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Abbreviations used in this issue:

HCV = hepatitis C virus; HR = hazard ratio; IB = inflammatory bowel disease; IBS = irritable bowel syndrome; OR = odds ratio; QOL = quality of life; SSA/P = sessile serrated adenoma/polyp; TCA = tricyclic antidepressant; UC = ulcerative colitis.

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Welcome to issue 31 of Gastroenterology Research Review.

Among the papers selected for inclusion in this issue, German investigators evaluated the efficacy and safety of effervescent tablet and viscous suspension formulations of budesonide for the short-term treatment of eosinophilic oesophagitis. Researchers from the US developed a novel scoring system, CARDS (C. difficile-associated risk of death score), for predicting in-hospital mortality in admitted patients with Clostridium difficile infection. The role of statins for reducing cirrhosis decompensation and death was assessed in US veterans with HCV and compensated cirrhosis. This issue concludes with research showing that ramosetron was able to improve stool consistency and QOL in women with IBS with diarrhoea.

I hope you enjoy reading this issue’s selected research, and that you find the comments helpful.

Kind Regards,
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Quantification of adequate bowel preparation for screening or surveillance colonoscopy in men

Authors: Clark BT et al.

Summary: Data from 438 male US veterans who had undergone screening or surveillance colonoscopies and repeat colonoscopy examinations within 60 days by a different endoscopist were analysed to establish an objective definition of adequate bowel preparation based on the BBPS (Boston Bowel Prep Scale; 0–3) score; a total of 1161 colon segments were tested. There were 347 men (79.2%) with a BBPS score ≥2 in all segments, 2 or 3 in 10.7% [3.2%–18.1%]). Screening and surveillance intervals based only on the first examination findings would have been incorrect for 16.3%, 15.3% and 43.5% of men with BBPS scores of 3 in all segments, 2 or 3 in 10.7% [3.2%–18.1%]). Screening and surveillance intervals based only on the first examination findings would have been incorrect for 16.3%, 15.3% and 43.5% of men with BBPS scores of 3 in all segments, 2 or 3 in all segments and 1 in ≥1 segments, respectively. The authors of an editorial in the same issue discussed the findings and encouraged readers to adopt the BBPS, which they note is validated and easily learnt.

Comment: Colonoscopy is well established to reduce the risk for colorectal cancer and its related mortality. Quality and diagnostic yield of colonoscopy depends on the operator (i.e. a high adenoma detection rate is associated with a lower risk for interval cancer) and the patient, particularly with respect to the quality of the bowel preparation. Current guidelines require an ‘adequate’ bowel preparation, defined as ability to identify polyps >5mm, to determine screening intervals. The aim of the current study was to clarify the level of bowel preparation at which detection rate of polyps >5mm is unacceptably decreased. The study employed validated BBPS – in brief, 3 = little to no staining of mucosa, 2 = minor staining, 1 = significant staining and 0 = unprepared colon, with right colon, transverse colon and left colon scores summed up to a total of 0–9. Miss rates for adenomas >5mm were 15.9% with a segmental BBPS of 1 and thus significantly higher than with scores of 2 (5.2%) or 3 (5.6%). Thus, the authors recommend repeat colonoscopy in 12 months if at least one segment scores 0 or 1, while scores of 2 or 3 in all segments should follow screening intervals as per guidelines. Notably, the study did not address the relationship between detection of serrated adenomas and bowel preparation. Finally, it must be considered that even with an excellent bowel preparation, 2% of adenomas >10mm and 13% of adenomas 6–9mm are still missed, and thus the average risk interval cancer remains at 1 in 1000 even with a normal colonoscopy.


Abstract

Editorial


Abstract

Editorial

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A randomised, double-blind trial comparing budesonide formulations and dosages for short-term treatment of eosinophilic oesophagitis

Authors: Miehlke S et al.

