

## **A Pilot Study in the Treatment of ECD**

A pilot study in the treatment of Erdheim-Chester Disease is being conducted by Dr. Augusto Vaglio of Parma, Italy. He is studying the use of sirolimus (a drug most often used by transplant patients as an anti-rejection medicine) and prednisone. Dr. Vaglio has shared the study writeup and protocol with the ECD Global Alliance as found on the following pages.

If anyone is interested in knowing more about this study/protocol they are encouraged to have their doctor call Dr. Vaglio directly. His contact information is as follows:

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The following pages contain the details pertaining to the study as provided by Dr. Vaglio. This information is not necessarily meant for a lay person, but is provided here in hopes it will promote information sharing among the community of knowledgeable physicians and provide guidance to those searching for additional treatment options.

## SIROLIMUS PLUS PREDNISONE FOR ERDHEIM-CHESTER DISEASE. A PILOT STUDY

### Background Information:

Erdheim-Chester disease (ECD) is an extremely rare form of non-Langerhans cell histiocytosis which typically affects the connective and adipose tissue. ECD can arise at any age. It clinically presents with a broad range of manifestations, ranging from a focal isolated to a diffuse infiltrative disease, which often affects multiple organ systems and has a high mortality rate<sup>1</sup>.

A number of clinical and histological findings characterise ECD: the typical finding is the involvement of long bones, especially of the lower limbs, with the development of osteosclerosis. Osteosclerotic areas can be detected by simple radiograms, but whole-body bone scintigraphy with Tc-99m is probably the most useful imaging technique since it can show a diffuse hyperaccumulation of Tc-99m in the long bones<sup>1</sup>.

The most common extra-skeletal manifestations are found at different sites, including the CNS, the retroperitoneum, the retro-orbital tissue, the heart, the lungs, the liver and the skin<sup>1</sup>.

Diabetes insipidus, due to direct involvement of the hypothalamic-pituitary axis is the most common CNS manifestation. Retro-orbital tissue involvement usually causes exophthalmos. Lung manifestations include interstitial fibrosis and pleural thickening<sup>2</sup>. Heart failure and pericardial effusion with tamponade may also occur. Retroperitoneal infiltration usually involves the soft tissues surrounding the abdominal aorta, the iliac arteries and the kidneys; peri-renal involvement usually distinguishes ECD from idiopathic retroperitoneal fibrosis, which characteristically affects the peri-aortoiliac space only<sup>3</sup>. In some cases, peri-aortic infiltration may also extend to involve the thoracic aorta, with a clinical picture which is referred to as "coated aorta".

On histology, ECD is characterized by the presence of "foamy" histiocytes, which stain positive for CD68 but negative for CD1a and S100; on ultrastructural examination, these cells do not show Birbeck granules<sup>2</sup>. These aspects help differentiate ECD from classical Langerhans cell histiocytoses, which show S100<sup>+</sup> CD1a<sup>+</sup> cells with Birbeck granules in more than 20% of the cases. Additionally, in ECD biopsies the histiocytic infiltrate usually coexist with a chronic inflammatory infiltrate composed of plasma cells and lymphocytes<sup>1,2</sup>.

The etio-pathogenesis of ECD is still poorly understood. A recent study showed an intense expression of different chemokine- and chemokine receptor pairs in the diseased tissues, thus leading to the hypothesis that ECD is mainly driven by an inflammatory process rather than by a primitive proliferative disorder<sup>4</sup>. On the other hand, there is no clear evidence concerning the mono-, oligo- or polyclonal origin of the infiltrating cells<sup>5</sup>.

The treatment of ECD is still empirical, and no standardized approaches exist. The outcome of patients with systemic manifestations is definitely poor, and the reported mortality rates at 3 years approach 60%; the deaths are mainly due to cardio-pulmonary causes<sup>1</sup>.

