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Juvenile Idiopathic Arthritis

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1. WHAT IS JIA

1.1 What is it?

Juvenile idiopathic arthritis (JIA) is a chronic disease characterised by persistent joint inflammation; the typical signs of joint inflammation are pain, swelling and limitation of movement. "Idiopathic" means that we do not know the cause of the disease and "juvenile", in this case, means that the onset of the symptoms usually occurs before 16 years of age.

1.2 What does chronic disease mean?

A disease is said to be chronic when the condition persists – this means that the appropriate treatment does not necessarily bring about a cure of the condition but results in an improvement of symptoms and laboratory tests.
This also means that when the diagnosis is made, it is impossible to predict for how long that the child may be ill.

1.3 How frequent is it?

JIA is a relatively rare disease that affects about 1-2 individuals in every 1,000 children.

1.4 What are the causes of the disease?

Our immune system protects us from infections caused by various microbes such as viruses or bacteria. It is able to distinguish what is potentially foreign and harmful and should be destroyed from what

belongs to us.
Chronic arthritis is believed to be an abnormal response of our immune system, which to a degree, loses capacity to distinguish "foreign" from "self" cells and results in attack to its own body components leading to inflammation (e.g. of the joint lining). For this reason, diseases such as JIA are also called "autoimmune", meaning that the immune system reacts against the patient’s own body.
However, like most human chronic inflammatory diseases, the precise mechanisms that cause JIA are unknown.

1.5 Is it a hereditary disease?

JIA is not a hereditary disease since it cannot be transmitted directly from parents to their children. Nevertheless there are some genetic factors, with more as yet undiscovered, that predispose individuals to the disease. The scientific community agrees that JIA is the result of a combination of genetic predisposing factors and exposure to environmental influences (probably infections). However, even when there may be a genetic predisposition, it is very rare to have two children affected in the same family.

1.6 How is it diagnosed?

The diagnosis of JIA is based on the presence and persistence of arthritis and by careful exclusion of any other disease through the medical history, physical examination and laboratory tests.
JIA is when the disease starts before the age of 16, symptoms last for more than 6 weeks and all other diseases that may be responsible for arthritis have been ruled out.
The reason for this 6 week period is to allow the exclusion of other forms of transient arthritis such as those which may follow various infections. The term JIA includes all forms of persistent arthritis of unknown origin with onset in childhood.
JIA includes different forms of arthritis that have been identified (see below).

1.7 What happens to the joints?

The synovial membrane is the thin inner lining of the joint capsule; in

arthritis this becomes much thicker, filled with inflammatory cells and tissue resulting in an increased amount of synovial fluid inside the joint. This causes swelling, pain and limitation of movement. A characteristic feature of joint inflammation is joint stiffness which occurs after prolonged rest periods; it is therefore particularly pronounced in the morning (morning stiffness).
The child often tries to reduce pain by keeping the joint in a semi-flexed position; this position is called "antalgic" to emphasise the fact that it is aimed to reduce pain. If maintained for prolonged periods (usually more than 1 month), this abnormal position leads to the shortening (called contracture) of muscles and tendons and to the development of flexion (bent) deformity.
If not properly treated, joint inflammation may cause joint damage through two main mechanisms: the synovial membrane gets very thick, becoming boggy (with the formation of what is known as the synovial pannus) and through the release of various substances that provoke damage and loss of joint cartilage and bone. On x-rays this appears as holes in the bone that are called bone erosions. The prolonged maintenance of the antalgic position causes muscle atrophy (wasting and loss of muscle), stretching or retraction of muscles and soft tissues, leading to flexion deformity.

2. DIFFERENT TYPES OF JIA

2.1 Are there different types of the disease?

There are several forms of JIA. They are mainly distinguished by the number of joints affected (e.g oligoarticular – less than 5 joints - or polyarticular JIA – 5 or more joints) and by the presence of additional symptoms such as fever, rash and others (see following paragraphs). Diagnosis of the different forms is made by observing the symptoms during the first 6 months of the disease. For this reason, they are also often referred to as onset-forms.

