STRIDE II Podcast

Dr. Julie Ann Lough (00:06):

Hello and welcome to the EMG-Health Podcast. My name is Dr. Julie Ann Lough and I am a Science Communicator and TV Producer and today I am pleased to be presenting a podcast on inflammatory bowel disease that has been sponsored by Abbvie.

The episode will be exploring the journey from publication to practice of the selecting therapeutic targets in inflammatory bowel disease initiative, otherwise known as STRIDE-II. Joining me for the discussion today are three experts in the field of IBD.

We have Prof. Dan Turner, Director of the Institute of Paediatric Gastroenterology and Nutrition and a specialist in inflammatory bowel disease at Shaare Zedek Medical Centre in Jerusalem, Israel, Prof. Iris Dotan, Director of the Division of Gastroenterology at the Rabin Medical Centre in Petah Tikva, Israel and Prof. Dr. med. Axel Dignass. He is Head of the Department of Medicine and Professor of Medicine at Agaplesion Markus Hospital in Frankfurt, Germany.

Together, they will explore the creation of treat-to-target guidelines, discuss the different considerations for monitoring in Crohn's disease and ulcerative colitis and reveal how to implement, treat-to-target guidelines in patient care. Welcome to the podcast. So, let's start off, first of all, with you Prof. Dotan. Let's go back a few years and just discuss the original selecting therapeutic targets in inflammatory bowel disease. So, the original STRIDE work from 2015. You worked on that piece of work, as well as the STRIDE-II work. What were the main findings? And I suppose, why have we had to review it to bring us up to date with STRIDE-II?

Prof. Dotan (01:47):

Thank you so much for that question, Julianne, this is very important as when we talk about STRIDE-II, we always need to remember where we came from. So actually the "selecting therapeutic targets part one" was reported in 2015 after a group of physicians from the International Organization for the Study of Inflammatory Bowel Diseases gathered together in an attempt to formalize recommendations that actually did not exist in such a way until then, to formalize recommendation for follow-up and therapeutic targets. What are the therapeutic targets for patients with inflammatory bowel diseases? Now, of course, this was based both on expert opinion to move on and progress further as more and more data and more and more options as well as new therapeutic targets were available as we had more advanced therapies, if we want to be more specific.

(02:47) So for instance, in the STRIDE-II compared to the STRIDE-I, there was an addition of the time to expected response, remission and endoscopic healing with different treatments that have been introduced to incorporate treatment targets. So, this was something important that was not included in STRIDE I. Clinical response and remission, as well as normalization of C-reactive protein were introduced as immediate and short-term targets. Faecal calprotectin, right? We had six more years of experience. So, reduction of faecal calprotectin to an acceptable range was a formal intermediate treatment target. The paediatric targets, of course, very important. They were not included in the first report – it was an important part. And of course, addressing quality of life that in the six years that were in the interval between, STRIDE-I and STRIDE-II, granted that the work on STRIDE-II began long before it was published, of course, so restoration of quality of life. I think today we will all acknowledge the importance of it. And absence of disability was added to endoscopic healing for instance, as long-term targets.

Dr. Julie Ann Lough (03:59):

A follow up question that maybe yourself might like to answer Prof. Dotan, or Prof. Dignass, or Prof. Turner: You talk there about the importance of valuing the quality of life. Had clinicians been

really overlooking this with patients or is it just, we have better tools for measuring quality of life outcomes now?

Prof. Dotan (04:20):

So, a very important question, and it's not that physicians and clinicians have been overlooking it; I think that this is the first thing that we ask a patient when a patient is entering the room, we ask: "How are you?" So, the answer to "how are you?" is also quality of life and it includes also patients reported outcomes, of course, right? "I feel well, or I do not feel well. I have, two, three or 12 bowel movements a day and my abdominal pain is such and such." So the quality of life is included in that, but it's of course much more than that and I think that first of all, we acknowledge more that there are important disabilities, and the derangements of quality of life in patients with inflammatory bowel diseases, loss of work, loss of work days, loss of student time, loss of activities in the family and personal interactions and quality of life in general, fatigue, unhappiness, mental and emotional issues that are related with some of the symptoms that go with inflammatory bowel diseases, as well as some of the biologic mechanisms that relate to that.

(05:37) So, first of all, we have more knowledge and second, we are a bit (and in that we are still far from being perfect), we are a bit better in measuring quality of life. I think that also having more tools to measure quality of life is some progress that we made, but we're still a long way from being where I think we need to be.

