EMJ GASTROENTEROLOGY

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+ UEG WEEK VIRTUAL 2020

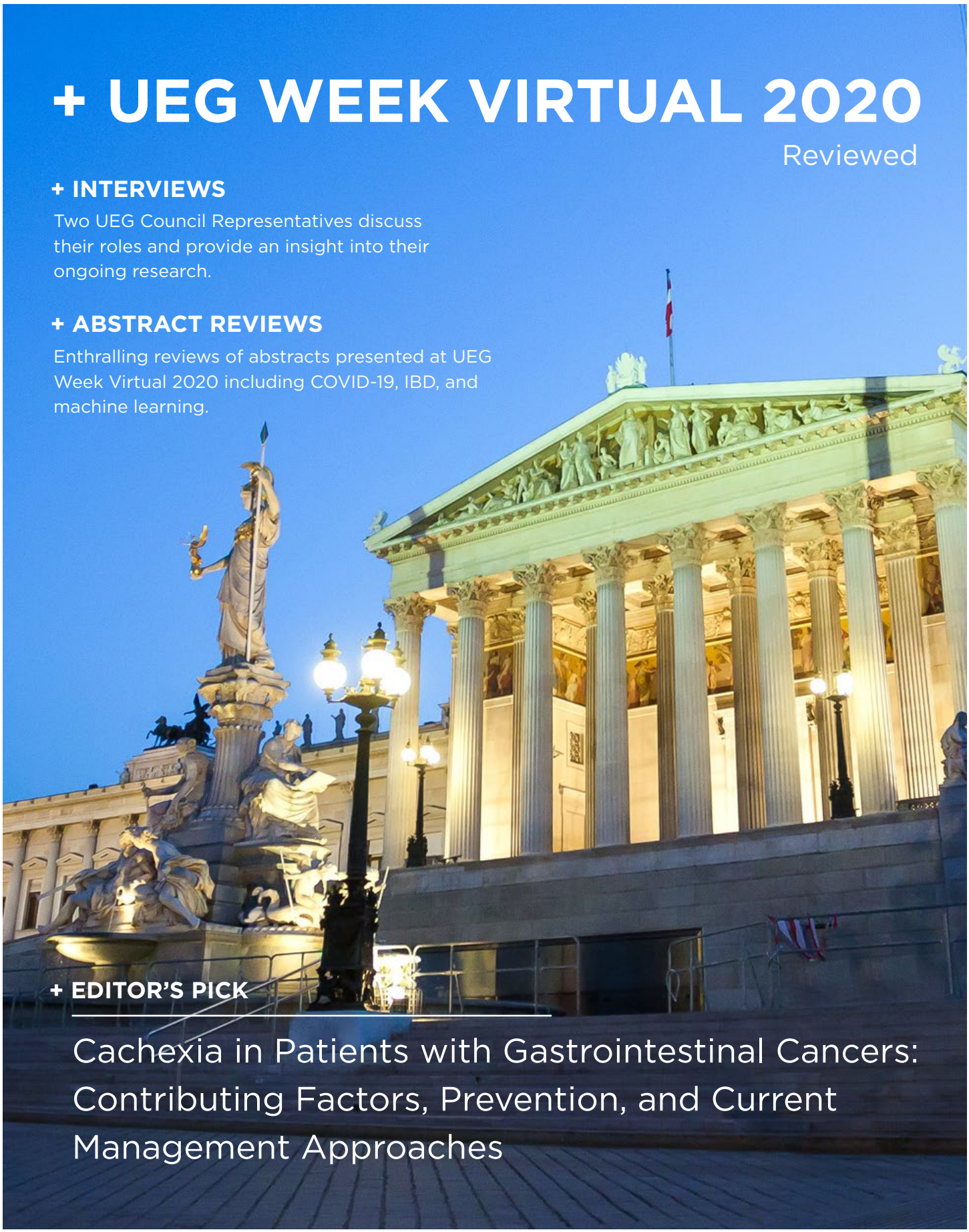
Reviewed

+ INTERVIEWS

Two UEG Council Representatives discuss their roles and provide an insight into their ongoing research.

+ ABSTRACT REVIEWS

Enthralling reviews of abstracts presented at UEG Week Virtual 2020 including COVID-19, IBD, and machine learning.



+ EDITOR'S PICK

Cachexia in Patients with Gastrointestinal Cancers: Contributing Factors, Prevention, and Current Management Approaches

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"The articles in this year's issue are once again fascinating reads, with authors sharing expert insights into a plethora of topics in gastroenterology."

Spencer Gore, CEO

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EMJ allows healthcare professionals to stay abreast of key advances and opinions across Europe.

EMJ aims to support healthcare professionals in continuously developing their knowledge, effectiveness, and productivity. The editorial policy is designed to encourage discussion among this peer group.

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EMJ Gastroenterology 9.1

Welcome

Dear Readers,

Welcome to the latest issue of *EMJ Gastroenterology*, an eJournal brimming with the latest developments in the field. As always, we bring you a detailed review of the United European Gastroenterology (UEG) Week, alongside articles written by experts in the field.

In response to the ongoing coronavirus disease (COVID-19) pandemic, UEG made the decision to hold this year's UEG Week virtually. The society did not shy away from the challenge of holding their congress online for the first time, delivering an extraordinary platform filled with presentations from experts in gastroenterology from around the world. The virtual congress platform, which saw over 10,000 participants in attendance, offered nearly 200 live sessions, more than 500 on demand sessions, and over 1,400 e-posters. The highlights of the scientific programme have been collated for your reading pleasure on the following pages, including summaries of key industry symposia and abstracts presented at the congress.

Complementing the review of UEG Week Virtual 2020, we had the pleasure of interviewing two influential members of UEG: Prof Asbjørn Mohr Drewes, UEG Council General Gastroenterology Representative, and Prof Laurent Castera, UEG Council Liver Representative. In these interviews, the board members provided a unique insight into their areas of expertise, including gut–brain interactions and noninvasive methods for liver fibrosis assessment. Another interview included in this year's issue is with Dr Radislav Nakov, President of the Association of Young Hepatogastroenterologists in Bulgaria and President of Bulgarian Society of Neurogastroenterology and Motility, who draws attention to the important ongoing work on rare diseases in gastroenterology and imparts advice to those starting their career in this rewarding specialty.

The articles in this year's issue are once again fascinating reads, with authors sharing expert insights into a plethora of topics in gastroenterology. Grundmann et al. explore the realm of cachexia in patients with gastrointestinal cancers and Menassa et al. delve into the exciting possibilities of stem cell therapies for inflammation-associated sigmoid colon diseases, both of which are fundamental reads. Bhattacharya and Cross also review upcoming therapeutics, this time traversing novel and emerging therapies for inflammatory bowel disease. Also on this topic, Chapman and Jones highlight the important link between depression and inflammatory bowel disease, focussing on the role of inflammatory cytokines.

I would like to take this moment to thank all those who have contributed to this year's *EMJ Gastroenterology*, an issue I am confident you all will find value in.

Spencer Gore

Chief Executive Officer, EMG-Health

Foreword

Dear Colleagues and Friends,

Greetings from the desk of your Editor-in-Chief and allow me to warmly welcome you all to the 2020 issue of *EMJ Gastroenterology*. I feel both privileged and excited to close a second year as Editor-in-Chief of this beloved, international peer-reviewed journal. As its name states, *EMJ Gastroenterology* focusses on basic, translational, clinical, and outcomes research in all fields of gastroenterology, a huge, multidisciplinary speciality including internists, endoscopists, digestive surgeons, oncologists, nutritionists, and many others subspecialists, who work together in multidisciplinary teams to offer the newest evidence-based treatment to patients with digestive diseases.

Due to the coronavirus disease (COVID-19) pandemic, the 28th United European Gastroenterology (UEG) Week, which was to be held in Vienna, Austria, was replaced by the first ever virtual UEG Week. Even though a digital congress does not allow physical contact and personal discussions between colleagues and friends, the UEG Week Virtual 2020 was a tremendous success, with 10,738 participants. The organisers made it possible to explore a new virtual world and showcased state-of-the-art science and developments in digestive health. UEG Week remains the premier venue for researchers from across the globe to present their latest findings. In this issue's Congress Review, EMJ report on the event, highlighting the news stories that really matter and giving a voice to researchers and presenters who regaled attendees with the results of their studies that will propel us forward in our understanding of the digestive system.

The articles included in *EMJ Gastroenterology* comment on some of the biggest topics from UEG Week Virtual 2020 and offer some interesting food for thought. Further included is my Editor's Pick for this issue by Grundmann et al. on cachexia in patients with gastrointestinal cancers. Additionally, the journal features two interesting papers on inflammatory bowel disease: one about the novel and emerging therapies (Bhattacharya & Cross), and the other about the role of inflammatory cytokines in depression among these patients (Chapman & Jones). Menassa et al. present on stem cell therapy, a novel therapeutic approach for inflammation-associated sigmoid colon disease. These and more are included for your reading pleasure, and I hope that they generate compelling debates among peers.

I am sure that you will find this latest issue an interesting read, which will provoke lively discussions and debates. Lastly, I would like to extend my appreciation to all *EMJ Gastroenterology* editorial board members and EMJ's diligent editorial team for putting this fantastic issue together; I hope you enjoy it as much as I did.

Sorin T. Barbu

Professor of Surgery, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

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Congress Review

Review of the United European Gastroenterology (UEG) Week Virtual 2020

Location: UEG Week Virtual 2020

Date: 11th–13th October 2020

Citation: EMJ Gastroenterol. 2020;9[1]:12-20. Congress Review.

"WILLKOMMEN IN WIEN" were the words that delegates expected to hear when arriving in Vienna, Austria, to participate in the United European Gastroenterology (UEG) Week. Instead of walking through Austria's architecturally stunning scientific hub, where more than 2,000 large-scale meetings and events are hosted annually, or enjoying a relaxing evening in one of the imperial cities renowned coffee houses or cosy wine taverns, delegates joined the 28th UEG Week virtually from the comfort and safety of their homes. Despite the unprecedented impacts of the coronavirus disease (COVID-19), UEG seamlessly provided one of the most spectacular events this year: the UEG Week Virtual 2020.

"We hope that this will give you everything that you have had in your previous UEG weeks and more."

UEG chose a unique approach to ensure that the UEG Week Premiere session was as lively and interactive as possible: the session opened with DJ Melinda Stoika, who provided uplifting beats to elevate the mood and enliven everyone for the 3-day event ahead. Award-winning broadcaster Jonathan McCrea, a communication specialist with a love for technology and science, was undoubtedly the perfect moderator to host the session. Live from the UEG studio in Vienna, delegates were welcomed by McCrea's opening words: "Good evening everyone, to gastroenterologists across the world, to researchers, physicians, and all of those working in digestive health. To say this year has been a challenging one is an understatement." He proceeded to discuss the challenges that the COVID-19 pandemic has brought to healthcare and other industries, whilst also congratulating the UEG Week Virtual 2020 for being extraordinarily special: "The communities of those invested

in gastrointestinal health and the outcomes of their patients can come together to hear from renowned experts, learn from the latest science, discuss and debate new therapies and new ideas, and come together and connect in a way that was never possible before." He continued: "We hope that this will give you everything that you have had in your previous UEG weeks and more." He then welcomed the top UEG Council members: President Prof Axel Dignass, Frankfurt, Germany; Vice President Prof Helena Cortez-Pinto, Lisbon, Portugal; and Scientific Committee Chair, Prof Herbert Tilg, Innsbruck, Austria.

Prof Dignass positively stated: "I'm here and I'm really proud and happy to see you all throughout the world." He then delineated the precautions taken to ensure that the UEG Week remained a safe experience, and explained that, as UEG is a very multidisciplinary organisation, it took some time for the decision to be made to transfer the congress online. Prof Dignass further outlined how the COVID-19 pandemic was a significant challenge for him personally because it greatly affected his research and abilities to network as President of UEG. When questioned how the UEG team coped with changing to a virtual event, he stated: "This is probably one of the biggest assets that UEG has. The headquarters have an outstanding team, they were so flexible. While changing over to a virtual congress, we were also delivering our usual content of educational materials, webinars, and meetings, which all other societies had stopped."

Scientific Committee Chair, Prof Herbert Tilg, emphasised that the original programme for UEG had been completed in March 2020 and had taken 1.5 years to put together. Therefore, the UEG Scientific Committee had to restart the process and condense the programme. Though compressed, the 3-day event boasted 117 live streamed sessions, more than 1,400 eposters, 2,788 submitted abstracts, 1,915 presented

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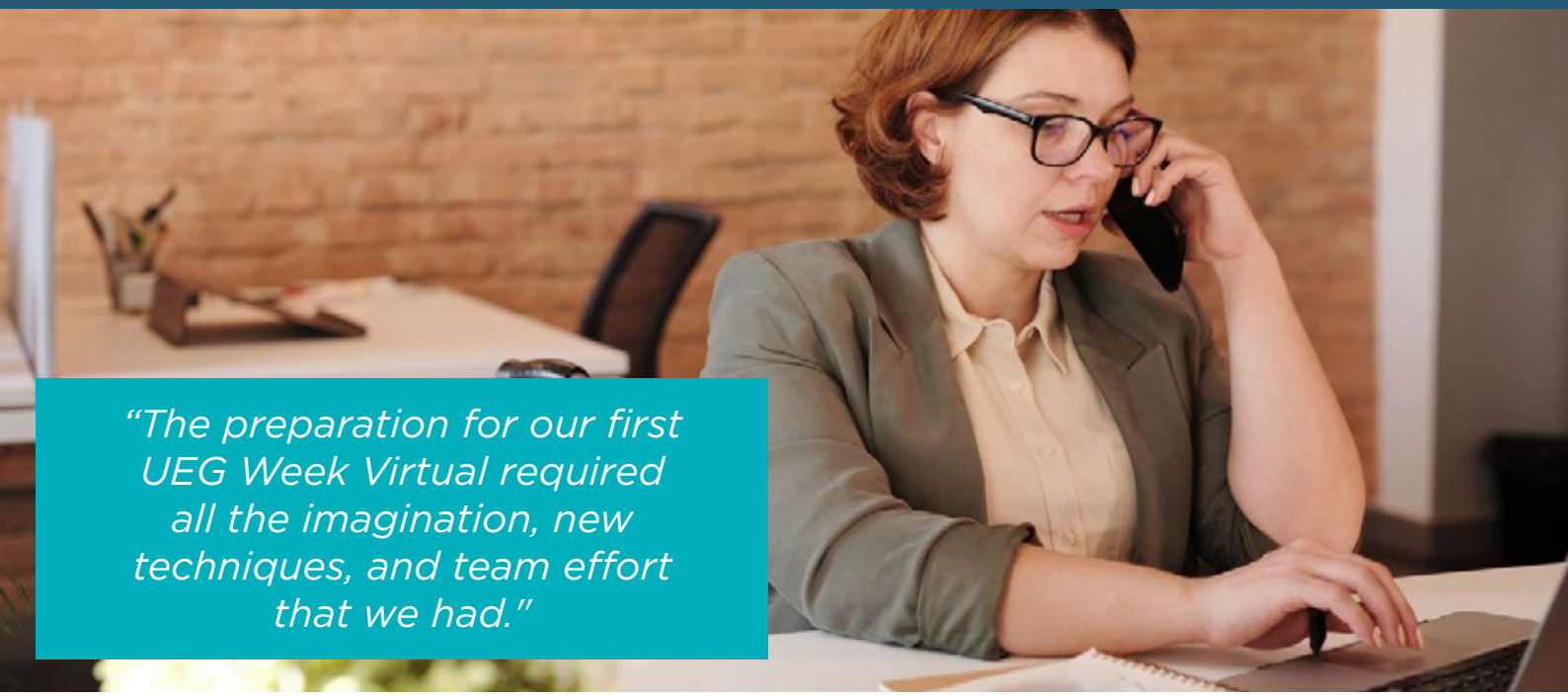


"The preparation for our first UEG Week Virtual required all the imagination, new techniques, and team effort that we had."

abstracts, and 12 sponsored symposia, and attracted nearly 11,000 participants. The content covered all gastroenterology specialities, including hot topics such as faecal microbiota transplantation, COVID-19, artificial intelligence and robotics in endoscopy, and novel treatment options and strategies in inflammatory bowel disease (IBD).

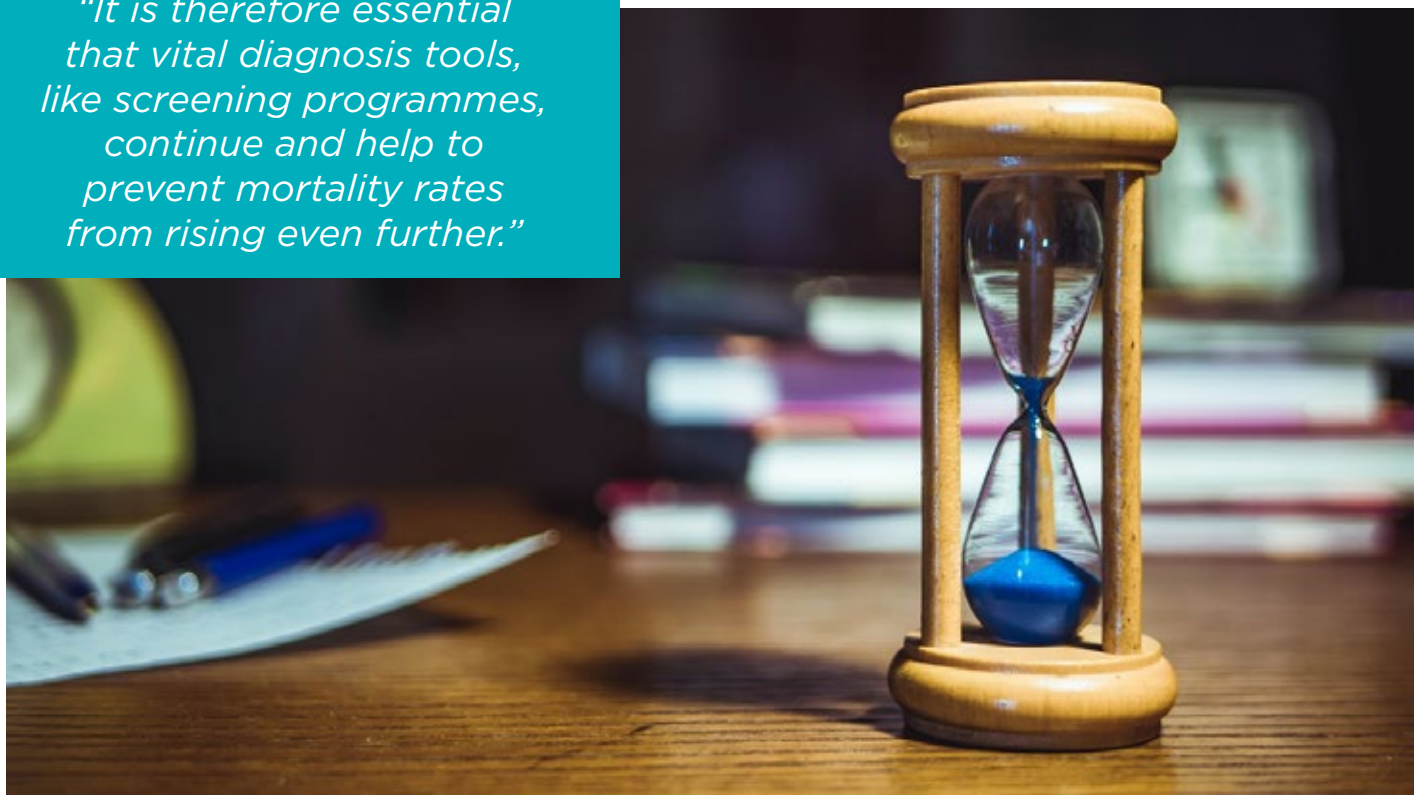
The UEG platform was second to none, and enabled participants to explore the latest science with interactive virtual sessions and live demos. To make the experience more representative, everyone even received a virtual congress bag to collect and keep track of documents. However, UEG Week was not only about the science. Participants were invited to the 'Chill Zone' to relax, learn healthy cooking recipes, and had a choice of three yoga classes. The fun did not stop there, as sightseeing tours of Vienna were available to watch, and participants were encouraged to take part in the virtual congress treasure hunt to win a free registration to UEG Week 2021.

The primary award presented at this year's congress, the distinguished UEG Research Prize, was awarded to Prof Stephan Schreiber for his outstanding project "Therapeutic mechanisms of controlled-ileocolonic-releasee nicotinamide (CICR-NAM) in IBD." In the following pages, we have compiled some of the late-breaking research highlights, with topics including the lower associated risk of pancreatic cancer through reduced weight loss surgery, a revolutionary endoscopic ablation procedure to reduce insulin dependence in patients with Type 2 diabetes mellitus, and COVID-19 fears among patients with IBD. We have also enlisted stand-out abstract summaries from UEG Week presenters, which detail the use of machine learning algorithms to predict rebleeding and mortality of oesophageal variceal bleeding in cirrhotic patients, the impact of prenatal stress on visceral sensitivity and intestinal homeostasis in adulthood, and more.

Th UEG Week Premiere session concluded with the 'Presidential Address' by Prof Dignass, in which he reiterated that UEG is built on support, respect, awareness, and co-operation. UEG has grown profoundly since beginning in 1992. Collaborating with 48 national societies and 17 speciality societies, with a community of more than 50,000 experts strong, UEG is committed to building a close-knit digestive health community. "The preparation for our first UEG Week Virtual required all the imagination, new techniques, and team effort that we had. I'm sure you will appreciate this," Prof Dignass stated, while inviting everyone to "meet, exchange, and evolve virtually while at the best gastroenterology congress in the world." Concluding the session, he wished everyone strength, positivity, and perseverance during these unprecedented times. This supportive attitude was embraced throughout the entirety of the Virtual UEG Week 2020, and we look forward to the continuation of this spirit until next year's UEG Week, planned again for Vienna, Austria.

UEG 2020 REVIEWED →

"It is therefore essential that vital diagnosis tools, like screening programmes, continue and help to prevent mortality rates from rising even further."



COVID-19-Related Delays Estimated to Increase Colorectal Cancer Mortality Rates

DELAYS in receiving fundamental medical care have been experienced worldwide this year because of resources being reallocated to tackle the coronavirus disease (COVID-19) pandemic. One service in particular that has seen such delays is the screening of colorectal cancer (CRC), and according to research presented at UEG Week Virtual 2020 and reported in a press release dated the 12th October, these delays could have a significant negative impact on CRC mortality.

As the second most common cause of cancer deaths and the most common digestive cancer in Europe, the importance of identifying CRC at an early stage is well established. Screening is a crucial tool for the detection of CRC, with a steady decline in CRC mortality rates being associated with the rollout of screening programmes across Europe. Suspensions to essential screening programmes have been widespread since the COVID-19 pandemic started, and researchers from the University of Bologna, Bologna, Italy, conducted a study to assess the impact of these suspensions on CRC outcomes.

The researchers developed a model to estimate the impact of delays in receiving a colonoscopy on CRC disease stage progression and mortality. For a delay period of 0–3 months, it would be expected that 74% of CRC cases be Stages I–II, with a 2% increase seen with delays of 4–6 months. Furthermore, the researchers predicted that longer delays of 7–12 months and >12 months would increase the incidence of advanced CRC cases from 26% to 29% ($p=0.008$) and 33% ($p<0.001$), respectively. When assessing the impact on mortality rates, a 12% increase in CRC deaths was estimated for a change from a delay of 0–3 months to >12 months. Prof Luigi Ricciardiello, lead author of the study, commented on the significance of the findings: "It is therefore essential that vital diagnosis tools, like screening programmes, continue and help to prevent mortality rates from rising even further." He added: "Healthcare authorities need to act urgently on how they reorganise activities during COVID-19, without compromising the diagnosis of other high-impact diseases like this research shows."

Pancreatic Cancer Risk Reduced by Weight Loss Surgery

> *"Our research shows that this surgery is a viable way in reducing the risk of pancreatic cancer in this growing, at-risk group."*

SURGERY to address obesity significantly reduces the risk of developing pancreatic cancer, according to findings of a 20-year analysis, shared at UEG Week Virtual 2020 and in a press release dated 12th October 2020.

The study considered 1,435,350 patients who were obese and had diabetes, over a period of 20 years; 10,620 of these patients underwent bariatric surgery during this period. The prevalence of pancreatic cancer in those patients who had undergone bariatric surgery was significantly less than those without surgery (prevalence of 0.19% versus 0.32%; $p<0.05$).

Pancreatic cancer is increasing in incidence, with cases in the European Union increasing by 5% between 1990 and 2016, the greatest rate of increase of the top five cancers in the EU. Over that period, survivability of pancreatic cancer has not improved significantly, so prevention is important. Lead author Dr Aslam Syed, Allegheny Health Network, Division of Gastroenterology, Pittsburgh, Pennsylvania, USA, emphasised the impact of pancreatic cancer: "The average survival time at diagnosis is particularly bleak for this silent killer, at just 4.6 months, with patients losing 98% of their healthy life expectancy. Only 3% of patients survive more than 5 years."

As rates of both obesity and diabetes are increasing, these study findings are particularly timely. More than one-half the adult population of the EU are obese or overweight, with associated health risks including increased risk of pancreatic and other cancers. Dr Syed highlighted the impact of the findings in this context: "Obesity and diabetes are well-known risk factors for pancreatic cancer via chronic inflammation, excess hormones and growth factors released by body fat. Previously, bariatric surgery has been shown to improve high blood sugar levels in diabetic patients and our research shows that this surgery is a viable way in reducing the risk of pancreatic cancer in this growing, at-risk group."

IBS Risk Increased for Childhood Asthma and Food Allergy Patients

IRRITABLE bowel syndrome (IBS) at age 16 years is more of a risk for those who experienced asthma and food hypersensitivity at age 12 years, according to a new study that was reported in a press release at UEG Week Virtual 2020, dated 12th October 2020.

The study, by researchers from the University of Gothenburg, Gothenburg, Sweden, and the Karolinska Institute, Stockholm, Sweden, involved a total of 2,770 children who were analysed from birth to age 16 years. The patients and their parents were required to complete questionnaires on asthma, allergic rhinitis, eczema, and food hypersensitivity at ages 1, 2, 4, 8, 12, and 16 years.

At age 16 years, those who had IBS were around twice as likely to have had asthma at the age of 12 years (11.2% versus 6.7%). Additionally, 40.7% of 16-year-olds with IBS had reported food allergy at age 12 years, compared to 29.2% of 16-year-olds without IBS. The research team also found an association between asthma, food hypersensitivity, and eczema and an increased risk of concurrent IBS at age 16 years.

"Previous studies on allergy-related diseases and irritable bowel syndrome are contradictory."

Dr Jessica Sjölund, who led the population-based cohort study, was pleased to have found evidence for an association that has been previously unclear: "We knew that allergy and immune dysregulation had been suggested to play a role in the development of irritable bowel syndrome, but previous studies on allergy-related diseases and irritable bowel syndrome are contradictory."

The team are now hopeful that this knowledge could led to new treatment developments for those with adolescent IBS, which could focus on the low-grade inflammation observed in allergy-related diseases.

Revolutionary Procedure to End Insulin Treatment in Diabetes

DUODENAL mucosal resurfacing (DMR) is the novel, minimally invasive, endoscopic ablation procedure which has been tested and shown to reduce dependence on insulin in a group of patients with Type 2 diabetes mellitus. Research on this therapeutic procedure was presented at UEG Week Virtual 2020 on 13th October.

The new technique rejuvenates the lining of the duodenum and was used in combination with daily administration of glucagon-like receptor peptide agonists and light lifestyle counselling. The pilot study enrolled 16 insulin-dependent patients with Type 2 diabetes mellitus with an average BMI of 29.8 kg/m^2. The results showed that 75% of patients no longer depended on insulin 6 months after the study and had HbA1c levels <7.5%, which decreased to 6.7% 12 months after the study. Other positive responses included reduced average BMI after 12 months to 25.5 kg/m^2 and reduced percentage fat in the liver from 8.1% to 4.6% after 6 months. The results of the study were promising in terms of improving overall metabolic health and reducing risk factors for the development of metabolic syndromes such as diabetes. In those who did not respond to the new procedure and remained on insulin after 6 months (25%), median insulin dose decreased from 35 units per day to 17 units per day at 12 months.

Performed in an outpatient setting, DMR is performed with an integrated over-the-wire catheter attached to a custom console that performs a synchronised lifting of the duodenal mucosa and then ablation of the treatment area. The mechanism underlying the novel technique is not yet fully understood but may be associated with the change observed in mucosal cells in response to a diet high in fat and sugar, affecting the production and signalling of key hormones implicated in insulin resistance and diabetes. The act of resurfacing the lining of the duodenum may rejuvenate and reset this effect.

Dr Suzanna Meiring, study lead from Amsterdam University Medical Centre, Amsterdam, the Netherlands, commented on the prospects of the new results and the impact on patients: "This could be a game-changing approach in the treatment of metabolic syndrome. Many patients with Type 2 diabetes [mellitus] are very happy to be able to discontinue insulin therapy since insulin therapy comes with weight gain and hypoglycaemic events." She also confirmed that a large, randomised controlled trial will further investigate these results.

"This could be a game-changing approach in the treatment of metabolic syndrome."

COVID-19 Fears Among IBD Patients

A global survey by the European Federation of Crohn's & Ulcerative Colitis Associations (EFCCA) has shown that patients with inflammatory bowel disease (IBD) are worried that their medication may increase the risk of contracting coronavirus disease (COVID-19). This is according to a press release by the EFCCA that was presented at UEG Week Virtual 2020, dated 11th October.

To investigate the current COVID-19 concerns and fears from IBD patients, EFCCA, with the collaboration of Prof Silvio Danese, Head of the IBD Center at the Humanitas Research Hospital, Milan, Italy, launched the survey between March 30th and April 16th 2020. It focussed on the most recurrent questions that patients asked their physicians during the COVID-19 outbreak.

The survey reached 3,815 IBD patients in 51 countries and results showed that a vast number of respondents were worried about contracting COVID-19 (85%) or infecting others (87%). Furthermore, 63% reported the worry that their medication might be putting them at increased risk of infection; however, the majority of patients (88%) did not want to discontinue their IBD medications during the pandemic and only 4% stopped taking their medication on their own initiative.

Close co-operation with all stakeholders could provide greater patient compliance and provide aligned, consistent, and reassuring recommendations.

The survey also investigated what factors alleviated concerns about COVID-19; patient associations represented the most reassuring factor (42%) followed by relatives (27%) and international authorities (14%). Friends, physician consultation, and psychologists scored 7%, 6%, and 4%, respectively.

These results suggest that patient organisations play an important role in linking all stakeholders involved in IBD patient management. During periods of crisis that cause greater worry and disruption to people living with chronic diseases, such as the COVID-19 pandemic, close co-operation with all stakeholders could provide greater patient compliance and provide aligned, consistent, and reassuring recommendations.

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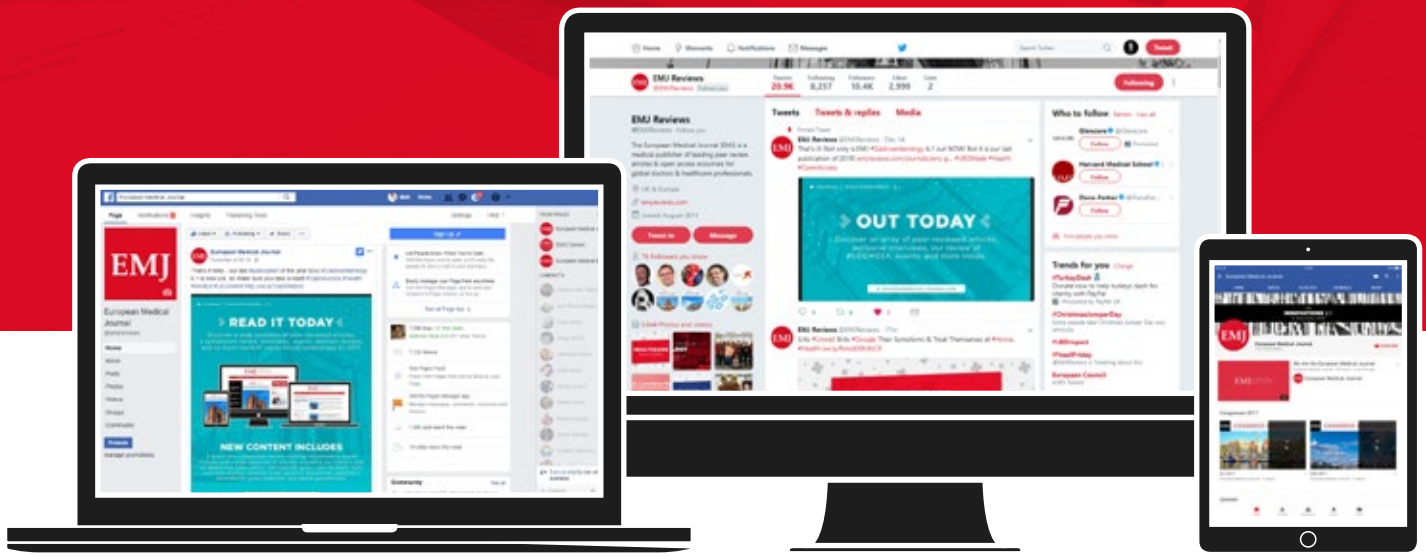

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Dynamic Management of Crohn's Disease: Reaching a New Dimension in Patient Care

This symposium took place on 13th October 2020, as part of the United European Gastroenterology (UEG) Week Virtual 2020

Speakers: Silvio Danese,[1] Subrata Ghosh,[2] Torsten Kucharzik,[3] Laurent Peyrin-Biroulet[4]

1. Humanitas Research Hospital, Milan, Italy
2. Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK
3. Klinikum Lüneburg, Lüneburg, Germany
4. Nancy University Hospital, Vandoeuvre-lès-Nancy, France

Disclosure: Prof Danese has provided research support for and/or was a principal investigator for, has been a consultant for, and has participated in speaker bureaus for AbbVie, Allergan, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Ferring, Hospira, Johnson & Johnson, Merck, MSD, Takeda, Mundipharma, Pfizer, Sandoz, Tigenix, UCB, and Vifor Pharma. Prof Ghosh has provided research support and/or was a principal investigator for AbbVie, GlaxoSmithKline, and Vertex; has been a consultant for AbbVie, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Dr Falk Pharma, Ferring, Galapagos, Gilead, Janssen, Pfizer, Receptos, Roche, and Takeda; and has participated in speaker bureaus for AbbVie, Ferring, Janssen, Pfizer, and Takeda. Prof Kucharzik has provided research support and/or was a principal investigator for AbbVie, Janssen, Celgene, Celltrion, Hospira, Mundipharma, Dr Falk Pharma, Roche, Galapagos, Gilead, Takeda, and MSD; has been a consultant for AbbVie, Biogen, Celgene, Celltrion, Hospira, Mundipharma, Dr Falk Pharma, Galapagos, Gilead, Janssen, MSD, Novartis, Takeda, and UCB; and has participated in speaker bureaus for AbbVie, Dr Falk Pharma, Ferring Arzneimittel GmbH, MSD, Pfizer, Roche, Takeda, and UCB. Prof Peyrin-Biroulet has provided research support and/or was a principal investigator for AbbVie, Janssen, MSD, Pfizer, and Takeda; has been a consultant for AbbVie, Amgen, Biogaran, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Ferring, Genentech, H.A.C. Pharma, Hospira, Index Pharmaceuticals, Janssen, Eli Lilly, Lycera, Merck, Norgine, Pfizer, Pharmacosmos, Samsung Bioepis, Sandoz, Takeda, Tillots Pharma AG, and Vifor Pharma; and has participated in speaker bureaus for AbbVie, Ferring, H.A.C. Pharma, Janssen, Merck, Takeda, Tillots Pharma AG, and Vifor Pharma.

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Meeting Summary

The symposium entitled "Dynamic management of CD: reaching a new dimension in patient care" took place on 13th October 2020 during the United European Gastroenterology (UEG) Week Virtual 2020. Distinguished experts Prof Danese, Prof Ghosh, Prof Kucharzik, and Prof Peyrin-Biroulet highlighted the latest developments in Crohn's disease (CD) management, with a focus on the ground-breaking

STARDUST treat-to-target (T2T) trial and the STARDUST intestinal ultrasound (IUS) substudy. The specialists discussed how dynamic management of CD is evolving toward having an emphasis on proactive management, including patient-reported outcomes and endoscopic targets, with the goal of preventing disability and bowel damage. The data from the STARDUST trial illustrated how a T2T strategy could be an additional tool for clinicians, to assist them in making informed treatment-dosing decisions and help patients with CD achieve their treatment goals. The results from the IUS substudy showed how this technique could be useful in the noninvasive monitoring of treatment response in patients with CD. The speakers concluded that, in the current CD treatment landscape, dynamic management strategies can be used to adapt to the patient's needs, with the goal of providing long-term disease control.

