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Juvenile Idiopathic Arthritis

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3. DIAGNOSIS AND THERAPY

3.1 What laboratory tests are needed?

At the time of diagnosis, certain laboratory tests are useful along with joint examination and eye checks. These tests help to define the type of JIA and to identify patients at risk of developing specific complications such as chronic iridocyclitis.
Rheumatoid factor (RF) is a laboratory test detecting an autoantibody, which, if positive and persistent in high concentration, indicates the JIA subtype.
Antinuclear antibodies (ANA) are often positive tests in patients with oligoarticular early-onset JIA. This population of JIA patients are at high risk of developing chronic iridocyclitis and therefore should have scheduled eye screenings using a slit-lamp (every three months).
HLA-B27 is a cellular marker which is positive in up to 80% of patients with enthesitis-associated arthritis. It is positive in only 5-8% of healthy individuals.
Other examinations such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) that measure the extent of general inflammation are useful; however, diagnosis as well as treatment decisions are based much more on clinical assessment than on laboratory tests.
Depending on the treatment, patients may need periodic tests (such as blood cell count, liver function test, urine test) to check for side effects of the treatment and to assess potential drug toxicity that may cause no symptoms. The inflammation in the joint is evaluated mainly by clinical examination and sometimes imaging studies such as ultrasound. Periodic X-rays or magnetic resonance imaging (MRI) may be useful to assess bone health and bone growth and therefore to tailor the therapy.

3.2 How can we treat it?

There is no specific therapy to cure JIA. The aim of treatment is to relieve pain, fatigue and stiffness, prevent joint and bone damage, minimize deformities and improve mobility preserving growth and development for all types of arthritis. In the last ten years there have been tremendous advances in the treatment of JIA with the introduction of drugs known as biologic agents. However, some children might be "treatment resistant", meaning that the disease is still active and the joints inflamed despite treatment. There are some guidelines for deciding treatment, although treatment must be individualised for every child. Parental participation in the treatment decision is very important.

Treatment is based mainly on the use of drugs that inhibit systemic and/or articular inflammation and on rehabilitation procedures that preserve joint function and contribute to preventing deformities. Therapy is quite complex and requires the co-operation of different specialists (paediatric rheumatologist, orthopaedic surgeon, physical and occupational therapist, ophthalmologist).

The next section describes the current treatment strategies for JIA. More information on specific drugs can be found in the Drug Therapy section. Note that each country has a list of approved drugs; hence, not all the drugs listed are available in all countries.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) have traditionally been the main treatment for all forms of juvenile idiopathic arthritis (JIA) and other paediatric rheumatic diseases. They relieve symptoms of inflammation (i.e anti-inflammatory) and are antipyretic (i.e. keep fever down) medications; they do not induce disease remission but do help control symptoms due to inflammation. The most widely used are naproxen and ibuprofen; aspirin, although effective and inexpensive, is used much less today, mainly due to risk of toxicity (namely, systemic effects in case of high blood levels and liver toxicity especially in systemic JIA). NSAIDs are usually well tolerated: gastric discomfort, the most common side effect in adults, is uncommon in children. Occasionally, one NSAID may be effective where another has failed. Combining different NSAIDs is not indicated. The optimal effect on joint

inflammation occurs after several weeks of therapy.

Joint injections

Joint injections are used if there are one or more joints with inflammation inhibiting normal movement of the joint and / or are very painful for the child. The drug injected is a long-acting corticosteroid preparation. Triamcinolone hexacetonide is preferred for its prolonged effect (frequently many months): absorption into systemic circulation is minimal. It is the treatment of choice for oligoarticular disease and used in combination with other treatments in the other forms of JIA. This form of therapy can be repeated several times in the same joint. The joint injection can be performed with local anaesthesia or general anaesthesia (usually in the younger age) depending on the age of the child, the type of joint and the number of joints to be injected. More than 3-4 injections per year in the same joint are usually not recommended.
Usually joint injections are associated with other treatment to achieve rapid improvement of pain and stiffness or they may be used as "bridging agents" when starting other medications which may take several weeks to work.

Second level drugs

Second level drugs are indicated in children that have severe or progressive polyarthritis despite adequate therapy with NSAIDs and corticosteroid injections. Second level drugs are generally added to previous NSAIDs therapy, which is normally continued. The effect of most second level drugs becomes fully evident only after several weeks or months of treatment.

