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“Challenges in the Care of IBD in Patients of All Ages”

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With Big Ben in the background: inflammatory bowel diseases in young and old

by Dr. Beate Fessler

“We are proud to be holding this meeting here in London”, **Prof. A. Forbes**, University College Hospital, London, said as he opened the Falk Symposium 190 “Challenges in the Care of IBD in Patients of All Ages” in the British metropolis. He and the other two scientific organizers, **Prof. A. Levine**, E. Wolfson Medical Center, Holon, and **Prof. C. Probert**, University of Liverpool, he continued, had managed to find “global experts and excellent speakers”, who had attracted over 1000 gastroenterologists from more than 60 countries to the bank of the Thames. With Big Ben in the background, they engaged in an intensive exchange of ideas and detailed discussions. In fact, this topic – inflammatory bowel disease in the very young and the very old – constantly manages to surprise.

Considerable differences: natural course of Crohn’s disease and ulcerative colitis

Although Crohn’s disease and ulcerative colitis are both inflammatory bowel diseases (IBD), they differ considerably in their course and accordingly in their treatment goals. Ulcerative colitis is characterized by acute inflammatory flare-ups and the treatment goal is thus to prevent recurrence and colorectal carcinoma, according to **Dr. E. Domènech**, Hospital Universitari Germans Trias i Pujol, Barcelona. Crohn’s disease, by contrast, exhibits persistent inflammatory activity associated with complications such as strictures, abscesses, and fistulae. These can already be detected at disease onset in 20–40% of patients and in up to 80% 20 years later, Dr. Domènech summarized. In such cases, the goal is to stop the progression to a stricturing or penetrating disease. Location of Crohn’s disease is relatively stable. It only spreads in 10–15% of cases. In 10% of patients complications are localized perianally at diagnosis and in 12% in the further course.

Childhood-onset more aggressive than adult-onset

The clinical course of IBD that onset in childhood is particularly aggressive. According to a Scottish comparative study of the clinical course of childhood-onset and adult-onset IBD, children with Crohn’s disease more frequently presented with a “pan-enteric” phenotype (43% vs. 3.2%). Over 80% of children with ulcerative colitis started out with pancolitis; in adults, the figure was around half. According to **Prof. D.C. Wilson**, University of Edinburgh, the differences cannot be explained solely by genetics. But data on epigenetics-related environmental influences have not so far produced any clear conclusions either. “We just don’t know”, he was forced to admit.

Predictors? Look at the clinical picture

An intensive search is underway for predictors that can be used to predict the natural disease course and so help guide the choice of therapy. Despite all the research into endoscopic, serologic, and genetic markers, clinical characteristics still remain the best predictors. **Prof. E. Louis**, C.H.U. Sart Tilman, Liège, emphasized the need to determine individual risk, based on, for example, disease location, extent of disease, lesion depth, or age. The discussion also covered the small but subtle distinction between parameters that are actually predictive and parameters that are “merely” associated.

Paris classification differentiates more precisely between children

Precise classification of IBD is, according to **Prof. J.S. Hyams**, Connecticut Children's Medical Center, Hartford, important for different reasons: on the one hand, from a scientific perspective but on the other hand also as a basis for informing patients and their relatives, particularly in the case of pediatric patients. Unlike the Montreal classification, which aggregates all patients under 17, the Paris classification differentiates between children over 10 and under 10. The recent discovery of monogenetic IBD in children under two, in the view of Prof. Hyams, makes a further distinction necessary, "since these children require specialized therapy."

Azathioprine delays progression to complications

Can the natural course of IBD be affected by drugs? Thiopurines, at least, often seem to do little to improve the situation. In one five-year study, a similar number of patients receiving thiopurines progressed to a stricturing (B2) or penetrating (B3) disease as the total study population. Data from Olmsted County exhibits a non-significant drop in the risk for B2 or B3 patients receiving treatment with 6-mercaptopurine (6-MP)/azathioprine. In-house data from **Prof. J.F. Markowitz**, Cohen Children's Medical Center, New York, in children, however, suggests that azathioprine can delay at least the onset of complications. The effect on the incidence of intestinal responses appears rather low. This changes if they are administered at an early stage. When they are applied in the first year after diagnosis, operation rates can be reduced significantly ($R = 0.47$).

