KEEP CALM AND USE BIOMARKERS IN IBD

The chronic, progressive nature of IBD has a significant impact on patients' lives, and presents an ever growing burden on society. Recent evidence supports the regular monitoring of objective markers to maintain tight disease control. In a satellite symposium, sponsored by Abbvie, the role of biomarkers in driving a treat-to-target approach in IBD was discussed.

In his welcoming address, Chair Prof Remo Panaccione, Canada, talked about the rising incidence of IBD in industrialised countries.

– There has been an industrialisation and Westernisation of countries in Asia, Middle East and South America – and emerging cases of IBD in these countries. This has an impact on the global burden of IBD, he pointed out.

Unfortunately, IBD onset usually occurs between 15 and 40 years of age – a time when individuals are economically and educationally productive, Prof Panaccione continued.

– We want to normalise their quality of life to what they had before they were diagnosed. That is what we should strive for.

Peter Bossuyt, Remo Panaccione and Jonas Halfvarson

Helpful tools

Dr Jonas Halfvarson, Sweden, talked about biomarkers.

– Frequent use of endoscopy for monitoring is costly and invasive. A god surrogate marker for endoscopic activity would reduce the number of endoscopies needed. CRP and faecal calprotectin (FCP) are the best surrogate markers currently available, Dr Halfvarson said.

CRP is a helpful tool in the diagnosis – a surrogate marker of disease activity, a helpful marker of ongoing inflammation monitoring and predictor of response and relapse. Short term normalisation is predictive to response to therapy, and ongoing elevation is a predictor of relapse.

– But as you know, CRP is a marker of *general* inflammation, and may therefore not always be an accurate measure of inflammation in the bowel, he continued.

FCP is also useful tool. Decreasing levels correlate with clinical response and mucosal healing. It can help predict relapse and post-operative recurrence.

– FCP is also useful to decide when – and in whom – a more invasive endoscopy or disruptive MRI should be performed.

Dr Halfvarson underlined that further research is needed.

– This to define optimal cut-off values for diagnosis and follow up, characterise intra-individual variations in FCP and to determine optimal timing and frequency of stool sampling and measurement.

If we are going to measure this in a chronic patient over long time, we need at-home FCP tests for routine monitoring of disease activity. He presented *IBDoc*, as a suitable tool for this task.

– In Sweden we have integrated this with our IBD registry SWIBREG, Dr Halfvarson ended his lecture.

Evidence for tight control

Dr Peter Bossuyt, Belgium, presented data from the CALM study. In this trial on Crohn's disease (CD), half of patients (122) were randomised to clinical management driven by CDAI and prednisone use, and the other half (122) to tight control: Escalation driven by CDAI, FCP, CRP and prednisone use.

– Patients had a very short duration of CD when they entered the trial, he said.

Data from week 48 showed a better outcome for the tight control arm.

– Monitoring is one thing, taking action is another thing. If you adapt treatment after monitoring, you get *better* results. If you combine CRP and FCP you get even better results, Dr Bossuyt stressed.

So can we trust biomarkers in IBD management?

– We have been lacking evidence for this – until now. CALM shows that we can. Biomarkers are the main drivers of treatment decisions during monitoring, they reflect endoscopic outcomes and are independent of disease location.

Prof Panaccione ended the symposium with an economic analysis comparing the two treatment strategies in CALM.

– Modelled into 2 years, it shows that tight control is less costly and more beneficial. It is saving society money, he stated.

Per Lundblad

ANTI-TNF IN IBD: INVENTORY AND OUTLOOK

At a satellite symposium in the format of an interactive discussion forum, sponsored by Biogen, a faculty discussed their personal experiences of integrating biosimilars into daily clinical practice.

Chair Prof Gert van Assche, Belgium, greeted all delegates welcome. He continued by talking about the expanding IBD treatment landscape.

– Biosimilars have opened up that landscape, I think anti-TNFs are going to remain important as a treatment option, he said.

Fraser Cummings, Yoram Bouhnik, Gert van Assche, Raya Atreya and Geert D'Haens

Gain share

When one change from a reference product to a biosimilar, this is called a "switch". Dr Fraser Cummings, UK, described how they did a switch in the UK.

– We found that a managed switching programme, using a gain share agreement, delivered significant cost savings and service development while maintaining similar patient reported outcomes, biochemical response and adverse events profile, he said.

Gain share means the money that is saved is shared with the unit, and don't just disappear. According to Dr Cummings this is a very important model.

He underlined the importance to ensure that *all* staff members had confidence in what they were doing.

– The infusion Nurse is a key figure!

