The magazine that covers major international congresses and symposia focusing on inflammatory bowel disease (IBD)

UEG WEEK · IBD NORDIC CONFERENCE · TAILORED THERAPIES FOR IBD · NEXT STEP IN IBD TREATMENT · PREDICTING RESPONSE TO TREATMENT · MUCOSAL HEALING IN THE REAL WORLD
For the third time, Nordic doctors and nurses with an interest in IBD gathered for a Meeting dedicated to IBD. On the 11 - 12th of October in 2018 it took place in Malmö, the third largest city in Sweden situated on the south-west coast of the country.

Approximately 240 delegates had found their way to Hotel View, that overlooks the bridge that spans across the sea to Denmark. They were all welcomed by Prof Tom Øresland, Norway, who was the Chair of the Scientific & Program Committee.

In his welcoming address, Prof Øresland spoke about the program, designed to cover most of the pertinent clinical issues of today. He also encouraged them all to interact with each other and to create networks across national borders.

Perhaps we are using our drugs too late
The first speaker was Dr Johan Burisch, Denmark, who asked the question if the disease course of IBD has changed in the biological era.

He presented older data on disease progression over time in Crohn’s disease (CD) that showed only 30 % of patients had not developed organ damage after 10 years. Much more recent data from a cohort of CD-patients showed no difference in disease progression in patients that had received anti-TNF treatment or not.

- A global meta-analysis on disease extension in ulcerative colitis (UC) showed a colonic extension over 5 years to be 17.8 %. After 10 years it was 31.0 % – that is no difference from older cohorts, Dr Burisch continued.

Danish data on surgery rates in CD shows a decrease.
- But the most dramatic decrease was before we got biologicals, he pointed out.
- Data on surgery rates between 2003 and 2015 in both CD and UC do not show a big change.
- A proportion of our patients are destined for surgery, and we can’t change that.

However, data from Canada on colectomy rates do show a reduction in the number of elective, but not emergent, colectomies – corresponding with a greater utilisation of immunomodulators and infliximab.
- Perhaps we are using our drugs too late in our patients, Dr Burisch commented.

The impact of biologicals remains to be proven
The median time to start a biologic treatment is long.
- If we treat our patients to target – and change the therapy when we have to – this can change outcomes. This was demonstrated in the CALM study last year, Dr Burisch said.

Data from 2018 show that early anti-TNF treatment delays progression of CD, but not early surgery, in children.
- We lack clinical predictors on which patients that are going to need surgery. Serology, genetics etc are not feasible in clinical practice, due to being time-consuming and expensive.

In his conclusions, he underlined that CD and UC are associated with disease progression and thereby also worsened prognosis. Despite changes in medical treatment, their impact on disease course remains to be proven.
- Contemporary population-based cohorts of patients diagnosed in the biological era are lacking. Identification of high-risk patients may improve the treatment paradigm and improve outcomes.

CD – Paneth’s disease?
It is largely known that CD can affect the intestinal microbiota. The role of defensins in CD has been generated more and more interest in IBD research. One researcher who early put his attention to defensins is Prof Eduard F. Stange, Germany, who had a lecture with an update entitled “Where are we with defensins?”

Defensins are antimicrobial peptides, and their role are both antibacterial and immunomodulatory. They are produced in Paneth cells, and are expressed in most surfaces such as skin, gastrointestinal mucosa, genitourinary tract and lung.
- Every single cell in your body that is
exposed to bacteria, express defensins, Prof Stange explained.

Paneth cells co-express alpha-defensins and NOD-2. Paneth cells also constitute the niche for Lgr5 stem cells in intestinal crypts.

– Ileal CD is linked to Paneth cell differentiation. If you knock out Paneth cells in mice, they get ileitis. So I say that CD of the small intestine should be called Paneth’s disease, Prof Stange continued.

In Paneth cells of CD autophagosomes engulf and destroy defensin containing granules – independent of inflammation and ATG16L1 or NOD2 mutations. This is linked to autophagy, and the sensitivity for CD is 90 %, he told the audience.

