

Research trial protocol.

**Treatment of idiopathic recurrent pericarditis with anakinra. A multicenter randomized controlled clinical trial.** AIR TRIP trial: AnakInRa - Treatment of Recurrent Idiopathic Pericarditis (ClinicalTrials.gov, number NCT02219828;). Study design and rationale

**Background.** Colchicine resistant and corticosteroid dependent patients with recurrent pericarditis are a major management challenge. We aimed to assess the safety and efficacy of anakinra, a recombinant form of the naturally occurring interleukin-1 (IL-1) receptor antagonist, in patients with cortico-dependent recurrent pericarditis and resistant or intolerant to colchicine.

**Study design.** AIR-TRIP trial will enroll at least 20 patients in a prospective, double-blind, randomised controlled withdrawal trial of anakinra compared to placebo in patients with recurrent cortico-dependent and resistant or intolerant to colchicine. The primary efficacy end points are the recurrence rate and time to flare in the double-blind phase after randomization. Secondary end points were responder status and time to response in the open label phase (time frame: 60 days) and percentage off corticosteroids at 6weeks in the initial open label phase.

**Implications.** This trial will provide important evidence regarding the possible benefit of the use of anakinra in the most troublesome complication of pericarditis.

## **Background**

In acute pericarditis, recurrences represent the most troublesome complication and occur in up to 30% of patients (1). In general, the first attacks are the most severe, while subsequent episodes are milder. The number of recurrences and the interval between the episodes vary among patients. The optimal regimen for preventing recurrences has not been clearly established; treatment modalities include non steroidal anti-inflammatory drugs (NSAIDs), corticosteroids (CS), colchicine, immunosuppressive agents, and pericardiectomy (1-4). Although long term prognosis is generally good (1-5), in frequently relapsing cases CS side effects may be relevant and the quality of life severely affected.

We have recently reported a dramatic therapeutic response to interleukin (IL)-1 beta recombinant receptor antagonist (anakinra) in three pediatric patients with CS dependent idiopathic recurrent pericarditis (RP). In all three patients anakinra withdrawal, after the achievement of a complete remission, was followed after a few weeks by a disease recurrence. The reinstatement of anakinra was again associated with an immediate response, and continuous treatment allowed steroid withdrawal and prevented new disease relapses (6).

The dramatic effect of anakinra, together with clinical and laboratory features (serositis, fever, increased C reactive protein - CRP), suggests that RP may represent another autoinflammatory condition in which IL-1 plays a pivotal role (6).

1. Brucato A, Brambilla G, Moreo A, Alberti A, Munforti C, Ghirardello A, et al. Long-term outcomes in difficult-to-treat patients with recurrent pericarditis. *Am J Cardiol* 2006; 98: 267-71
2. Imazio M, Brucato A, Adler Y, Brambilla G, Artom G, Cecchi E, et al Prognosis of idiopathic recurrent pericarditis as determined from previously published reports. *Am J Cardiol* 2007; 100: 1026-8
3. Imazio M, Bobbio M, Cecchi E, Demarie D, Pomari F, Moratti M, et al. Colchicine as first-choice therapy for recurrent pericarditis: results of the CORE (Colchicine for REcurrent pericarditis) trial. *Arch Intern Med* 2005; 165: 1987-91
4. Imazio M, Brucato A, Cemin R, Ferrua S, Belli R, Maestroni S, Trincherò R, Spodick DH, Adler Y; on behalf of the CORP (COLchicine for Recurrent Pericarditis) Investigators. Colchicine for Recurrent Pericarditis (CORP) A Randomized Trial. *Ann Intern Med.* 2011; 155(7): 409-14
5. Imazio M, Spokisck D, Brucato A, Trincherò, Adler Y. Controversial aspects in the management of pericardial diseases. *Circulation* 2010;121(7): 916-28
6. Picco P, Brisca G, Traverso F, Loy A, Gattorno M, Martini A. Successful treatment of idiopathic recurrent pericarditis in children with interleukin-1beta receptor antagonist (anakinra): an unrecognized autoinflammatory disease? *Arthritis Rheum.* 2009; 60: 264-8.

### **Study objectives**

This prospective, randomized, double-blind, placebo-controlled, withdrawal, multicenter trial will evaluate the efficacy and safety of anakinra in the treatment of cortico-dependent recurrent pericarditis resistant or intolerant to colchicine. Anakinra will be considered as a monotherapy or in

adjunct to colchicine, while corticosteroids must be completely withdrawn. The trial design is shown in the attached **Figure 1**.

