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Drug Therapy

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Introduction

This section reports information on drug therapies that are commonly used to treat paediatric rheumatic diseases. Each section is divided into 4 main parts.

Description

This section provides a general introduction to the drug with its mechanism of action and expected side effects.

Dosage/modes of administration

This section provides the dose of the drug, usually in mg per kg per day or mg per body surface area (square metres), as well as information on the mode of administration (e.g. pills, injections, infusions).

Side effects

This section provides information on the most widely known side effects.

Main paediatric rheumatic diseases indications

This final section reports the list of paediatric rheumatic diseases for which the drug is indicated. Indication means that the drug has been specifically studied in children, and regulatory authorities such as the European Medicines Agency (EMA) or the Food and Drug Administration (FDA) of United States and others allow its use in children. In certain cases, your doctor may decide to prescribe the drug, even if a specific authorisation is not available.

The paediatric legislation, the label and off-label use and future therapeutic possibilities

Until 15 years ago, all drugs used to treat JIA and many other paediatric diseases had not been properly studied in children. This meant that physicians were prescribing drugs based on personal experience or on

studies conducted in adult patients.
Indeed, in the past, conducting clinical trials in paediatric rheumatology has been difficult, mainly because of the lack of funding for studies in children and the lack of interest by pharmaceutical companies for the small and non-rewarding paediatric market. The situation changed dramatically a few years ago. This was due to the introduction of the Best Pharmaceuticals for Children Act in USA and specific legislation for paediatric medicines development (Paediatric Regulation) in the European Union (EU). These initiatives essentially forced pharmaceutical companies to study drugs in children as well.
The USA and EU initiatives, together with the existence of 2 large networks, the Paediatric Rheumatology International Trials Organisation (PRINTO at www.printo.it), which unites more than 50 countries worldwide, and the Paediatric Rheumatology Collaborative Study Group (PRCSG at www.prcsg.org), based in North America, had a very positive impact in paediatric rheumatology, in particular on the development of new treatments for children with JIA. Hundreds of families of children with JIA treated by PRINTO or PRCSG centres worldwide have participated in these clinical trials, allowing all children with JIA to be treated with drugs specifically studied for them. Sometimes, participation in these studies requires the use of a placebo (i.e. a tablet or infusion with no active substance) to be sure that the drug under evaluation does more benefit than harm.
Because of these important developments, several drugs are specifically approved for JIA today. This means that regulatory authorities, such as the Food and Drug Administration (FDA), the European Medicines Agency (EMA) and several national authorities, have reviewed scientific information coming from clinical trials and have allowed pharmaceutical companies to state in the drug label that it is efficacious and safe for children.
The list of drugs specifically approved in the treatment of JIA includes methotrexate, etanercept, adalimumab, abatacept, tocilizumab and canakinumab.
Several other drugs are currently being or will be studied in children, so your child might be asked by his/her doctor to participate in such studies.
There are other drugs that are not explicitly approved for use in JIA, such as several non-steroidal anti-inflammatory drugs (NSAIDs), azathioprine, cyclosporine, anakinra and infliximab. These drugs are

used without an approved indication (so called off-label use) and your doctor might propose their use especially if there are no other available treatments.

Adherence

Adherence to treatment is of the greatest importance for maintaining good health both on a short and long term basis.
Adherence to treatment entails following the course of treatment prescribed by your doctor; this may include various components: taking medicine on a consistent basis, routine checkups at the clinic, regular physiotherapy, routine follow-up of lab work (blood tests), etc. These various components work together, creating a complementary program which fights the disease, strengthens your child's body and keeps him/her healthy. The frequency and dosage of medications are determined by the need to maintain certain levels of the drug in the body. Lack of adherence to this protocol can result in ineffectively low levels of medication and increase the chance of a flare up of the disease. In order to stop this from happening, it is important to take both shots (injections) and oral medications (tablets or syrup) regularly. The most common reason for lack of success in treatment is not adhering to the recommended treatments. Adherence to all details of the medical program prescribed by the doctor and medical team greatly increases the chance of remission (no active arthritis). Maintaining the various components of treatment can sometimes be taxing on parents and guardians. Nevertheless, it is up to them to make sure that the child receives the best chance for a healthy outcome. Sadly, as a child progresses in age, especially as he/she enters the teenage years, lack of adherence becomes more of an issue. Teenagers resist defining themselves as patients and skip inconvenient parts of their treatment. Consequently, flare ups are very common during these years. Adhering to the medical treatment regime ensures the best chances for remission and improvement in quality of life.