Summary: Adults with active eosinophilic oesophagitis were randomised to receive budesonide 1mg tablets (n=19) or two 2mg tablets (n=19), budesonide viscous suspension 2×5mL (0.4 mg/mL; n=19) or placebo (n=19) daily in a double-blind, double-dummy manner and were followed for 2 weeks. Compared with placebo, the budesonide 1mg and 2mg efﬁcacious tablets and the suspension were associated with signiﬁcantly greater histological remission rates (mean of <16 eosinophils per mm² high-power ﬁeld; primary endpoint: 100%, 94.7% and 94.7%, respectively, vs. 0% [p<0.0001]) and significantly greater improvements in total endoscopic intensity score. All groups had improvements in dysphagia after treatment, but this was only sustained in the budesonide 1mg efﬁcacious tablet recipients compared with placebo (p=0.0196). No serious adverse events were recorded, and two budesonide recipients in each group developed local fungal infections. Eighty percent of participants preferred the efﬁcacious tablets.

Comment: Eosinophilic oesophagitis is a chronic condition with signiﬁcant symptoms and increasing incidence worldwide. While oral budesonide has been shown to be effective, no oral formulation per se is currently available outside clinical trials or from inhalants. The current study addressed this by testing orally dispersible budesonide in tablet form at 1mg or 2mg twice a day or as an oral liquid as compared with placebo. Budesonide was highly effective in inducing histological remission and improved endoscopic intensity scores. Oral fungal infections occurred in two patients, and the efﬁcacious tablet form was preferred by patients over the liquid. Notably, the lower dose (1mg) tablet achieved a 100% remission rate. The study highlights the difﬁculty in terms of assessing symptoms in response to treatment and the lack of a validated scoring system, and as a matter of fact, symptoms improved even in the placebo group. Overall, this study, which is the largest randomised clinical trial in eosinophilic oesophagitis so far, clearly shows the potency of oral budesonide in inducing remission. However, there are still substantial questions about long-term treatment, symptom resolution and maintaining remission in patients with eosinophilic oesophagitis.


Abstract

Clinical and endoscopic predictors of cytological dysplasia or cancer in a prospective multicentre study of large sessile serrated adenomas/polyps

Authors: Burgess NG et al.

Summary: This was an analysis of prospective data on 268 SSA/Ps (sessile serrated polyps) recorded, and two budesonide recipients in each group developed local fungal infections. Eighty percent of participants preferred the efﬁcacious tablets.

Comment: SSA/Ps account for 20–30% of sporadic cancers. As they are often difﬁcult to detect, SSA/Ps remain an important risk factor for interval cancers, which remains 5–7% after colectomy. Additionally, SSA/Ps are often only partially resected. The current study addressed the lack of information on clinical and endoscopic characteristics of SSA/Ps with cytological dysplasia. Dysplasia in SSA/Ps may assume serrated or conventional morphology, which can result in underappreciation of the underlying lesion. In this large prospective cohort study of 268 large SSA/Ps (>20mm), dysplasia was found in 32.4%. Submucosal invasive cancer was found in 3.9%. Dysplasia was associated with age, lesion size, adenomatous pit pattern (Kudo III, IV or V; 3.98 [1.94–8.15]) and any 0-ls component within an SSA/P (3.10 [1.19–8.12]). An adenomatous pit pattern was more likely in conventional type dysplasia than serrated dysplasia. Presence of high-grade dysplasia or cancer was seen in 7.2%, with associations with each decade increase in age (OR 2.0 [95% CI 1.33–3.56]) and any Paris 0-ls component (10.2 [3.18–32.4]).


Abstract

Beyond endoscopic mucosal healing in UC: histological remission better predicts corticosteroid use and hospitalisation over 6 years of follow-up

Authors: Bryant RV et al.

Summary: These researchers compared histological remission (Truelove and Richards’ index) with endoscopic mucosal healing (Baron score <1) for predicting UC outcomes in 91 patients with established disease at baseline; median follow-up was 72 months. There was moderate concordance between endoscopic and histological remission (κ=0.56 [95% CI 0.36–0.77]); inﬂammation persisted in 24% of patients despite endoscopic remission. Corticosteroid use and hospitalisation for acute, severe colitis were predicted by histological remission (respective HRs 0.42 [95% CI 0.2–0.9] and 0.21 [0.1–0.7]), but not endoscopic mucosal healing (0.86 [0.3–1.7] and 0.83 [0.3–2.4]).