Dr. Julie Ann Lough (05:57):

Great. Prof. Turner and Prof. Dignass: Do you have anything you would like to add to that?

Prof. Turner (06:02):

STRIDE-II took the notion of STRIDE-I to the next level putting everything into perspective and the right context. So yes, removal of inflammation is still the most important part of the long-term goal of treating our patients. I think with the time, the STRIDE-II puts the patient in the centre, not only in the sense of long-term consequences of the inflammation, but also relating to symptoms and how the patient feels.

Prof. Dignass (06:34):

I think our treatment approaches have been changing significantly over the past 70 years. So, we nowadays have a more holistic approach. We look at all the different sides of the patients and we also are in the time of shared decision-making and we have very good evidence and very good data that patient's perspectives and physician's perspectives sometimes really differ significantly. So, there's something very important about benefit-risk ratio, what we are always taking care of. Patients sometimes do not care for histological healing or for some lab healing, they want to be in clinical remission, they want to have no adverse effects of their treatment, and they want to have the best and greatest quality of life to enable them to do their work, to have a normal social life, and I think this is something which is very important, and I think this is really reflected in the new STRIDE-II guidelines. There are different new targets that should be achieved and I think they are much more balanced than in the previous STRIDE guidelines or STRIDE recommendations.

Dr. Julie Ann Lough (07:49):

I suppose, Prof. Dignass ,that brings me on to my next question, where you were talking about the importance of both the patient and the physician working together around management of these conditions and the importance of patients understanding where they're going.

So one of the big things that's changed in terms of the treatment for ulcerative colitis and for Crohn's disease is around the area of biologics and small molecules. How are they changing the landscape of treating patients with IBD?

Prof. Dignass (08:21):

I think there has been a significant change in the landscape giving us new tools in our hands, which allow for instance, to achieve mucosal healing, so endoscopic healing, even histological healing. If we go back 50, 60 years, we had only steroids and we know quite well that in most of the patients they can improve clinical symptoms, they can achieve clinical response, clinical remission, but only in a very, very, very minor part of patients endoscopic healing, or even histological healing is seen. So, I think even if we go a little bit before the era of biologics, we have the great data from Scandinavia, the IBSEN cohort, showing that if you achieve mucosal healing, you have a much better disease course of both Crohn's disease and ulcerative colitis. But in the past 20 years, we had great studies, I think even in the last 10 years, we had great studies showing that having a more tight monitoring of the patients, tight control, treat-to-target, we can achieve a little bit more.

(09:30) So one study, for instance, I would like to highlight is the CALM study, led by Jean-Frederic Colombel, our great friend, showing that if you have patients with early Crohn's disease and you treat them either in one arm (it was a randomized controlled study) with a more tight control approach, so these patients were monitored, not only clinically with CDAI and PROs, but there was also control of faecal calprotectin, CRP, and these are great tools we have now in our hands, and they were compared to patients that were just treated according to the regular clinical management at this time, so it was just the CDAI and the prednisolone use in these patients and these patients were treated throughout one year and there was a significant benefit with better long-term outcomes, better remission, better endoscopic healing compared to the clinical management arms.

(10:35) I think this was one study showing that if we have this tight approach, we can achieve something more. We have now still the ongoing REACT 2 study, we had the POCER trial also with post-operative disease. We have still unpublished, but presented in abstract form data from the STATUS trial with ustekinumab, so there are several biologics, very, very good evidence that we can achieve certain targets, and we have much, much more in our hands, in the very near future. So, I think with the small molecules, and I'm talking about the JAK inhibitors, I'm talking about S1P modulation, I talk about the new IL-23 molecules we will have in our hands. We have a great armamentarium where we can achieve targets that we could not achieve like 10 years or even like five years ago.

Dr. Julie Ann Lough (11:33):

So, it really does seem that a lot of these new drugs coming on board are real game changers in the area of IBD, so I can only imagine how exciting it must be.

One of the things that you touched on there was how we're understanding biomarkers a little bit better. Have improvements in monitoring and in detecting metabolites made a big difference as well and why you can decide which targets can be treated?

Prof. Dignass (12:02):

Yeah, I think calprotectin is not really that new, but there have been so many clinical studies showing that calprotectin is an easy tool and is quite reliable showing the intestinal activity relatively, not in 100%, but similar to an endoscopy. And this is a non-invasive tool, so I think this is great. We still use the old CRP which in my opinion is very helpful in patients with Crohn's disease, not that much in patients with ulcerative colitis, where you can have a completely normal CRP, but there is significant inflammation and these are two non-invasive and I think very easy to use tools.

