PIBD IN BARCELONA 2017

The fourth International symposium on paediatric IBD – PIBD – was held in Barcelona, 13th - 17th of September 2017. It attracted 527 delegates from 57 countries and 5 continents to come to the Spanish city. The Meeting was organised by European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN).

The symposium has so far been held every third year, but at the Opening Session in Barcelona Dr Javier Martín de Carpi, Spain, and Prof Dan Turner, Israel, who both represented the organizers, told the audience that from now on this will a biannual Congress.

– The next will be given in Budapest 2019, Prof Turner said.

The delegates were also greeted welcome by Prof Julian Panes, President of ECCO.

– In ECCO, we are working with you paediatricians as much as we can. Our paediatric content at the ECCO Congress will continue to increase, Prof Panes said.

Pitfalls of primary non-response

Prof Maria Dubinsky, USA, gave a lecture on how to manage the unsatisfactory response to anti-TNF treatment. This she began by identifying three types of patients with unsatisfactory response:

– It could be the patient is not responding – a primary non-responder. Or a patient who *loses* response, and finally a patient who refuses your therapeutic recommendations, she said.

Prof Dubinsky started with primary non-response. This could be due to a biological mechanism (e.g. not TNF-driven), or that the cause of disease is not inflammation – or the patient suffers from an infection, especially *C.difficile*.

– It could also be a dose failure: Underdosage, or exposure issues – e.g. loss of monoclonals in stool.

The approach to primary non-response should be to use objective measures of disease activity, rule out strictures and infection and confirm adherence.

– Consider a switch from subcutaneous to intravenous anti-TNF. Ask yourself where the drug is going – understand who is at risk for needing more drug: Those with high inflammatory burden, low albumin or high CRP, males and those with a high BMI.

She presented a study from 2015 on faecal loss of infliximab that had concluded that this loss may contribute to primary non-response in severe IBD colitis.

There are many pitfalls of primary non-response: Giving up too early, waiting to long, not engaging surgery early – or even *first*, inappropriate dosing (usually underdosing)

and inability to assess pharmacokinetics.

– Patients at risk of developing anti-drug-antibodies (ADA) are patients receiving episodic therapy and "pseudo-episodic" therapy – by that I mean subtherapeutic serum drug levels, or having drug clearance between doses.

Recognizing reason for failure can guide treatment

Combination therapy enables multiple mechanisms of disease control and a reduction in ADA.

– The benefit of combination therapy with azathioprine and infliximab is primarily due to azathioprine's influence on the pharmacokinetics of infliximab, Prof Dubinsky explained.

She presented a study on prospective therapeutic drug monitoring to optimise infliximab maintenance therapy in IBD. The conclusion was that dose optimisation increases the probability of remaining on infliximab up to 5 years.

– Proactive infliximab drug monitoring is associated with less surgery and hospitalisation, according to a study presented at DDW earlier this year.

In her summary, Prof Dubinsky stressed that recognising reason for failure can guide decision making. Measuring anti-drug-antibodies and drug levels can help guide treatment decisions.

– Optimised monotherapy with proactive monitoring may be an effective and safer option. Individualised and dashboard guided dosing is closer than we think, Prof Dubinsky ended her lecture.

Vedolizumab safe and effective in children

How to use new biologics in children? Prof Robert N. Baldassano, USA, talked about this.

After taking a quick look on what is in the pipeline of therapies for paediatric IBD, he turned his attention to present available biologics, and the evidence for gut-selectivity for vedolizumab.

– Three trials in paediatric children found that patients randomised to placebo had a *higher* rate of infections compared to those on active drug, Prof Baldassano said.

Published papers on paediatric use of vedolizumab all show that for ulcerative colitis (UC) the response came quicker.

– For Crohn's disease (CD), the patients took longer time to respond – but they eventually did.

Two studies are ongoing on measuring drug levels in children on vedolizumab, he added.

In his summary, Prof Baldassano underlined that paediatric UC patients responded earlier – and had higher remission rates – than their CD counterparts.