Comment: Endoscopic mucosal healing, i.e. complete resolution of endoscopically visible inflammation, is a well-established treatment goal in UC as it is associated with clinical remission and lower rates of colectomy. However, inﬂammation is often present on histology even in the context of endoscopic and clinical remission; only limited uncontrolled data are available regarding the role of histological remission for patient outcomes in UC. In this study 91 patients with UC were followed over 6 years. The study included 27% with proctitis, 49% with distal disease and 21% with extensive disease. At baseline, 53% of patients were on 5-aminosalicylic acid agents alone and 3% were on antitumour necrosis factor therapy. Not unexpectedly, there was only moderate agreement between clinical, endoscopic and histological measures of disease activity. However, only histological remission predicted reduced future corticosteroid requirements (HR 0.42). Twenty-two percent of study participants required hospital admission for acute, severe colitis with histological remission predicting reduced rates of hospitalisations in contrast to endoscopic remission, which did not. Neither clinical, endoscopic nor histological remission predicted colectomy. However, the study was likely underpowered given that the colectomy rate was only 12%. Overall, this study suggests that revisiting histological remission as a treatment endpoint may be a useful and readily available opportunity to better identify patients at risk of poor outcomes and therefore requiring more intense therapy.


Abstract

Clostridium difficile associated risk of death score (CARDS): a novel severity score to predict mortality among hospitalised patients with C. difficile infection

Authors: Kassam Z et al.

Summary: A novel Clostridium difficile infection risk score (CARDS) for predicting mortality was developed using 2011 US data from 374,747 cases of C. difficile infection among 77,776 hospitalisations; the in-hospital mortality rate was 8%. A multivariate analysis identified the following eight severity score predictors: age, cardiopulmonary disease, malignancy, diabetes, IBD, acute renal failure, liver disease and ICU admission. Weighting for these predictors ranged from –1 for diabetes to 5 for ICU admission. A significant increase in mortality was seen as CARDS increased. CARDS ranged from 1 (1.2% mortality) to 15 (100% mortality). Validation using data from the same database may prove helpful in terms of identifying patients at risk of poor outcome, used by hospitals to track the severity of presentations and assist with studies as a validated assessment tool for C. difficile infection severity.


Abstract
Please review the Approved Product Information before prescribing. Full Product Information is available from Gilead Medical Information: 1800 806 112.

**PBS Information:** HARVONI is PBS listed for the treatment of chronic genotype 1 hepatitis C infection in adults. Dual General Schedule and S100 [HSD] listing. Authority required. Refer to PBS Schedule for full authority information.

**Minimum Product Information.** HARVONI (ledipasvir/sofosbuvir) 90/400 mg tablets.

**INDICATIONS:** Chronic hepatitis C (CHC) genotype 1 infection in adults.

**DOSAGE AND ADMINISTRATION:** One tablet daily, orally.

**CONTRAINDICATIONS:** Hypersensitivity, concurrent use with other medicinal products containing any of the same active components.

**PRECAUTIONS:** Symptomatic bradycardia when coadministered with amiodarone. Use with potent P-gp Inducers. HCV/HBV co-infection. Patients with decompensated cirrhosis, patients with prior exposure to HCV direct-acting antivirals. Pregnancy (Category B1).

**DRUG INTERACTIONS:** Acid reducing agents, antiarrhythmics (amiodarone), anticonvulsants, anticoagulants, antimycobacterials, antiretrovirals, simprevir, St John’s wort, HMG-CoA reductase inhibitors.

**ADVERSE REACTIONS:** Fatigue, headache, nausea, diarrhoea and insomnia, symptomatic bradycardia when coadministered with amiodarone. This is not a full list – for more details/complete list of adverse events refer to full Product Information. Date of preparation 21st July 2015.

References:
Statins are associated with a decreased risk of decompensation and death in veterans with hepatitis C-related compensated cirrhosis

Authors: Mohanty A et al.

