



Welcome to the first issue of Adacolumn Newsletter for 2007. In this issue you will find a summary of Dr Hanai's editorial "Positions of selective leukocytapheresis in the medical therapy of ulcerative colitis" that was recently published in the World Journal Gastroenterology.

Two of our Travel Grant winners for 2006 presented their interesting reports at the First European Symposium on Paediatric Inflammatory Bowel Disease which was held in Rome last November. You will find a summary in this Newsletter.

We are happy to inform that there is a new Otsuka Travel Grant for ESPGHAN 2007 in Barcelona. If you would like to apply, read more about it on page 3.

How and why Adacolumn induces remission of inflammatory bowel disease – including steroid refractory cases.

In a recent editorial in the World Journal of Gastroenterology, Dr Hanai¹ provides a comprehensive view on how the depletion of peripheral granulocytes and monocytes by using Adacolumn produces high remission rates in patients with inflammatory bowel disease (IBD). The paper recaps the results from a large number of clinical studies in different patient groups. In many patient groups, steroids could be avoided or were tapered to a minimum dose.

The Adacolumn

Adacolumn is a selective granulocyte, monocyte device; the patients' blood is passed through a column, which is filled with especially designed cellulose acetate beads. The beads adsorb most of the granulocytes and monocytes which express Fc- γ -R and complement receptors. As a consequence, the number of effector cells in the inflamed bowel wall is decreased.

Patients differ in clinical response

The editorial summarises reports of clinical responses when using Adacolumn to treat different groups of patients. It is concluded that steroid naïve ulcerative colitis (UC) patients demonstrate the best response to Adacolumn, although steroid dependent and steroid refractory UC patients also show a high degree (83-85%) of clinical response. In 79% of the refractory cases, remission was maintained after one year. In patients suffering from Crohns' disease, there is less data on the use of Adacolumn than in UC, but the studies reviewed indicate a remission rate of 52% in steroid refractory patients, and 70% in steroid dependent patients. Similarly, Adacolumn maintained remis-

sion in 62% of IBD patients with a high level of faecal calprotectin (a neutrophil specific protein), compared to 24% in untreated patients.

What can explain the sustainability of the clinical response

The remission in most patients is maintained for a long time after the last Adacolumn GMA session. Factors contributing to the long-term efficacy are not understood yet. However, there seems to be a sustained suppression of pro-inflammatory cytokines which are released by peripheral leukocytes. Additionally, during the process, significant amounts of soluble TNF-alpha receptors are released in the column which reach the patients' circulation via column outflow blood. Soluble TNF-alpha receptors are known to neutralize TNF without invoking TNF-like action.

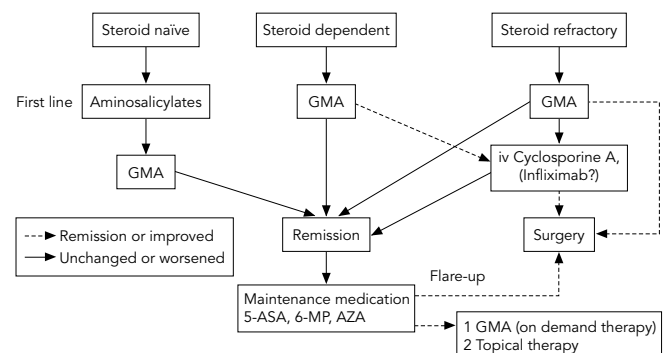


Figure from Hanai¹. Treatment algorithm for ulcerative colitis without corticosteroids. Based on this scheme, patients at any stage of their disease might benefit from Adacolumn GMA and avoid corticosteroids or other drug based medications.

1. Hanai, H. Positions of selective leukocytapheresis in the medical therapy of ulcerative colitis. World J Gastroenterol, 2006. 12(47): 7568-77.

First European Symposium on Paediatric Inflammatory Bowel Disease, Rome 2006

For the first time an international conference on IBD in children and adolescents was held. Around 400 researchers, paediatricians and nurses gathered at a three-day conference in Rome in November 2006.

The first day of the symposium was devoted almost entirely to new discoveries regarding the significance of heredity for IBD. To summarise, no precise answer exists to this question.

The correct diagnosis has been the theme of the European work group consisting of paediatricians working with and doing research on paediatric IBD. The results of the group's work were presented on the second day. Similarities in the method of investigation are of benefit to the patient, not to mention research.

One of the topics discussed was "Is there a large difference in IBD between children and adults?" Being ill while growing up affects the child, and paediatricians need to consider the child's disease, growth and development. In Rome the question was discussed of whether it is actually another type of disease that starts earlier or whether it is just a coincidence that one falls ill as a child. Children and adolescents with Crohn's disease have more inflammation higher up in the gastrointestinal tract than adults. Inflammation throughout the colon is also more common in children than in adults.

Nutrition, growth and personal development must be supported in young people with IBD. It was therefore pointed out many times that the care provided requires several categories of health professionals with a high level of competence and the ability to cooperate with one another. The American paediatricians maintained that a liquid diet treatment for teenagers is a non-starter, a view sharply criticised by both Canadians and Europeans. Being able to give treatment with

something quite as harmless as a liquid diet is an invaluable asset for patients and those giving treatment.

New treatments and the risks of adverse reactions were presented and discussed on the final day. There is some disquiet among doctors concerning the lack of clarity regarding links between treatment with new drugs and tumour diseases. These are difficult questions, which were dealt with in a very informative way.

To round off the conference, the results of stem cell treatment were presented as one possible way perhaps of curing IBD. For the time being this involves considerable risks, which are not balanced by potential benefits.