Dynamic Management in Crohn's Disease

Professor Laurent Peyrin-Biroulet

Prof Peyrin-Biroulet started the symposium by describing how the focus of inflammatory bowel disease (IBD) therapy is moving toward disease modification.[1] Early targeting in CD offers a novel opportunity to change the course of long-term disease evolution, helping patients to lead a normal life by preventing disabilities.[1] Using paradigms such as T2T, incorporating composite endpoints such as clinical and endoscopic remission, and applying adjunctive measures such as biomarkers, helps provide optimal disease monitoring and management for patients with IBD (Figure 1).[2]

As evidence has accumulated, the more ambitious goal of complete endoscopic remission has seemed attainable. However, data from the CALM study showed that complete endoscopic remission was achieved in only approximately 20% of patients treated with a tight-control strategy at Week 48, suggesting that this target could have been too ambitious;[3] new strategies and therapies with new mechanisms of action may, therefore, be needed to meet endoscopic remission goals. Early disease control may be the best way to change patients' lives and alter the disease course, as data show that the early use of disease-modifying anti-inflammatory therapies can impact the natural history of CD.[1]

Novel initiatives in IBD management promote an emphasis on disease modification, firstly to help achieve disease and symptom control, followed by disease remission for long-term disease modification. Defined endpoints can include several measures focussing on patient quality of life and the prevention of disease complications. Recent studies have also shown that transmural healing is a better outcome compared to endoscopic healing as it results in less surgery, fewer hospitalisations, and has a positive impact on the disease course.[4]

Prior to the development of the STRIDE guidelines, physicians focussed mainly on symptomatic remission and possible achievement of biomarker remission using reactive management strategies. Now, in the era of STRIDE guidelines that recommend tight control and T2T strategies, clinicians are practising proactive management, focussing on achievement of deep remission with an absence of symptoms and severe endoscopic lesions, with the ultimate goal of preventing disability and bowel damage in patients with CD.[5]

Exploring STARDUST

Professor Silvio Danese

The STARDUST trial[6] was the first T2T, randomised trial of adult patients with CD, using endoscopy at Week 16 as a decision point for dose adjustment of ustekinumab, an IL-12/23 inhibitor. The objective of the trial was to test the hypothesis that a maintenance strategy with ustekinumab, based on early endoscopy, regular assessment of biomarkers (e.g., faecal calprotectin [fCal] and C-reactive protein [CRP]) and clinical symptoms (e.g., Crohn's Disease Activity Index [CDAI]), and subsequent treatment adjustment to achieve the treatment target, is more successful in obtaining endoscopic improvement than a maintenance strategy using standard of care (SoC) with ustekinumab.[7]

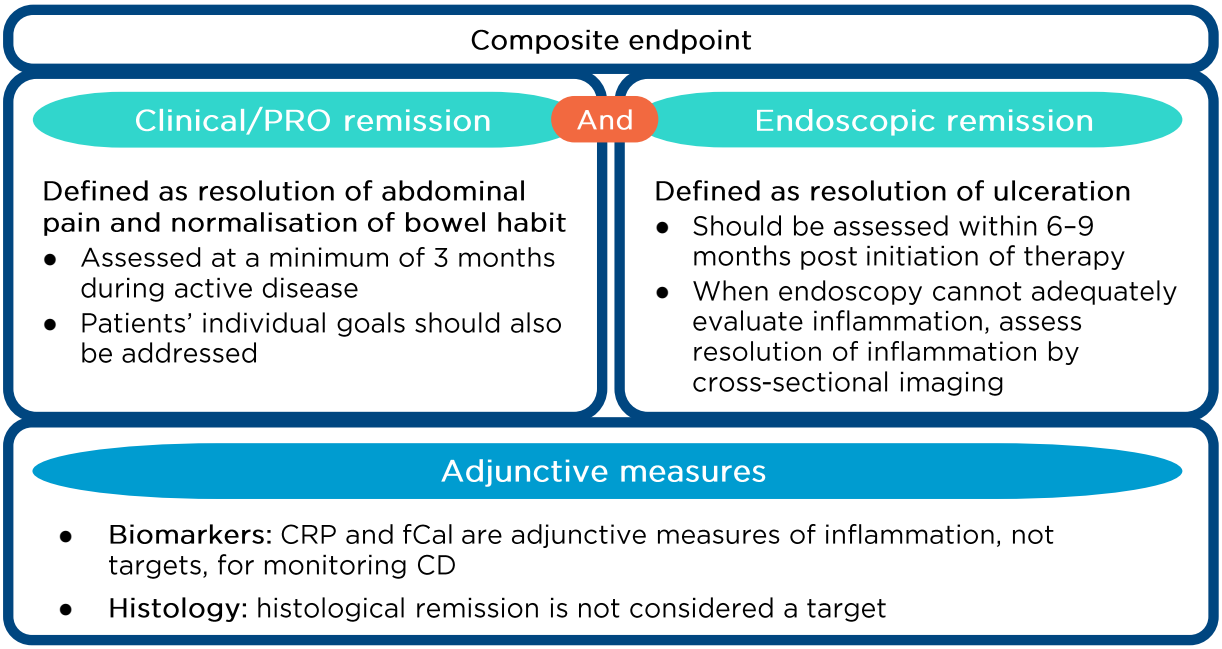

Figure 1: Treat-to-target recommendations in Crohn's disease.

CD: Crohn's disease; CRP: C-reactive protein; fCal: faecal calprotectin; PRO: patient-reported outcome.

Adapted from Peyrin-Biroulet et al.[2]

The study also applied IUS examinations as a noninvasive tool to assess the response to treatment in a subgroup of patients.[8,9]

Patients with moderate-to-severe active CD, who were either biologic-naïve or had been exposed to one previous biologic, were included in the study. Patients received an induction dose (approximately 6 mg/kg intravenously [IV]) of ustekinumab at Week 0, followed by maintenance therapy with ustekinumab (90 mg subcutaneously [SC]) starting at Week 8. An interim analysis was performed at Week 16; if patients achieved the first target (CDAI 70 response), they were randomised to the T2T or SoC arm.

Patients in the T2T arm either received ustekinumab every 8 weeks (q8w) or 12 weeks (q12w), based on the change in the Simple Endoscopic Score for Crohn's Disease (SES-CD) from baseline. Patients in the T2T arm received maintenance treatment, with possible dose adjustments based on symptoms and biomarkers, while patients in the ustekinumab SoC arm received dose adjustments as per the label, based solely on physician-confirmed disease flare. The primary endpoint at Week 48 was a 50% reduction from the baseline SES-CD value (Figure 2).[6]

During the study maintenance period, CDAI, CRP, and fCal measures were assessed to examine whether patients had achieved the treatment target, defined as a CDAI <220 and ≥70 point improvement in CDAI score from baseline, and a CRP value ≤10 mg/L or an fCal value ≤250 µg/g. If patients had achieved the target, they could continue with the assigned dose. If the target was not reached, they were eligible for dose escalation. If patients did not achieve the target while receiving a dose every 4 weeks, they discontinued the study.[10]

The patient disposition results showed that 490 patients received ustekinumab induction, with a large proportion of patients achieving CDAI response; 79% of patients in the T2T arm and 87% in the SoC arm completed the study. Discontinuation in the T2T and SoC arms was mainly caused by lack of efficacy and withdrawal by the participant. The dose distribution showed that the majority of patients who received the q12w dose were still receiving that dose at Week 48 (59.8% and 63.8% in the T2T and SoC arms, respectively). Similarly, 40.5% and 78.4% of patients receiving the q8w dose in the T2T and SoC arms, respectively, were still receiving that dose at Week 48.[10]

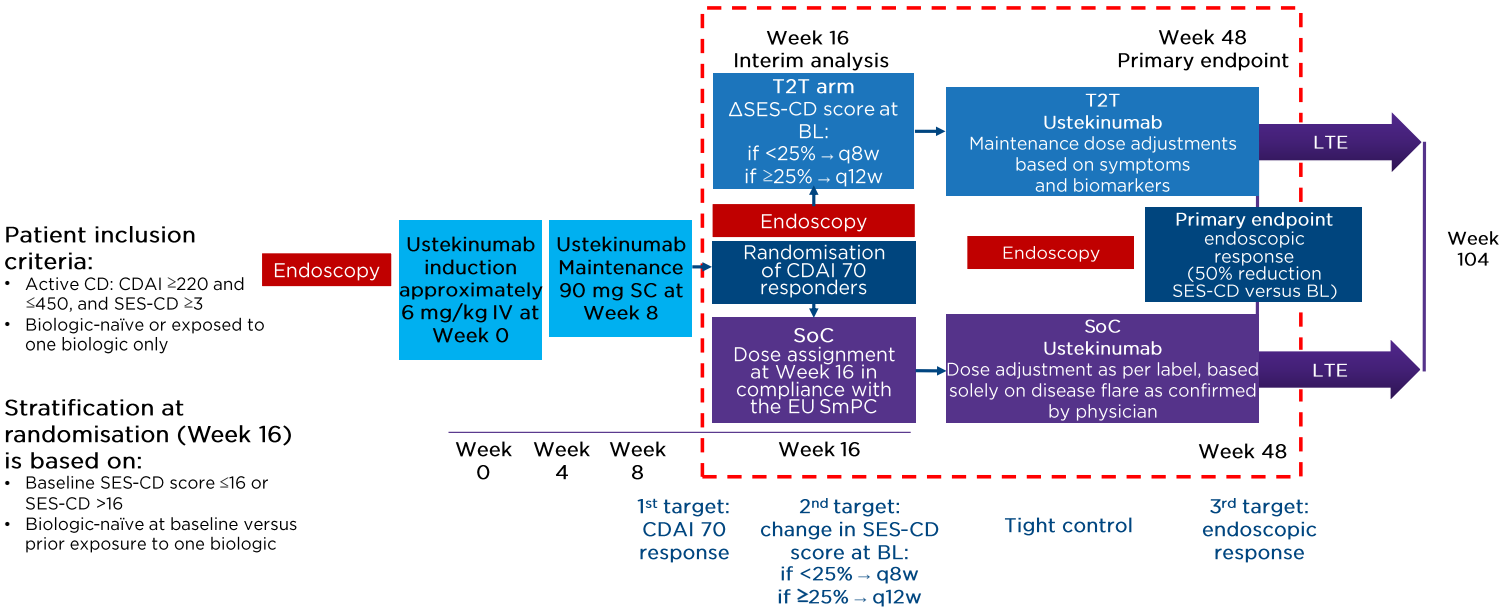

Figure 2: STARDUST study design.

BL: baseline; CD: Crohn's disease; CDAI: Crohn's Disease Activity Index; EU: European Union; IV: intravenously; LTE: long-term extension; q8w: every 8 weeks; q12w: every 12 weeks; SC: subcutaneously; SES-CD: Simple Endoscopic Score for Crohn's Disease; SmPC: summary of product characteristics; SoC: standard of care; T2T: treat-to-target.

Adapted from Janssen-Cilag Ltd.[6]

The results of the STARDUST study show that the nonresponder imputation (NRI) analysis of the endoscopic response primary endpoint with SES-CD improvement ≥50% at Week 48 was achieved by 37.7% of patients in the T2T arm, compared with 29.9% of patients in the SoC arm (p=0.09). The analyses of the last observation carried forward (LOCF) and the NRI, which only included patients who discontinued because of lack/loss of efficacy, showed that a significant proportion of patients in the T2T arm achieved the primary endpoint, compared with patients in the SoC arm (p=0.049 and p=0.036, respectively).[10] There were no between-group differences in the NRI and LOCF analyses for the endoscopic outcomes at Week 48.[10] The changes in SES-CD over time from baseline to Week 48 showed a clear and rapid effect of ustekinumab at Week 16 of treatment, characterised by a substantial decrease in mean (95% confidence interval) scores from baseline to Week 16 (13.4 versus 8.8, respectively; Δ-4.6 [-5.5 to -3.7]) in the T2T arm.[10] There was no significant difference in SES-CD score between the T2T and SoC arms at Week 48 (8.5 versus 8.6, respectively).

Clinical outcomes at Week 48 for the NRI and LOCF analyses demonstrated that both the T2T and SoC regimens were associated with high efficacy; >70% of patients achieved the CDAI 70 target and >60% of patients were in clinical remission at Week 48 in both groups.[10] As seen in the change in endoscopy scores over time, mean CDAI scores also showed a dramatic drop between baseline and Week 8 of treatment in both treatment arms, which was further boosted by treatment optimisation at Week 16 (LOCF analysis).[10] Normalisation of biomarker responses (fCal, CRP) at Week 48 was observed in approximately 25% of patients in the NRI and LOCF analyses for both the T2T and SoC arms. Changes in biomarkers over time showed a similar trend, compared with the CDAI 70 data over time for both the T2T and SoC arms, which showed a marked drop between baseline and Week 8 in both treatment groups.[10]

The safety summary at Week 48 indicated that there were no major differences between the T2T and SoC groups, confirming the well-known safety profile of ustekinumab in patients with CD.[10] Prof Danese concluded by reiterating that in the STARDUST study, 48 weeks of treatment with ustekinumab resulted in a numerically higher endoscopic response in patients in the T2T arm compared with SoC, with high clinical remission

and biomarker responses also observed in both arms. The safety and tolerability of ustekinumab was consistent with the known safety profile. T2T could, therefore, represent an additional tool for clinicians, to guide ustekinumab dosing decisions for patients with CD.

Can We Reach the Stars with Ultrasound?

Professor Torsten Kucharzik

Prof Kucharzik presented the data from the STARDUST IUS substudy, noting that IUS can be used to determine disease activity and severity in patients with IBD, and to detect complications in patients with CD. It is a noninvasive, low-cost, patient-centred technique that has comparable accuracy to MRI and CT scanning (Figure 3).[11-13]

The aims of the STARDUST IUS substudy were to assess the effectiveness of ustekinumab in achieving IUS response and remission, and to explore the relationship between IUS response and changes in clinical and endoscopic parameters over time.[8,9]

IUS can reflect transmural disease activity, and the most prominent parameter to measure this activity is bowel-wall thickness (BWT). The IUS substudy examined BWT in the ileum and the colon in patients with CD; increased BWT was defined as increases of >2 mm in the terminal ileum and >3 mm in the colon, as determined in the transversal and longitudinal sections of the most affected part of the segment. An IUS response was defined as ≥25% reduction in BWT, compared with baseline.[14-16] Vascularisation using colour Doppler signal, echo stratification assessment, and inflammatory mesenteric fat assessments were also used to assess transmural disease activity.[15]

IUS remission, or transmural healing, was defined as normalisation of BWT, normal vascularisation (colour Doppler signal of 0 or 1), normal bowel-wall echo stratification, and the absence of inflammatory mesenteric fat, based on the most affected part of the bowel.[17] IUS was performed at baseline, as well as at Weeks 4, 8, 16, and 48.

The baseline characteristics showed that the ileum was the most affected part of the bowel in 50 of the 77 patients participating the substudy (65%), and the colon, including the caecum, was the most affected part in 27 patients (35%).[16] The overall percentage change in BWT over time showed a significant decrease compared with baseline values, starting at Week 4 of treatment ($p<0.01$) and continuing at Week 8 ($p<0.0001$), Week 16 ($p<0.0001$), and Week 48 ($p<0.0001$). There was a more pronounced decrease in BWT in the colon compared with the ileum, but both areas showed significant decreases over time.[16]

Analyses of IUS response and transmural healing over time showed that 25% of patients showed a response to treatment as early as Week 4, with approximately 24% of patients showing complete transmural healing and complete normalisation of all IUS parameters at Week 48 of treatment.[16] The IUS response was observed early, at Week 4, in both the colon and ileum, though the response was more pronounced in the colon.[16] There was a progressive increase in the number of patients showing improvements in BWT in both the ileum and colon over time. For the most affected part of the bowel, the proportion of patients with normalisation of vascularisation, bowel-wall stratification, and mesenteric fat increased through to Week 48.[16]

Prof Kucharzik presented an example IUS image from a selected patient case from the STARDUST study, demonstrating transmural healing in the terminal ileum at Week 48 of ustekinumab treatment, with complete normalisation of all pathological parameters compared with baseline.

The IUS substudy results showed that there was a 92.3% agreement between IUS and endoscopy in defining the most affected part of the bowel at baseline for the ileum, indicating that IUS may be a useful tool, in addition to endoscopy, to help determine the most affected part of the bowel.[16] There was also reasonable reliability between IUS response of the most affected part of the bowel at Weeks 4, 8, 16, and 48 and the endoscopic response and biomarker outcomes at Week 48.[16]

Prof Kucharzik concluded by emphasising that IUS responses to ustekinumab were detected as early as Week 4 of treatment and improved over time up to Week 48. Furthermore, a clinically meaningful percentage of patients achieved transmural healing at Week 48, primarily in the colon.

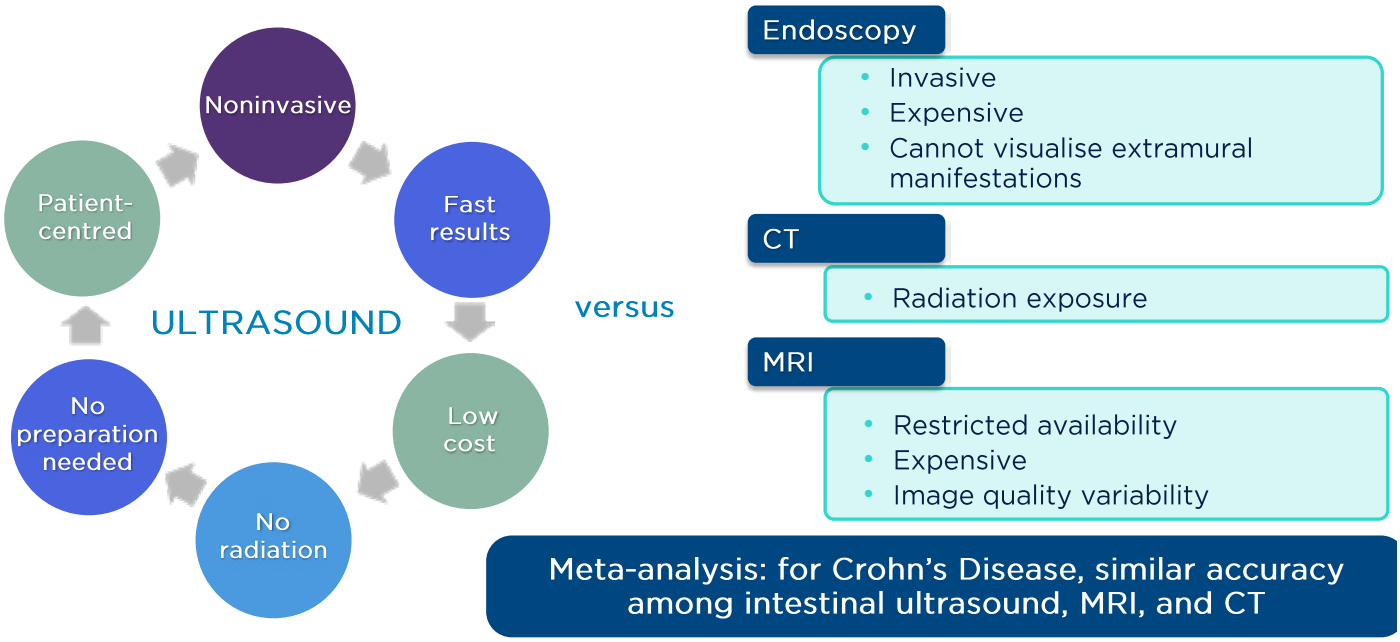

Figure 3: What is currently known about intestinal ultrasound.

Adapted from Panés et al.,[11] Horsthuis et al.,[12] and Yoon et al.[13]

There was high agreement at baseline between IUS and endoscopy in defining the most affected part of the bowel, as well as reliability between IUS response as early as Week 8 and endoscopic response and biomarker outcomes at Week 48. The results show that IUS can be a useful tool in predicting later endoscopic response with ustekinumab in patients with CD and underline the potential benefits of using IUS as part of a personalised approach to treatment.

Dynamic Management: A Case-Based Approach

Professor Subrata Ghosh

Prof Ghosh demonstrated how the evolving principles of CD management can be applied to current practices, using a case-based approach. He presented the case of a 28-year-old male patient, diagnosed with CD characterised by ileocolonic disease. The patient had started treatment with adalimumab 4 months earlier but had not responded to treatment. Laboratory tests showed modestly elevated CRP and fCal levels, with extensive colonic ulceration during colonoscopy (SES-CD=15), deep ulcers on MRI, and increased BWT and narrowing of the ileum on IUS.

The patient began receiving a single dose of ustekinumab 6 mg/kg IV, followed by maintenance therapy of ustekinumab 90 mg SC q8w after 8 weeks. At 14 weeks of treatment, the patient reported feeling better, with no abdominal tenderness and improvements in laboratory test measures. Colonoscopy revealed ulcerations in the distal ileum, though there was significant healing in the transverse colon.

Prof Ghosh presented several possible treatment choices for the patient, including options for optimising ustekinumab therapy or switching to a different drug class. The patient continued to receive ustekinumab 90 mg SC q8w. At Week 42 of treatment, he reported further reduced symptoms, with corresponding improvements in biomarker responses and BWT, and no ulcerations found on colonoscopy. Prof Kucharzik noted that the initial video showed markedly increased BWT, which had improved at Week 42, indicating a good IUS response, and recommended continuing treatment with ustekinumab q8w to achieve complete transmural healing. The panel agreed that continuation of treatment with ustekinumab q8w, based on the

current outcomes, could help the patient achieve this transmural healing goal.

Prof Ghosh highlighted that the initial rapid clinical and endoscopic response to treatment during the induction phase benefited from the IV infusion, and that long-term control and reduction of the disease burden, or even normalisation, can be achieved over time by administering the correct maintenance dosing of the drug at the correct intervals, as well as monitoring appropriately with biomarkers, endoscopy, or ultrasound scan.

Question and Answer Session

The question and answer session included several queries from the virtual audience and focussed on T2T strategies. When asked about the STARDUST results, Prof Danese remarked that one of the strengths of the trial was that it provided robust data regarding the efficacy of ustekinumab in patients who were naïve to biologic therapies and those who had previously received one biologic treatment; there were no significant differences in treatment responses between these patients, with comparable endoscopic and biomarker outcomes. He also commented that the long-term data from the STARDUST trial will be available in the future. When asked about the future of IUS in clinical practice, Prof Ghosh remarked that endoscopy will still have a role in the future; however, going forward, a combination of symptom assessment, patient-reported outcomes, biomarkers, and IUS outcomes is likely to provide the majority of data.

The audience also asked about the future of T2T strategies, commenting that tight monitoring strategies, such as T2T, might represent an increased monitoring burden for patients. Prof Ghosh responded that if patients receive an initial explanation of the goals of the T2T strategy and are included in the treatment decision-making process, most understand the treatment strategy and are generally satisfied with their experience. He added that using IUS techniques also helps them to visualise their improvements. Prof Danese agreed that using IUS provides a noninvasive tool for detailed point-of-care assessments, supporting patients in achieving their treatment goals.

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Ulcerative Colitis: Today, Tomorrow, and the Future

This symposium took place on 12th October 2020, as part of the United European Gastroenterology (UEG) Week Virtual 2020

Chairperson: Jean-Frederic Colombel[1]

Speakers: Jean-Frederic Colombel,[1] Silvio Danese,[2] Laurent Peyrin-Biroulet[3]

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Meeting Summary

This was a Gilead- and Galapagos-sponsored symposium devoted to today, tomorrow, and the future of ulcerative colitis (UC), as part of the United European Gastroenterology (UEG) Week Virtual 2020.

Prof Colombel welcomed the audience and provided the first talk, summarising the current treatment landscape and unmet needs in UC, and highlighting the limitations of pharmaceutical and surgical therapies for UC, as well as the divergent views of the condition by patients with UC and their physicians.

Prof Danese discussed the late-stage clinical development of sphingosine-1-phosphate (S1P) receptor modulators, IL-23 inhibitors, leukocyte adhesion inhibitors, and JAK/tyrosine kinase 2 (TYK2) inhibitors for the treatment of UC, and considered how these new drugs could change clinical practice.

Finally, Prof Peyrin-Biroulet shared his vision of what the future might hold for the treatment of patients with UC. He summarised the late-stage clinical development pipeline for potential UC therapeutics and shared his view on how the increasing deployment of biosimilars, as well as novel treatment concepts such as dual-targeted biologics and biologic/small-molecule combination therapies, may change the way that UC is treated in the future. He also highlighted the importance of personalised treatment targets and how patient education and patient-specific treatment guidelines could empower patients with UC, to help close the existing gap between routine real-world clinical practice and best practice for the management of UC.

Ulcerative Colitis: Today

Professor Jean-Frederic Colombel

Crohn's disease (CD) and UC are chronic inflammatory bowel diseases (IBD) that lead to digestive disorders and inflammation in the digestive system.[1] Very often, UC is seen as a minor disease; however, UC is a progressive gastrointestinal inflammatory disease of the colon. The extent of colorectal inflammation fluctuates over time and may result in long-term complications, which can be aggravated by structural changes such as strictures, pseudopolyposis, bridging fibrosis, and neoplastic transformation. Functional abnormalities are important because they can cause distressing symptoms, such as urgency and incontinence, and they are linked to decreased contractility and impaired colonic motility. In addition, anorectal dysfunction may lead to 'lead pipe' colon, rectal narrowing, widening of the presacral space, and impaired continence.[2,3]

Systemic, gastrointestinal, and psychological symptoms cause severe disease burden for patients with IBD as they occur with high frequency and severity, and cause significant distress. The top six symptoms include lack of energy, bowel urgency, diarrhoea, flatulence, feeling bloated, and worrying.[4] In particular, the lack of energy, experienced as fatigue, and the impact of the psychological burden, such as worrying, were highlighted by Prof Colombel as very important causes of distress in patients with IBD. The prospective, multicountry, observational ICONIC study assessed the cumulative burden in adult patients with UC under routine care, and reported a disconnect between physicians' and patients' perceptions, as approximately 40% of patients classified their disease activity differently from their physicians.[5] Patients also reported being highly concerned about the disease treatment and potential complications, particularly the potential to require an ostomy bag or to need surgery, unwanted effects of their medication, uncertainty about the course of their disease, and decreased energy levels.[6]

Although a wide range of therapies are currently approved for the treatment of UC, including anti-IL, anti-integrins, and, more recently, small molecules targeting intracellular processes, (Figure 1),[7-10] unmet needs in the treatment of UC remain, both in clinical trials and in clinical practice, with many patients still not able to achieve adequate disease control.[11] For anti-TNF drugs, nonresponse rates of 20–40% have been reported in clinical trials and 10–20% in real-world studies.[12] Similarly, real-world nonresponse rates of 49–57% have been reported for the α4β7 integrin inhibitor vedolizumab, 38–49% for the IL-12/IL-23 inhibitor ustekinumab in the UNIFI study, and 40–45% for the JAK inhibitor tofacitinib in the OCTAVE study.[13,14]

Another concern is the plateauing in the rates of steroid-free remission. The proportion of treated patients not achieving steroid-free remission has been reported to be 60–84% with adalimumab or infliximab,[15-17] 62–87% with vedolizumab in the GEMINI 1 and VARSITY studies,[18,19] 58–62% for ustekinumab in the UNIFI study,[20] and 72% for tofacitinib in the OCTAVE study.[14] Although the definitions of steroid-free remission vary between studies, the concept remains useful as a high-hurdle endpoint.

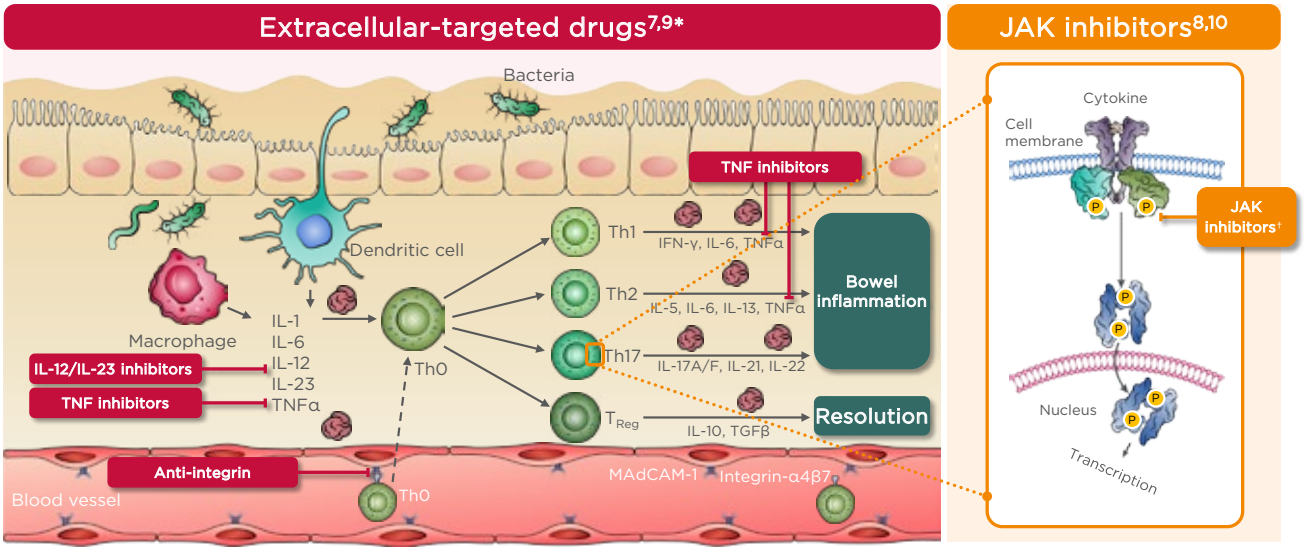

Figure 1: Schematic overview of therapies currently approved for ulcerative colitis.[7-10]

*Cells and cytokines listed are examples and do not provide an exhaustive list.

†Th17 cells are not the only cells targeted by JAK inhibitors and are used an example to illustrate their action on an intracellular pathway.

MAdCAM-1: mucosal addressin cell adhesion molecule-1; P: phosphate; T_{Reg}: regulatory T cell.

An excessive use of steroids has also been noted in patients diagnosed with IBD and seems to be associated with treatment initiation outside of specialist care, or by a gastroenterologist in training.[21] Steroid dependency, defined in the European Crohn's and Colitis Organisation (ECCO) guidelines as either the prescription of ≥1 steroid over 12 months, the inability to wean from steroids within 3 months, or a disease flare within 3 months of steroid cessation, also remains problematic, particularly in patients with UC.[22] An additional burden of steroid therapy is that it may lead to fatigue, which has been reported by nearly 50% of patients with IBD.[23]

Furthermore, in the real world, not all responders persist on treatment. A real-world study of patients with UC being treated with vedolizumab or infliximab reported that <80% of induction responders persisted for 24 months on treatment.[24] Similarly, the Dutch Initiative on Crohn and Colitis (ICC) registry study reported that only 60% of patients who initiated treatment with tofacitinib remained on treatment after 24 weeks.[25] Taken together, these illustrate that there is a clear unmet need for new, long-term, effective treatment options for patients with UC.

Colectomy is a major surgical procedure that may significantly affect both mortality rates and the quality of life of patients with UC.[26] Although UC colectomy rates have been decreasing since the introduction of biologics,[27,28] they still remain high in the long term.[29] Furthermore, a majority of patients may not be able to benefit on this decrease in colectomy rates, due to the still limited use of biologics in UC, coupled with an excessive use of steroids.[22,30]

The research of today shows that UC has a high economic and treatment burden, and patients and physicians do not always share the same view on the disease. There are clear treatment unmet needs, as many patients do not achieve long-term, steroid-free remission without colectomy. Despite updated clinical evidence, new guidelines, and aggressive treatment targets, the early use of effective therapies remains surprisingly uncommon. However, Prof Colombel concluded that the gastroenterological community has nevertheless come a long way: there is now a recognised predictive biomarker (faecal calprotectin) for treatment monitoring, more stringent clinical trial endpoints in the form of long-term remission and histological endpoints, and the Selecting Therapeutic

Targets in Inflammatory Bowel Disease (STRIDE) guidelines help to codifying ambitious treatment targets.[31-34]

Ulcerative Colitis: Tomorrow

Professor Silvio Danese

Emerging therapies for UC currently undergoing Phase III development fall under four main mechanisms of action: leukocyte retention in lymphoid organs by S1P receptor modulators (etrasimod and ozanimod), IL-23 inhibitors (mirikizumab, guselkumab, brazikumab, and risankizumab), JAK/TYK2 inhibitors (filgotinib and upadacitinib), and leukocyte adhesion inhibitors (integrin blockers and etrolizumab).[35]

S1P modulators are structural analogues of the lipid signalling molecule S1P, with antagonist actions leading to selective immunosuppressive action through the sequestration of lymphocytes in secondary lymphoid tissues and a rapid reduction of peripheral blood lymphocytes.[36] In the True North study,[37] the S1P modulator ozanimod demonstrated highly statistically significant ($p<0.0001$) results for the induction of clinical remission at Week 10 and in maintenance at Week 52. Key secondary endpoints of clinical response and endoscopic improvement at Week 10 and at Week 52 were also met, and the safety profile of ozanimod was consistent with that observed in previously reported trials. The leukocyte adhesion inhibitor etrolizumab selectively targets the β7 subunit of both α4β7 and αEβ7 integrins and blocks interactions with their respective ligands, mucosal vascular addressin cell adhesion molecule 1 and E-cadherin, to reduce gut-specific lymphocyte trafficking to the inflamed colon.[38] In the HICKORY study, etrolizumab met its primary endpoint of inducing remission versus placebo for patients with UC but failed to meet its primary endpoint versus placebo as maintenance therapy.[38] Additionally, in people who had received prior anti-TNF treatment, etrolizumab met the primary endpoint at induction but not at maintenance.[39]

JAK inhibitors are orally administered small molecules that, by temporarily blocking signalling through the JAK/signal transducer and activator of transcription pathway, inhibit key mechanisms of the innate and adaptive immune response.[40] They differ in their selectivity for different JAK: tofacitinib is more selective for JAK1/2/3 than for TYK2, upadacitinib is more selective for JAK1/3 than for JAK2, and filgotinib is more selective for JAK1 than for JAK2.[41-43] The blocking of specific JAK kinases by selective JAK inhibitors may be of clinical relevance, as it may translate into therapies with improved safety and efficacy.[10]

Tofacitinib is the only JAK inhibitor approved for the treatment of moderate-to-severe UC but has shown no efficacy in CD, which has been speculated to be at least partly because of the design of the Phase II and III studies of tofacitinib in CD.[42,44,45] Infections and infestations, including a herpes zoster virus safety signal, have been reported for tofacitinib in the OCTAVE Induction 1 and Induction 2 studies,[14,46] and a similar safety profile was recently reported in the real-world TROPIC consortium study of 260 patients with UC.[47]

Preferential JAK1/3 inhibitors, such as upadacitinib, are currently in clinical development for UC.[35] Upadacitinib was evaluated in the Phase II part of the U-ACHIEVE study and found during the induction phase to have a safety profile similar to that of placebo; the study is currently recruiting for Phase III.[48]

Filgotinib, a preferential JAK1 inhibitor, has been evaluated for UC in the combined Phase IIb/III study SELECTION.[49] The primary objective of the Phase III part of SELECTION was to evaluate the safety and efficacy of filgotinib in the induction and maintenance treatment of moderately to severely active UC in participants who were either biologic-naïve (n=659) or biologic-experienced (n=689).[49,50] The primary endpoints were remission based on components of the Mayo Clinic Score at Weeks 10 and 58, and the use of steroids was tapered during the maintenance phase of the study.[49,50] Filgotinib 200 mg demonstrated superior clinical remission in both the biologic-naïve and the biologic-experienced treatment arms, with more patients achieving clinical remission with filgotinib than with placebo during the induction and maintenance phases (11% and 26%, respectively; Figure 2).[49,50]

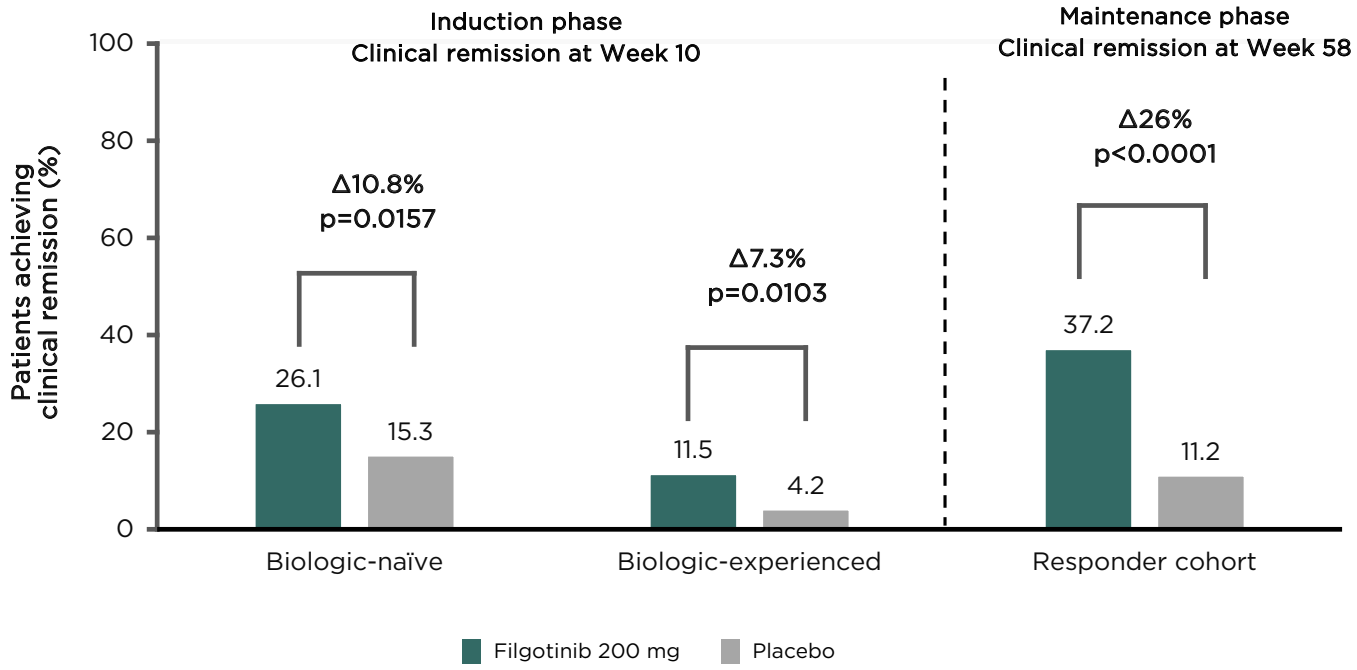

Figure 2: SELECTION primary endpoint results at induction and maintenance.

