IBD NORDIC CONFERENCE IN STOCKHOLM 2017

For the second time, *IBD Nordic Conference* was held in Stockholm on the 5th and 6th of October. Delegates from all Nordic countries came to listen to a mix of international key-note speakers that came both from the Nordic countries and beyond.

Prof Tom Øresland was the Chair, and he greeted all of them welcome to the Swedish capital.

– Our Meeting is the only Nordic Meeting on IBD. But the Nordic countries are small – so I urge you to interact and to create networks with your colleagues when you are here, he said.

He then declared the Meeting opened.

A pre-clinical period may be amenable to prevention

One of the prominent international speakers was Prof Jean-Frédéric Colombel, USA. He spoke about the road to prevention in IBD – challenges and opportunities.

– Why strive for prevention? Because IBD affects young people in the most productive years of their life, there is no known cure, therapy de-escalation is not feasible in the long term – there is a high rate of relapse, and therefore therapies are life-long and associated with very high costs, he explained.

There are three traditional frameworks of prevention: Primary prevention in healthy individuals, secondary prevention with early detection in high-risk patients and tertiary prevention with improved care for patients with established disease.

Prof Colombel pointed out that we are making progress with new drugs and therapies, but they have – at best – an efficacy of 50 % or below. We also have new strategies – biomarkers predicting response, earlier diagnosis and intervention and drug combinations were some he mentioned.

– At secondary prevention the goal is to detect disease at an early, treatable stage so its long-term sequelae may be avoided. Strategies are applied to persons at risk of disease, but still asymptomatic.

Prof Colombel presented data that showed that immune-mediated diseases have a pre-clinical period which may be amenable to prevention.

– This is a very good time for secondary prevention. Now, our colleagues in RA are doing just that.

A fantastic tool

Prof Colombel reported of several studies on preclinical IBD – with data from Nurses Study in the US, and the PREDICTS study. In the latter, preclinical samples are obtained from soldiers in the US army later diagnosed with Crohn's disease (CD) or ulcerative colitis (UC).

– They've got millions of samples – and some of them will develop IBD. It is a fantastic tool to investigate what takes place *before* onset of IBD, he said.

But there are many challenges in prevention in IBD. Biomarkers and predictive algorithms should have high predictive value to justify potential adverse effects from screening – including emotional stress – inappropriate health care costs due to false positivity, and potentially toxic and costly interventions. A predictive algorithm should also inform on timing to diagnosis.

– There is a need for better understanding: *Which* therapies or interventions can ameliorate or reverse the immunological changes in the preclinical phase? And which therapies or preventive measures would high-risk individuals be willing to accept – with a probability of developing disease?

His final question was for how long a preventive therapy or strategy should be continued in order to prevent or halt disease progression.

Appendectomy before diagnosis of UC protective for colectomy

The appendix is a reservoir of commensal bacteria. It was previously thought that evolution had made it expendable, that it had no function any more, said Prof Christianne Buskens, The Netherlands.

– But then a study published in 1987 found that appendectomy at childhood protects against UC. Interest in the appendix was regained, and since then a total of 38 studies has been performed, she continued.

On the function of the appendix, evolutionary studies have found that it is involved in handling intestinal bacteria. The

inner layer of the appendix is a safe house for commensal bacteria, that enables re-inoculation of the gut after gastrointestinal infection.

– So could it be that appendectomy *prevents* re-colonisation? In mouse models, appendectomy delays onset of UC and decreases disease activity, Prof Buskens said.

However, data from the largest epidemiological study shows that if one perform appendectomy *before* diagnosis of UC, it is protective for colectomy.

– But if you do it after diagnosis, the procedure increases the risk for colectomy!

An ongoing randomised, controlled trial – ACCURE – is investigating the effect of appendectomy on the clinical course in UC.

– We have to wait for the result, but I think I can conclude that the appendix is involved in UC, and that appendectomy prevents development of UC. But there are many questions: Does appendectomy modulate the clinical *course* of UC? And *how* is the appendix involved in UC, Prof Buskens ended her lecture.