Methotrexate

There is no doubt that methotrexate represents the second level drug of first choice worldwide for children with JIA. Several studies have demonstrated efficacy as well as safety profile of methotrexate used for several years. The medical literature has now established the maximum effective dose (15 mg per square metre by either oral or parenteral route, usually by subcutaneous injections). Therefore, weekly methotrexate is the drug of first choice especially in children with polyarticular JIA and is effective in the majority of patients. It has anti-inflammatory activity but it is also able, in some patients and through

unknown mechanisms, to reduce disease progression or even induce disease remission. It is usually well tolerated; nausea / vomiting and increase in liver transaminase levels represent the most common side effects. During treatment, potential toxicity needs monitoring with periodic blood tests and laboratory examination.
Methotrexate is now approved for use in JIA in many countries all over the world. Combining methotrexate treatment with folic or folinic acid (a vitamin that reduces the risk of side effects especially on liver function), is also recommended.

Leflunomide

Leflunomide is an alternative to methotrexate, especially for children who do not tolerate the latter. Leflunomide is administered in tablets and this treatment was studied in JIA and its efficacy has been proven. However, this treatment is more expensive than methotrexate.

Salazopyrin and cyclosporin

Other non-biologic drugs, such as salazopyrin, have also been shown to be effective in JIA but are usually less well tolerated than methotrexate. Experience with salazopyrin is much more limited compared to methotrexate. To date, no proper studies have been conducted in JIA to assess the efficacy of other potentially useful drugs such as cyclosporin. Salazopyrin and cyclosporin are currently less used, especially in countries where availability of biologic agents is more widespread. Cyclosporin is a useful drug, in association with corticosteroids, for the treatment of macrophage activation syndrome in systemic JIA; this is a severe and potentially life-threatening complication of systemic JIA and secondary to a massive general activation of the inflammatory process.

Corticosteroids

Corticosteroids are the most effective available anti-inflammatory drugs but their use is limited because, in the long-term, they are associated with several significant side effects, including osteoporosis and stunted growth. Nevertheless, corticosteroids are valuable for the treatment of systemic symptoms that are resistant to other therapies, for life-threatening systemic complications and as a "bridge" drug to control acute disease while waiting for the second level drugs to take effect. Topical corticosteroids (eye drops) are used in the treatment of iridocyclitis. In more severe cases, periocular corticosteroid injections

(inside the eye globe) or systemic corticosteroid administration may be required.

Biologic agents

New perspectives have been introduced in the last few years with drugs known as biologic agents. Physicians use this term for drugs produced with biological engineering, which, unlike methotrexate or leflunomide, are primarily directed against specific molecules (tumour necrosis factor or TNF, interleukin 1, interleukin 6 or a T cell stimulatory molecule). Biologic agents have been identified as important ways to block the inflammatory process typical of JIA. There are now several biologic agents almost all specifically approved for use in JIA (see paediatric legislation below).

Anti-TNF drugs

Anti-TNF drugs are agents that 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 so far has been shown to be good at least for few years of treatment (see safety section below); however, longer follow-up is 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; for example, etanercept is administered subcutaneously twice or once per week, adalimumab subcutaneously every 2 weeks and infliximab by monthly intravenous infusion. Others are still under investigation (e.g. golimumab and certolizumab pegol) in children, and there are other molecules being studied in adults that may become available for children in the future.
Usually, anti-TNF therapies are used in most of the JIA categories, with the exception of persistent oligoarthritis, which is usually not treated with biologic agents. They have more limited indications in systemic JIA, where other biologics are normally used, such as anti-IL-1 (anakinra and canakinumab) or anti-IL-6 (tocilizumab). The anti-TNF agents are used either alone or in combination with methotrexate. Like all other second level drugs, they must be administered under specialist supervision.

Anti CTL4Ig (abatacept)

Abatacept is a drug with a different mechanism of action directed

against a type of white blood cell called T lymphocytes. Currently, it can be used to treat children with polyarthritis who do not respond to methotrexate or other biologic agents.

Anti interleukin 1 (anakinra and canakinumab) and anti interleukin 6 (tocilizumab)

These drugs are specifically useful for treating systemic JIA. Normally the treatment of systemic JIA starts with corticosteroids. Although effective, corticosteroids are associated with side effects, especially on growth, so when they are not able to control disease activity within a short time period (typically a few months), physicians add anti-IL-1 (anakinra or canakinumab) or anti-IL-6 (tocilizumab) drugs to treat both the systemic manifestation (fever) and arthritis. In children with systemic JIA, the systemic manifestations sometimes disappear spontaneously but the arthritis persists; in these cases, methotrexate could be introduced alone or in combination with anti-TNF or abatacept. Tocilizumab can be used in systemic and polyarticular JIA. It was first proven for systemic and later for polyarticular JIA and it can be used in patients who donot respond to methotrexate or other biologic agents.