Figure portrays the proportion of biologic-naïve or biologic-experienced patients with ulcerative colitis achieving clinical remission during the induction phase (Week 10) and for the rerandomised responder cohort during the maintenance phase (Week 58) in SELECTION.

Reproduced with permission from Peyrin-Biroulet[49] and Feagan.[50]

Although adverse events such as infections and infestations were more prevalent in patients treated with filgotinib compared with patients that received placebo during the induction period, rates of herpes zoster were in line with placebo during the maintenance phase (Week 58)[50] and were also consistent with the rates observed for patients with rheumatoid arthritis, including those treated with adalimumab or methotrexate.[51] Venous thromboembolism rates in SELECTION were also consistent with the low rates observed in rheumatoid arthritis.[49,51] Additionally, in the Phase II DARWIN 2 study, filgotinib 200 mg increased the mean levels of low-density lipoprotein (LDL), high-density lipoprotein (HDL), and total cholesterol. The LDL:HDL ratio, however, fell slightly over the study period, which indicated that the JAK1 selectivity of filgotinib might lead to proportionally greater increases in HDL cholesterol compared with the increases seen for LDL cholesterol.[52]

In animal studies, histologic changes have been observed in the testis and in the epididymides at filgotinib doses several-fold higher than the dose recommended for human use. No testicular toxicity has been observed with doses equivalent to the 200 mg dose.[53] However, as a precaution and follow-up to this potential safety signal, the randomised, placebo-controlled Phase II studies MANTA (in males with UC or CD) and MANTA-RAy (in males with rheumatic diseases) have been initiated to evaluate the testicular safety of filgotinib in humans.[54,55]

For adults with moderately to severely active UC, investigational new treatments could, once approved, fit into existing treatment algorithms during both the induction and maintenance phases, with the goal of maintaining steroid-free, clinically and endoscopically defined remission in patients diagnosed with UC (Figure 3).[22] Several of the new investigational therapies, such as ozanimod and filgotinib, appear to have benign safety profiles and may, from a safety point of view, be suitable as both first- and second-line therapies (i.e., both before and after biologics). Regarding efficacy, these new molecules could be considered as both first- and second-line therapies, including for long-term maintenance therapy.[22]

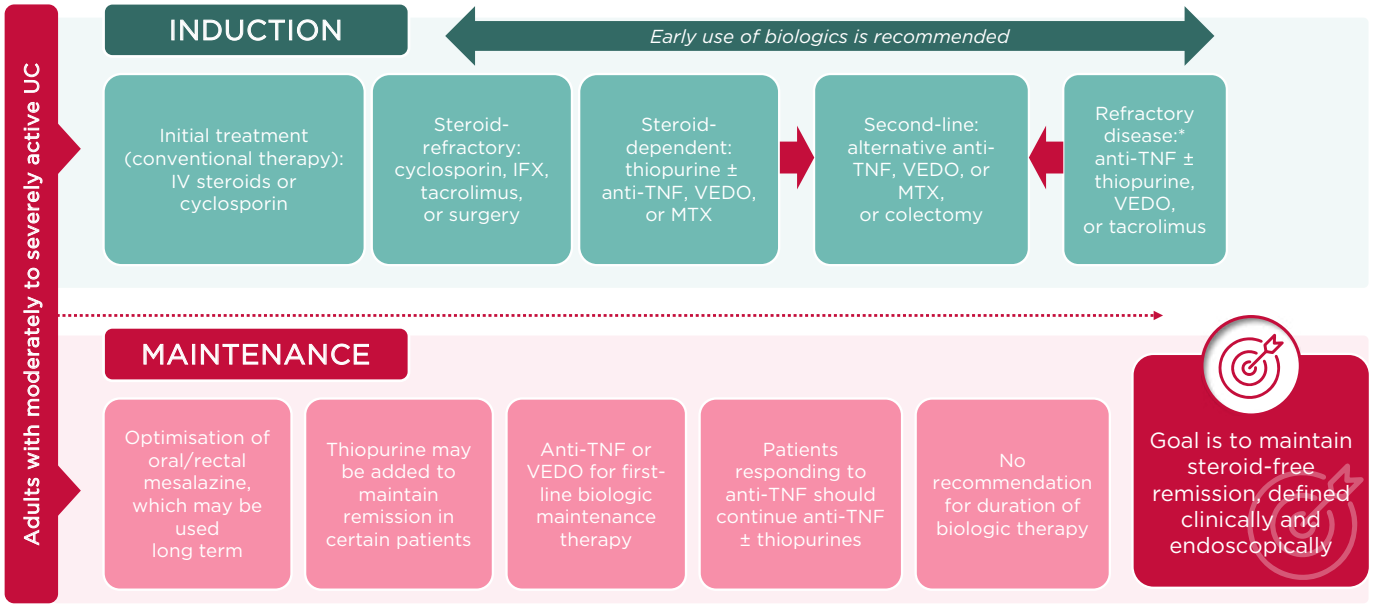

Figure 3: Potential roles of new therapies for the treatment of adults with moderately to severely active ulcerative colitis.

*Refractory to oral steroids or immunomodulator therapy.

IFX: infliximab; IV: intravenous; MTX: methotrexate; UC: ulcerative colitis; VEDO: vedolizumab.

However, patient preferences for oral, intravenous, or subcutaneous modes of administration need to be considered, as modes of administration are becoming more important considerations for novel therapies, particularly as the efficacy and safety profiles of available drugs are plateauing.[56] Drug preferences are also influenced by cost, reflected in the higher uptake of biosimilars in Europe compared with the USA, which are more affordable compared with their reference biologics.[57] In summary, multiple new therapeutic modalities are in clinical development for UC, and several of these new molecules have shown favourable benefit–risk profiles in late-stage clinical trials.

Ulcerative Colitis: the Future

Professor Laurent Peyrin-Biroulet

Biologics used to treat immunologic conditions such as UC are large molecular weight (>1 kilodaltons [kDa]) protein therapeutics requiring parenteral administration, which preferentially interact with extracellular drug targets. Small molecule therapeutics, on the other hand, are small molecules (<1 kDa) of synthetic origin designed to modulate either intra- or extracellular targets, and are most commonly administered either orally or topically.[58,59] Although low trough concentrations of both biologics and small molecule drugs may result in breakthrough symptoms, only biologics are known to be potentially immunogenic, which may lead to the neutralisation of the therapeutic effect of the biologic.[60]

Biosimilars are defined as biologics with no clinically meaningful differences in efficacy or safety from their licensed originators. The lower cost of biosimilars stimulates market competition and facilitates patient access to biologics because of their lower costs.[61] Biosimilars have significantly reduced the treatment cost for biologics both in the European Union (EU) and in the USA, exemplified by the approval of several biosimilar anti-TNF therapeutics for the treatment of immune disorders such as IBD.[62-65]

Several head-to-head trials are expected to provide some answers regarding the drugs that will constitute the future of IBD therapy. The outcomes of a study,[66] which compared the adalimumab biosimilar candidate BI 695501 with

EU-approved Humira® (Boehringer Ingelheim, Ingelheim am Rhein, Germany), have recently been reported,[67] and results are expected in 2020 from the GARDENIA (etrolizumab versus infliximab) and HIBISCUS (etrolizumab versus adalimumab) Phase III studies.[68] In 2021, readouts are expected from the Phase II EXPEDITION trial, which evaluates brazikumab versus vedolizumab in UC,[69] and from the Phase III SEAVUE trial comparing adalimumab with ustekinumab in UC.[70] Results are also expected in 2022–2023 from the Phase II/III study INTREPID,[71] which compares brazikumab with adalimumab, and from the Phase III study VIVID-1,[72] which evaluates mirikizumab versus ustekinumab. Outcomes of the Phase II/III study GALAXI,[73] which investigates guselkumab versus ustekinumab in patients with moderately to severely active CD, are expected in 2024. In addition, studies evaluating combinations of two different biologics for achievement of remission are being conducted; one example is the Phase II VEGA study, evaluating combination treatments of guselkumab and golimumab in patients with UC.[74]

"Small molecules have a number of advantages in the treatment of UC" – Prof Silvio Danese, 2020

Although biologics have revolutionised the management of autoimmune diseases,[75] small molecules have a number of advantages for the treatment of UC. This is mainly because of their oral mode of administration, effectiveness in patients previously treated with TNF inhibitors, short serum half-life, potential high cost–effectiveness ratio, lack of immunogenicity, previous treatment experiences from other patient types and in other diseases, potential as first-line therapy after aminosalicylates and steroids, rapid absorption time, and potential for use in mild, moderate, and severe UC.[76] Prof Peyrin-Biroulet indicated that the lack of immunogenicity associated with small molecule drugs also opens up the possibility of treatment holidays for patients with IBD on small molecule therapies; however, additional research is needed to define which patients and disease stages are most suited for stop/start treatment regimens in IBD.

The immunosuppressive mechanisms of action of drugs used to treat IBD result in reductions in disease activity; however, they are also associated with an increased risk of infections and a potential increase in the risk of developing cancers.[77,78] The I-CARE study, a European-wide, prospective, longitudinal, observational, multicentre cohort study, has been designed to evaluate the risk of developing cancer or serious infection in patients that are using immunosuppressive and biologic therapies.[79] I-CARE has thus far enrolled >10,000 patients with IBD, and the first results are expected to be presented at ECCO 2021.[80]

Dual-targeted, or bispecific, antibodies have been proposed as a novel therapeutic approach for the treatment of immune disorders such as IBD. This unique class of biologics combines two distinct binding specificities within a single therapeutic entity, which allows for the simultaneous targeting of two different disease-causing cytokines or pathways by the same therapeutic. Several bispecific biologics are currently in preclinical or clinical development for the treatment of a variety of autoimmune and inflammatory diseases.[81]

Another approach is combination therapy, in which separate biologics and small molecule drugs are administered concomitantly.[82-84] The selection of drugs that might be suitable for combination therapies needs to be based not only on safety profiles, but also on mechanisms of action. However, challenges remain in predicting how effects of crosstalk and synergy from the combination of two different drugs will influence the overall safety and efficacy of a combination therapy. Filgotinib, for example, appears to have a favourable safety profile so could be considered for combination therapy trials with other drugs with favourable safety profiles, such as vedolizumab, ozanimod, or etrolizumab.

Additionally, experimental treatment concepts to modulate immune dysregulation conditions such as IBD are currently being explored, including targeting the human genome, where approximately 99% of the DNA sequence has unknown function, and the gut microbiome.[85,86]

The future of UC management is envisioned as a stepwise approach, starting with symptom remission (patient-reported outcomes Stages 1–2), followed by endoscopic, histologic, and ultimately molecular healing.[87]

"The good physician treats the disease; the great physician treats the patient who has the disease" – Sir William Osler, 1903

To achieve this, STRIDE guidelines have been published that include evidence- and consensus-based recommendations for selecting the goals for treat-to-target strategies in patients with IBD. The treatment of patients with UC should target the resolution of rectal bleeding and the normalisation of bowel habits, and outcomes should be assessed every 3 months until symptom resolution and every 6–12 months thereafter. Similarly, the treatment of intestinal inflammation should aim for a Mayo endoscopic subscore of 0 as the optimal target, with a Mayo endoscopic subscore of 1 as a minimum target within 3–6 months after the start of therapy. Histopathology may be used as a sensitive measure of inflammation but not as a target, and available biomarkers, such as C-reactive protein and faecal calprotectin, should be used as adjunctive measures of inflammation for monitoring in patients with UC.[34]

These ambitious treatment targets may be supported by the implementation of home-based biomarker monitoring, virtual clinics, and telemedicine, which may lead to increased adherence rates and improved treatment outcomes.[88] Interest in, and development of, telemedicine and remote monitoring has been greatly accelerated by the ongoing coronavirus disease (COVID-19) pandemic.[89]

Prof Peyrin-Biroulet outlined his 5-year perspective on the treatment of UC: this included reduced reliance on endoscopy in UC, except for colorectal cancer screening; patients being able to receive treatment from home; targets based on symptoms, endoscopy, and/or histology; and treatments tailored to individual patients and not to molecular pathways, with the ultimate goal of achieving a normal life with UC. Unfortunately, there is still a significant gap between current healthcare practice and optimal treatment strategies in UC[90] and more education needs to be aimed at patients rather than at healthcare providers, for example through the development of patient guidelines to educate patients on which treatment options are available.[91] The focus also needs to shift from inflammation toward disease modification and quality of life improvements, with the ultimate aim of improving overall patient outcomes.

Conclusion

Although therapies such as biologics and novel small molecule drugs targeting different immune pathways have revolutionised the treatment of autoimmune disorders including IBD in recent decades, unmet needs remain. A new generation of drugs for IBD are in clinical development, including S1P modulators, IL-23 inhibitors, leukocyte adhesion inhibitors, and preferential JAK1 inhibitors. Novel treatment concepts such as bispecific biologics and biologic/small molecule drug combination therapies are also being developed. In parallel, the clinical management of IBD is being improved through the implementation of personalised treat-to-target strategies, biomarker-based disease activity monitoring, and empowerment of patients through improved patient education.

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The Gene Expression Signature Modulated by Dupilumab is Correlated with Histological Severity and Endoscopic Features of Mucosal Inflammation and Remodelling in Eosinophilic Oesophagitis

This oral presentation took place on 12th October 2020, as part of the United European Gastroenterology (UEG) Week Virtual 2020

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Summary

Dupilumab is a monoclonal antibody that inhibits IL-4 and IL-13 signalling in multiple Type 2 inflammatory disorders, including eosinophilic oesophagitis (EoE). This article reviews the oral presentation given by Dr Collins at the United European Gastroenterology (UEG) Week Virtual 2020 and describes the results of a post hoc analysis of a Phase II proof-of-concept study of dupilumab in adults with active EoE. The aim of the analysis was to ascertain whether there were any correlations between gene expression and disease severity in patients enrolled in the study.

Background

EoE is a chronic inflammatory disease triggered by an abnormal Type 2 inflammatory response to allergens, and is characterised by eosinophilic inflammation of the oesophagus and histological abnormalities.[1] Patients with EoE have an altered oesophageal transcriptome compared with healthy controls, including dysregulation of genes associated with epithelial barrier function and proliferation, collagen and fibrosis pathways, and Type 2 inflammation.[2]

IL-4 and IL-13 are key and central drivers of Type 2 inflammation in multiple diseases, including EoE. Dupilumab is a fully human monoclonal antibody that binds specifically to IL-4Rα, the shared receptor component of IL-4 and IL-13, and thus inhibits the dual signalling pathways of both cytokines.[3-6]

Materials and Methods

In a double-blind, placebo-controlled, Phase II proof-of-concept study, adults with active

EoE were randomised 1:1 to receive 12 weeks of subcutaneous dupilumab 300 mg weekly or placebo.[7] Dupilumab demonstrated efficacy in reducing dysphagia, histological severity (as assessed by EoE histological scores and peak oesophageal intraepithelial eosinophil count), and endoscopic features of mucosal inflammation and remodelling (as assessed by the EoE endoscopic reference score [EoE-EREFS]), and had an acceptable safety profile. In this post hoc analysis of the study, the authors investigated the correlation between gene expression and both histological severity and the macroscopic features of mucosal inflammation and remodelling in 41 of the patients enrolled in the study.

Pinch biopsies were collected from the proximal, mid, and distal oesophagus at baseline and Week 12, and RNA was extracted for transcriptome analysis. Gene expression per patient was averaged across the three samples at each time point. The top 50 most upregulated and top 50 most downregulated genes in EoE that were normalised by dupilumab treatment were used to create a normalised enrichment score (the DpxOme-EoE™ NES). The NES allowed conversion of the expression level of multiple genes to one score that reflected the overall molecular phenotype of a sample. Spearman correlation analysis was performed to compare the DpxOme-EoE NES or individual gene expression with total histological scoring system (HSS) scores, tissue eosinophil count, and EoE-EREFS. The EoE-HSS assessed the severity of histological changes in the oesophagus (grade score) and the extent of tissue that was abnormal (stage score). The EoE-EREFS measured the severity of endoscopic findings.

Results

Dupilumab normalised the expression of 1,302 genes after 12 weeks of treatment, whereas no significant changes were seen in the placebo group. In the dupilumab group, this normalisation resulted in a transcriptome similar to that seen in healthy controls; the transcriptome in the placebo group remained similar to published transcriptome data from patients with EoE.[2]

Spearman analysis showed strong, significant (all $p<0.001$) correlations between the DpxOme-EoE NES and the total EoE-HSS grade score (correlation coefficient: 0.832), the EoE-HSS stage score (correlation coefficient: 0.787), and peak oesophageal intraepithelial eosinophil counts (correlation coefficient: 0.773) (Table 1). A moderate correlation (correlation coefficient: 0.562; $p<0.001$) was observed with EoE-EREFS. A high correlation was found with individual genes, including those related to epithelial proliferation, such as *ANO-1*; those related to barrier function, such as *SPINK8*; those related to inflammatory mechanisms, such as *CTSC* and *CRISP3* (coding for the proinflammatory protease cathepsin C and for a cysteine-rich secretory protein, respectively); and *GPR97*,[8] a gene highly expressed on airway eosinophils following allergen challenge.

Conclusion

These data demonstrate that dupilumab normalises several pathways known to be dysregulated in EoE. The post-dupilumab treatment transcriptome in patients with EoE, i.e., the DpxOme-EoE NES, was strongly correlated with EoE-HSS grade score, EoE-HSS stage score, and peak oesophageal intraepithelial eosinophil count, and was moderately correlated with EoE-EREFS. Strong correlations were seen for individual genes associated with epithelial proliferation, barrier function, and inflammatory mechanisms. The expression of genes associated with remodelling in EoE were also among those normalised by dupilumab. Additional analyses are ongoing to further evaluate intrapatient variability. This present analysis suggests that the improvements in histological and endoscopic measures that occur following dupilumab treatment in patients with EoE are due, at least in part, to direct effects on oesophageal epithelial gene expression.

Table 1: Correlations between the post-dupilumab transcriptome and histological and endoscopic endpoints.

Correlation with DpxOme-EoE™ NES	Correlation coefficient	p value
EoE-HSS grade score		
Overall correlation	0.832	<0.001
Top positively correlated gene: *CTSC*	0.826	<0.001
Top negatively correlated gene: *CRISP3*	-0.813	<0.001
EoE-HSS stage score		
Overall correlation	0.787	<0.001
Top positively correlated gene: *NCF2*	0.791	<0.001
Top negatively correlated gene: *CRISP3*	-0.796	<0.001
Peak oesophageal intraepithelial eosinophil count		
Overall correlation	0.773	<0.001
Top positively correlated gene: *GPR97*	0.812	<0.001
Top negatively correlated gene: *ZNF416*	-0.781	<0.001
EoE-EREFS		
Overall correlation	0.562	<0.001
Top positively correlated gene: *BC043620*	0.623	<0.001
Top negatively correlated gene: *EPB41L3*	-0.613	<0.001

DpxOme-EoE™ NES: normalised enrichment score of the top 50 most upregulated and top 50 most downregulated genes in eosinophilic oesophagitis that were normalised by dupilumab treatment; EoE-EREFS: eosinophilic oesophagitis endoscopic reference score; EoE-HSS: eosinophilic oesophagitis histological scoring system.

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Abstract Reviews

Contained in the following pages are summaries of captivating abstract reviews from the United European Gastroenterology (UEG) Week Virtual 2020, written by the presenters themselves.

Impact of COVID-19 on Patients with Inflammatory Bowel Disease: Update from an International Registry

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Keywords: Coronavirus disease (COVID-19), immunosuppression, inflammatory bowel disease (IBD).

Citation: EMJ Gastroenterol. 2020;9[1]:44-46. Abstract Review No. AR1.

BACKGROUND AND AIMS

Patients with inflammatory bowel disease (IBD) are frequently on immunosuppressive treatments that increase the risks of infection. To date, there are limited data on the disease course of coronavirus disease (COVID-19) in patients with IBD, including the impact of clinical characteristics and medications. The authors utilised the Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD), an international registry of patients with IBD who have had COVID-19, to evaluate the association of demographics, clinical characteristics, and immunosuppressant treatments on COVID-19 outcomes. This work was an updated analysis of SECURE-IBD following the first publication from this database.[1]

MATERIALS AND METHODS

Age-standardised mortality ratios were calculated using reference populations from China, Italy, and the USA.[2-4] The primary outcome was severe COVID-19, defined as a composite of intensive care unit admission, ventilator use, and/or death. Multivariable logistic regression was used to understand the independent impact of variables on severe COVID-19.

Table 1: Multivariable analysis of risk factors for severe coronavirus disease (COVID-19).

Variable (referent group)	ICU/ventilator use/death (odds ratio [95% CI]) (n=948)	p value
Age (years)	1.04 (1.02–1.06)	<0.0001
Male (female)	1.04 (0.63–1.73)	0.88
Diagnosis Crohn's disease (ulcerative colitis or IBD unspecified)	0.99 (0.56–1.76)	0.99
Disease severity Active disease (remission)	0.90 (0.52–1.57)	0.71
Systemic corticosteroid (none)	5.20 (2.47–10.92)	<0.0001
TNF antagonist (none)	0.98 (0.53–1.82)	0.96
Current smoker	0.96 (0.29–3.15)	0.95
BMI ≥30	1.62 (0.82–3.20)	0.16
Comorbidities (none) 1 ≥2	 2.60 (1.34–5.01) 4.80 (2.40–9.61)	 0.004 <0.0001
5-ASA/sulfasalazine (none)	2.03 (1.14–3.61)	0.02

5-ASA: 5-aminosalicylic acid; CI: confidence interval; IBD: inflammatory bowel disease; ICU: intensive care unit.

RESULTS

A total of 959 cases from 40 countries were reported (median age: 43 years; 52% male). A total of 86 patients (9%) had severe COVID-19, 320 (33%) were hospitalised, and 37 patients died (3.9% case fatality rate). Age-standardised mortality ratio for patients with IBD were 2.0 (95% confidence interval [CI]: 1.4–2.7), 1.7 (95% CI: 1.1–2.2), and 1.9 (95% CI: 1.3–2.5), relative to data from China, Italy, and the USA, respectively. On multivariable analysis, risk factors for severe COVID-19 among patients with IBD included increasing age, ≥1 comorbidities in addition to IBD, systemic corticosteroids, and sulfasalazine or 5-aminosalicylate use (Table 1). TNF antagonist treatment was not associated with severe COVID-19 (adjusted odds ratio: 0.9; 95% CI: 0.5–1.8).

CONCLUSIONS

Strengths of the study included a large, international population of patients with IBD. Limitations included the fact that this was a convenience sample, with potential for reporting bias. The clinical implication of these findings is that patients with IBD who are older with multiple comorbidities, and those on systemic corticosteroids, are at higher risk of severe COVID-19. In contrast, TNF antagonists do not appear to increase the risk of poor outcomes, and these data provide reassurance that patients should continue these medications. Future research is needed to better understand the impact of other IBD medications, including different classes of biologics.

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Use of a Machine Learning Algorithm to Predict Rebleeding and Mortality for Oesophageal Variceal Bleeding in Cirrhotic Patients

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Keywords: Artificial intelligence, gastrointestinal haemorrhage, liver cirrhosis, machine learning, oesophageal and gastric varices, prognosis.

Citation: EMJ Gastroenterol. 2020;9[1]:46-48. Abstract Review No. AR2.

BACKGROUND AND AIMS

Oesophageal variceal bleeding (OVB) is one of the most common complications of cirrhosis. Mortality rates range from 15% to 20% in the first episode.[1,2] Therefore, identifying patients with high chances of survival is paramount to allocate resources into treatment with accuracy.[3] The purpose of this study was to use a machine learning algorithm to predict rebleeding and mortality for OVB in patients with cirrhosis and to analyse its accuracy.[4-6]

MATERIALS AND METHODS

A historical cohort study was conducted, analysing data from hospital charts from January 2010 to December 2016. Patients were found by searching every use of terlipressin during the time period. Medical charts were hand-analysed. Patients over 18 years old with laboratory and imaging data supporting the diagnosis of cirrhosis and with a definitive diagnosis of OVB were included.

This analysis used data from 74 patients with cirrhosis, taking into account 36 variables, which had OVB as a complication. The preliminary analysis of the study was Pearson correlation, which compared the 36 variables in the study with outcomes of death and rebleeding, aiming to verify the linear correlation strength, positive or negative.

When artificial intelligence was applied, an artificial neural network (ANN) was utilised to recognise patterns in outcomes through supervised learning. The results were analysed on a confusion matrix, which presented the probabilities of the positive predictive value, negative predictive value, sensitivity, specificity, and network accuracy. A receiver operating characteristic (ROC) curve analysis was then performed.

RESULTS

Electronic search retrieved 177 hospital admissions with use of terlipressin, 101 of which were due to OVB. All-cause mortality was 36.0%, 41.5%, and 50.4% for 30-, 90-, and 365-day, respectively. Mean age was 56 years and 79% were male. The most frequent cause of cirrhosis was alcohol abuse, followed by hepatitis C.

The Pearson correlation analysis showed that the variables had values of linear correlation ranging from -0.34 to 0.30 for mortality and -0.31 to 0.21 for rebleeding. Both values represent weak correlations with the outcomes. Thus, it is notably difficult to define which variables are the ones with major leverage on the outcomes. Therefore, the use of artificial intelligence could be a key tool to identify the patterns in such a complex data-evolved situation.

For patients who had a rebleeding outcome, the specificity value showed that the ANN was able to identify 66.7% of cases. The predictive value showed when the ANN predicted rebleeding, 100% of the patients did indeed rebleed. The overall accuracy was 97.4% and the area under the ROC curve (AUROC) was 0.942.

For patients who had a mortality outcome, the specificity value showed that the ANN was able to identify 95.0% of cases. The predictive value shows when the ANN predicted mortality, 95.0% of the patients did indeed die. The overall accuracy was 97.4% and the AUROC was 0.993, which demonstrates a high performance of the network.

CONCLUSIONS

The ANN could more accurately predict mortality by OVB when compared with two other assessment tools, Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) and Model for End-stage Liver Disease (MELD) Score.[7,8,9] The AUROC of CLIF-SOFA found in the literature for the outcome death was 0.943 and the AUROC of the MELD score was 0.80,[10] whereas the AUROC of the ANN was 0.993. Therefore, machine learning could be a useful tool to improve clinical practice, with the possibility of outperforming the current tools.

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Impact of Prenatal Stress on Visceral Sensitivity and Intestinal Homeostasis in Adulthood

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Keywords: Gut microbiota, irritable bowel syndrome (IBS), prenatal stress (PS), visceral hypersensitivity.

Citation: EMJ Gastroenterol. 2020;9[1]:48-50. Abstract Review No. AR3.

INTRODUCTION

Irritable bowel syndrome (IBS) affects 10–15% of the world population. It is the most common cause of primary gastroenterology visits and affects twice as many females than males.[1] IBS is characterised by visceral pain associated with alterations in bowel transit (either diarrhoea, constipation, or a mix of both). IBS greatly affects quality of life and is highly correlated with psychological comorbidities; 30–50% of patients with IBS report anxiety or depression.[2] The pathophysiology of IBS is complex and differs among patients. It can include visceral hypersensitivity, increased paracellular permeability, and gut microbiota dysbiosis, classifying IBS as a pathology of the gut-brain axis.[2] Among IBS risk factors, stress, in particular neonatal stress, increases both the incidence of the disease and the worsening of the symptoms.[3] Prenatal stress (PS), which induces gut microbiota dysbiosis, has recently been identified as a risk factor for anxiety and depression, both of which are IBS comorbidities.[4,5] However, the causal link has not been established, and the authors hypothesised that PS in mice would predispose the adult offspring to visceral hypersensitivity and intestinal homeostasis disruption, as observed in IBS.

METHODS

PS was induced in C57bl/6 mice by using a bright light (coupled to restriction) for 30 minutes three times a day between Days 13 and 18 of gestation. Visceral hypersensitivity to colorectal distention was assessed in male (n=20) and female (n=20) 8-week-old offspring by recording abdominal contractions in response to pressures of colorectal distension at 15, 30, 45, and 60 mmHg. The paracellular cellular permeability of the offspring was measured by 4 kDa fluoresce in isothiocyanate–dextran (FiTC)-dextran (10 mg/mice) gavages, followed by fluorescence measurement in the plasma 4 hours later. *Cxcl2,*

Tgfb, Ccl5, Reg3g, Muc2, Occln, Ttf3, Mmp7, Penk, and *Ifng* colonic expressions were monitored by real-time quantitative reverse transcription-PCR. The fecal microbiota composition was assessed by the MiSeq-based microbial taxonomic method and its organisation as a biofilm was evaluated by 16S RNA FISH staining.

RESULTS

In the offspring of both sexes, PS induced hypersensitivity to colorectal distensions expressed as the area under the curve for the lowest (15–30 mmHg) and the highest (45–60 mmHg) pressures of distension (Figure 1).

Female mice were significantly more hypersensitive to colorectal distension for both types of pressure, while the increased sensitivity in the male offspring was significant only for the lowest pressures of distension (Figure 1). Paracellular permeability and gene expression in the colon remained unaltered by PS in both males and females. PS mice gut microbiota analyses revealed a dysbiosis as well as an alteration of the biofilm organisation. Indeed, *Akkermansia muciniphila* was increased in stressed male and female mice, while *Desulfovibrio spp* and *Lactobacillus animalis* were decreased in males and females, respectively. The alteration of the gut microbiota biofilm in PS mice was marked by bacterial infiltrations in the sterile mucus layer.

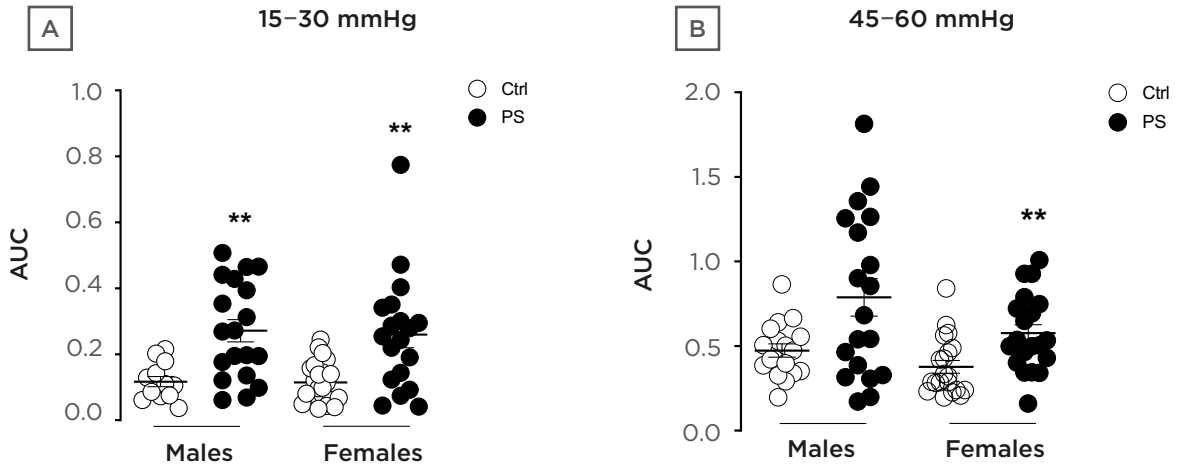

Figure 1: Area under the curve of the visceromotor response to colorectal distension of **(A)** 15–30 mmHg and **(B)** 45–60 mmHg in control (white circles) male (n=20) and female (n=20) and prenatal stress (black circles) offspring.

** p<0.01 compared to control.

AUC: area under the curve; Ctrl: control; PS: prenatal stress.

Finally, spearman correlations showed the existence of an inverse correlation between the abundance of *L. animalis* in the female faeces and visceral hypersensitivity for the lowest (R= -0.6; p=0.006) and highest (R= -0.61; p=0.007) pressures of distension. The same correlation was found in males, but only for the highest pressures. (R= -0.6; p=0.005).

CONCLUSION

This study shows that PS is sufficient to induce visceral hypersensitivity, gut microbiota dysbiosis, and biofilm disruption in mice. Therefore, PS could represent an important priming event for the development of IBS in adulthood.

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Acute Infusion Reactions to Vedolizumab in Inflammatory Bowel Disease

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Citation: EMJ Gastroenterol. 2020;9[1]:50-51. Abstract Review No. AR4.

BACKGROUND AND AIMS

Vedolizumab is a fully humanised, monoclonal IgG1 antibody, directed toward α4β7-integrin. It is effective at inducing and maintaining a response in one-third of patients with inflammatory bowel disease (IBD).[1] Clinical monitoring for 2 hours is recommended after the two first infusions at Weeks 0 and 2, and for 1 hour after all the subsequent infusions because, as a biotherapy, it may induce an infusion reaction (IR). The occurrence of IR is well described with chimeric monoclonal antibodies (mAb), such as infliximab (IFX).[2] In contrast, vedolizumab is a fully humanised mAb and the frequency of IR and immunisation against the drug in studies appears to be low.[3-5] However, precise description, time to onset, and severity of acute IR are often lacking in the literature.

METHODS

The authors conducted a multicentre retrospective review of patients with IBD treated with vedolizumab in four French university hospitals. All consecutive patients who received at least one infusion of vedolizumab for ulcerative colitis or Crohn's disease in one of these four centres from May 2014 until February 2018 were included. Vedolizumab was administrated at a standard dose of 300 mg at Weeks 0, 2, and 6, and then every 8 weeks (or every 4 weeks in cases of treatment optimisation). No patient received

premedication before the infusions. The primary outcome was the rate of acute IR, defined by adverse events occurring during the infusion or within 2 hours afterwards. There is no consensus to define acute IR, but because monitoring lasts a maximum of 2 hours, the authors focussed on events that occurred during the course of the infusion or within 2 hours of its completion. IR can be identified by the criteria proposed by Sampson et al.[6]

RESULTS

A total of 550 patients (260 males; 47%) with a mean age of 43±16 years (range: 17–88) were included. Among them, 299 patients (54%) had Crohn's disease, of whom 59% had an ileocolonic location and 43% had fistulising disease; and 251 patients (46%) had ulcerative colitis, of whom 58% had pancolitis. At time of vedolizumab initiation, the median duration of IBD was 11 years (range: 1–55). The vast majority of patients received at least one anti-TNF treatment prior to vedolizumab infusion, and of these patients, 367 (67%) received at least two anti-TNF treatments before starting vedolizumab. A total of 6,459 infusions of vedolizumab (average: 12 infusions per patient) were administered during the study period and only six acute IR (0.1%) occurred in the 550 patients. All IR were reported during infusion and five out of six happened during the induction phase of vedolizumab (i.e., the first three infusions). No severe reaction and no anaphylactic shock were registered, athough vedolizumab was definitely discontinued in two cases. The authors performed a univariate analysis using a chi-square test, but they failed to identify risk factors associated with the occurrence of IR. There was a tendency of an increased risk of IR to vedolizumab in patients with a previous history of IR to infliximab, but it was not statistically significant (p=0.07).