Tom Øresland

Christianne Buskens

De-escalation may be considered when target is achieved

Prof Edouard Louis, Belgium, talked about treatment de-escalation in CD.

– There are many reasons for considering this – safety, patients concern, adherence and costs are among them, he said.

"SINGLE PORT LAPAROSCOPY HAS MANY POTENTIAL BENEFITS"

There are two ways to de-escalate: By decreasing the dose, or to withdraw treatment.

– I want to underline that cyclic treatment is *not* on-demand treatment. The first and undisputable aim of IBD treatment is full disease control! The idea of cyclic treatment is to aim at the lowest immunosuppressive/biological use still compatible with full disease control, Prof Louis underlined.

Hence a treat-to-target strategy seems the most appropriate for IBD.

– Once the target has been reached, treatment de-escalation may be contemplated, he stated.

De-escalation is associated with an increased risk of relapse, but may offer a favourable benefit/risk cost profile in a subset of patients, was Prof Louis final conclusion.

Small bowel cancer in CD is a puzzle

IBD and intestinal cancer, was the title of a talk given by Prof Tine Jess, Denmark.

– When I was a medical student, all evidence on disease progression in IBD came from a few studies, mostly from US referral centres. But of course, patients in these centres are not the same as in your everyday clinic, she said.

Prof Jess continued by presenting a prospective study from Denmark, presented at DDW in 2000, that had found *no* increased risk for cancer in IBD – only a mildly increased risk for small bowel cancer in CD.

– Later however, a slightly increased risk for colorectal cancer (CRC) was found – interestingly most in CD.

A meta-analysis from 2012 on UC and CRC after a median of follow-up for 14 years showed a very small increased risk for CRC in UC.

– This a very important take-home message! And data from Denmark from 1979 - 2008 on 35.000 patients – the whole country was one cohort – shows a *decreasing* risk of CRC in UC patients. The pattern of mortality in CRC in Denmark follows the same pattern.

She ended her lecture by stating that small bowel cancer remains a puzzle.

– But it is a very rare disease, and difficult to study cases. There have only been 40 cases totally in Denmark, Prof Jess said.

Many benefits for single port laparoscopy

Laparoscopy in IBD reduces surgical site infections and abdominal abscesses – but there are no significant differences in rates of reoperation, GI bleeding and mortality, compared to open surgery.

This was pointed out by Prof Anthony de Buck van Overstraaten, Canada, who talked about transanal/single port ileal pouch-anal anastomosis (IPAA) surgery.

– There are three types of surgery: Open surgery, laparoscopy and NOTES (Natural orifice transluminal endoscopic surgery), he explained.

Single port laparoscopy has many potential benefits – for cosmesis and body image, for reinforcing the laparoscopic advantages and decreased pain in the postoperative period. Prof van Overstraten showed a film on the procedure.

He presented his study on transanal versus transabdominal minimally invasive completion protectomy with IPAA in UC, published in 2017. Among the findings were the same rate of complications, no difference in anastomotic leak, a lower conversion rate in transanal IPAA and a shorter hospital stay for patients undergoing the transanal procedure.

– 93 % of patients in a survey said they prefer single incision laparoscopy surgery, and 66 % state they would go to another hospital for this.

In his conclusions, Prof van Overstraaten said that single incision laparoscopy surgery (SILS) and transabdominal minimally invasive surgery (TAMIS) is feasible,

with a possibly better outcome.

– But the impact of transanal access on pouch function needs to be assessed. Also a cheaper transanal platform is necessary.

"A new, potent mode of action for CD"

Prof Arthur Kaser, UK, talked about anti-interleukin-12/23 therapies in IBD.

The first study on an anti-interleukin-12 antibody for active CD was published in NEJM in 2004.

– It was a small study, with a small number of patients. But it did well against placebo, Prof Kaser said.

He continued by describing the function and mechanism of interleukin-12. It is an interleukin that is naturally produced by dendritic cells, macrophages, neutrophils, and human B-lymphoblastoid cells in response to antigenic stimulation.

– Ustekinumab is the antibody we at present have available. Others are in development. Interestingly, a phase II study indicted that those who failed anti-TNF, were those to have a benefit from ustekinumab, Prof Kaser underlined.