One other tool, which is also now included in the STRIDE-II guideline is the intestinal ultrasonography. This is something that has not been discussed in most parts of the world. It's something in Italy and in Germany because we have used it for more than 20 years, 30 years and it's like our extended clinical exam. We can do it on a daily basis because the gastroenterologists are doing it and this is a non-invasive tool where you can see inflammation in Crohn's disease, you can even see the transmural activity, you can see complications like fistulizing disease, like abscess formation and I think with

these three tools that can be used at the bedside and now are more implemented in many countries all over the world, we have a much, much better armamentarium to really assess our patients because in the STRIDE-I there was one key assessment (they were already the PROs) but there was a lot of endoscopy and endoscopy is not that much liked by our patients, especially because of the bowel cleansing, and it's an invasive procedure.

Dr. Julie Ann Lough (13:53):

So, Prof. Turner, you're one of the first authors of this very substantial piece of work. Take us inside the room and talk us through the challenges in getting the consensus here. How did you manage to work through all the thought process in the field of IBD at the moment to come up with this excellent piece of work?

Prof. Turner (14:16):

Truthfully, at the beginning we didn't envision the work as it turned out. So, the beginning was to try and update STRIDE-I in a more limited effort to look at just briefly the updated literature that was published since, and to provide some limited highlights. But when we went back to our friends, Axel and myself, to the International Organization of IBD, the IOIBD, the feedback that we received was that this is an important work that might influence the care of patient worldwide and we should go to scratch and do a proper literature search and review all the manuscripts in a systematic way. So, we recruited the four brilliant bibliographic fellows who reviewed over 11,000 abstracts, and retrieved the hundreds of full text manuscripts and all the data by targets and by topics and by year and very soon we managed to see the pattern of the published data until now and how all the targets come together. Once we had done that, we could send all the data and the results of the systematic review to all the members of the IOIBD and we had like a limited Delphi process until we reached a consensus.

(15:50) In that regard the COVID-19 pandemic was an advantage because people got used to working with Zoom, so with IOIBD's previous projects this required the face-to-face discussions, but quickly we switched to what became standard for everyone with the Zoom meetings and that facilitated the consensus. So, a few more debates and a few more turn arounds of the tables and we ended up with that document. When we saw the systematic review by the fellows, it was really a substantial piece of work. They reviewed so many papers, and we decided to have a shorter manuscript just with the bottom line, but to keep the extensive review for those who want to dig in to the details as a supplementary material. So, the review of the literature and the supplementary material is a gigantic piece of work made by four brilliant fellows.

Dr. Julie Ann Lough (17:00):

It certainly is a very substantial piece of work. I'd recommend anybody reads the supplemental information if they really want a good overview of some of the exciting things that are happening around treat-to-target.

So, Prof. Dotan, that links in quite nicely with the fact that, you know, you've worked on the original STRIDE and STRIDE-II and as you were saying, it was a massive collaborative effort. When you decide which targets you're going to try and treat, what is it that makes the ideal target to aim to treat across all IBD patients?

Prof. Dotan (17:32):

I think a major point needs to be that it needs to be patient relevant and meaningful. And what does meaningful mean? So of course, it is easy to see why clinical outcomes would be meaningful because the patient says, "I feel okay, or I feel better, or I'm improving". So clinical targets such as the stool frequency, abdominal pain, rectal bleeding, and so on and so forth are important. So that's quite easy to see. And of course, when you have clinical remission, we already know that for patients in clinical remission (and it is relevant for Crohn's disease and ulcerative colitis, similarly) it is associated with further beneficial outcomes. So it is easy to think why clinical markers are important and targets. When

we move to endoscopic targets - one of the differences we have is data to suggest today that patients in endoscopic healing have better outcomes that are relevant, depending, again, if you measure for ulcerative colitis or Crohn's disease, but generally you have better outcomes, better quality of life, less hospitalizations, less complications, and less surgeries.

(18:46) Now with some of the targets. And this is why for instance, in STRIDE-II, histology and histologic healing in ulcerative colitis was still not stated as an outcome, but suggested as an outcome because there is emerging data to suggest that it is becoming a meaningful target, specifically because it is related with better outcomes, but the data until now are mostly retrospective, not controlled, the level of the quality of the data may be less optimal and so on. So this is how you choose your targets, that they are meaningful, that they're relevant for patients, that you have enough data to say that is an important target. And I think we didn't say it until now, but when we say "that is an important target", that has clinical implications, and maybe we will discuss it in the end. But if this is a target that is important, that means that if we treated the patient with drug A and we didn't reach that target even after optimization, it means that I will need to add drug B to drug A, to change drug A, to drug C and so on and so forth. So this is a very responsible "statement" to say, "this is a target". Thus, we need to choose them very carefully.