Pediatric patients: biologics or early resection?

Prof. P.L. Lakatos, Semmelweis University, Budapest, has seen operation rates fall since TNF-alpha inhibitors were introduced. Data over the short and medium term indicates that mucosal recovery is achieved and hospitalization rates reduced. There is little data on the effect of biologics on the disease course in children, according to **Prof. M.C. Dubinsky**, University of California, Los Angeles. In her view, changing the disease course must actually denote prevention, not simply the closure of a fistula. "We should not just be looking at the mucosa but also at whether the children can lead a normal life," she emphasized. A look at what little data there is shows a reduction in operation rates in pediatric IBD patients treated with biologics. This is logical, since mucosal recovery should be associated with fewer strictures and fistulae and thus also with fewer operations. But Prof. Dubinsky remains skeptical and asks whether the quality of mucosal recovery achieved is good enough or whether early resection followed by biologics administration is the better strategy where complications arise. The simple strategy followed by **Prof. R.N. Baldassano**, Children's Hospital of Philadelphia, is: "We have to treat the disease as long as it remains inflammatory." The goal must be long-term remission and prevention of complications, as is the case in other chronic diseases such as hypertension, diabetes and rheumatoid arthritis.

Reaction on intestinal flora

Is Crohn's disease associated with a loss of tolerance towards resident intestinal flora or dysfunction of autophagy? Both, explained **PD Dr. M. Scharl**, Zürich University Hospital. The link between the two could be the NOD2 gene. The effect of the poorly absorbed antibiotic rifaximin on intestinal flora for maintaining remission in Crohn's disease was investigated by **Dr. A.O. Jigarano**, "Saint Spiridon" Emergency Hospital, Iasi. Following standard treatment with a steroid, placebo-controlled treatment was provided over 12 weeks. At the end of the study and after 24 weeks, the antibiotic was shown to be superior to the placebo.

If TNF-alpha blockers fail

Treatment with anti-TNF-alpha fails within 12 months in up to 50% of patients. The treatment interval can then be halved or, as patients generally prefer, the dosage increased. If this does not succeed, there is an argument for increasing antibody titers and decreasing TNF-alpha levels. Treatment can then be switched to another TNF-alpha blocker. However, escalating the dose further can also be successful. "In some patients this can overcome the antibodies," said **Dr. S. Ben-Horin**, Sheba Medical Center, Tel Hashomer. Another option is simply to wait. "'Wait and see' works with some patients," said Dr. Ben-Horin. If two TNF-alpha antibodies fail, the immunomodulator methotrexate can be used. It restores immunogenicity, reducing antibody levels and increasing API levels. In order to pre-empt a drop in efficacy, it should be used in combination with azathioprine since this reduces the risk.

Prof. M. Allez, Hôpital Saint-Louis, Paris, also recommended looking for other causes – complications such as abscesses, strictures, malignant lesions, or infection in patients refractory to treatment. It would be better to distinguish between responders and non-responders in advance of treatment. This may become possible using PIMS (Physiological Intermolecular Modification Spectroscopy), as **Dr. P. Eftekhari**, INOVEM Scientific, Strasbourg, showed in a blinded cross-sectional study. PIMS allowed responders to infliximab to be predicted with a high degree of probability.

Consider enteral nutrition

Nutritional therapy instead of steroids? – This is certainly an option, explained Prof. Levine. In children, high remission rates of between 75% and 85% can be achieved with special enteral nutrition as well as enteral tube feeding. Post-operative recurrence can be reduced considerably using enteral nutrition. Pathogenetic studies indicate an association between Crohn's disease and a diet high in sugar and animal fats. Emulsifiers in particular pose a risk for the intestinal barrier. In his view, it is therefore worthwhile considering enteral nutrition more intensively and clarifying outstanding issues.