To sum up, we know more about the importance of heredity in inflammatory bowel disease, plus the fact that the environment also plays a role. We now know that a thorough investigation of the gastrointestinal tract is important to enable us to assess the spread of the disease. There is a high degree of consensus about how inflammatory bowel disease should be investigated and treated in Europe.

Lena Grahngquist, Paediatrician, Senior Physician and Head of the Gastroenterology and Nutritional Unit, Astrid Lindgren Children's Hospital, Karolinska University Hospital. (Translation by Intervendum. The whole report is available at our home page www.otsuka.se.)

The first 100 patients treated in Scandinavia

Data on the first 100 patients in Scandinavia who were treated with the Adacolumn have been published in the *Scand J Gastroenterol*. The results show Adacolumn significantly improved symptoms of inflammatory bowel disease in 68% of patients, mostly with drug refractory IBD; 46% achieved complete remission during the observation period. You can order a reprint from us, reprints@otsuka.se.



Report from the First European Symposium on Paediatric Inflammatory Bowel Disease (Rome, 23–25 November 2006)

The first European conference on paediatric IBD took place at the end of November 2006.

On the first day a discussion took place primarily of immunopathogenesis, genetics and bacterial flora in IBD, which brought us clinicians right up to date in the field.

Also discussed was research needed in paediatric IBD. What differences are there between paediatric and adult IBD? How does early differ from late IBD?

Another important question was the link between genotype and phenotype in paediatric IBD. The paediatric phenotype appears to differ from that of the adult, and the onset of the paediatric disease also seems to be more aggressive.

The second day was devoted to the clinical treatment of paediatric IBD. A central question was the definition of remission. Is mucosal healing really the golden standard or can one be satisfied with a good clinical response? Is it possible to obtain prolonged remission with mucosal healing?

Anne Griffiths from Canada then gave a fantastic overview of growth disturbances in IBD.

Severine Vermeire from Belgium spoke about new

and old serological markers in IBD. The “new” markers are antimicrobial antibodies.

The third day concluded with heated discussions about biological drugs for IBD. At what stage should the disease be treated with biological drugs? The outcome is probably better with a top-down strategy, where better endoscopic healing could be shown.

There are altogether eight reports of lymphoma (hepatosplenic T-cell lymphoma, HTSCL) in patients with Crohn's who were treated with both azathioprine and infliximab. The question therefore was whether one can combine these two drugs. Is azathioprine really the villain of the piece? In the group of patients heterozygotic for TPMT, there seems to be a greater risk of lymphoma and brain tumour.

To sum up, this was a most inspiring meeting of the highest technical quality, at which light was shed on a lot of interesting clinical problems, while at the same time leaving room for discussion with colleagues from Sweden as well as other countries.

Dr Susanne Schmidt, Pediatric Unit, Södra Älvsborgs Sjukhus, Borås. (Translation by Intervendum. The whole report is available at our home page www.otsuka.se.)

Adacolumn[®] Travel Grants to ESPGHAN May 9–12, 2007 in Barcelona

5 travel grants of 500 EUR each – for the purpose of visiting ESPGHAN 2007 in Barcelona will be presented by Otsuka to gastroenterologists and gastro-nurses. The winners will be chosen by Dr. Tarja Ruuska, Department of Paediatrics, Tampere University Hospital and Prof. Robert Löfberg, IBD unit, Sophiahemmet, Stockholm. The winners will be notified personally by e-mail no later than March 27, 2007 and their names will be published in the Adacolumn Newsletter.

Conditions

- The applicant should be working with gastroenterology as main occupation.

- The applicant should state specific and well defined reasons why he or she is applying for the grant.
- The grant is personal and can not be transferred to any other person. If not used the grant should be returned to Otsuka Pharma Scandinavia AB.
- The winners are expected to write a short report from their visit to ESPGHAN which will be published in the Adacolumn Newsletter.

To apply send an e-mail to grants@otsuka.se no later than March 15, 2007 with the following details:

Name; Hospital and Department name; E-mail; Reasons.

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- Positions of selective leukocytapheresis in the medical therapy of ulcerative colitis** *Hiroyuki Hanai, Department of Medicine, Hamamatsu University, Hamamatsu, Japan.*
- Granulocyte, monocyte/macrophage apheresis for inflammatory bowel disease: The first 100 patients treated in Scandinavia** *Tryggve Ljung^{1,11}, Ole Østergaard Thomsen², Morten Vatn³, Per Karlén⁴, Lars Norman Karlsen⁵, Curt Tysk⁶, Stefan U. Nilsson⁷, Anders Kilander⁸, Rolf Gillberg⁸, Olof Grip⁹, Stefan Lindgren⁹, Ragnar Befrits¹, Robert Löfberg^{1,10}.* ¹Department of Gastroenterology and Hepatology, Karolinska University Hospital, Stockholm, Sweden, ²Department of Gastroenterology, Herlev Hospital, University of Copenhagen, Denmark, ³Rikshospitalet, University of Oslo, Oslo, Norway, ⁴Department of Gastroenterology, Söder Hospital, Stockholm, Sweden, ⁵Department of Medicine, Rogaland Hospital, Stavanger, Norway, ⁶Department of Gastroenterology, Örebro University Hospital, Örebro, Sweden, ⁷Department of Medicine, Kristianstad Hospital, Kristianstad, Sweden, ⁸Section of Gastroenterology and Hepatology, Sahlgrenska University Hospital, Göteborg, Sweden, ⁹Department of Gastroenterology and Hepatology, Malmö University Hospital, Malmö, Sweden, ¹⁰IBD Unit, Sophiahemmet, Stockholm, Sweden, and ¹¹Otsuka Pharma Scandinavia AB, Stockholm, Sweden.

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This form can be sent by post to the address below, by fax or send a request by e-mail to reprints@otsuka.se.

Please let us know your comments or if you have any questions:

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