## **Methods**

### **Study population**

The study population will consist of male and female patients  $\geq 2$  and  $\leq 70$  years old with a diagnosis of idiopathic recurrent pericarditis in continuous treatment with corticosteroids and colchicine-treated. In order to randomize at least 20 patients it is expected to assess for eligibility approximately 24 patients in 3 tertiary hospitals in Italy in a period of 6 months.

### **Inclusion criteria:**

Patients eligible for inclusion in this study have to fulfill all of the following criteria:

1. Patient's written informed consent for  $\geq 18$  years of age before any assessment is performed. Parents' or legal guardian's written informed consent and child's assent, if appropriate, are required before any assessment is performed for patients  $< 18$  years of age.
2. Age  $\geq 2$  years and  $< 70$  years at screening visit;
3. Recurrent pericarditis defined as a first episode of acute pericarditis followed by recurrences (at least two recurrences for this study). First episode of pericarditis is diagnosed when at least two of the following criteria were present: pericarditic typical chest pain (sharp and pleuritic, improved by sitting up and leaning forward), pericardial friction rubs, widespread ST segment elevation or PR depressions not previously reported, and new or worsening pericardial effusion. Recurrence is diagnosed when chest pain recurs and one or more of the following signs is present: fever, pericardial friction rub, ECG changes, echocardiographic evidence of new or worsening pericardial effusion, and elevations in the white blood cell count, erythrocyte sedimentation rate or C-reactive protein. To be enrolled in this study, elevation of C-reactive protein is mandatory both in the first attack and in the following recurrences.
4. Specific etiologies excluded, including tuberculous, neoplastic or purulent etiologies, post-cardiac injury syndromes, systemic diseases including rheumatic autoimmune diseases and autoinflammatory diseases such as familial Mediterranean fever (FMF) and tumour necrosis factor receptor-associated periodic syndrome (TRAPS).

5. Records to document the number of prior pericardial recurrences, the time interval between them as well as prior treatments must be made available from the medical charts.
6. Troponin values during at least one previous attack is recorded.
7. QuantiFERON (QFT-TB G In-Tube) test or positive Purified Protein Derivative (PPD) test has been previously made and recorded.
8. Patients will be enrolled at the time of a recurrent episode (at least the second recurrence, i.e. third episode) or “relapse” of pericarditis documented by the following criteria:
  - recurrent pericardial pain (with a score of least 5 on the 21 circles VAS) AND
  - increase in CRP  $\geq 1$  mg/dL (being normal value = 0 - 0.5 mg/dL ), AND
  - one or more of the following signs: fever ( $\geq 37^{\circ}\text{C}$ ), pericardial friction rub, pertinent ECG changes, echocardiographic evidence of of new or worsening pericardial effusion (see definition above)
9. Continuous treatment with CS, the dose of which must not have been increased in the three days preceding enrolment
10. Women of child bearing potentials (WCBP), defined as pre-menarche females aged 8 years and above or all women physiologically capable of becoming pregnant, sexually active, must use an effective form of contraception.

**Exclusion criteria:**

Patients fulfilling any of the following criteria are not eligible for enrollment in this study:

1. Pregnant or nursing (lactating) women
2. History of being immunocompromised, including a positive HIV at screening (ELISA and Western blot) test result.
3. Positive QuantiFERON (QFT-TB G In-Tube) test or positive Purified Protein Derivative (PPD) test ( $\geq 5$  mm induration) performed after the first attack of pericarditis. Patients with a positive PPD test ( $\geq 5$  mm induration) at screening may be enrolled only if they have either a negative chest X-ray or a negative QuantiFERON test.
4. Live vaccinations within three months prior to the start of the trial, during the trial, and up to three months following the last anakinra dose.
5. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases

6. History of significant other medical conditions, which in the Investigator's opinion would exclude the patient from participating in this trial including current pericarditis due to known diseases (e.g. tuberculosis, neoplastic or purulent causes, connective tissue diseases, acute rheumatic fever, etc.)
7. History of recurrent and/or evidence of active bacterial, fungal, or viral infection(s).
8. History of Type I hypersensitivity to anakinra.
9. History of poor compliance.
10. Use of any investigational drug (or biologic), or device within five half-lives of the drug prior to study entry or during the study.

### **Investigational drug**

Anakinra and placebo will be provided by SOBI (Sweden) as an unrestricted research grant. SOBI will have no role in the planning of the study, analysis of the data, or writing of this manuscript.