2.1.1 Systemic JIA

Systemic means that various organs of the body may be involved, in addition to the arthritis.
Systemic JIA is characterised by the presence of fever, rash and intense

inflammation of various organs of the body that may appear before arthritis or during the course of arthritis. There is recurrent high fever and a rash that appears mainly during fever spikes. Other symptoms may include muscle pain, enlargement of liver, spleen or lymph nodes and inflammation of membranes around the heart (pericarditis) and lungs (pleuritis). Arthritis, usually involving 5 or more joints, may be present at disease onset or can appear several weeks later. The disease may affect boys and girls at any age, but it is especially common in toddlers and preschool children.
About half of patients have limited periods of fever and arthritis; these patients tend to have the best long-term prognosis. In the other half, fever often tends to subside, while arthritis becomes more important and sometimes difficult to treat. In a minority of these patients, fever and arthritis persist together. Systemic JIA accounts for less than 10% of all JIA cases; it is typical of childhood and is seldom observed in adults.

2.1.2 Polyarticular JIA

Polyarticular JIA is characterised by the involvement of 5 or more joints during the first 6 months of the disease in the absence of fever. There are blood tests that evaluate Rheumatoid Factor (RF) that can distinguish between two types: RF negative and RF positive JIA.
RF positive polyarticular JIA: this form is very rare in children (less than 5% of all JIA patients). It is the equivalent of adult RF positive rheumatoid arthritis (the most common type of chronic arthritis in adults). It often causes symmetrical arthritis affecting initially mainly the small joints of the hands and feet and then extending to the other joints. It is much more common in females than in males and has onset usually after 10 years of age. It is often a severe form of arthritis.
RF negative polyarticular JIA: this form accounts for 15-20% of all JIA cases. It can affect children at any age. Any joint can be affected and usually both large and small joints are affected.
For both forms, the treatment must be planned early, as soon as the diagnosis is confirmed. It is believed that early and appropriate treatment leads to better results. Nevertheless, response to treatment is difficult to predict in its early stages. The response to treatment varies greatly from one child to another.

2.1.3 Oligoarticular JIA (persistent or extended)

Oligoarticular JIA is the most frequent JIA subtype, accounting for almost 50% of all cases. It is characterised by the presence, in the first 6 months of the disease, of fewer than 5 joints involved in the absence of systemic symptoms. It affects large joints (such as knees and ankles) asymmetrically. Sometimes only one joint is affected (monoarticular form). In some patients, the number of joints affected increases after the first 6 months of disease to 5 or more; this is called extended oligoarthritis. If the joints involved are less than 5 throughout the course of the disease then this is termed persistent oligoarthritis. Oligoarthritis usually has its onset before the age of 6 and is primarily observed in females. With timely and appropriate treatment, joint prognosis is often good in patients in which the disease remains limited to a few joints; it is more variable in those patients who develop an extension of articular involvement into polyarthritis.

A significant proportion of patients may develop eye complications, such as the inflammation of the eye (anterior uveitis). Since the anterior part of the uvea is formed by the iris and the ciliary body, the complication is named either chronic iridocyclitis or chronic anterior uveitis. In JIA, this is a chronic condition which develops insidiously without causing any overt symptoms (like pain or redness). If unrecognized and left untreated, anterior uveitis progresses and may cause very serious damage to the eye. Early recognition of this complication is therefore of utmost importance. Because the eye does not become red and the child does not complain of blurred vision, anterior uveitis may not be noticed by parents or clinicians. Risk factors for developing uveitis are early onset of JIA and positive ANA (Anti-Nuclear Antibody).

It is therefore imperative for children at high risk to have regular eye checks by an ophthalmologist using a special appliance known as a slit-lamp. The frequency of examinations is usually every 3 months and should be maintained long-term.

2.1.4 Psoriatic arthritis

Psoriatic arthritis is characterised by the presence of arthritis associated with psoriasis. Psoriasis is a skin inflammatory disease with patches of scaling skin often located over elbows and knees. Sometimes only the nails are affected by psoriasis or there is a family history of psoriasis.

