

ECD Global Alliance Synopsis of 2013 Erdheim-Chester Medical Symposium (October 31, 2013)

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On October 31st 2013, the first ever Erdheim-Chester Disease Global Alliance Medical Symposium was hosted by the ECD Global Alliance at the Marriott Marquis and Marina in San Diego, California. The symposium provided an opportunity for leading specialists in the field to come together and discuss for the first time their most recent data relating to diagnosis, treatment and prognosis of ECD. Following the success of the event, an official medical review discussing in detail the current status of ECD will be published at a later date by the principal investigators who attended. However, in the meantime, we have put together a summary of what was discussed by each speaker on the day, for those who were unable to attend.

Dr. Julien Haroche from Hôpital Pitié-Salpêtrière, Paris, France, spoke about the history and current state of ECD knowledge. He said that there have been around 500 cases reported since 1930. It is a disease resulting from tissue infiltration by foamy histiocytes. Bone involvement occurs in 96% of cases and 50% have tissue involvement around the kidneys (forming the so-called hairy kidney on radiographic imaging.) A biopsy is needed to prove ECD and this biopsy is CD68+, CD1a- and S100-. The presence/absence of these markers provides the main disease characteristics. Bone pain is seen in 50% of patients and 15-25% have central nervous system (CNS) involvement. Cardiac manifestations include peri-aortitis (the so called “coated aorta”, involving the thoracic and/or abdominal aorta) and infiltration of the right atrium. Some treatments for ECD include interferon alpha

(IFN α), which is considered at the moment the initial therapy for the disease, various chemotherapies such as cladribine, tyrosine kinase inhibitors such as Imatinib, and drugs that target cytokines such as *Infliximab* and *Anakinra* (for mild forms of ECD, not for CNS effects), and in rare cases, double autologous hematopoietic stem cell transplantation (patients have relapsed 10 years later). Dr. Haroche also spoke about the cytokine profile in ECD patients. This generally shows an increase in IL-12, IFN- α , MCP-1 and a decrease in IL-4 and IL-7, thereby suggesting a skewing of T-helper cell direction towards Th1 over Th2 cells.

Dr. Ken McClain from Baylor College of Medicine, Texas, said that the classification of LCH and ECD as a cancer-like disease or as a disease of immune dysregulation remains unclear. They have shown that 63% of Langerhans cell histiocytosis (LCH) patients have the BRAF-V600E mutation. However, they have not yet seen any significant correlation between those patients with or without the mutation and the ultimate outcome of the disease. LCH is an inflammatory myeloid neoplasm, and BRAF-positive cases may benefit of treatments with BRAF-inhibitors. Apparently, patients who have the BRAF mutation maintain it over time, i.e. patients don't lose the mutation and become wildtype. He also mentioned that they have been able to find BRAF mutation in CD34+ hematopoietic stem cells which may indicate that a mutated hemopoietic precursor might be the origin of the disease. They speculate that ECD may follow a similar model. The BRAF-V600E may be useful as a diagnostic tool.

Dr. Maria Ferrarini from the San Raffaele Scientific Institute Milan, Italy, said that ECD histiocytes do not express proliferation markers, but do express cytokines and chemokines. Cytokines are proteins that act as regulators of inflammation or signaling molecules. Chemokines are a family of proteins involved in the recruitment of inflammatory cells to the lesion site. She mentioned how the cytokine/chemokine profile may lead to histiocyte activation. They also saw that the presence of a of specific chemokines and cytokines, including tumor necrosis factor alpha, in pericardial fluid of ECD patients, is able to affect endothelial function, by

promoting lymphomonocyte chemotaxis and endothelial permeability, indicating that factors released by ECD histiocytes are pathogenetic.. They are currently working on assessing the effects of different drugs, including cytokine- and BRAF-inhibitors, that might be used for the disease in an in vitro bio-reactor model. This model can be further exploited to predict the impact of selected drugs in a given patient.

David Bell PhD, from Therapure Biopharma in Canada spoke about a new therapeutic approach of targeting drug delivery, possibly for ECD patients. Histiocytes express CD163 on their cell surface (this is the hemoglobin-haptoglobin receptor) which allows for the possibility to target CD163 cells to treat ECD. CD163 is also expressed on macrophages and by targeting these macrophages; they may be able to switch them to an M2 phenotype, providing a greater opportunity for immunomodulation. This means of drug delivery may also reduce systemic toxicity, due to the targeted, highly concentrated delivery.

