Dear newsletter readers,

I am happy to provide you with this year’s first issue of Adacolumn Newsletter. This is actually the 28th issue since it was started in 2004. (archived versions from 2006 are available on our website – www.otsukapharma.info – under Medical professionals – Adacolumn – Service center – Newsletters.)

We attended the ECCO-IBD Meeting in Hamburg as one of the exhibitors, and held a satellite symposium which contained the topics of Selective Leukocyte Apheresis: Advances in Mode of Action (by Prof. Ola Winqvist) and the Sharing the Clinical Realities: When to Perform GMA Apheresis (by Prof. Dignass). It was visited by many, and 94% of the attendants (of which 73% were GI specialists) replied positively to the question: “the symposium has met my expectation”.

In this issue, Dr. Tarja Ruuska has kindly written a short summary of her recent publication on 38 pediatric patients treated with Adacolumn (GMA) in the Nordic region. And, we’re proud to present an Adacolumn clinical update leaflet, based on our meeting held in Brussels last year. Please inquire to your Otsuka contacts to receive your copy. Do not hesitate to visit our homepage to explore the continuously growing Adacolumn literature database. There are over 130 searchable publications on Adacolumn in IBD at your disposition, including the first independent meta-analysis by Sauerland and Habermalz in Dig Dis Sci.

Finally, I wish you very pleasant summer!

Mari Liljefors
Communications Director,
EU Marketing Coordinator, Adacolumn
Otsuka Pharma Scandinavia AB

No 1, July 2009

On Mode of Action and Shared Clinical Realities – Adacolumn® at ECCO-IBD 2009

The annual European Crohn’s and Colitis Organisation (ECCO) congress has become the most important scientific EU forum in IBD. It was attended by approx. 1700 persons this February in Hamburg, Germany. One of the Adacolumn-related core messages was the independent meta-analysis by Sauerland and Habermalz, IFOM, Cologne integrating 6 randomized controlled trials including the US UC sham (Sands) trial. The full paper on the meta-analysis is available electronically in Dig. Dis. Sci.

An ECCO Award of Distinction was won by the investigator study group and OFRI (Otsuka Frankfurt Research Institute) for the CESA 5.10 trial poster. This trial included the same type population as the Sands sham trial in the US. In both treatment arms, remission and response levels were on about the same level as reported in prior trials from EU and Japan, with an overall remission rate of 40.7% and an overall response rate of 58.8%. Interestingly, the results of this so far biggest randomized controlled trial with Adacolumn® in UC in Europe did thus not confirm the results of the US trials.

Fully complementary to these scientific topics, Otsuka had the pleasure to host the official Adacolumn Satellite Symposium on February 5. This open, CME-credited event was visited by ca. 180 participants; 50 % more visitors than expected. Prof. Ola Winqvist, Karolinska Hospital, Stockholm and Prof. Axel Dignass, Markus Hospital, Goethe University, Frankfurt, presented advances in Mode of Action research and shared clinical experience with Adacolumn, focusing on the most appropriate indications. Reinforcing Prof. Tohshifumi Hibi’s message about Adacolumn being already an integral part of the IBD treatment algorithms in Japan earlier that day during an ECCO plenary congress session, the questions and feedback from the audience showed again high interest in granulocyte monocyte/macrophage (GMA) apheresis as a therapeutic option of choice.

The very positive feedback survey results collected from the specialist audience will further contribute to targeting precisely the increasing demand after sharing the clinical realities among experienced and new Adacolumn users.

Dr. Raphael Gruber, MD, PhD
Director, Adacolumn Business Unit – EU

Together with colleagues from Sweden, Denmark and Finland we have collected data from 37 patients whom received GMA treatment in order to evaluate the efficacy and safety of the treatment in pediatric patients.

