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CASE REPORT

Tumour necrosis factor inhibitors in critical care: Case report with review of the literature

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S U M M A R Y

This is a case report of a patient with Crohn's disease admitted to hospital with a typical flare. The main symptoms were abdominal pain and haemorrhagic diarrhoea. During the current admission she was commenced on her first course of Infliximab.

The clinical benefits of monoclonal TNF-alpha inhibitors are described. The anxieties relating to infectious complications that may be, in part related to the TNF-alpha inhibition are also discussed. At present the impact of these agents on critical illness is unclear but as the use of these effective drugs increase it is inevitable there will be an increase in patients presenting with critical illness who are concurrently on this treatment. Some of the implications are outlined.

1. Case report

A 47-year-old lady with a 17-year history of Crohn's disease was admitted to hospital with a typical flare, her main symptoms being abdominal pain and haemorrhagic diarrhoea. The Crohn's disease had previously been complicated by a colo-vesicular fistula requiring sub-total colectomy, and recurrent bouts of small bowel obstruction. During the current admission she was commenced on her first course of Infliximab.

She developed profound sepsis a few days after admission, requiring full ventilator and inotropic support. CT scan showed dilated small bowel loops with no evidence of perforation. She was commenced on Cefuroxime and Metronidazole. Following further clinical deterioration, a repeat CT scan revealed free fluid in the peritoneal cavity and multi focal areas of free gas, with subphrenic and paracolic collections. Disseminated intravascular coagulopathy was treated prior to laparotomy, at which faecal peritonitis was seen. Two large abscess cavities were resected and the abdomen washed out. The small bowel was necrotic necessitating and an end ileostomy with rectal stump formation. As the small bowel was dusky in appearance a laparostomy was formed.

A fistula developed.

Recurrent laparotomies for peritoneal washout and removal of intraperitoneal haematoma were performed. Bone marrow failure persisted requiring regular transfusion and she developed a refractory coagulopathy. There was a respiratory deterioration with new left-sided patchy consolidation on a chest radiograph.

A florid "punched out" vesicular rash of herpes simplex (HSV type 2) with lower lip stomatitis developed. High dose intravenous acyclovir and zovirax cream were commenced.

By day 19 multi-organ failure was present with ARDS, an open abdomen, disseminated intravascular coagulopathy, and HSV type II infection.

Left-sided facial twitching developed. A computed tomography scan of the brain was reported as consistent with a diagnosis of encephalitis. An EEG confirmed right temporal lobe periodic epileptiform discharge.

The seizure activity progressed despite escalating doses of anti-seizure medication (lorazepam, diazemuls, thiopentone, phenobarbitone, sodium valproate and infusions of propofol) and treatment doses of acyclovir.

By day 26 the pupils were dilated and responded sluggishly to light. Rescue measures for elevated ICP had been employed (including mannitol) but on day 33 post intensive care admission, bradycardia developed followed by asystole, and the patient died.

2. Discussion

2.1. Introduction

Crohn's disease is a controllable inflammatory condition of unknown cause, which affects the gastrointestinal tract. It is characterised by transmural inflammation, and can affect any portion of the GI tract, although the small intestine is most commonly affected (up to 80% of cases). At present Crohn's disease usually comes to the

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attention of Critical Care Physicians as post-operative high-dependency patients. Advances in therapy, however, may change that. In the future Crohn's patients may present more commonly with secondary infectious complications of therapy, as with the case under discussion. These complications have largely been linked to the use of TNF-alpha inhibition.

T-helper cells produce numerous cytokines which are implicated in the induction and maintenance of immune disease. The cytokines produced by Th1 and Th2 helper cells tend to have opposite effects on each other. In very simplistic terms, therapies for immune disorders have been developed to either down-regulate Th1 proinflammatory cytokines, or upregulate Th2 anti-inflammatory cytokines,

TNF-alpha is expressed by activated T-cells, B-cells and NK cells,[1] as well as macrophages in response to infectious or inflammatory stimuli. Synovial macrophages typically produce TNF-alpha.

TNF-alpha is a multi-potent proinflammatory cytokine, and is a pivotal co-factor for the regulation of other cytokines involved in the pathogenesis and progression of immune conditions such as Crohn's disease.

It occurs as a trimer (formed of three monomeric subunits), both as a soluble factor in plasma, and as a transmembrane factor. Binding to THR1 or THR2 receptors facilitate its biological activity.