Summary: This retrospective analysis of US veterans records identified 40,512 patients with HCV-related compensated cirrhosis; 2802 of the cohort filled prescriptions for statins. A propensity score model was developed, using variables associated with statin prescription, in which 685 statin users were matched with 2062 nonusers. Discrimination of the propensity score model was 0.92. Compared with statin nonusers, statin users had lower risks of decompensation and death (relative HRs 0.55 [95% CI 0.39–0.77] and 0.56 [0.46–0.69]); the findings persisted after adjustments (0.55 [0.39–0.78] and 0.55 [0.45–0.68]). This study was also summarised by the Journal’s Section Editors.

Outcomes of esophageal dilation in eosinophilic esophagitis: safety, efficacy, and persistence of the fibrostenotic phenotype

Authors: Ruhe TM et al.

Summary: The safety and long-term efficacy of esophageal dilation were investigated in a large retrospective cohort of 509 patients with eosinophilic esophagitis; 164 patients underwent 486 dilation procedures, with 95 requiring repeated procedures (75% within 1 year). Compared with patients who did not undergo dilation, those who did had a longer predilation duration of symptoms (11.1 vs. 5.4 years [p<0.001]). Smaller baseline esophageal diameter was the only predictor of needing multiple dilations. There were no major bleeds, perforations or deaths, and the overall complication rate was 5%, mostly related to postprocedural pain.

Imipramine for treatment of esophageal hypersensitivity and functional heartburn

Authors: Limsrivilai J et al.

Summary: Patients with established eosophageal hypersensitivity or functional heartburn were randomised to receive imipramine 25mg (n=43) or placebo (n=40) once daily for 8 weeks. There was no difference between imipramine and placebo recipients for >50% reductions in gastroesophageal reflux disease scores (primary endpoint) in intent-to-treat and per-protocol analyses (37.2% vs. 37.5%; OR 0.99 [95% CI 0.41–2.41] and 45.5% vs. 41.2%; 1.19 [0.45–3.13], respectively); similar results were seen in subgroup analyses assessing eosophageal hypersensitivity and functional heartburn separately. Imipramine significantly improved QOL on the 36-Item Short Form Health Survey versus placebo in the per-protocol analysis (p=0.048), but not in the intent-to-treat analysis (p=0.26). Overall adverse events were similar between the groups, but constipation was more common among imipramine than placebo recipients (51.2 vs. 22.5% [p=0.01]). The findings of this study were also discussed in an editorial in the same issue of the journal.

Comment: Patients with eosophageal hypersensitivity and functional heartburn respond poorly to therapy with proton-pump inhibitors. While TCAs (tricyclic antidepressants) have been recommended in this context, placebo-controlled data for TCAs are limited. In the current study, the TCA imipramine showed a similar symptom rate to placebo with ~37% of patients achieving a >50% decrease in eosophageal symptoms. However, QOL scores were more likely to improve with imipramine. Similar results have been observed in a large randomised clinical trial in IBS where the TCA desipramine was compared with placebo (Gastroenterology 2010). While desipramine improved ‘satisfaction with treatment’ score, no improvement was seen with actual IBS symptoms; i.e. while symptoms remained stable, coping with symptoms became easier. Thus, the real aim for introducing TCAs in this context needs to be better QOL and not necessarily immediate symptom relief. Understanding this and more importantly communicating this to our patients is crucial to manage expectations and compliance.

Comment: While oral steroids have proven efficacy in inducing remission in eosinophilic esophagitis, dilation is often considered in the context of a stricture for rapid symptom relief. However, while esophageal dilation for symptomatic eosinophilic esophagitis and particularly eosinophilic esophagitis-related strictures is performed not infrequently, the actual long-term outcomes are not well studied. The current retrospective study included 164 patients with eosinophilic esophagitis undergoing 486 dilations and 345 patients with eosinophilic esophagitis not receiving dilation therapy recruited over 12 years. In keeping with the concept that fibrosis due to chronic inflammation plays an important part in the structuring in eosinophilic esophagitis, patients requiring dilation had been symptomatic for a significantly longer time than this not needing endoscopic therapy (11.1 vs. 5.4 years). Symptoms associated with need for dilation were dysphagia, food impaction and absence of heartburn or abdominal pain. Endoscopic factors were presence of rings and abnormal baseline endoscopy. In general, dilation was tolerated well with a 5% complication rate and no major bleeds; perforations or deaths. Fifty-eight percent of dilated patients required a second dilation with 75% of these requiring it within the first 12 months. Thus, overall, dilation of eosinophilic esophagitis was safe and resulted in good symptom relief, albeit with the need for repeat procedures in the majority of patients.
Classifying back pain and peripheral joint complaints in inflammatory bowel disease patients