Other complementary treatments

Rehabilitation

Physical therapy and rehabilitation is an essential component of management; it includes appropriate exercises as well as, when indicated, the use of splints to maintain joint position in a comfortable posture to prevent pain, stiffness, muscle contractures and joint deformities. It must be started early and should be performed routinely to improve or maintain healthy joints and muscles.

Orthopaedic surgery

The main role for orthopaedic surgery is prosthetic joint replacement (mostly hips and knees) in case of articular destruction and surgical releasing of soft tissues in case of permanent contractures.

3.3 What about unconventional/complementary therapies?

There are many complementary and alternative therapies available and this can be confusing for patients and their families. Think carefully

about the risks and benefits of trying these therapies as there is little proven benefit and they can be costly both in terms of time, burden to the child and money. If you want to explore complementary and alternative therapies, then please discuss these options with your paediatric rheumatologist. Some therapies can interact with conventional medications. Most doctors will not be opposed to alternative therapies, provided you follow medical advice. It is very important not to stop taking your prescribed medications. When medications such as corticosteroids are needed to keep the disease under control, it can be very dangerous to stop taking them if the disease is still active. Please discuss medication concerns with your child’s doctor.

3.4 When should therapies start?

Today, there are international and national recommendations that help physicians and families to select the treatment.
International recommendations have been recently issued by the American College of Rheumatology (ACR at www.rheumatology.org) and others are being currently being prepared by the Paediatric Rheumatology European Society (PRES at www.pres.org.uk).
According to these recommendations, children with a less severe disease (few joints involved) are usually treated primarily with NSAIDs and corticosteroid injections.
For more severe JIA (several joints involved), methotrexate (or leflunomide to a lesser extent) is administered first and if this is not sufficient, a biologic agent (primarily an anti-TNF) is added alone or in combination with methotrexate. For children who are resistant or intolerant to treatment with either methotrexate or biologic agents, another biologic could be used (another anti-TNF or abatacept).

3.5 What about paediatric legislation, label and off-label use and future therapeutic possibilities?

Until 15 years ago, all drugs used to treat JIA and many other paediatric diseases were not properly studied in children. This means that physicians were prescribing drugs basing on personal experience or 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 of specific legislation for paediatric medicines development (Paediatric Regulation) in the European Union (EU). These initiatives essentially forced pharmaceutical companies to also study the drugs in children.
The USA and EU initiatives, together with 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, have had a positive impact in paediatric rheumatology development, 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 placebo (i.e. a tablet or an infusion with no active substance) to be sure that the study drug does more benefit than harm.
Because of this important research, several drugs are nowadays, specifically approved for JIA. This means that regulatory authorities, such as the Food and Drug Administration (FDA), the European Medicine Agency (EMA) and several national authorities have revised 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 for JIA includes methotrexate, etanercept, adalimumab, abatacept, tocilizumab and canakinumab. Several other drugs are currently being 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 formally approved for use in JIA, such as several non-steroidal anti-inflammatory drugs, azathioprine, cyclosporine, anakinra, infliximab, golimumab and certolizumab. These drugs may be used even without an approved indication (so called off-label use) and your doctor might propose their use especially if there are no other available treatments.

3.6 What are the main side effects of therapy?

The drugs used in the treatment of JIA are usually well tolerated. Gastric intolerance, the most frequent side effect of NSAIDs (which should therefore be taken with some food), is less common in children than in adults. NSAIDs can cause an increase in the blood levels of some liver enzymes but this is a rare event with the exception of aspirin.
Methotrexate is also well tolerated. Gastro-intestinal side effects, such as nausea and vomiting, are not uncommon. To monitor potential toxicity it is important to monitor liver enzymes using routine blood counts. The most frequent laboratory abnormality is an increase in liver enzymes, which normalizes with drug withdrawal or with methotrexate dose reduction. The administration of folinic or folic acid is effective in reducing the frequency of liver toxicity. Hypersensitivity reactions to methotrexate rarely occur.
Salazopyrine is reasonably well tolerated; the most frequent side effects include skin rash, gastrointestinal problems, increased liver enzymes, leukopenia (lowering of white blood cells leading to risk of infections). Like for methotrexate, regular laboratory tests are therefore needed.
The long-term use of corticosteroids in high dosage is associated with several important side effects. These include stunted growth and osteoporosis. Corticosteroids at higher doses cause a marked increase in appetite, which may lead to obesity. It is therefore important to encourage children to eat food that can satisfy their appetite without increasing calorie intake.
Biologic agents are usually well tolerated at least in the initial years of treatment. Patients should be carefully monitored for the possible occurrence of infections or other adverse events. However, it is important to understand that the experience with all drugs currently used for JIA is limited in size (just a few hundred children participated in clinical trials) and in time (biologic agents have only been available since 2000). For these reasons, there are now several JIA registries to follow up children on biologic treatment at the national (e.g. Germany, United Kingdom, USA and others) and international level (e.g. Pharmachild, which is a project conducted by PRINTO and PRES) with the purpose of closely monitoring children with JIA and to see if safety events might occur in the long term (several years after the drugs have been administered).