It has many associations and plays a part in apoptosis, cell activation, cell recruitment and differentiation, the expression of adhesion molecules and the release of pro-coagulant factors. It also paradoxically participates in host resistance.[2] It does the latter through co-ordinating the orderly recruitment of leukocytes to target organs, and by granuloma formation. The role of TNF-alpha in host resistance raises concerns that anti-TNF-alpha agents may be associated with an increased risk of infection and malignancy. It may interfere with the integrity of the immune system, which is essential not only for defence against infectious organisms bit also the control of tumour antigens. Factors which predispose patients to infection, amongst which is TB[3] include the severity of the underlying disease but also the concomitant use of immunosuppressant therapy.[4] Crohn's disease, per se, does not predispose patients to opportunistic infections but the sequelae of Crohn's does.

In inflammatory bowel disease there is an increase in gram-negative sepsis. The mechanism for this is uncertain but it has been postulated that gut translocation, villous atrophy, gut wall breakdown and hypoperfusion of the gut are all implicated.

2.2. Therapy of inflammatory bowel disease

Pharmacological therapy for inflammatory bowel disease usually follows an 'escalating ladder' pattern. More toxic agents are added when the more benign agents have failed. Typically common regimes involving the use of 5-aminosalicyclic acid related drugs with antibiotics will escalate to steroids, and finally immunosuppressive agents. These include azathioprine and, more recently, tumour-necrosis factor inhibitors. Some authorities have begun adopting a 'top down' approach, where more powerful (and more toxic) agents are used first. It is unclear which of these strategies are more effective.[5]

Several TNF-alpha inhibitors have been developed and are increasingly being used in the management of Crohns. Table 1 lists the range of conditions which to date have been effectively treated with TNF-alpha inhibition.

There are two pharmacological approaches. Soluble TNF-alpha receptor fusion proteins such as Etanercept and monoclonal antibodies to tumour necrosis factor-alpha. These include infliximab, adalimumab, certolizumab pegol and golimumab. The latter three agents can be administered subcutaneously and are administered every four weeks. Certolizumab and golimumab are not yet approved for use in Europe. The monoclonal antibodies have the theoretical advantage of binding to TNF-alpha when it is still bound to the membrane, whereas etanercept only binds soluble TNF-alpha.

Infliximab, a chimeric human/mouse (70/30) IgG1 monoclonal antibody is an intravenously administered TNF-alpha inhibitor. It has high specificity for human TNF-alpha and binds with high affinity to both monomeric and trimeric forms of TNF-alpha. It forms very stable complexes with both soluble and transmembrane TNF and scarcely releases either once bound to them.[6] It is given every two weeks.

2.3. Clinical experience with TNF-alpha inhibition

Infliximab was approved for the treatment of Crohn's disease in 1998. Compelling evidence of efficacy was provided by a 12-week phase 2 trial in 108 patients,[7] followed by a 36 week extension trial[8] and a small phase 3 trial in 94 patients.[9]

Due to the safety concerns, patients were restricted to those with moderate to severely active Crohn's, or fistulating Crohn's disease which had been unresponsive to a full course of corticosteroid and immunosuppressant therapy.

Infliximab reduces the signs and symptoms of Crohn's disease in patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional treatment. It can induce and maintain remission of Crohn's disease that is refractory to standard therapy, whilst reducing or abolishing the need for steroid therapy. It is likely it will reduce the number of draining entero-cutaneous fistulae in patients with fistulating Crohn's disease. As such it is becoming an established part of the treatment of this disease. Elsewhere, the use of infliximab appears to be in evolution and it has now been studied in a wide range of other inflammatory conditions such as rheumatoid arthritis and the seronegative spondyloarthropathies.

2.4. Complications

A number of complications have become evident with the increased use of TNF-alpha inhibitors. These include injection site reactions, infusion reactions and increased infections complications. Demyelinating disease, heart failure, malignancy, and the induction of autoimmunity, have also been reported in association with infliximab use.

2.4.1. Infectious complications

There are numerous case reports, phase 3 trial, and post-marketing surveillance reports of infectious complications with the use of TNF-alpha inhibition. These were predominantly mild – upper respiratory and urinary tract infections although there are also more significant problems.

The issue is made more complex because concomitant treatments such as corticosteroids[12] or azathioprine[13] may also result in infectious complications including more severe complications such as abdominal abscess, sepsis and death. As overall mortality rates (0.4–1.3%) are comparable to those in studies of the natural history of Crohn's disease it is unclear whether the crude annual mortality rate is actually higher in patients taking TNF-alpha inhibitors.[10,11]

This is becoming clearer. A recent survey in the UK found that infectious complications are more likely within the first ninety days of starting treatment.[15] There is also limited evidence in the literature that surgical site infections may be more common if orthopaedic patients are taking TNF-alpha inhibitors at the time of surgery.[16] In a study of 500 consecutive patients treated at the Mayo Clinic, 48 patients had an infective episode. Of these, in 41