Corticosteroids, alone or combined with alkylating agents such as cyclophosphamide are often used. They seem to be effective in patients with exophthalmos, renal and bone manifestations. Other cytotoxic drugs such as vinblastin, vincristin, adriamycin, and etoposide have been used in different combinations but often with poor results, and it is reported that a number of deaths in ECD patients treated with such approaches were probably treatment-related<sup>7-9</sup>. A recent study reported on the use of interferon- $\alpha$  in a series of eight ECD patients: during therapy some ECD manifestations (e.g. exophthalmos, xantelasma) disappeared but the patients with CNS and cardiovascular involvement failed to respond, and the mortality rate was 25% over the study period (median follow-up, 23 months)<sup>10</sup>.

In conclusion, no standard treatment has been established for ECD: it seems suitable that agents other than alkylating or chemotherapy drugs can be used in combination with steroids; given the chronic clinical course of ECD, they need to be well-tolerated and suitable for a long-term treatment, and they should allow steroid tapering.

### Scientific/Medical Rationale and Objective:

Rapamycin (sirolimus) is a lipophylic macrolide isolated from a strain of *Streptomyces hygroscopicus*. The intracellular receptor of rapamycin is a small molecule of 12 kd named FK506-binding protein; the rapamycin-FK506-binding protein interacts with the target molecule mTOR (mammalian target of rapamycin), and thus inhibits several processes such as cell proliferation, particularly in cells activated by mitogenic stimuli (eg, IL-2). The inhibition of mTOR activity is able to inhibit the rejection of a transplanted organ by impairing lymphocyte proliferation induced by IL-2. However, rapamycin also has anti-neoplastic effects, the underlying mechanism of action being similar to that leading to its immunosuppressive properties<sup>11</sup>. In vivo studies have shown that rapamycin may inhibit the growth of colon adenocarcinoma<sup>12</sup>. Clinical studies have also demonstrated that renal transplant patients who develop Kaposi sarcoma show regression of skin lesion after switching from cyclosporin to rapamycin<sup>11</sup>.

In addition to the oncologic and transplant fields, rapamycin has also been successfully used in autoimmune diseases such as systemic lupus erythematosus, particularly for patients refractory to conventional therapies<sup>13</sup>.

The immunosuppressive and anti-proliferative properties of sirolimus make it a potentially effective agent in the treatment of ECD, a disease characterized by an intense inflammatory component which usually coexists with an infiltrating oligo- or monoclonal histiocytic population.

Our group has described the case of an ECD patient who was refractory to different combination therapies (steroids plus tamoxifen, steroids plus cyclophosphamide) and responded well to the association of steroids and sirolimus: the patient had a diffuse bone and retroperitoneal involvement, and has now concluded the third year of treatment with sirolimus and prednisone. The disease is still in remission. The association with sirolimus allowed tapering of prednisone, which is now being continued at a very low-dose (2.5 mg/day). This case has been reported in abstract form<sup>14</sup>.

Another patient, who was diagnosed with ECD with systemic involvement (cardiac, retroperitoneal, bone, aortic) at our centre, is now receiving prednisone and sirolimus and, after treatment was started, no disease progression has been observed. He has now ended the seventh month of treatment.

### References

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**Study Design**

This is an open-label, prospective, non-randomised multicentre trial that aims at investigating the effectiveness and safety of the combination sirolimus plus prednisone in the treatment of ECD. This is a pilot study on a relatively small series of consecutive ECD patients.

Prednisone and sirolimus will be started simultaneously. The prednisone dose will be 0.75 mg/kg/day (single daily dose) for the 1<sup>st</sup> month, 0.50 mg/kg/day for the 2<sup>nd</sup> month, 0.25 mg/kg/day for the 3<sup>rd</sup> and 4<sup>th</sup> months, 0.125 mg/kg/day for the 5<sup>th</sup> and 6<sup>th</sup> months. After the end of the 6<sup>th</sup> month, prednisone will be tapered to a maintenance dose of 5-2.5 mg/day.

