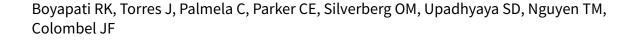


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[Intervention Review]

Withdrawal of immunosuppressant or biologic therapy for patients with quiescent Crohn's disease

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ABSTRACT

Background

Crohn's disease (CD) is a chronic, relapsing and remitting disease of the gastrointestinal tract that can cause significant morbidity and disability. Current treatment guidelines recommend early intervention with immunosuppressant or biological therapy in high-risk patients with a severe disease phenotype at presentation. The feasibility of therapeutic de-escalation once remission is achieved is a commonly encountered question in clinical practice, driven by patient and clinician concerns regarding safety, adverse events, cost and national regulations. Withdrawal of immunosuppressant and biologic drugs in patients with quiescent CD may limit adverse events and reduce healthcare costs. Alternatively, stopping these drug therapies may result in negative outcomes such as disease relapse, drug desensitization, bowel damage and need for surgery.

Objectives

To assess the feasibility and safety of discontinuing immunosuppressant or biologic drugs, administered alone or in combination, in patients with quiescent CD.

Search methods

We searched CENTRAL, MEDLINE, Embase and the Cochrane IBD Group Specialized Register from inception to 19 December 2017. We also searched the reference lists of potentially relevant manuscripts and conference proceedings to identify additional studies.

Selection criteria

Randomized controlled trials (RCTs) and prospective cohort studies that followed patients for a minimum duration of six months after drug discontinuation were considered for inclusion. The patient population of interest was adults (\geq 18 years) with CD (as defined by conventional clinical, endoscopic or histologic criteria) who had achieved remission while receiving immunosuppressant or biologic drugs administered alone or in combination. Patients then discontinued the drug regimen following a period of maintenance therapy of at least six months. The comparison was usual care (i.e. continuation of the drug regimen).



Data collection and analysis

The primary outcome measure was the proportion of patients who relapsed following discontinuation of immunosuppressant or biologic drugs, administered alone or in combination. Secondary outcomes included: the proportion of patients who responded to the reintroduction of immunosuppressant or biologic drugs, given as monotherapy or combination therapy; the proportion of patients who required surgery following relapse; the proportion of patients who required hospitalization for CD following relapse; the proportion of patients who developed new CD-related complications (e.g. fistula, abscesses, strictures) following relapse; the proportion of patients with elevated biomarkers of inflammation (CRP, fecal calprotectin) in those who stop and those who continue therapy; the proportion of patients with anti-drug antibodies and low serum trough drug levels; time to relapse; and the proportion of patients with adverse events, serious adverse events and withdrawal due to adverse events. For dichotomous outcomes, we calculated the risk ratio (RR) and 95% confidence interval (95% CI). Data were analyzed on an intention-to-treat basis where patients with missing outcome data were assumed to have relapsed. The overall quality of the evidence supporting the primary and secondary outcomes was assessed using the GRADE criteria.

Main results

A total of six RCTs (326 patients) evaluating therapeutic discontinuation in patients with quiescent CD were eligible for inclusion. In four RCTs azathioprine monotherapy was discontinued, and in two RCTs azathioprine was discontinued from a combination therapy regimen consisting of azathioprine with infliximab. No studies of biologic monotherapy withdrawal were eligible for inclusion. The majority of studies received unclear or low risk of bias ratings, with the exception of three open-label RCTs, which were rated as high risk of bias for blinding. Four RCTs (215 participants) compared discontinuation to continuation of azathioprine monotherapy, while two studies (125 participants) compared discontinuation of azathioprine from a combination regimen to continuation of combination therapy. Continuation of azathioprine monotherapy was shown to be superior to withdrawal for risk of clinical relapse. Thirty-two per cent (36/111) of azathioprine withdrawal participants relapsed compared to 14% (14/104) of participants who continued with azathioprine therapy (RR 0.42, 95% CI 0.24 to 0.72, GRADE low quality evidence). However, it is uncertain if there are any between-group differences in new CDrelated complications (RR 0.34, 95% CI 0.06 to 2.08, GRADE low quality evidence), adverse events (RR 0.88, 95% CI 0.67 to 1.17, GRADE low quality evidence), serious adverse events (RR 3.29, 95% CI 0.35 to 30.80, GRADE low quality evidence) or withdrawal due to adverse events (RR 2.59, 95% CI 0.35 to 19.04, GRADE low quality evidence). Common adverse events included infections, mild leukopenia, abdominal symptoms, arthralgias, headache and elevated liver enzymes. No differences between azathioprine withdrawal from combination therapy versus continuation of combination therapy were observed for clinical relapse. Among patients who continued combination therapy with azathioprine and infliximab, 48% (27/56) had a clinical relapse compared to 49% (27/55) of patients discontinued azathioprine but remained on infliximab (RR 1.02, 95% CI 0.68 to 1.52, P = 0.32; GRADE low quality evidence). The effects on adverse events (RR 1.11, 95% CI 0.44 to 2.81, GRADE low quality of evidence) or serious adverse events are uncertain (RR 1.00, 95% CI 0.21 to 4.66; GRADE very low quality of evidence). Common adverse events in the combination therapy studies included infections, liver test elevations, arthralgias and infusion reactions.