1. NSAIDs – Non-Steroidal Anti-Inflammatory Drugs

1.1 Description

Non-steroidal anti-inflammatory drugs (NSAIDs) have traditionally been the main treatment for many paediatric rheumatic diseases. Their role

remains important and most children are prescribed NSAIDs. They are symptomatic anti-inflammatory, anti-febrile (antipyretic) and anti-pain (analgesic) medications; symptomatic means that they do not clearly affect the course of the disease. They might have limited effects on the progression of the disease (as described in adults with rheumatoid arthritis), but their main benefit is to control symptoms due to inflammation.
They act mainly by blocking an enzyme (cyclooxygenase) that is important for the formation of substances that can cause inflammation, called prostaglandins. These substances also have a physiological role in the body that includes stomach protection, regulation of blood flow in the kidneys, etc. These physiological effects explain most of the side effects of NSAIDs (see below). Aspirin was widely used in the past because it is cheap and effective, while today it is used less due to its side effects. The most widely used NSAIDs are naproxen, ibuprofen and indomethacin.
More recently, new generations of NSAIDs, known as cyclooxygenase (COX)-2 inhibitors, have been made available, but only a few have been studied in children (meloxicam and celecoxib). Even so, there is still no widespread use of these substances in children. These drugs seem to have less gastric side effects than other NSAIDs while maintaining the same therapeutic power. COX-2 inhibitors are more expensive than the other NSAIDs and the debate over their safety and efficacy compared to traditional NSAIDs is not yet concluded. Experience with COX-2 inhibitors in paediatric patients is limited. Meloxicam and celecoxib have proven to be effective and safe in children in a controlled trial. There are differences in the response of children to different NSAIDs, so one NSAID may be effective where another has failed.

1.2 Dosage/modes of administration

A 4 to 6 week trial of a single NSAID is necessary to assess its efficacy. However, since NSAIDs are not disease-modifying drugs (i.e. they are not able to modify the course of the disease), they are used more to treat pain, stiffness and fever associated with systemic arthritis. Most can be given in liquid or pill form. They should be given with food or immediately after meals to reduce gastric irritation
Only a few NSAIDs are approved for use in children: the most common are naproxen, ibuprofen, indomethacin, meloxicam and celecoxib.

Naproxen

Naproxen is administered at 10-20 mg per kg per day in 2 doses.

Ibuprofen

Ibuprofen is administered in children from 6 months to 12 years at a typical dose of 30 to 40 mg/kg/day in 3 to 4 divided doses. Children normally start at the lower end of the dosing range and then gradually increase the dose as needed. Children with milder disease may be treated with 20 mg/kg/day; doses greater than 40 mg/kg/day may increase the risk of serious adverse effects; doses greater than 50 mg/kg/day have not been studied and are not recommended. The maximum dose is 2.4 g/day.

Indomethacin

Indomethacin is administered in 2- to 14-year-olds at 2 to 3 mg/kg/day given in 2-4 divided doses. The dose is titrated upward to a maximum of 4 mg/kg/day or 200 mg per day.

Meloxicam

Meloxicam is administered in children greater than or equal to 2 years of age at 0.125 mg/kg orally once daily with a maximum dose of 7.5 mg orally daily. There is no additional benefit demonstrated by increasing the dose above 0.125 mg/kg once daily in clinical trials.

Celecoxib

Celecoxib is administered in children 2 years or older: 10 to less than or equal to 25 kg at a dosage of 50 mg orally twice daily; for children greater than 25 kg, the dosage is 100 mg orally twice daily.

