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New biological agents for the treatment of the "high risk" IBD patients

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Abstract. – *Background:* **Several new biological drugs have been introduced in the last decade or are under investigation for the treatment of IBD. They include anti TNFα agents, anti adhesion molecules, anti IL-12/23, anti IL-6R and others. Their role in IBD therapy will be discussed in regard of the association of chronic inflammation and cancer in the gut. The risk of colorectal cancer is increased in ulcerative colitis (UC) and, to some extent, in Crohn's disease (CD). This association is well known from many years. However, the mechanisms linking chronic inflammation and carcinogenesis are beginning to be elucidated only recently.**

Results and Conclusions: **Experimental data indicate that several cytokines could play a role in promoting tumour development. In this perspective, the anti cytokine agents could be not only powerful tools in treating inflammation but also efficacious in preventing the onset of inflammation associated colorectal cancer.**

Key Words:

Inflammatory bowel diseases, Colorectal cancer, Proinflamatory, Cytokines, Chemokines, Interleukines, Antagonists of TNF, Infliximab, Adalimumab, Certolizumab pegol.

Introduction

Cancer Risk in Inflammatory Bowel Disease

Several studies demonstrated that patients affected by inflammatory bowel disease (IBD), have an increased risk of colorectal cancer development. In Ulcerative Colitis (UC) the risk is estimated to be 2% after 10 years of disease, 8% after 20 years, 18% after 30 years, according to cumulative probabilities from a meta-analysis (1). The cancer risk seems to be higher in UC patients with long-standing and extensive disease. In Crohn's Disease (CD) the chance of developing cancer is also elevated: most cancers occur in those tracts with extensive inflammatory damage, but were also detected in bypassed or excluded segments of bowel. Moreover, other types of neoplasms were observed in CD patients, such as lymphoma and carcinoid tumors.

However, population based studies published within the past 5 years suggest that cancer risk has decreased over time, despite lower frequency of colectomies. The screening program of colonscopic surveillance has an important role in cancer prevention, although surveillance program in IBD remains controversial: recent studies found that colonscopy screening may not improve survival[2]. The reduction of bowel neoplasia in IBD patients, has been possibly related, in part, to the wider use of maintenance treatments.

Table I resumes factors associated with colorectal cancer risk in IBD[3].

In colon carcinogenesis, chronic inflammation of colonic mucosa in IBD has a critical role and the molecular processes leading to colitis-associated cancer are different from those of sporadic colorectal cancer. Recent evidence demonstrated the role of various cytokines, released by epithelial and immune cells, in the pathogenesis of cancer associated with colitis.

Mechanisms Linking Chronic Inflammation and Cancer

In inflammatory bowel disease, the well controlled balance of the intestinal immune system is disturbed at all levels. Luminal antigens gain access to the underlying mucosa through a leaky barrier and an impaired innate immune response of the epithelial layer. Dendritic cells recognize commensal microbes as pathogens and change their status from tolerogenic to activating. So naive T cells differentiate into effector T cells (Th1, Th17, Th2) and natural killer T cells. Ef-

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Table I. Factors associated with colorectal cancer risk in IBD*.

Factors that increase CRC risk	Factors that decrease CRC risk
Longer duration of colitis	Prophylactic total proctocolectomy
Greater extent of colonic involvement	Regular doctor visits
Family history of colorectal cancer (CRC)	Surveillance colonscopy
Primary sclerosing cholangitis (PSC)	Chemioprevention
Young age of IBD onset (some studies)	
Backwash ileitis	
Severity of histological inflammation	
History of dysplasia	

*Modified from ref. 3.

fector cells (Th1, Th17, Th2) predominate over regulatory T cells (Th3, Tr). Activated T cells through proinflammatory cytokines stimulate macrophages to secrete large amounts of TNFα, IL-1 and IL-6. Leukocytes enter from the mucosal vasculature and release chemokines which amplify and perpetuate this vicious circle with chronic tissue damage[4].

Persistent release of reactive nitrogen and oxygen species leads to genome damage, thus contributing to tumorigenesis. Inflammatory cells and their products, cytokines, chemokines and growth factors play a role in cancer promotion and progression steps.

