IBD 2017 – THERAPEUTIC AND BIOLOGICAL BARRIERS

Falk Symposium 209 had a program that aimed to shed light into the better understanding of the intestinal microflora and the subsequent interaction with the host. Novel therapeutic concepts, barriers and challenges we all face in our daily IBD practice were discussed and summarised. The Symposium was held in Berlin in October 6 - 7, 2017. Prof Britta Siegmund, Germany, was Chair of the Scientific Organisation. IBD Congress News sat in on the second of the two days.

The first lecture on this day was given by Prof Raja Atreya, Germany. He talked about luminal therapy with small molecules.

– Small molecules have low molecular weight, and are physically stable small organic compounds. They have short serum half-life, are non-antigenic and their form of application is variable – mostly oral, he said.

Combining treatments for IBD is likely

Luminal therapy with small molecules have made the transfer from bench to bedside. They show signs of efficacy with a good safety profile.

He first talked about GED-0301which is an oral SMAD7 antisense oligonucleotide. Inhibition of SMAD7 production restores TGF-beta signalling, thereby suppressing inflammatory cytokine production.

In a Phase II multicenter randomised clinical trial (RCT) on patients with active CD, GED-0301 for 12 weeks demonstrated 67 % of patients had a clinical response (defined as CDAI decrease from baseline with 100 or more) – and clinical remission (CDAI less than 150) in 48 %.

However, GED-0301 with the brand name Mongersen, has been withdrawn by its manufacturer due to lack of efficacy in Phase III.

Prof Atreya also presented other trials on small molecules. A Phase IIa study on submucosal STNM01 (a chemical synthetic double strand RNA oligonucleotide) in ulcerative colitis (UC) had good results.

– More trials are awaited. Effective therapy for IBD will probably require combin-

ing treatments to affect multiple targets – i.e. luminal therapy with small molecules in *combination* with biologicals or sequential induction-maintenance, Prof Atreya summarised.

Thiopurines and methotrexate

New tricks, known drugs was the title of Dr Peter Higgins, USA, talk.

– I will discuss multiple off-label uses. These approached are not supported by prospective, rigorous randomised clinical trials – much of the data I will present is anecdotal, Dr Higgins underlined.

So why would we need tricks?

– Many therapeutic choices are now available for IBD. Clinical trials tell us whether, and at what dose, a drug works for the *average* subject – but patients vary. We would like to get the best value from all our IBD drugs, he explained.

He started with optimising thiopurines.

– Simplify your practice – pick either 6-MP or azathioprine. Azathioprine is a bit easier to fine-tune. There are a lot of papers produced on metabolites, but they are not very useful. Pharmacodynamic markers are better, and can produce better clinical outcomes.

Methotrexate (MTX) is effective for CD, and in some cases for UC – but persistence is poor, Dr Higgins continued.

– Use of short-term MTX can be very helpful in setting of abscess in CD. A large and complicated abscess is a contraindication to systemic steroids or anti-TNF therapy.

MTX is a structural cousin of trimethoprim (an antibiotic used mainly in the treatment of bladder infections). Maximising MTX requires dose titration, consideration of drug interactions and support through adverse effects. It has moderate anti-microbial effects, and can be given for mucosal inflammation in the setting of an abscess for 3 - 6 months. It is often helpful for achieving drainage and for abscess resolution – but watch for MTX-antibiotic interactions.

– Challenges are that there are no useful biomarkers to monitor MTX, drug interactions and that it is teratogenic – so MTX is contraindicated in pregnancy.

"INFLIXIMAB RESCUE HAS BEEN FOUND TO HELP ACUTE SEVERE UC"

Protocol lowered colectomy rates

Tofacitinib metabolism interacts with azoles (antifungal treatments), which increase exposure to tofacitinib more than two times, although this can vary by patient.

– This means that tofacitinib can be optimized at lower cost with azoles, so we can get more out of the drug, Prof Higgins pointed out.

Response metrics can identify responders to vedolizumab at week 6, by using laboratory value-based algorithms.

