Selected Summaries

Colon rescue therapy in acute severe ulcerative colitis

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SUMMARY

The investigators from GETAID (Groupe d'Etudes Therapeutiques des Affections Inflammtoires Digestives) did a randomized, parallel, open-label, multicentre trial over a 3-year period. Consecutive patients ≥18 years of age who had an acute severe flare of ulcerative colitis (UC) (disease extent being left-sided colitis or pancolitis) as defined by a Lichtiger score >10 points and did not respond to intravenous (i.v.) corticosteroids (0.8 mg/kg of methylprednisolone or equivalent given for at least 5 days) were randomized to receive cyclosporin A (CyA, 2 mg/kg/day i.v.) or infliximab (IFX, 5 mg/kg i.v.). Subsequent doses of CyA were titrated to obtain CyA blood levels of 150–250 ng/ml and patients with a clinical response at day 7 were switched to oral CyA (dose of 4 mg/kg and the dosage was accordingly adjusted to maintain blood CyA levels of 150–250 ng/ml). Further doses of IFX were given at 2 and 6 weeks (at a dose of 5 mg/kg i.v.) only if there was clinical response at day 7. All the included patients were naive to CyA, IFX and azathioprine (Aza)/6-mercaptopurine (6-MP) unless Aza/6-MP had been started within 4 weeks of inclusion in the study. Aza (dose of 2–2.5 mg/kg/day) was given to all patients who had a clinical response at day 7. Prophylaxis for *Pneumocystis jirovecii* was given to all the patients who received CyA. The patients were followed up till day 98.

The primary outcome measure was treatment failure at any time. Treatment failure was defined as the presence of any of the following: (i) absence of clinical response at day 7; (ii) relapse between days 7 and 98 (defined as an increase of Lichtiger score by at least 3 points lasting for at least three consecutive days and leading to modification of treatment); (iii) absence of steroid-free remission at day 98 (steroid-free remission was defined as a Mayo disease activity index score ≤2 with an endoscopic subscore ≤1); (iv) occurrence of a severe adverse event leading to treatment interruption; (v) colectomy; and (vi) death. The investigators hypothesized that CyA was better than IFX and the sample size was calculated with an intent to detect a 30% difference in failure rate between the CyA and IFX groups, with a power of 80% and type I error of 5%. As the observed failure rate was 45% in the IFX group based on the data analysis of the initial 30 patients, it was calculated that a total of 116 patients would have to be randomized to fulfil the sample size as per the above assumption.

A total of 115 patients were randomized in a 1:1 manner to receive either CyA (58 patients) or IFX (57 patients). The baseline characteristics with respect to age, sex, duration or extent of disease, duration of i.v. steroid treatment, laboratory values (haemoglobin, albumin, C-reactive protein), Mayo disease activity index, Mayo endoscopic subscore, quality-of-life assessment by inflammatory

bowel disease (IBD) questionnaire score were similiar in both the groups. The mean age of the patients was 39 years in the CyA group and 36 years in the IFX group. However, the Lichtiger score was higher in the CyA group compared to the IFX group.

Treatment failure was seen in 60% (35 of 58) of patients in the CyA group compared to 54% (31 of 57) in the IFX group; this was statistically insignificant, i.e. the primary end-point assessed namely treatment failure was similar in both the treatment groups. On multivariate analysis, the independent predictors of treatment failure were age >40 years and haemoglobin level >12.5 g/dl.

The authors also assessed some secondary end-points—86% patients in the CyA group had a clinical response at day 7 compared to 84% in the IFX group. The rate of decrease of Lichtiger score between days 0 and 7 was faster in patients who received IFX compared with those who received CyA. The median time to clinical response was 4 days in the IFX group and 5 days in the CyA group. Also, 47% of patients in the CyA group had mucosal healing compared with 45% in the IFX group. The quality-of-life assessed by the IBD questionnaire score increased by 78 points in the CyA group and by 100 points in the IFX group.Seventeen per cent (10 of 58) of patients in the CyA group and 21% (12 of 57) in the IFX group required a colectomy. Severe adverse events occurred in 16% (9) of patients in the CyA group and 25% (14) in the IFX group; the most common of these was worsening of disease activity. No deaths were reported. None of the secondary end-points assessed were statistically significant between both the treatment groups except for the rate of decrease of Lichtiger score between days 0 and 7.