He presented data from the UNITI-1 and 2 studies.

– In induction we saw a dose-dependent response rate – and also in maintenance week 44. Perhaps even more impressive, we saw a dose-dependent change in CDAI score and CRP from week 0 in the IM-UNITI study on maintenance.

Risankizumab is an anti-IL-23 antibody being investigated for the treatment of multiple inflammatory diseases.

– The drug has shown good results in psoriasis.

Prof Kaser presented data from a phase II study on risankizumab in CD. They demonstrated a clear effect over placebo.

Another Phase II study has shown similar results for MEDI2070, also an antibody against IL23.

– Only patients who had failed anti-TNF were included!

In his summary, Prof Kaser pointed out that anti-IL-12/23 monoclonal antibodies represent a new, potent mode of action in CD. Ustekinumab is an option for patients with loss of response to anti-TNF.

– And new anti-IL-23 monoclonal antibodies show promising phase II data. And these drugs are remarkably safe, he stated.

Risks associated with anti-TNF

– For some years now, anti-TNFs have been the best selling drugs in the world,

said Prof Tine Jess, who returned to the podium.

She talked about risks associated with anti-TNF in patients with IBD.

Prof Jess underlined that in trials that lead to drug approval today, children and elderly patients are excluded – as well as pregnant patients. Therefore, phase IV studies are needed.

– In Scandinavia, we are lucky enough to have unique personal identifiers and can link that to registries, she continued.

A phase IV trial can never be a randomised controlled trial (RCT), Prof Jess stressed.

– So there is a large risk for confounding by indication. To handle that, we have propensity scores – that estimate the propensity for treatment as a function of covariates for each patient, both treated an untreated.

On the subject of anti-TNF and cancer, previous meta-analyses of RCTs in IBD show no increased risk. However SABER study – an observational study – shows a slightly increased risk.

– A large Danish nationwide cohort study, adjusted for propensity, found no increased risk of any cancer in fully adjusted risk estimates.

Prof Jess also presented a study on the risk of site-specific infections.

– It found an increased risk of infections during the first 90 days. The question is if this was due to increased awareness. The study found no increased risk of opportunistic infections.

Tine Jess

Fatigue in IBD is frequent and burdensome

Clinical nurse specialist Palle Bager, Den-

mark, gave a lecture about fatigue in IBD.

– It is not easy to define what fatigue is. My best suggestion is: "Overwhelming tiredness - resistant to rest and sleep", he said.

For some people fatigue is a normal feature in life, and it is common in chronic diseases. *How* common is it?

– In remission or in mild IBD, up to 40 % of patients has fatigue. In moderate to severe IBD, up to 77 %. 25 % of IBD patients suffer from chronic fatigue, Nurse Bager told the audience.

There are many things that can cause fatigue. Inflammation, iron deficiency and depression are evident. For anaemia, medication and micronutrients there are no clear evidence – and for sleeplessness there is some evidence.

– It is really a black box, but it has to do with inflammation. Maybe fatigue should be added as an EIM of IBD.

His take-home messages were that fatigue in IBD is frequent and burdensome. Physical fatigue is dominant.

– Women have more fatigue than men, and several factors correlates with fatigue in IBD.

No cure has been found yet – and intervention studies are needed, Nurse Bager finished his lecture.

Gert van Assche

Arthur Kaser

"INVEST IN NEW TREATMENT OPTIONS AND MAKE TREATMENTS MORE AFFORDABLE"

Treat the patient – not the disease

Costs and benefits of our treatments was the title of a talk from Prof Gert van Assche, Belgium.

– There are three ways to improve the value quotient: To improve quality at the same cost, to decrease cost at the same quality – or to implement a combined change in quality and cost, resulting in a net increase in value, Prof van Assche initially stated.

An integrated IBD unit strives to optimize resource utilization, and increase benefit to risk ratio of medical therapy and surgery.

– Avoid too early surgery – and too late surgery. *Both* are costly!

Also the IBD unit should empower patients to cope with their disease and to reduce disability, he added.

Shared decision-making is also important.