Dr Cummings also said that he thought that a switch from a subcutaneous drug to an infusion is going to be opposed by patients.

CREOLE study

Prof Raya Atreya, Germany, pointed out that we for the last years have seen very convincing and robust data for biosimilar infliximab.

– In my unit we decided to switch 160 patients early last year. This enabled us to employ a second physician – which also is a gain share.

He explained that they saw no statistical difference in clinical outcome or trough levels after 6 months in those patients.

Dr Yoram Bouhnik, France, said that they in his department decided not to switch immediately.

– From a scientific point of view, we eventually found that we had enough evidence, so our head of department finally decided to do it. The patients have to agree though, and now most of them do.

He also presented data from the CREOLE study, on the efficacy of adalimumab in patients with Crohn's disease and symptomatic small bowel stricture.

– The success rate was 64 %.

– We were very scared to use anti-TNF in strictured patients. But you have showed us that it works. It proves that there is an inflammatory ingredient in strictures, said Prof Geert D'Haens, The Netherlands.

Tell the patient what you know

The SECURE study was on a switch from reference infliximab to biosimilar infliximab. The data was presented by Prof D'Haens.

– We measured serum concentrations at week 8 and 16, and there were no differences between the biosimilar and the reference product.

For immunogenicity, the figures were again very reassuring, he continued.

– With these data from 100 patients, we went to our patients and asked them to switch. It took us a year, but now 95 % of them are on the biosimilar.

The keynote, according to Prof D'Haens, is to tell the patients what you know.

What about a second switch?

– I think that's OK if the one you are changing to is manufactured by the same producer. If not, I would be hesitant. We lack data on second switching – and that is something we need.

The symposium ended with a discussion on pharmacy switch, i.e. the pharmacy switches on its own – despite what the physician has prescribed.

– It is not an issue in Germany, the pharmacist will give the patient what they have been prescribed, said Prof Atreya.

– In the Netherlands the hospital decides. But you can't be sure where this is going, said Prof D'Haens.

– I think we need to know what is going on – if we are going to take responsibility for our patients, said Dr Cummings.

Per Lundblad

ENTERING A NEW ERA OF PATIENT-REPORTED OUTCOMES IN IBD

IBD can have a significant impact on patients' well being and health-related quality of life. To tackle disease burden and provide benefits meaningful to patients, health authorities are recommending assessing disease activity with objective markers of inflammation, together with patient-reported outcomes (PRO). In a satellite symposium, sponsored by Takeda, the ongoing evolution of PROs in IBD was discussed.

Prof Peter Higgins, USA, was the Chair.

– PROs reflect how patients feel and function at present, whereas objective measures of inflammation predict future disease activity and clinical outcomes. So they complement each other, he said.

Currently, no validated ulcerative colitis (UC) and Crohn's disease (CD) PROs exist that qualify for FDA labelling claims.

– Development of a valid PRO is a complex and lengthy process. While we are waiting, symptom-based PROs adapted from Mayo score or CDAI are useful in the interim – to keep clinical development going, Prof Higgins continued.

Brian Faegan, Peter Irving and Peter Higgins

Interim PROs are consistent with meaningful benefits

Prof Brian Faegan, Canada, stated that physicians always underestimate patients' symptoms.

– The use of PRO instruments is part of a general movement toward the idea that the patient, properly queried, is the best source of information about how he or she feels. This is the FDA's position, Prof Faegan said.

He continued by describing how in infliximab trials 20 years ago, a rectal bleeding score of 1 was accepted as clinical remission. However today, FDA states that it should be 0.

– And 20 years ago we used the CDAI score in CD. But that is not approved by FDA anymore, Prof Faegan said.

He presented data from a post-hoc analysis of the GEMINI 1 on vedolizumab in UC. In the placebo arm 13,5 % of patients had Mayo 0 rectal bleeding. compared to 32, 8 % for vedolizumab. Also in the vedolizumab trial for CD, both trial-defined remission and symptom-based PRO remission were higher than placebo,

– Results from interim PROs are consistent with meaningful benefits in both UC and CD patients. Interim POs will ultimately be replaced by fully validated instruments, Prof Faegan concluded.

IBD control questionnaire is recommended

The use of PROs in management of patients with UC or CD can focus visits on the issues patients care about, Dr Peter Irving, UK, said.

He talked about IBDQ-32, which is a PRO instrument, commonly used in IBD trials.

– A change in IBDQ total score matches clinical response, as demonstrated in the ACT 1 and 2 trials for UC.

However, IBDQ – although widely used – has limitations.