Authors: van Erp SJ et al.

Summary: This research prospectively followed patients with IBD, including 13 with chronic back pain, 80 with peripheral joint complaints, 62 with axial/peripheral joint complaints and 100 controls with no such complaints. Factors independently associated with the presence of joint or back pain were smoking, female gender and IBD disease activity. Criteria for axial/peripheral spondyloarthritis were met by 12.3% of patients, with 9.7% receiving a rheumatological diagnosis of arthritis. Most patients reported stable joint/back pain during the 12-month follow-up period.

Comment: Joint and back pain are the most extra-intestinal manifestations in patients with IBD. This prospective observational study followed IBD patients with >3 months of back/joint pain (n=155) as compared with 100 IBD patients without joint problems over a follow-up period of 1 year. Not unexpectedly, smoking, gender and IBD disease activity were associated with IBD back/joint problems. Spondyloarthritis was common among IBD patients with back/joint pain. This study highlights the vigilance required in IBD patients regarding extra-intestinal manifestations of IBD and the need for counselling regarding smoking in this patient group.

Reference: J Crohns Colitis 2016;10(2):166–75

Ramosetron reduces symptoms of irritable bowel syndrome with diarrhea and improves quality of life in women

Authors: Fukudo S et al.

Summary: Female outpatients with IBS with diarrhea were randomised to receive ramosetron 2.5μg (n=284) or placebo (n=286) once daily for 12 weeks. Compared with placebo, significantly greater proportions of ramosetron recipients reported global improvement (50.7% vs. 32.0%; relative risk 1.58 [95% CI 1.29–1.94]; number needed to treat, 6) and increased stool consistency (40.8% vs. 24.3% [p<0.001]). Ramosetron was also associated with significant reductions in abdominal pain and discomfort (p=0.001) and greater QOL improvement (p=0.002), and it induced constipation in 11.0% of recipients.

Comment: IBS is a common disease with significant impact on QOL. The 5-HT₃ (5-hydroxytryptamine-3; serotonin) receptor antagonist ramosetron has been shown to be efficacious in Asian men but not women with IBS with diarrhea [Clin Gastroenterol Hepatol 2014]. The current, adequately powered phase 3 study found that ramosetron improved symptoms, stool consistency and QOL. Adverse events were noted in significantly more patients in the ramosetron group (52.7%) compared with the placebo group (41.5%); however, serious adverse events, i.e. one case of anaemia and one of enterocolitis, were only described in the placebo group. The current study therefore convincingly shows that ramosetron is efficacious and safe, not just in males but also females. Importantly, no case of ischaemic colitis, which has been reported for some of the other 5-HT₃ receptor antagonists, has been seen so far in over 2000 patients with IBS with diarrhea treated with ramosetron.

Reference: Gastroenterology 2016;150(2):358–66

Independent commentary by Associate Professor Golo Ahlenstiel,
Gastroenterologist and Hepatologist at Westmead Hospital, Sydney. After completing his medical and doctoral degrees at the University of Bonn, Germany, Golo Ahlenstiel received research fellowships from the National Institutes of Health (NIH, USA) and the German Research Foundation (DFG, Germany) to pursue research into the immunopathogenesis of viral hepatitis at the National Institutes of Health, Bethesda, MD, USA. Apart from his clinical duties as a staff specialist at Westmead Hospital, he also leads a Liver Immunology group at The Westmead Institute for Medical Research.