3.7 How long treatment should last?

Treatment should last as long as the disease persists. Disease duration is unpredictable; in the majority of cases, JIA goes into spontaneous remission after a course ranging from few to many years. The course of JIA is often characterised by periodic remissions and exacerbations, which lead to important changes in therapy. Complete treatment withdrawal is considered only after arthritis is "quiet" (i.e in remission) for a long time (6-12 months or longer). However, there is no definitive information on the possible recurrence of the disease once a drug is stopped. Physicians usually follow up children with JIA until they become adults, even if the arthritis is quiet.

3.8 Eye examination (slit-lamp examination): how often and for how long?

In patients at risk (especially if ANA positive), slit-lamp examination is performed at least every three months. Those that have developed iridocyclitis should have more frequent examinations, depending on the severity of eye involvement determined during ophthalmologic visits. The risk of developing iridocyclitis decreases with time; however, iridocyclitis may also develop many years after arthritis onset. It is therefore prudent to have eye examinations for many years, even if arthritis is in remission.

Acute uveitis, which can occur in patients with arthritis and enthesitis, is symptomatic (red eyes, eye pain and uncomfortable exposure to light or photophobia). If there are such complaints, prompt ophthalmologic referral is required. Unlike iridocyclitis, there is no need for periodic slit-lamp examinations for early diagnosis.

3.9 What is the long-term evolution (prognosis) of arthritis?

The prognosis of arthritis has improved significantly over the years, but still depends on the severity and type of JIA and early and appropriate treatment. There is ongoing research to develop new drugs and biologic agents and also to make treatment available to all children. Arthritis prognosis has considerably improved in the last ten years. Overall, around 40% of children will be off medication and without symptoms (remission) 8-10 years from disease onset; the highest rates of

remission are in the oligoarticular persistent and systemic types.
Systemic JIA has a variable prognosis. About half of patients have few signs of arthritis and the disease is characterised mainly by periodic disease flares; the ultimate prognosis is often good as the disease frequently goes into spontaneous remission. In the other half of patients, the disease is characterised by persistent arthritis while systemic symptoms tend to fade with years; severe articular destruction may develop in this subset of patients. Finally, in a minority of this second group of patients, systemic symptoms persist together with articular involvement; these patients have the worst prognosis and may develop amyloidosis (a severe complication that requires immunosuppressive therapy). The progress of target biologic therapy with anti-IL-6 (tocilizumab) and anti-IL-1 (anakinra and canakinumab) will probably greatly improve the long-term prognosis.
RF positive polyarticular JIA more often has a progressive articular course that may lead to severe joint damage. This form is the childhood counterpart of rheumatoid factor (RF) positive rheumatoid arthritis in adults.
RF negative polyarticular JIA is complex, both in clinical manifestations and in prognosis. However, the overall prognosis is much better than for RF positive polyarticular JIA; only about one quarter of patients develop articular damage.
Oligoarticular JIA often has a good articular prognosis when the disease remains limited to a few joints (so-called persistent oligoarthritis). Patients in which the articular disease extends to involve several joints (extended oligoarthritis) have a similar prognosis to patients with polyarticular RF negative JIA.
Many patients with psoriatic JIA have a disease which is similar to oligoarticular JIA, while others are similar to adult psoriatic arthritis.
JIA associated with enthesopathy has also a variable prognosis. In some patients the disease goes into remission, while in others it progresses and may involve sacroiliac joints.
Currently, in the early stage of the disease there are no reliable clinical or laboratory features available and doctors cannot predict which patient will have the worst prognosis. Such predictors would be of considerable clinical importance since they would allow the identification of patients who should be prescribed a more aggressive treatment from onset of disease. Other laboratory markers are still under study to predict when it is time to stop treatment with

methotrexate or biologic agents.

3.10 And that of iridocyclitis?

Iridocyclitis, if left untreated, may have very serious consequences including cloudiness of the lens in the eye (cataract) and blindness. However, if treated at an early stage, the inflammation and any symptoms usually settle with therapy that consists of eye drops to control inflammation and dilate the pupils. If symptoms cannot be controlled using eye drops, then biologic treatment may be prescribed. However, there is no clear evidence yet to suggest the best choice for treating severe iridocyclitis, because of the variable response to treatment from child to child. Early diagnosis is therefore the major determinant of prognosis. Cataracts can also be the consequence of long-term treatment with corticosteroids, especially in systemic JIA patients.