### **Study drug administration**

All patients fulfilling study entry criteria receive open-label treatment with anakinra (adults: 100mg/day; children: 2 mg/kg/day up to 100 mg) subcutaneously (s.c.) daily. Treatment with anakinra will be continued until day 60 in responder patients, when responders patients will be randomized in a double blind fashion to continue with anakinra or to be switched to placebo for another 6 months.

### **Co-medications**

Patients may enter study on whatever medications they were using to treat their pericarditis except for other IL-1 blockers.

The dose of corticosteroids must not have been increased in the three days preceding enrolment.

A dose increase of analgesics (paracetamol or tramadol) and NSAIDs (e.g. aspirin, ibuprofen, indomethacin) is allowed to relieve pain prior to anakinra therapy. Co-medication must remain unchanged in responder patients until Day 8.

In responder patients at day 8 all medications other than CS (azathioprine, methotrexate, cyclosporine, cyclophosphamide, hydroxychloroquine, chloroquine, and NSAIDs) will be tapered off and withdrawn within 15 days from response. Colchicine withdrawal is optional.

Corticosteroid therapy will be progressively tapered off and stopped within 6 weeks from response. Suggested prednisone (or equivalent) tapering might be 5 mg every week in adults and by 0.2 mg/kg every week in children.

In case of early trial discontinuation (at Day 3) or in case of important pericarditis worsening (as defined by the attending physician) during the first 8 days, the patient will be discontinued from the trial and receive rescue therapy as per physician decision and will be withdrawn from the study and followed for safety

## **Study design**

The study is a 8-month, multicenter, randomized, double-blind, placebo-controlled, medication - withdrawal study to evaluate the efficacy , tolerability, and safety of anakinra in adults and children with idiopathic recurrent pericarditis (RP). The study is approved by the ethics committees at each participating center. It consists of two parts: Part 1 is an open-label treatment period in which Anakinra is administered daily for 60 days and the response is assessed. Part 2 is a double-blind withdrawal period of other 180 days, in which patients who had a sustained complete response in part 1 are randomly assigned to receive either anakinra or placebo daily for up to 6 months. The end of the study is the end of part 2 or the time of relapse, whichever occurs first. All the patients are then followed for other 4 months, to assess safety (Figure 1).

All patients entering the study or their parents provide written informed consent. Authors wrote the protocol (MI, MG, AB and AM), hold the data, make all the analyses, The study is conducted at 3 centers in Northern Italy: Maria Vittoria Hospital, Torino, Ospedale Papa Giovanni XXIII, Bergamo, and Istituto Gaslini, Genova.

RP patients will be enrolled at the time of a recurrent episode (at least the second recurrence, i.e. third episode) of pericarditis (i.e., relapse) (see inclusion criteria), until a population of at least 20 patients to be randomized at day 60 will be reached. RP patients fulfilling study entry criteria will receive anakinra (100mg/day or 2 mg/kg/day up to 100 mg if children) subcutaneously (s.c.). A clinical, laboratory, ECG and echocardiographic assessment will be performed at study Day 1 (baseline), Day 4 (72h of treatment) and day 8.

On Day 4 patients will be divided in 2 categories. Those with a reduction by  $\geq 30\%$  in baseline pericardial pain on a 21 circle visual analogue scale (VAS), and a  $\geq 30\%$  decrease in CRP levels, and no increase in pericardial effusion at the echocardiography will continue in the study. Patients who will not meet these criteria will be considered “early treatment failures” will receive rescue therapy as per physician decision, and will be withdrawn from the study and followed for safety.

Responder status will be assessed at Day 8 with the following three criteria all to be met (**one secondary outcome**):

1. no or mild pericardial pain (a score  $\leq 2.5$  on a 21 circle VAS), AND
2. normal CRP levels (CRP  $\leq 0.5$  mg/dL), AND
3. absent or mild ( $\leq 10$  mm) echocardiographic effusion.

“Non-responders” at Day 4 (early treatment discontinuation) or at Day 8 will perform the end of study assessments and will be followed for safety up to 3 months.

At Day 8, “responders” will withdraw NSAIDs as well as any other concurrent medication within two weeks. Corticosteroid (CS) therapy will be progressively tapered off and stopped within 6 weeks (see *Comedications* for tapering criteria). Colchicine withdrawal is optional.

Treatment with anakinra will be continued until day 60 when 20 patients will be randomized in a double blind fashion to continue with anakinra (10) or to be switched to placebo (10) for another 6 months.