– Use GEMINI trial data to predict week 52 biologic remission. Then use machine learning on lab values at week 6 – after 2 infusions – to train prediction model on 70 % of the data set, selected randomly. Then test the prediction on the remaining 30 % of the data set. These are highly generalisable data from multicenter clinical trials – but they would benefit from prospective validation.

Finally, Prof Higgins talked about protocolising acute severe colitis care.

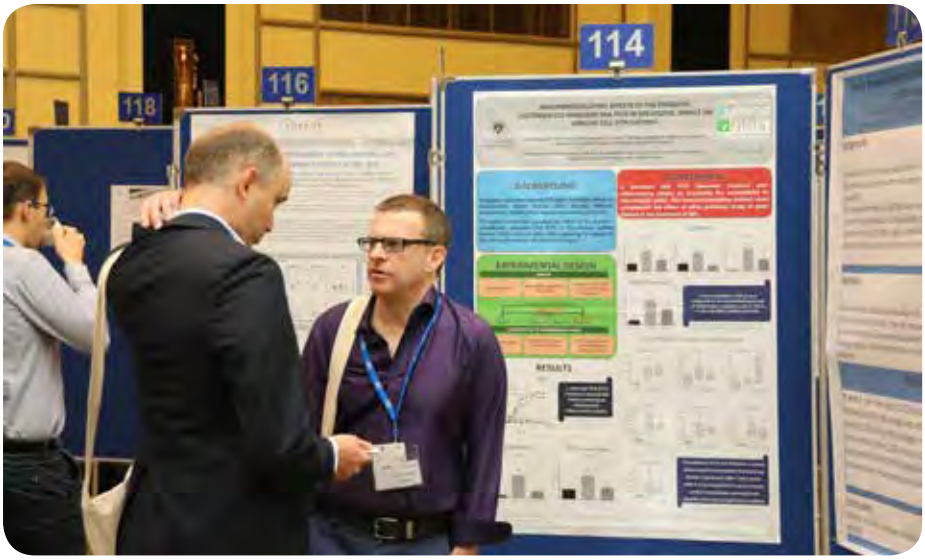
– We have developed and refined acute severe UC protocol in Michigan. This has given us more consistency in care, and a more rapid rescue medication – or surgery. The colectomy rate has gone down from approx. 30 % to approx. 20 %. The protocol is freely available at *www.med.umich.edu/ibd/docs/severeucprotocol.pdf* and it is updated annually.

Infliximab rescue has been found to help acute severe UC, but an increasing number of patients have already failed infliximab.

– But tofacitinib can produce rapid responses. There are no issues with antibodies to drug, and a short half-life (3,5 hours) so it can clear rapidly if surgery is needed, Prof Higgins stated at the end of his lecture.

Raja Atreya

Peter Higgins



No efficacy for pre- or synbiotics in IBD

Registered dietician Lihy Godny, Israel, presented data on the increasing sales in the pro- and prebiotic market. She continued with the changes in the gut microbiome in IBD.

– The key question is if this is an abnormal immune response to a normal microbiota – or if it is a normal immune response to an abnormal microbiota?

Then she turned to her topic of pre-, pro- and synbiotics. Probiotics are live microorganisms/ microbial products that alter the microbiota and confer a health benefit to the host. Synbiotics are products in which the prebiotic compound(s) selectively favour the probiotic organism(s).

– Microbial manipulation is an important strategy in treating IBD, but there is no shown efficacy for probiotic therapy in CD, Ms Godny said.

Instead probiotic therapy should be considered for UC – inducing remission in mild to moderate disease, and for maintaining remission. Also in pouchitis – for primary and secondary prevention.

– Caution should be taken with critically ill patients. And there is no efficacy for the use of pre- or synbiotics in IBD, she continued.

Further research is warranted – on homogenous phenotypes, controlling the diet and other external factors and standardized sampling, storing and analysis.

– These should be longitudinal rather than single-point-in-time. Sampling should take place at the likely site of action: mucosal sampling, small intestine and the colon. We also need high quality RCTs, RD Godny said.