Dr. Giulio Cavalli also from the San Raffaele Scientific Institute Milan, Italy, spoke about the presentations and manifestations of ECD. They performed a literature review of every published case of ECD and summarized the findings. 71% of ECD patients are between the ages of 40-70 years and the median age is 53. The most common symptoms are bone pain, diabetes insipidus (excessive thirst and excretion of large amounts of severely diluted urine due to loss of anti-diuretic hormone), neurological and/or constitutional symptoms (meaning non-specific general symptoms, including fever, weight loss, fatigue). If a patient doesn't have diabetes insipidus or constitutional symptoms then usually these will not develop later on. Patients under 40 more often endure pulmonary, cardiac or retroperitoneal involvement. Middle age patients have more frequent pulmonary, cardiac and retroperitoneal involvement. Elderly patients usually show more cardiac manifestations. In their retrospective review, bone pain was the most common symptom observed. Neurological symptoms included exophthalmos (bulging of the eye out of the orbit), visual disturbances, ataxia (lack of voluntary

coordination of muscle movements), radiculopathy (pain, numbness and tingling due to nerve compression), seizures, and dysarthria (difficulty speaking). Diabetes insipidus and retroperitoneal involvement were also seen. Additionally, kidney failure was observed and kidney symptoms included hydronephrosis (water inside the kidney), nephron-vascular hypertension (stenosis of the renal artery causing hypertension) and back pain. Pulmonary symptoms were seen in 12% of cases and symptoms included dyspnea (shortness of breath) and cough. Cardiovascular symptoms included pericardial effusions (fluid around the heart), coated aorta, infiltration of the right atrium, and diastolic heart failure (decline in the performance of the ventricles of the heart).

Dr. Augusto Vaglio from University Hospital of Parma, Italy, spoke about the cardiovascular involvement in ECD. Pericardial thickening and effusions leading to tamponade (build-up of fluid up in the pericardial space, which prevents the heart from pumping effectively), coronary artery disease which could lead to a heart attack, right atrial masses, valvular heart disease and periaortic fibrosis have been observed. 6 patients were studied and 4 patients showed cardiovascular symptoms on a cardiac MRI – results indicated the presence of pseudo masses in the right atrium. It is recommended that those with ECD have a systematic cardiac and aortic evaluation as cardiovascular involvement leads to a worse prognosis.

Dr. Filip Janku from the University of Texas spoke about the outcomes of patients with ECD at MD Anderson. He said that the previous reports suggesting that more than half of those with ECD die in 3 years is not true. 5 year survival has been shown to be 80% by more recent observations. Following their 16 patient study; 81% showed bone involvement, 69% had pulmonary involvement, 69% cardiac involvement, 56% CNS symptoms, 56% renal involvement and 13% showed signs skin involvement. Diabetes insipidus was seen in 56% of patients. Dr. Janku discussed their therapeutic experience with *Imatinib*, a tyrosine kinase inhibitor. However, he also emphasized the importance of identifying the full patient molecular profile, before moving forward to gene therapy.

Dr. Julien Haroche from Hôpital Pitié-Salpêtrière, Paris, France, gave a second talk on his study of 96 patients from 1992 to 2013. He showed that 39% of his patients had bone involvement, 29% had diabetes insipidus, 33% showed pulmonary involvement and he also mentioned that effects to the dentate nuclei in the cerebellum were the most problematic aspect of CNS involvement. It was therefore recommended that patients also have an MRI of the brain with specific studies on the cerebellum. Dr. Haroche also mentioned the importance of renovascular hypertension and that this should be systemically looked for. The overall prognosis of ECD depends on the CNS involvement. First line treatment is IFN α which is associated with improved survival. Pegylated-IFN α can be used but there are dose equivalence problems - 105 patients so far have been treated with 87 patients treated with IFN α . It was mentioned that *Anakinra* improves systemic effects and helps in mild cases of ECD, but there have been no proven effects on CNS or cardiovascular involvement. Also the therapeutic effects of infliximab are variable among different patients. *Cladribine* may be another option option for LCH. 51% of patients had a BRAF mutation. Apparently there are no significant difference in disease outcome between wildtypes and those with the mutation. There appears to be a link between the BRAF mutation and those patients with diabetes insipidus. 7 patients that could not tolerate IFN α were treated with the BRAF inhibitor, *Vemurafenib*, with sustained and positive results.