Dr. Julie Ann Lough (20:03):

That brings me onto a follow-up.

One of the big things that you look at is patient reported outcomes. Can clinicians do more, or are there more tools available to help us better quantify those PROs so that we could follow them much better and to make them a better target for treatment?

Prof. Dotan (20:22):

Thank you for this question. So of course, the patient reported outcomes may be a little complex to quantify, and because this is something that is subjective, right? This was part of the criticism on the Crohn's disease activity index that included general feeling of patients. As a sub-statement, I will say that while subjective, it is important to include how patients feel. Today we have new tools. We have the IBD Disk, we have ways to follow up on patients' outcomes. We have ways to quantify, and we have a lot of, of course, digital and app related data to help us quantify how patients indeed feel on a day-to-day basis. So, I think that this is very useful, to follow up on patients.

Dr. Julie Ann Lough (21:14):

So, let's get into some of the nitty gritty of the detail now. So, UC and Crohn's disease are both classed as inflammatory bowel diseases, but with UC only impacting on the colon, this leads to different targets in the treat-to-target approach. Can you talk us through a little bit in what was identified as good targets for Crohn's disease?

Prof. Dignass (21:34):

Yeah, Julie, I think this is very important. We recommended a composite endpoint or composite endpoints, and it's a combination of patient reported outcomes. It's endoscopic healing, it's the use of biomarkers and it's quality of life and disability. And why did we go for this? Clinical indices or PROs are sometimes subjective, they are very, very important, but we all know there's also an overlap between IBD and IBS, and sometimes it's difficult to distinguish if we were just to rely on patient report outcomes. So, for Crohn's we have the PRO-2, we have abdominal pain and stool frequency that we will use and PCDAI for the children, and we have some recommendations in the paper, what should be achieved. Endoscopic healing moves us to a more objective marker, and it has been classified as a more long-term target, so this is also important and can be assessed by sigmoidoscopy or colonoscopy, or perhaps by capsule endoscopy. And it's very complicated to discuss the score, so I will not go into further detail in this respect, but we also have the biomarkers and nominization of CRP is something we were knowing for a long, long time, but now the faecal calprotectin is really lifted up because

we know that it's much, much more sensitive in certain areas and really reflects in a better way the inflammation in the bowel. So, it's very close to what we see in endoscopy. Quality of life as mentioned earlier, is very important for the holistic approach of the patient and the ultimate goal we would like to achieve is absence of disability and really normalization of the health-related quality of life. And then there are some further points and I think Iris already mentioned and discussed it a little bit.

(23:40) For instance, transmural healing. This is extremely important for a transmural disease, but several years ago, we could not really even monitor this. And now with MRI, with the ultrasound, we can monitor this, but we still do not have enough and perfect data to really show that we can achieve that, so this was not a formal target. It was considered to be assessed and perhaps in STRIDE-III, with more data coming up, it will become even more important. And if we move to histology, for histology at this point of time, we didn't even mention it for Crohn's disease. It's a formal target for ulcerative colitis, but the data on histological healing, histological improvement for Crohn's disease was really scarce and we didn't know how to define it. And this is also very complicated for instance, in patients with Crohn's disease, when a majority of patients have ileal or small bowel disease, and we cannot even reach the area which is important to assess the histology. So, I think there will be more discussion over the next years.

Dr. Julie Ann Lough (24:54):

So, Prof. Turner, we've obviously just heard about the targets around Crohn's and how that's different than for the treatment of UC. So, what are the different targets that should be treated for patients with the presentation of UC?

Prof. Turner (25:08):

