Cyclosporine rescue therapy in acute severe ulcerative colitis combined with Clostricium difficile infection

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Introduction

Ulcerative colitis (UC) is a chronic inflammatory disorder of the large bowel characterised by clinical relapses and symptom-free periods. Acute severe ulcerative colitis (ASUC) is one of the most severe manifestation of UC which needs hospital admission and intensive medical therapy. In case of lack of prompt improve these patients need colectomy.

However phenomenon of ASUC is defined by the Truelowe-Witts scoring system, the differential diagnostic modalities are highly important before medical-, even the surgical therapy. Stool culture is a mandatory examination to be performed before starting immunosuppressants as a bowel rescue.

Clostridium difficile is a gram positive anaerob bacteria, causing pseudomembranous colitis. It manifests with severe diarrhoea, most frequently after antimicrobial therapy or in nosocomial circumstances. It may lead to complications like toxic megacolon, perforation, sepsis or death. Concomitant C. difficlie infection (CDI) is a frequent phenomenon in relapse of inflammatory bowel disease (IBD). It is more frequent in UC than in Crohn's disease (CD). Excluding C. difficile infection before bowel rescue therapies, like corticosteroids, infliximab (IFX) or cyclosporine (CsA) is extremely important.

Synchronous CDI and ASUC is a great challenge in a daily clinical practice due to the overlapping symptoms. Course of the disease might be more severe, and outcome might be more unfavourable in CDI combined ASUC (CDI-ASUC). There are no robust evidences regarding safety of initiating corticosteroid, immunomodulator or biologic therapy as a rescue therapy in CDI-ASUC. Guideline of American College of Gastroenterology (ACG) on CDI recommends simultaneously starting of empirical antibiotic therapy for CDI and immunotherapy for IBD flare until having the microbiological results - with a low level of evidence (D). However, using a combination of immunomodulators and antibiotics in CDI-ASUC was observed to have worse outcomes than using antibiotics alone in a multicentric study organised by the European Crohn's Colitis Organisation (E). Among 143 cases there were only 6 cases treated with CsA.

Here we report a case of CDI-ASUC patient who were treated with CS.

Case report

Ulcerative pancolitis (UC) was diagnosed in october of 2019 in a 37 years old female patient. Due to steroid resistance we started to administer infliximab as an induction therapy. A severe acute relapse started after the second induction dose. A cyclosporine rescue therapy was planned, but CDI was diagnosed after her clinical admission. Oral vancomycin and parenteral methronidasol was introduced and continued for 7 days. Mild clinical improvement, and significant decrease of CRP concentration was observed. After a repeated rectosigmoidoscopy but without a second toxin test we introduced parenteral cyclosporine in 3mg/bwkg dose. Serum drug concentration was checked regularly. Bowel movements decreased rapidly, we were able to discharge this patient in a good clinical and laboratory parameters on the 25th day after her admission. There was no any complication of cyclosporin during her hospitalisation.

Discussion

C. difficile is a gram-positive, spore-forming, anaerobic bacteria which able to form toxins leading to severe pseudomembranous colitis. In the late seventies it was identified as a causative agent of antibiotic related diarrhoea. After coming up of a virulent strain (NAP1/BI/027CDI became more frequent in hospitalised patients, and disease course became more severe also. Approximately 8-10% of adults residing in hospitals carry C. difficile, and about 5-15% of healthy population is a carrier of the bacteria (D).

CDI has been reported in 2.8%–11.% of the patients hospitalised for UC and 10.7%18.3% in outpatients with ileo pouch anal anastomosis (IPAA) (A). The overall risk for an UC patient to have clinically significant CDI was observed as high as 3.4% (95% confidence interval (CI): 2.5–4.6%) in a Canadian cohort between 2002 and 2009 (F).

Risk factors for CDI in IBD could be different compared to non-IBD population. Evidence is contradictory regarding antibiotic use as a risk factor for CDI in IBD patients, but proton pump inhibitors and non-steroid anti-inflammatory drugs may play a role in CDI (A). There are inconsistent evidences regarding corticosteroids and biological therapy in this context. A retrospective cohort study among 999 IBD patients (737 CD and 262 UC) observed that maintenance immunomodulator therapy (OR = 2.56, 95%CI: 1.285.12, p=0.008) and colonics disease is an independent risk factor for CDI (I). A retrospective study of 10662 IBD inpatients observed a greater risk of CDI within 3 months of corticosteroid initiation (RR = 3.4; 95%CI: 1.96.1) but no increased risk with preceding biologic therapy (J).

There are only scarce data regarding safety of initiating rescue immunomodulator therapies in CDI-ASUC patients. ACG 2013 guidelines on proved CDI recommend to continue ongoing immunosuppressants, but beware of escalation of these drugs in the setting of untreated CDI. ACG has no strict statement regarding initiate of rescue therapy in CDI-ASUC, but avoids from initiating of corticosteroids or IFX it the first 72 hours of anti-CDI therapy (E). Guideline of American Gastroenterological Association (AGA) advises to treat CDI with antibiotics for 3-4 days before escalating immunosupressants in case of worsening symptoms (M).

Effects of combined antibiotic and immunomodulator therapy was investigated in a multi-center study organised by the ECCO (F). It was observed that additive immunomodulator therapy leads to a worse outcome (likelihood ratio: 11.9; CI, 0.9 –157; p=0.06) compared to antibiotic therapy alone regarding death and colectomy rate within 3 months of admission. Treatment with 2 or 3 immunomodulators was correlated with the same outcomes, independent of disease severity at presentation (OR: 17; CI, 3.2–91; p=0.01). There were only six patients treated with CsA as a rescue, four of them reached these unfavourable primary endpoints.

Cylosporin is a calcineuron inhibitor molecule. It is administered as a rescue therapy in ASUC, however it is administered much more rare since Infliximab was introduced for the same indication. It might cause deterioration of kidney functions, hypertension, and serum triglyceride alterations. It predisposes respiratory infections.

There are no data in the literature regarding its safety in CDI-ASUC. There is not enough data even in the transplant literature. Only one retrospective study among lung transplant patients (n=217) treated with CsA or tacrolimus compared the potential of these drugs to cause CDI. Twenty patients (18.9%) in the CsA group had been registered with CDI compared to 31 patients (27%) in the tacrolimus group (p= 0.16) (K). Cyclosporin elaborated the colonisation, toxin production and consequential epithelial damage, cryptitis and acute inflammatory changes in mouse model (L).

There was no any adverse events regarding CsA therapy in ASUC in this patient. Further data collection is needed to make a recommendation regarding CsA use in CDI infected ASUC patient.

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