Sirolimus will be administered at a dose of 2 to 3 mg/day (single daily dose), in order to achieve trough levels ranging from 8 to 12 ng/mL. The dose of sirolimus will be kept stable throughout the study period.

Additional drugs such as proton-pump inhibitors, calcium, vitamin D, bisphosphonates or statins may be added to the treatment regimen to prevent or minimize the side-effects (e.g. osteoporosis, hypercholesterolemia) induced by prednisone and sirolimus.

The overall duration of treatment will be 24 months. After the end of this period, the investigators will decide whether to continue or withdraw treatment on the basis of the clinical status of the disease and/or the treatment-related side-effects experienced by the patients. For instance, if a patient experiences a stable disease remission (eg, lasting > 12 months), the investigator(s) will suggest treatment withdrawal. Conversely, if the patient has reached remission within the last 12 months, treatment will be continued for an additional 6-12 months. In summary, the aim of treatment will be to induce a stable clinical remission. In case of a disease flare during treatment (after remission has been induced), the doses of the immunosuppressive drugs will be increased (keeping of sirolimus trough levels within the range will be mandatory though). In case of disease relapse after treatment has been stopped, sirolimus and prednisone will be resumed (if they proved to be effective in the initial treatment course).

**Subject Population to be Included:**

The study will include only patients with a clinical or biopsy-proven diagnosis of ECD. The diagnosis of ECD must fulfill the criteria reported by Veyssier-Belot et al. (*Medicine (Baltimore)* 1996; 75:157-169).

Newly diagnosed, untreated patients and patients who experience progressive disease (both treated with other regimens and not undergoing treatment) will be enrolled.

**Number of Subjects:**

The study aims to enrol a minimum of 8 subjects. The results of this pilot investigation can be submitted for publication in a peer-reviewed journal only after having studied a 8-subject sample.

If this study yields positive results, a pilot multicentre randomised trial will be designed, with the aim of comparing the efficacy and safety of sirolimus plus prednisone vs interferon- $\alpha$  alone in ECD patients.

**Primary and Secondary Efficacy Endpoints:**

The study will aim to assess whether (and if yes, to what extent) the combination of sirolimus and prednisone may prolong progression-free survival.

Secondary end-points will include the induction of disease remission at the different diseased sites: because it is known that some of the ECD manifestations are usually more resistant to therapy than others, the rate of remission will be considered per affected organ or system.

There are no established criteria to define "remission" of ECD lesions.

The disease status will be primarily defined on clinical grounds (patients' symptoms and signs). Measurable lesions will be assessed as follows: we establish that any modification in size of the ECD lesions that is  $\pm 10\%$ , as assessed clinically (eg, in the case of skin lesions) or radiologically (eg, CT scan for retroperitoneal fibrosis), will be defined as *stable disease*; modifications in size exceeding 10% will be defined as progression or *partial remission*. The complete disappearance of the lesions will be defined as *complete remission*.

Other laboratory tests will help to define the disease status: for instance, normalisation of the acute-phase reactants ESR (erythrocyte sedimentation rate) and CRP (C-reactive protein)- if high at diagnosis- could support the concept of disease remission.

Remission will be defined as disappearance (complete remission) or reduction of ECD lesions, as assessed by means of appropriate imaging or laboratory techniques (eg, CT scan evaluation for lung or retroperitoneal disease, bone scintigraphy or X-rays for skeletal lesions, C-reactive protein levels to assess global disease activity).