The age range of children was between 5 and 17 years, (mean 13.2 years) and the duration of illness 2.4 years. Twenty-two of our patients had ulcerative colitis, 13 had Crohn\'s disease and 2 had intermediate colitis. Most patients were either corticosteroid dependent (55 %) or corticosteroid resistant (24 %). Patients received 5-10 apheresis sessions (mean 5.8). Response to the treatment was evaluated by using IBD activity indices PUCAI and PCDAI for UC and Crohn\'s disease respectively, as well as corticosteroid tapering. The mean PUCAI score was 38.8 before treatment, 10.1 following treatment and 4.6 points 3 months later (p=0.0002). A significant decrease (>20 points), was seen in 15 UC patients. In the CD group the mean PCDAI were 31.1 before treatment, 23.2 following treatment and 8.2 three months later (p=0.025). A significant decrease in PCDAI scores (>12.5) was seen in 5 children with Crohn\'s disease.

Corticosteroids were used at the commencement of treatment in 19 UC patients, at the end of treatment in 15 and 3 months later in 11 cases. Doses were significantly reduced (p=0.012). Eight children with Crohn\'s disease received corticosteroids at the beginning of the treatment, 9 at the end of treatment and 6 three months later, and although there was a tendency for dose reduction, it did not reach statistical significance.

GMA was proven to be safe, and no notable side-effects were seen.

This retrospective study demonstrates a good response to GMA treatment in pediatric IBD. A lot of questions, however, need to be answered: 1. which patients would benefit mostly from the GMA treatment, 2. how many sessions would be optimal and 3. whether GMA is useful for maintenance therapy.
The BSG congress, Glasgow

The BSG is the largest annual gastroenterology conference in the UK. This year it was held in Glasgow, with 3,000 gastroenterologists attending. OPUK had a presence there in the form of a brand new Adacolumn® stand. We encountered a great deal of interest from UK delegates. Since Otsuka is always keen to deepen our understanding of delegates’ opinions regarding Adacolumn®, we invited them to fill out a questionnaire. The results were very interesting. 90% of them agreed that Adacolumn® can induce remission, and 86% agreed that it has an excellent safety and tolerability profile. Encouragingly, a large proportion of participants (81%) agreed that a treatment guarantee would enable them to consider Adacolumn® as a treatment option for their patients.

In conclusion, in this sample of UK delegates the vast majority confirmed that Adacolumn® can induce remission and response in IBD, has an excellent safety and tolerability profile, and is a treatment option for their patients.

Melanie Rochford, Commercial Manager, Otsuka Pharmaceuticals (UK) Ltd.

Adacolumn marketing survey – ECCO-IBD meeting

The 4th ECCO-IBD congress (Feb. 5 – 7, 2009) was held in Hamburg, Germany this year with a yet increased number of participants (1676 IBD specialists). Otsuka was one of the exhibitors and had the pleasure to host and distribute the much demanded ECCO abstract CD-ROM at our booth.

Our exhibition booth displayed elements of Otsuka’s Japanese heritage together with Adacolumn branding, underlining the slogan – “A gentle revolution in IBD therapy”. A Japanese calligraphist offered to write booth visitors’ first names in Japanese on simple notebooks, an equally highly appreciated attraction.

A survey on Adacolumn among congress visitors was conducted. More than half of the participants were GI specialist, 14% GI trainees, and 8% were IBD nurses. About one fifth of all congress visitors have chosen to take part in this survey. Results show a very good perception of Adacolumn safety and capacity of steroid-sparing, rendering it an option also in pediatric IBD. We would like to thank all associates for their help with conducting this important survey at ECCO.

Mari Liljefors
EU Marketing Coordinator
The online survey conducted by the Italian IBD patient organization (A.M.I.C.I.)

The Adacolumn leukocyte aphaeresis (GMA) was performed on 669 patients who were not responding or intolerant to pharmacological therapy (3%). 53% of the patients presented an optimal or a good response to the aphaeresis, maintained between 6 to 24 months and indicated an improved quality of life. In case of relapse, one cycle of leukocyte aphaeresis was repeated. The only side effects recorded were headache (1 case) and inadequate venous access (1 case). The results obtained are in line with the scientific literature, showing a clinical remission in 50% of patients, with maintenance of the benefit obtained on average for one year.

Carmen Ferrara, Clinical Specialist Adacolumn, Otsuka Pharmaceutical S.A.

