Tumor Necrosis Factor-α does not play a role in the pathogenesis of Crohn's disease

Gijs R. van den Brink
Department of Gastroenterology & Hepatology
Leiden University Medical Center
Leiden, the Netherlands
g.r.van_den_brink@lumc.nl

Department of Gastroenterology & Hepatology
Genève

Tumor Necrosis Factor (TNF)-α is a potent pro-inflammatory cytokine, produced by monocytes, macrophages and T-cells. Levels of TNF-α are increased in the mucosa and stool of patients with Crohn's disease which give rise to the idea that locally produced TNF-α may play an important role in the pathogenesis of Crohn's disease.
Infliximab, a chimeric humanized anti-TNF-α monoclonal antibody was originally designed for but unsuccessful in the treatment of patients with severe sepsis. In 1993 a young girl with debilitating and completely therapy resistant Crohn's disease was treated for the first time with Infliximab. Treatment resulted in rapid clinical improvement and complete endoscopic remission, lasting for three months (Lancet. 1993;342:173). This first successful treatment resulted in widespread and successful application of anti-TNF-α targeted therapy in patients with Crohn's disease.
Etanercept, a human soluble tumor necrosis factor receptor: Fc fusion protein which was equally effective in patients with Rheumatoid arthritis as infliximab. Strangely, when Etanercept was tried in a clinical trial in patients with Crohn's disease no effect was observed at all (Gastroenterology. 2001;121:1088).
The speaker will discuss published and unpublished data that support the recent concept that infliximab does not act by neutralizing soluble TNF-α in patients with Crohn's disease but instead induces apoptosis of activated lamina propria T lymphocytes.(Gastroenterology. 2003;124:1774) It does so by binding to membrane bound TNF-α on activated T cells. The apoptotic response depends in the induction of reverse intracellular signaling via the intracellular tail of membrane-bound TNF-α.
The story of Infliximab is an example of the fact that even in the days of targeted therapies novel drugs work in unexpected ways.