It is important that only one non-steroidal anti-inflammatory drug (NSAID) is taken at any time. Thus if taking one NSAID regularly, do not take additional ibuprofen for pain such as a headache as there is risk of gastric irritation. If additional pain relief is needed, paracetamol can be taken.

1.3 Side effects

NSAIDs are usually well tolerated and side effects are less common than in adults. Gastro-intestinal tract problems are the most common side effect, with gastric ulceration commonest (injuries to the lining of the stomach). Symptoms range from mild abdominal discomfort after taking the medication to severe abdominal pain and bleeding from the stomach that may appear as black and loose stools. Gastrointestinal toxicity of NSAIDs in children is poorly documented, but in general it is

considerably less than that observed in adults. However, parents and patients should be advised to always take the medication with food to minimize the risk of gastric upset. The utility of antacids, histamine2-receptor antagonists, misoprostol and proton pump inhibitors for prophylaxis against serious NSAID-induced gastrointestinal complications in children with chronic arthritis is unclear and no official recommendations exist. Side effects on the liver can cause an increase in liver enzymes but it is of negligible significance, except in the case of aspirin.
Kidney problems are rare and only occur in children who have previous dysfunctions of the kidneys, heart or liver.
In patients with systemic JIA, NSAIDs (as other medications) may trigger macrophage activation syndrome, a sometimes life-threatening activation of the immune system.
NSAIDs can affect blood clotting but this response is not clinically significant except in children who already have a blood clotting abnormality. Aspirin is the drug that causes more clotting problems; this effect is exploited for the treatment of diseases in which there is an increased risk of thrombosis (formation of pathologic blood clots inside the vessels); in this case, aspirin in low doses is the drug of choice.
Indomethacin can be useful to control fever in medication resistant systemic juvenile idiopathic arthritis.

1.4 Main paediatric rheumatic diseases indications

NSAIDs may be used in all paediatric rheumatic diseases.

2. Cyclosporine A

2.1 Description

Cyclosporine A is an immunosuppressive drug, initially used to prevent organ rejection in patients who underwent transplant operations, but now also used for paediatric rheumatic diseases. It is a potent inhibitor of a group of white blood cells that have a fundamental role in the immune response.

2.2 Dosage/modes of administration

It can be given in liquid or pill form at a dosage of 3-5 mg per kg per day in 2 doses.

2.3 Side effects

Side effects are quite frequent, especially at high doses, and may limit the use of the drug. They include renal damage, high blood pressure, liver damage, gum enlargement, hair growth over the body, nausea and vomiting.
Treatment with cyclosporine therefore requires regular clinical and laboratory check-ups to assess drug side effects. Children must check blood pressure regularly at home.

2.4 Main paediatric rheumatic diseases indications

Macrophage activation syndrome.

Juvenile dermatomyositis.

3. Intravenous immunoglobulins

3.1 Description

Immunoglobulin is a synonym for antibody. Intravenous immunoglobulins (IVIG) are prepared from large pools of plasma from healthy blood donors. Plasma is the liquid component of human blood. IVIGs are used to treat children who lack antibodies as a result of a defect in their immune system. However, their mechanisms of actions are still unclear and may vary in different situations. IVIGs have also been shown to be helpful in some autoimmune and rheumatic diseases.

3.2 Dosage/modes of administration

They are given by intravenous infusion, with different schedules depending on the disease.

3.3 Side effects

Side effects are rare and include anaphylactoid (allergic) reactions,

muscle pain, fever and headache during infusion, headache and vomiting due to non-infective meningeal irritation (which physicians call aseptic, meaning that there is inflammation of the membranes around the brain) about 24 hrs after the infusion.
These side effects resolve spontaneously. Some patients, particularly those with Kawasaki disease and hypoalbuminaemia, may develop abnormalities of their blood pressure when receiving IVIG; these patients need careful monitoring by an experienced team.
IVIGs are free of HIV, hepatitis and most of other known viruses.