Granulocytapheresis with Adacolumn® in IBD – Naples

On September 30th 2008 at Hotel delle Terme di Agnano in Naples, the first meeting was held on Granulocytapheresis in IBD. The “Seconda Università” and Federico II University in Naples were the promoters of the meeting. The organizer presented their results, as well as those of an European clinical study of great scientific value on Granulocytapheresis in ulcerative colitis CESA 5.10 (5 Adacolumn vs 10) to the participants. The meeting was very interesting also for the multidisciplinary nature of its program, thanks to the lectors including transfusion doctors, immunologists and gastroenterologists who took part in this meeting. Of particular interest was the round table discussion, open to the whole audience, which had Prof. Riegler and Prof. Ciacci as moderators. The discussion led to an optimal positioning of the use of Adacolumn® in the therapy of inflammatory bowel diseases.

Edoardo Damiano, Product Specialist Adacolumn, Otsuka Pharmaceutical S.A.

Poster awarded

Recently we have reported on the finalization of the largest European trial with Adacolumn GMA apheresis in Europe, the CESA 5.10 trial. This trial has shown that 5 weekly GMA apheresis treatments improve the symptoms of ulcerative colitis nearly equally good as 10 treatments do. The results of this randomized, dose controlled trial have been accepted as poster with oral presentation at the ECCO-IBD in Hamburg. The poster of the primary investigator, Prof. Dignass from Markus Hospital in Frankfurt, Germany, was awarded as poster “highly commended”.

We have noticed that the CESA poster presentation during DDW in Chicago has attracted an enormous audience.

Watch out for the publication of CESA 5.10 in the next months.
Commitment by the Italian nephrologists

During the national congress of the Italian Society of Nephrology (SIN) held in Rimini 8-11 October 2008, the SD Emodepurative Therapy, Department of Medical Services’ Clinicizzato Ospedale “SS. Annunziata – ASL Chieti presented a poster with the title: The leukocyte aphaeresis in chronic Inflammatory Bowel Diseases: further commitment of the nephrologists. Sirolli V., Di Cesare M., D’Ettorre D., Carlini F., Di Liberato L., P. Cappelli Brummer U, Bonomini M.

The result of the study was especially interesting. Indeed, a cycle of aphaeresis led to a significant improvement in overall clinical condition of patients after six months of follow-up in patients who had not shown signs of recovery of disease activity. The clinical benefits were also supported by the resolution of the ulcerative lesions at endoscopic level. Promoters of the study believe that treatment and a further valid “commitment” by the nephrologists, called increasingly to solve problems not only of renal origin.
I would firstly like to thank for the ADACOLUMN Travel Grant I received, which enabled me to go to Hamburg for this year’s ECCO/NECCO meeting.

This was my first ECCO/NECCO experience, and it is greatly recommended. I listened to highly qualified people give highly qualified speeches on subjects of my interest. I have chosen only to report on NECCO, as this is “my area”.

After the official opening remarks we listened to Karin Menzel’s presentation on IBD epidemiology and how “it all started”, going back to Florence and Dr. John Snow, how it has developed, what we think and know, incidence, demographics, ethnicity, and genetics. We think a lot, but don’t know as much for sure.

Jean-Frédéric Colombel spoke of recent advances in the safety of immunomodulators and biologics. We learned about developments in IBD treatment, patient concerns, side effects such as infections and malignancies, and of awareness, especially for side effects.

Christian Felley presented on leucocytapheresis in IBD, which is an excellent, and in my opinion, especially good idea for patients who fail to tolerate medical treatments. The greatest problem with leucocytapheresis may be the lack of efficacy in blinded studies.

Liesbeth Moortgat spoke about dealing with fatigue in IBD, another very relevant but overlooked topic in patient care. Although we cannot rid of it, we can try to help patients cope by changing the vicious cycle into a positive one.

Lone Jorgensen talked about disease outcome measurements and diaries used in IBD patients. She spoke interestingly about the tools we use and to the difficulties of comparing the mixture of clinical measurements and “feelings” between studies and between patients. She spoke conclusively of other ways to monitor disease and disease progression.