CONCLUSION

In this large multicentre cohort, the rate of acute IR was very low, at 0.1%. No severe IR were reported and none of the IR occurred within the 2 hours of recommended monitoring. These data, consistent with the literature, confirm the safety profile of vedolizumab. This therefore allows clinicians to question the need for clinical monitoring after the first two injections of vedolizumab. The withdrawal of this clinical monitoring seems possible in terms of safety, but is also desirable to improve the quality of life of patients with IBD and to reduce the indirect costs of treatment.

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The Incremental Benefit of Dye Chromoendoscopy Compared to High-Definition White Light and Virtual Chromoendoscopy for Lesion Assessment and Prediction of Submucosal Invasion

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BACKGROUND AND AIMS

The identification of a demarcated area (DA), where a regular microvascular or pit pattern appears disordered, is a fundamental principle of optical evaluation and can predict the presence of submucosal invasive cancer (SMIC) in large (≥20 mm) nonpedunculated colorectal polyps (LNPCP).[1-3] While virtual chromoendoscopy (VCE) is the primary method for performing optical evaluation, it has shown modest performance for LNPCP. Dye-based chromoendoscopy (DBC) is an alternative which has shown excellent performance characteristics with traditional magnification.[4] The authors therefore sought to evaluate the incremental benefit of DBC in addition to high-definition white light (HDWL) and VCE for DA identification and the prediction of SMIC in LNPCP.

METHODS

A prospective observational study of consecutive LNPCP at a single tertiary referral centre was performed.[5] Prior to resection, all LNPCP were initially assessed for a DA with HDWL plus VCE (Narrow Band Imaging [Olympus Corporation, Tokyo, Japan]) and then by DBC, by two trained independent observers. DA diagnostic performance (sensitivity, specificity, positive predictive value, and negative predictive value) and interobserver agreement (k statistic) were calculated.

RESULTS

Over 22 months to September 2019, 205 consecutive LNPCP (median size: 38mm; interquartile range: 30-50 mm; 46.8% right colon) were enrolled. The overall frequency of SMIC was 9.3%. The absence of a DA had a negative predictive value of 95.6% (95% confidence interval: 92.2–97.6%) for SMIC, independent of the use of DBC. A high rate of interobserver agreement was recorded for the identification of a DA with HDWL plus VCE (99.5%; k=0.98) and with HDWL plus VCE plus DBC (99%; k=0.95).

DISCUSSION

Lesion assessment is a critical component in determining the suitability of endoscopic resection for LNPCP.[6-8] In this study, the authors demonstrated that the use of HDWL combined with VCE had a high rate of interobserver agreement for DA identification, independent of the use of DBC. More importantly, they showed that the absence of a DA on the surface of LNPCP is a very strong predictor for the absence of SMIC, also independent of the use of DBC. Taken together, there is no role for the universal application of DBC in addition to HDWL plus VCE for LNPCP. Moreover, the results supported that LNPCP not demonstrating a DA, and in absence

of lesion characteristics associated covert SMIC, can be safely resected by piecemeal endoscopic mucosal resection. These study findings do require validation outside of an expert setting and provide an avenue for future research.

CONCLUSION

In conclusion, the absence of a DA within LNPCP is strongly predictive for the absence of SMIC. It can be determined without the need for DBC with a high rate of interobserver agreement among experts.

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Congress Interviews

United European Gastroenterology (UEG) Representatives Prof Drewes and Prof Castera spoke to EMJ about their roles in the society, as well as their personal research interests.

Prof Asbjørn Mohr Drewes

UEG Council General Gastroenterology Representative
Mech-Sense and Centre for Pancreatic Diseases, Department of Gastroenterology & Hepatology, Aalborg University Hospital, Aalborg, Denmark

Q1 You are a widely recognised expert in pancreatology, visceral pain, pharmacology, and gut-brain interactions, but what originally drew you to the field of gastroenterology?

It was coincidental as I was originally in training as a rheumatologist, but during a stay at the department of gastroenterology, I became fascinated with endoscopy and gastrointestinal (GI) diseases. To some degree, I believe it was also inherited as my father wrote his doctoral thesis on motility disorders and diabetes, which is also one of my main research areas.

Q2 As the Cofounder and Director of Mech-Sense at Aalborg University Hospital, could you please inform our readers as to why this research centre was established, and what are its long-term goals?

Like most things in life, it was also rather spontaneous. In Alborg, my colleague Prof Hans Gregersen was interested in gut biomechanics and my interests were pain and GI sensations in the gut. Therefore, we joined forces and founded Mech-Sense (focussing on gut mechanics and sensations) in 2003. Since then, our research has moved more towards motility disorders, diabetes, pharmacology, imaging, and especially pancreatology. The characteristics of the centre are that it is very multidisciplinary; among the 22 employees we have 10 specialities and collaborations with a vast number of national and international institutions. The long-term goal of the centre is similar to elsewhere, however, we wish to improve medicine using a multidisciplinary approach by bridging borders between specialities and using that to move science forward.

Q3 A major research interest of yours is gastrointestinal pain in health and disease and you sponsored the clinical trial 'A Study of Local Effect and Safety of a Single PPC-5650 Dose on Reflux Pain During Pain Stimulation in the Esophagus'. Why are you interested in this specific topic and what were the major outcomes of the trial?

Well, we have always had an interest in pharmacology and GI sensations, and we have participated in approximately 50 different trials including medications spanning from Phase 1b to 4, but we are mainly focussing on Phase 2 studies. The study mentioned investigated a new possible way to block acid-sensing ion channels. This was in line with our interests at that time, when we did a lot of research in oesophageal diseases. Since then our focus has moved more to the small and large intestine with associated organs.

Q4 In 2018 you received the prestigious "Hagedorn Prize" from the Danish Association of Internal Medicine in recognition of your excellent work in establishing the relationship between the brain and the gut. Could you elaborate further on this correlation?

The prize was given due to several aspects of my research and the brain-gut interactions was only one of them. I believe the main reasons was the model of our centre, spanning from basic and translational to clinical research, and because we then use this knowledge to provide new indications for medications or clinical guidelines. The brain-gut axis is of course crucial to understanding sensations in the gut and for more than 25 years, we have used electrophysiology and imaging methods to explore this area.

Q5 In your expert opinion, how has the current coronavirus disease (COVID-19) pandemic affected the field of gastroenterology, and is this something your research focusses on?

We are not doing research on COVID-19 specifically; however, we have had a lot of problems due to it. The pandemic resulted in a lockdown of our labs and patients not coming to the hospital unless necessary, which has heavily affected our ongoing research and ability to recruit patients for trials. Furthermore, we have a lot of international collaborations which have been halted due to the situation of the pandemic. Interactions have been greatly impacted; congresses and meetings have been cancelled and therefore networking, and particularly negotiating with industry partners, has become harder. The pandemic has also resulted in issues with us receiving permissions. Health authorities

"Many big organisations have devoted their grants to COVID-19 research, making less available for other areas such as GI research."

have prioritised COVID-19 studies, which means that we are waiting much longer for applications not related to the pandemic. Additionally, many big organisations have devoted their grants to COVID-19 research, making less available for other areas such as GI research. Lastly, a huge proportion of the hospital has been involved with COVID-19 patients and therefore they needed rooms and have taken some of our research laboratories away from us and so I only have one laboratory left currently, making it harder to do research.

Q6 How did you become involved with the UEG council and what was the goal you set out to achieve when you joined?

As member of the European Society of Neurogastroenterology and Motility (ESNM) I was elected as a member of the medical block where 11 societies are represented. Because there are now so many medical societies, two members have been allocated to the UEG Council and among the applicants from the medical block, I was elected as one of them. Although my areas of interest are neurogastroenterology and pain research, I represent the medical block and as such I have to represent as many of the 11 medical specialities in the block as possible. This is also why I am trying to promote more interdisciplinary work between these specialities at sessions at the UEG Week.

"This is also why I am trying to promote more interdisciplinary work between these specialities at sessions at the UEG Week."

Q7 What elements does your role as the United European Gastroenterology (UEG) Council General Gastroenterology Representative entail, how do you contribute to the annual congress, and what do you enjoy the most about the role?

There are many aspects, and it is difficult to rule one out. My main interest is to ensure that the medical block is heard in the council, and that diseases across the specialities are dealt with at our meetings. As such, I try to establish new sessions that are more interdisciplinary and involve, for example, the transition from childhood to adulthood or other interdisciplinary matters. At the UEG Week I try to be as active as possible, especially as a speaker in sessions within pain, motility, and pancreatology and I also aim to network and comment on posters and other news. If you ask me what I enjoy the most, I enjoy tandem sessions where we discuss different opinions for certain topics.

Q8 At UEG Week you presented and advocated for the surveillance of pancreatic cancer in the session "Long term management of patients with chronic pancreatitis: beyond pain." For those that did not attend, what were your arguments for surveillance?

It was an interesting session and I never tried a tandem session online before. I was not able to find evidence for cancer screening in patients with chronic pancreatitis in general, but the arguments I put forward were the following: 1) pancreatic cancer results in about 8% of the cancer deaths worldwide with a very bad prognosis; 2) some patients with chronic pancreatitis such as smokers and those with a family disposition and mutations (germline and *PRSS1*) have a higher risk and should be screened; however, other risk factors such as metabolic syndrome, alcohol, etc. should also be taken into consideration; 3) when discovered early, the prognosis is much better; however, the problem is that when patients are not screened the cancer progresses to an advanced stage; 4) new treatment options and surveillance of selected groups have shown to improve the prognosis dramatically; 5) new magnetic resonance and endoscopic ultrasound methods are promising, and in the near future, there may be blood tests that can be used as biomarkers. Therefore, it should soon be possible to screen outside very specialised centres especially for the patients with the risk factors I mentioned.

Prof Laurent Castera

Department of Hepatology, Beaujon Hospital, University of Paris, Clichy, France
UEG Council Liver Representative

Q1 You are currently the UEG Council Liver Representative. Please could you tell us about your duties in this role and any key projects that are associated?

As a founding member of UEG, the European Association for the Study of the Liver (EASL) has a liver representative within the council. My role is to ensure communication and crosstalk between the two societies and that the liver, an important player in digestive diseases, is represented in the different aspects of UEG activities, including education, research, and patient care. As an example, a partnership has been established between EASL and UEG for lobbying for digestive health with one unified voice at the European Parliament in Brussels, Belgium.

Q2 Noninvasive methods for liver fibrosis assessment is one of your research interests. What is it about this area that interests you most?

The implementation of noninvasive tests for liver fibrosis assessment has been one of the major advancements in hepatology over the last decade. Their use has really changed the practice of hepatology worldwide, leading to a dramatic decrease in the number of liver biopsies performed, especially for viral hepatitis. I had the privilege of chairing the first international guidelines (EASL-Latin American Association for the Study of the Liver [ALEH] Clinical Practice Guidelines on the use of noninvasive tests), which were published 5 years ago, and that will be updated next year. The focus is now on the follow-up of cured hepatitis C virus patients with cirrhosis and, most importantly, on the detection of advanced fibrosis in patients with nonalcoholic fatty liver disease (NAFLD).

Q3 You recently published the article 'Non-invasive tests for liver fibrosis in NAFLD: creating pathways between primary healthcare and liver clinics'. What are the main take-away messages from this?

NAFLD is now becoming the leading cause of chronic liver disease worldwide, affecting approximately 20–30% of the general population. The main challenge in clinical practice is the identification of patients with NAFLD with advanced liver fibrosis or cirrhosis, who are at the greatest risk of developing complications and should thus be referred to a specialist. Liver biopsies are unrealistic for this purpose because of the high number of NAFLD patients, most of them being seen in primary care. The current situation is that <10% of NAFLD patients are referred to a specialist.

We need to increase the awareness of general practitioners: if risk factors such as diabetes, obesity, hypertension, and hypercholesterolemia are present, the probability of having NAFLD is very high (80–90%). NAFLD can be confirmed by simple liver tests (elevated transaminases) and steatosis on ultrasound. The most promising strategy to stratify patients with NAFLD who should be referred to a specialist is the sequential use of noninvasive tests, serum tests such as FIB-4 (age, transaminases, and platelet count), followed by the measurement of liver stiffness using elastography.

Finally, establishing pathways between primary care and liver clinics to create a better linkage to care of NAFLD patients will be a critical challenge in the coming years.

Q4 You are involved in The LiverScreen Project and gave a presentation on this at the UEG Week Virtual 2020. Could you tell

our readers about the project and what has been learnt from this so far?

As you know, chronic liver diseases are silent killers as they evolve over several decades without any symptoms and are responsible for approximately 2 million deaths each year. Once you reach the stage of cirrhosis, it is usually too late and most of the patients are diagnosed at the stage of decompensated cirrhosis. The objective of the LiverScreen Project is to devise and evaluate a screening strategy for detecting chronic liver diseases early enough to take action. The strategy is simple, using transient elastography, a point-of-care noninvasive test, to detect fibrosis. We are aiming to enrol 30,000 subjects from the general population across eight European countries. So far, around 9,000 subjects have already been screened. This project is led by the LiverScreen consortium and has received Horizon 2020 funding.

Q5 With artificial intelligence encompassing many fields of medicine, do you see it being adopted in your area of research?

Very likely! Artificial intelligence is already a part of our everyday life. It is really going to change the field of medicine as well, not only in radiology or pathology but in all aspects of medicine. For instance, if you want to design a study at a population level in NAFLD, risk factors are well known and artificial intelligence could be applied to design new algorithms for detecting people at risk and aid in increasing awareness. So yes, I am pretty convinced that in the next coming years it will be an important factor.

Q6 The Nobel Prize in Physiology or Medicine this year was awarded to the scientists who identified the hepatitis C virus. How has the research of those scientists shaped the field of hepatology today?

Profs Harvey Alter, Michael Houghton, and Charles Rice have been awarded the Nobel Prize for the discovery of the hepatitis C virus, a bloodborne virus affecting more than 70 million persons worldwide and causing 400,000 deaths per year from cirrhosis and liver cancer. This award has been long expected and is a great recognition for our community. The irony is that none of these great scientists are hepatologists. Prof Alter was a transfusionist at the National Institute of Health (NIH) and Prof Houghton and Prof Rice are virologists. The first step was the identification in the 1970s of "non-A, non-B" hepatitis in recipients of blood transfusions by Prof Alter, who was also involved in the discovery of the hepatitis B virus with Dr Baruch Blumberg, another Nobel prize recipient. The second step was the discovery of the virus in 1989, by Prof Houghton, through intensive sequencing for 6 years using novel molecular biology techniques. The last step was the development by Prof Rice of *in vitro* and *in vivo* study models, allowing for better understanding of the virus biology and, most importantly, the identification of therapeutic targets, paving the way for designing effective drugs. Today, direct acting antivirals are able to achieve cure in 99% of patients whereas 30 years ago interferon could cure <10%. Finally, the World Health Organization (WHO) is aiming for global hepatitis C virus elimination by 2030.

The discovery of hepatitis C virus is quite unique, not only because it is a story of incredible persistence, creativity, and fruitful collaboration, but also because it took less than 40 years from the discovery to the cure of hepatitis C virus and this is quite unprecedented.

"It took less than 40 years from the discovery to the cure of hepatitis C virus and this is quite unprecedented."

Interview

Dr Radislav Nakov

President of the Association of Young Hepatogastroenterologists in Bulgaria; President of Bulgarian Society of Neurogastroenterology and Motility; Queen Yoanna University Hospital, Medical University of Sofia, Sofia, Bulgaria

Q1 What motivated you to specialise in gastroenterology over other disciplines?

As a medical student, I was fascinated by gastroenterology because it combines the intelligence of internal medicine and the boldness of surgery. In other words, you can use your brain and hands every single day. Therefore, the every day of the gastroenterologist is never boring.

Moreover, gastroenterology is an ever-improving field. We have witnessed cornerstone moments in the field: the discovery of *Helicobacter pylori*, biological therapy, and hepatitis C treatment. Nowadays, gut microbiota and artificial intelligence in endoscopy are receiving a lot of attention.

Q2 What are you currently researching and what areas of gastroenterology do you believe merit wider attention by the gastroenterology community?

I have started my scientific career with a PhD thesis in inflammatory bowel disease, in which I have assessed noninvasive markers such as fecal calprotectin and trefoil factor 3 for follow-up of patients with ulcerative colitis and Crohn's disease.

Subsequently, I have been fascinated by the beauty of gut microbiota. Here I would like to thank Dr Gianluca Ianiro from Gemelli University Policlinic in Rome, Italy, who inspired and motivated me. I am proud that we have succeeded in creating the first stool bank in an Eastern European country (Bulgaria) and that we have reported the first series of successful and safe fecal microbiota transplantations (FMT) in Bulgaria.

In the last 2 years, our team have performed a few internet-based epidemiological studies on the prevalence of irritable bowel syndrome and functional dyspepsia. These were the first studies describing the prevalence of these gut-brain interaction disorders in Bulgaria. Moreover, in another study, we found that gastrointestinal (GI) symptoms were significantly more prevalent in the Bulgarian population during the coronavirus disease (COVID-19) lockdown than under normal circumstances.

The topic that I am most inspired by and that merits wider attention by the gastroenterology community are rare diseases in gastroenterology. For the last few years, I have been a member of the Bulgarian Centre of Excellence (CoE) for transthyretin amyloidosis, a rare disease presenting symptoms ranging from the peripheral nerves, heart, and GI tract. We have shown that

GI manifestations are common in hereditary amyloidogenic transthyretin (ATTRv) amyloidosis and are present even before the onset of the polyneuropathy in some cases. Unfortunately, delays in diagnosis of ATTRv amyloidosis with GI manifestations commonly occurs because of the fragmented knowledge among gastroenterologists and general practitioners. Therefore, recently we have organised a working group of European gastroenterologists and neurologists that have now prepared recommendations for the diagnosis and management of transthyretin amyloidosis with GI manifestations.

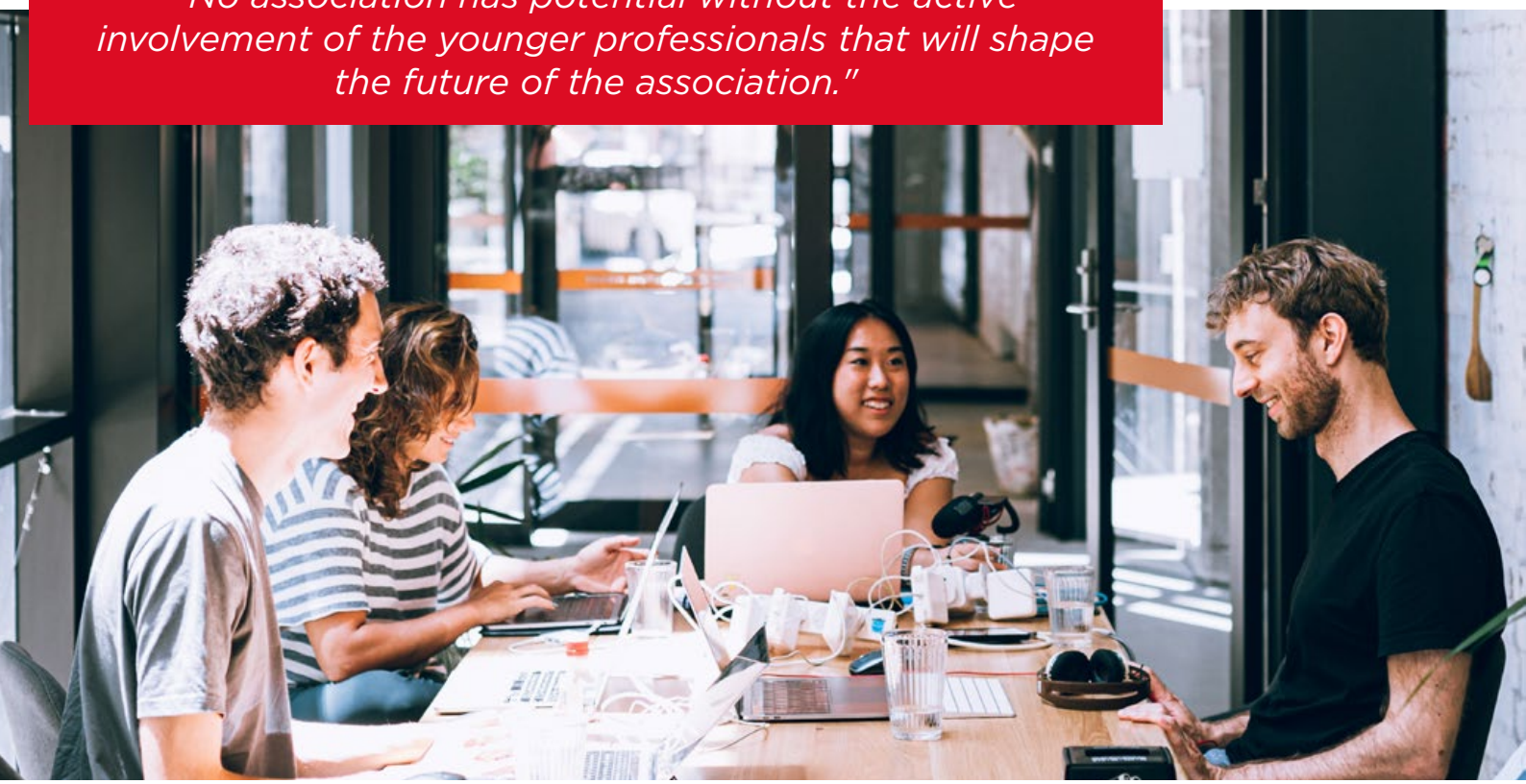
Furthermore, I would like to congratulate the European Association for Gastroenterology, Endoscopy, and Nutrition (EAGEN) for organising a postgraduate course on rare diseases in gastroenterology.

Q3 How did you become involved with the Young Hepatogastroenterologists in Bulgaria and what is your role as President?

No association has potential without the active involvement of the younger professionals that will shape the future of the association. Unfortunately, a few years ago, a young gastroenterologist could not present a study at the National Congress of Gastroenterology in Bulgaria (BSGE); they were not involved in any activities of the National Society. Therefore, a group of young residents in Bulgaria were motivated to organise a conference for young gastroenterologists in Bulgaria. It was a great success and attracted more than 150 young doctors. The next year, we created the Association of Young Hepatogastroenterologists in Bulgaria. However, we were not recognised as an official gastroenterology section by the National Society. Here came the support of the United European Gastroenterology (UEG) Board and UEG Young Talent Group, who helped us to be recognised by the mother society by starting the dialogue between us.

Nowadays, the young gastroenterology section of Bulgaria is now one of Europe's most active ones, actively organising a congress for young gastroenterologists with lectures and hands-on training in Bulgaria, helping to organise the European conference for young gastroenterologists, and actively increasing its participation in the UEG's (educational/support) programmes.

"No association has potential without the active involvement of the younger professionals that will shape the future of the association."



Q4 Similarly, what were the goals you set out to achieve when you became the President of the Bulgarian Society of Neurogastroenterology and Motility (BgSNM) and what is the long-term goal of this society?

The BgSNM was founded at the BSGE in 2019. There was an immense need to form such a group that united the Bulgarian gastroenterologists interested in neurogastroenterology and motility. The forming members of BgSNM are mainly young consultants and residents in gastroenterology who organised the first national population-based study for functional GI disorders prevalence in Bulgaria.

Our mission is to reduce the burden of disorders of the gut-brain interaction in Bulgaria by raising awareness and motivating scientific innovation and advances in medical care in the field of neurogastroenterology.

Our goals are to organise an annual scientific meeting, various workshops, and educational events. We would like to become active members of the European Society of Neurogastroenterology and Motility (ESNM) and collaborate with colleagues from all around Europe. As a young society, we have a lot to learn, and we believe that our experienced colleagues from Europe will help us to achieve our goals and develop as an organisation.

Q5 What would be your advice to fellow young gastroenterologists starting their careers and, in your opinion, what qualities are needed to become successful?

Nowadays, more young physicians should be inspired to do research. I believe that by performing studies, we ask ourselves essential clinical questions, which eventually make us better doctors. Therefore, in my opinion, the best clinicians are also excellent researchers.

Furthermore, communication and collaboration are crucial. Medicine is teamwork, and we should participate in working groups in order to improve ourselves. I would like to advise young gastroenterologists to apply for international clinical and research fellowships, to visit international congresses every year like the UEG Week, and to network with as many peers and experts as possible. I would also like to recommend every young gastroenterolgist to dive into the UEG Talent Pool and to apply to and actively participate in UEG programmes and positions in UEG committees and task forces.

Q6 You participated in a live case-based discussion titled 'Endoscopy in patients with foreign body' at this year's UEG Week. What were the main takeaway messages from this session?

'Foreign bodies in endoscopy' was a very vivid and interactive session! It was a pleasure to discuss this topic with such great experts as Dr Ulrike von Arnim, Prof Alexander Meining, and Prof Peter Siersema. The main takeaway messages were to always assess patients with foreign bodies for a concomitant psychotic disorder, to be aware that a patient with food impaction may have underlying eosinophilic oesophagitis, and to use a suitable extraction device according to the type and location of the ingested foreign object.

Moreover, it is essential to know that if we have an asymptomatic patient with ingestion of a blunt and small object (except for batteries and magnets), we should observe him only clinically, without needing endoscopic removal.

Q7 Faecal microbiota transplantation is gaining prominence in the treatment of gastrointestinal diseases. What are the current concepts and future challenges?

The truth is that FMT has only been proven to be a safe and effective treatment for Clostridioides difficile infection; however, increasing evidence supports the role of FMT in other gastrointestinal and extraintestinal diseases. FMT has many potential applications, including in irritable bowel syndrome, inflammatory bowel disease, liver disorders, critically-ill patients, metabolic disorders, and neurological disorders. The use of FMT in chronic disorders such as inflammatory bowel disease is a real challenge because repetitive infusions are needed, and we still do not know how many FMT we need, what the interval between them should be, and what results to expect.

The future of FMT applications should focus on the urgent need for standardisation of regulations and protocols for donor screening to ensure patient safety. Moreover, another fundamental challenge is identifying the disorders for which microbiota modification may have an apparent clinical effect.

Cachexia in Patients with Gastrointestinal Cancers: Contributing Factors, Prevention, and Current Management Approaches

EDITOR'S PICK

My Editor's Pick for this issue is the excellent paper by Grundmann et al., which is focussed on cachexia's pathophysiology, emerging diagnostic criteria with potential biomarkers, prevention strategies, and novel treatment approaches. We all hope for a more effective management and for a quicker amelioration of cachexia which negatively affects quality of life, responsiveness to chemotherapy, and survival in advanced cancer patients.

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Abstract

Cancer cachexia is highly prevalent among patients with the advanced stage of cancers and leads to a higher risk of mortality. Delayed management of cachexia results in suboptimal treatment outcomes and irreversible progression to refractory cachexia. The purpose of this review is to provide the pathophysiology of cancer cachexia, emerging diagnostic criteria with potential biomarkers, prevention strategies, and novel treatment approaches. Cachexia is characterised by the presence of an inflammatory process in conjunction with muscle mass and unintentional body weight loss. Various biomarkers such as leptin, ghrelin, TNFα, essential amino acids, total amino acids, and C-reactive protein are indicative of cachexia. Increased circulating levels of β-dystroglycan, myosin heavy-chain, and dystrophin are indicators of shortened survival time as skeletal muscle tissues break down. Despite muscle wasting being a hallmark of cachexia, recommended cachexia management is limited to nutritional counselling and administration of an appetite stimulant and corticosteroids for a short period, which often fail to reverse cancer cachexia. It is critical to monitor weight loss using the cachexia grading system for early detection, to halt progression to refractory cachexia and improve the survival of patients with cancer cachexia.

INTRODUCTION

Cancer cachexia is highly prevalent among patients with the advanced stages of cancers, affecting an estimated 12 million people worldwide and being causative in up to 2 million deaths annually as of 2016.[1] A distinguishing feature of cachexia is the loss of musculoskeletal lean body mass, with or without fat mass loss, in conjunction with weight loss of >5% over the course of 6 months.[2] These metabolic derangements delineate it from age-related sarcopenia or malnutrition, which can be reversed with proper nutritional supplementation or exercise.[3]

Cancer-associated cachexia is often linked to increased morbidity and mortality given its underdiagnosis and delayed treatment.[4,5] Delayed diagnosis of cachexia decreases quality of life, and may delay optimal patient care if systemic inflammation and gastrointestinal (GI) symptoms hinder the administration of necessary chemotherapy.[6] Approximately 80% of patients with advanced cancers experience cachexia, at which point intervention measures are often too late to reverse the condition and the progressive nature of the malignancy is accelerated by the complex cachectic metabolic derangement. Patients with advanced GI cancers may present with a higher incidence of cachexia given the aggressive nature of chemotherapy, the nutritional deficiency caused by the malignancy, and the relative proximity of localised inflammation and systemic responses.[7] This review addresses the pathophysiology of cancer cachexia, emerging diagnostic criteria and potential biomarkers, prevention strategies, and current as well as novel treatment approaches that either slow, halt, or reverse the progression of cachexia in patients with GI cancer.

PATHOPHYSIOLOGY OF CANCER CACHEXIA

The multifactorial nature of cancer development itself is highly complex, so it comes as no surprise that the pathophysiology of cachexia within this specific setting remains poorly understood. However, cachexia can be clearly differentiated from both malnutrition and sarcopenia by the presence of an inflammatory process in conjunction with muscle mass and body weight loss.[3] The systemic metabolic derangement caused by the malignancy is a result of hypercatabolism, hypermetabolism, systemic inflammation, and an imbalance in protein synthesis regulation.[8,9] Regulation of caloric intake is mediated through a variety of hormones, among them the adipocyte-generated cytokine-associated hormone leptin, the orexigenic peptide ghrelin present primarily in the GI tract, and the neuropeptide α-melanocyte-stimulating hormone.[10-12] Under physiological conditions, upon food intake leptin is released into the blood circulation to stimulate the production of proopiomelanocortin, leading to the release of cortisol and ultimately suppression of further food consumption (Figure 1).[13] Its opposing hormone, ghrelin, stimulates appetite by increasing the release of neuropeptide Y and orexin in the central nervous system, leading to increased gastric acid secretion (Figure 1).[13,14] A higher amount of leptin is expressed in patients with GI cancers, while a lower amount of ghrelin is present in this population, contributing to a deranged metabolism and lower caloric intake.[15] The imbalance between leptin and ghrelin is primarily attributed to systemic inflammation, an early hallmark of cancer and a necessary contributor to the development of cachexia. In fact, weight loss of <5% over 6 months but increasing inflammatory markers may indicate a precachectic state that warrants intervention to prevent progression.[16,17] It has also been observed that patients with cachexia develop resistance to ghrelin even if the hormone is being supplemented to stimulate appetite.[18]

A nonspecific marker of systemic inflammation is C-reactive protein (CRP), which increases in the early stages of malignancy. More specific to GI cancers are elevated plasma levels of TNFα, IL-1β, and IL-6, as well as a reduction in serum albumin and adiponectin levels.[15] While TNFα is not a specific marker of cancer cachexia, its increased blood levels in conjunction with rising IL-6 levels correlate with the progression from malnutrition to cachexia (Figure 1).[15] Interestingly, expression levels of IL-1β were found to be elevated in adipose and tumour tissues of GI cancer patients with cachexia versus those without cachexia, indicating more pronounced crosstalk between the tumour and surrounding tissues as a contributing factor in the development of cachexia.[19] Along with higher

IL-1β expression in patients with cachexia comes an increase in fibrosis and macrophage infiltration in subcutaneous adipose tissue compared to weight-stable patients with cancer, suggesting both an inflammatory and morphological differentiation in GI cancer cachexia.[20]

Because of a shift in metabolic and catabolic activity, both lipid and protein, as well as muscle-related biomarkers, may indicate sarcopenia and malnutrition. Increased local and systemic inflammation due to the tumour cause muscle proteolysis, in conjunction with malabsorption of nutrients due to the localised presence of the malignancy. The ratio of essential amino acids to total amino acids and CRP in plasma was higher in patients with GI cancer who lost psoas muscle area compared to those who maintained or gained psoas muscle.[21] This association between inflammation, increased proteolysis, and loss of muscle mass indicates that patients with advanced GI cancer have deranged metabolic/catabolic activity that cannot be compensated with nutritional supplementation alone. Other indicators of loss of muscle mass are increased plasma levels of β-dystroglycan, myosin heavy-chain, and dystrophin, which play a vital role in providing structural integrity to muscle tissues.[22] Increased circulating levels are indicators of shortened survival time and refractory cachexia as skeletal muscle tissues are breaking down.

EMERGING DIAGNOSTIC CRITERIA AND BIOMARKERS

Patients with GI cancer remain at high risk of developing cancer cachexia and a majority are diagnosed too late for effective prevention or treatment to slow or reverse the progression of muscle and weight loss.

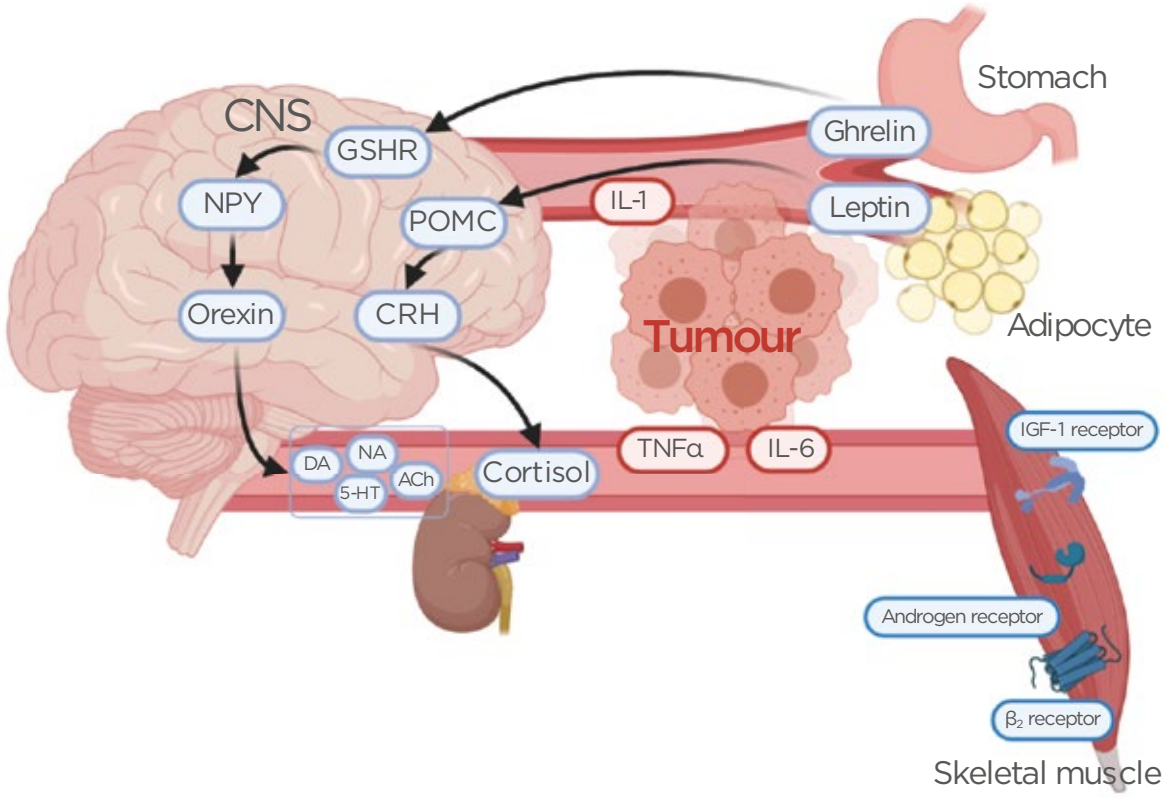

Figure 1: Effects of ghrelin and leptin secretion on the release of hormones and neurotransmitters from the central nervous system.

Release of inflammatory mediators from the tumour alters ghrelin and leptin homeostasis, leading to reduced skeletal muscle tissue. Also shown are potential targets for pharmacotherapeutic intervention, such as GSHR, IGF-1 receptor agonists, androgen receptor agonists, and adrenergic β_2 receptor antagonists.

ACh: acetylcholine; CNS: central nervous system; CRH: corticotropin-releasing hormone; DA: dopamine; GSHR: ghrelin receptor agonists; IGF-1: insulin-like growth factor-1; NA: noradrenaline; NPY: neuropeptide Y; POMC: proopiomelanocortin; 5-HT: serotonin.