3.4 Main paediatric rheumatic diseases indication

Kawasaki disease.
Juvenile dermatomyositis.

4. Corticosteroids

4.1 Description

Corticosteroids are a large group of chemical substances (hormones) that are produced by the human body. The same or very similar substances can be manufactured synthetically and used for the treatment of various conditions including paediatric rheumatic diseases. The steroid given to your child is not the same as those used by athletes to enhance performance.
The full name for the steroids used in inflammatory conditions is glucocorticosteroids or more briefly corticosteroids. They are very potent and fast-acting drugs, suppressing inflammation by interfering with immune reactions in quite a complex manner. They are often used to achieve more rapid clinical improvement of a patient’s condition before other treatments used in combination with the corticosteroids start to work.
Apart from their immunosuppressive and anti-inflammatory effects, they are also involved in many other processes within the body, e.g. in cardiovascular function and stress reaction, water, sugar and fat metabolism, blood pressure regulation and others.
Along with their therapeutic effects, there are considerable side effects, associated mainly with long-term therapy with corticosteroids. It is very important that a child is under the care of a physician who is

experienced in management of the disease and in minimizing the side effects of these drugs.

4.2 Dosage/modes of administration

Corticosteroids can be used systemically (swallowed or injected into a vein) or given locally (by injection into a joint or topically on the skin or as eye drops in case of uveitis).
Dose and route of administration are chosen according to the disease to be treated, as well as the severity of patient’s condition. Higher doses, especially when given by injection, are powerful and act rapidly.
Oral tablets are available in different sizes containing different amounts of the drug. Prednisone or prednisolone are two of the most commonly used.
There is no generally accepted rule for drug dosing and frequency of administration.
A daily dose (often in the morning), usually up to a maximum of 2 mg per kg per day (maximum 60 mg per day) is given. An every other day dose may have less side effects but is also less effect than a daily or split daily dose, which is sometimes necessary to maintain disease control. In severe disease, physicians might prefer to choose high-dose methylprednisolone, which is given as an infusion into the vein (intravenous), usually once daily for several days in a row (up to 30 mg per kg per day with a maximum of 1 g per day) and in hospital setting. Sometimes daily intravenous administration of smaller doses may be used when absorption of oral medication is a problem.
Injection of long-acting (depot) corticosteroid into the inflamed joints (intra-articular) is a treatment of choice in juvenile idiopathic arthritis. Depot corticosteroids (usually triamcinolone hexacetonide) have the active steroid substance bound on small crystals; once they have been injected into the joint cavity, these spread around the inner joint surface and release corticosteroid for prolonged periods, often achieving long-term anti-inflammatory effect.
The duration of this effect is highly variable but usually last many months in most patients. One or more joints can be treated in one session using individual combinations of topical analgesia (e.g. skin anaesthetic cream or spray), local anaesthesia, sedation (midazolam, entonox) or general anaesthesia, depending on the number of joints to be treated and the age of the patient.

4.3 Side effects

Two main types of corticosteroid side effects occur: those resulting from prolonged use of large doses and those resulting from withdrawal of therapy. If corticosteroids are taken continuously for more than one week, they cannot be stopped suddenly, as this might cause severe problems. These problems develop because of insufficient production of steroids by the body, suppressed by the administration of the synthetic preparation. The efficacy, as well as the type and severity of corticosteroid side effects, is individual and therefore difficult to predict. The side effects usually relate to the dose and administration regimen; e.g. the same total dose would have more side effects if given in divided daily doses than in a single morning dose. The main visible side effect is increased hunger, resulting in weight gain and development of stretch marks on the skin. It is very important for children to keep a well-balanced diet low in fat and sugars and high in fibre to help to control weight gain. Acne on the face can be controlled by topical skin treatment. Problems with sleeping and mood changes with feelings of being jittery or shaky are common. With long-term corticosteroid treatment, growth is often suppressed; to avoid this important side effect in children, doctors prefer to use corticosteroids for the shortest possible period and at the lowest dosage. A dosage below 0.2 mg per kg per day (or a maximum of 10 mg per day, whichever is lower) is thought to avoid growth problems.