The skin disease may precede or follow the onset of arthritis. Typical signs suggestive of this JIA subtype include swelling of the whole finger or toe (so called "sausage" finger or dactylitis) and nail changes (pitting). Presence of psoriasis in a first degree relative (a parent or sibling) can also occur. Chronic anterior uveitis may develop and therefore regular eye checks are recommended.
Disease outcome varies, as response to treatment may be different for skin and joint disease. If a child has arthritis in fewer than 5 joints the treatment is the same as for the oligoarticular type. If the child has more than 5 affected joints, the treatment is the same as for the polyarticular forms. The outcome may be related to the treatment response for both arthritis and psoriasis.

2.1.5 Arthritis associated with enthesitis

The most common manifestations are arthritis affecting mainly the large joints of the lower limbs and enthesitis. Enthesitis means inflammation of the "enthesis", the point of insertion of tendons over bones (the heel is an example of enthesis). Localised inflammation in this area is usually associated with intense pain. Most commonly enthesitis is located on the soles and the heels, where the Achilles tendons are inserted. Sometimes these patients develop acute anterior uveitis. Unlike uveitis with other JIA forms, it usually presents with red and watery eyes (lachrymation) and increased sensitivity to light. Most patients are positive for a laboratory test called HLA B27: this tests for a family predisposition to the disease. This form affects predominantly males and the arthritis usually begins after 6 years of age. The course of this form is variable. In some patients, the disease becomes quiescent after time, while in others it also spreads to the lower spine and to the joints attached to the pelvis, the sacroiliac joints, limiting the movements of back. Low back pain present in the mornings and associated with stiffness is highly suggestive of spinal joint inflammation. Indeed, this form resembles some spine diseases occurring in adults called ankylosing spondylitis.

2.2 What causes chronic iridocyclitis? Is there a relationship with arthritis?

Eye inflammation (iridocyclitis) is caused by an abnormal immune

response against the eye (autoimmune). However, the precise mechanisms are unknown. This complication is mainly observed in patients with early onset JIA and a positive test for ANA.
The factors linking eye to articular disease are unknown. However, it is important to remember that arthritis and iridocyclitis may follow an independent course; periodic slit-lamp examinations must be continued even if the arthritis goes into remission as the eye inflammation can relapse without symptoms and even when the arthritis is better. The course of iridocyclitis is characterised by periodic flare-ups that are also independent from those of arthritis.
Iridocyclitis usually follows the onset of arthritis or may be detected at the same time as arthritis. More rarely it precedes arthritis. These are usually the most unfortunate cases; since the disease is asymptomatic, late diagnosis may result in visual impairment.

2.3 Is the disease in children different from the disease in adults?

Mostly yes. The polyarticular RF positive form, which is responsible for about 70% of adult rheumatoid arthritis cases, accounts for less than 5% of cases of JIA. The oligoarticular form with early onset represents about 50% of JIA cases and is not seen in adults. Systemic arthritis is characteristic of children and is seldom observed in adults.

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, l=15*q13.1.1>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.

4. EVERYDAY LIFE

4.1 Can diet influence the course of the disease?

There is no evidence that diet can influence the disease. In general, the child should follow a balanced, normal diet for his/her age. Overeating should be avoided in patients taking corticosteroids, as these drugs increase appetite and food with high calories and sodium should be

avoided during corticosteroid treatment, even if the child is taking a small dose.

4.2 Can climate influence the course of the disease?

There is no evidence that climate can affect the disease manifestations. However, morning stiffness may persist longer in cold damp weather.

4.3 What can exercise and physical therapy add?

The purpose of exercise and physical therapy is to enable the child to optimally participate in all daily activities of life and fulfil all desired social roles. Furthermore, exercise and physical therapy can be used to encourage active healthy living. To be able to achieve these goals, healthy joints and muscles are important. Exercise and physical therapy can be used to achieve better joint mobility, joint stability, muscle flexibility, muscle strength, coordination and endurance (stamina). These aspects of musculoskeletal health allow the child to successfully and safely engage in school activities and extra-curricular activities, such as active leisure time activities and sports. Treatment and home exercise programmes can be helpful to reach the required strength and fitness level.