– It is designed to be a 4-domain – bowel, systemic, social and emotional – health-related quality of life instrument. But there are problems, such as double-barrelled questions. For example – fear of not finding a washroom, should it be in the emotional or bowel domain?

Some IBDQ items my carry more weight than others for patients. Dr Irving presented the top 15 most important symptom concepts for patients. The top 4 were abdominal pain, increase in bowel movements, tiredness/fatigue and diarrhoea.

– So it may be more beneficial to study treatment effects based on individual selected items, instead of a total score, he commented.

ICHOM stands for international consortium for health outcomes measurement. They have a standard set for IBD – the IBD control questionnaire. It is unanimously recommended as a PRO tool for use in healthcare settings.

In clinical practice, Dr Irving recommended to autosend the questionnaire 7 days before visit via a web portal.

– PRO e-monitoring tools may help improve how we deliver value-based healthcare. Continuing development and application of PROs in daily practice can also positively affect clinical care of our patients, was Dr Irving's summary.

Per Lundblad

PHYSICIAN: SHERLOCK AND SAVIOUR

IBD can have substantial psychosocial implications, limiting the lifestyle of IBD patients. Patients with microscopic colitis (MC) are often stepchildren in IBD, but they also have a severe impaired quality of life. In a satellite symposium, sponsored by Tillotts Pharma, the importance of quality of life (QoL) in IBD patients was discussed – and how a prompt diagnosis and treatment may improve QoL in MC patients.

The Chair was Prof Axel Dignass, Germany, and he introduced Dr Yoram Inspector, UK. He talked about the psychiatric and the psychological burden of IBD on QoL.

Yoram Inspector, Axel Dignass and Andreas Münch

Chronic inflammation affects the brain

– People have known since the beginning of time that the body is one whole unit. Also that a lot of stress goes into the bowel, Dr Inspector started by saying.

This goes through what is called the brain-gut axis, an autonomic nervous system modulating a wide range of GI target cells.

– Chronic inflammation affects the brain – and a study from 2013 revealed that intestinal inflammation may result in decreased sensitivity to positive emotions, Dr Inspector underlined.

Research has shown that no statistically significant difference was found between ulcerative colitis (UC) and Crohn's disease (CD) in all health-related quality of life (HRQoL).

– Also that IBD patients in remission experience better HRQoL, compared to patients with active disease. So induction of remission should become the main stay of care regarding improvement in HRQoL, he summarised.

A significant impact on quality of life

MC is all about quality of life, said Dr Andreas Münch, Sweden

– It is a disabling disease – more common in Sweden than CD, he continued.

Data presented at UEG Week last year showed a steep increase in incidence of MC.

– Someone thought of taking biopsies from patients with chronic diarrhoea, Dr Münch commented.

That is what characterise MC – chronic, watery diarrhoea. Mainly it affects women over 65 years of age. Biopsies are essential for diagnosis, and Dr Münch showed the histological spectrum of MC in images – there are three subtypes: Collagenous colitis, lymphocytic colitis and incomplete MC.

The clinical criteria for disease activity in MC are as follows: Clinical remission is defined as less than 3 stools per day and less than 1 watery stool per day. Clinical activity is defined as 3 or more stools per day – *or* 1 or more watery stool per day.

– Patients with clinically active MC have a significant impact on their quality of life, probably due to that sudden onset of symptoms is reported in 55 %. They are afraid of going out, drive a car etc.

Therefore he stated that all patients with chronic diarrhoea should be referred to colonoscopy.

– Stool *consistency* influences quality of life more than stool *frequency,* and therefore treatment can be justified also when patients have less than 3 watery stools per day.

A common chronic inflammatory bowel disease

There is effective treatment for MC – budesonide has been shown to be effective both in inducing and maintaining clinical remission.

– After diagnosing MC, consider if it can be drug-induced and consider smoking cessation. Smoking has a significant association with watery diarrhoea, Dr Münch underlined.

Treat with budesonide 9 mg/daily for 6 - 8 weeks. Initially this will get approximately 80 % of patients in remission.

– But 60 % relapse. If so, try maintenance with a lower dose, up to 6 mg/daily of budesonide.

If there is no response or intolerance – reconfirm MC diagnosis and consider differential diagnoses. Then adalimumab or infliximab can be tried – or an ileostomy.

At the end of his lecture, Dr Münch pointed out that MC is a common chronic inflammatory bowel disease.

– Abdominal pain is common in MC, so make sure to rule out IBS. Be aware of the consequences of watery diarrhoea – as urgency and faecal incontinence, he said.