Focus on: post-operative use of azathioprine in Crohn's disease

Despite developments in drug strategies, operation rates in Crohn's disease remain high. But what can be done to prevent post-operative recurrence? Seven randomized controlled studies and two meta-analyses indicate that 5-ASA has a minimal favorable effect. Studies indicate a non-significant effect for probiotics and the same applies for interleukin-10. The focus is now on azathioprine. It has been shown to be superior to 5-ASA endoscopically in one meta-analysis and also clinically in a further study. The TOPPIC (Trial of Prevention of Post-operative Crohn's Disease) study is now investigating 240 patients over three years to discover whether 6-MP can prevent or delay post-operative recurrence in Crohn's disease, explained **Dr. I. Arnott**, University of Edinburgh. The results are expected in 2015. Prof. Forbes drew attention to the problem of undernourishment in patients following bowel resection. This is too often underestimated. It is often associated with high levels of inflammatory activity. In his opinion, therefore, food supplements are important in patients who are clearly undernourished.

No response to azathioprine? Try metabolite monitoring

Azathioprine is being deployed increasingly frequently and earlier in maintenance treatment following drug-induced remission of Crohn's disease. The same applies to TNF-alpha inhibitors. The decision to use an API must, according to **Dr. D. Rampton**, The Royal London Hospital, be made on an individual basis taking into account various parameters such as duration and extent of disease and also patient characteristics such as age, smoking, weight progression, drug complications, or compliance. "One size fits all" does not apply to treatment of patients with Crohn's disease, said Dr. Rampton. If thiopurines are used, **Dr. P. Irving**, Guy's and St. Thomas' Hospital, London, believes, metabolite monitoring should always be performed if the patient does not respond to adequate doses within 12–16 weeks. Where 6-thioguanine nucleotide (TGN) levels are low and 6-methyl mercaptopurine (MMP) levels are high, i.e. where there is thiopurine resistance, the biochemical shunt can be adjusted by additionally administering allopurinol, which inhibits azathioprine metabolism to thiouric acid and improves efficacy.

Fecal microbiotics transplantation in ulcerative colitis too?

Should treatment focus on microbiotics rather than cytokines and T cells? A good question, as the importance of microbiotics in IBD pathogenesis is now undisputed. Reduced diversity of the microbiome is detected in children with severe ulcerative colitis. So far, strategies such as probiotics to treat changes in microbiota have been disappointing, explained **Prof. E. Wine**, University of Alberta, Edmonton. As in *Clostridium difficile* infections, fecal microbiotics transplantation is now also being attempted in children and young adults with mild to moderate ulcerative colitis. Seven out of nine patients responded to the therapy, six of them over one month. Three patients achieved clinical remission within a week (see also interview).

Always ask pediatric non-responders about compliance

Children with ulcerative colitis have a poorer response to steroids and are colectomized significantly more frequently. If drug therapy fails, particular attention should be given to their compliance. Here it is also important, says **Prof. D. Turner**, Shaare Zedek Medical Center, Jerusalem, to talk to the children on their own, without their parents, and to check API levels regularly. The possibility of other diseases should also be weighed up such as presence of an irritable bowel or lactose intolerance.

Preventing recurrence with xilei-san

If proctitis does not respond to standard treatment, according to **Dr. S. Keshav**, John Radcliffe Hospital, Oxford, intensive systemic therapy such as i.v. corticosteroids or cyclosporine should be initiated without delay. Biologics are also an option. However, Dr. Keshav also referred to new experimental approaches that appear eminently promising. These include treatment with suppositories containing xilei-san. This is a plant used in Chinese medicine that can reduce the risk of recurrence, as demonstrated by at least one small placebo-controlled study. An appendectomy may also reduce the risk of recurrence.

Keep an eye on AS and PSC

Extraintestinal manifestations may trouble patients more than the colitis itself. According to **Prof. T. Orchard**, St. Mary's Hospital, London, of relevance here is ankylosing spondylitis (AS). It develops in up to 5% of patients and is strongly associated with HLA-B27. Primary sclerosing cholangitis (PSC) is also strongly associated with ulcerative colitis. It is clinically relevant, since whereas patients with ulcerative colitis tend to live longer than the average population, mortality is considerably elevated in patients with concomitant PSC, explained **Prof. R.W. Chapman**, John Radcliffe Hospital, Oxford. PSC is a premalignant condition, he explained: "It is the most important cofactor for dysplasia and colon carcinoma in patients with ulcerative colitis." Findings on the use of ursodeoxycholic acid in chemoprevention are inconclusive, but "I believe it is significant," said Prof. Chapman. Achieving normal AP serum levels is a crucial factor for survival. If they improve to below 1.5 times the normal level, the outcome is considerably better.