When we started to draft the manuscript, we had two different tables and figures, one for Crohn's disease and one for ulcerative colitis, but what we noticed quite soon was that many of the targets in the end can be articulated in the same way. So symptomatic response, symptomatic remission, faecal calprotectin, CRP, ESR, endoscopic healing, all these are the same important targets for both diseases. So, the way we measure each target may differ and therefore we added a table to specify how to define each of the concepts in Crohn's disease and ulcerative colitis. For instance, if you want to have histological healing in ulcerative colitis, you want the threshold of calprotectin of less than a hundred or less than 70. If you want just endoscopic healing Mayo 0 or 1, perhaps less than 250 is good enough. In Crohn's disease you get different thresholds to differentiate endoscopic healing from transmural healing and there are some data on that as well. And obviously how you measure symptomatic response might be much easier in ulcerative colitis than in Crohn's disease, because the association between symptoms and endoscopic healing is much closer in UC. So roughly those will be in complete clinical remission in ulcerative colitis, without any symptom, one full stool per day without any blood. The likelihood that this patient will have at most mild colitis, Mayo endoscopic sub-score of 0 or 1 is 80%. And if you add to that also a normal faecal calprotectin that also increases to nearly a hundred percent or 95%. In the case in Crohn's disease, we should rely more on objective markers on CRP and ESR. Now, it doesn't mean that in ulcerative colitis, we don't look at ESR and CRP, and it doesn't mean that in Crohn's disease, we don't care about symptoms, but it's just the emphasis and the way we measure the threshold that would differ between the two diseases and in the margin, as Axel previously said, there is the histological healing in ulcerative colitis, which seem to be more significant in the outcome of the patient than in Crohn's disease.

(27:39) Since ulcerative colitis is a more abrupt disease, it's not rare to see significant inflammation in UC and then two months later, normal mucosa and then you can be with complete endoscopic healing for a year and then again, one month later, you go into the mucosa, to the bowel and everything is severely inflamed. In Crohn's disease it's a more indolent course, so it will develop more slowly, you will get more inflammation with time, it will respond more slowly to treatment. So, the way we look at the treatment target in these two diseases maybe a little bit different although the concept will be the same

Dr. Julie Ann Lough (28:22):

Prof. Turner, nothing's going to quite be a magic bullet with patients feeling better overnight. How is it that clinicians can reassess the targets and adjust their treatments accordingly and be realistic with patients about how long it might be until they see results.

Prof. Turner (28:38):

So, one of the challenges that physicians faced when the notion of STRIDE-I was delivered as endoscopic healing was, so what do we do now between six and 12 months? Do we not have a specific target that we need to look at? Well, obviously we all do it, so there was a little gap between clinical practice and the overall true goal that was proposed. And the different time dependent targets tried to mirror what we as clinicians do in clinic. So, when you give a treatment, first thing, you want to see a clinical response, and then you want to see a clinical remission. If someone has three bloody diarrhoeas per day, you don't care about the CRP or imbalanced calprotectin. Obviously, this patient is very active and we are not doing what we need to do, and we're going to change treatment based on the clinical symptoms and not more than that, but this needs to be very short.

(29:42) We say that sometimes it takes for steroids to work three weeks, but you wouldn't wait with the treatment for three weeks to decide on treatment, there is another stage in between that means response. So you want to see a trend, you want to see, okay, in a week time, something's happening, there is a trend, the patient is improving and therefore we're going to wait another week to see whether we get to the point of clinical remission after two or three weeks, then if after one week of treatment of steroids, you see zero response, maybe we need to do something else or you're at that point, but we'll have a few time points, we'll have time for response for clinical response, time for clinical remission, time for endoscopic remission, for normalization or induction in faecal calprotectin value and it's getting a little bit more complicated than just endoscopic healing yes or no, but we are going to do it anyway in clinic, **(30:41)** So we are starting a treatment or medication with the patient. We are going to tell them, "Don't worry about it, it's going to take a week or two weeks before you feel better." I mean, this is part of what we're doing every day, so STRIDE-II took this everyday clinic scenario and just tabulated it in a more intuitive figure or time dependent targets. With that we added another table to time to remission and response to each of the different interventions and that was based on a systematic review of the evidence, but also in the Delphi group when we ask the AD experts of IOIBD from their experience, how long does it take to work? And we hope that this table is helpful for clinicians.

Dr. Julie Ann Lough (31:30):

It's certainly very clearly laid out in that paper. Before we go to a general discussion, I'm going to end my final question to Prof. Dotan.

So, we've heard about the suggested targets-to-treat and the approaches that should be used, when you compare this with the first stride report, what do you think is the key added value? Like how have we moved the field forward with these STRIDE-II guidelines?

Prof. Dotan (31:55):

I think that there is an important progress between of course, STRIDE-I and STRIDE-II. It's actually amazing to see how many changes and updated statements work. But I think that the key messages that need to be highlighted first of all, is that an important treatment target is first and foremost, symptomatic relief in symptomatic response. So that is being ranked as highest still and that's most important. Now then we want to have symptomatic remission and normalization of C-reactive protein, then decreasing calprotectin to acceptable range and normal growth in children. And I think that that needs to be highlighted. And in the end, the targets that were chosen today are endoscopic healing, the normalization in quality of life and the absence of disability. So those would be the long-term targets. So, I think that first of all this is the scheme as we see it and of course, this can be seen in

the STRIDE manuscript and of course in every presentation, I think since then, when we're discussing treatment targets. The updates are actually very important.

