



<https://printo.it/pediatric-rheumatology/IE/intro>

## **Deficiency of IL-1 Receptor Antagonist (DIRA)**

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### **1. WHAT IS DIRA**

#### **1.1 What is it?**

Deficiency of IL-1 Receptor Antagonist (DIRA) is a rare genetic disease. Affected children suffer from severe skin and bone inflammation. Other organs such as the lungs may be involved. Untreated, the disease may lead to severe disability and even death.

#### **1.2 How common is it?**

DIRA is very rare. Currently, less than 10 patients have been identified worldwide.

#### **1.3 What are the causes of the disease?**

DIRA is a genetic disease. The responsible gene is called IL1RN. It produces a protein, IL-1 Receptor antagonist (IL-1RA), that plays a role in the natural resolution of inflammation. IL-1RA neutralizes the protein interleukin-1 (IL-1), which is a powerful inflammatory messenger in the human body. If the IL1RN gene carries a mutation, as it does in DIRA, the body cannot produce IL-1RA. Therefore, IL-1 is no longer opposed and the patient will develop inflammation.

#### **1.4 Is it inherited?**

It is inherited as an autosomal recessive disease (which means that it is not linked to gender and that neither parent needs to show symptoms of the disease). This type of transmission means that to have DIRA, an

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individual needs two mutated genes, one from the mother and the other from the father. Both parents are carriers (a carrier has only one mutated copy but not the disease) and not patients. Parents who have a child with DIRA have a 25% risk that a second child will have DIRA as well. Antenatal diagnosis is possible.

### **1.5 Why does my child have this disease? Can it be prevented?**

The child has the disease because it was born with the mutated genes that cause DIRA.

### **1.6 Is it infectious?**

No, it is not.

### **1.7 What are the main symptoms?**

The main symptoms of the disease are skin inflammation and bone inflammation. The skin inflammation is characterised by redness, pustules and scaling. The changes can affect every part of the body. Skin disease comes on spontaneously but it can be exacerbated by local injury. For instance, intravenous cannulae often lead to local inflammation. The bone inflammation is characterised by painful bony swellings, often with the overlying skin appearing reddened and warm. Many bones can be involved, including the limbs and the ribs. The inflammation typically involves the periosteum, the membrane covering the bone. The periosteum is very sensitive to pain. Therefore, affected children are often irritable and miserable. This may lead to poor feeding and impaired growth. Inflammation of the joint space is not typically a feature of DIRA. The nails of DIRA-patients can become deformed.

### **1.8 Is the disease the same in every child?**

All affected children have been seriously ill. However, it is not the same in every child. Even within the same family, not every affected child will be equally ill.

### **1.9 Is the disease in children different from the disease in**

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## **adults?**

DIRA has only been recognized in children. In the past, before effective treatment became available, these children would die before reaching adulthood. Hence, the features of DIRA in adulthood are unknown.

## **2. DIAGNOSIS AND THERAPY**

### **2.1 How is it diagnosed?**

First there must be a suspicion of DIRA based on the disease features of the child. DIRA can only be proven by genetic analysis. The diagnosis of DIRA is confirmed if the patient carries 2 mutations, one from each parent. Genetic analysis may not be available in every tertiary care centre.

### **2.2 What is the importance of tests?**

Blood tests such as erythrocyte sedimentation rate (ESR), CRP, whole blood count and fibrinogen are important during disease activity to assess the extent of inflammation.

These tests are repeated after the child becomes symptom-free, to observe if the results are back to or near normal.

A small amount of blood is also needed for the genetic analysis.

Children who are on life-long anakinra treatment must provide blood and urine samples regularly for monitoring purposes.

### **2.3 Can it be treated or cured?**

The disease cannot be cured but it can be controlled with life-long use of anakinra.

### **2.4 What are the treatments?**

DIRA cannot be adequately controlled with anti-inflammatory drugs. High doses of corticosteroids can partially control disease symptoms, but usually at the expense of unwanted side effects. Painkillers are usually needed to control bone pain until treatment with anakinra has taken effect. Anakinra is the artificially produced form of IL-1RA, the protein that DIRA patients lack. Daily injection with anakinra is the only

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therapy that has been effective in the treatment of DIRA. In this way, the shortage of natural IL-1RA is corrected and the disease can be brought under control. Disease recurrence can be prevented. With this therapy, after the diagnosis is made, the child will need to inject this drug for the rest of his/her life. If administered daily, symptoms disappear in most patients. However, some patients have shown partial response. Parents should not modify the dose without consulting the physician.

If the patient stops injecting the drug, the disease will return. Since this is a potentially deadly disease, this must be avoided.

### **2.5 What are the side effects of drug therapy?**

The most troublesome side effects of anakinra are the painful reactions at the site of injection, comparable to an insect sting. Especially in the first weeks of treatment, these can be quite painful. Infections have been observed in patients treated with anakinra for diseases other than DIRA. It is unknown whether this effect applies equally to DIRA patients. Some children treated with anakinra for other disorders appear to gain more weight than desired. Again, we do not know whether this is applicable to DIRA. Anakinra has been used in children since the beginning of the 21st century. Therefore, it remains unknown if there are side effects in the very long term.

### **2.6 How long should treatment last for?**

Treatment is life-long.

### **2.7 What about unconventional or complementary therapies?**

There is no therapy of this kind available for this disease.

### **2.8 What kind of periodic check-ups are necessary?**

Children being treated should have blood and urine tests at least twice yearly.

### **2.9 How long will the disease last?**

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The disease is life-long.

### **2.10 What is the long term prognosis (predicted outcome and course) of the disease?**

If treatment with anakinra is started early and continued indefinitely, children with DIRA will probably live a normal life. If there is a delay in diagnosis or lack of compliance with treatment, the patient risks progressive disease activity. This may lead to growth disturbances, severe bone deformities, crippling, skin scarring and eventually death.

### **2.11 Is it possible to recover completely?**

No, because it is a genetic disease. However, life-long therapy gives the patient the opportunity to live a normal life, without restrictions.

## **3. EVERYDAY LIFE**

### **3.1 How might the disease affect the child and the family's daily life?**

The child and the family face major problems before the disease is diagnosed. After the diagnosis is made and treatment has been instituted, many children lead an almost normal life. Some children must deal with bone deformities that can seriously interfere with normal activities. The daily injections may be a burden, not just because of the discomfort, but also because the storage requirements of anakinra may interfere with travel.

Another problem may be the psychological burden of life-long treatment. Patient and parent education programmes can address this issue.

### **3.2 What about school?**

When the disease has not led to permanent disability and is fully controlled by anakinra injections, there are no restrictions.

### **3.3 What about sports?**

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When the disease has not led to permanent disability and is fully controlled by anakinra injections, there are no restrictions. Skeletal damage incurred early in the disease may limit physical activities but there is no need for additional restrictions.

### **3.4 What about diet?**

There is no specific diet.

### **3.5 Can climate influence the course of the disease?**

No, it cannot.

### **3.6 Can the child be vaccinated?**

Yes, the child can be vaccinated. However, parents need to contact the treating physician for the live attenuated vaccine.

### **3.7 What about sexual life, pregnancy, birth control?**

At present, it is not clear whether anakinra is safe for pregnant women.