Complicated: pregnant women – unclassified IBD – monogenic disposition

All women of childbearing age with IBD must, according to **Prof. J. van der Woude**, Erasmus Medical Center, Rotterdam, be asked directly whether they want to have children. If this is not the case, they should use reliable contraception methods. Otherwise, folic acid supplementation should be started. Even at this early stage, important issues such as fertility, heredity etc. should be discussed with patients. If a female patient is being treated with methotrexate (MTX) at the point of pregnancy, Prof. van der Woude believes this is no reason to terminate the pregnancy immediately. In these cases, he recommends immediately discontinuing MTX, administering high doses of folic acid, and investigating fetal health using 3D ultrasound. Treatment of unclassified IBD is just as problematic. Up to 10% of pediatric IBD diagnoses are unclassified. Treatment is as for ulcerative colitis, said **Dr. R.K. Russell**, Yorkhill Children's Hospital, Glasgow, until the diagnosis is clarified during follow-up. Babies that develop an IBD in the first few weeks generally have a monogenic disposition such as IL-10 axis defects or defects in apoptosis or a mutation in XIAP (X-linked inhibitor of apoptosis). Hematopoietic stem cell therapy may then be the correct course, as **Prof. F. Ruemmele**, Hôpital Necker Enfants Malades, Paris, showed.

Perianal sepsis in ulcerative colitis? It might actually be Crohn's disease!

According to a population-based cohort study in New Zealand, around a quarter of patients with Crohn's disease suffer perianal symptoms. In most cases, the symptoms are already present at diagnosis. In cases of non-septic presentations such as hemorrhoids or fissures, **Dr. K. Nugent**, Southampton General Hospital, advised against surgical intervention. The situation is different for septic conditions or strictures. The risk of perianal sepsis is particularly high where there is distal inflammation. If this is the case, proctectomy is often the only remaining option. Patients with ulcerative colitis develop perianal sepsis considerably less frequently. In these cases, a check should therefore always be made to discount Crohn's disease.

Awarding the Herbert Falk Prize

This year's Herbert Falk Prize, presented by **Prof. D.P. Jewell**, University of Oxford, went to **Prof. C. Fiocchi**, The Cleveland Clinic Foundation. Prof. Fiocchi's work culminated in the conclusion that the risk for IBD is essentially determined by the exposome and epigenetics. In his view, nutrition in particular has an essential effect on "genome, microbiome and immunome", essentially determining whether a IBD will develop.

Overcoming complications

Ulcerative colitis may have numerous concomitant complications including infections. "Exacerbation of ulcerative colitis may be associated with CMV infection", said **Prof. M. Novelli**, UCL Medical School, London. But salmonella or Clostridium difficile can also exacerbate the disease. In refractory ulcerative colitis a concomitant infection should therefore always be discounted first. **Prof. X. Hébuterne**, Hôpital de l'Archet, Nice, placed special emphasis on the 15% of IBD patients in whom the disease only manifests itself after 65. Particular care is advised when treating this group with immunosuppressants, biologics and steroids. Studies indicate, amongst other things, that the risk of severe infections is particularly high in older people treated with TNF-alpha inhibitors. Comorbidity rates must also increasingly be taken into account. The increased risk of colorectal carcinoma in patients with IBD is believed to be reduced by 5-ASA, explained **Dr. M.D. Rutter**, University Hospital of North Tees, Cleveland (GB). According to more recent studies, azathioprine can also reduce the risk of high-grade dysplasia and carcinoma in patients with long-term ulcerative colitis. Dr. Rutter referred in

particular to a study in which this risk was reduced by 72% compared to patients who had never been administered a thiopurine. The topic of “neoplasia” is entirely relevant even for children with IBD. In the first 8–10 years according to **Prof. P.A. Rufo**, Boston Children’s Hospital, however, it can still be disregarded. Overall, however, it is higher than in patients with adult onset, with a cumulative risk of 10.8% after 20 years versus 8.6%, according to the results of a meta-analysis. The relative risk of a carcinoma is 43 times higher in patients who contract the disease before their 20th year. They must be followed up particularly intensively.