Per Lundblad

CHANGE MANAGEMENT IN IBD – ARE WE MASTERING IT

At a satellite symposium, sponsored by Ferring pharmaceuticals, personalised treatment and the role for 5-ASA in treat-to-target strategies was discussed.

Prof Subratra Ghosh, UK, who was the Chair, talked about the "real price" of IBD.

– Indirect costs relate to higher rates of unemployment, sick leave and disability, and these costs may exceed direct costs, he said.

Prof Ghosh continued with tailored management in IBD. First thing to do is to establish management goals in conjunction with the patient.

– Management can make a big difference here, and make a dent in these costs, he underlined.

He also pointed out that in clinical practice, we now deal with fatigue, sexual dysfunctions etc.

– IBD care in the clinic is more multidimensional than in clinical trials.

Paolo Gionchetti, Subratra Ghosh and Bas Oldenburg

5-ASA in UC and CD

Prof Paolo Gionchetti, Italy, then talked about the treat-to-target (T2T) approach in mild to moderate IBD.

– IBD is a very heterogeneous disease, so we can not have just *one* approach, he said.

Therefore we need personalised treatment – and that is what T2T is all about, Prof Gionchetti continued.

– It means that one should set a target, monitor and alter therapy if the target is not met.

Categorise patients effectively – with understanding of the patient's clinical characteristics and prognosis. Then establish the management plan – with selection of appropriate initial therapy, and with monitoring and adaptation of therapy moving forwards.

In ulcerative colitis (UC), rectal 5-ASA should be considered a first-line therapy for patients with mild to moderately active distal UC. A Cochrane review 2016 found that oral 5-ASA once daily is as effective and safe as conventional drug dosing for maintenance of remission in quiescent UC, Prof Gionchetti told the audience.

– A meta-analysis of mucosal healing rates found that 5-ASA preparations achieved mucosal healing in nearly 50 % of patients with UC. There were no significant differences between the various 5-ASA agents in either oral or rectal treatment groups.

In Crohn's disease (CD), a Cochrane systematic review found that 5-ASA was not more effective than placebo. However, the pooled analysis suggests that 5-ASA preparations may be superior to placebo for the maintenance of surgically induced remission in patients with CD, even if this benefit is modest.

– In population based studies, there is a significant amount of CD patients that only received treatment with 5-ASA and never received steroids, he ended his talk.

Non-adherence is common

The incidence of IBD is increasing, even in a high prevalence country such as the Netherlands, said Prof Bas Oldenburg, The Netherlands.

He talked about the COIN study, a large national study on costs of IBD in the country.

– It found that IBD-related costs remained stable over the two years investigated – but the proportion of anti-TNF related healthcare costs *increased*, while hospitalisation costs *decreased*.

The study had also investigated self-reported non-adherence data, and found these to be very high.

– And since they were self-reported, they are probably even higher in reality. Non-adherence is associated with loss of response.

