Can we simplify the journey in UC?

JYSELECA is a once-daily oral treatment* that provides long-term efficacy**[1,2] and improves patient quality of life†[1,3]

SCAN ME

MACE, Major adverse cardiovascular event; UC, Ulcerative colitis; VTE, Venous thromboembolism.

*Available as a convenient, once-daily, oral tablet for both induction and maintenance therapy. Recommended maintenance dose is 200 mg once daily; 100 mg once daily in adults at higher risk of VTE, MACE, and malignancy.[1]
**Long-term clinical and histologic remission at Week 58.[1]
†~50–80% of patients achieved clinically meaningful HRQoL improvements across IBDQ, EQ-5D VAS, and WPAI at Week 10 ($p<0.05$ vs. placebo).[3]

1. JYSELECA SmPC, May 2023; 2. Feagan BG, *et al. Lancet* 2021;397(10292):2372–2384; 3. Schreiber S, *et al. J Crohns Colitis* 2023;17(6):863–875.

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Surveillance for individuals at high-risk of pancreatic cancer: Are we finally heading toward evidence?

At least 5% of pancreatic ductal adenocarcinoma (PDAC) cases arise in the context of a genetic predisposition either due to known syndromes such as Peutz-Jeghers syndrome (PJS), hereditary pancreatitis (HP), familial melanoma (FAMMM), Lynch syndrome, in *BRCA*/*PALB*/*ATM* mutation carriers or in individuals with multiple affected family members and no detected mutation (FPC). Owing to a high risk of developing PDAC, yearly surveillance with endoscopic ultrasound (EUS) or magnetic resonance imaging (MRI) is recommended in these high-risk individuals (HRIs). In this issue of the *United European Gastroenterology Journal*, de Mestier et al.[1] report data of a patient-level meta-analysis aimed at evaluating the appropriateness of pancreatic surgery in HRIs undergoing surveillance. Of 1747 patients from 13 studies undergoing surveillance by means of MRI and/or EUS, 90 (5.1%) were operated on. The authors considered surgery to be appropriate if a pancreatic intraepithelial neoplasia (PanIN) with high-grade dysplasia (PanIN-3), a branch-duct intraductal papillary mucinous neoplasm (IPMN) with high-grade dysplasia, a main-duct IPMN, a PDAC or a malignant pancreatic neuroendocrine tumor were diagnosed at final pathology report, and inappropriate in all other cases. These lesions are indeed considered a successful target of surveillance. Factors associated with appropriateness were the presence of an identified germline mutation, age older than 50 years and having detected a high-risk lesion defined as either with "worrisome features" (WFs) or "high-risk stigmata" (HRS) for IPMNs or a solid mass. The authors developed a score system based on these three factors that can guide decisions on surgical indication in HRIs.

Notably, this is the fourth meta-analysis of results of HRIs surveillance published in the past year, suggesting an increased perception of the need to gather evidence on this topic. All these studies examined slightly different aspects of almost the same published cohorts. Paiella and colleagues[2] also aimed at investigating the rate of correct and unnecessary surgery. When examining 16 studies with 1551 HRIs, 105 (6.3%) received surgery, which was deemed unnecessary in 68% of cases. In another meta-analysis, Signoretti et al.[3] examined the pooled prevalence of screened HRIs with diagnosis of lesions considered a successful target of surveillance. This rate was 3.3% among 1588 HRIs from 16 studies, being similar when either EUS or MRI was employed. Notably, this rate changed in subgroups, being 3% in FPC, 4% in HP, 5% in FAMMM, 6.3% in *BRCA* mutation carriers, and 12.2% in PJS. Finally, Corral and colleagues[4] examined results from 19 studies with 1660 screened HRIs. The overall diagnostic yield of screening for high-risk pancreatic lesions was 0.74 per 100 patients per year, and the number needed to screen to identify one patient with a high-risk lesion was 135, being much higher in HRIs with PJS (1 in 71) and FAMMM (1 in 51) compared with other subgroups. EUS yield was slightly but not significantly higher compared with that of MRI. All these meta-analyses suffer from the limitations of the previous studies such as the relatively small number of HRIs enrolled in each cohort, with only some 25% enrolling more than 150 individuals and the follow-up being often very short. Some more recent publications provide, however, further interesting evidence. Paiella et al. reported data of the first round of surveillance of HRIs in the Italian Association for the Study of the Pancreas Registry.[5] The rate of malignancy in the 187 enrolled HRIs was 2.6%, and age older than 50 years, smoking and having more than two relatives with PDAC were independently associated with detection of premalignant and malignant lesions. Finally, Canto and colleagues[6] investigated the incidence of PDAC in 354 HRIs with a median follow-up of more than five years undergoing surveillance in the CAPS (Cancer of the Pancreas Screening) studies in the United States. The large sample size and long follow-up time allowed the identification of modifications that were associated with the appearance of malignant lesions. A progression toward malignancy or high-grade dysplasia was indeed observed in 7% of the cohort, and 93% of these patients showed some WFs before. The observed WFs (solid mass, mural nodule, thickened cyst wall, rapid cyst growth rate, and main pancreatic duct greater than 5 mm) are similar to those considered suspicious in individuals with IPMNs. The outcome of patients diagnosed with PDAC in this surveillance protocol was much improved compared with nonscreened sporadic cases, as 90% of PDAC cases

were resectable and 85% of patients were alive at three years after diagnosis. Notably, the progression to malignant lesions occurred at a median age of 67 years and after a median follow-up of almost five years. This study provides evidence of the importance of long-term follow-up in HRIs and underlines the central role of morphology in selecting patients for surgery. These latter results bring us back to the score proposed by de Mestier et al.[1] that include age, germline mutations and morphological WFs or HRS. However, major limitations of the surveillance protocols necessitate individualizing them depending not only on morphology but also on the basis of genetic background, which should be carefully investigated, and environmental risk factors such as smoking. As an example, whereas surveillance does not seem necessary before age 50 in FPC, it should start earlier and possibly be more intense in FAMMM and PJS. Moreover, these surveillance protocols seem able to diagnose early PDAC cases arising from IPMNs, but the lack of detection of high-grade PanINs remains an unsolved issue. Recently, intriguing data on the association of pancreatic juice biomarkers[7] with morphologic lesions in HRIs have been reported, but there is a need for validation in large prospective cohorts. Finally, as the rate of unnecessary surgery in these cohorts is not negligible, with consequent morbidity and psychological discomfort, these programs should still be limited to high-volume centers with specific expertise.

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