Non-invasive diagnosis by VOC profile

Invasive diagnostic techniques in IBD are generally very distressing for patients and are not without risk. It may soon be possible to “sniff out” the disease from the odor of the stool. Gas chromatography detection of volatile organic compounds (VOC) from feces is at least a real possibility for distinguishing between Crohn’s and colitis patients and healthy subjects, explained Prof. Probert. Infants with necrotizing enterocolitis already exhibit a different VOC profile from healthy babies. There are also differences in the VOC profile between irritable bowel syndrome and active IBD as well as between active and inactive ulcerative colitis.

Cannabis yes, emulsifiers no

That cannabis can certainly be an option in IBD was made clear by **Dr. T. Naftali**, Meir Medical Center, Kfar Saba, based on in-house retrospective data taken from 30 patients with Crohn’s disease who had on average smoked one to three joints daily for three years. 70% of patients improved clinically. In particular, however, far fewer patients needed steroids than without cannabis use (4 vs. 26). Intensive research is also being conducted into APIs that improve intestinal barrier disorders as a cause of IBD. Above all, however, the intestinal barrier must not be damaged further. Intake of emulsifiers with food should therefore be avoided as much as possible, warned **Prof. J.M. Rhodes**, University of Liverpool.

Interview with Prof. Dr. Gerhard Rogler, Zurich University Hospital

“Individualized treatment can be achieved with accelerated step-up therapy”

Professor Rogler, the right therapy for the right patient at the right time: This individualized approach is increasingly demanded when treating chronic inflammatory disease, including at this symposium. How can this be implemented in clinical practice?

Prof. Rogler: First of all, it means that strategies with rigid schemata such as “top-down therapy” for all is wrong. That’s because it prevents the individual patient’s needs and particularities from being addressed in detail. But it also means that you have to look at each patient in detail and see them frequently, especially at disease onset and if the disease course changes. You have to be very familiar with the course of the disease to treat it individually. Individualized treatment is achieved, for example, with accelerated step-up therapy, since the priority is not to lose too much time. If you waste more than two years before diagnosis in Crohn’s disease or it takes more than two years from diagnosis to achieve the optimum therapy, the outcome is considerably worse and operation rates double. We demonstrated this in the Swiss cohort. If the disease is very severe in a very young patient, in these exceptional cases I would start straight away with a combination of immunosuppressants and biologics.

The search for predictors for aggressive progression is underway at all levels. What is currently certain for high risk patients?

Prof. Rogler: The clinical picture is crucial. A very young patient under 25 with a primary penetrating progression with abscesses and fistulae or stenosis should be immune-suppressed at an early stage or be given TNF-alpha inhibitors. On the other hand, a simple ileitis is not a reliable indication of poor prognosis even if the patient is young, smokes, or has other risk factors. Even initial steroid use per se is not in my opinion a definitive indication that the course of the disease will be severe. However, we do not yet have reliable molecular markers.

Given all the calls for individuality, where does that leave the guidelines?

Prof. Rogler: In my view, the guidelines have an increasing problem: The more updates there are, the more “eminence-based” medicine creeps in. Increasingly often, recommendations surface with level 5 evidence („expert opinion“). Guidelines are suitable for patients that are simpler to treat and, in these cases, they are very

helpful. They contain recommendations that relate to published literature. Here they can be an important aid for practising doctors. But patients with a complicated clinical course should be treated by specialists and for them these guidelines are certainly just a guide and not a prescription. Unfortunately, the ECCO Guidelines, for example, are becoming increasingly more detailed: There are guidelines for imaging and shortly also for extra-intestinal manifestations. In my view, this is not always helpful for gastroenterologists in clinical practice since it becomes difficult to maintain an overall view.

Pediatric gastroenterology is one theme of this symposium. Progression is particularly severe when disease onset is in childhood. Do we know the reasons for this?