– Anti-TNF naive paediatric patients had experienced remission in higher rates than those with previous anti-TNF exposure. Preliminary data are suggesting that shortening infusion interval to 4 weeks may improve effectiveness in some patients.

"SURGERY MAY BE CONSIDERED AS AN ALTERNATIVE TO MEDICAL THERAPY"

This led him to the following conclusions:

– These studies present encouraging data that vedolizumab is safe and effective in paediatric UC, and to a lesser extent also in CD. However, rigorous dose finding efficacy trials are necessary. We should all participate!

Avoid extensive resections of the small bowel

One of the sessions in Barcelona concerned guidelines and position papers. Dr Jorge Amil Dias presented, on behalf of the IBD working group of ESPGHAN, the guidelines for surgical management of CD in children.

– Remember that surgery in CD is treatment, he stressed.

The guideline states that surgery may be considered as an alternative to medical therapy when a patient has active disease limited to short segments, despite optimised medical treatment.

– Surgery should be considered in children in prepubertal or pubertal stage if growth velocity for bone age is reduced over a period of 6 - 12 months – in spite of optimised medical and nutritional therapy, Dr Dias continued.

The evaluation of a refractory patient must be thorough.

– A complete assessment of the patient's general and bowel condition is recommended prior to elective surgery in order to optimise the surgical approach, minimise the length of bowel resection, and reduce the risk of complications. It should include history, physical examination, endoscopy imaging studies, screening for concomitant infections and nutritional defiencies.


Maria Dubinsky


Robert N. Baldassano

Extensive resections of the small bowel should be avoided as they pose a long-term risk of development of short bowel syndrome.

– When a patient has pancolonic disease, the choice of surgery is subtotal colectomy and ileostomy. Later ileorectal anastomosis can be performed if the rectum is spared and there is no significant perianal disease. One stage ileorectal anastomosis is generally *not* advised.

Post-operative medical treatment should be based on ileocolonoscopy assessment and not solely on symptoms or serum inflammatory markers. Repeated faecal biomarkers testing may aid in deciding in the timing of endoscopy.

– Thiopurines may be used for preventing post-operative recurrence in moderate risk. When thiopurines have failed preoperatively, their post-op use requires careful risk-benefit analysis, Dr Dias stated.

The role of capsule endoscopy

Dr Salvatore Oliva, Italy, presented endoscopy guidelines.

– *Why* do we need endoscopy guidelines in paediatric IBD? Because there are none – and we have new classifications, advances in endoscopic tools and the importance of mucosal healing, he explained.

Dr Oliva started with monitoring.

– *When* should we do this? Before major treatment changes – escalating or de-escalating. Also in symptomatic patients when it is not clear whether the symptoms are inflammation-related.

In CD, monitoring should be performed to ensure mucosal healing during clinical remission. In UC, monitoring should be performed to ensure mucosal healing only if faecal calprotectin is high. Ideally, mucosal healing would mean lack of inflammation (SES-CD and Mayo/UCEIS = 0). Endoscopic remission is defined as SES-CD 2 or less and Mayo/UCEIS 1 or less. Endoscopic response is defined as a decrease from baseline of more than 50 %.

– So, how *frequent* should we do this? Following a bowel resection, endoscopy should be performed 6 - 12 months later – faecal calprotectin could assist with the exact timing, Dr Oliva continued.

The need for endoscopic reassessment should be individualised according to disease type, severity, risk of relapse and risk of progression.

– To date, the 6-month assessment seems to be a reliable endoscopic time point for the first mucosal healing evaluation after a major change of therapy in high risk CD.

On the small bowel, the guidelines state that capsule endoscopy is complementary to MR enterography (MRE) for evaluating the small bowel in children with suspected CD. In established small bowel CD, capsule endoscopy can detect residual inflammation even in the presence of normal serum and faecal inflammatory markers and MRE. It can also confirm small bowel mucosal healing after commencing a new treatment.

Finally Dr Oliva talked about surveillance.