Delayed diagnosis leads to increased morbidity and mortality, lower quality of life, and suboptimal therapeutic outcomes.[4,5] Early and frequent evaluation of patients with GI cancer is of critical value to detect weight loss as well as early changes in clinical and metabolic status. Such changes fall in the category of precachexia if inflammatory and/or nutritional markers are changing, and nutritional needs evolve either independently or based on chemotherapy or radiation treatment (Table 1).[23] The most common diagnostic criteria are nutritional assessments, weight loss >5% over 6 months without starvation, >2% of weight loss if BMI <20 kg/m^2, and/or demonstration of sarcopenia via skeletal muscle index measurement.[2]

Nutritional assessment tools are often used in conjunction with weight changes and quality of life observations in diagnosed patients. Among the established scales, the Nutrition Risk Screening-2002 (NRS-2002), Malnutrition Universal Screening Tool (MUST), and the Malnutrition Screening Tool (MST) are frequently used in clinical practice to establish nutritional and metabolic derangements.[16] If a patient has been identified to be at risk for developing cachexia or is precachectic, a more in-depth evaluation of nutritional intake, physical activity, and body composition has to be considered, along with nutrition assessment tools, such as the Subjective Global Assessment (SGA) or Minimal Nutrition Assessment (MNA), to evaluate the degree of malnutrition and existing cachexia.[16,24] The combined use of physical diagnostic criteria and nutritional screening or assessment tools has been given strong recommendations by the European Society for Clinical Nutrition and Metabolism (ESPEN) despite a "very low" level of available evidence.[16,25] This has been further refined as a two-step model for risk screening and diagnosis assessment of malnutrition by the Global Leadership Initiative on Malnutrition (GLIM), first convened in 2016.[26]

Table 1: Stages and characteristics of cachexia.

Precachexia Weight loss <5% Clinical and metabolic changes	Monitor weight and manage nutritional needs
	Frequent evaluation of inflammatory markers (TNFα, IL-1, IL-6) and nutrition markers (ghrelin and leptin)
	Consider changes in chemotherapy or radiation regimen to prevent progression
Cachexia Weight loss >5% Different phenotypes	Evaluate organ function, especially liver and kidney
	Counsel on diet and exercise, suggest additional protein intake per European Society for Clinical Nutrition and Metabolism (ESPEN) recommendations
	Pharmacotherapy intervention to increase appetite and anabolism
	Counselling on weight maintenance or recovery, depending on cancer stage
Refractory Cachexia Refractory catabolic cancer disease	Palliative care to reduce pain and maintain the level of quality of life
	Associated with poor outcomes and high mortality in patients with cancer
	Pharmacotherapeutic options can be exhausted according to patient well-being
	Consider parenteral nutrition support and maintenance of hydration

Adapted from Grundmann et al.[23]

The latest GLIM criteria as of 2019 include unintentional weight loss, low BMI, and reduced muscle mass as phenotypic criteria, and reduced food intake and inflammation or disease burden as aetiologic criteria, of which at least one phenotypic and aetiologic criterion need to be present to diagnose malnutrition.[26]

Patients with a weight-stable condition and BMI ≥25 kg/m^2 demonstrated longer survival than the patients who lost weight.[27] While cachexia is characterised by lean muscle loss, the association of BMI by % of weight loss can predict the prognosis of patients with cachexia, quality of life, and symptom burden. The cachexia grading system (ranged 0–4), based on % of weight loss and BMI, is beneficial for early detection to manage cancer cachexia.[27,28]

Thus, the ideal goal would be to prevent the development of cancer cachexia in the first place by recognising potential cachexia in patients with GI cancers. Once cachexia has progressed past a particular point, muscle degradation and loss of physical functioning are irreversible and impact the success of therapy and outcome. Patients with GI cancers are at higher risk of death if they had developed cachexia or refractory cachexia, lower grades in phase angle, decreased handgrip strength, and an increased CRP.[29] Together with weight loss, these measures can be utilised to evaluate the progression of muscle strength loss and increased inflammation to provide potential intervention. The phase angle, a composite measure obtained by bioelectrical impedance analysis, can predict nutritional status and overall health status.[30]

Another early marker of cachexia in GI cancer is carnosine dipeptidase 1, which has been associated with weight loss, malnutrition, lipid breakdown, and low circulating albumin as well as insulin-like growth factor 1.[31] The plasma levels of the enzyme, which plays a role in several disease states and is primarily expressed in the central nervous system and the liver, is significantly reduced in patients who develop cachexia compared to weight-stable patients with GI cancer. Carnosine is highly concentrated in muscle tissue, serving as a pH buffer to balance aerobic and anaerobic metabolism and catabolism activity.[32] Because muscle integrity and degradation is a contributing factor to cachexia, elevated plasma levels of β-dystroglycan can serve as specific biomarkers for the diagnosis of GI cancer cachexia, while elevations in dystrophin and myosin heavy-chain may predict poor survival.[22] Another potential predictor of muscle degradation in patients with GI cancer with cachexia are serum levels of carnitine, an essential compound needed in fatty acid energy metabolism in skeletal muscle cells.[33] Carnitine serum levels were significantly lower in patients with GI cancer with cachexia compared to other patients with cachexia and healthy controls, potentially providing a specific marker for the severity of cachexia in patients with cancer.

Despite these emerging biomarkers for cachexia development and progression, none are routinely used in clinical practice or have been tested widely as screening tools.

Current clinical practice guidelines for cachexia diagnosis primarily rely on the overall patient status by evaluating subjective symptoms, taking a history, a clinical examination, body composition measures, general laboratory values, and activity monitoring (Table 2).[16,34] While this approach can identify cachexia, it is often not specific or sensitive enough to monitor the development of progression in a timely manner for providing appropriate intervention. Clinicians may, therefore, consider additional laboratory measures as discussed above to guide important pharmacologic and nonpharmacologic treatment decisions to prevent or halt the progression of cancer cachexia before it advances to the mostly treatment-resistant refractory cachexia stage (Table 1).

PREVENTION STRATEGIES FOR GASTROINTESTINAL CANCER CACHEXIA

Cancer cachexia contributes to an increased risk of premature death in patients with GI cancer; hence, preventing its development remains a primary challenge and opportunity to improve quality of life and patient outcomes. Given that sudden and unexpected weight loss is both a hallmark indicator for tumour growth and anorexia-cachexia, it may serve as a nonspecific but leading sign for clinicians to investigate further. Any patient diagnosed with cancer is at risk of developing cachexia and therefore should

be frequently monitored for weight loss, changes in appetite and caloric intake, decrease in muscle strength, and increased inflammation.

Given the profound loss of lean muscle mass and metabolic derangement, nutritional intervention serves as an initial and ongoing therapeutic intervention to prevent or potentially halt or reverse the progression of cancer cachexia. Specifically, protein intake should be increased to at least 1 g/kg/day, ideally to 1.5 g/kg/day, in combination with regular physical activity or exercise.[16] Regular physical activity or exercise in conjunction with adequate nutrition is essential to maintain muscle strength, physical functioning, and metabolic activity.[35]

Rising serum levels of CRP, TNFα, and IL-6, in conjunction with >5% weight loss over 6 months and decreased muscle strength, is a strong indicator for a cachexia diagnosis.[36] Hence, a prevention strategy that is commonly employed in patients with cancer has been physical exercise to maintain muscle strength and nutritional support for caloric intake.[37,38] Physical exercise has been studied in several clinical trials for the prevention and treatment of cachexia in patients with cancer, and evaluated in a systematic Cochrane review.[39] Despite agreement among clinicians and researchers that exercise does benefit patients with precachexia and cachexia, heterogeneity in study design and neglect to include cachexia staging and assessment prevent consistent evaluation of the safety and efficacy of exercise in cachexia. Hence, its benefit remains undetermined and clinicians are left to consider its recommendation on an individual patient basis. Similar to physical exercise, nutritional support is a commonly employed and clinically utilised adjunct therapy to prevent and treat anorexia, malnutrition, and cachexia.

However, enteral nutrition support with omega-3 fatty acids, arginine, glutamine, and polyribonucleotides has not shown consistent improvements or increased survival in patients with GI cancer, and may only benefit patients with good functional status and an overall better prognosis.[40,41] Systemic inflammation remains a major contributing factor in the development of cancer cachexia and also serves as a biomarker for its diagnosis as previously discussed. Both the tumour and the immune response contribute to the development of a precachectic state that leads to a metabolic instability, hastening weight and muscle loss.[42]

Table 2: Current guidelines to diagnose cancer-associated cachexia.

Subjective symptoms	Appetite, early satiety, nausea, vomiting, disturbances of taste or smell, other GI symptoms, weakness, disease-related burden, quality of life
History	Weight change, speed of weight loss, % of normal dietary intake
Clinical examination	Inspection of mouth, abdomen, hydration status, oedema, body weight, perceived physical strength
Laboratory values	CRP, blood sugar profile, testosterone
Activity monitoring	Performance status (ECOG or Karnofsky Performance Scale), upper limb hand-grip dynamometry, body-worn activity meters
Body composition	Cross-sectional imaging (CT or MRI), dual energy X-ray imaging (DEXA), anthropometry (mid-arm muscle area), bioelectrical impedance analysis

CRP: C-reactive protein; DEXA: dual-energy X-ray absorptiometry; ECOG: Eastern Cooperative Oncology Group; GI: gastrointestinal.
Adapted from Radbruch et al.[34]

Reducing or suppressing systemic inflammation can potentially reduce both the progression of the malignancy as well as the development of a cachectic state. The use of anticytokine drugs, such as thalidomide, that target a range of proinflammatory cytokines (TNFα, IL-6, IL-1β, etc.) has shown mixed results in treating or preventing cachexia in clinical trials to date, primarily due to a heterogeneous patient population and testing in late disease states.[43] There is a potential correlation between the use of anti-inflammatory drugs, in particular the long-term use of aspirin, and lowering the risk of colorectal cancer development, as has been shown in several longitudinal studies.[44,45]

CURRENT AND NOVEL APPROACHES TO CANCER CACHEXIA TREATMENT

The two primary goals in the prevention and treatment of cancer cachexia are to increase or maintain appetite and to prevent a loss of muscle mass. Although weight and appetite loss are associated, they are not always an indication of cachexia since chemotherapy and radiation therapy themselves can impact appetite and weight changes through systemic and local inflammation themselves.[46] Because the imbalance in catabolism and anabolism is caused by systemic inflammation, the most common first-line pharmacotherapies remain glucocorticoids and progesterone derivatives that aim to stimulate appetite and maintain or increase weight via anabolism.[47,48] However, both drug classes have limited long-term benefits and do not improve physical functioning. Megestrol acetate remains the primary agent used to prevent and treat all stages of cancer cachexia and clinical studies indicate weight stabilisation or weight gain with its short-term use.[49] Combination therapy with nonsteroidal anti-inflammatory agents to suppress inflammation did not show a benefit over treatment with megestrol acetate alone, and thus remains limited to use in clinical trials.[50,51] Other agents that are occasionally used with mixed or equivocal success are cannabinoids, anticytokine and anabolic agents, and β-blockers (Figure 1).[23] Each class of agents has limitations and none of the experimental off-label uses has shown consistent benefits in halting or reversing cachexia in patients with GI cancer specifically or patients with advanced cancer in general. Such is the case with the combined use of agents that stimulate protein synthesis, such as short-term use of glucocorticoids or omega-3 fatty acids,[52] and agents that prevent catabolism, specifically thalidomide, which downregulates the ubiquitin-proteasome proteolysis pathway involved in protein degradation.[48] Thalidomide remains controversial due to its known genotoxic and other adverse effects and has not been approved for the prevention or treatment of cancer cachexia. Its benefit in this population is also questionable given limited evidence from clinical studies.[53] Newer drugs that are being investigated target specific signalling pathways involved with food intake. Among them is the ghrelin receptor agonist anamorelin that has shown some benefits in patients with non-small cell lung carcinoma (ROMANA1 and ROMANA2 studies, including a total of 979 patients)[54,55] and one multicentre study in 50 patients with GI cancer.[56] Anamorelin does modestly improve body weight and lean body mass over the course of 12 weeks in patients with cancer cachexia compared to those receiving placebo; however, the European Medicines Agency (EMA) did not grant market approval for this indication in non-small cell lung cancer. Aside from increased strength exercises, physical functioning remains unaddressed in clinical trials to date.

Pharmacological approaches have limitations due to side effects and added burden to patients with cachexia, who are taking multiple medications and experiencing treatment-associated side effects. Several nonpharmacological approaches are utilised to improve the quality of life and mitigate the limitations of current pharmacotherapy to overcome the adverse effects of cancer chemotherapy. Such approaches involve targeted acupuncture to reduce specific GI and cachexia symptoms,[57] nutritional counselling, psychosocial interventions, and dietary supplements.[58] Recent guidelines recommended using enteral tube feeding and parenteral nutrition only with caution, and not treating patients with these approaches consistently.[59]

CONCLUSION

Cancer-associated cachexia has received increased attention for the last two decades. The definition of cachexia has been generally agreed

upon in the cachexia research community; however, diagnostic measures using the biological markers are still mainly under investigation. Recently, evaluation of the skeletal muscle index and psoas muscle index is often used to assess the loss of muscle mass for measuring cachexia. Despite various pharmacological agents having undergone clinical trials and some shown promising results, currently no medications are available to treat cachexia. Most recent guidelines for cancer cachexia management recommend dietary counselling, megestrol acetate as an appetite stimulant, or short-term use of dexamethasone.[58] These medications may be helpful to stimulate appetite but should not be taken for a long time due to various side effects. Also, these medications or nutritional counselling may not slow down lean muscle loss or treat cachexia. If possible, nonpharmacological approaches that would not be burdensome for patients may be a promising solution for patients with cachexia, who are affected by fatigue, decreased energy levels, nausea, and decreased appetite.

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Stem Cell Therapies: A Review of Current Therapeutic Approach for Inflammation-Associated Sigmoid Colon Diseases

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Abstract

Chronic inflammation is the single major contributor to the pathogenesis of sigmoid colon inflammatory diseases such as segmental colitis associated disease and inflammatory bowel disease (IBD). Existing conventional anti-inflammatory treatments have not proven to be a sufficient long-term solution for management of symptoms due to the immunosuppressive nature of these agents. Stem cell (SC) transplantation is a novel approach to treatment that could improve the prognosis of IBD patients in the long term by preventing inflammation, restoring defective immune balance, and promoting mucosal healing. Multiple studies have shown that bone marrow SC, mesenchymal SC (MSC), and most recently intestinal SC (ISC) have had marked success in improving immune functionality in cases of IBD. Effects of bone marrow SC did not show the kind of longevity that researchers initially anticipated, leading them to instead pursue thorough study of MSC. The tolerogenic effects of MSC have proven them to be a key player in the development of SC therapy; however, their exact mechanism of action has yet to be fully characterised. Due to existing discrepancies in the data detailing the association between MSC and colorectal cancer risk, ISC have since become of interest with the intention of finding a more reliable alternative source of SC. Preliminary studies have shown that ISC may be capable of achieving the same immunomodulatory effects as MSC but with reduced colorectal cancer risk, suggesting them to be the most promising new method of treating inflammatory-based sigmoid colon diseases under study thus far.

INTRODUCTION

The authors of this review aim to provide the latest information on the correlation between immunopathology of sigmoid colon inflammatory diseases and the application of innovative therapies using stem cells (SC). The anatomical approach, regarding the sigmoid colon, is based on the overlap of many diseases of this part of large colon either in their histopathological diagnosis and treatment or their epidemiological trends and risk factors.

Characteristic diseases of the sigmoid, such as diverticulitis, segmental colitis associated

disease, and inflammatory bowel disease (IBD) have a common hallmark: chronic inflammation. The problematic inflammatory process taking place in the gastrointestinal (GI) tract is the deleterious effect of an otherwise well-balanced host defence system.

This review article presents the immune system mechanisms of the GI tract, molecules associated with chronic inflammation, and new options of treatment based on the immunomodulatory properties of the haematopoietic (HSC) and mesenchymal stem cells (MSC) transplantation or transfusion, as well as intestinal stem cells (ISC) grown *in vitro* used as donor cells for transplantation, which are termed organoids.

SC treatment for IBD has recently attracted much interest and generated numerous publications. Among the different inflammatory diseases of the sigmoid colon these innovative treatment solutions with SC, which are in different phases of clinical research, are analysed mainly in patients with ulcerative colitis (UC). In other words, the authors will draw upon the present articles on UC to give the latest information on the current knowledge regarding this new treatment. Experimental work has yielded encouraging results; however, several aspects remain unresolved. The complexity of the issues involved raises many questions requiring further study and clarification.

This article is a comprehensive presentation of the most relevant data available in the existing literature emphasising the pathways of these multifaceted and complex interactions.

FUNCTIONAL FEATURES OF SC IN THE INTESTINAL EPITHELIUM

The sigmoid mucosa is covered by a single columnar epithelium that form one layer of cells linked together with tight junctions. These cells, enterocytes, goblet cells, and neuroendocrine cells, have a common progenitor: the so called ISC LGR5+, also known as crypt base columnar cell (CBC).[1] SC reside at the base of the crypts, forming a small niche. Under normal conditions the intestinal epithelium has a renewal rate every 3–8 days.[2]

SC are capable of differentiating into many mature types of intestinal epithelial cells, regenerating and repairing mucosal epithelium and they also adjust to a diverse environment created by microorganisms due to their properties of cellular plasticity as presented by Es et al.[3]

The underlying mechanisms of SC regeneration in response to injury are mostly unclear, although cytokine STAT5 seems to have a functional role in this process. Depletion of STAT5 leads to reduced proliferation of SC, whereas overexpression has the opposite effect.[4] Further studies will reveal the active role of SC in the understanding of epithelial homeostasis in the intestine.

INTRODUCTION OF THE ROLE OF SC AS THERAPEUTIC AGENTS TO IBD

It is well established that IBD, a collective term for the chronic inflammatory conditions UC and Crohn's disease (CD), can affect the sigmoid colon and has various immunologic and pathogenic features that motivate the prospective for more innovative therapies in the coming years.

UC is a chronic IBD characterised by ulcers of the distal sigmoid and rectum leading to diarrhoea, haematochezia, intense abdominal pain, and GI bleeding. UC signifies a defective autoimmune response leading to the excessive inflammation of the GI mucosa due to dysregulated cytokine production by CD4+ T cells and dendritic cells (DC), coupled with a loss of immunotolerance due to low numbers of T-regulatory lymphocytes (Treg).[5] Activation of IFNγ and TNFα promotes proliferation of CD4+ Th1 cells, and without Treg to counteract this activity, damage to the epithelial mucosa lining the GI tract will occur (Figure 1).[5] While there is no definitive cure for UC, it has been shown in recent years that therapeutic measures to reduce the activation of these CD4+ Th1 cells through a reset of the immune system can lead to cessation of IBD symptomatology.[5]

Conventional treatments, such as surgical operations or drug administration, have been used over the years, with the risk of colorectal cancer (CRC) development remaining high. Patients with chronic severe and protracted UC present an increased risk of CRC, which is approximately 5%.[6]

The effects of a variety of anti-inflammatory agents on the progression of UC have been

closely studied. Corticosteroids (CS) were the first anti-inflammatory measures that demonstrated marked success in the treatment of UC, but subsequent studies have proven an association between long-term CS therapy and complications, such as deep vein thrombosis, osteoporosis, and infection, to name a few.[7] For these reasons, CS are not recommended for prolonged use and are best utilised to achieve only the initial immunosuppression necessary to promote symptom regression.

Researchers have seen moderate success with the utilisation of TNFα inhibitors in attempt to prevent hyperactivity of proinflammatory cytokines and sustain symptom remission, but this method has shown decreased efficacy in immunocompromised individuals due to complications that arise from unrelated infections and exacerbation of GI bleeding.[5] Other anti-inflammatory drugs, such as JAK inhibitors, anti-integrin agents, and thiopurines have been studied for use as well, but each of these therapies have still carried substantial infection risk and have not proven to be superior in long-term maintenance of UC.[8] While each of these advancements have largely proven to be beneficial in improving the prognosis of UC, the immunosuppressive nature of these agents is an inherent overlying complication to consider. With this in mind, a novel approach to treatment of UC as well as other IBD conditions has been found to be through SC transplantation, and this has been attempted in a few different approaches.

Recent published articles implicate many different types of SC in the treatment of IBD, which are HSC, bone marrow stem cells (BMSC), MSC, and ISC.[9] The aim of these SC-based interventions is to reset the defective immune system by regenerating immune cells that will improve overall functionality. The alternative immunological reactions seen with anti-inflammatory drugs are not seen with SC, suggesting them to be a more effective therapy.

Researchers first saw success with the transplantation of HSC, but preliminary trials have proven that the association between this therapy and adverse events suffered after transplantation is too strong to justify further use.[10] Autologous BMSC, which can aid in replenishing functional adaptive immunity that is typically lost in cases of IBD, were determined to be a much safer alternative.[10] Table 1 presents some of the work that has been done regarding SC-based therapy in UC.

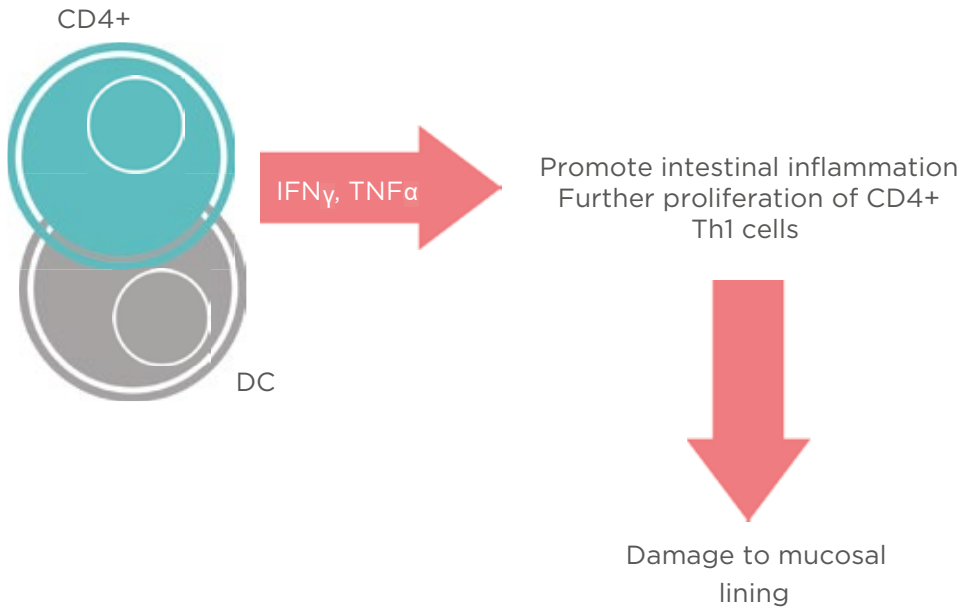

Figure 1: Schematic representation of different pathways that mesenchymal stem cells use to upregulate T-regulatory lymphocytes.

CD: cluster of differentiation; DC: dendritic cells.

Table 1: Summarised data of some recent experimental studies about the applications of stem cells in ulcerative colitis.

Stem cell	Source type	Route of administration	Condition	Outcome	Reference
BMSC	Autologous bone marrow	Submucosal injection through colonoscopy, intravenous administration	UC	Alleviation of symptoms, decreased bleeding and oedema, C-reactive protein reduced to normal values, no relapse after 2 years.	Xiang et al.,[10] 2016
MSC	Allogeneic bone marrow and umbilical cord	Intravenous administration	UC	Improvement of symptoms such as diarrhoea and abdominal pain, endoscopic healing, reduced inflamed area, and lymphocytic infiltrate.	Liang et al.,[22] 2012
MSC	Culture-derived allogeneic bone marrow	Intravenous administration	UC	Increase in the duration of remission, reduced recurrence and frequency of hospital admissions.	Ocansey et al.,[11] 2020 Lazebnik et al.,[23] 2010
MSC	Culture-derived human umbilical cord	Intravenous administration	UC	Reduction in the formation of ulcers.	Hu et al.,[24] 2016
ISC	Culture derived Lgr5+ colonic stem cells	Transplantation into the mouse colon	IBD (UC and CD)	Colon repair and regeneration of damaged epithelium.	Watanabe[36] 2018

BMSC: bone marrow stem cells; CD: Crohn's disease; IBD: inflammatory bowel disease; ISC: intestinal stem cell; MSC: mesenchymal stem cell; UC: ulcerative colitis.

The application of BMSC is limited due to their painful and invasive method of sampling and the possible side effects of cyclophosphamide administered for transplantation purposes.[11] Furthermore, the effects from single BMSC treatment have proven to be transient, and this has since led researchers to instead investigate the use of autologous MSC and ISC therapy.[10,11] More promising data have been released so far about the therapeutic applications of MSC.

THE ROLE OF MSC AS THERAPEUTIC AGENTS IN UC

The idea of designing innovative and more promising biological therapeutic methods is well depicted in the attempts of using human MSC to treat IBD. These SC are non-haematopoietic SC derived from bone marrow, umbilical cord blood, or adipose tissue. Evidenced by several studies, it is well known that they play an important role in sites of inflammation and tissue injury due to their ability to migrate to these areas. Inflammatory tissue damage and loss of

regulation of the chronic immune responses are the main features in IBD pathogenesis and MSC target them by using various molecular and cellular mechanisms.[12-16]

Both innate and adaptive immune responses are involved. Innate immune cells, such as antigen-presenting DC, macrophages, and natural killer cells, play major roles in the initiation of the inflammatory process in IBD. MSC react to inflammatory signals by secreting particles that suppress inflammation and proliferation of DC and natural killer cells.[12,13] Moreover, it has been shown that MSC secrete cytokines that can restore a balance between M1 and M2 macrophages via inducing a switch of the M1 inflammatory phenotype to the M2 anti-inflammatory/healing phenotype.[14] Experimental research has documented that MSC are important immunoregulators, enhancing the production of a variety of anti-inflammatory cytokines and growth factors, such as TGFβ, indoleamine-pyrrole 2,3-dioxygenase, prostaglandin E, IL-4, IL-10, IL-11, and IL-13, and inhibiting other proinflammatory agents, such as IL-6, IL-12, IL-23, and IL-21.[15,16]

Several studies found that MSC *in vitro* express low levels of MHC Class I and no MHC Class II molecules. As a result, they do not elicit a T lymphocyte rejection response in cases of transplantation. The privilege of low immunogenicity of MSC is essential to overcome the barriers of the adaptive immunity, allowing their application across syngeneic and allogeneic immune systems.[17]

Furthermore, the adaptive immune responses are modulated by the upregulation of Tregs through various cellular mechanisms. Firstly, there has been a growing attention in the experiments where MSC drive DC to differentiate into regulatory cells, triggering the production of Tregs, which leads to a more enhanced suppression of the already established inflammation.[18] Secondly, increased expression of Tregs is also presented by the secretion of exosomes and other soluble factors (TGFβ1, IL-10, prostaglandin E2) released from MSC.[11,19] Lastly, MSC interfere with the dysregulation of the balance that Bax protein (proapoptotic) and Bcl-2 protein (antiapoptotic) have, resulting in enhanced T-cell apoptosis. Apoptotic T cells induce macrophages to produce high levels of TGFβ, which upregulate Tregs, thus suppressing the immunologic response (Figure 2).[20,21]

THERAPEUTIC APPLICATIONS OF MSC IN IBD SUMMARISED BY RECENT CLINICAL DATA

The immunomodulatory functions of MSC have led to an increased trend for their study in clinical research and therapeutic application in UC. Clinical studies on allogeneic MSC, from umbilical cord or bone marrow, reported a better clinical outcome in the disease prognosis.[22] In one of these trials analysed by Lazebnik et al.,[23] bone marrow-derived allogeneic MSC administered intravenously in UC patients showed a significant increase in the duration of remission, as well as reduced recurrence and frequency of hospital admissions in these patients.[11] In addition, in a nonrandomised study, umbilical cord-derived MSC given by the same route reported reduction in the formation of ulcers in 30/36 patients with UC (Table 1).[24]

Similar studies of MSC in IBD are in different phases of clinical trials and applied in CD with promising clinical results.[25] MSC have also shown efficacy in fistula healing in cases of perianal fistulising CD, demonstrated in a study by Dige et al.,[26] in which 12/21 patients experiencing complete fistula healing 6 months following initial treatment with adipose-derived MSC and an additional four patients experiencing a marked reduction of symptoms.

THERAPEUTIC APPLICATIONS OF MSC IN COLITIS-ASSOCIATED CRC SUMMARISED BY RECENT CLINICAL DATA

Exploring the immunologic applications of progenitor cells in IBD let the authors consider their questionable utility for colitis-associated CRC treatment. Some recent data have demonstrated that MSC could migrate to CRC tissue from bone marrow. Due to their distinctive ability to home into neoplasia, these cells can be used as vehicles in the tumour microenvironment to target tumour sites. Modified MSC, such as TNF-related apoptosis inducing ligand MSC, MSC delivering cluster of differentiation markers, and MSC transfected with cytosine deaminase or the

symporter sodium iodide and CCL5/RANTES, have been tested so far with positive correlation with the tumour regression.[27] In addition, it has been reported that bone marrow MSC are able to secrete particular cytokines limiting CRC cell growth and spread.[28]

The immunohistochemical marker Ki67 could be a future guide to microscopically assess the therapeutic outcome of MSC transplantation examined in CRC biopsy specimens. The antitumour effect of MSC treatment has been previously studied and correlated with reduced Ki67 index. One study by Zheng et al.[29] proved tumour cells treated with MSC and stained with Ki67 proliferation index presented a decreased expression of this marker.

According to the above data, it seems quite safe to presume that MSC could limit or decrease the survival of tumour cells. This fact demands systematic investigation in this field in order to enlighten the specific role of MSC as therapeutic agents to colitis-associated CRC.

While MSC have proven to be predominantly effective in mediating tumour regression due to their anti-inflammatory and immunosuppressive effects, it is necessary to consider the demonstrated instances in which they have also led to outcomes opposite of this desired effect. The exact mechanism of action of MSC upon tumour cells has yet to be fully characterised; however, recent studies have shown that MSC transplantation has the potential to cause tumour growth. This is thought to be partially attributed to the tolerogenic nature of MSC as well as their preferential migration to tumour sites, which allow for creation of an optimal environment for tumour proliferation under the right circumstances.[30,31] Their origins could also play a role, as evidenced in a study from Ritter et al.,[32] in which it was found that certain adipose-tissue derived MSC in particular were associated with increased proliferation of malignant tumour cells, while MSC derived from the umbilical cord suppressed this growth. Patients who received allogeneic HSC transplants followed for more than two decades post-transplant showed an increased risk for secondary malignancies.[33]

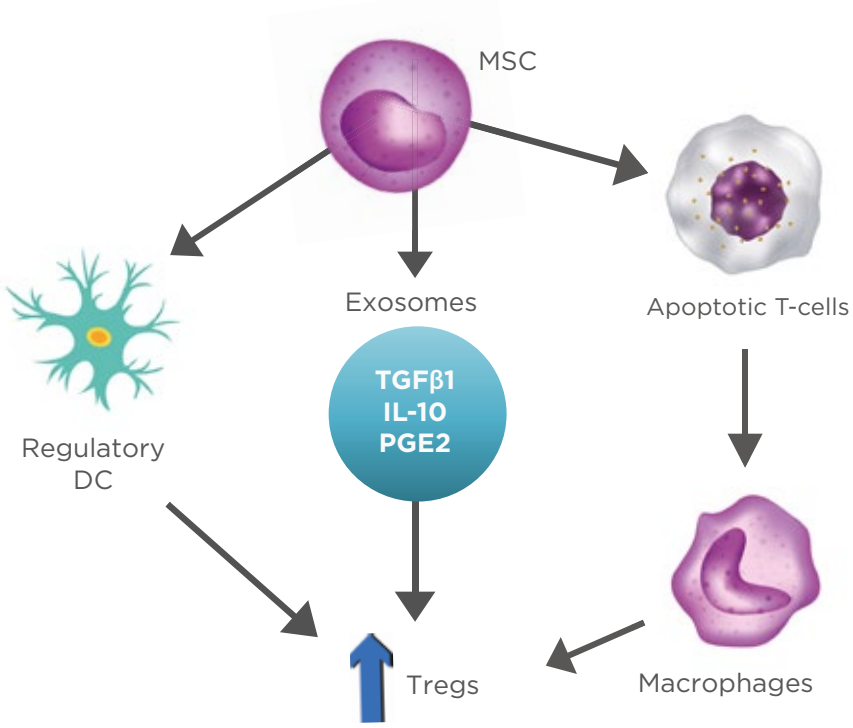

Figure 2: Representation of stem cells and their ability to modulate inflammation through production of various cytokines.

DC: dendritic cells; MSC: mesenchymal stem cells; PGE2: prostaglandin E2; Tregs: T-regulatory lymphocytes.

Additionally, MSC are capable of producing vascular endothelial growth factor, which plays a key role in tumour development by inducing angiogenesis, with help from TNFα and IFNγ.[34]

In a study by Fu et al.,[35] cancer cell lines were analysed according to their malignant phenotype, which was characterised by the proliferation rate, resistance to apoptosis, metastatic potential, and the tumorigenesis of these cells. Introductory research based on the co-culture of MSC and cancer cells suggests that these tumour-promoting effects of MSC can be exacerbated depending upon the metastatic abilities that the tumour cells possess. This indicates that it could be beneficial to first closely analyse the lineage of the existing cancerous cells in a patient before deciding to implement this therapeutic measure. MSC have been found to exert minimal influence in worsening the tumorigenic qualities of cancer cells that are already highly invasive and proliferative, in contrast to their effect on less proliferative cancer cells, in which their presence is more likely to induce tumour growth.[35]

Further research is necessary to better understand the discrepancies associated with MSC and their role in tumorigenesis.

THE ROLE OF ISC AS THERAPEUTIC AGENTS TO IBD AND CRC

ISC are another source that can be used for treatment. Results from preliminary studies of these therapies have proven to be promising new approaches in the treatment of UC.

Autologous transplantation of ISC has been described by Watanabe et al.[36] as a safe and simple therapeutic option for patients with serious GI epithelial injuries (Table 1). Researchers anticipate transplantation of new ISC to be effective in reducing the cancer risk associated with colitis, since they are capable of replacing old ISC that often accumulate cancer-initiating mutations.[37] However, further research is necessary to confirm this hypothesis and determine whether autologous ISC from IBD patients versus healthy donor ISC will have the same results after transplantation. Studies have shown that organoids extracted from CD patients have displayed the same growth capabilities as organoids from healthy individuals, which makes ISC therapy a highly positive prospect for future implication in IBD management.[37] It will also be necessary to confirm that the presence of ISC does not function to aid in the progression of malignancy as is occasionally seen with MSC.

In the contest of individualised therapy in CRC patients, *in vitro* disease models have emerged. Samples from CRC patients establishing colon cancer organoids have contributed to the investigation of mechanisms regarding molecular markers that could contribute to therapeutic options in colon cancer.[38] Biobanks of cancer organoids as well as pharmacological and genetic profiles are emerging as powerful *in vitro* disease models. Molecular analyses and gene profiles analysed in *ex vivo* ISC could help in the stratification of patients with the highest risk of developing CRC. A strong marker for ISC identified in human and mouse models from patients with IBD is a Wnt-independent cell-adhesion glycoprotein called olfactomedin 4. On the other hand, ISC from CRC patients overexpress achaete-scute-like2, a Wnt-dependent basic helix-loop-helix transcription factor.[39]

Vitamin D deficiency is known to be associated with IBD and CRC development, and recent studies have proven that vitamin D receptor is expressed *in vivo* in concurrence with the crypt SC marker LGR5.[40] This discovery is significant because it demonstrated that calcitriol, a vitamin D metabolite, plays an important role in mediating ISC homeostasis. In one recent study, normal and tumour colon organoids from fresh human tissues were used to analyse the effect of calcitriol. Calcitriol inhibited the proliferation of both normal and cancer SC while simultaneously inducing cancer SC differentiation, making vitamin D receptor agonists an attractive therapeutic agent to combat CRC progression.[40]

CONCLUSIONS

Clinical and experimental data have shown remarkable results about the therapeutic role of SC in UC. More clinical trials are mandatory to demonstrate the efficacy of such therapies based on the cell origin, dosage, and route of administration. The establishment of reliable assessment criteria is necessary to measure the pathological and clinical effects of SC. Since many diseases of the sigmoid colon are based

on chronic inflammation, further studies on the immune system could provide a more rational approach. Colitis-associated CRC and the application of SC therapies remain a challenge and an open field for more detailed research.

Altogether, right now, SC therapies constitute a novel option for treatment approach for UC and a potential new therapeutic option for other inflammatory-based sigmoid colon diseases and cancer. Future research will reveal the answers for a better orientation and the know-how to deal with therapies based on SC applications.

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That Gut Feeling: The Role of Inflammatory Cytokines in Depression Among Patients with Inflammatory Bowel Disease

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Abstract

There is mounting evidence of an associative link between inflammatory bowel disease (IBD) and clinical depression. In the first major treatise on the eponymous disease, Burrill Crohn himself noted that: "The number of cases of ileitis that have been rescued from institutions for the treatment of mental diseases emphasises not the personality but the end results of the drain of the disease upon the psychic constitution of the sufferer." In the 70 years since that prescient statement, a high incidence of neuropsychiatric symptoms (depression, anxiety, cognitive fatigue, and sleep disorders) in patients with IBD has been frequently observed. Since patients with depression have significantly increased rates of relapse, surgery, hospitalisation, and suicide, recognising and treating depression is of paramount importance. In this narrative review, the authors will trace some of the biochemical connections between intestinal inflammation and neuropsychiatric symptoms and focus on strategies to manage both. Additionally, the authors offer a cautionary reflection on the extant need for widespread screening for depression among patients with IBD.