Lihy Godny

Jacques Moreau

Tools to limit the number of consultations

IBD is an ideal ground for therapeutic education.

– They are often young subjects, with a chronic disease that cause personal and social problems. We have today more sophisticated treatments and more ambitious treatment goals – but frequent non-adherence, Prof Jacques Moreau, France, pointed out.

He described the ECIPE study, which main aim was to demonstrate that an educational program could have a significant impact on IBD patient's skills with regard to their disease.

– The conclusion was that educational programs do improve the skills of IBD patients. The benefit is maintained for at least 12 months after discontinuation of the program, Prof Moreau reported.

He also talked about e-health.

– The best combination for the future is therapeutic education plus telemedicine. But we need to find good biomarkers, and we need to have more educators – physicians, IBD nurses, psychologists, dieticians and expert patients. Finally we need to develop good web platforms.

To use these tools allows potentially to limit the number of consultations, of hospital admissions and phone calls.

– It allows to improve the reactivity for good therapeutic decisions, improved adherence and to control side-effects – and perhaps to limit complications. Finally it will save time and costs for healthcare, Prof Moreau finished his talk.

Define patient and provider specific goals

Dr Millie D. Long, USA, talked about the patient's perceptions of treatment of IBD. Cancer risks is the highest concern for patients, she underlined.

– We must think on how to communicate those risks. *Absolute* risk of a disease is your risk of developing the disease over a time period and can be expressed in different ways: 1 in 10 risk, 10 % risk and 0,1 risk. *Relative* risk is used to compare the risk in two different groups of people – one need to know the absolute risk to frame this risk, Dr Long explained.

Her advice was that absolute risk is better in communication of risk to patients.

– Avoid decimals (such as 0,06), keep common denominators (such as x/10 000) and provide visual aids help (i.e. turn numbers into pictures). Also give a perspective to other disease and life risks.

In Dr Long's conclusions she stated that one should define patient and provider specific goals of therapy, as those may differ – for example social/quality of life outcomes *and* endoscopy.

– Discuss risks of therapy with patients, and pay particular concern of malignancy. Use absolute numbers and provide data in setting of risks of disease itself.

Providers and patients prioritize a research agenda differently.

– There is more emphasis on diet and complementary agents for patients. A patient input on aspects of study design and relevant outcomes for clinical trials is needed. Combining these agendas may lead us to better IBD outcomes, was Dr Long's final statement.

Targets in IBD

Treat-to-target (T2T) - is this a meaningful paradigm? This was the topic for two lectures, one in favour, and one that did not agree. The first speaker was Dr Filip Baert, Belgium, who was pro T2T.

– We have moved from clinical response to deep remission as our target. Why? Because in CD, there is a big difference between symptoms and ongoing tissue damage, he stressed.

Dr Baert presented data that showed that mucosal healing predicts sustained clinical remission in CD. He continued with the CALM study, the latest evidence for the benefit of T2T.

– In CALM, one arm had patients that were escalated if target was not met, the other arm had standard of care. The difference was significant for the T2T arm at the endpoint after 48 weeks after randomisation.

So what should be the targets in IBD? According to Dr Beart, in the short term it should be clinical remission and minimising the side effects. Also normalisation of biomarker remission and mucosal healing.

– In the longer term they should be to avoid disease progression (in CD) and to avoid complications and serious adverse events. For UC – cancer and colectomy, for CD – repeated surgery in patients with extensive small bowel disease.

He ended with a quote from the American Baptist minister Benjamin Mays: "The tragedy of life does not lie in you not reaching your goal. The tragedy lies in having no goal to reach".

Targets need to be individualised

Prof Gerhard Rogler, Switzerland, did not agree.

– There are many misconceptions in the T2T paradigm, he said.

There are both benefits and disadvantages: T2T 's benefits are improved outcomes through better disease monitoring, and disease modification that can lead to reduction of damage, Prof Rogler admitted.

– But the risks include unrealistic targets: Mucosal healing is only achieved in 40 % of patients, a rapid rotation of drugs is possible – which leads to frustrated patients and physicians. Also over-treatment with the risk for costs and safety.

