PRESS RELEASE

RESULTS OF AUTOLOGOUS HAEMOPOETIC STEM CELL TRANSPLANTATION FOR REFRACTORY CROHN'S DISEASE: A RANDOMISED CLINICAL TRIAL

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Nottingham, Friday, December 11, 2015 – Results from the Autologous Stem Cell Transplantation International Crohn's Disease (ASTIC) trial published in the *Journal of the American Medical Association* (JAMA) on December 15, 2015 show that autologous Haematopoietic stem cell transplantation (HSCT) was not significantly better than conventional therapy at inducing sustained disease remission (clinical remission off all medical therapy for 3 months with no evidence of active disease on endoscopy and GI imaging) **at one year in patients with treatment refractory Crohn's disease.** However, exploratory analyses did demonstrate benefit of HSCT over conventional treatment that warrants further study. Thus, compared to the control group, significantly more HSCT patients were able to withdraw all immunosuppressive therapy for the three months prior to the primary endpoint. Furthermore, at the primary endpoint, numerically (but not significantly) more patients undergoing HSCT had been in clinical remission for 3 months and were free of disease on endoscopic / radiological assessment (p= 0.054). Importantly, there were significant benefits of HSCT compared to conventional treatment in the absolute reduction of clinical and endoscopic disease activity.

Nearly everybody has had an attack of gastroenteritis at some time, and will remember the dreadful pain and diarrhoea it causes. Patients with Crohn's disease have this experience every day, with the problem starting at a young age, persisting on a lifelong basis and accompanied by malnutrition, fatigue and ill health. About one in 200 people in developed countries suffer from Crohn disease or ulcerative colitis. Crohn disease is one of life's most challenging chronic diseases. Although there have been major advances in understanding and treatment recently, some patients are resistant to all treatments and lead lives that are severely curtailed and of poor quality.

It was to address the needs of such patients that the ASTIC trial was set up. It is a unique ground-breaking collaborative project conducted by leading entities in the fields of Bone Marrow Transplantation and Gastro-enterology: the European Society for Blood and Marrow Transplantation (EBMT) and the European Crohn´s and Colitis Organisation (ECCO) and funded by the Broad Medical Foundation and the Nottingham Digestive Diseases Centres.

ASTIC systematically investigated the effect of immunoablation and autologous HSCT on objective signs of disease, symptoms and need for treatment and is the only controlled trial to have done so. The treatment aims to eliminate aberrant immune reactions that the body has developed against itself and replace them with uncommitted stem cells, a sort of immunological spring clean.

ASTIC trial is an international, multi-centre, investigator-based, open label, phase III trial that involved 11 JACIE-accredited transplant units in 7 countries from July 2007 to March 2013. A total of 45 patients aged 18-50 years with impaired quality of life from active Crohn's disease not amenable to surgery, despite treatment with ≥3 immunosuppressive/biologic agents have entered the trial. It was stimulated by reports some of which suggested that long-term regression of disease amounting to potential cure could be achieved. But the treatment is hazardous with major potentially lethal

risks, so recruitment to the trial was cautious and the most stringent criteria ever developed were used for the trial's primary endpoint. In fact the criteria were so stringent (no symptoms, no signs of disease on total bowel examination and no need for treatment) that few patients achieved them. Nevertheless, there were improvements in the individual measures underlying the composite endpoint and objective signs of disease disappeared in about a quarter of patients.

All patients underwent stem cell mobilisation before randomisation (1:1 permuted block design) to immunoablation and HSCT (n=23) or control treatment (HSCT deferred for one year, n=22). If patients improved, corticosteroids and immunosuppressive/biologic drugs were systematically weaned. The main outcome was sustained disease remission, a composite primary endpoint comprising clinical remission (Crohn Disease Activity Index (CDAI) < 150) without corticosteroids or immunosuppressive/biologic drugs for at least the last 3 months and no endoscopic/radiological evidence of active (erosive) disease anywhere in the GI tract at one year assessment. Secondary outcomes were individual components of the primary composite outcome and other measures of disease activity, laboratory results, quality of life and functional status, and GI tract imaging.
All criteria for sustained disease remission were achieved in two HSCT patients versus one control patient (p=0.600). Fourteen HSCT patients (61%) vs five (23%) were off immunosuppressive drugs for >3 months (p=0.012). Ten vs two patients had a CDAI $\leq$ 150 (remission) at the final evaluation, eight vs two for $\geq$ 3 months (p=0.052). Eight vs two patients were adjudicated free of active disease on endoscopy and radiology at final assessment (p=0.054). There were 76 serious adverse events in HSCT patients vs 38 in controls. One HSCT patient died.