INTRODUCTION

In the first major treatise on the eponymous disease, Burrill Crohn himself noted that: "The number of cases of ileitis that have been rescued from institutions for the treatment of mental diseases emphasises not the personality but the end results of the drain of the disease upon the psychic constitution of the sufferer" (emphasis added).[1] In the 70 years since that prescient statement, a high incidence of neuropsychiatric symptoms (depression, anxiety, cognitive fatigue, and sleep disorders) in patients with inflammatory bowel disease (IBD) has been consistently observed.[2-4] As with IBD, depression lacks clear biomarkers for definitive diagnosis,

and frequently involves complex treatment regimens. Unfortunately, there is no parallel imaging technique to colonoscopy for the brain that is comparably simple and widely available. As a result, diagnosis and treatment of depression presents unique challenges alone, and those challenges are compounded both by systemic inflammation and by various medications. Since patients with depression have significantly increased rates of relapse, surgery, hospitalisation,[5] and suicide,[6] recognising and treating depression is of paramount importance. In this narrative review, the authors will trace some of the biochemical connections between intestinal inflammation and neuropsychiatric symptoms and focus on strategies to manage both.

COMMON THREADS: CYTOKINES

To illuminate the connections between the immune system, peripheral inflammation, and neuropsychiatric effects, it is instructive to observe the psychological effects when systemic inflammation is induced by an immediate immune challenge. One common method for inflammation induction is injection of *Salmonella abortus equi* endotoxin.[7] In healthy volunteers, endotoxin rapidly activates the host-defence system, inducing both TNFα and IL-6 (see below), resulting in a constellation of disrupted neurological functions referred to as 'sickness behaviour'. Among the disruptions are extraintestinal symptoms well known to legions of those with IBD: anxiety, depressed mood, fatigue, and memory impairment. In the context of treating IBD, it is important to note that both the anxiety and depressed mood normalised in parallel with decreases in the cytokine concentrations. Similar mood effects are seen with *Salmonella Typhii* vaccine[8] and Bacillus Calmette–Guérin vaccine,[9] with concomitant elevation of the same cytokines. It is also worth remembering that these were healthy volunteers, subjected to a short-duration, low-dose immune challenge in which both the cytokine levels and neuropsychiatric symptoms typically resolve in a timescale of hours. By contrast, patients with IBD have chronic immune activation, and frequently higher circulating amounts of those same cytokines, even in remission.[10] Patients with IBD are, therefore, subject to prolonged alterations in brain function leading to anhedonia, anxiety, and cognitive fatigue.[2-4]

Perhaps the most insightful example for this discussion is exogenous IFNα, used for both chemotherapy and hepatitis C. There are two advantages to using IFNα therapy as a comparative study. First, given the widespread use of IFNα, there is a large dataset with robust documentation of systemic effects and mechanisms in both animals and humans. Second, owing to repeated and higher dosings over weeks and months, IFNα treatment more closely aligns with the chronic inflammatory state typically presented in IBD. As above, IFNα induces a rapid and sustained increase in other inflammatory cytokines, particularly TNFα and IL-6.[11] Significantly, up to 50% of patients being treated with IFNα experience major depressive symptoms, with 80% reporting sickness behaviour.[12,13] While those percentages are initially alarming, numerous large studies of patients with IBD have estimated between 20 and 45% of patients with IBD experienced at least some depressive symptoms,[14] and elevated rates of depressive disorder of 15% or higher.[2]

TNFα

TNFα has been ascribed a central role in chronic inflammation not only in IBD, but also rheumatoid arthritis (RA), plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, and systemic lupus erythematosus. TNFα interacts with the Type 2 receptor, leading to an inflammatory cascade via NF-κB activation. NF-κB is a transcription factor for an enormous number of inflammatory genes,[15,16] including virtually every molecule discussed in this review, including itself.

Along with, and because of, the dysregulation of so many critical factors for neurotransmission, it is little surprise that circulating TNFα is strongly associated with a variety of psychiatric effects, including depression, anxiety, cognitive fatigue, and sleep disturbances.[7,8,11,17-21]

Serum TNFα levels have been found to be significantly elevated in patients in the acute phase of major depressive disorder (MDD).[17] While levels decreased during antidepressant treatment, they remained elevated in the chronic phase of MDD. Similarly, post-mortem examination of individuals with depression has found elevated levels of TNFα in a variety of

areas of the brain.[18] Perhaps unsurprisingly, both TNFα protein and mRNA were also elevated in the prefrontal cortex of teenage suicide victims,[19] as well as in plasma of some adults attempting suicide.[20] In clinical trials, systemic TNFα infusion was tested for proapoptotic activity with certain cancers.[22] Many patients developed dose-dependent, reversible, attentional deficits, memory disorders, fatigue, confusion, and in some cases neurotoxicity.

In 1998 the U.S. Food and Drug Administration (FDA) approved infliximab for Crohn's disease, the first biologic inhibitor for TNFα, heralding a new age in the treatment of IBD. Almost overnight, anecdotal reports of rapid antidepressant effects surfaced, with later imaging studies demonstrating observable changes in brain function in 48 hours,[21] and biochemical changes within 24 hours.[23] As a result, in 2013, a clinical trial of infliximab for treatment-resistant depression was undertaken.[24] While inhibition of TNFα was not shown to be uniformly effective, it was effective in a subgroup of patients with higher levels of C-reactive protein (CRP). This trial suggested that depression is not purely an inflammatory process, but is certainly exacerbated by existing inflammation, and treatable by suppressing inflammatory cytokines, adding to the results observed in IBD, RA, and psoriasis.[25]

Notably, antidepressant effects of TNF blockade are not exclusive to infliximab, nor even to antibodies. Thalidomide, which acts as a small-molecule inhibitor of TNFα, also shows antidepressant effects.[26]

IL-6

Along with TNFα, IL-6 is elevated in virtually all autoimmune inflammatory disorders, and has a strong association with depression.[27] Among its pleiotropic roles are induction of CRP,[28] weakening of tight junctions at the intestinal epithelial barrier and the blood–brain barrier (BBB),[28] and differentiation of T helper cells into Th17 (IL-17 producing) cells. IL-6 expression is controlled, at least partially, by NF-κB. In Crohn's patients, IL-6 is highly upregulated in active disease, and is strongly downregulated in infliximab responders.[29] In animal studies, IL-6 has been shown to directly pass through the BBB and into the brain.[30] As with TNFα, average IL-6 levels have been found to be elevated in the brains of successful suicides and in the cerebrospinal fluid of attempters. There is a rich literature demonstrating the strong relationship between IL-6 and dopamine in the symptoms of anhedonia,[27,28,31,32] a core symptom of MDD. Even a comparably low level of IL-6 is strongly tied to motivational effort,[32] and as such is a likely contributor to the high degree of treatment nonadherence observed in IBD patients.[33]

Unlike TNFα, where exogenous cytokine was tested only on ill patients, the effects of IL-6 have been directly tested by subcutaneous injection of the recombinant protein into healthy volunteers.[34] Within 4 hours, self-reported measures of concentration, self-reliance, and 'high spirits' had all dropped significantly, while fatigue, sadness, and anxiety had all increased. Sleep analysis of this same cohort showed a significant decrease in time spent in the rapid eye movement phase of sleep. As emphasised above, these were healthy volunteers with a single low-dose acute stimulus over a short time period. As with TNFα, it appears that a significant portion of patients with IBD do not have sufficient biochemical adjustment to increased IL-6 levels, and thereby experience more chronic versions of the short-term effects listed above, manifested in sleep and mood disorders.

Given early success in blocking TNFα and subsequent focus on more gut-specific inflammation (vedolizumab), IL-6 inhibitors have not yet been used extensively in IBD despite successful clinical trials. However, studies in RA have shown that blockage of the IL-6 signalling (either antibodies to IL-6[35] or to the IL-6 receptor[36]) has positive effects on depression and anxiety symptoms, as well as improvements to sleep.

IL-17A

Of the cytokines commonly associated with both IBD and depression, IL-17A is particularly enigmatic. Th17 cells are induced either by IL-6 or by IL-23, leading to the production of IL-17A. Similar to IL-6, IL-17A is directly involved in weakening both the intestinal epithelial barrier and the BBB. In the brain, IL-17A is associated with a host of neurological diseases, including multiple sclerosis, ischaemic brain injury, and Alzheimer's disease.[37] IL-17A also appears to directly induce microglia into the reactive state, leading to significant monoamine neurotransmitter issues

(see below).[38] One IL-17A inhibitor in particular, Ixekizumab, demonstrated parallel results to those mentioned above in improving depressive symptoms in patients with plaque psoriasis.[39] Despite initial failure as a therapeutic target in Crohn's disease, IL-17A is still a potentially useful biomarker because IL-17A levels are associated with antidepressant effectiveness[40] and even with infliximab response.[41]

Other Targets

While not as frequently implicated in depression, both IL-12 and IL-23 have been associated with depressive symptoms. Inhibition of both IL-12/IL-23 (ustekinumab)[42] or IL-23 alone (guselkumab)[43] improve depression and anxiety scores. Somewhat more surprising is the finding that vedolizumab, an α4β7-integrin inhibitor acting virtually exclusively in the gut, also ameliorates depression and anxiety, and improves sleep quality.[44] In fact, a 2016 meta-analysis showed that inhibition of virtually any single cytokine involved in inflammation improved symptoms of depression.[25]

TRANSMISSION TO THE BRAIN

There are three distinct pathways for transmission of inflammation from the intestines to the brain: the neural, the humoral, and the cellular. It is very likely that all three are in play with IBD.

In the neural pathway, cytokines bind directly to afferent fibres of the vagus nerve, transmitting the signal directly to the brain. Since this signalling does not require any molecular transport across the BBB, the transmission is fastest. There is a wealth of data on direct vagus stimulation (albeit not from the intestines) for treatment-resistant depression.[45]

In the humoral pathway, cytokines and other molecular miscreants directly cross the BBB into the brain, either passively or by active transport. This is perhaps the best studied of the three pathways, because BBB leakage is implicated in any number of neurological disorders, and it becomes more pronounced with age;[46] while active transport of cytokines and other immunomodulators is partly circadian, and is associated with sleep disruptions.[47] It is worth noting that the epithelial barriers of the intestine, the retina, and the brain are similarly constituted and disrupted by many of the same factors.[48] For example, Calarge et al.[49] were recently able to show that increased intestinal permeability is directly associated with depressive symptoms, specifically in unmedicated adolescents. This aligns well with other data demonstrating that both IL-6 and IL-17 alter the integrity of the BBB from the periphery, while activated microglia also act to disrupt the BBB and express cytokines and chemokines from the inside.[50]

At least partially, the humoral pathway opens the door to the cellular pathway, both by loosening the tight-junction regulation and by increased expression of monocyte chemotactic protein (MCP-1/CCL20) in brain endothelial cells, thereby permitting cell trafficking of monocytes and macrophages into the brain.[51]

EFFECTS ON MONOAMINE NEUROTRANSMITTERS

Mechanistically speaking, the effects of inflammatory cytokines represent a form of 'perfect storm' for effects on the brain, and specifically on the synthesis and availability of monoamine neurotransmitters. Figure 1 and 2 illustrate a number of the pathways leading to neurological effects of inflammation.

The Indole-2,3-dioxygenase pathway: The Monoamine Crossroads

One of the most well documented alterations in neurotransmitter levels is brought about by indole-2,3-dioxygenase (IDO1), a uniquely destructive nexus in the synthesis, signalling, and release of monoamines. As shown in Figure 1, this enzyme catabolises tryptophan, thereby inhibiting serotonin synthesis, increases excitotoxic glutamatergic signalling and glutamate release, and in turn hinders dopamine release. When it was discovered, IDO1 was thought to be an intestinal variation of the tryptophan-2,3-dioxygenase (expressed primarily in the liver). Later studies demonstrated that IDO1 is induced by cytokines and transcribed by NF-κB. One proposed rationale for this particular enzyme is an evolutionary defence against pathogens by lowering the amount of available tryptophan, with depressive symptoms restricting social behaviour and thereby transmission of infectious agents.[52]

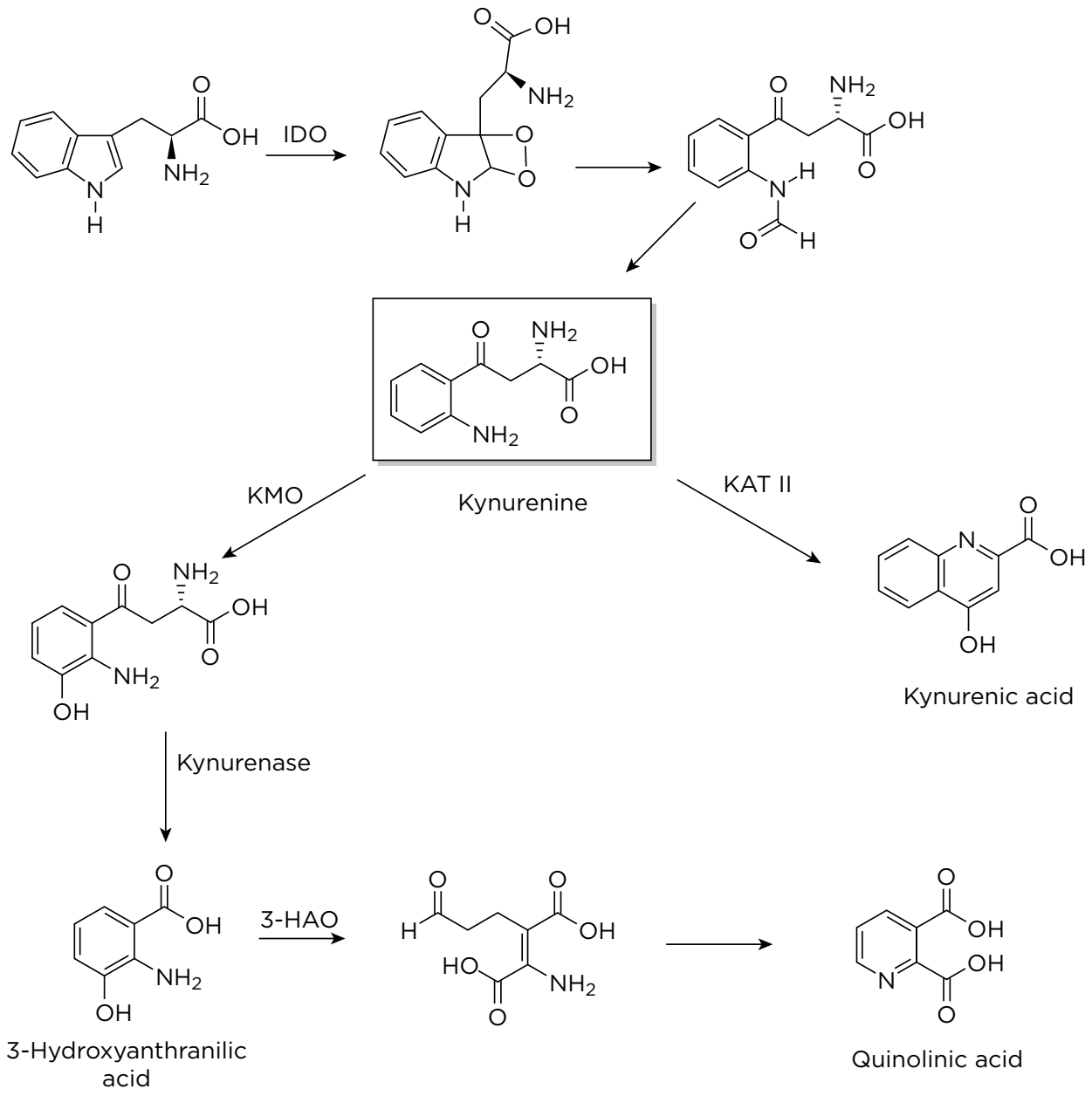

Figure 1: Indole-2,3-dioxygenase pathway.

3-HAO: 3-hydroxyanthranilic acid oxidase; IDO: indole-2,3-dioxygenase; KAT II: kynurenine aminotransferase II; KMO: kynurenine 3-monooxygenase.

Overexpressing this defence mechanism has the unfortunate consequence of also depleting not only available serotonin, but by extension melatonin, the monoamines most commonly associated with depressive symptoms and sleep disorders. This diversion may help explain the blunted response to selective serotonin reuptake inhibitors (SSRI) found in many patients with IBD, since SSRI drugs act downstream of neurotransmitter synthesis. While most studies of IDO1 are focussed on depletion of serotonin, it is important to note that melatonin is an important inhibitor of MMP-9,[53] an upregulated enzyme that causes epithelial barrier damage. As such, depletion of melatonin likely plays a role in both intestinal and BBB permeability. Infliximab treatment strongly downregulates the expression of IDO1, and this may be a significant explanation for the antidepressant effects of anti-TNF treatment, as well as its effects on sleep quality.[29]

Additionally, in animal models, inhibition of IDO1 by 1-methyltryptophan had comparable

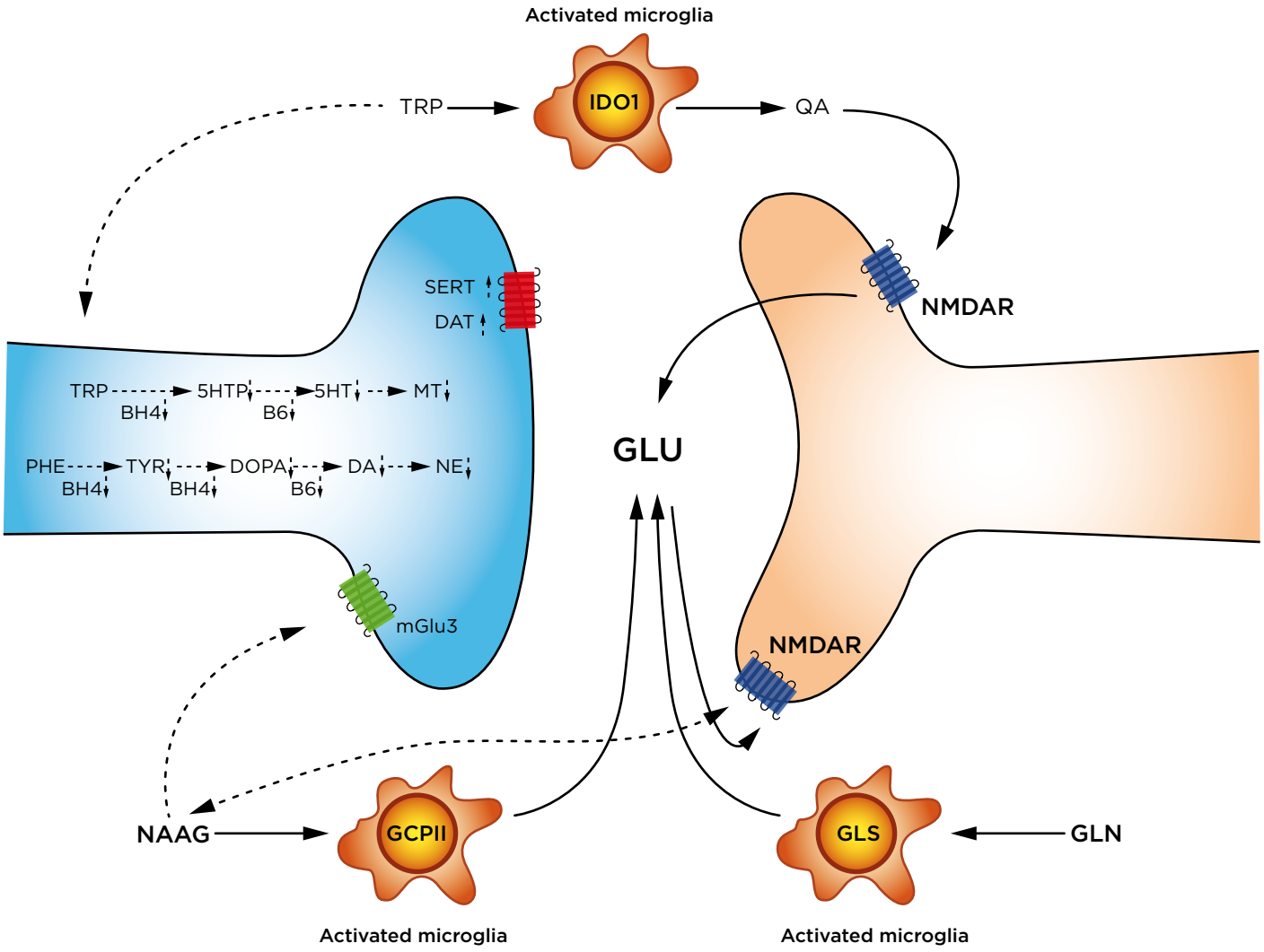

Figure 2: Inflammation-altered pathways in neurotransmission.

Synthesis of 5HT, MT, DA, and NE are slowed by lowered availability of BH4 and B6. BH4 is a cofactor in the hydroxylation of TRP, PHE, and TYR. B6 is a cofactor in the decarboxylation of DOPA to form DA, and the decarboxylation of 5HTP to form 5HT. Reuptake of DA by the DAT and of 5HT by the SERT are increased.

Activated microglia express three enzymes responsible for increased glutamate and glutamatergic signalling: 1) IDO1 catabolises TRP to QA. QA is an agonist at the NMDAR, leading to GLU release. 2) GCPII cleaves NAAG to N-acetylaspartate (not shown) and GLU. As a result, NAAG signalling at both the mGlu3 and the NMDAR are decreased. 3) GLS hydrolyses GLN to GLU. Removal of excess GLU by the GLT1/EAAT2 is also downregulated (not shown).

Impaired or downregulated pathways are shown with dotted arrows.

5HT: serotonin; 5HTP: 5-hydroxytryptophan; BH4: tetrahydrobiopterin; B6: pyridoxyl-5'-phosphate; DA: dopamine; DAT: dopamine transporter; DOPA: L-3,4-dioxyphenylalanine; EAAT2: excitatory amino acid transporter 2; GCPII: glutamate carboxypepsidase-II; GLN: glutamine; GLS: glutaminase; GLT1: glutamate transporter-I/; GLU: glutamate; IDO1: Indole-2,3-dioxygenase; mGlu3: metaboglutamate-3 receptor; MT: melatonin; NAAG: N-acetylaspartylglutamate; NE: norepinephrine; NMDAR: N-methyl-D-aspartate receptor; PHE: phenylalanine; QA: quinolinic acid; SERT: serotonin transporter; TRP: tryptophan; TYR: tyrosine.

effects on depressive behaviour to treatment with infliximab, suggesting that IDO1 may be a viable drug target for inflammation-mediated depression.[54] There are multiple clinical trials investigating IDO1 inhibitors as add-on therapy for cancer treatments, so there may well be an approved drug in this class in the next several years.

Glutamate–N-methyl-D-aspartate receptor

As a continuation of the effects of IDO1, a primary catabolite of tryptophan is quinolinic acid (QA; Figure 1). QA is an N-methyl-D-aspartate receptor (NMDAR) agonist, leading to increased glutamate signalling, release of additional glutamate, and inhibition of the release of dopamine. QA binds preferentially to NMDAR in the forebrain, in areas critical to mood, memory, and sleep regulation.[55] Multiple studies have shown that the cognitive fatigue in IBD is postsynaptic in origin, and it therefore seems likely that NMDAR signalling plays a critical role.[21] One of the purported sites for the rapid antidepressant action of ketamine in treatment-resistant depression is the NMDAR. In humans with treatment-resistant depression, low-dose ketamine as an add-on therapy dropped levels of both TNFα and IL-6,[56] while one animal study showed it also lowered the levels of QA and microglia.[57] It remains to be seen how effective ketamine will be in patients with IBD, but the studies above suggest a more complex and useful anti-inflammatory role in addition to its use as an antidepressant.

Excitotoxicity in the immediate term is most likely manifested by anhedonia and 'brain fog'. However, in the long term, excitotoxicity destroys neurons, specifically dopaminergic neurons. This destruction is exactly the type of process thought to lead to Parkinson's disease. Notably, IBD has long had a particularly strong association with development of Parkinson's disease,[58] and NMDAR glutamate signalling could be a significant contributor. In support of this hypothesis, consider that IDO1 catabolites are increased in the cerebrospinal fluid of Parkinson's patients,[59] and animal models of Parkinsonism are partially induced with QA.[60]

Not only is glutamate release and signalling increased thanks to QA, but also by upregulations of glutamate carboxypeptidase II[61] and glutaminase.[62] By hydrolysing either N-acetylaspartylglutamate or glutamine, additional glutamate is released, augmenting the glutamatergic (excitotoxic) responses. Increased glutamate is indeed visible in the brain by proton magnetic resonance spectroscopy.[63] Along with increased release, signalling, and synthesis of glutamate, the primary reuptake transporter (EAAT2/GLT1) is downregulated.[64] Added to that, decarboxylation of glutamate to GABA by GAD1 is likely regulated by NF-κB, and requires vitamin B6 as a cofactor (see below). With these enzymes combined, glutamate excitotoxic signalling almost certainly plays a central role in the neuropsychiatric comorbidities of IBD.

Tetrahydrobiopterin and Neopterin

Along with upregulation of IDO1, cytokines also are associated with diversion of the catabolic synthesis of tetrahydrobiopterin (BH4), a critical cofactor for hydroxylation of phenylalanine, tyrosine, and tryptophan, the rate-limiting step en route to the catecholamines and serotonin/melatonin. Depletion of BH4 actually occurs in two ways. First, large upregulation of the first enzyme in the BH4 synthesis (GTP cyclohydrolase) creates a synthesis bottleneck, overwhelming the second enzyme in the pathway.[65] As a consequence, the critical BH4 precursor is unhelpfully diverted to neopterin. Second, cytokines strongly induce nitric oxide synthase and reactive oxygen species, both of which require BH4 as a cofactor,[66] depleting the available supply. Both processes decrease the availability of monoamine neurotransmitters, and are associated with anxiety, fatigue, and anhedonia. In one particularly elegant study by Felger et al.,[67] reverse microdialysis of L-DOPA into the brains of rhesus monkeys reversed the symptoms of IFNα-induced depression, suggesting that hydroxylation (controlled by BH4 levels) was the dominant issue, and subsequent decarboxylation and vesicular transport (via VMAT2) might be functioning normally.

Pyridoxyl-5'-Phosphate: Vitamin B6

The final step in the synthesis of serotonin from 5-hydroxytryptophan, dopamine from L-DOPA, and GABA from glutamate is decarboxylation by the amino acid decarboxylases. As with the

hydroxylases discussed above, these enzymes are dependent on the availability of a cofactor: in this case, pyridoxal-5'-phosphate (the active form of Vitamin B6), of which patients with IBD are frequently deficient.[68] Studies on RA suggest that deficits in active B6 are not an absorption issue, but rather alterations in processing and metabolism.[69] While there are considerably less data available, it has been reported that tryptophan metabolites inhibit the phosphorylation of pyridoxal.[70] A recent animal study showed that NF-κB knockout mice had a downregulation of AOX1, the principal metabolic enzyme responsible for converting pyridoxal-5'-phosphate to pyridoxic acid.[71] While this finding does not prove AOX1 is upregulated by NF-κB, it certainly fits the pattern of NF-κB playing a central controlling role in inflammatory responses in the brain.

CONCLUSIONS AND FINAL THOUGHTS

Reflecting the mounting evidence, the American College of Gastroenterology (ACG), the British Society for Gastroenterology (BSG), the American Gastroenterological Association (AGA), the World Gastroenterology Organisation (WGO), and the Crohn's & Colitis Foundation have all added some level of psychiatric assessment and management to their respective clinical guidelines. This is an important step toward successfully treating patients with IBD. However, as an example, the ACG recommendation (strong recommendation, very-low level of evidence)[72,73] points out a larger problem in the need for broad screening. As an illustration, in a 2017 report, >4,000 patients were asked to self-evaluate, with only 20% of patients with Crohn's disease and 14% of patients with ulcerative colitis claiming to be depressed. However, by using a short questionnaire (Patient Health Questionnaire depression scale [PHQ-8]), an alarming 38% of patients with Crohn's disease and 32% of patients with ulcerative colitis in the same cohort met the criteria for depression.[5] Given the antidepressant effects of some treatments (see above), the actual percentages in treatment-naïve patients could be considerably higher. Since depression has such strong effects on motivation (including adherence with diagnostic and treatment protocols),[74] devastating effects on disease progression, and significant increases to mortality, the need for psychiatric screening as part of disease management cannot be overstated.

There are two additional problems to be addressed in screening and reporting. First, the phrase "antidepressant usage" found in many studies is wholly insufficient. This phrase is comparable to using "IBD medication" in gastroenterology. Different antidepressant classes are as mechanistically dissimilar from each other as aminosalicylate and infliximab, possibly even more so. Given that some specific SSRI drugs (mirtazapine) are reported to worsen systemic inflammation,[75] while at least one norepinephrine–dopamine reuptake inhibitor (bupropion) is reported to lessen it,[76] such granular detail is critical.

Second, as mentioned in the introduction, there is a dearth of reliable biomarkers for depression and anxiety. As a result, diagnosis often relies on various questionnaires that are not entirely comparable. It would be wise of the advisory bodies of IBD treatment to recommend a diagnostic tool for depression alongside the aforementioned need for its diagnosis.

Using the statistics quoted above, roughly one in three patients with IBD is potentially depressed, and possibly as high as one in six has considered, or is considering, suicide as a result of that depression within the past year.[77] For a typical gastroenterologist, that translates to seeing multiple patients per week that could be actively suicidal. Would their approach change if aware that the next patient was slowly (or rapidly) losing the battle against depression exacerbated by IBD? One very small scale report from the Jackson County, Missouri, USA, Medical Examiner's Office might provide some insight.[78] Of 12 Crohn's patients that died from 2008 to 2010 (average age: 45 years), there were five suicides, three accidental drug overdoses, and one case of liver failure from alcohol abuse. Only two of 12 died of IBD complications. As the authors rightly point out, these numbers certainly will not scale to the whole population, and treatments have certainly improved in the past decade. However, this paper serves as a sobering reminder that the intestines are not the only battlefront for IBD patients, nor their caregivers.

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An Overview of Novel and Emerging Therapies for Inflammatory Bowel Disease

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Abstract

Inflammatory bowel disease, consisting of Crohn's disease and ulcerative colitis, causes chronic gastrointestinal symptoms and can lead to morbidity and mortality if uncontrolled or untreated. However, for patients with moderate-to-severe disease, currently available therapies do not induce or maintain remission in >50% of patients. This underscores the need for additional therapies. In this review, the authors detail the novel therapies vedolizumab, tofacitinib, and ustekinumab and delve into therapies which may come onto the market within the next 10 years, including JAK-1 inhibitors (filgotinib and upadacitinib), IL-23 inhibitors (guselkumab, mirikizumab, and risankizumab), the anti-β4β7 and anti-βEβ7 integrin monoclonal antibody etrolizumab, the sphingosine-1-phosphate subtypes 1 and 5 modulator ozanimod, and mesenchymal stem cells. Further studies are required before these emerging therapies gain approval.

INTRODUCTION

Inflammatory bowel disease (IBD), consisting primarily of ulcerative colitis (UC) and Crohn's disease (CD), are chronic diseases affecting the gastrointestinal tract. Symptoms include diarrhoea, with and without blood, and abdominal pain. UC and CD, if left untreated or uncontrolled, cause significant morbidity and mortality at rates higher than the general population.[1] Furthermore, the incidence and prevalence of IBD are increasing over time around the globe.[2]

Standard therapies in IBD include topical 5-aminosalicylate products such as mesalamine and sulfasalazine, thiopurines such as azathioprine and 6-mercaptopurine, and topical and systemic corticosteroids. Unfortunately, topical 5-aminosalicylate products are not recommended in moderate-to-severe UC because of a lack of efficacy in this cohort.[3] Thiopurines are only effective in about one-quarter of patients,[4] and corticosteroids are not recommended for maintenance of remission as a result of dose-dependent short and long-term adverse effects, such as increased risk of serious infection, weight gain, elevated blood sugar levels, bone loss, and cataracts.[5, 6]

Novel medications for IBD include biologics such as the anti-TNF agents infliximab and adalimumab, the anti-α4β7 integrin monoclonal antibody vedolizumab, the anti-IL-12/IL-23 monoclonal antibody ustekinumab, and small molecules inhibiting JAK such as tofacitinib. However, in patients with moderate-to-severe UC and CD, these medications have an average induction of remission and maintenance of remission rates <50%,[7-13] underscoring the need for additional therapies for nonresponders and those who lose response to treatment. These remission rates are even lower in patients with prior exposure to biologic therapy. In this paper, the authors discuss select new IBD therapies and emerging therapies that will likely come onto the market in the next 5–10 years (Table 1).[8-26]

NOVEL THERAPIES

Vedolizumab

Vedolizumab is an anti-α4β7 integrin monoclonal antibody that modulates gastrointestinal tract inflammation by inhibiting adhesion of peripheral blood lymphocytes to MAdCAM-1.[27] Because of this molecule's specificity to the gastrointestinal tract, the risk of progressive multifocal leukoencephalopathy (PML) is markedly decreased compared to that of natalizumab, an anti-α-4-integrin monoclonal antibody that causes systemic immunosuppression.[27]

In the Gemini 1 trial, in patients with moderate-to-severe UC, patients were randomised to either vedolizumab or placebo for induction.[8] In the maintenance arm, patients who responded to induction therapy were randomised to vedolizumab every 8 weeks, vedolizumab every 4 weeks, or placebo for up to 52 weeks. Higher rates of clinical response (the primary outcome) at Week 6 were seen in the vedolizumab arm than the placebo arm (47.1% versus 25.5%; p<0.001). Significantly higher rates of clinical remission were seen in the vedolizumab arms compared to placebo. Rates of serious infections were similar between the arms, including no cases of PML in either group.

The Gemini 2 and 3 trials studied vedolizumab in moderate-to-severe CD. Gemini 2 had a similar trial design as that of Gemini 1.[13] More patients on vedolizumab were in remission at Week 6 compared to placebo (14.5% versus 6.8%; p=0.02). In the maintenance arm, significantly more patients on vedolizumab were in remission at Week 52 than those on placebo. Of the most common adverse events (AE), only nasopharyngitis occurred more frequently in the vedolizumab arm. No cases of PML were reported and infections, serious infections, and serious AE occurred more frequently in the vedolizumab arm.

The Gemini 3 trial focussed on patients in whom prior therapy had failed, with 76% of patients having experienced anti-TNF failure[12] (whereas in Gemini 2 the number of patients who had failed these agents was limited to 50% of the total).[13] A nonsignificantly increased portion of anti-TNF agent nonresponders in the vedolizumab arm were in clinical remission at Week 6 versus those on placebo (15.2% versus 12.1%; p=0.443). A significantly higher number of patients were in clinical remission at Week 10 in the vedolizumab arm compared to placebo (26.6% versus 12.1%; nominal p=0.001). Rates of serious infections and serious AE were similar between the vedolizumab and placebo arms. Gastrointestinal infections occurred in slightly more patients in the vedolizumab arm. No cases of PML were reported.

Subcutaneous vedolizumab may be preferred by many patients given its convenience as compared to intravenous administration. In a UC trial of this formulation, patients received two doses of intravenous vedolizumab.[28] Those who responded were randomised to subcutaneous vedolizumab, intravenous vedolizumab, or placebo. Significantly more patients in the subcutaneous vedolizumab arm achieved clinical remission at Week 52 than in the other two arms. Safety profiles were similar between the subcutaneous and intravenous vedolizumab arms.

Results from the study investigating subcutaneous vedolizumab in CD have only been presented in abstract form.[29]

Tofacitinib

Tofacitinib is a small molecule that inhibits all JAK pathways implicated in the pathogenesis of IBD, especially JAK1 and JAK3.[30] Small molecules have some advantages over biologics, such as their ability to be administered orally. Furthermore, small molecules do not induce a host antibody

response so there is no need for concomitant administration of immunomodulators (such as azathioprine, 6-mercaptopurine, or methotrexate) that carry their own toxicities and AE. Overall, these properties suggest that small molecules are easier to administer, may have a more durable response, and may have a favourable safety profile in comparison to combination of anti-TNF and immunomodulator therapy.

Table 1: Overview of ovel and emerging therapies in inflammatory bowel disease.

