OPTIMISING MANAGEMENT USING COMBINATION THERAPY

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When tumour necrosis factor-α (TNF-α) inhibitor therapy is used, guidelines recommend combination therapy with an immunomodulator (thiopurine or methotrexate). This is often a difficult sell to the patient, for whom immunomodulators have often already failed, and who may fear increased risk with the combination. So what's new?

Evidence for combination therapy in Crohn's disease

Results of the Study of Immunomodulator Naive Patients in Crohn's Disease (SONIC) and Combination Of Maintenance Methotrexate-Infliximab Trial (COMMIT) in achieving steroid-free remission are well known. SONIC found a 57% rate for infliximab plus azathioprine vs. 44% for infliximab monotherapy at 26 weeks. COMMIT found a 76% rate for infliximab, corticosteroid, and methotrexate, vs. 78% for monotherapy at 14 weeks. There are no primary data on combination therapy with other TNF-α inhibitors, but a meta-analysis of 11 randomized controlled trials (RCTs) of infliximab, adalimumab, and certolizumab pegol showed combination therapy to be almost 80% more effective than monotherapy for infliximab (odds ratio [OR] 1.79; 95% confidence interval [CI] 1.06-3.01), but not adalimumab (OR 0.88, 95% CI 0.58-1.35), or certolizumab pegol (OR 0.93, 95% CI 0.65-1.34). Furthermore, unlike infliximab therapy, which benefits from addition of thiopurines at any stage, a similarly designed assessment of the effect of azathioprine on semesters in remission with adalimumab could not show this.

Evidence for combination therapy in ulcerative colitis

The single trial of combination therapy for ulcerative colitis (UC-SUCCESS) with infliximab plus azathioprine showed a greater magnitude of benefit than in Crohn's disease (40% steroid-free remission for the combination vs. 22% for infliximab monotherapy at 16 weeks), together with mucosal healing (63% vs. 55%) that was, not surprisingly, higher than the 46% vs. 30% seen in Crohn's disease.

Risks of thiopurines as part of combination

Comparative effectiveness RCTs and subanalyses of RCTs have not shown any impact of concomitant immunomodulators on the risk of serious infection compared to monotherapy. Although observational data suggest an increased risk of infection with combination therapy compared to infliximab alone, rates are similar to immunomodulator monotherapy. Observational data (registries and adverse-event reporting systems) are exposed to appreciable bias, with neither defined denominator nor duration of follow up. Pooled RCT data demonstrate that combination therapy may increase the risk of lymphoma above that in the general population, to levels that are similar to those seen with immunomodulator monotherapy (standardized incidence ratio [SIR] 3.2, 95% CI 1.5-6.9, but combination therapy vs. immunomodulator monotherapy SIR 1.7, 95%CI 0.5-7.1). No lymphomas have been reported on TNF-α inhibitor monotherapy in any of the RCTs and across all studies, so the finger of blame points at immunomodulators. The risk of hepatosplenic T-cell lymphoma appears to be related to the duration of thiopurine therapy (>2 years). Increasing age is the greatest risk factor for serious infection and lymphoma.

Further questions

Do you need to start immunomodulators before TNF-α inhibitor therapy? Do risks resolve when combination therapy stops? Can you safely reintroduce treatment after a serious infection or malignancy? What about combination therapy with golimumab, biosimilars, or other biological agents?

Conclusions

In most patients the benefit of combination therapy outweighs the risk, since it increases the effect and extends the durability of TNF-α inhibitor therapy. In young males, methotrexate may be preferred over azathioprine. Optimizing management includes discussion, explanation, early introduction, maintenance therapy, monitoring drug levels (see next presentation) and (probably!) monotherapy after 1 to 2 years of combination therapy.

Key Reference

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