1. Was the UC SUCCESS trial a failure?

Although both azathioprine and infliximab are effective for treatment of ulcerative colitis, the comparative efficacy of these two drugs or the combination IFX-Aza has not been previously evaluated in UC. A similar study (SONIC), showed superiority of combination over monotherapy in Crohn's disease (Colombel et al. – NEJM '10). In the industry-funded UC SUCCESS study, investigators evaluated the efficacy of Aza, IFX or combination therapy for induction of remission in patients with moderate-severe UC who had inadequate response to steroids. The study was terminated early at the decision of the sponsor when only 40% of the planned subjects were enrolled. More patients in the IFX-Aza group achieved steroid-free remission at week 16 (40%) compared with both IFX alone (22%) and Aza alone (23%). Mucosal healing also occurred more frequently in the combination therapy group than either monotherapy groups. There was no significant difference in the risk of serious adverse events between groups. Patients on combination therapy had lower risk of anti-IFX antibody development compared to those on IFX monotherapy.

Comments:
Due to its early termination at the decision of the sponsor, this study was significantly underpowered and, for this reason, most of the secondary end-points could not be adequately evaluated. The fact that IFX-Aza combination therapy is superior to Aza monotherapy at 16 weeks is not surprising but the answers to the more important comparisons between IFX combination and monotherapy as well as between IFX and Aza monotherapy, could not be provided by this study. The equivalence between azathioprine and IFX at 8 and 16 weeks is rather surprising but could be due to a type 2 error.

Source:

2. Is IBD associated with an increased risk of stroke and heart disease?

Chronic inflammation is a risk factor for atherosclerosis by promoting plaque formation and platelet and endothelial dysfunction. Active inflammation also predisposes to thrombosis through the coagulation cascade. Whether these processes are associated with an increased
risk of stroke (CVA) and ischemic heart disease (IHD) in IBD patients is unknown. Investigators have performed a systematic review and meta-analysis including 9 studies (6 case-control and 3 cohort) with over 150,000 patients. IBD was associated with a modest increase in the risk of CVA in women (OR 1.28) and young patients and a slight increase in the risk of IHD also in women (OR 1.26). Interestingly, IBD was not associated with an increased risk of peripheral arterial thromboembolic events. Considerable heterogeneity was seen among the studies.

Comments:
Although the findings of this study are biologically plausible, the effect size is so small that it is difficult to exclude the presence of known or unknown confounders. Aside from methodological limitations and heterogeneity among studies, there is also the risk of detection bias as patients with IBD are more closely scrutinized through increased healthcare use. Also, when “soft” endpoints such as transient ischemic attacks (TIAs) and “angina” are accounted for as diagnoses of interest there is also a substantial risk of ascertainment bias. The study was also unable to determine if the increased risk of cerebrovascular and cardiac events is related to the disease in general, active disease – inflammation or the medications used to treat IBD. The good news for patients is that, if there is an increased risk of cerebrovascular and coronary events in IBD, it is likely to be very small and certainly considerably smaller than the risk of venous thrombo-embolism which can be an important cause of morbidity and mortality in IBD patients.

Source:

3. Increased risk of non-melanoma skin cancer associated with thiopurine use in IBD
Thiopurines (azathioprine and 6-MP) have been associated with an increased risk of squamous and basal cell carcinoma in patients post-transplant or with rheumatological conditions. Increased sensitivity to DNA damage by UVA rays, decreased immune surveillance and chronic cutaneous viral infections have all been considered as putative mechanisms. The effect of thiopurines on skin cancer in patients with IBD has been the subject of several previous investigations. In this paper, the authors present the results of a meta-analysis of such studies. Pooled data from 8 studies representing more than 60,000 patients with IBD found that thiopurine use was associated with a more than 2-fold increased risk of non-melanoma skin cancer (hazard ratio 2.3). They found significant heterogeneity among studies primarily related to the study population (hospital- vs. community-based) and duration of follow-up. Population-based and longer-term studies found a lower risk of skin cancer.
Comments:
Just as it is the case with the previous meta-analysis, there are a number of methodological limitations in this study such as combining case-control with cohort studies as well as detection and ascertainment bias. The authors could not distinguish between squamous and basal cell cancers which have different prognoses. In addition, no information was provided about the dose-effect of thiopurines. That said, it is likely that thiopurines are associated with a slightly increased risk of non-melanoma skin cancer similar to their association with cervical cancer. Fortunately, given that most of the skin cancers occur in sun-exposed areas, the implication here is that an ounce of prevention literally translates into an ounce of sun-screen. Much like patients using biologics (both anti-TNF and leukocyte trafficking inhibitors), patients using thiopurines should be advised to use sun protection when exposed.

Source: