age is growth retardation, which is caused by several factors: resistance to growth hormone, reduction of growth hormone and insulin-like growth factor-1 levels as well as a direct action on growth plates.

Moreover, long-term use of corticosteroids may alter the physiological process of bone mass gain impairing peak bone mass and leading to an increased risk of osteoporosis later in life [1]. Fracture risk is greater at therapy onset and decreases after discontinuation. Bone densitometry (DXA) is recommended at baseline and periodically thereafter (every 6-12 months), in order to monitor the Z score in function of disease activity and corticosteroid therapy. Reaching disease control is essential to reduce the risk of osteoporosis. Calcium (300–500 mg/day according to age) and vitamin D (400 U/day) supplementation can be recommended. Bisphosphonates may be employed in cases of fractures or rapid decrease of bone density after specialized advice, although their use in children is still matter of debate. A vascular necrosis of bone is another complication of corticosteroids, especially when used at high doses.

Transient suppression of cortisol production is associated with therapeutic daily use of corticosteroids for more than 2 weeks. Normal pituitary-adrenal function can be recovered after corticosteroid discontinuation, however cortisol production can be slow to become again normal after prolonged therapy. Adrenal insufficiency may be a life-threatening condition leading to cardiovascular collapse if not promptly diagnosed and treated. Children at risk of adrenal insufficiency should receive an additional dose of corticosteroids in situation of stress (eg. infections, trauma, surgery).

In order to reduce corticosteroid toxicity, several strategies have been adopted. The use of the lowest effective dose for the shortest period of time as well as the early association with

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Table 1
Immunosuppressive agents used in pediatric rheumatology.

Drugs	Mechanism of action	Dose, frequency and route	Main side effects
Methotrexate	Reduces the production of pro-inflammatory cytokines and inhibits cell-mediated immunity	10–15 mg/m^2/weekly (max 25 mg/weekly) Oral (up to 15 mg/dose) or SC	Transient elevation of liver enzymes, nausea, vomiting or abdominal pain
Sulfasalazine	Interferes with production of leukotrienes and prostaglandins	Start with 10–15 mg/kg/day and increase weekly over 4 weeks up to 30–50 mg/kg BID or TID, oral	A maculopapular rash occurring within 2 days after institution of therapy (especially on sun-exposed skin), neutropenia, thrombocytopenia, rarely pancytopenia
Colchicine	Suppresses cytoskeletal transport	0.5–2 mg/day as needed QD, oral	Nausea, vomiting, abdominal pain, diarrhea
Azathioprine	Inhibits T cell function	Start with 1–1.5 mg/kg/day, increase as needed and as tolerated to 2 to 2.5 mg/kg/day, maximum 150 mg QD, oral	Oral ulcers, nausea, vomiting, diarrhea, epigastric pain Leukopenia, thrombocytopenia and anemia (check for Thiopurine methyl-transferase deficiency)
Mycophenolate Mofetil	Inhibits B and T cells proliferations	Start with 300 mg/m^2/dose and increase the dose in two weeks up to 600 mg/m^2/dose (max 3 g/daily) BID, oral	Nausea, vomiting or abdominal pain Leukopenia, anemia, thrombocytopenia, pancytopenia
Cyclophosphamide	Depletes B	IV 500–1000 mg/m^2 monthly Oral 2 mg/kg/day	Leukopenia (granulocytopenia) and thrombocytopenia, anorexia, nausea and vomiting and alopecia. Bladder toxicity, prophylactic Mesna should be used to prevent it. Infertility
Cyclosporine	Blocks IL-2 signaling and transcriptions of T cell genes	3–5 mg/kg/day BID, oral	Impaired renal function, hypertension, hepatic toxicity, tremor, mucous membrane lesions, and nausea and vomiting Hypertrichosis, paresthesias, and gingival hyperplasia
Thalidomide	Inhibits neutrophil chemotaxis, monocyte phagocytosis, and expression of TNF-α and IL-6 messenger RNA (mRNA)	2.5 to 5 mg/kg/day QD or BID, oral	Peripheral neuropathy. Drowsiness Carpal tunnel syndrome, muscle weakness and cramps, teratogenicity

SC: subcutaneous; QD: once daily; BID: twice a day; TID: three times a day.

another immunosuppressant as steroid sparing agent is advocated. Treatment with intravenous pulses of methylprednisolone (up to 30 mg/kg, 1 g maximum) followed by low to medium doses of daily oral prednisone can be effective in selected cases.

3. Biologics

Advances in physiopathological knowledge of autoimmune and autoinflammatory conditions and the availability of new therapies acting on specific targets have led to an important improvement of outcome in the past two decades. Biologic agents encompass a rapidly growing class of drugs including monoclonal antibodies and fusion proteins targeting the cytokines that play a main role in disease pathways.

Since their introduction, biologic agents have revolutionized the management of autoimmune/autoinflammatory diseases through selected inhibition of specific targets. They are usually employed when others immunosuppressants fail to achieve disease control. The targets of these drugs are pro-inflammatory cytokines (TNF-α, IL-1 β, IL-6) or molecules on surface of T cells (CTLA4) and B cells (CD20) (see Table 2).

Concerns on the safety profile of biologics have been raised since their introduction, although these drugs seem quite safe so far. Given the potential to lower immune system response, risk of serious infections was one of major worries [2].

The infectious risk among different biologics is similar and several studies have reported a risk of serious infections ranging from no increased risk to 2-fold risk compared with methotrexate, the most commonly prescribed non-biologic drug.

Moreover, high disease activity seems to increase infectious risk as shown in patients with juvenile idiopathic arthritis (JIA) treated with biologic agents [3]. Tuberculosis screening is recommended before starting biologic treatment especially anti-TNF-α agents.

The risk of malignancies with biologics is uncertain due to the presence of several confounding variables such as drug history and the background effect of inflammatory disease itself. In 2010, the Food and Drug Administration (FDA) reported several cases of malignancy in children diagnosed with JIA, inflammatory bowel diseases and other conditions treated with anti-TNF-α agents [4]. Indeed, the vast majority of cases had received other immunosuppressants. Furthermore, other studies demonstrated an increased background risk of malignancies in JIA patients ranging between 2 a 4-fold compared to non-JIA patients. Although reported data are reassuring so far, the overall long-term risk of malignancies related to biologic treatment is unknown [5].

4. Vaccinations

Children with pediatric rheumatic diseases have an increased risk of infections, which contributes to the morbidity of their disease. Immunogenicity of a vaccine in patients with rheumatic diseases can differ from the healthy population, due to the disease or its immunosuppressive treatment [6]. Over the years, awareness of infection prevention by vaccination in rheumatic diseases has increased. In 2011, a EULAR task force published evidence-based recommendations regarding vaccination of adults and children with rheumatic diseases [7]. Patients who use corticosteroids may show lower seroconversion rates or GMT (geometric mean antibody titers), but they generally still reach protective antibody titers to vaccines. A high dose of corticosteroids or concomitant use of other immunosuppressive drugs can be associated with lower, yet still protective, titers. Studies have shown that there is no general detrimental effect of low-dose corticosteroids on