Geert D’Haens talked about endoscopic measurements, and although I don’t perform endoscopies, it was interesting to learn the words used in patient files. Patricia Detré spoke about clinical research training, which was also very interesting as I didn’t know a formalised training for study nurses existed.

The meeting was finally closed by Lisa Young, whom introduced future NECCO activities. Altogether, this was a very inspiring congress and I do recommend participation next year.
Between February 4-7, 2009, I was in Hamburg at the ECCO meeting. I had received a travel scholarship from Otsuka that helped me with the costs.

The first one and a half day it was the ECCO Nurses Network meeting which I had great expectations on. The programme promised a lot of interesting topics, for example “Fatigue in IBD patients”, “The role of the IBD study nurse”, and of course “New and upcoming techniques of blood cells removals in the treatment of IBD”. But it was the talk about “IBD transition to adult health care” that became the best of all. Johanna Escher was great to listen to and I think all of us wanted to work with this brilliant paediatric gastroenterologist. It was also very nice to meet all these nurses working in the same area!

At lunch, the 5th of February the “big” meeting began. Suddenly the Congress Centre was full with people. A new, exciting programme was beginning. The first day became very heavy. The sessions were difficult and I had some problems to follow in all genetic talks! It was relieving to hear from others that they experienced the same thing. It was much better the day after. The best talk was “Stress in IBD”, both because of the interesting topic and because of David Rampton that made it so easy and exciting to listen to. His talk also is going to be helpful in my own research about what causes exacerbations in IBD. The poster session was on this day. For me this was important because I had a poster of my own. It was exciting to have to present my work in 1-2 minutes when the guided poster session arrived at my poster!

One of the most important things when you go to congresses like this is the people you meet. It is great to meet all this persons with the same interest! You make new friends, you exchange experiences, you discuss different ideas, and you have a good time together. Thank you, Otsuka, for very interesting days in Hamburg!

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### Adacolumn® European events 2009

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Granulocytapheresis versus methylprednisolone in patients with acute ulcerative colitis: 12-month follow up.
80 patients with UC. Activity of the disease was evaluated by clinical activity index and endoscopic index. Patients were randomly divided in two groups: Group A received a five-session (1 session/week) treatment with GCAP, Group B were treated with i.v. or i.m. methylprednisolone (MP). Remission was observed in 72.5% of those treated with GCAP versus 50% of those treated with MP.

Post Marketing Surveillance of Adacolumn GMA in a total of 697 patients treated for active UC in 53 medical institutions, 1999 - 2006. During the 7 year period, there was no serious AE related to GMA. Overall response rate was 77.3%. Clinical remission was 71.1%. Endoscopic assessment of efficacy showed very significant mucosal healing.

Investigation of IP-10 production in UC to examine its association with disease development. Serum IP-10 levels of active and inactive UC (n=29 and N21 resp.) and 20 controls measured by ELISA. IP-10 production by granulocytes and monocytes adsorbed to G-1 beads was examined. Serum IP-10 levels decreased following GMA treatment in responders, but not in nonresponders. Interestingly, serum IP-10 levels before GMA were higher in responders than in nonresponders. In parallel with the serum levels, IP-10-positive cells also decreased following GMA treatment.

Retrospective data collection of GMA in steroid resistant or dependent paediatric IBD (n=37) from 3 Nordic countries, for the evaluation its efficacy and safety. PUCAI, PCDAI decreased significantly in both UC and CD groups. Steroid dosage was reduced significantly in UC, and continued for 3 months. Relapse observed in 2 UC and 3 CD patients after 3 months follow-up.

Investigation of the impact of GMA on FOXP3, CD25high expressing regulatory T cells. Biopsies and blood samples obtained at baseline and post-GMA from 31 UC patients and 13 healthy controls were immunostained against FOXP3 and CD25high on Tregs.

Clinical Effectiveness of Selective Granulocyte, Monocyte Adsorptive Apheresis with the Adacolumn Device in Ulcerative Colitis. Habermalz B, Sauerland S. Dig Dis Sci 2009 June
First meta-analysis in UC-related RCTs with Adacolumn

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