Defence against infections may be also altered, resulting in more frequent or more severe infections, depending on the extent of immunosuppression. Chickenpox may run a serious course in immunosuppressed children who haven’t already had chicken pox, so it is very important to alert your doctor immediately when your child either develops the first signs or you realise that he or she has been in close contact with someone who subsequently developed the disease. Depending on the individual situation, injection of antibodies against the chickenpox virus and/or anti-viral antibiotics can be given.

Silent side effects should be monitored for closely during treatment. They include the loss of bone minerals, causing the bones to weaken and become more prone to fracture (osteoporosis). Osteoporosis can be identified and followed by bone densitometry imaging. It is believed that a sufficient supply of calcium (about 1000 mg daily) and vitamin D

may be useful to slow down the evolution of osteoporosis.
Eye side effects include cataracts and increased intraocular pressure (glaucoma). If increased blood pressure (hypertension) evolves, a low-salt diet is important. Blood sugar levels can rise, causing steroid-induced diabetes; in this case, a diet low in sugars and fat is needed.
Intra-articular steroid injections are infrequently associated with side effects. There is a risk of some leakage from the joint into the tissues, causing thinning of the fat layer under the skin (sub-cutaneous atrophy) or calcium deposits (calcinosis). The risk of steroid injection-induced infection appear to be extremely low (about 1 per 10,000 intra-articular injections) when performed by an experienced physician.

4.4 Main paediatric rheumatic diseases indications

Corticosteroids can be used in all paediatric rheumatic diseases; they are typically used for the shortest possible period and at the lowest dosage.

5. Azathioprine

5.1 Description

Azathioprine is a drug that decreases immunity.
It works by interfering with the production of DNA, a process that all cells need to undergo in order to divide. The inhibition of the immune function is in fact due to the effects of the drug on the growth of one kind of white cell of the blood (lymphocytes).

5.2 Dosage/modes of administration

It is administered orally at a dosage of 2-3 mg per kg per day, up to a maximum of 150 mg per day.

5.3 Side effects

Although usually better tolerated than cyclophosphamide, azathioprine can have some side effects that need close monitoring. Toxicity to the gastrointestinal tract (oral ulcers, nausea, vomiting, diarrhoea, epigastric pain) is uncommon. Liver toxicity may occur but is rare. A

reduction in the number of circulating white blood cells (leukopoenia) may occur and it is in most cases dose-related; less common is the reduction in the number of platelets or red blood cells. Around 10% of patients are at higher risk of haematological complications (cytopoenia, or a decrease in white blood cells, red blood cells or platelets) due to a possible genetic defect (partial thiopurine methyltransferase –TPMT-deficiency also known as genetic polymorphism). This can be tested for before starting the treatment and the monitoring of blood cell counts can be performed 7 to 10 days after treatment onset and then at regular monthly or bi-monthly intervals.
The long-term use of azathioprine may theoretically be associated with an increased risk of cancer but there is insufficient evidence thus far. As with other immunosuppressive agents, treatment exposes the patient to an increased risk of infections; herpes zoster infection in particular is observed with higher frequency in patients treated with azathioprine.

5.4 Main paediatric rheumatic diseases indications

Juvenile systemic lupus erythematosus.
Some paediatric systemic vasculitis.

6. Cyclophosphamide

6.1 Description

Cyclophosphamide is an immunosuppressive medication that reduces inflammation and suppresses the immune system. It works by interfering with the multiplication of cells, altering the synthesis of DNA and therefore it is particularly active on cells such as blood cells, hair and intestinal lining cells that proliferate very actively (cells need to make new DNA to reproduce). White blood cells, known as lymphocytes, are mostly affected by cyclophosphamide and their change in function and in number explains the suppression of the immune response. Cyclophosphamide has been introduced in therapy to treat certain forms of cancer. In rheumatologic diseases, where it is used in intermittent therapy, it has fewer side effects than in cancer patients.