Dr. Laurent Arnaud from Hôpital Pitié-Salpêtrière, Paris, France, spoke about an analysis done in 66 patients with ECD. Gene expression analysis showed 265 significantly up or downregulated transcripts between patients and the controls. 163 patients had increased and 23 had decreased mRNA expression. Some of the molecules and pathways already identified which are involved in ECD include, adhesion molecules, Matrix metalloproteinases, genes of the BCL-2 family members the TP53 apoptotic pathway and the BRAF/Erk pathway. These results reveal the identification of complex gene expression patterns which is a significant advance in this rare disease.

Dr. Juvianee Estrada-Veras from the NIH (National Institutes of Health), Bethesda, Maryland, spoke about the current ECD Natural History Study at the NIH. The first patient was seen in October of 2011 and the last was this past June of 2013. Patients come for a week. 32 patients have been seen and evaluated. During this time cells, urine, plasma and DNA are obtained. Clinical manifestations are studied and imaging studies such as CT scans, MRI's, advanced cardiac MRI's and PET scans are done. Patients see specialists in different departments such as neurology, cardiology, rehabilitation, ophthalmology and nutrition; however, the NIH cannot treat ECD. Many patients display low vitamin B12 levels (400pg/ml is the recommended level) and vitamin E may also be involved in the neurological manifestations. At the end of the week the patient receives a copy of all test results with recommendations. It is a great experience and patients report it helps them at the same time the knowledge can be used to help others. The NIH pays for most of the travel costs as well as the stay there. Research from the NIH has also shown that stimulated macrophages isolated from patients secrete IL-2, IL-10 and IL-13 and diffusion tensor imaging (DTI) is also currently being evaluated.

Dr. Lorenzo Dagna from the San Raffaele Scientific Institute Milan, Italy, spoke about the recent advances in ECD. It has been shown that ECD occurs as a result of a full blown chronic inflammatory reaction and the BRAF-V600E mutation in histiocytes is implicated. Dr. Dagna spoke about the current cytokine blockers being used, e.g. *Anakinra* (IL-1 receptor blocker) and *Infliximab* (TNF α inhibitor). He also showed some preliminary results of an ongoing trial using *Tocilizumab*, which blocks the soluble receptor of IL-6. Results to date show a decrease in CRP levels as well as a decrease in FDG intake. Tocilizumab was effective on the different localizations of the disease, but there were poor effects on CNS localization. He also presented recent data from his group using ultra-sensitive methods for detecting BRAF mutation, which showed that the BRAFV600E mutation was present in all the ECD patients studied (18 out of 18), both in the biopsies and the blood cells. He suggested that BRAF-negative patients may prove positive for the mutation if

studied with adequately sensitive methods. It was also shown that the MAP Kinase pathway is activated in peripheral blood monocytes and the Ras/Raf/MEK/Erk pathway is also activated in ECD patients.

Dr. Juvianee Estrada-Veras from the NIH, Bethesda, Maryland, spoke about the role of rehabilitation medicine in those with ECD. Patients display general symptoms of weakness, weight loss, fatigue and pain. 96% have skeletal involvement and 50% have bone pain. Early initiation of rehab services is needed.

Dr. Augusto Vaglio from University Hospital of Parma, Italy, presented results of an ongoing trial in Italy where 9 patients are receiving *Sirolimus* and *Prednisone* for ECD. *Sirolimus* is an mTOR inhibitor and an immunosuppressive drug with anti-proliferative anti-neoplastic properties. Patients were given *Sirolimus* at a dose of 2-3mg/day with a target trough level of 8-10 nm/ml. The mean follow-up was 41 months. 7 patients experienced inactive disease, 1 died from CNS involvement and 1 died from a small cell lung cancer. It is a potential treatment for patients with multisystemic ECD. It induces stabilization and is pretty well tolerated. Side effects include edema, high blood pressure and Cushing's syndrome related symptoms from steroid use. Also seen was high cholesterol, increased blood sugars, leg edema and the drug is not recommended for those with effusions. Steroids are not needed in combination with *Sirolimus*.