– You have to talk to your patients, otherwise they go to Dr Google who only talks about lymphoma, infections and cancer.

He ended with some advice on how we can improve the benefit to cost ratio.

– Use the appropriate drugs: Early biologics in disabling CD, early 5-ASA in UC. Ensure timely surgery when indicated.

Optimize biologics based on rational treatment algorithms including therapeutic drug monitoring in patients losing response.

– For payers and health care professionals: Invest in new treatment options and make treatments more affordable.

Facilitate head-to-head comparison trials to accurately assess incremental cost efficacy ratios of novel drugs.

– And treat the *patient* – not the disease – to decrease indirect, non-medical costs, was Prof van Assche's last advice.

Budesonide has a central role in treatment of MC

In the last session of the Conference, Dr Andreas Münch, Sweden, talked about microscopic colitis (MC).

– The epidemiology for MC in Sweden is 10 - 12 per 100.000 inhabitants, which is between CD (7,5/100.000) and UC (15,6/100.000) he said.

Data from Denmark show a increasing annual incidence for MC – in 2011 the figure was 24,7/100.000.

There is a diagnostic overlap between

MC and functional bowel disorders. One study found the prevalence of MC in functional disease was 7 %. MC consists of two diseases – lymphocytic colitis (LC) and collagenous colitis (CC).

– Genetically, HLA associations distinguish CC from LC.

Aquaporin-8 is a water channel protein, and Dr Münch showed data that this is downregulated in LC, and upregulated in CC. He also underlined that current smoking has a significant association with watery diarrhoea.

– Current and previous smokers have a significantly less likelihood to achieve clinical remission. Smokers also get CC earlier than non-smokers.

Budesonide is the drug of choice to treat MC. Dr Münch presented data from a double-blind, double-dummy phase III trial in which 57 patients from 30 centers participated. It showed that budesonide is more effective than mesalamine or placebo to induce remission in LC.

He ended by presenting a treatment algorithm for active MC, in which budesonide has a central role in different dosages. But what should one do with patients that don't respond? The audience was given a sneak peek on a poster that was to be presented at the UEG Week a few weeks later. It was on treatment of budesonide refractory patients with MC.

– The conclusion is that these patients can achieve clinical remission or response on anti-TNF agents. In the cases that failed anti-TNF, further treatment with vedolizumab, rituximab and ustekinumab did not improve the clinical condition.

European data registry

At the end of his lecture, Dr Münch wanted to advertise the ongoing project of establishment of a prospective data registry for MC in Europe: PRO-MC collaboration, founded by the European Microscopic Colitis Group (EMCG) in association with UEG.

– It is a good way to participate in research. If you are interested send a mail to **info@pro-mc.eu** or visit **www.emcg-ibd.eu**, he said.

Next year the Nordic IBD Conference will return in Stockholm. For details, keep checking the Congress Calendar in *IBD Congress News*.

Per Lundblad

Andreas Münch

Alvilde Ossum from Norway won the Best abstract award.

SATELLITE SYMPOSIUMS AT IBD NORDIC CONFERENCE

During the two days of the Meeting in Stockholm, a total of four satellite symposia were presented.

The first of these had the title *Keep calm and treat to target: Results and implications from the CALM study.* It was sponsored by Abbvie, and Prof Jonas Halfvarson was the Chair.

Treat-to-target versus standard clinical management

Prof Jean-Frédéric Colombel was the invited Speaker, and he talked about the CALM study. This he began by setting the background.

– The possible benefits of tight monitoring and treat-to-target are many: Treatment decisions are simplified and the strategy identifies patients with a poor prognosis or high risk of relapse. But the potential of a treat-to-target approach to change the progressive nature of IBD is largely unknown, he said.

CALM is a prospective, open-label, multicentre, active-controlled, Phase III study to evaluate two treatment algorithms in patients with CD: Clinical management, and treat-to-target – i.e. treatment escalation decisions based on close monitoring of biomarkers (serum CRP and faecal calprotectin).

All patients were naive to biologics and immunosuppressants.

– That is why they took ten years to recruit, he explained.

They all have had a flare of Crohn's disease (CD), and were randomised to the two arms. A total of 244 patients meant 122 in each arm.