Patients will perform clinical and laboratory evaluation at Months 1, 2, 4, 6, and 8 or at relapse whichever occur first.

In case of relapse, as defined below, during the first two months of open label therapy the patient will be considered a failure. If a relapse occurs during the withdrawal phase blinding of that patient will be broken and patients who received placebo will be treated with anakinra while patients receiving anakinra will be treated as per physician decision and considered late treatment failures. Analgesic drugs and NSAIDs as symptomatic medication will be allowed to relief pain in case a few days elapse between the onset of pain and the administration of anakinra.

### **Objectives:**

#### **Primary objective:**

To assess the efficacy and initial safety profile of anakinra in RP patients with a recurrent episode of pericarditis.

#### **Secondary objectives:**

1. To assess CS and concurrent medication sparing effects of anakinra over 8 months

### **End points.**

#### **Primary end points, in the double-blind withdrawal phase (Part 2);**

1. recurrence rate at 8 months,

2. time to flare after randomization.

### **Secondary end points , in the Open-Label Phase (Part 1)**

1. responder status and time to response in the open label phase (time frame: 60 days)
2. percentage off corticosteroids at 6weeks.

To assess the responder status in the open label phase at Day 8 and 60 the following three criteria all have to be met: no or mild pericardial pain (a score  $\leq 2.5$  on a 21 circle VAS), and normal CRP levels (CRP  $\leq 0.5$  mg/dL), and absent or mild ( $\leq 10$  mm) echocardiographic effusion.

The following items will be also assessed:

1. the change over time of the 3 outcome criteria, i.e. pericardial pain, CRP levels, and echocardiographic effusion;
2. the change over time in patient's/parent's global assessment of overall well being on a 21 circle VAS;
3. the change over time in the global evaluation of disease activity by physicians on a 21 circle VAS;
4. the tolerability and safety of the treatment, i.e. monitoring and recording all adverse events (AEs), with attention to local tolerability to s.c. injection, and serious adverse events (SAEs), and the regularly scheduled monitoring of hematology, blood chemistry, physical examinations, and vital signs including blood pressure over 8 months.

Assessments will be performed at Days 4, and 8 (study Period 1), and then at Day 30, and Months 2, 4, 6, and 8 or at recurrence, if not otherwise specified.

## **VISIT SCHEDULE WITH ASSOCIATED ENDPOINTS (see Appendix 1 - CRF protocol)**

- **Day 1:** complete collection of clinical data in a pre-definite format, including: sex, present age, age at first attack, etiology of pericarditis (only idiopathic pericarditis is included in this study), number of previous attacks, including the first, duration of the attacks, N. of recurrence per year in the previous year, previous therapies, current therapy.

Pericardial pain and global assessment of overall well-being on a 21 circle visual analogue scale.

Blood pressure, heart rate, presence/absence of pericardial rubs, physical examination.

ECG assessment, Echocardiographic assessment (effusion size determined measuring the greatest echo-free space in telediastole); CRP levels. Complete blood cell count, AST, ALT, creatinine.

- **Day 4 (72h) (=), Day 8:**

Pericardial pain and global assessment of overall well-being on a 21 circle visual analogue scale.

Blood pressure, heart rate, presence/absence of pericardial rubs, physical examination.

ECG assessment, Echocardiographic assessment (effusion size determined measuring the greatest echo-free space in telediastole); CRP levels. Complete blood cell count, AST, ALT, creatinine.

- **FOLLOW UP VISITS AT 1, 2, 4, 6, 8 and 12 MONTHS:** physical examination, ECG, Echocardiogram, CRP and Complete blood cell count, AST, ALT, creatinine.

- **UNSCHEDULED VISITS, in case of pericarditis RECURRENCES/RELAPSE**

- **UNSCHEDULED VISITS in case of SERIOUS ADVERSE EVENTS (SAEs).**

### **Data Analysis and Statistics**

**Sample size:** we estimate that 10 patient per arm will be enough to detect a difference in recurrence rate from 80% in the placebo arm to 10% in anakinra patients with a power of 90% at a confidence level of 95%.

### **Statistical analysis:**

A 2-sided logrank test will be used to compare the time to flare from randomization to month 8 in the two treatment arm.

The primary analysis will be based on the intention to-treat analysis in double-blind withdrawal phase (Part 2).

### **Data management**

Data will be collected using case report forms (see attachment), and the study database. Data will be managed blinded to treatment assignments.