Therapy	Mechanism of Action	Route of Administration	Landmark Trials	Currently used in clinical practice (versus investigational)	Used in Crohn's disease?	Used in ulcerative colitis?
Vedolizumab	Anti-α4β7-integrin monoclonal antibody	Intravenous injection, subcutaneous injection	Gemini 1[8] Gemini 2[13] Gemini 3[12]	Yes	Yes	Yes
Tofacitinib	JAK inhibitor (preferentially inhibits JAK1 and JAK3)	Oral	Octave 1[9] Octave 2[9] Octave Sustain[9]	Yes	No	Yes
Ustekinumab	Anti-IL-12/-23 monoclonal antibody	Intravenous injection, subcutaneous injection	UNITI-1[11] UNITI-2[11] IM-UNITI[11] Sands et al.,[10] 2019	Yes	Yes	Yes
Filgotinib	JAK1 inhibitor	Oral	FITZROY[14]	No	Yes	No
Upadacitinib	JAK1 inhibitor	Oral	U-ACHIEVE[15] CELEST[16]	No	Yes	Yes
Guselkumab	IL-23 inhibitor	Intravenous injection, subcutaneous injection	None published thus far	No	No	No
Mirikizumab	IL-23 inhibitor	Intravenous injection, subcutaneous injection	Sandborn et al.,[17] 2020	No	No	Yes
Risankizumab	IL-23 inhibitor	Intravenous injection, subcutaneous injection	Feagan et al.,[18] 2017 Feagan et al.,[19] 2018	No	Yes	No
Etrolizumab	Anti-α4β7 and anti-αEβ7 integrin monoclonal antibody	Subcutaneous injection	Rutgeerts et al.,[20] 2013 EUCALYPTUS[21]	No	No	Yes
Ozanimod	Sphingosine-1-phosphate subtypes 1 and 5 modulator	Oral	TOUCHSTONE[22]	No	No	Yes
Mesenchymal stem cells	Differentiation capacity of stem cells	Intrafistular application, intravenous injection	Garcia-Olmo et al.,[23] 2009 Ciccocioppo et al,[24] 2011 Duijvestein et al.,[25] 2010 Forbes et al.,[26] 2014	No	Yes	No

Results from the Octave Induction 1, Octave Induction 2, and Octave Sustain trials demonstrated the effect of tofacitinib on patients with moderate-to severe-UC.[9] In the Octave Induction 1 and 2 studies, patients were randomised to receive either tofacitinib 10 mg twice daily or placebo for 8 weeks. In the Octave Sustain trial, patients with a response to induction therapy were randomised to tofacitinib at either 5 or 10 mg twice daily or placebo for 52 weeks. In both induction trials, tofacitinib produced a significantly higher rate of clinical remission at Week 8. Similarly, maintenance of remission at 52 weeks was significantly higher in both tofacitinib groups.

Worsening of UC, nasopharyngitis, headache, and arthralgias were the most common AE reported. Serious AE were not more common in the tofacitinib arms. Infection rates were higher in the tofacitinib arms in both induction and maintenance trials. Five patients who had received tofacitinib experienced cardiovascular events. One episode of gastrointestinal perforation occurred in a patient with cytomegalovirus infection on prednisone. The discovery of increased rates of pulmonary embolism and mortality in older rheumatoid arthritis patients with at least one cardiovascular risk factor receiving higher dose tofacitinib[31] led the U.S. Food and Drug Administration (FDA) to issue a black box warning about tofacitinib.[31,32] Tofacitinib should be reserved for patients failing biologic therapy and it is recommended that the dose is reduced to 5 mg twice daily after successful induction with 10 mg twice daily. Results of the effect of tofacitinib in CD have not been as promising as in UC.[33,34]

Ustekinumab

Ustekinumab is a monoclonal antibody against the p40 subunit of the IL-12/-23 receptors. Results from the Phase III trials (UNITI-1, UNITI-2, IM-UNITI) were published after promising results from Phase IIa and IIb trials,[35,36] which consisted of an 8 week induction trial and 44 week maintenance trial in patients with moderate-to-severe CD.[11] The UNITI-1 trial consisted of patients who had primary nonresponse, secondary nonresponse, or AE from anti-TNF agents. The UNITI-2 trial consisted of patients who did not respond to or experience AE from immunosuppressants or glucocorticoids. In both the UNITI-1 and UNITI-2 trials, patients in either ustekinumab arm were more likely to achieve the primary endpoint (clinical remission at Week 6) compared to placebo. Similarly, in the IM-UNITI trial, more patients on ustekinumab were in clinical remission at Week 44, compared to patients on placebo. Rates of AE, including serious AE, were similar across arms in the induction and maintenance trials. Long-term extension trial results have been similarly promising.[37]

In an 8 week induction trial studying ustekinumab in UC, patients were assigned either fixed or weight-based doses of ustekinumab or placebo.[10] Patients that responded to ustekinumab were then randomised to one of two frequencies of ustekinumab or placebo in the 44-week maintenance trial. Patients in both ustekinumab arms of the induction trial were more likely to achieve clinical remission than those given placebo ($p<0.001$ for both comparisons). Patients in both ustekinumab arms of the maintenance trial were significantly more likely to achieve clinical remission than those in the placebo arm. In the induction trial, AE were similar across all three arms, with serious AE highest in the placebo arm. In the maintenance trial, higher rates of AE, including serious AE, were reported in the placebo arm.

EMERGING THERAPIES

JAK1 Inhibitors

Filgotinib

Whereas tofacitinib inhibits all JAK with a preference for JAK1 and JAK3,[30] filgotinib selectively inhibits JAK1 only.[38] In the Phase II FITZROY study, the safety and efficacy of filgotinib was tested in patients with moderate-to-severe CD.[14] In the first 10 weeks, patients were randomised to either filgotinib or placebo. In the following 10 weeks, patients were stratified based on prior clinical response, prior anti-TNF agent exposure, and baseline corticosteroid use, among other considerations, to one of two doses of filgotinib or placebo. More patients in the filgotinib group achieved clinical remission than those in the placebo group in the induction phase of the trial (47% versus 23%; p=0.0077). AE were similar between treatment and placebo arms, but serious AE occurred at higher rates

in the treatment arm, including four patients who developed serious infections. Additional trials studying filgotinib are underway in CD[39,40] and UC.[41,42]

Upadacitinib

Upadacitinib is a JAK inhibitor that selectively binds JAK1,[43] similar to filgotinib. This small molecule has been studied in Phase II trials in both UC and CD.[15,16] Results from the induction trial of the Phase IIb trial U-ACHIEVE, studied upadacitinib in moderate-to-severe UC.[15] All patients in the study had inadequate response to or loss of response to corticosteroids, immunosuppressives, or biologics. The study consisted of two 8-week parts. In the first part, eligible patients were randomly assigned to receive one of four doses of oral upadacitinib or placebo. In the second part, eligible patients were randomly assigned to one of two doses of upadacitinib.

The primary endpoint of clinical remission at 8 weeks was achieved in more patients receiving upadacitinib than those receiving placebo. Of the patients receiving the 7.5 mg dose, 8.5% achieved the primary endpoint. This increased to 14.3% in those receiving the 15 mg dose, 13.5% receiving the 30 mg dose, and 19.6% receiving the 45 mg dose, whereas 0.0% achieved clinical remission with placebo (respective p value comparisons with placebo: p=0.052, p=0.13, p=0.011, and p=0.002, respectively). Fewer patients who had previously failed anti-TNF agents responded to upadacitinib. More patients on upadacitinib demonstrated biologic, endoscopic, and histologic response. Rates of AE were similar between patients receiving upadacitinib and placebo, including serious AE and serious infections. Further studies of upadacitinib in UC are underway.[44,45]

Upadacitinib was studied in moderate-to-severe CD in the Phase II CELEST trial.[16] In the 16-week induction trial, patients were randomised to one of five upadacitinib doses or placebo, stratified by prior anti-TNF use and endoscopic disease severity. After the induction trial, patients were rerandomised to one of two upadacitinib doses or placebo for the 36-week maintenance trial. In the induction trial, the proportion of patients achieving clinical remission, the primary endpoint, or endoscopic remission were not significantly different between groups. In the maintenance trial, numerically, more patients in the 12 mg twice daily group were in clinical and endoscopic remission than the other groups. More AE occurred in the higher dose upadacitinib arms, but the majority were mild or moderate in severity. The most serious AE occurred in the 12 mg twice daily arm. The most frequent AE included worsening CD, urinary tract infection, nausea/vomiting, and headache. Further studies of upadacitinib in CD are in progress.[46-50]

IL-23 INHIBITOR

Guselkumab

Whereas ustekinumab blocks both IL-12 and IL-23 by inhibiting their shared p40 subunit, guselkumab is a more selective antagonist, targeting the p19 subunit of IL-23.[51] IL-23 activates the JAK-signal transducer and activator of transcription pathways (Figure 1).[51] The Th17 pathway is subsequently activated, leading to further production of cytokines such as IL-17, IL-21, IL-22, and IL-26. Guselkumab has already demonstrated efficacy without any serious AE and has been approved for moderate-to-severe plaque psoriasis. No clinical trials have been published yet on this agent; however, one published case report described a female with CD who achieved deep remission with guselkumab.[52] Clinical trials are underway and planned for study in UC and CD.[53-56]

Mirikizumab

Like guselkumab, mirikizumab is a monoclonal antibody that binds the p19 subunit of IL-23. Mirikizumab was studied in a Phase II trial in moderate-to-severe UC.[17] Patients were randomised to one of three doses of intravenous mirikizumab or placebo. Those that responded to mirikizumab at Week 12 were randomised to 200 mg subcutaneous mirikizumab every 4 or 12 weeks through to Week 52. Those that responded to placebo at Week 12 were continued on placebo through to Week 52.

Compared to placebo, more patients in the mirikizumab arms were in clinical remission at Week 12, the primary endpoint; however, these differences were nonsignificant. Significantly more patients receiving mirikizumab had a

clinical response by Week 12 compared to placebo. Significantly more patients in the 50 mg and 200 mg arms achieved endoscopic remission by Week 12. In the maintenance trial, by Week 52, 53.7% and 39.7% of patients given mirikizumab every 4 and 12 weeks, respectively, were in clinical remission, with similar rates between biologic-naïve and biologic-exposed patients. In the induction trial, the most frequent AE were nasopharyngitis, worsening of UC, and anaemia. In the maintenance trial, the most frequent AE were nasopharyngitis, upper respiratory tract infection, arthralgia, and influenza. Further trials are underway studying mirikizumab in UC[57-59] and CD.[60-62]

Risankizumab

Risankizumab also targets the p19 subunit of IL-23. A Phase II, 12-week induction study in patients with moderate-to-severe CD compared intravenous risankizumab to placebo.[18] Patients were randomised to either 200 mg or 600 mg of intravenous risankizumab or placebo, each administered every 4 weeks. Significantly more patients in the risankizumab groups achieved clinical remission at Week 12, the primary endpoint. Higher numbers of patients in the 600 mg compared with placebo group achieved clinical response, endoscopic remission, and deep remission. Mucosal healing, defined as absence of mucosal ulceration, was not achieved at higher rates in the risankizumab groups compared with placebo. Serious AE included worsening of CD and infections (n=3 [risankizumab groups]; n=3 [placebo group]).

Results from an open-label extension study were subsequently published.[19] Of the 44 patients in the open-label extension arm, 71% were in clinical remission at Week 52 and 81% demonstrated a clinical response. Further studies on risankizumab are underway in UC[63,64] and CD.[65-67]

Anti-α4β7 and Anti-αeβ7 Integrin Monoclonal Antibody

Etrolizumab

Etrolizumab is a monoclonal antibody against α4β7 and αEβ7 integrin and thereby prevents leukocyte binding with MAdCAM-1 and E-cadherin, respectively (Figure 2).[37] After promising Phase I results,[20] the Phase II trial (EUCALYPTUS) results were published.[68]

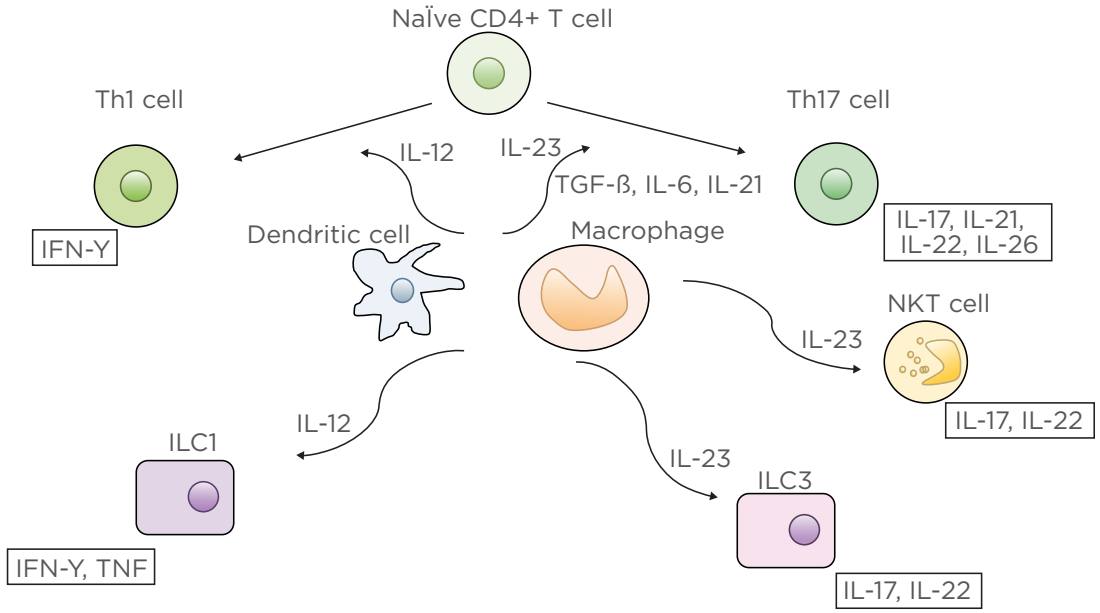

Figure 1: IL-12 and IL-23 differentiation pathways.

CD: cluster of differentiation; ILC: innate lymphoid cells; NKT: natural killer T.

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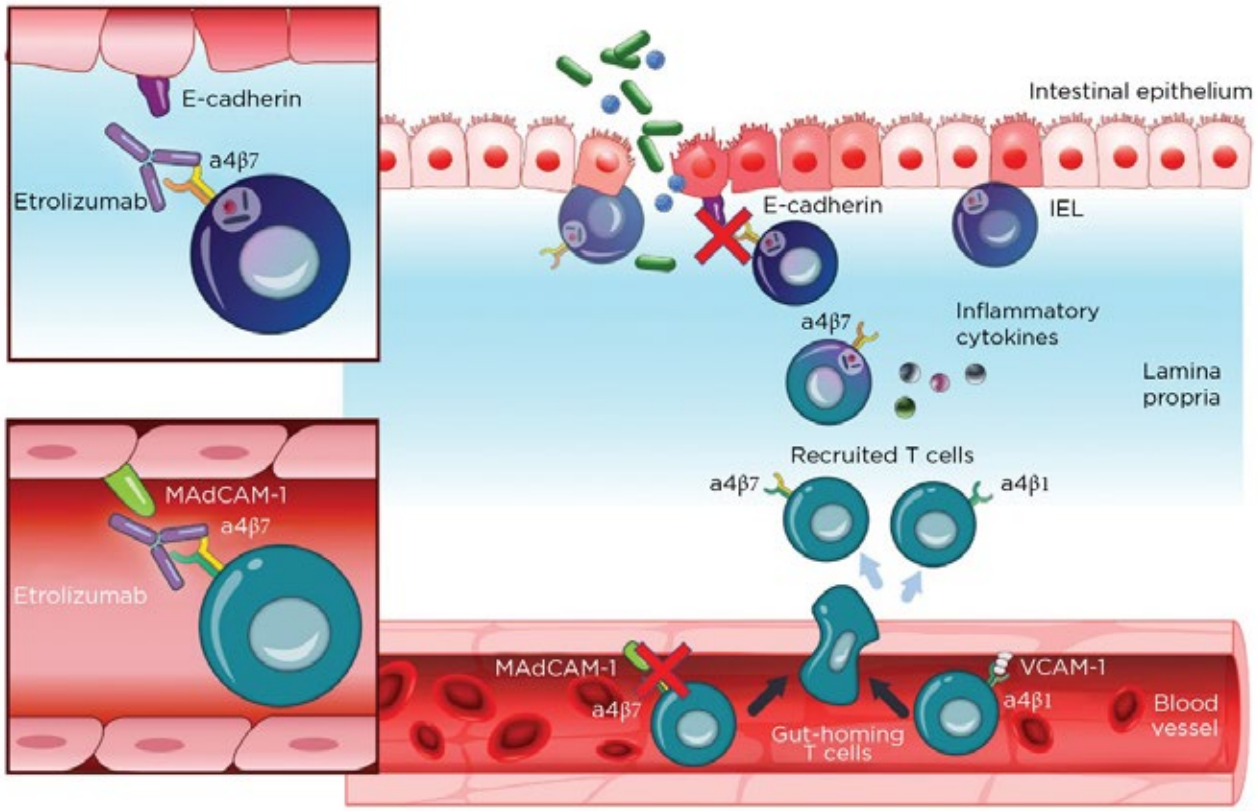

Figure 2: Etrolizumab mechanism of action.

IEL: Intraepithelial lymphocytes; MadCAM-1: mucosal addressin cell adhesion molecule 1; VCAM-1: Vascular cell adhesion protein 1.

From Sandborn et al.,[37] 2020. Creative Commons 4.0 International License (https://creativecommons.org/licenses/by-nc/4.0/).

In EUCALYPTUS, patients underwent randomisation with assignment to one of two doses of subcutaneous etrolizumab or placebo.

At 10 weeks, statistically more patients in the etrolizumab arms were in clinical remission compared to the placebo arm, the primary endpoint (21%, 10%, and 0% in the 100 mg etrolizumab, 300 mg etrolizumab plus loading dose etrolizumab, and placebo group, respectively, [comparisons p=0.0040 and p=0.048]). No significant differences were reported for clinical remission at Week 6, clinical response at Week 10, mucosal healing (defined as a Mayo Endoscopic Subscore 0 or 1) at Week 10, or histopathologic disease severity score. Numerically, more AE were reported in the placebo group. One serious infection was reported in the placebo group.

Further studies are underway, including open-label extension studies in UC (SPRUCE,[69] HIBISCUS I,[70] HIBISCUS II,[71] LAUREL,[72] GARDENIA,[73] HICKORY,[74] COTTONWOOD[75]) and CD (BERGAMOT,[76] JUNIPER[77]).[21]

Sphingosine-1-Phosphate Subtypes 1 and 5 Modulator

Ozanimod

Ozanimod is an oral small molecule that modulates sphingosine-1-phosphate 1 and 5 receptor subtypes. Sphingosine-1-phosphate subtype 1 has been demonstrated to play a key role in lymphocyte trafficking; when antagonised, lymphocytes are no longer able to travel from secondary lymphoid organs into the circulation.[78] The TOUCHSTONE Phase II trial studied ozanimod in moderate-to-severe UC.[22] In the induction phase, patients were randomised to

one of two doses of ozanimod or placebo for 8 weeks. Patients who responded in the induction trial continued, blinded, on the medication for 24 weeks. Those that did not respond during the induction trial were given the option to continue open-label treatment.

Significantly more patients in the 1 mg/day of ozanimod arm achieved clinical remission, the primary outcome, at Week 8 compared to placebo (16% versus 6%; p=0.048). Numerically, more patients in the 0.5 mg/day of ozanimod arm achieved clinical remission at Week 8 compared to placebo (14% versus 6%; p=0.14). Significantly more patients in both ozanimod arms demonstrated mucosal healing and Mayo Endoscopic Subscore 0 or 1 at Week 8, compared to placebo. Numerically, more patients in the ozanimod arms demonstrated histologic remission at Week 8 compared to placebo.

At Week 32, significantly more patients receiving 1 mg or 0.5 mg/day of ozanimod remained in clinical remission compared to placebo (21%, 26%, and 6%, respectively; p=0.01 and p=0.002 compared to placebo). Mucosal healing and histologic remission at Week 32 were achieved in significantly more patients in both ozanimod arms compared to placebo. More AE were reported in the placebo arm, including serious AE and AE leading to drug discontinuation.

Preliminary results from the Phase III trial studying ozanimod in UC[79] have been reported as promising, with significantly increased numbers of patients achieving clinical remission after induction therapy at Week 10 and maintaining remission up to Week 52;[80] published results are pending. Further studies are underway with ozanimod in UC[81-84] and CD.[85,86]

Mesenchymal Stem Cells

Mesenchymal stem cells (MSC) are adult stem cells which lack the immunogenicity required for preconditioning regimens. Trials have been performed using intrafistular autologous adipose-derived stem cells (ASC),[23] intrafistular bone marrow-derived mesenchymal stem cells (bmMSC),[24] and intravenous bmMSC in both fistulising[25] and luminal CD[26] with mixed results. Numerous future studies are underway to evaluate the role of MSC in both CD and UC.[87-90]

CONCLUSION

Here, the authors have given an overview of novel and emerging therapies for use in the management of CD and UC. Given the rates of induction of remission and maintenance of remission with current therapies, future agents with new mechanisms of action are needed. It is promising that primary endpoints of clinical remission are reported in >50% of patients with agents such as mirikizumab and guselkumab, higher rates than achieved by agents currently approved for CD and UC. One network meta-analysis analysing rheumatoid arthritis data suggests that filgotinib is more effective than tofacitinib, with upadacitinib following tofacitinib.[91,92]

Future studies are also required to gain additional knowledge regarding positioning of agents. Personalised medicine or matching optimal medical therapies to patients based on their individual characteristics requires further study, although some predictive characteristics are emerging.[93,94] To date, the only head-to-head trial of biologics compared vedolizumab and adalimumab (the VARSITY trial) and the authors of the study concluded that vedolizumab outperformed adalimumab.[95] In addition to efficacy, the safety profiles of each medication will play a large role in the selection of agents for each patient. Targeted therapies with higher specificty are potentially safer than existing therapies; for example JAK-1 inhibitors have been compared in the rheumatology literature to tofacitinib, a nonselective JAK inhibitor.[96] Furthermore, medications with gut selectivity are likely to have more acceptable long-term safety profiles. Therapies that can be topically administered, such as MSC, are likely to play a significant role in the future management of perianal fistulising disease in CD. Overall, these new therapies for the management of IBD are exciting and are likely to help more patients achieve induction and long-term maintenance of remission with fewer AE.

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Pneumoperitoneum, Pneumothorax, and Pneumoretroperitoneum Post Colonoscopy: A Case report and Review of Literature

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Abstract

Colonic perforation post colonoscopy is rarely seen; however, when coupled with massive pneumoperitoneum in haemodynamically stable patients, a real dilemma for surgeons is created. The decision between watchful waiting versus surgical intervention is the real challenge and while most surgeons will urge for surgical intervention, conservative management on the other hand can be safely applied in selected haemodynamically stable patients.

INTRODUCTION

Colonoscopy is a common and safe procedure commonly used in clinical practice for the investigation and treatment of a multitude of gastrointestinal pathologies, including both benign and malignant conditions.[1] Although rarely seen, this procedure is associated with a risk up to 0.3% of serious complications, such as colonic perforation and bleeding.[2,3] This risk is seen mainly when a therapeutic approach is used during the procedure.[4] Pneumoperitoneum is seen in more than 90% of micro or macrocolonic perforation, and it is defined as free air within the peritoneal cavity. The management dilemma is when the pneumoperitoneum is asymptomatic without signs of peritonitis. Traditionally, antibiotics and surgical management are opted for as first choice in the management of asymptomatic pneumoperitoneum.[3,5] However, conservative management is becoming more common in such complication, especially in haemodynamically stable patients with nonsurgical abdomen. Here, the authors present a case of benign massive pneumoperitoneum associated with retro-pneumoperitoneum, pneumothorax, and subcutaneous emphysema, diagnosed 2 weeks post diagnostic colonoscopy.

CASE REPORT

This is a case of a 64-year-old Caucasian male with comorbid conditions of coronary artery disease, dyslipidaemia, hypertension, and atrial fibrillation who was transferred to the authors institute 2 weeks post screening colonoscopy with severe abdominal distension. At the time of colonoscopy, no risk factors for perforation were documented and no technical challenges were encountered.

During the physical exam, the patient's vitals were stable, with soft but distended abdomen with hypoactive bowel sound and no signs of peritoneal irritation. In addition, decreased bilateral air entry was noted over the lung field on auscultation.

Chest X ray showed pneumothorax and pneumoperitoneum (Figure 1). Kidney, ureter, and bladder X ray (KUB) examination was done in a supine and erected position and showed bowel loop of normal calibres with a large pneumoperitoneum and air fluid levels (Figure 2).

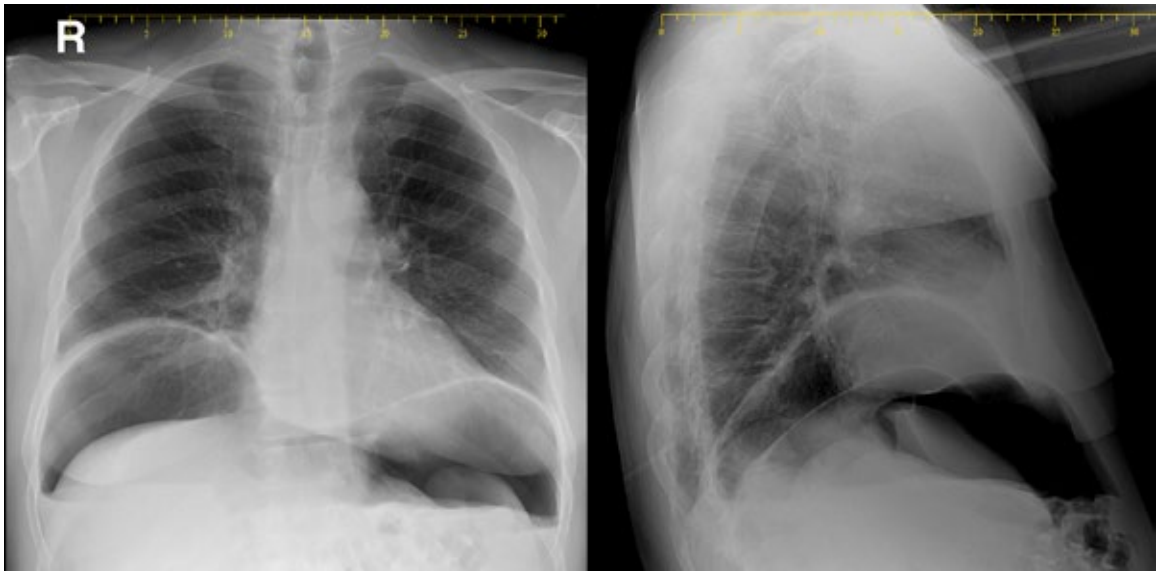

Figure 1: Pneumothorax and pneumoperitoneum.

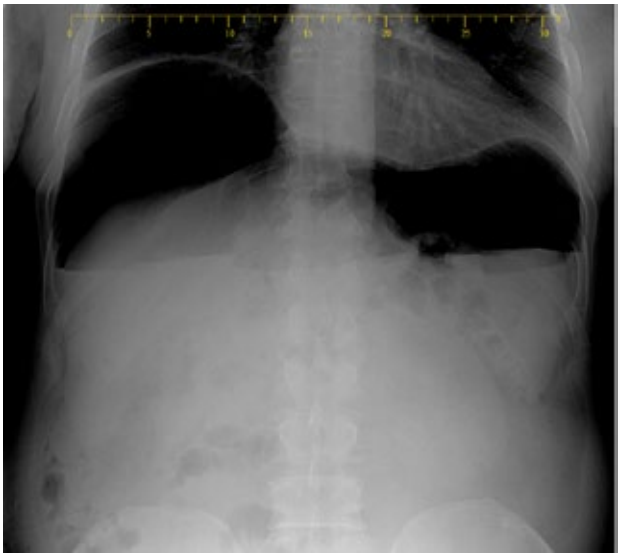

Figure 2: Bowel loop of normal calibres with a large pneumoperitoneum and air fluid levels.

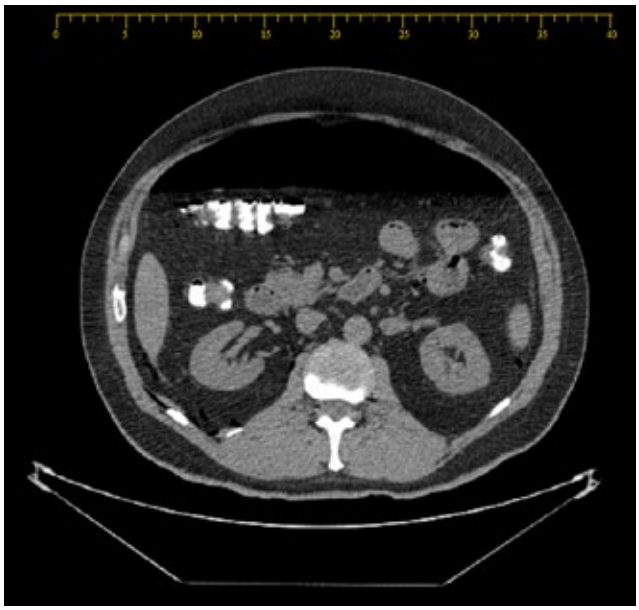

Figure 3: Large pneumoperitoneum in the anterior aspect of the abdomen.

Laboratory tests revealed elevated white blood cell count and C-reactive protein of $16.0x10^3$ cells/L and 26.3 mg/L, respectively.

The patient underwent a chest, abdomen, and superior pelvis CT scan, which revealed large pneumoperitoneum in the anterior aspect of the abdomen, free air in the mesentery close to the spleen and liver, free air close to the lesser curvature of the stomach, a thickened sigmoid, thickening in distal ileal loops with fat streaking, pneumoretroperitoneum, and subcutaneous emphysema. The chest CT scan showed pneumothorax and pneumomediastinum and findings were suggestive of a sigmoid perforation (Figure 3).

The patient was haemodynamically stable and afebrile. The decision was taken for a conservative management backboned by keeping the patient nil by mouth; serial repetition of vitals, physical exam, lab tests, KUB; and intravenous antibiotics (amoxiclav, metronidazole and ciprofloxacin) for a total of 7 days, this regimen was started abroad and continued at the authors institute.

Over the next 3 days, the patient's abdominal distension was improving mildly, and his inflammatory markers (white blood cell, neutrophils, and C-reactive protein) improved towards normalisation. On the other hand, his pneumoperitoneum and pneumothorax were relatively stable over the course of his hospitalisation. After 4 days of hospitalisation, the patient developed low-grade fever of (38.5 °C), while the patient's abdominal physical exam was normal except for distention. This latter fact posed a real dilemma on the origin of the fever, which could be due to lung origin, but any other abdominal cause cannot be ruled out without the diagnostic laparoscopy. Thus, a diagnostic laparoscopy was scheduled aiming to explore the abdominal cavity and at the same time decompress the retained pneumoperitoneum, which would eventually help re-establish the pressure equilibrium between the thoracic and abdominal cavity.

The abdomen was assessed using a 10 mm under-vision trocar then two 5 mm trocars were inserted under direct vision. Perihepatic fluids were identified and then sent to culture and cytology, results for which came back negative for malignancies or bacteraemia. No purulent or faecal materials were detected. Severe inflammatory reaction was noted at the level of the sigmoid with loops of small bowel adherent to the sigmoid, in favour of a contained or walled off sigmoid perforation. The decision was made to drain the abdominal cavity using a 24 French gauge Blake drain placed in the pelvis and near the presumed sigmoid perforation.

On postoperative Day 2, the patient started a full liquid diet, which was tolerated and advances in diet were not made until soft gastric low residue was reached on Day 4 post operation. The patient was discharged home on Day 6 post diagnostic laparoscopy, without antibiotics. The patient opted to repeat his colonoscopy in 6–8 weeks time, as he was staying in the country for medical care only, if his physical exam and follow-up laboratory workup were normal, and at 3 months if any abnormality was noted.

DISCUSSION

The authors review of literature revealed only a few reported cases of massive pneumoperitoneum secondary to colonic perforation from colonoscopy that were managed conservatively. Even rarer, is the delayed presentation of patients with post colonoscopic perforation 2 weeks after colonoscopy. In fact, the frequency of perforations due to colonoscopy ranges from as low as 0.2% when diagnostic purpose is targeted and can reach as high as 2.0% when aiming for therapeutic intent.[3,6] In fact, 9% of the colonoscopic perforations were identified at least 2 weeks after the procedure. In this case, colonic perforation was detected after 14 days. Colonic perforation when coupled with massive pneumoperitoneum in haemodynamically stable patients creates a real dilemma for surgeons nowadays. The decision between watchful waiting versus surgical intervention is the real challenge. While most surgeons will urge for surgical intervention, conservative management on the other hand can be safely applied in selected haemodynamically stable patients. Thus, conservative treatment for massive pneumoperitoneum is suitable based on the patient's symptoms and clinical condition. If the abdominal pain was mild and localised and no severe sepsis or peritonitis was perceived, watchful waiting is adequate.[5] Henceforth, the decision for the trial of a conservative management in the authors' case was made: the patient presented with no signs of peritonitis and was haemodynamically stable.

The picture of a massive pneumoperitoneum can be shocking at the time of diagnosis but understanding the pathophysiology of its occurrence supports the decision of nonsurgical management. In the cases of a viscus perforation enteric contamination occurs and only a small amount of air escapes.[6] However, the picture of massive pneumoperitoneum is mainly encountered in nonsurgical cases since no signs of peritonitis or sepsis are present and consequently more air enters the peritoneal cavity.[6]

To the authors' knowledge, no defined algorithm exists at the moment for the management of these clinical scenarios. But what is undebatable is that the most significant aspect that the physician should base their decision upon is the general condition of the patient. Indeed, conservative management is successful in cases of massive pneumoperitoneum, and close monitoring of the patient's vitals and serial abdominal physical exam are enough. Alarming signs such as peaks of fever and increased intensity of abdominal pain shall urge the surgeon to reconsider their decision for a conservative management.

CONCLUSION

In conclusion, management of massive pneumoperitoneum is always challenging in haemodynamically stable patients and treatment should consider a balance between conservative management versus surgical intervention.

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Achalasia Cardia: A Comprehensive Review

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Abstract

Achalasia cardia is the best characterised oesophageal motility disorder. It is characterised by progressive ganglion cell degeneration in the oesophageal myenteric plexus, which results in impaired lower oesophageal sphincter (LES) relaxation upon swallowing and aperistalsis in the distal smooth muscle segment of the oesophagus. The usual presenting features are dysphagia to both liquids and solids from onset, regurgitation of undigested food, retrosternal pain, heartburn, and weight loss. Initial investigations include upper gastrointestinal (GI) endoscopy and timed barium oesophagogram, whereas high resolution manometry is diagnostic. Therapy in achalasia cardia is directed towards biochemical or mechanical reduction in LES pressures. If candidates are fit for surgery, pneumatic dilatation, peroral endoscopic myotomy, and laparoscopic Heller's myotomy are the mainstays of therapy that act by mechanical disruption of LES. On the other hand, botulinum toxin and pharmacotherapy (nitrates and calcium channel blockers) act by biochemical reduction of LES and are reserved for surgically unfit patients with limited life expectancy because of their short-lived efficacy. Oesophagectomy is reserved for treating refractory longstanding cases, who have previously failed multiple therapies.

INTRODUCTION

Achalasia cardia is a rare oesophageal motility disorder caused by autoimmune neurodegeneration of the oesophageal myenteric plexus.[1] Although rare, it is the most common and best characterised oesophageal motility disorder. The primary distinction from other motility disorders (e.g., Jackhammer oesophagus and distal oesophageal spasm) is the failure of lower oesophageal sphincter (LES) relaxation in achalasia. Therefore, most of the therapies are directed towards reduction in LES pressures. Manometrically, achalasia cardia can be divided into three subtypes that aid treatment decision-making and hence have prognostic significance.[2,3] There has been renewed interest in this motility disorder in the past few years with the advent of third space endoscopy, such as peroral endoscopic myotomy (POEM), which has revolutionised the endoscopic management of achalasia.[4] In this review, the authors discuss the epidemiology, pathogenesis, diagnosis, and treatment of achalasia cardia.