Dr. Julien Haroche from Hôpital Pitié-Salpêtrière, Paris, France, spoke about the use of *Vemurafenib* in ECD. IFN α is the first line of treatment and is effective in 70% of cases. Half of patients are found to have the BRAF mutation. *Vemurafenib* is a BRAF inhibitor shown to improve those with metastatic melanoma and hairy cell leukemia. 9 patients were given *Vemurafenib* after failure of first line drug. The initial dose given is 960mg twice per day (4 tablets twice/day), however, this was always tapered to 2 tablets twice a day due to side effects. It seems to be effective in those with cardiac and CNS involvements. Side effects include keratosis, photosensitivity, hair loss and body aches. Also, 1 patient did develop squamous cell

carcinoma and treatment was discontinued – this is something that needs to be monitored carefully in the future. New BRAF inhibitors are becoming available, e.g. *Dabrafenib* as well as combined inhibitors, e.g. *Trametinib*. Their use will need to be monitored in the future. The next vital step in this trial is to identify the long-term effects of *Vemurafenib*, i.e. what happens when a patient is taken off the treatment – do the symptoms return? How long should a patient be treated with *Vemurafenib*? And should those who don't have the BRAF mutation also be treated? These are all still open questions. A collaborative “Long-term Outcome after *Vemurafenib* in ECD” (LOVE) Study was proposed as a method to answer these questions.

There was a panel discussion on developing centers of excellence, so that those with ECD will have the opportunity to go and see specialists. They discussed what can be done in the future to help doctors caring for those diagnosed with ECD. It is hoped to have more discussions on this in the future.

There was also a panel discussion based on the most effective treatment protocol at present. It is felt that IFN α treatment is associated to improved survival. It appears that most ECD-investigators believe that those with cardiac and CNS symptoms should try IFN α first. If there is no improvement, or if it is not well tolerated, switching to another treatment is warranted. *Vemurafenib* (provided the BRAF mutation is present) or another BRAF-inhibitor, may be a next step. Some doctors advise the use of *Anakinra*, *Sirolimus*, *Imatinib*, *Methotrexate*, *Cladribine*, *Infliximab*, or *Tocilizumab* as other treatment options.

(Doctors at Memorial Sloan-Kettering Cancer Center, MD Anderson, and other institutions in the US and Europe are currently participating in a *Vemurafenib* trial. Other trials are expected to open for *Dabrafenib/ Trametinib* treatments in 2014. *If at all possible, patients and their treating doctors are encouraged to make efforts to have treatments administered under a clinical trial so that patient response can be followed and used to gain approval status from the appropriate governing bodies, e.g., FDA.*)

The next medical symposium and patient meeting has been tentatively scheduled for September 18th at the NIH in Bethesda, Maryland., USA.

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ECD Global Alliance
2013 ECD Medical Symposium ECD Investigator
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2013 ECD Medical Symposium Attendees. From left to right: Kathy Brewer; Per Johansson, MD PhD; David Hyman, MD; Babar Kahlon, MD, PhD; Filip Janku, MD, PhD; Kate Matthews, MSc; Eli Diamond, MD; David Bell, PhD; Marina Ferrarini, MD; Lorenzo Dagna, MD; Elisabetta Ferrero, PhD; Giulio Cavalli, MD; Tim Vollmer, MD; Tom Colby, MD; Ken McClain, MD, PhD; Omar Abdel-Wahab, MD; Laurent Arnaud, MD, PhD; Augusto Vaglio, MD; Juvianee Estrada-Veras, MD; Mark Heaney, MD, PhD; Glenn Padnick; Julien Haroche, MD, PhD; Pam Fleming. Not shown: Carrie Bjonback, MD; Nancy K. Feeley, NP; Karen Kushner, LCSW; Jason Poole, PhD; Paul J Scheel, Jr, MD; Cecile-Rose Vibat, PhD