6.2 Dosage/modes of administration

Cyclophosphamide is administered orally (1-2 mg per kg per day) or more frequently intravenously (usually monthly pulses of 0.5–1.0 g per square meter for 6 months and then 2 pulses every 3 months or, alternatively, pulses of 0.5g per square meter every 2 weeks for a total of 6 infusions).

6.3 Side effects

Cyclophosphamide is a drug that greatly reduces immunity and has several side effects that need close laboratory monitoring. The most common are nausea and vomiting. Reversible thinning of the hair does occur.

Excessive reduction in the number of circulating white blood cells or platelets may occur and may need dose adjustments or temporary withdrawal of the drug.

Bladder alterations (blood in urine) may occur but are much more common in daily oral treatment than in monthly vein injections. Drinking plenty of water helps to avoid this problem. After vein injection, large volumes of fluids are usually given to wash out cyclophosphamide from the body. Long-term treatments run the risk of fertility impairment and increased cancer frequency; the risk of these complications depends on the cumulative dose of the drug taken by the patient over years.

Cyclophosphamide reduces the immune defences and therefore increases the risk of infections, particularly if given in association with other agents that interfere with immunity such as high dose corticosteroids.

6.4 Main paediatric rheumatic diseases indications

Juvenile systemic lupus erythematosus.

Some systemic vasculitis.

7. Methotrexate

7.1 Description

Methotrexate is a drug that has been used in children suffering from a

number of different paediatric rheumatic diseases for many years. It was initially developed as an anti-cancer drug because of its ability to slow down the rate of the cell division (proliferation).
Nevertheless, this effect is only significant in higher doses. At low intermittent doses used in rheumatic diseases, methotrexate reaches its anti-inflammatory effect through other mechanisms. When used at such small doses, the majority of the side effects seen with larger doses either do not occur or are easy to monitor and manage.

7.2 Dosage/modes of administration

Methotrexate is available in two main forms: tablets and injection liquid. It is given only once weekly, on the same day of the week. The usual dose is 10-15 mg per square meter per week (usually to a max 20 mg per week). Addition of folic or folinic acid 24 hours after MTX administration reduces the frequency of some side effects.
The route of administration, as well as the dose, is chosen by the physician according to the individual patient’s condition.
Tablets are better absorbed when taken before a meal and preferably with water. Injections can be administered just under the skin, similarly to insulin injections for diabetes, but can also be given into the muscle or very rarely into a vein.
Injections have the advantage of better absorption and usually less stomach upset. Methotrexate therapy is usually long-term up to several years. Most physicians recommend treatment to continue for at least 6-12 months after disease control (remission) is achieved.

7.3 Side effects

Most children on methotrexate have very few side effects. They include nausea and stomach upset. These can be managed by taking the dose at night. A vitamin, folic acid, is often prescribed to prevent these side effects.
Sometimes using anti-sickness drugs before and after the methotrexate dose and/or changing to injectable form can help. Other side effects include mouth ulcers and less commonly skin rash. Cough and breathing problem are rare side effects in children. An effect on the number of blood cells, if present, is usually very mild. Long-term hepatic damage (liver fibrosis) appears to be very rare in children, because

other hepatotoxic factors (toxic to the liver), such as alcohol consumption, are not present.
Methotrexate therapy is typically interrupted when liver enzymes increase and re-started when they fall back to normal. Regular blood tests are therefore needed during methotrexate therapy. The risk of infections is usually not increased in children treated with methotrexate.
If your child is a teenager, other considerations may become important. Alcohol intake should be strictly avoided, as it may increase the liver toxicity of methotrexate. Methotrexate may harm an unborn baby, so it is very important that contraceptive precautions are taken when a young person becomes sexually active.

7.4 Main paediatric rheumatic diseases indications

Juvenile idiopathic arthritis.
Juvenile dermatomyositis.
Juvenile systemic lupus erythematosus.
Localized scleroderma.