Trial Chief Investigator Prof Chris Hawkey, Professor of Gastroenterology in Nottingham and Chairman of Core Charity said "Haematopoietic stem cell transplantation is probably the most effective treatment for Crohn's disease but also the most toxic. It cannot be recommended for widespread use at the present time but may be a risk worth taking for a small number of patients that have run out of treatment options". The ASTIC team are now turning their attention to identifying those most likely to benefit, with minimal toxicity. Professor Dominique Farge Bancel, Saint Louis Hospital in Paris and Chair of the EBMT Autoimmune Disease Working Party, adds that "Although autologous HSCT therapy showed more toxicity in early stages of the follow-up in Crohn's patients, long term results after HSCT treatment may shed new lights on the expected benefit, as observed in Scleroderma, another autoimmune disease where the proof of a HSCT superiority over conventional therapy was obtained only after long term follow-up at the price of higher early toxicity. Further research combining double expertise from ECCO and EBMT specialists as in ASTIC trial will allow to improve patients selection and a HSCT regimen with endpoints comparable to those currently used for testing new biotherapies so as to unravel the final clue: who are the best candidates that will benefit from a HSCT?"

ASTIC was funded by the **Broad Medical Research Program.** Our Mission: To cure Crohn's disease and ulcerative colitis, and to improve the quality of life of children and adults affected by these diseases.

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About the European Crohn´s and Colitis Organisation (ECCO) - www.ecco-ibd.eu
The ECCO is a fast growing and highly active non-profit association focusing on Inflammatory Bowel Disease (IBD). ECCO acts mainly in Europe and encourages collaboration beyond Europe´s borders allowing anyone around the globe interested in IBD to benefit from our programme and services.
Mission

ECCO's mission is to improve the care of patients with IBD in all aspects through international guidelines for practice, education, research and collaboration in the area of IBD.

Aims

A key goal of ECCO is to promote, sponsor and steer national and international IBD research efforts. ECCO successfully influences IBD management through the development, publication, dissemination and teaching of IBD guidelines and other educational materials such as workshops and the e-CCO learning platform. ECCO facilitates and promotes the education of healthcare professionals in the field of IBD. It enhances the quality of research in the field of IBD, both in basic and clinical science. ECCO takes a political voice in Europe and collaborates with organisations sharing an interest in IBD, including medical societies, patient organisations and industries. Furthermore ECCO participates in the activities of the United European Gastroenterology (UEG) and in the organisation of the annual United European Gastroenterology Week (UEG Week).

Country Members

Since the foundation in 2001, ECCO has embraced 35 Country Members who are the driving force and are considered as ambassadors spreading the ECCO Spirit, such as Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Cyprus, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Latvia, Lithuania, Moldova, Norway, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, The Netherlands, Turkey, Ukraine, United Kingdom.

History

ECCO was founded in Vienna, Austria, in 2001 as an umbrella organisation for national Inflammatory Bowel Diseases (IBD) study groups in Europe. It expanded from an organisation with 14 Country Members to an association comprising 35 affiliated countries in 2015.

About the European society for Blood and Marrow Transplantation (EBMT) and the EBMT Autoimmune Disease Working Party (ADWP) - www.ebmt.org

The EBMT is a not-for-profit medical and scientific organisation established in 1974. It is dedicated to fighting life-threatening blood cancers and diseases and improving patients' lives. The EBMT Members - more than 4,000 physicians, nurses, scientists and other healthcare professionals - participate in a unique collaborative network of peers involved in haematopoietic stem cell transplantation (HSCT) and cellular therapy research. The membership encompasses at least 600 centres who are performing or are involved in HSCT in more than 60 countries. The EBMT holds a central role in performing co-operative studies and disseminating state-of-the-art knowledge aimed at increasing survival rates and enhancing the quality of life of patients with life-threatening blood cancers and diseases.

Since 1997, the EBMT Autoimmune Disease Working Party (ADWP) is dedicated to foster awareness and clinical collaboration on Stem Cell Transplantation for Autoimmune Diseases. The EBMT ADWP database is the largest collaborative platform of the field and it has actively contributed to the completion of clinical and research studies for more comprehensive understanding of best available current therapeutic strategies in Autoimmune Diseases in rapidly progressive or severe Systemic Sclerosis, Multiple Sclerosis, Lupus, Rheumatoid Arthritis and Juvenile Arthritis, Immune Cytopenia, Inflammatory Bowel diseases and other ADs, and more recently in Early Acute Insulin Dependent Diabetes.

For further information about the EBMT, please visit the website: www.ebmt.org and follow us on Twitter: @TheEBMT

The Nottingham Digestive Diseases Centre (**NDDC** - www.nottingham.ac.uk/nddc/) is the UK's Biomedical Research Unit for gastroenterology and hepatology. NDDC comprises over 100 academics and NHS associates. NDDC conducts research to make novel observations regarding mechanisms underlying digestive health and diseases in order to develop innovative tests, devices and treatments to improve digestive health.

Core, the UK funding charity (www.corecharity.org.uk) is committed to fighting all digestive diseases. These are conditions that affect the gut, liver and pancreas. Collectively they are a factor in 1 in 8 deaths in the UK – and more than a quarter of cancer deaths are from cancers found in the digestive system. Core supports medical research to save lives. By increasing our understanding of disease we can diagnose earlier and provide more effective treatment. To enable patients to take control of their conditions, Core provides evidence-based information. And we want to make sure that nobody suffers through ignorance or embarrassment so we work to raise awareness of digestive diseases, their symptoms and impact.
As a charity Core needs donors. We receive no government funding for any of our work. You can find out more about all of Core's activities, and make a donation, by visiting www.corecharity.org.uk.

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