COMMENT

Exacerbation of acute severe UC requires hospitalization in 18%–25% of patients.[1,2] For such patients, i.v. corticosteroids have been the mainstay of treatment since Truelove and Jewell published the first controlled trial of this treatment regimen in 1974, which led to a significant decrease in the associated morbidity and mortality.[3] Complete response to intensive medical treatment regimen with i.v. corticosteroids was reported in just over 40% of patients whereas incomplete response was reported in nearly 30% and the remaining patients required colectomy in the same admission.[4]

Surgery has been the standard of management in patients with severe exacerbation of UC who did not respond to intensive medical treatment. Delaying surgery in such non-responders leads to a higher mortality.[5] However, the preferred surgical choice which is restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) has been associated with complications. In a systematic review, the pooled incidence rates of pouch failure, pelvic sepsis and pouchitis were found to be 4.3%, 7.5% and 26.8%, respectively. With regard to the functional outcome, it was found that the pooled incidence of mild and severe faecal incontinence was 14.3% and 6.1%, respectively with the mean 24-hour defaecation frequency and night-time frequency being 5.9 and 1.5, respectively.[6] Also, there are issues such as fertility in women after IPAA. Hence, there is a need to explore possible medical treatment options in the management of steroid-refractory severe UC.

CyA and IFX are agents which have been used as rescue therapies in patients with steroid-refractory severe UC and are thus referred to as colon-salvage therapies.[7] There have been mainly uncontrolled studies though there are a few controlled studies too reporting the efficacy of these therapeutic options in patients with steroid-refractory severe UC. A few retrospective studies have compared CyA with IFX.

Intravenous CyA was shown to be more effective than a placebo in the immediate short term (success rate of 82% in patients who received CyA *v.* 0% in patients who received placebo) in a small randomized controlled trial of 20 patients with severe flare of UC who did not respond to 7 days of treatment with i.v. corticosteroids.[8,9] Similar response rates in the short-term were reported in a retrospective case series with CyA. However, the long-term remission rates were found to be low. Nearly 68%–88% of patients required a colectomy in the long-term.[10] Patients being treated with CyA need strict monitoring of blood levels to minimize side-effects.

IFX was shown to be superior to placebo (colectomy rate of 29% in patients who received IFX *v.* 67% in patients who received placebo, in the initial 90 days) in patients with acute severe or moderately severe UC who did not respond to i.v. steroids.[11] Similar results in the short-term were reported in retrospective case series.[12,13] However, the high cost of biological agents, side-effects including reactivation of tuberculosis are a major concern for their use, especially in developing countries. There have also been concerns about an increased risk of postoperative complications including pelvic sepsis in patients who received IFX,[14] though these findings need to be confirmed as evidence regarding such complications has been conflicting.[15,16]

Retrospective observational studies have compared the effectiveness of CyA and IFX in patients with steroid-refractory severe acute UC. A meta-analysis of these revealed that there was no significant difference between these two in the 3-month and 12-month colectomy rates, adverse drug reactions and post-operative complications.[17] However, a direct comparison of these drugs in a prospective study is required to compare and assess the effectiveness of these therapies in severe acute UC not responding to i.v. steroids. The investigators of this study attempted to answer the question.

The strengths of this trial are the relatively large number of patients, the multicentric nature of the study and a robust study design. This is the only randomized controlled study comparing the effectiveness of CyA and IFX in patients with steroid-refractory severe acute UC. However, there are a number of limitations. The investigators hypothesized CyA to be superior to IFX and calculated the sample size assuming a 30% difference in effectiveness between these two drugs. It means that a lesser degree of superiority would be missed by this study. The Lichtiger score was used to assess patients for inclusion into the study as well as to assess the treatment response. However, this index has not been validated and hence its usefulness is questionable. Also, there was a dichotomy in the results as more patients than expected had endoscopic remission (47% in the CyA group and 45% in the IFX group) at the end of the study period and this number exceeded the number of patients who had clinical response with therapy as assessed by the Lichtiger index. This might indicate that the ongoing symptoms in at least some of the patients could be due to irritable bowel syndrome rather than due to active inflammation related to UC. The results of this trial are applicable only to those patients who in the past have not received CyA, IFX or Aza. The administration of CyA was well tailored and titrated by close monitoring of blood levels of the medication but such therapeutic monitoring and dose modification was not done for IFX and this could have had a bearing on the efficacy as well as adverse effect profile. As only short-term results are currently available, no assessment can be made on the long-term results or the optimal long-term medical regimen in these settings.