8. Leflunomide

8.1 Description

Leflunomide is an alternative option for patients unresponsive or intolerant to methotrexate. However, experience with this drug in childhood arthritis is still scarce and the drug is not approved for JIA by regulatory authorities.

8.2 Dosage/modes of administration

Children with a weight less than 20 kg receive 100 mg of leflunomide orally for one day, followed by a maintenance dose of 10 mg every other day. Children weighing 20 to 40 kg are given 100 mg of leflunomide for two days, followed by a maintenance dose of 10 mg per day. Children weighing more than 40 kg receive 100 mg of leflunomide for three days, followed by a maintenance dose of 20 mg per day.
Because leflunomide is teratogenic (can cause malformation to the foetus), young females of childbearing potential must have a negative

pregnancy test before starting this medication and must adopt appropriate contraception.

8.3 Side effects

Diarrhoea, nausea, vomiting are the main side effects. In case of toxicity, treatment with cholestyramine under medical control is needed.

8.4 Main paediatric rheumatic diseases indications

Juvenile idiopathic arthritis (the drug is not approved for use in juvenile idiopathic arthritis).

9. Hydroxychloroquine

9.1 Description

Hydroxychloroquine was originally used for the treatment of malaria. It has been shown to interfere with several processes related to inflammation.

9.2 Dosage/modes of administration

It is given once daily in the form of a tablet, up to 7 mg per kg per day, with a meal or a glass of milk.

9.3 Side effects

Hydroxychloroquine is usually well tolerated. Gastrointestinal intolerance, mainly nausea, may occur but is not severe. The major concern is toxicity to the eye. Hydroxychloroquine accumulates in a part of the eye called the retina and persists for long periods of time after it has been discontinued.
These alterations are rare but may cause blindness, even after use of the medication has been stopped. However, this eye problem is extremely rare at the low doses currently used.
Early detection of this complication prevents visual loss if the medication is discontinued; periodic eye examinations are therefore

indicated, although there is a debate about the need and frequency of these measures when hydroxychloroquine is administered at low doses, as in rheumatic diseases.

9.4 Main paediatric rheumatic diseases indications

Juvenile dermatomyositis.
Juvenile systemic lupus erythematosus.

10. Sulfasalazine

10.1 Description

Sulfasalazine is a combination of an antibacterial and an anti-inflammatory drug. It was developed many years ago when adult rheumatoid arthritis was thought to be an infectious disease. Despite the fact that the rationale for its use was subsequently revealed to be wrong, sulfasalazine has been shown to be effective in some forms of arthritis, as well as in a group of diseases characterized by chronic gut inflammation.

10.2 Dosage/modes of administration

Sulfasalazine is administered orally at 50 mg per kg per day, to a max 2 g per day.

10.3 Side effects

Side effects are not uncommon and require periodic blood tests. They include gastrointestinal problems (poor appetite, nausea, vomiting and diarrhoea), allergy with skin rash, liver toxicity (elevated transaminases), reduced number of circulating blood cells, decreased serum immunoglobulin concentration.
This drug should never be given to systemic JIA or JSLE patients because it can induce a severe flare up of the disease or macrophage activation syndrome.

10.4 Main paediatric rheumatic diseases indications

Juvenile idiopathic arthritis (mainly enthesitis-related JIA).

11. Colchicine

11.1 Description

Colchicine has been known for centuries. It is derived from the dried seeds of colchicum, a genus of flowering plants in the family Liliaceae. It inhibits the function and numbers of white blood cells, in this way blocking inflammation.

11.2 Dosage/modes of administration

It is given orally, usually up to 1-1.5 mg per day. In some cases, higher dosages (2 or 2.5 mg per day) may be required. Very rarely, in resistant cases, the drug is given intravenously.

11.3 Side effects

Most side effects are related to the gastrointestinal system. Diarrhoea, nausea, vomiting and occasional abdominal cramps may improve with a lactose-free diet. These side effects usually respond to transient dose reduction.