## DEFINITIONS AND ASSESSMENT SCALES

### PERICARDIAL EFFUSION SIZE: MILD/MODERATE/SEVERE

The size of the effusion can be determined measuring the sum of the greatest echo-free space in telediastole (usually in the parasternal long axis-view for circumferential effusions but also in several off-axis views especially for loculated effusions). Pericardial effusion is classified as small (<10 mm usually only posterior), moderate (10-20 mm, usually circumferential), and large (>20 mm). This simple classification of the size of the effusion is clinically significant because it can be easily accomplished also with a little confidence with echocardiography, and has been used in several studies on pericardial diseases.

1. Weitzman LB, Tinker WP, Kronzon I, Cohen ML, Glassman E, Spencer FC. The incidence and natural history of pericardial effusion after cardiac surgery : an echocardiography study. *Circulation* 1984;69:506-11.
2. Imazio M, Brucato A, Trincherò R, Adler Y. [Diagnosis and management of pericardial diseases](#). *Nat Rev Cardiol*. 2009;6:743-51.
3. Imazio M. Asymptomatic post-operative pericardial effusions: Against the routine use of anti-inflammatory therapy. *Ann Intern Med* 2010; 152: 186-7.

### PAIN IN PERICARDITIS

Pain is the main symptoms in pericarditis, often excruciating and resistant to therapies in the acute phase. With the resolution of the acute attack pain sharply declines, but a small proportion of patients (approximately 20%) will continue to report a mild pain. This phenomenon has been described in the literature (Imazio et al, Recurrent pain without objective evidence of disease in patients with previous idiopathic or viral acute pericarditis. *Am J Cardiol* 2004;94:973-975). For this reason the goal of the therapy cannot be the complete absence of pain, and the persistence of a mild pain is accepted even in case of complete response. For this reason CRP elevation was mandatory to be included in AIR-TRIP study.

### ECG CHANGES

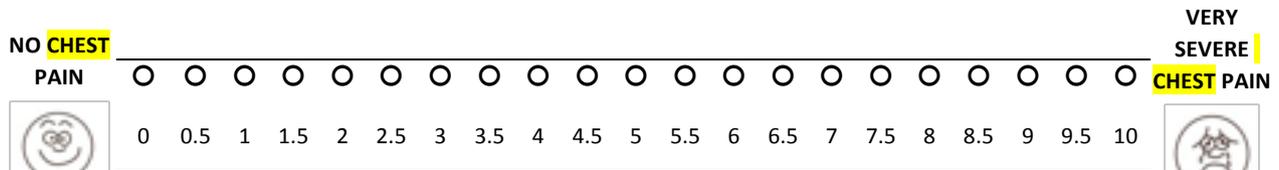
The 12-lead electrocardiogram in patients with acute pericarditis classically shows widespread upward concave ST-segment elevation and PR-segment depression (*N Engl J Med* 351;21;2195-2202). The electrocardiographic abnormalities may evolve through four phases: diffuse ST-segment elevation and PR-segment depression (stage I); normalization of the ST and PR segments (stage II);

widespread T-wave inversions (stage III); and normalization of the T waves (stage IV). Typical ECG changes are recorded in 50-80% of cases (submitted).



## PATIENTS RATING OF THE INTENSITY OF CHEST PAIN

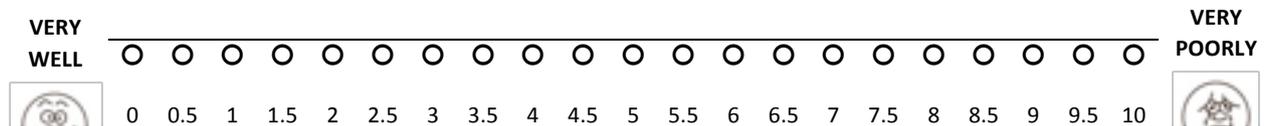
How much **CHEST** pain do you think you had because of your illness **IN THE PAST WEEK**?



Please fill a circle below to indicate how severe your pain has been:

## PATIENTS RATING OF THE OVERALL WELL-BEING

Considering all the ways in which the illness affects yourself **AT THIS TIME**, please indicate



below how you are doing by filling a circle:

Filocamo G, Davi S, Pistorio A, Bertamino M, Ruperto N, Lattanzi B, Consolaro A, Magni-Manzoni S, Galasso R, Varnier GC, Martini A, Ravelli A. Evaluation of 21-numbered circle and 10-centimeter horizontal line visual analog scales for physician and parent subjective ratings in juvenile idiopathic arthritis. *J Rheumatol* 2010;37:1534-41