To conclude, this trial has shown that both CyA and IFX were equally effective in the short-term for induction of remission and avoiding colectomy with reasonably low side-effects in a proportion of patients with steroid-refractory severe acute UC.

The effectiveness of such treatment tended to decrease with time even in the short-term follow-up of 98 days despite addition of maintenance therapy with azathioprine. The long-term effectiveness, avoidance of colectomy and side-effects need to be ascertained by following up the patients included in this study. The various limitations notwithstanding, the current study generated the much needed evidence for rescue medical therapies in patients with severe acute UC refractory to i.v. steroids.

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Preventing infection in the intensive care unit: Targeted or universal decolonization

Huang SS, Septimus E, Kleinman K, Moody J, Hickok J, Avery TR, Lankiewicz J, Gombosev A, Terpstra L, Hartford F, Hayden MK, Jernigan JA, Weinstein RA, Fraser VJ, Haffenreffer K, Cui E, Kaganov RE, Lolans K, Perlin JB, Platt R; CDC Prevention Epicenters Program; AHRQ DECIDE Network and Healthcare-Associated Infections Program. (University of California Irvine School of Medicine, Orange; Hospital Corporation of America, Houston and Nashville; Texas A&M Health Science Center, Houston; Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston; Rush Medical College and John Stroger Hospital of Cook County, Chicago; Centers for Disease Control and Prevention, Atlanta; Washington University in St Louis, St Louis, USA.) Targeted versus universal decolonization to prevent ICU infection. *N Engl J Med* 2013;**368:**2255-–65.

SUMMARY

This study—the Randomized Evaluation of Decolonization versus Universal Clearance to Eliminate Methicillin Resistant *Staphylococcus aureus* (REDUCE MRSA)—a pragmatic, cluster-randomized trial of 74 256 patients, compared three strategies to prevent MRSA clinical isolates and infections in 74 adult intensive care units (ICUs) in the USA. In group 1 (screening and isolation), MRSA screening of the nares was performed on admission to ICU and, if positive, contact precautions were implemented. In group 2 (targeted decolonization), in addition to contact precaution, patients who had colonization or infection with MRSA underwent daily bathing with chlorhexidine-impregnated clothes and were given intranasal mupirocin twice-daily for 5 days. In group 3 (universal decolonization), no MRSA screening was done and all patients were given intranasal mupirocin for 5 days and daily bathing with chlorhexidine-impregnated clothes.

For the primary outcome of ICU-attributable MRSA-positive clinical cultures, when compared with the baseline period (12 months), the modelled hazard ratios for MRSA clinical isolates during the intervention period (18 months) was 0.92 for group 1 (crude rate 3.4 isolates per 1000 days during the baseline period *v*. 3.2 isolates per 1000 days during the intervention period), 0.75 for group 2 (4.3 *v*. 3.2 isolates per 1000 days) and 0.63 for group 3 (3.4 *v*. 2.1 isolates per 1000 days). For the secondary outcomes, ICU-attributable bloodstream infections caused by MRSA and ICU-attributable infections caused by any pathogen, targeted or universal decolonization did not significantly impact MRSA bloodstream infections, although a significant reduction in bloodstream infections by any pathogen was demonstrated with both universal and targeted decolonization. The number needed to treat with decolonization to prevent one MRSA-positive clinical culture was 181 and for bloodstream infection by any pathogen it was 54. Adverse effects with chlorhexidine were mild and occurred in only 7 patients.

COMMENT

Healthcare-associated or hospital-acquired infections are not uncommon. They contribute to increased healthcare cost and result in morbidity and mortality. Nosocomial infections are associated with a higher mortality, not only in acute care and long-