After the disappearance of these signs, an attempt to slowly increase the dose to the original level can be made. There might be a decrease in the number of blood cells; therefore periodic monitoring of blood cell counts are required.

Muscle weakness (myopathy) may be seen in patients with renal and/or liver problems. Prompt recovery is achieved after discontinuation of the drug.

Another rare side effect is alteration of the peripheral nerves (neuropathy), and in these rare cases the recovery may be slower. Rash and alopecia (hair thinning) may be observed occasionally.

Serious poisoning may occur after ingestion of a large quantity of the drug. Treatment for colchicine intoxication (poisoning) requires medical intervention. Gradual recovery is usually observed but rarely the overdose may be fatal. Parents should be very cautious that the drug is not within the reach of small children. Colchicine treatment in Familial Mediterranean Fever could be continued throughout pregnancy after

consultation with a gynaecologist.

11.4 Main paediatric rheumatic diseases indications

Familial Mediterranean Fever.
Some other autoinflammatory conditions including recurrent pericarditis.

12. Mycophenolate mofetil

12.1 Description

In some paediatric rheumatic diseases, part of the immune system is over-activated. Mycophenolate mofetil inhibits the proliferation of B and T lymphocytes (these are specific white blood cells); in other words, it decreases the rate of development of some of the immune active cells. This effect starts after some weeks.

12.2 Dosage/modes of administration

The drug can be given as tablets or powder for solution from 1 to 3 g per day. It is recommended that mycophenolate mofetil is consumed between meals, as food intake may decrease the absorption of this substance. If a dose is missed, the patient should not take a double dose the following time. The product should be stored in the original packaging, tightly closed. Ideally, drug concentrations should be determined by analysing several blood samples taken the same day at different times; this allows proper adjustment of the dosage in an individual patient.

12.3 Side effects

The most common side effect is gastrointestinal discomfort, seen in 10-30% of cases, especially at the beginning of treatment. There may be diarrhoea, nausea, vomiting or constipation. If these side effects persist, a reduced dose may be taken or a shift to a similar product (myfortic) can be considered. The drug might lead to a decrease in white blood cells and/or platelets; hence, these should be monitored monthly. Administration of the drug should be temporarily withdrawn in

the event of a decrease in white blood cells and/or platelets.
The drug can cause an increased risk of infections. Drugs that suppress the immune system can result in an abnormal response to live vaccines. It is therefore recommended that your child should not receive live vaccines such as the measles vaccine. Consult with a physician before vaccinations and before travelling abroad. Pregnancy should be avoided during mycophenolate mofetil therapy.
Routine clinical examinations (monthly) and blood and urine testing are necessary to detect and respond to possible side effects.

12.4 Main paediatric rheumatic diseases indications

Juvenile Systemic Lupus Erythematosus.

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.

14. New drugs under development

New drugs are being developed by pharmaceutical companies and clinical researchers belonging to the Paediatric Rheumatology International Trials Organisation (PRINTO) and the Paediatric Rheumatology Collaborative Study Group (PRCSG at www.prcsg.org). PRINTO and PRCSG are involved in revising protocols, case report forms, data collection, data analysis and data reporting in the medical literature.

Before your doctor can prescribe a new drug, it must be carefully tested to assess its safety and its ability to treat patients must be established in clinical trials. In general, development in children follows development in adults, so some drugs may be available only for adults at this point. With a growing number of drugs available, off-label use should occur less frequently. You may wish to help in the development of a new medicine by participating in a clinical trial.

Further information can be found on the following websites:

PRINTO www.printo.it www.pediatric-rheumatology.printo.it

PRCSG www.prcsg.org

On ongoing clinical trials:

www.clinicaltrialsregister.eu/

www.clinicaltrials.gov
Agreed plans for development of new medicines for children in Europe:
www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/pip_search.jsp&mid=WC0b01ac058001d129
Authorised medicines for use in children:
www.ema.europa.eu
http://labels.fda.gov http://labels.fda.gov