– After 48 weeks, a significant difference was seen to the benefit for the treat-to-target group – 45 % met the specified criteria of steroid-free remission, as compared to 30 % in the clinical management arm.

"We can control inflammation in 80 % of patients"

– This is the first study to demonstrate that a treat-to-target approach, using biomarkers of inflammation, leads to superior endoscopic and clinical outcomes in CD compared with symptom-driven care, Prof Colombel stated.

Jonas Halfvarson

Jean-Frédéric Colombel

Managing patients with CD by clinical symptoms alone may not adequately control underlying inflammation, was his conclusion.

– We could also see that the treat-to-target approach did not lead to increased safety signals.

In the discussion afterwards Prof Colombel stated that he is convinced that we can control inflammation in approximately 80 % of CD patients.

– But then we have to treat early – and treat to target. What we don't know today is the long-term effect of treat-to-target. That is a trial we have to perform, he ended his lecture and with that the symposium.

5 years data on vedolizumab

Prof Halfvarson was also the Chair for the next satellite symposium: *When to swap or switch – are all biologics the same in the long run?* It was sponsored by Takeda.

He started with a slide of drugs being in development for IBD.

Edouard Louis

– This is good news for the patient – but poses a problem for doctors and nurses. How to pick the right treatment for the individual patient? Prof Halfvarson asked.

All IBD patients are not the same, and their profiles influence the treatment choices.

– *Clinical* characteristics include age and

gender, comorbidities, previous infections and anatomic distribution of inflammation among others. *Patient* characteristics include compliance, patient's preferences and daily life, he pointed out.

Prof Edouard Louis continued with the safety and efficacy in biologics. He presented 5-year data from GEMINI OLE study on vedolizumab in UC.

– This trial provides more robust week 152 data, and an additional 2 years to what had been published previously, he pointed out.

The conclusions from this study was that clinical benefits and health related quality of life improvements continued with up to 5 years of cumulative vedolizumab treatment. Safety profile was consistent with that published for the 3-year interim analysis.

Jørgen Jahnsen

Bjørn Moum

– Patients clinical profiles and preferences may help to choose among biologic agents in UC. Vedolizumab offers sustained efficacy and safety in clinical trials and real life experience, Prof Louis summarised.

Several switches

Prof Bjørn Moum then presented a case of a female patient with CD, born -81. She was intolerant for azathioprine, due to hair loss.

– First she started on adalimumab and came gradually in clinical and laboratory remission. But after two years this was stopped because of increasing skin erosions with excema and arthralgia/arthritis in her left knee, Prof Moum told the audience.

After a switch to infliximab biosimilar, the first infusion induced a response. But after the 4th infusion she started to relapse. Low drug levels had been measured at infusion 3.

– We increased the dose, and added methotrexate. But more neutralizing antibodies were detected.

A year ago the patient was switched to vedolizumab monotherapy.

– She is now doing fine, and has no arthralgia, Prof Moum said.

– One of the benefits of vedolizumab treatment is safety, so I agree with that choice, Prof Louis remarked at the end of the symposium.

Earlier use of anti-TNF with biosimilars

Treating the patients of tomorrow, was the headline for a satellite symposium sponsored by Janssen pharmaceuticals. Dr Michael Eberhardson was the Chair.

Michael Eberhardson

He began by stating that of what the physician can offer an IBD patient today, many are not helped – and we see a lot of loss of response over time.

– This is really a challenge for us, he said.

He presented the step-wise approach in drug therapy for IBD.

– We still have to stick to these steps, and we do not have the markers to tell us which one to use for which patient, Dr Eberhardson commented.

Biosimilars will likely change the situation. There will probably be an increased use of anti-TNFs earlier in disease progression in Sweden, due to the arrival of biosimilars, he envisioned.

– The question is if anti-TNF will be the new azathioprine?

Coming treatments might preliminary be used in patients post-anti-TNF.

– In the future we will probably have more patients post-anti-TNF with a need for optimisation of treatment – this will be challenging because we will have high demands on the treatment efficacy, i.e. mucosal healing, was Dr Eberhardson's last message.