Prof. Rogler: Children with ulcerative colitis frequently start their disease career with pancolitis, whilst those with Crohn's disease often start out with the penetrating form of the disease. Why this is the case remains unclear. There is of course a genetic predisposition that may accumulate in these children. However, the evidence for this is weak. Environmental factors are also of interest as triggers. Accumulated environmental factors could have an effect very early on in children. We observe families in which the disease recurs increasingly earlier across generations. So it will be interesting to look for potential environmental factors in these children that have led to this early onset of the disease.

The severe progression makes aggressive therapy necessary over the long term. How has that worked?

Prof. Rogler: Pediatricians tend to be reluctant to use TNF-alpha blockers. They use methotrexate, for example, more frequently. But even here a dose with a high risk of cumulative toxicity is reached after five to seven years. We often have adolescents referred who have already been treated with a biologic for five or eight years that cannot be discontinued due to the course of the disease, or who have already been receiving methotrexate for similar periods. The children generally tolerate the medication well and appear to suffer from a classical loss of efficacy less frequently than adults. Regular immune monitoring is important for follow-up. In patients undergoing combined therapy with azathioprine and biologics especially, an eye should be kept on the lymphocyte count. The safe range is between 600 and 1500/ μ l. Where values are lower (below 500/ μ l) it must be assumed that the T helper cell count is below 200/ μ l, i.e. a severe immunodeficiency has been induced as with AIDS. Very severe infections therefore predominantly present where lymphocyte counts are below 500/ μ l.

So is it not better to colectomize early on in cases of ulcerative colitis?

Prof. Rogler: I am particularly skeptical about "prophylactic" use of colectomies at a young age. In my view, a strict approach to the indication must be maintained. 30 years after colectomy, up to 25% of patients are incontinent. In addition, mortality rates in ulcerative colitis are no lower in countries that perform high numbers of colectomies. Patients also die from perioperative complications such as pulmonary embolisms in these countries. Nevertheless mortality is up to 1% for colectomies. These risks should not be entered into simply on grounds of a potential long-term therapy, unless a severe or fulminating inflammation is present.

Research is currently focusing on intestinal barrier dysfunction, the etiologic cause of IBD. So far, probiotics have hardly been resoundingly effective.

Prof. Rogler: Research into probiotics is handicapped by its tendency to look for a single bacterium that can be patented. It would be better to look for a complex ecosystem that has a favorable impact or indeed extend testing of fecal transplantation in clinical trials. But it is still unclear how the intestinal immune system responds to a "stool transplant". No bacterial cocktail similar to the patient's own microflora should be administered to patients with ulcerative colitis since the patients' immune system responds badly to this in particular. However, we know that external flora generally activates the immune system. A bacterium that is in itself quite harmless may actuate the immune system. So, clearly the need is simply to make more efforts to identify the "optimum" mix of microflora. So, I have not yet given up hope that at some point manipulation of bowel flora will be one of the standard methods.

Phosphatidylcholine and pig whipworm eggs also act against intestinal barrier disorders. Both principles are currently being studied intensively in ulcerative colitis/Crohn's disease. What is your opinion on this?

Prof. Rogler: These are exciting approaches, above all because they appear to be very low in terms of adverse reactions. And it is in principle good to tread new paths in view of the numerous failed trials of biologics. Currently, phosphatidylcholine is the only substance in clinical trials principally targeting barrier disorder. And the use of pig whipworm eggs is also an exciting approach. If what has been shown in the laboratory is confirmed, the therapy actually leads to a metamorphosis of the immune system. Data on both substances will be available in the next few months. Then we will know.

Cannabis in IBD – Does that make sense?

Prof. Rogler: Some patients control their ulcerative colitis with an evening joint. Patients not only feel better but the inflammation also decreases. The tetrahydrocannabinoids contained in cannabis quite clearly have an immune-modulating effect. Derivatives with only peripheral action appear to be less effective. So it certainly makes sense to investigate the cannabis effect further.

We have also had good experiences with blueberries. In an open pilot study with patients already receiving azathioprine and TNF-alpha blockers remission was induced in the majority of patients. It is likely that the anthocyanins they contain have a direct antiinflammatory effect.

Perhaps when developing drugs that intervene less in the immune system and have a good safety profile we should pay attention to what patients tell us. After all, the information about the positive effects of blueberries came from patients.

Professor Rogler, thank you very much for the interview.

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