Prof Rogler added the increased complexity of treatment algorithms, increased immunogenicity and endoscopic procedures and invasive tests to his list of risks.

– There is a lack of common definition on mucosal healing, he pointed out.

To treat to mucosal healing is a major reason for depression in IBD patients and physicians, and the rates for mucosal healing in recent clinical trials in CD are low – from 17,2 to 45,9 %.

– Risk-benefit studies on T2T are missing – and the paradigm is now more critical seen also in other diseases. Treatment targets need to be individualised, Prof Rogler ended his talk.

Both speakers ended their talk together with agreeing on the targets in IBD:

– To treat to steroid-free remission: Yes – this is a minimum, but it takes time and effort. Involve your patient, and utilize multidisciplinary care. Individualise treatment and seek objective confirmation of response. Endoscopic remission is a good prognostic factor in the absence of other markers.

Reactive monitoring

Drug monitoring in biologicals was the topic of a talk given by Dr Gionata Fiorino, Italy.

– Anti-TNF does not work in all patients from start, he began by reminding he audience.

Then there is secondary loss of response to anti-TNF. For infliximab the annual risk for this is 13 % per patient-year of fol-

Millie D. Long

Filip Baert

low-up and for adalimumab the figure is 20 % per patient-year of follow-up.

Dr Fiorina continued by talking about factors impacting on anti-TNF pharmacokinetics and anti-drug antibodies (ADA).

– We know there is a correlation between ADA and through levels. Data shows that higher trough serum concentrations are associated with better outcomes, he said.

This is where therapeutic drug monitoring comes in. Dr Fiorino presented a proposed algorithm for *reactive* therapeutic drug monitoring (TDM) of anti-TNF maintenance therapy in IBD.

– If trough levels show supra-therapeutic values, or therapeutic trough count more than 10 - 15 mg/ml of drug – discontinue it. Change to a non-anti-TNF drug or refer to surgery. If undetectable or sub-therapeutic trough count and no ADA:

Gerhard Rogler

Gionata Fiorino

Escalate dose or reduce interval between infusion and consider adding an immunomodulator. IF ADA are found in *low* levels, do the same. If ADA are high, discontinue drug, switch to another anti-TNF, or change to a non-anti-TNF drug or refer to surgery, he explained.

"TDM BY DOSING TROUGH COUNT AND ANTIBODIES CAN EFFICIENTLY GUIDE THERAPY OPTIMISATION"

Proactive monitoring

Then he presented a proposed algorithm for *proactive* TDM in maintenance. If trough count is supra-therapeutic, de-escalate dose or increase interval.

– If the patient is on combination treatment, consider stopping the immunomodulator and continue on mono-therapy.

In case of therapeutic trough count (5 - 10 mg/ml) continue on same dosing. Continue proactive TDM every 6 - 12 months.

– If ADA appears, add immunomodulator or optimise dosing on combo-therapy.

If trough count shows undetectable or sub-therapeutic trough count: If no ADA, escalate. If ADA are present, but low – escalate and consider adding an immunomodulator. Finally, if ADA are high – discontinue drug, switch anti-TNF or change to a non anti-TNF drug.

ECCO Statement

In his conclusions, Dr Fiorina said that a significant proportion of patients require optimisation while being under biological therapy. TDM by dosing trough count and antibodies can efficiently guide therapy optimisation.

– Proactive and reactive TDM are both efficient strategies for therapeutic management, but more evidence is needed to define minimal effective exposure thresholds. Further RCTs comparing the efficacy and safety of early optimised therapy based on TDM to target trough concentration versus standard induction dosing are needed!

He ended his lecture with ECCO Statement 6I:

"Confirmed loss of response to an anti-TNF agent should be first managed by dose optimisation. Dose increase or interval shortening are equivalent strategies. If dose optimisation is ineffective, switching to another anti-TNF is recommended. Where available, measurement of serum anti-TNF through levels and anti-drug antibodies could be used to guide optimisations strategy".

Per Lundblad