Epidemiology

Achalasia is equally common in both sexes. Most commonly diagnosed between 40 and 60 years of age, achalasia can present in

any age group.[3] Most of the epidemiological data is derived from retrospective studies as population-based studies are scarce because of the rarity of achalasia.[5] Because of its rarity and chronicity, the prevalence is much higher than the incidence of achalasia. According to the Dutch healthcare insurance data from 2018, the incidence and prevalence of achalasia were 2.2 per 100,000 population per year and 15.3 per 100,000 population, respectively.[5] Similarly, Asian data from Korea showed incidence and prevalence of 0.4 per 100,000 population per year and 6.3 per 100,000 population, respectively, in 2014.[6] According to these studies, the incidence of achalasia is increasing.[3]

Aetiopathogenesis

Autoimmune progressive degeneration of ganglion cells in the oesophageal myenteric plexus in genetically susceptible individuals (human leukocyte antigen [HLA]-DQ variants DQA1*0103 and DQB1*0603) is the most plausible pathogenetic event leading to achalasia, according to current available evidence.[7] There is a preferential loss of inhibitory nitrinergic neurons, which secrete nitric oxide and vasoactive intestinal peptide, and variable a loss of excitatory cholinergic neurons, which secrete acetylcholine, in oesophageal smooth muscles, leading to incomplete LES relaxation and failure of peristalsis.[8] The triggering factor for ganglion cell loss is presumed to be latent/chronic viral infections such as herpes simplex virus 1.[9] Autoimmune degeneration is mediated by both cytotoxic T cells (cell-mediated immunity) and antibodies to enteric neurons and complement activation (humoral immunity). Achalasia cardia is associated with other neurodegenerative diseases like Parkinson's disease, as evidenced by the presence of Lewy bodies in ganglion cells.[10] Achalasia, like oesophageal dysmotility, can be caused by ganglion cell degeneration by *Trypanosoma cruzi*, which causes Chagas disease (endemic in South America).[11] The combination of achalasia, alacrima, and adrenal insufficiency is known as Allgrove syndrome, or triple A syndrome, which is a rare autosomal recessive disorder.[12]

DIAGNOSIS

History and Clinical Examination

Dysphagia to both solids and liquids from the onset (occurs in 85–91% of patients) is the most common presenting feature of achalasia, as liquids require better neuromuscular co-ordination than solids for oesophageal emptying. Postures like raising the arms in an erect position increase the intraoesophagael pressure and propel food in the aperistaltic oesophagus, as the oesophagus is compressed between the spine and the manubrium sterni. Regurgitation of undigested food (occurs in 75–91% of patients) is the second most common presenting symptom. Food is regurgitated prior to reaching the stomach, unlike in gastroesophageal reflux (GERD) or gastric outlet obstruction. Retrosternal chest pain and heartburn can be seen in 40–60% of patients, which often leads to misdiagnosis as GERD and a delayed diagnosis of achalasia. Fermentation of undigested carbohydrate produces lactate and causes heartburn.[13,14] Chest pain is least responsive to treatment compared to other symptoms but it can resolve spontaneously, unlike others.[15] Weight loss can occur but it is not as substantial as in mechanical causes of dysphagia (e.g., oesophageal cancer or stricture). The Eckardt score is based on the degree of dysphagia, regurgitation, chest pain, and weight loss, and is used to evaluate treatment efficacy in achalasia.[16] Cough and fever caused by aspiration pneumonia (8–10%) can be one of the presenting symptoms of achalasia.[14] Another rare but noteworthy symptom in achalasia is impaired belching caused by compression of the membranous trachea by a dilated oesophagus and inadequate relaxation of the upper oesophageal sphincter.[17] Clinical examination is usually unremarkable. Few patients may have emaciation and oral ulcerations caused by regurgitation. Diminished breath sounds, dull percussion notes, and crepitations in areas of consolidation can be found in cases of aspiration pneumonia.[14]

INVESTIGATIONS

Upper GI endoscopy and timed barium oesophagogram are the initial investigations to rule out mechanical obstruction. High resolution manometry (HRM) is diagnostic

and helps to classify achalasia.[18] The principal differential diagnoses of achalasia are GERD, pseudoachalasia, other oesophageal motility disorders, and mechanical dysphagia, which can be differentiated based on the investigations above. (Table 1A).

Upper Gastrointestinal Endoscopy

Upper GI endoscopy helps to rule out mechanical dysphagia caused by oesophageal malignancy and stricture. Endoscopy in achalasia shows a dilated and tortuous oesophagus (Figure 1A), intermittent tertiary contractions caused by spontaneous contractions of the oesophageal smooth muscles, and undigested food or liquid. The oesophageal mucosa is usually normal, but gastric stasis can cause erythema/ulceration and oesophageal candidiasis. A pulsion-type oesophageal epiphrenic pseudodiverticulum can be seen, which makes endoscopic therapy challenging. The contracted LES can be traversed with a gentle endoscope pressure unlike in malignancy/strictures.[14,19]

Timed Barium Oesophagogram

Timed barium oesophagogram (TBE) is the imaging of choice in achalasia. After swallowing 100–250 mL of barium (45% weight/volume) over 15–20 seconds, an X ray is performed at 1, 2, and 5 minutes.[20] Oesophageal emptying is evaluated by the height and width of the remaining barium column in the oesophagus at 1, 2, and 5 minutes (Figure 1B). Delayed emptying of the barium from the oesophagus, tertiary contractions, and bird-beak appearance on the X-ray are the characteristic features. Post-treatment TBE is compared to pretreatment TBE to assess response to therapy. In late stages of achalasia, megaoesophagus (oesophageal diameter: >7 cm) and sigmoid oesophagus (dilated, tortuous oesophagus) can be seen, which implies decompensated disease poorly responsive to therapy.[3] Oesophageal epiphrenic diverticulum can also be found, albeit rarely, on barium oesophagograms in association with achalasia. [19]

High Resolution Manometry

HRM has higher sensitivity and reproducibility than conventional oesophageal manometry and hence has replaced it for diagnosis and classification of achalasia. Achalasia can be classified into three subtypes according to the Chicago classification version 3.0.[2] Integrated relaxation pressure of more than an upper limit of normal with 100% failed peristalsis differentiates achalasia from other motility disorders (e.g., Jackhammer oesophagus or distal oesophageal spasm). In Type I AC, there is no oesophageal contractility or pressurisation. It represents late-stage disease with a dilated, atonic oesophagus caused by minimal oesophageal smooth muscle contractility (Figure 1C). Type II AC is characterised by panoesophagael pressurisation (in >20% swallows) between the upper and lower oesophageal sphincter, caused by disorganised oesophageal neuromuscular activity, which is indicative of intact oesophageal contractility (Figure 1D). [2,3] Thus, Type II AC represents the early stage of disease and is most responsive to pneumatic dilatation (PD).[21] Type II achalasia is also the most common subtype. Type III AC is least common and least responsive to therapy, and is characterised by premature contractions (distal latency <4.5 seconds in >20% swallows) and segmental pressurisation of the distal oesophagus (Figure 1E).[22]

OTHER INVESTIGATIONS

As part of the work-up for endoscopic/surgical myotomy requiring general anaesthesia, complete blood count, serum creatinine, and electrolytes, liver function tests and thyroid profiles can be performed. Chest X-ray helps to identify aspiration pneumonia and CT of the chest and endoscopic ultrasound (EUS) can be useful to rule out pseudoachalasia. Marked (>10 mm), asymmetric lower oesophageal wall thickening on EUS suggest underlying malignancy.

Management

Symptomatic relief of dysphagia and associated complications are the goals of achalasia treatment. As pathophysiology is poorly understood, there is no currently available treatment directed towards pathogenetic factors. Treatment is guided by surgical risk of the patient and achalasia subtype.[3] In patients with low surgical risk, pneumatic dilatation, laparoscopic Heller's myotomy (LHM), or POEM are the mainstays of treatment. Botulinum toxin (BT)/pharmacotherapy is reserved for patients with high surgical risk/limited life expectancy.[3]

Table 1: A) Comparison of diagnostic modalities; **B)** treatment options; and **C)** various guidelines in achalasia cardia.

A) Comparison of diagnostic studies in achalasia cardia			
	Upper gastronintestinal endoscopy	**Timed barium oesophagogram**	**High-resolution manometry**
Sensitivity	Identify one-third of patients in early stage Sensitivity increases with stage of disease	Identify two-thirds of patients in early stage Sensitivity increases with stage of disease	Sensitivity >95% Few patients may show changes of diffuse oesophageal spasm in early stages
Advantages	1. Rules out mechanical dysphagia 2. Helpful in pseudoachalasia where manometric/radiographic features may mimic achalasia	1. Assessment of oesophageal emptying and EGJ morphology. 2. Helpful in cases where manometry results are equivocal 3. Enable achalasia severity assessment and treatment outcome evaluation	1. Gold standard for diagnosis 2. Helps in classifying achalasia subtypes which is useful in predicting response to therapy
Disadvantages	1. Poor sensitivity (may be normal in early cases) 2. Can only suggest achalasia, needs confirmation by other tests	1. May miss one-third of early cases of achalasia 2. Other motility disorders and mechanical dysphagia can mimic radiographic features of achalasia	1. Mechanical obstruction can cause impaired EGJ relaxation and aperistalsis on manometry mimicking achalasia. 2. Assessment of lower oesophageal sphincter parameters can be difficult in cases with hugely dilated esophagus, precluding placement of catheter beyond EGJ
B) Comparison of therapeutic options in management of achalasia (in candidates fit for surgery)			
	Pneumatic dilatation	**Laparoscopic Heller's myotomy**	**Peroral endoscopic myotomy**
Overall treatment efficacy	44–84% (Type II best >Type I>Type III) Poor in young male (aged <40 years), Type I/III achalasia	57.0–89.3% (Best in Type II)	75–97% (Better than other modalities for Type III with long myotomy)
Follow-up data available	≥5 years	≥5 years	1–3 years
Incidence of posttreatment GERD	2–3%	2–33% (reduced substantially by fundoplication)	20–54% (>80% are responsive to PPI)
Limitations	Many patients require redilatation (one-third)	Results are suboptimal in sigmoid Oesophagus and Type III achalasia	High rates of GERD Requires expertise in third-space endoscopy
Complications	Oesophageal perforation (3–5%), haematoma formation, diverticula formation	Insufflation-related adverse events, bleeding (early and delayed), mucosal perforation (2.6%), GERD	Oesophageal perforation (1–7%), recurrent dysphagia caused by incomplete myotomy (3–10%), GERD (2–26%), postvagotomy diarrhoea/dumping syndrome (caused by division of the vagus nerve) and splenic injury (1–5%)

Table 1 continued.

C) Comparison of various guidelines for achalasia			
	Seoul Consensus 2019[3]	**ESGE guidelines[69]**	**ASGE guidelines[68]**
Choice of treatment	PD/LHM as initial treatment, POEM outcomes comparable to LHM, POEM as first-line in Type III achalasia	Based on patient characteristics and preference, possible side effects, expertise (comparable efficacy of PD, LHM, and POEM), and manometric subtypes	Treatment based on type of achalasia, expertise, and patient preference LHM, PD, and POEM: all are effective modalities. For Type I/II, LHM and PD are comparable
Role of botulinum toxin	For patients in whom general condition renders unsuitable for surgery	Reserved for surgically unfit patients and in whom definitive treatment is deferred	Recommends against use of botulinum toxin as definitive therapy, only for candidates not suitable for definitive therapy
Post-POEM reflux	Acid suppressive therapy for symptomatic patients/ erosive oesophagitis	Follow-up endoscopy recommended. Symptomatic patients with normal endoscopy should undergo time barium oesophagogram, empirical PPI, and/or 24-hour pH monitoring, lifelong PPI for oesophagitis>Grade A	Counsel patient regarding higher risk of GERD with POEM compared to PD/LHM, manage reflux by measuring oesophageal acid exposure, long-term PPI, and surveillance endoscopy
Comparative efficacy of POEM and LHM	LHM and POEM comparable in treatment naïve, POEM better in Type III	LHM and POEM comparable efficacy, consider age and achalasia subtype to decide treatment	Comparable in Type I/II, POEM better in Type III
Management of Type III achalasia	POEM>LHM because of provision of extended myotomy	POEM appears to be superior to LHM	POEM preferred
Rescue treatment in failed myotomy (POEM/ LHM)	Rescue treatment after failed endoscopic treatment (PD/POEM) and failed LHM	LHM failure: PD/POEM/ redo LHM POEM failure: Re-POEM/ LHM/PD	PD or redo myotomy (same or alternative myotomy technique such as POEM/LHM)

ASGE: American Society for Gastrointestinal Endoscopy; EGJ: oesophagogastric junction; ESGE: European Society of Gastrointestinal Endoscopy; GERD: gastroesophageal reflux; LHM: laparoscopic Heller's myotomy; PD: pneumatic dilatation; POEM: peroral endoscopic myotomy; PPI: proton-pump inhibitors.

Botulinum Toxin

The rationale of using BT in achalasia is because of the associated blockade of acetylcholine from the presynaptic cholinergic neurons, which are relatively preserved in comparison to the selective loss of inhibitory nitrinergic ganglion cells in achalasia.[23,24] During endoscopy, 100 units of BT powder is dissolved in sterile saline solution and 25 units each is injected with a sclerotherapy needle at 1 cm above the Z line/squamocolumnar junction into all four quadrants. Doses >100 units have not shown higher efficacy. In one-third of patients, LES pressure decreases and in two-thirds dysphasia is improved.[25] The effect of therapy is short lived because of the growth of new cholinergic neurons. Hence, 50% of patients require reinjection after 6–12 months. Repeat injections can be technically difficult because of fibrosis from prior injections. Therefore, BT is reserved for patients with high surgical risk and limited life expectancy. BT is usually safe,

although side effects such as oesophageal perforation, mediastinitis, and heartburn/chest pain has been reported.[26]

Pharmacological Therapy

Although several pharmacological agents like calcium channel blockers, nitrates, anticholinergics, phosphodiesterase inhibitors, and β agonists have been tested in achalasia, most of them provide short-lived benefits at most, with risk of developing tolerance on continued treatment as well as potential side effects.[27] Most of the agents do not improve oesophageal peristalsis except anticholinergic cimetropium bromide, which is not widely available and seldom used.[28] Most commonly used agents are calcium channel blockers (nifedipine) and nitrates (isosorbide dinitrate). Doses of isosorbide dinitrate 5–10 mg sublingually 10–15 minutes prior to every meal relaxes LES pressure by 66% for 90 minutes. Headache is a common side effect when using nitrates. Nifedipine 10 mg sublingually 10–15 minutes premeal relaxes LES by 30–40% for 60 minutes. Peripheral oedema, orthostasis, and headache are common side effects of nifedipine.[29]

Pneumatic Dilatation

PD is one of the recommended initial treatments for achalasia and is widely performed across various centres.[3] Rigiflex™ balloon dilator (Microvasive, Milliford, Massachusetts, USA), available in three sizes: 30, 35, and 40 mm, is used for performing PD. Initially, the 30 mm balloon is used, followed by progressively larger balloons (the graded approach).[30,31] After index dilatation by the graded approach, repeated dilatations on follow-up for recurrent symptoms is known as the 'on demand approach'. After overnight fasting, the procedure is performed under fluoroscopic guidance with conscious sedation. A novel technique under endoscopic guidance without fluoroscopy has also been described.[32] After passing a guidewire into the stomach by endoscopic guidance, the endoscope is withdrawn into the gastroesophageal junction (GEJ) and the length from the incisors to the GEJ is noted along the length of the endoscope. The Rigiflex balloon is passed over the guidewire corresponding to the measured distance. Radiographic contrast injection can also be done to mark the GEJ. The Rigiflex balloon is then placed across the GEJ under fluoroscopic guidance and is inflated with air to 10–15 psi until the balloon waist disappears.

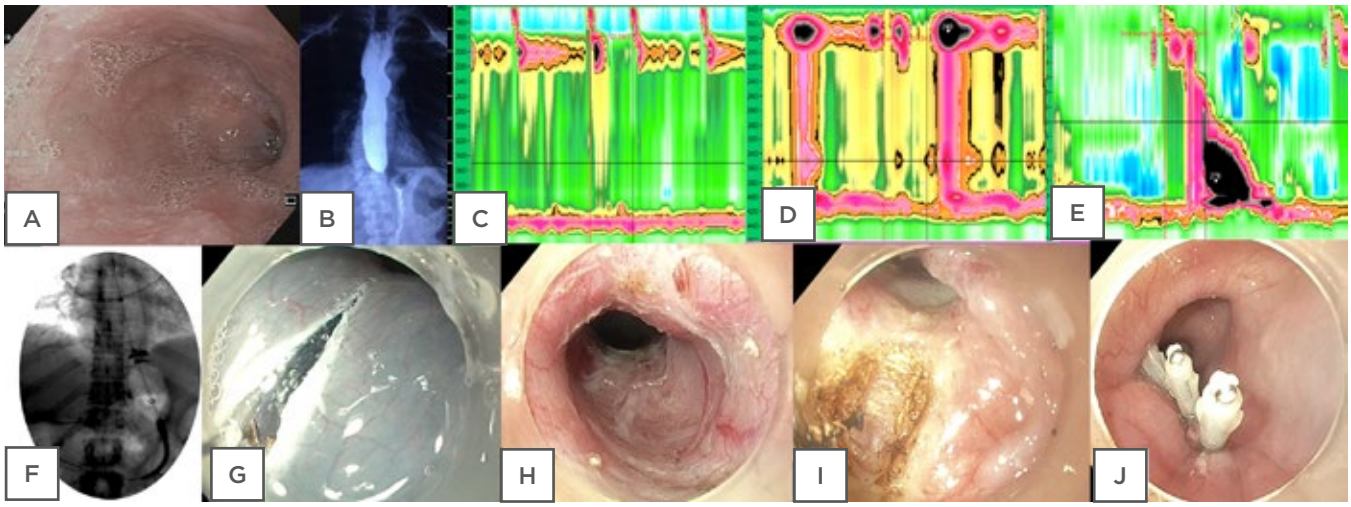


Figure 1: Diagnostic investigations and treatment modalities in achalasia.

A) Endoscopy showing a dilated, tortuous oesophagus in a case of achalasia. **B)** Timed barium oesophagogram at 5 minutes in a case of achalasia cardia showing retention of barium in the oesophagus. **C)** High-resolution manometry picture of Type I achalasia. **D)** High-resolution manometry picture of Type II Achalasia. **E)** High-resolution manometry picture of Type III Achalasia. **F)** Pneumatic dilatation in achalasia by Rigiflex™ balloon dilator (Microvasive, Milliford, Massachusetts, USA). **G)** Mucosal incision in peroral endoscopic myotomy (POEM). **H)** Submucosal tunneling in POEM. **I)** Circular myotomy in POEM. **J)** Closure of mucosal incision in POEM.

The waist of the balloon is seen between the two crus of the diaphragm and radiopaque marks can be seen in the balloon catheter in Figure 1F. Pressure is maintained for 1 minute. Waist obliteration, blood staining of the balloon, chest pain, and mucosal tear/widening of GEJ on postdilatation endoscopy confirms adequate dilatation.

Oesophageal perforation (3–5%), haematoma formation, and diverticula formation are the known adverse events.[33] Tachycardia and/or persistent chest pain persisting for >4 hours are indicators of probable perforation and warrant a contrast eosophagogram. Conservative treatment with antibiotics and parenteral nutrition is warranted for small perforations, whereas urgent thoracotomy and repair is required if there is large perforation with free flow of contrast into the mediastinum. This is the reason why only patients with low surgical risk should be subjected to PD.[33,34] Incidence of GERD post-PD is approximately 2–4%.[35] Poor predictors of treatment with PD are age <40 years, chest pain, and Type III achalasia. Response rate for chest pain is approximately 50%.[35] In trials comparing BT with PD, the safety and cost effectiveness of BT is offset by the requirement of repeated injections.[36] According to a meta-analysis of randomised controlled trials (RCT), PD was comparable with LHM in regard to efficacy, except in young males of whom 24% required redilatation, compared to 14% with LHM.[37,38] In a recent RCT, PD was shown to have a significantly lower success rate (54%) at 2 years in comparison to POEM (92%).[38] The response rate of PD in the recent RCT would have increased by 76% if the 40 mm balloon was used instead of the 30–35 mm.[38]

Peroral Endoscopic Myotomy

POEM is a natural orifice transluminal endoscopic surgery that uses submucosal endoscopy and has revolutionised endoscopic treatment of achalasia.[4] It is useful in treatment naïve, treatment failure, and Type III achalasia. General anaesthesia with endotracheal intubation and carbon dioxide insufflation is used for the procedure.[39] Mucosal incision, submucosal tunnel creation, myotomy of oesophageal circular muscles, and closure of mucosal incision are the principal four steps of performing POEM (Figure 1G-1J).[40] After injecting indigo carmine diluted with normal saline at approximately 13 cm proximal to GEJ, a 2 cm longitudinal incision is made anteriorly (at '1 o'clock') or posteriorly (at '5–6 o'clock') with the use of a triangular tip (Figure 1G). The choice of anterior or posterior POEM depends on the operator/clinical scenario and data from RCT and meta-analysis have shown comparable results with shorter time for the posterior approach.[41-46] In redo myotomy/distorted anatomy, greater curvature myotomy (at '8 o'clock') can be performed. However, greater curvature myotomy is not popular as it leads to disruption of the 'angle of HIS', which is a predisposition to GERD. An endoscope with a transparent cap is inserted into the submucosal tunnel and extended by injection and cautery, which should be around one-third of the oesophageal circumference and extend 3 cm distally to the GEJ (Figure 1H). The mucosal layer is preserved by keeping the endoscope close to the circular muscle layer. Myotomy of circular muscles is performed by starting at 2–3 cm distal to the mucosal entry using a triangular tip knife until the longitudinal muscles are visible. This is continued between circular and longitudinal muscle fibres, up to 2–3 cm beyond GEJ (Figure 1I). Longer myotomy (>4 cm) can lead to severe erosive oesophagitis.[47] Mucosal incision is closed by applying clips (Figure 1 J). Current guidelines do not recommend antibiotic lavage prior to closure of the mucosal incision.[48] A contrast oesophagogram is carried out at postoperative Day 1 to exclude a possible leak and to evaluate the treatment response by seeing adequacy of barium emptying. Patients tolerating an oral diet, in whom contrast oesophagogram has shown no leak, can be started on a liquid diet on postoperative Day 1, followed by a regular diet on subsequent days.[40] The initial clinical success and intermediate-term efficacy after 2 years are 82–100% and 78–91% respectively.[49-51]

Various adverse events (0.5–3.3% of cases) with POEM include insufflation-related events (pneumoperitoneum: 6.8%; pneumomediastinum: 1.1%; and mediastinal and subcutaneous emphysema: 7.5%); bleeding, either early or delayed; and mucosal perforation in 2.6%.[52] Insufflation-related adverse events can be minimised with extra low-flow carbon dioxide. A tense pneumoperitoneum (with high end-tidal carbon dioxide) can be treated with decompression by a Veress needle.[40]

Minor bleeding is treated with a coagrasper or electrocautery knife, whereas delayed bleeding (0.7% of cases) may require re-entry into the tunnel to coagulate the bleeding vessel.[53] The risk factors for mucosal perforation are previous myotomy, submucosal fibrosis, mucosal oedema, and a long tunnel >13 cm. Closure of mucosal perforation by clips and/or Endoloops® (Johnson & Johnson, New Brunswick, New Jersey, USA), fibrin glue, OverStitch™ Endoscopic Suturing (Apollo Endosurgery, Austin, Texas, USA), or fully covered metal stents have been described.[54] The prevalence of increased oesophageal acid exposure, reflux oesophagitis, and GERD symptoms after POEM ranges from 13–58%, 18–65%, and 17–40%, respectively.[55] Patients should be counselled for increased risk of GERD post-POEM. However, most of the GERD after POEM are mild, asymptomatic, and proton-pump inhibitor responsive. An endoscopy should be performed at follow-up to check for reflux oesophagitis. If present, proton-pump inhibitors are the first line of management. If symptoms of reflux are present without changes of oesophagitis on endoscopy, 24 hour pH monitoring can be performed.[3] Novel modifications of POEM by addition of fundoplication (POEM-F), such as in LHM, has been shown to reduce reflux in pilot studies.[56] However, the need for fundoplication to treat GERD post-POEM is very low. Increased procedure time, cost, and uncertain durability are the drawbacks of POEM-F. Preservation of sling fibres, by identifying two penetrating vessels at the distal end of myotomy, have shown to reduce the degree of oesophagitis.[57]

Two recent RCT have demonstrated the efficacy of POEM to be superior to PD and noninferior to LHM.[58,59] In Type III achalasia, results of POEM are more successful than LHM because of the ability to perform long myotomy based on the length of the spastic distal segment of the oesophagus.[3] POEM is preferred over LHM in patients with a sigmoid oesophagus and other spastic motility disorders.[60]

Laparoscopic Heller's Myotomy

LHM is the first-line surgical therapy for achalasia; it has a response rate of 90–97% with recurrent dysphagia in 3–10% of patients. Laparoscopic incision is made anteriorly from 6 cm above the GEJ to 3 cm beyond, preserving cardio-oesophageal fat and the anterior vagus nerve. Extended gastric myotomy (3.0 cm) is associated with lower rates of repeated surgery and hence is preferred over standard gastric myotomy (1.5 cm). Post-LHM GERD with extended myotomy can be minimised by concurrent fundoplication (posterior Toupet fundoplication at 270° is a better antireflux procedure than anterior Dor fundoplication at 180°). The minimally invasive, laparoscopic approach is associated with shorter hospital stays, reduced postoperative pain, and lower disability. The laparoscopic approach is preferred over the thoracoscopic approach because of the shorter operating time and lower probability of conversion to open myotomy.

Adverse events with LHM include oesophageal perforation (1–7%) caused by inadvertent mucosal injury, recurrent dysphagia caused by incomplete myotomy (3–10%), GERD (2–26%), postvagotomy diarrhoea/dumping syndrome caused by division of the vagus nerve, and splenic injury (1–5%). In sigmoid oesophagus and Type III achalasia, the results of LHM are suboptimal. LHM has equal efficacy compared to PD with greater durability in young males.

POEM was noninferior to LHM with regard to clinical success at 2 years (83.0% and 81.7%, respectively) and associated with lower risk of serious adverse events (2.7% versus 7.3%, respectively) but higher incidence of reflux oesophagitis (44% versus 29%, respecively) according to a recent RCT.[59]

INTERDISCIPLINARY AND NUTRITIONAL APPROACH IN MANAGEMENT OF ACHALASIA

A multidisciplinary approach to achalasia management is crucial and should include gastroenterologists, surgeons and radiologists, dieticians, nurses, and actively participating family members.[60] Highly individualised dietary management modifying food texture and fluid viscosity can help avoid malnutrition. Family members have a crucial role in encouraging adherence to dietary modifications. Malnourished patients awaiting surgery and those with poor oral intake and high risk of aspiration should be treated with tube feeding to reduce postoperative complications. In rare cases of end-stage

achalasia, radiologic percutaneous gastrostomy feeding is effective. Intrajejunal feeding may be required in cases where pulmonary aspiration occurs with gastrostomy feeding.[61]

PROGNOSIS AND LONG-TERM COMPLICATIONS

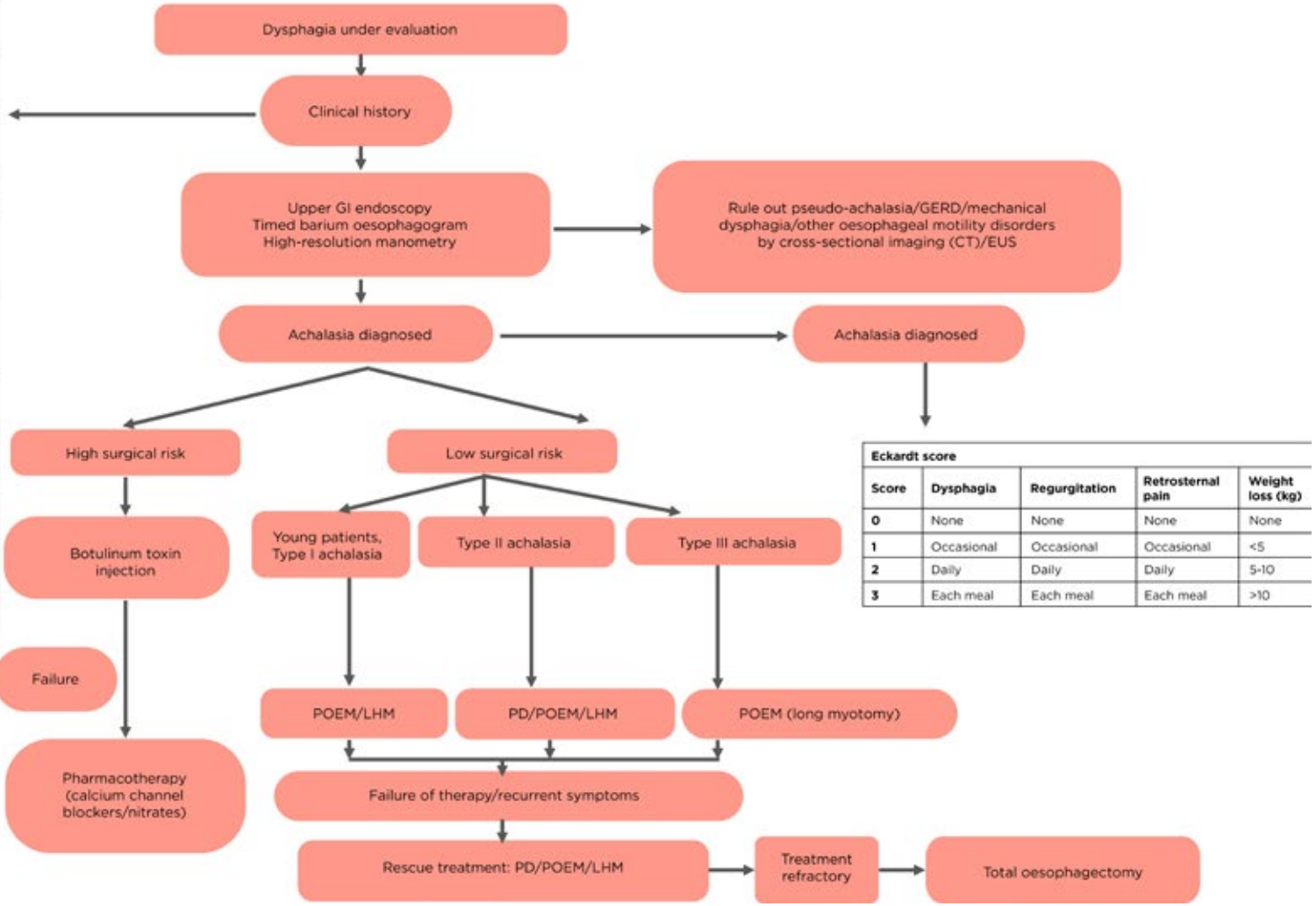
Achalasia is a chronic neurological disorder which is not cured by LES-directed therapies and hence requires lifelong follow-up. Long-term complications include development of end-stage achalasia/megaoesophagus or oesophageal squamous cell carcinoma. Progressive dilation of the oesophagus is developed in 10–15% of patients, which leads to megaoesophagus/end-stage achalasia even posttreatment, and eventually 5% require oesophagectomy.[62] The rate of squamous cell cancer is 1 in 300 patient-years, but surveillance endoscopy is not routinely recommended (number needed to detect one cancer is 400 endoscopies).[63] However, after longstanding disease (10–15 years), a 3 yearly follow-up is recommended by many experts.[64]

Efficacy of current endoscopic/surgical modalities (POEM, PD, LHM) decreases over time. After 5 years of initial treatment, 18–21% and 25–35% patients require retreatment in LHM and PD, respectively.[65,66] After POEM, at 49 months of median follow-up, 13% of patients have recurrence;[67] more long-term data is required for POEM. These patients can be successfully treated with other modalities, and a small proportion will require oesophagectomy.

CONCLUSIONS

Achalasia can be diagnosed with appropriate clinical history as it is often misdiagnosed as GERD. Endoscopy and barium swallow can be helpful to rule out mechanical dysphagia. HRM is diagnostic and useful in classification, which affects prognosis and guides treatment. Treatment of achalasia should be individualised and based on surgical risk and achalasia subtype according to various guidelines (Table 1B and 1C).[3,68,69] Patients with high surgical risk should undergo BT/pharmacotherapy. PD, LHM with fundoplication, and POEM are options for patients with low surgical risk. In young patients (<40 years) with Type I achalasia, POEM/LHM should be the first option of treatment as response rates to PD is low. In Type II AC, PD can be used as an initial treatment option (with LHM/POEM), as results of PD are best in Type II AC. POEM with extended myotomy is recommended for Type III achalasia (Figure 2).[3,70] Upon failure of therapy, either of the three modalities can be used. Oesophagectomy should be reserved for patients with longstanding disease who are fit for surgery and have had repeated failure to various therapies.

	Esophageal motility disorder	Esophageal motility disorder
Duration	Longstanding	Short in malignant
Course	Intermittent	Progressively increasing
Relation with food and posture		
Relation with type of food	Both liquids and solids from onset	Solids initially then liquids later on
Relation with posture	Decreased with raising arms and erect position	None
Relation with temperature of food	More in extreme temperatures (hot and cold)	None
Associated symptoms		
Regurgitation	Common	Unusual
Chest pain	Episodic pain highly suggestive	Usually painless
Weight loss	None or minimal	Profound



Eckardt score

Score	Dysphagia	Regurgitation	Retrosternal pain	Weight loss (kg)
0	None	None	None	None
1	Occasional	Occasional	Occasional	<5
2	Daily	Daily	Daily	5-10
3	Each meal	Each meal	Each meal	>10

Figure 2: Stepwise diagnosis and management algorithm for achalasia cardia.

EUS: endoscopic ultrasonography; GERD: gastroesophageal reflux disease; GI: gastrointestinal; PD: pneumatic dilatation; POEM: peroral endoscopic myotomy; LHM: laparoscopic Heller's myotomy.

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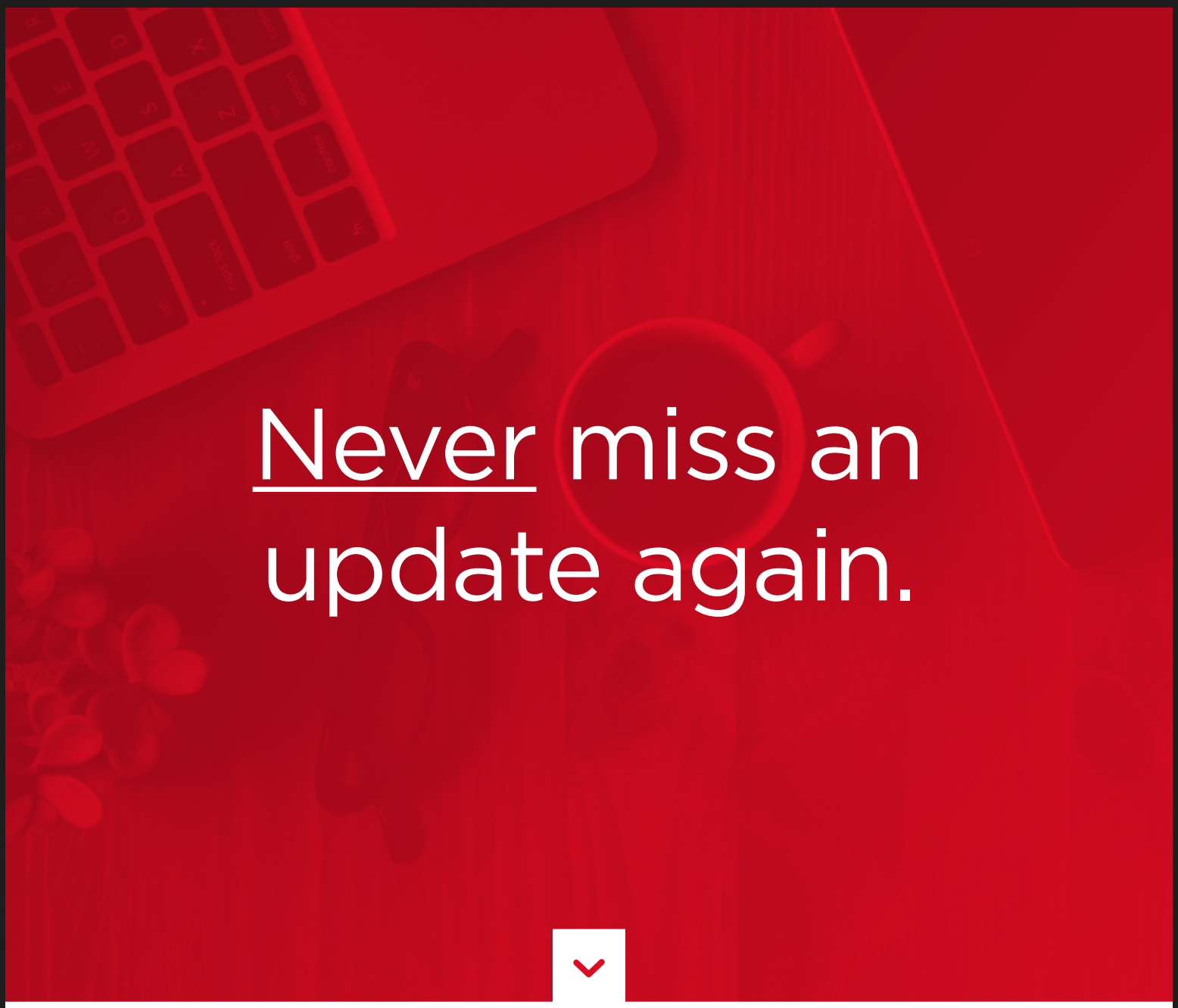

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