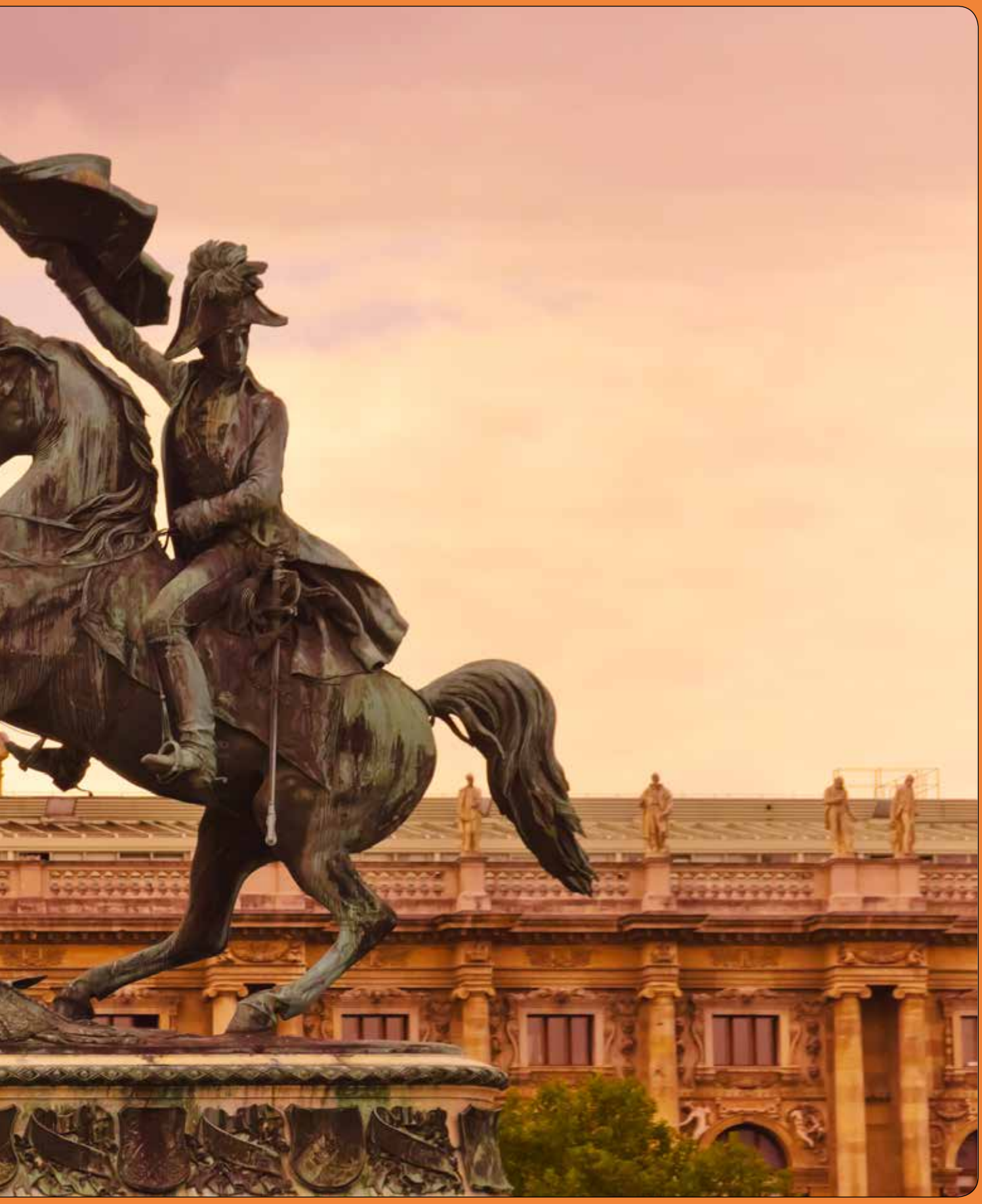
Prof Oldenburg presented a randomised study on mesalamine dose escalation in patients with quiescent UC. It had shown that this reduces faecal calprotectin.

– So it might be a good idea to take calprotectin also in UC patients that are maintained in remission with 5-ASA.

In his conclusions, Prof Oldenburg stated that non-adherence and low-dosing is common in IBD. Medication costs of IBD are high, but might be balanced by a decrease in hospitalisations and surgery.

– Targeting non-adherence and optimisation of drug dosing have a great potential for preventing relapse and/or the need for step-up!

Per Lundblad



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CONGRESSES 2018–2019

Falk Symposium 210: Crossing New Borders in IBD: Thoughts and Demands - From Mechanisms to Treatment
20-21 April 2018
Lisbon Portugal
www.falk-foundation-symposia.org/uploads/

Digestive Disease Week (DDW)
2-5 June 2018
Washington DC USA
www.ddw.org/home

Falk Symposium 212: IBD and Liver: East meet West
7-8 September 2018
Kyoto Japan
www.falk-foundation-symposia.org

European Society of Coloproctology
26-28 September 2018
Nice France
www.escp.eu.com/conference-and-events/escp-nice-2018

Falk Symposium 213: Tailored therapies for IBD: A look into the future
5-6 October 2018
Milan Italy
www.falk-foundation-symposia.org/uploads/ tx_tocfpshoperw/S213_Milan_2018_Announcement.pdf

IBD Nordic Conference
11-12 October 2018
Quality Hotel View
Malmö Sweden
www.ibdnordic.se

UEG Week
20-24 October 2018
Vienna Austria
www.ueg.eu/week/past-future/ueg-week-2018/

Japan Digestive Disease Week 2018
1-4 November 2018
Kobe Japan
www.jddw.jp/english/index.html

Asian Pacific Digestive Week
15-18 November
Seoul Korea
www.apdw2018.org

ESPGHAN 4th Paediatric IBD Masterclass
25-27 November 2018
Copenhagen Denmark
www.espghan.org/index.php?id=569&eventId=140

Advances in IBD
13-15 December 2018
Orlando USA
www.advancesinibd.com

Crohn's & Colitis Congress
7-9 February 2019
Las Vegas USA
www.crohnscolitiscongress.org/CCC1/Public/Enter.aspx

ECCO Congress
6-9 March 2019
Copenhagen Denmark
www.ecco-ibd.eu/ecco19.html

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