(33:07) If you go into the details, the time to expected response, and that was discussed just now by Prof. Turner, so I will not go back into that, but I think that putting timeframes into our targets is very important. The clinical responses were in remission as well as the normalization of CRP as immediate in short term targets, meaning that we need to use our drugs, but not wait six or 12 months to achieve what is defined as short-term targets. The reduction of faecal calprotectin to acceptable range and there was much debate on what is an acceptable range, but first of all, that there will be a reduction in faecal calprotectin was important and added as a formal intermediate treatment target and of course the paediatric targets are an important addition. The restoration of quality of life and absence of disability, to write in black and white, that this is a treatment target that is defined by the IOIBD, I think it is very important and not only to define mucosal healing is a very important, long-term target. And of course, the suggestion that is already suggested while not stated, the transmural healing and histologic healing are important treatment targets in Crohn's disease and in ulcerative colitis respectively. So, I think that these are very important additions between STRIDE-I and STRIDE-II.

Dr. Julie Ann Lough (34:32):

So, we certainly have moved on substantially. I suppose, the key takeaway for practitioners and clinicians would be: there are clear targets that you can treat and then it's review reassess - review reassess and be realistic on the timelines.

Dr. Dotan (34:47):

Absolutely. You summarized it so nicely and I think that what all of us need to know that this is not just a scheme to discuss, present, or learn by heart, but as you said, that this has important clinical implications, and we need to adjust our treatment programs based on these targets and of course, to be realistic. So, there's no requirement or assumption that if we don't reach you know, a certain short-term target within two weeks, then we need to change the whole strategic plan. I think we need to highlight that as well. So, we see sometimes patients that within a few months changed three or four mechanisms of action. Today, we have multiple mechanisms of action, so there's no need to do that, but there is this guidance and again, the guidance is an important guidance, but just guidance. So be realistic, be pragmatic, but also adjust to what is important for your patients. And I think the requirement is that we don't stay forever on the same drug if we didn't hit our targets. So, the clinical implications are very important.

Dr. Julie Ann Lough (35:56):

Great. So, we've gone through a lot there about the targets that we can aim to treat. Prof. Dotan: It's not always possible for a lot of reasons to exactly treat-to-target. I mean, if that happens with patients, should physicians and clinicians give up all hope or what are the alternatives there, and how do we know when we've done enough for our patients, and that maybe to accept that for some it may just not be possible to treat-to-target in some patients.

Prof. Dotan (36:25):

So this is an extremely important question, actually, that we touch upon not enough I think, because some patients are more difficult to treat, and by the way, there is another IOIBD initiative now trying to define exactly who are these patients that are difficult to treat. But I think that as a general rule, we should not accept that we should abandon all hope and there's always hope for patients and for treatment. I think that first of all, we need to acknowledge that not everything is in drugs. And when I say not everything is in drugs, so we need to address diet as support for patients and as treatment of patients, there's more support for that in patients with Crohn's disease and of course it's preliminary support and now there are larger scale studies to look at that in a more controlled and objective way, but diet can always be an added treatment or added intervention that might move things from almost there to there.

(37:30) We always need to remember that surgery is a valid option for patients with Crohn's disease earlier and earlier today. And also, for patients with ulcerative colitis with somewhat more complex outcomes, potentially. So, diet and surgery from potentially two sides of the spectrum of drugs are important interventions. We need to remember that the drug of today might be part of the treatment armamentarium of tomorrow. So, if we're almost there, we need to see what can be done to improve the situation of a patient, knowing that in half a year or a year, the patient may be eligible for a clinical trial for an additional drug that will be approved. So, there's always hope in the sense of drugs as well. And of course, we need to see if there are correctable factors that actually contributed to this patient not making the best from the intervention that we suggested for him or her, for instance, is the patient taking non-steroidals? Is there something in the patient environmental arena that makes the situation still not in complete remission as we would have liked it? **(38:40)** And again, many of this is for drugs that we recognize or for supplements that the patient is taking in that we are not aware of, or for certain behaviours of the patients. So, I think we can take all of that into account in a very comprehensive, a very holistic approach. So holistic approach to patients, and I think that as a general statement, we never say never in medicine, but I think that's to say never say we abandon all hope is very important, it's also important for the patients to know that there's always something else that we can think of.