– A surveillance program should be considered in paediatric UC after 10 years from the onset of disease. As early as 8 years for extensive colitis, high burden of the colitis over time and family history. PSC should prompt even earlier surveillance. The screening program should be performed by an experienced endoscopist in this particular field.

Stem cell transplants

How to manage CD when medications are not working, was the title of a talk from Dr Athos Bousvaros, USA.

– Overall, I would say our aims of treating IBD are twofold – to improve quality of life and to reduce the likelihood of complications, he said.

But in this patient population, decision making is difficult. Often the patient has been sick for a long time and has been living with severe disability.

– Surgical intervention often means long term ileostomy, with no guarantee of success. A majority of these difficult patients have severe ileocolonic or panenteric CD.

Athos Bousvaros

Gert van Assche

And there is always another medication that can be tried.

This led Dr Bousvaros to stem cell transplants.

– Allogenic (= from a healthy donor) is probably the treatment of choice in many *monogenic* conditions that result in very early onset IBD. Autologous stem cell transplant (=cells are removed from a person, stored, and later given back to that same person) in adult type IBD is a very high risk procedure of unclear efficacy and safety. It should be limited to high quality centres, with a very strong clinical and research program and done under internal ratings based supervision. The procedure should probably be limited to patients with extensive small bowel CD that cannot be treated surgically, he continued.

The last resort

Diverting ileostomy can be extremely helpful in patients with refractory CD of ileum and colon, Dr Bousvaros established.

– Make sure you know the status of the proximal small bowel before you divert. Optimise nutritional status – and make sure the patient knows that the ileostomy may well be a long term condition.

Parenteral nutrition is usually used short term.

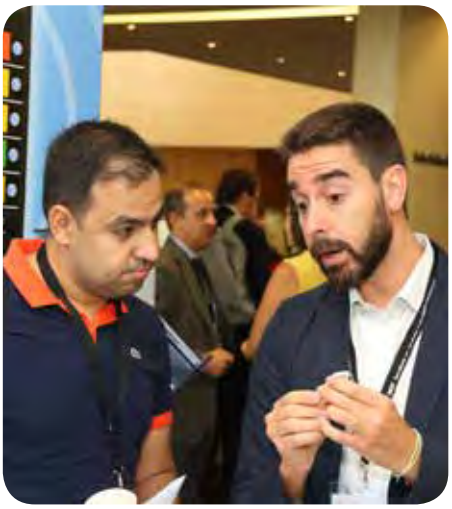
– There are some open label data on induction of remission and healing of fistulae – with around 50 % efficacy. But it is not recommended for long term use due to the risks of thrombosis, infection and cholestasis.

Small bowel transplant is the last resort. Indications include panenteric CD with intestinal failure and short bowel syndrome. Complications include rejection with or without graft failure and infection – bacterial translocation and opportunistic infection.

– Outcomes of 134 adults with CD were 69 % with 1 year survival and 62 % with 5 years survival.

In his conclusions, Dr Bousvaros said that a small subset of patients with CD will be refractory to multiple medical treatments.

– Stem cell transplant may be the treatment of choice in certain monogenic cases of IBD, but should be considered risky and experimental in conventional CD. Diverting ileostomy improves quality of life in selected patients with colonic or perianal CD, but may not heal the inflamed bowel, he ended his talk.



Cost consideration the main driver

Another session contained the adult versus the paediatric perspective. "Do our patients need continuous treatment for life", was the question that was asked. Prof Gert van Assche, Belgium, started with the adult perspective.

– Exit strategies for early top-down therapy in CD are always a trade-off – should you stop the anti-TNF or the immunosuppressor? Since patients are not the same, we can't have rules, he said.

Prof van Assche told the audience that data from Korea on children showed that only 19 % relapsed when they were stopped.

– So *perhaps* it is better to stop in children, but that has to be followed up.

There are no fixed stopping rules for biologics or immunosuppressives. Prospective data are mainly with infliximab and azathioprine.

– And there are no data for adalimumab and methotrexate.

Therapeutic decisions should therefore be patient centred.