4.4 Are sports allowed?

Playing sports is an essential aspect of the everyday life of a healthy child. One of the aims of JIA therapy is to allow children to conduct a normal life as far as possible and to consider themselves not different from their peers. Therefore, the general recommendation is to allow patients to participate in sport activities and to trust that they will stop if a joint hurts, while advising sport teachers to prevent sport injuries, in particular for adolescents. Although mechanical stress is not beneficial for an inflamed joint, it is assumed that the minimal damage that could result is much smaller than the psychological damage of being excluded from playing sports with friends due to the disease. This choice is part of a more general attitude that tends to encourage the child to be autonomous and able to cope by himself with the limits imposed by the disease.

Apart from these considerations, it is better to favour sports in which

mechanical stress to the joints is absent or minimal, such as swimming or riding a bike.

4.5 Can the child attend school regularly?

It is extremely important that the child attends school regularly. Limited mobility can be a problem for school attendance; it may cause difficulty walking, fatigue, pain or stiffness. It is therefore important in some cases to get the school team and peers to be aware of the child's limitations, to provide mobility facilities, ergonomic furniture and aids for handwriting or writing (e.g laptop). Physical education and sports participation are encouraged within the limitations of mobility due to disease activity. It is important that the school team has an understanding of JIA and is also aware of the disease course and that unpredictable relapses may occur. Plans for home teaching may be needed. It is also important to explain the child's potential needs to teachers: proper tables, regular movements during school hours to avoid articular stiffness, possible difficulty in writing. Patients should take part, whenever possible, in gym classes; in this case, the same considerations discussed above in terms of sports should be taken into account.
School for a child is what work is for an adult: a place where he/she learns how to become an autonomous person who is productive and independent. Parents and teachers must do whatever they can to encourage sick children participate in school activities in a normal way in order to have academic success, but also a develop social skills with peers and adults in order to be accepted and appreciated by friends.

4.6 Are vaccinations allowed?

If a patient is being treated with an immunosuppressive therapy (corticosteroids, methotrexate, biologic agents), vaccination with live attenuated microorganisms (such as anti-rubella, anti-measles, anti-mumps, anti-polio Sabin and BCG) must be postponed or avoided due to the potential risk of infections spreading as a result of reduced immune defences; ideally, these vaccinations should be given before starting therapies with corticosteroids, methotrexate or biologic agents.
Vaccines that do not contain living microorganisms but only infectious proteins (anti-tetanus, anti-diphtheria, anti-polio Salk, anti-hepatitis B,

anti-pertussis, pneumococcus, haemophilus, meningococcus) can be administered; the only risk is vaccination failure due to the condition of immunosuppression, in such a way that the vaccine provides less protection. However, it is recommended that the vaccine schedule is followed for young children, even with less protection.

4.7 Will the child have a normal adult life?

This is one of the main goals of therapy and it can be achieved in the majority of cases. Therapy of JIA has indeed improved dramatically and, with the new drugs, it will be even better in the future. The combined use of pharmacological treatment and rehabilitation can now prevent joint damage in the majority of patients.

Close attention should also be paid to the psychological impact of the disease on the child and family. A chronic disease like JIA is a difficult challenge for the whole family and, of course, the more serious the disease, the harder it is to cope with it; child will cope less well with the disease if the parents don’t. The parents have a strong attachment towards their child and, in order to prevent the child from any possible problem, they may become overprotective.

A positive-thinking attitude of parents who support and encourage the child to be independent as much as possible, despite the disease, will be extremely valuable; this will help the child to overcome difficulties related to the disease, to successfully cope with their peers and to develop an independent, well-balanced personality.

Psychosocial support should be offered by the paediatric rheumatology team when needed.

Families association or charities might also help families to cope with the disease.