Dr. Julie Ann Lough (39:16):

So, there is always hope, and there's always a try again, or maybe modifications need to be made. Prof. Dignass, some of the criticisms of this treat-to-target approach are that it's very prescriptive and then there's other suggestions that it's maybe too simplistic. What would you say to those criticisms?

Prof. Dignass (39:34):

I think this is a very important point, and I think my dear friends and colleagues Iris, and Dan have already addressed a lot of these points. Some physicians treating IBD patients would like to have a cookbook where they can just have a recipe and they give the drugs and they make the monitoring, but as we are all aware, we are talking about IBD and this is not only Crohn's disease and ulcerative colitis, its indeterminate colitis, it's patients with extraintestinal manifestations, so it maybe it's just even an over-simplification. We are talking about two or three diseases and they are lumped together and it maybe perhaps 50 different diseases. So why is a Crohn's disease patient sometimes getting only small bowel involvement, why large bowel involvement, why fistulizing disease. So, I believe it's not that simple, but I'm really, really happy with the STRIDE-II recommendations because they offer a basis for an individual and more personalized treatment of our patients.

(40:36) So you have a very nice timeframe, you can define targets, you have a time dependent targets, you can have several approaches to treat and to monitor the patients and I think it would be even better and even nicer, if we could tell, start with a medication X and then use medication Y or use a combination of X and Y, and if this will not work, do it in the other way, but we are talking about evidence, about clinical data, and we have not these data at the moment and I think nobody in the whole world is able to say which would be the perfect sequence in which combination, and this makes it so complicated. But I think at the moment, the balance is right. And it's really a helpful suggestion because as I already mentioned earlier, I see a lot of patients have been treated within the course of one year with eight different treatments.

(41:37) None of them has really been assessed and at the moment when I see the patient in my practice, I even cannot really say, did something work? Did it not work? Because the treatments were not reassessed. So were they achieved or not? The patient doesn't even know, like one question I always ask the patient is, "So did you feel some improvement?" "Yeah, it was better, but I was told there is still some blood in the stool." And this I believe is very helpful with these recommendations that really can be used in a daily clinical practice. And I think it's a major advantage compared to STRIDE-I because I remember when these were initially presented, there were like these endoscopies

every three months, and everybody's like, this is ridiculous. How can you scope a patient every three months? Now with these different targets, different approaches to monitor non-invasive monitoring, I think the STRIDE recommendations offer something which is really helpful for the clinician who is experienced in treating IBD patients. It's not something for the general practitioner seeing one IBD patient per year, because there is not the experience which drugs you can use in which sequence.

Dr. Julie Ann Lough (42:52):

I think that's probably a great place to end on it, that these are good guidelines, it's not a one size fits all because IBD patients are all unique in the way that their disease manifests itself, in the way that they cope with it and their quality of life. And that, as you were saying, Prof. Dotan, there's always hope, there's an option of, if this drug doesn't work with the target, we now have more practical targets. So we're not having to do invasive scopes on patients more often, we're able to get easily accessible targets and look at those. And then there are options of reviewing it, "If that's not working, maybe I need to adjust my medication and try things a little differently", so that it is a good handbook for people to use in terms of guidelines.

There's a final question I want to have for all of you here, which is a couple of you mentioned the likelihood of there being STRIDE-III. What is it that's in the field of IBD at the moment that's exciting you the most, and what answers would you like to see provided to the big questions in STRIDE-III? We'll start off with Prof. Turner.

Prof. Turner (43:59):

Quite frankly now with the era of STRIDE-II we are not so good in predicting disease. So that's why we moved away towards targets that are more like evaluating response to treatment. I think if we can sharpen our ways, might be machine learning, different -omics, more profound analysis of the samples that we get, biomarkers that provides an integrative approach, that more accurately assess who responded and who will respond to the next drug, that could sharpen a lot the way that we put the targets one after another in one timeline. We might go back a little bit on prediction, so already at the onset we will know better which drugs to give to which patients, and once we give the right drug, then the success rate will be higher and maybe we can skip some of the intermediate targets that we have now and replace them with more sophisticated integrative targets. And the other thing is of course, histology and transmural healing but it's a work in progress, but I don't think this will be waiting until STRIDE-III. I think in the next couple of years these two modalities will be ready for use.

Dr. Julie Ann Lough:

Prof. Dignass?