– Combination therapy increases the efficacy of infliximab therapy for at least one year, but continued combination adds a safety risk. Age is an important modifier for decisions on combination therapy – elderly patients are more at risk.

Prof van Assche pointed out that most patients can safely be re-exposed to infliximab if immunosuppressives are continued.

– And finally we have to say that cost considerations has been the main driver for attempts to stop biologics.

A 3 year interval can be beneficial

Prof Frank Ruemmele, France, then presented the paediatricians perspective.

– What is the real challenge in IBD? It is to bring our patients in remission and prevent damage – not to find exit strategies, he started by saying.

There is no literature on stopping treatment in children. Prof Ruemmele pointed out that there is a higher inflammatory activity in paediatric IBD, compared to adult-onset IBD.

– So why stop therapy? There is a risk of disease relapse, which can affect growth, quality of life, disease symptoms, prevention of complications and disease progression and treatment optimisation, he continued.

On the other side of the scale there is the risk of adverse events with medication – infections, malignancies and induction of immune-mediated diseases, as well as treatment costs and life quality, Prof Ruemmele admitted.

So exit strategies in paediatric onset IBD can be discussed.

– If the patient is in deep, prolonged remission and has no height retardation. It has to be steroid-free, or steroid sparing strategies. One has to have a discussion with the family on relapse rates – that can be up to 50 %.

Also one has to take into account adolescents risk behaviour, he underlined.

– They are at the age of tobacco introduction. And that's not a good time to stop.

In the debate between the two after their talks, Prof Ruemmele also pointed out that most patients respond if therapy is reintroduced.

– So a 3 year interval can be beneficial in many aspects.

Prof van Assche said that it is important to make a decision on stopping not only based on symptoms.

– We all know that teenagers don't like to talk about their symptoms, he said.

Always try to optimise therapies

In the last session Dr Javier Martín de Carpi talked about some misunderstandings of paediatric IBD.

These included that IBD is understood as a purely remitting-relapsing disease.

– And a few years ago we thought that an obese patient could not have CD, he pointed out.

We should not forget that our – more or less successful – practice can influence, modify, or determine the future evolution of the disease and of the patient, Dr de Carpi continued.

He underlined that follow-up in paediatric IBD should not only be organised on a demand basis. Instead the follow-up must be close, anticipatory and pro-active.

– When a patient previously in remission starts with symptoms, we must ask *why* does the medication fail? Is it loss of response, disease progression/extension/complication – or due to non-adherence? We must correlate symptoms with objective markers. If there is a discordance, it is mandatory to rule out non-inflammatory causes.

Javier Martín de Carpi

Frank Ruemmele

> **"WE SHOULD CONSTANTLY TRY TO IMPROVE THE ATTENTION GIVEN TO OUR PATIENTS"**

10 abstracts on therapeutic drug monitoring were presented at the Meeting, and Dr de Carpi stressed that TDM is coming more and more in paediatric IBD.

– When a change in medication is needed, be extremely careful with the decision – the options are limited. Always try to optimise the therapies, and remember that all loss of responses are not the same. Check adherence – many adolescents are not compliant. And think of the need of surgery due to disease progression.

The care given can be crucial

We should constantly try to improve the attention given to our patients, Dr de Carpi stated.

– This includes the use of new technologies, social networks and telemedicine. Create networks with patient's associations, schools, colleagues and primary care practitioners.

There are multiple benefits from a multidisciplinary approach, including paediatric gastroenterologists, surgeons and nurses.

– Also dieticians, pharmacists, psychologists, and social workers. In accordance with paediatric IBD nature, our care should be open to changes, dynamic and innovative.

He underlined that development of structured paediatric IBD units is mandatory.

– The only way to really improve the quality of care given to our patients is trough active collaboration of all paediatric "IBD-ologists" all over the world. So: Look deep, look closer, look further, look beforehand – and look jointly. Do not forget that the care given to our patients during paediatric age can be crucial – and for adaptation to the disease for the rest of their lives!

And with these words, PIBD in Barcelona 2017 had come to an end.

Per Lundblad