– We know there is a diminished bacterial diversity in CD – but if this is the chicken or the egg, we don’t know. But we do know that if you give a faecal microbiome transplantation from a sick monkey to a healthy monkey, the healthy monkey gets ill.

This means there are possibilities for interventions, and research is ongoing. Prof Stange ended his talk by stating that defensins have an important future in the development of therapies for IBD.

– It works, he stated.

Perianal CD requires higher serum and tissue concentrations of drug

Dr Christianne Buskens, The Netherlands, then joined Prof Stange on the podium for a tandem-talk on perianal CD.

Approximately 35 % of CD patients have one or more fistula episode. Active rectal disease, male gender, age at diagnosis and smoking are known associated risk factors, she said.

– For a low fistula, fistulotomy have a success rate of 90 % – but low fistulas are rare in CD, Dr Buskens continued.

So how to treat high and complex fistulas? Prof Stange presented a meta-analysis from 2016 on anti-TNF versus placebo. It showed a complete closure of 30 % for anti-TNF and 12 % for placebo. The corresponding figures for partial closure were 24 % for placebo and 44 % for anti-TNF. However, it also found a 50 % reopening of fistula after cessation of medication.

– Successful treatment of perianal CD with anti-TNF may require higher serum and tissue concentrations, he said.

Prof Stange also presented recent data on new drugs. Vedolizumab was found to actively drain fistula in 14 weeks in 28 %, versus 11 % for placebo. Data from 52 weeks were 31 % versus 11 %. For ustekinumab, a subgroup from the CERTIFI study showed 24 % versus 16 %.

– We can see a trend – but not the solution of the problem, Prof Stange said.

Promising – but not overwhelming – results

Dr Buskens then talked about seton drainage. This is recommended for complex fistula by ECCO (Statement 9 H).

– 10 studies, with a total of 305 patients, on closure after chronic seton reported a complete closure in 16.6 - 100 %. Partial closure was not reported, and the recurrences reported were 0 - 83.3 %. But the quality of the studies were low. I think that if you combine seton with anti-TNF, you might fare better, she said.

Advancement plasty and ligation of intersphincteric tract (LIFT) were other surgical techniques Dr Buskens described.

Prof Stange continued with stem-cell therapy.

– It is an internal medicine procedure, he pointed out.

A randomised controlled trial (RCT) from 2016 on expanded allogenic adipose-derived mesenchymal stem cells for complex perianal fistulas in CD showed convincing differences to placebo.

– The results were promising – but not overwhelming. The downside was that 13 % of patients developed an anal abscess.

He also underlined that critique has been given to that study.

– The surgeons were unmasked – but the internists were blinded. Clinical healing was defined as no secretion upon “gentle” compression. But what about solid surgical compression? We don’t know. And there was no change of quality of life in patients.

This was a single study, and Prof Stange ended by stating that he would like to see more studies on the topic.

Adaptive trial designs

Dr Peter Irving, UK, said he thinks there is a crisis in the world of trials in IBD.

– There are too many trials, and too few patients – and the wrong sort of patients. We struggle with difficult endpoints, and are too slow to allow new drugs to get to market, he stated.

Dr Irving continued by focusing on
three problems, of which endpoints was the first.
– In CD, Crohn’s Disease Activity Index (CDAI) is often used. It is both subjective and non-specific – it’s not a patient reported outcome (PRO). Therefore it does not correlate with objective measures of disease activity. Its use as an entry criterion and an outcome measure, has been associated with unacceptably high placebo rates.

Dr Irving also underlined that CDAI is not useful in evaluating important subtypes of the disease, such as fistula and post-op recurrence.
– IOBD came up with STRIDE (Selecting targets of remission in IBD) in order to combine endpoints, including PROs on pain and stool frequency. STRIDE also takes endoscopic outcomes into account.