Authors' conclusions

The effects of withdrawal of immunosuppressant therapy in people with quiescent Crohn's disease are uncertain. Low quality evidence suggests that continuing azathioprine monotherapy may be superior to withdrawal for avoiding clinical relapse, while very low quality evidence suggests that there may be no difference in clinical relapse rates between discontinuing azathioprine from a combination therapy regimen, compared to continuing combination therapy. It is unclear whether withdrawal of azathioprine, initially administered alone or in combination, impacts on the development of CD-related complications, adverse events, serious adverse events or withdrawal due to adverse events. Further high-quality research is needed in this area, particularly double-blind RCTs in which biologic therapy or an immunosuppressant other than azathioprine is withdrawn.

PLAIN LANGUAGE SUMMARY

Is withdrawal of drug therapy feasible in patients with CD who have achieved remission?

Background

Crohn's disease is a serious, chronic, inflammatory disease of the small and large intestine. Symptoms include abdominal pain, diarrhea, bleeding and weight loss. When people with Crohn's disease are experiencing symptoms the disease is 'active'. When the symptoms stop, it is called 'remission'. When people in remission experience symptoms it is called a 'relapse'. Immunosuppressant drugs (e.g. azathioprine, 6-mercaptopurine and methotrexate) and biologic medications (e.g. infliximab, adalimumab, vedolizumab and ustekinumab) are commonly used alone or in combination to treat Crohn's disease. While effective for initially controlling disease (i.e. inducing remission), there are safety and cost concerns regarding the long-term use of these drugs for the prevention of relapse in people with Crohn's disease in remission.

Study characteristics

We performed a comprehensive literature review and identified six randomized controlled trials (an experiment in which participants are randomly assigned to receive two or more interventions and the results are compared) that involved a total of 326 participants. Four of the six studies assigned patients who had been receiving azathioprine alone to either continue or discontinue therapy (215 participants).



Two of the six studies assigned patients who had been receiving azathioprine in addition to infliximab to continue therapy or discontinue azathioprine (111 participants).

Key results

Clinical relapse occurred in 13% (14/104) of patients who continued azathioprine monotherapy compared to 32% (36/111) of patients who discontinued azathioprine monotherapy. No differences were observed for Crohn's disease-related complications, side effects, serious side effects and withdrawal due to side effects. Common side effects included infections, mild decrease in the number of white blood cells, abdominal symptoms, joint pain, headache and elevated liver enzymes. Among patients who continued combination therapy with azathioprine and infliximab, 48% (27/56) had a clinical relapse compared to 49% (27/55) of patients discontinued azathioprine but remained on infliximab. No differences in side effects, serious side effects or withdrawal due to side effects were observed. Common side effects reported in the combination therapy studies included infections, liver test elevations, joint pain and infusion reactions (a hypersensitivity reaction to the biologic medication).

Quality of evidence

Overall, the quality of evidence for each outcome was low due to a high risk of study bias and small numbers of patients evaluated.

Conclusions

The effects of withdrawal of immunosuppressant therapy in people with Crohn's disease in remission are uncertain. Low quality evidence suggests that continuing azathioprine monotherapy may be superior to withdrawal of azathioprine for avoiding clinical relapse in people with Crohn's disease in remission. Low quality evidence suggests that stopping the immunosuppressive after combination therapy does not seem to impact on the risk of relapsing. It is unclear whether the withdrawal of azathioprine, initially administered alone or in combination, impacts on the development of Crohn's disease-related complications, side effects, serious side effects, or withdrawal from the studies due to side effects. Additional research is needed in this area to better inform clinical practice, particularly high-quality randomized controlled trials examining outcomes when biologic therapy is withdrawn.