**Inclusion Criteria:**

- Clinical or biopsy-proven diagnosis of ECD

- Written informed consent
- Age: 18-75 years
- Newly diagnosed or active progressive disease

## 12. Exclusion Criteria:

- Concurrent neoplasms or serious active infections
- Hypersensitivity to the study drugs
- GFR < 40 mL/min; WBC count < 4000/uL; proteinuria > 1g/24h; serum cholesterol >300 mg/dL and triglycerides > 350 mg/dL
- Patients experiencing stable disease remission
- Pregnant women
- Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (e.g., infectious disease) illness must not be enrolled into this study.
- Subjects participating concurrently in another clinical trial

## Study Procedures:

The enrolled patients will undergo the following clinical, laboratory and imaging examinations:

- *Routine clinic visits*: outpatient visits will be programmed at 2 and 4 weeks, and then every month for the first year of therapy; during the second year, the patients will be seen bimonthly. During every visit the patients' vital parameters will be recorded, then the patients will undergo physical examination and they will be monitored for any treatment-related side effects or signs/symptoms related to disease remission/progression.
- *Laboratory examinations*: during each visit, the patients will also undergo routine lab tests, including sedimentation rate, serum C-reactive protein levels, IL-6 levels, alkaline phosphatase, creatinine, BUN, cholesterol, tryglycerides, fasting glucose, and urinalysis)
- *Imaging studies*: the diseased sites (e.g. lungs, retroperitoneum) will be re-evaluated by means of appropriate imaging studies; CT or MRI scans will be performed at months 4, 8, 12, 18, and 24. Whole-body PET-CT scan will be performed at 12 and 24 months. Additional imaging or biopsy studies will be performed as appropriate.

The study will be coordinated by Prof Carlo Buzio and Dr. Augusto Vaglio at the Dept. of Clinical Medicine, Nephrology and Health Science of Parma University, Italy.

The list of the participating centres includes:

- Rheumatology Service, Arcispedale S. Maria Nuova, Reggio Emilia, Italy (Dr. Carlo Salvarani, [salvarani.carlo@asmn.re.it](mailto:salvarani.carlo@asmn.re.it))
- Nephrology Division, Policlinico Hospital, Milano, Italy (Dr. Gabriella Moroni, [gmoroni@policlinico.mi.it](mailto:gmoroni@policlinico.mi.it))
- Nephrology Division, Arcispedale S. Maria Nuova, Reggio Emilia, Italy (Dr. Lucio Manenti, [lucio.manenti@asmn.re.it](mailto:lucio.manenti@asmn.re.it))

The patients' data will be collected in an appropriate database. The investigators will have a meeting every six months to discuss the problems regarding the ongoing trial.

Additional centres will be included if they are willing to participate, in order to increase the recruiting potential of this study. The inclusion of any new centre in the list of the participating centres will be subject to approval of the study protocol by the local Ethics Committee.

## Safety Endpoints:

All the potentially treatment-related side effects will be investigated at each visit during the follow-up, as reported in the previous paragraph, and they will be recorded in the patients' appropriate safety data set.

Considering the most common sirolimus-related side effects, particular care will be taken in monitoring peripheral blood cell counts, serum levels of cholesterol and tryglycerides, urinalysis including proteinuria, and any laboratory or clinical signs suggestive of opportunistic infections.

Pleural, pericardial or peritoneal effusions will be monitored as potentially sirolimus-related side effects.

All recorded adverse events will be listed in the safety data set, including any physical examination findings, ECG results, chest X-ray results.

Adverse events will be described as mild, moderate, severe or very severe. Severity and relationship of an adverse event to study drug(s) will be determined by the Investigator.

**Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Approval:**

This trial has already been approved by the Ethics Committee of the University Hospital of Parma.

The patients will get the study drugs from their pharmacies and a total reimbursement will be provided by the Italian National Health System since they suffer from a disease included in the group of Rare Disease, according to ongoing Italian regulations.

**Informed Consent/Privacy Authorization:**

The protocol approved by the Ethics Committee also included an Informed Consent to the Patient, an informative Letter to the Patient and a Letter to the Family Doctor. All of these forms have been written in Italian language and are included with the relevant documentation approved by the Ethics Committee on 13 November, 2007.