Problem number two was recruiting patients.
– Patients enrolled in RCTs do not represent the IBD patient population. A paper found that – when recruiting – 34 % of patients with CD were eligible, and 26 % of those with UC. Patients excluded were those with stricturing or penetrating CD who took high doses of steroids, had comorbidities, prior exposure to biologics or had received topical therapies.

The final problem is there are too many trials and too few patients. Trials are big, so it is a slow process to find eligible patients.
– How do we address that? Perhaps with adaptive trial designs.

Dr Irving explained he would like to see integrated double-blind phase II dose-finding and phase III dose confirming inductions studies with a maintenance study. It uses accumulating data to decide on how to modify aspects of the study – without undermining the validity and integrity of the trial.

– It should be pre-planned and sequential, and involve interim analysis and adaptations or decision-making based on interim results. This would improve quality, speed and efficiency in trial execution and decision-making.

– Maybe we should be so bold that we have multiple mode of actions versus one mode of action? It’s time for a radical rethink, Dr Irving summarised his lecture.

How can we do a better job?
Anti-TNF therapy is most effective in early disease. Earlier disease treatment leads to better outcomes, Prof Silvio Danese, Italy, established.
– Yet diagnostic delay is quite common in CD patients, and leads to a negative disease course, he said.

Early CD (i.e. within 18 months of onset, as voted by experts) is characterised by inflammation – there are no fistulas, abscesses or strictures, as in late CD.
– Even so, 39,4 % of CD patients diagnosed in two referral centres had bowel damage at diagnosis. They will do badly in their disease course, Prof Danese continued.

There are many contributory factors for diagnostic delay.
– It could be a delay in seeking medical help – insidious symptoms, misinterpretation of symptoms or other factors such as psychosocial, cultural and language etc. Or there could be a delay in consideration of diagnosis by initial medical contact – misdiagnosis or failure to follow up the patient or non-adherence.

CD is quite rare, and carries a lack of specific symptoms. There is also a fragmentation of pathways between primary and secondary care and a wide disparity in organisation structure among centres. Finally there is also a lack on multidisciplinary teams that can refer earlier.
– So how can we do a better job, Prof Danese asked.

A way to ensure early referral
He described the development of a “red flags index” for early referral of adults with symptoms or signs suggestive of CD. It is an IOIBD initiative. A red flag index of 8 or more, derived from a 21-item questionnaire, is able to identify subjects with high suspicion of CD.

– The index is likely to discriminate CD from non-CD. Now we have real-life validation ongoing, with 150 GPs involved with 2 - 10 IBD referral centres. We expect 600 subjects, and the duration of the study is 12 months. Although we have just begun recently, 3 diagnoses have been found – with a disease course of only two months, Prof Danese said.

Early referral and close collaboration between GPs and IBD specialists plays a key role in improving early diagnosis – and a combination of early diagnosis and treatment can raise the bars for CD natural history, were his conclusions.

Children should talk to a surgeon early on
General goals for IBD therapy are endoscopic and microscopic remission and a good quality of life.
– Goals for children and adolescents also include normal growth and puberty, said Dr Pernilla Stenström, Sweden, who was talking about IBD surgery in children.

She explained that as a paediatric
What is considered CAM constantly changes
The abbreviation CAM stands for complementary and alternative medicine. Dr Randi Opheim, Norway, talked about CAM in IBD.

- CAM consists of a group of diverse medical and health care systems, practices and products not presently part of the conventional medicine, she explained.

These CAMs could be divided into subgroups – natural products, mind and body therapies and other CAM approaches.

Dr Opheim presented two studies, one from Sweden and one from Norway, on the use of CAM in IBD. Both presented data that showed that almost half of patients used CAM. Data from the Norwegian IBSEN study revealed no change in prevalence of CAM use between 10 and 20 years since diagnosis.

- Therapies used included massage, homeopathy, probiotics, fish oil and acupuncture among others, Dr Opheim said.

Going back to the IBSEN study, she could show that there has been a change in type of therapies used by IBD patients. Homeopathy use has gone down, and acupuncture, healing and herbals has gone up.