Prof. Dignass (45:29):

I would say, to add a little bit on to Dan's point, I think prediction of disease is very important. I believe what is also very important is prediction of response to any of the treatments we have, like the oncologists, they can measure markers and they know that that drug will not work at all and that drug will work much, much better, so this would help to prevent patients treated with drugs that cannot work and may cause side effects. So I believe this is very important and I'm looking for this. Iris mentioned in the beginning, we need molecular monitoring and I think better non-invasive tools to monitor our patients to do something without endoscopy. So I'm talking about Star Trek and we are in 2050, 2300... we will have perhaps some tools in our hands that we do not need these invasive markers.

(46:28) There is already some data for instance, from Markus Neurath, Raya Atreya, where they tried to see which drugs will respond better. This is far too complicated. You cannot use it in a clinical setting, but I think these are the first steps. And what I am really looking forward is big data analysis and then artificial intelligence to help us to get all the data, these 1,100 papers, 11,000 papers we will use for the next STRIDE-III, to assess them, to bring all the data together and with this help to

implement certain algorithms that will make treatment much, much, much easier. And then to be really honest, I'm looking for new drugs coming up or new treatment combinations, because most of the targets we would like to achieve, we can still not achieve for IBD. So if we move to psoriasis, it's very simple, you reach a lot of these targets in 90% of the patients. With all we have in our hands at the moment, we are 50% or even lower. And for instance, the new JAKs are showing something, which is significantly better to all we have now, but I personally believe it's not all good and not perfect, so I'm looking forward to combination treatment of drugs, with different mechanisms of action, hoping that with this, we will even have more mechanisms in our hands to really achieve the targets we are looking forward to achieve.

Dr. Julie Ann Lough (48:01):

Fantastic. And finally, Prof. Dotan, and what are you looking forward to most?

Prof. Dotan (48:04):

So, first of all, between STRIDE-II and STRIDE-III, which undoubtedly, I think will come, I think that first of all, we need to look at where we were in STRIDE-II. Specifically, are histologic healing and transmural healing really the statements that we'll start with in STRIDE-III. So I'm looking forward first of all, to support, to show that indeed if we are able to get to these targets, is patient outcome becoming better (that's first) and second, what is the price of that? So what's the number needed to treat them and what is the number needed to harm and is that outcome that we are bringing for our patients really meaningful? So I think this will be very exciting because if we will reach histologic healing and transmural healing in Crohn's disease, then theoretically, we are going back to a situation of a normal bowel.

(48:56) So this is as close to cure as was ever possible. So if we can do that with drugs that are existing now in certain combinations or in the drugs that will come in the coming few years, that will be extremely exciting. Additionally, I do think that we will see more and more microbiome based and metabolite-based targets. I think that we will target our drugs to achieve also more homeostasis of the bowel content, whether we will be looking at a stool samples or transcription or mucosal samples, so I think that that will provide more sophisticated potentially targets than we have today. Granted that these might be very local and probably not representing all areas of the bowel. So I'm sure we'll address these thoughts in the coming few years and talking about intervention, so of course we are all looking forward to interventions. I don't think there will be magic bullets. However, I think that there will be additional approaches for instance combination therapies, important new small molecules and new mechanisms of action. And as I had mentioned already, I'm a great believer in diet as an intervention, not only as a support nutritional support, but also as an intervention that might be therapeutic for patients. So I'm looking forward to that being one of the interventions that we will be include in a table in the STRIDE-III, to tell us how long should we wait until an addition of dietary intervention is assisting a mechanism of action, A or B in our patients. So I think that the future is very exciting.

Dr. Julie Ann Lough (50:38):

And what a great note to end things on.

So to summarize what we've seen from STRIDE-II: there are plenty of achievable targets, which are now more accessible in terms of monitoring and maybe less invasive for patients. The importance of reassessing if treatment to those targets is happening within acceptable timeframes and reassessing accordingly if it's not and considering multiple pathways, and then we've got the positive notes to end on and there's some very exciting treatments coming down the line, and there is very likely to be a STRIDE-III, possibly a STRIDE-IV as we understand more and more about the pathways of treating IBD.

Thank you all very much for joining me on this podcast. That's it for this episode, I hope you found today's overview of the implementation of the findings from STRIDE-II as informative as I did. So,

thank you to Prof. Dan Turner, Prof. Iris Dotan, Prof. Axel, Dignass, all of you for your time and your insight. To all our listeners, if this episode interested you, don't forget to subscribe wherever you listen to your podcasts, so you don't miss the next one. We have new episodes out every Friday. Meanwhile, be safe and stay well, bye for now.

ABBV-AA-00309-FM

Version 1.0

Approved December 2021