Paradoxical psoriasis side effect of anti-TNF therapy

Dr Jørgen Jahnsen presented a case of CD in a 10 year old boy. Enteral nutrition (EN) and azathioprine was started, but the patient could not manage EN so infliximab was started.

– After the first infusion, the patient went into remission. But after 20 months of treatment, skin lesions started to appear, Dr Jahnsen said.

He presented a study that showed that paradoxical psoriasis is a relevant side effect of anti-TNF therapy. The incidence rate is 5 per 100 person-years.

– Smoking is a risk factor, and a combination with an immunosuppressant leads to a reduced risk.

When paradoxical psoriasis happens, one should not stop therapy. Instead discuss with a dermatologist, and try local topical therapy.

– And that is what we did, but it did not work, Dr Jahnsen continued.

He presented a list of 5 publications on combinations of biologics in patients with IBD.

– It's not much. The first is a study – on infliximab and natalizumab from 2007 – the other four are case reports.

Skin lesions disappeared

One of the case reports was on a 22 year old woman with refractory CD who had undergone subtotal colectomy and end ileostomy but still had active ileitis and skin lesions. She had tried infliximab, adalimumab, certolizumab, natalizumab and vedolizumab. The woman was treated with a combination of ustekinumab and vedolizumab – and had significant improvement.

– So we tried that with our patient, and the skin lesions went away. But after stopping ustekinumab, they came back, Dr Jahnsen said at the end of the symposium.

Sub-optimal long-term remission rates

Dr Eberhardson was also the Chair for the fourth and final satellite symposium, entitled *New insights and technologies to improve patient management and outcomes in UC patients*. It was sponsored by MSD.

Prof Gert van Assche talked about UC as an accelerating global disease, and pointed out that China had their first case in 1956.

– It's going to be an unmet need to treat all patients with IBD.

Long term remission rates are suboptimal in UC, even with biologics. Between 16 and 35 % are in clinical remission at one year in treat-through studies on infliximab and adalimumab – and between 23 and 42 % in re-randomisation studies on vedolizumab and golimumab.

– Steroid free and durable remission rates are even lower! This means we have to make better use of existing therapies – and develop new treatment options.

For patients, regaining control over IBD also involves living a normal life away from hospitals and physicians – with no disability, no fatigue and no anxiety of the future, he said.

Optimising therapy means higher induction doses for anti-TNFs, use of therapeutic drug monitoring and home monitoring.

Gert van Assche

New drugs are on their way – and JAK-inhibitors are first in line.

Several challenges

Tele-monitoring technology in IBD care is developed to decrease the burden of chronic disease by minimising clinic visits without compromising the monitoring of continuous disease control, Prof van Assche continued.

But there are challenges: The first is to remain open to patients who are unable or unwilling to start tele-monitoring.

– Integrate the monitoring in an already busy practice and to allow personal interaction when needed, are others. Finally, to bring all stakeholders on the same page – GPs, other gastroenterologists and payers – is a big challenge, Prof van Assche ended his talk.

IOIBD definition of targets

What this technology also can help out with was inadvertently demonstrated by Prof Walter Reinisch, who was scheduled to give the next lecture, but had been unable to travel to Stockholm. So he gave it with the aid of a link from Austria – a "tele-talk".

In this he presented the definitions from IOIBD (International organisation for the study of IBD) on treatment targets in UC. Resolution of rectal bleeding and normalisation of bowel habit should be the clinical target.

– Resolution of symptoms alone is not the target. Objective evidence of inflammation in the bowel is necessary when making clinical decisions, Prof Reinisch said.

A Mayo endoscopic subscore of 0 is the optimal endoscopic target, but a subscore of 1 should be a minimum target.

– Endoscopic assessment should be performed 3 - 6 months after the start of therapy for a patient with symptoms, he continued.

PURSUIT is a study on golimumab in moderate to severe UC.

– In response, mucosal healing and clinical remission, PURSUIT showed significant differences over placebo at week 6.

In his conclusion he stated that tight control and patient reported outcomes on stool frequency and rectal bleeding enables physicians to achieve targets relevant to patients.

Per Lundblad