- What is considered to be CAM constantly changes. When it comes to acupuncture, no quality study has shown an anti-inflammatory effect. But patients says it takes the pain away – so it is symptomatic treatment.

Dr Opheim added that changing the microbiota with probiotics now can be excluded from CAM, and enter evidence-based medicine instead.

Physicians have to be aware of these therapies
She continued by talking about cannabis.

- Some patients with CD use it in order to control symptoms. There are few controlled studies, but those that exist reported. For vedolizumab the data is insufficient.

A laparoscopic surgical approach can be used safely in children.

- However, the sizes and types of the instruments must be carefully elected for children. Use shorter tips – there is limited intraabdominal space, and shorter instruments because the patients are smaller with shorter distances.

The child’s small and narrow pelvis makes it difficult to operate beneath the peritoneal fold – it is easier with laparoscopy.

- Hand sewing is more common in children, due to a lack of instruments in suitable sizes, Dr Stenström pointed out.

In the future she envisioned both national and international centres for surgery in children.

- And we need suitable instruments for small children – also for robotic surgery! We also need national and international longitudinal registries that covers childhood, adolescence and adulthood, she stated at the end of her lecture.
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Erika M. Klintberg says it improves sleep, gives pain relief, decreased diarrhoea and stimulates the appetite.

Mind-body therapies – such as relaxation, yoga, mindfulness hypnosis and meditation – has been shown to reduce stress and induce well-being. There are very few side-effects with these, she underlined.

– But there is a gap between the frequency of use and evidence-based efficacy of the therapies. However, a study found that only 48% of IBD patients regarded scientific foundation for the therapies as being important, Dr Opheim continued.

The users are often of female gender, of a younger age and have a higher education. They’ve experienced side effects, and perceived a lack of effect from, conventional medicine. They also scored better on SF-36 scores (used to indicate health status of particular populations).

– That shows that there is a positive effect.

The reasons for patients to use CAM are several – it allows them to take an active role and personal control, there is a movement toward patient autonomy and the communication between patient and doctor is often not optimal, were those Dr Opheim mentioned.

– Physicians should be aware of the various types of these therapies – in order to be able to discuss the pros and cons of complementary therapies with their patients, she finally stated.

Gaps in the universe of reproduction
What do we know about reproductive issues in men and women with IBD? This question was also the headline for a talk given by Prof Bente Nørgaard, Denmark.

– We know a lot, although there are still knowledge gaps, she started by saying.

The reason for these gaps is not a lack of interest – this has been comprehensive, she added.

– But, despite decades of research, it is still difficult to give qualified answers to several simple questions.

The problems are related to the nature of our data sets – they are not large nor good enough, according to Prof Nørgaard.

– There are also problems related to the complexity of factors we have to take into account. And the number of relevant reproductive outcomes to study is at least equal to the number of outcomes in non-IBD patients.

She presented a study on assisted reproductive technology (ART) treatments in women with IBD. It found that the chance of a live birth in women was decreased after ART.

– But once clinically pregnant, our results suggested a normal chance of maintaining the fetus throughout the pregnancy until delivery. But our results have to be confirmed in other settings. The reasons for a possible reduced chance of implantation is so far unknown.

Prof Nørgaard emphasised once again there are plenty research gaps in the universe.

– To summarise these gaps, we lack evidence on fertility related aspects, on early pregnancy loss and mechanisms of adverse birth outcomes. We also lack evidence on the impact of maternal IBD medication during pregnancy, and long-term health outcomes in the offspring.

Physicians should be aware of the gaps in the universe of reproduction.

– Physicians should be aware of the gaps in the universe of reproduction.

An with this, IBD Congress News also finishes its report from IBD Nordic Conference. At the end, Chair Prof Øresland announced that it will return to Malmö in November 28 - 29 in 2019. Needless to say, everyone is invited – not only doctors from the Nordic countries. So mark your calendar!

Per Lundblad