TNFα, TGFβ, IL-6, members of IL-12 family, such as IL-12, IL-23, IL-27 seem to be involved in inflammation associated carcinogenesis. Instead, IL-10 is an anti-tumor and anti-angiogenic cytokine. Obviously these molecules are potential drug targets[5].

Endo et al.[6] demonstrated that Activation-Induced Cytidine Deaminase (AID), an inducer of somatic hypermutations in the immunoglobulin gene, required for immunoglobulin class switch recombination, links between chronic inflammation and development of colitis-associated colorectal cancer. Th2 cytokines (IL-4 and IL-13) induce aberrant AID expression in human colonic cells and there is an association between AID expression and preferential mutation of the tumor suppressor gene p53 in human colonic cells.

Among the large number of cytokines and growth factors released during inflammation that may influence the process of carcinogenesis, IL-6 upregulates anti-apoptotic factors trough a process known as trans-signalling: so it may be implicated in colitis associated-cancer. Moreover, colorectal cancer cells may acquire the capacity to express IL-6[7].

Popivanova et al.[8] underlie the crucial role of TNFα as a mediator of colitis inflammation and associated-cancer. Wild-type mice treated with azoxymethane (AOM) followed by dextran sulfate sodium (DSS) develop severe ulcerative inflammation of colonic mucosa similar to human UC and successively progress to colon cancer. High levels of TNFα and its receptor TNF-Rp55 were expressed in the lamina propria and submucosal colonic regions. It was demonstrated that mice deficient in TNF-Rp55, treated with AOM and DSS, had less inflammatory infiltrate, less tissue damage and few neoplastic cells. Moreover etanercept, a TNFα antagonist, was administrated to wild-type mice treated with AOM and DSS. In these mice, the TNFα blockade reduced the colonic infiltration by macrophages and neutrophils and the number of tumoral cells. Furthermore, etanercept reduced the numbers of COX-2 expressing cells, that are involved in both cancer neovascularization and β-catenin activation. This study suggests a possible role of TNFα antagonists in the prevention of colitis-associated colon cancer.

Biologic Agents in IBD Therapy: Drug Targets

In the last 30 years, several medical treatments have been introduced for the management of IBD. These therapies are based on the modulation of autoimmune and inflammatory response.

Three TNFα antagonists are currently available: infliximab, a chimeric anti-TNFα monoclonal antibody; adalimumab, a fully human IgG1 anti-TNFα monoclonal antibody; certolizumab pegol, a pegylated humanized Fab' fragment that binds TNFα.

Infliximab

Evidence coming from the study published by Targan et al.[9] documented that a single infusion

of infliximab is an effective short-treatment for patients with moderate to severe CD that is refractory to standard treatment. The ACCENT I clinical trial[10] suggested that patients with CD who respond to an initial dose of infliximab are more likely to be in remission at weeks 30 and 54, to discontinue corticosteroids, and to keep on their response for a longer period of time, if infliximab treatment is maintained every 8 weeks. Furthermore, Present et al.[11] evaluated the efficacy of infliximab in healing enterocutaneous fistulas[11]. The ACCENT II study[12], the largest controlled trial on infliximab maintenance therapy in perianal and enterocutaneous fistulizing CD, underlies that long-term therapy is more effective than the short-term one.

As regards UC, two randomized double-blind, placebo-controlled studies evaluated the efficacy and safety of infliximab: ACT I and ACT II demonstrated that an induction regimen of 3 doses of infliximab followed by maintenance infusions every 8 weeks in patients with moderate to severe active UC was superior to placebo in achieving clinical response and remission, mucosal healing, and corticosteroid-sparing effects during 30 to 54 weeks of therapy[13].

Adalimumab

Adalimumab, was superior to placebo for inducing clinical remission and response in anti-TNF naive subjects with moderate-severe Crohn's disease, as demonstrated in CLASSIC I trial[14]. Results of GAIN trial suggest also that adalimumab therapy is superior to placebo for inducing remission and response in patients with moderate to severe CD who were intolerant of infliximab or had previously responded to infliximab and then lost response[15]. Subcutaneous administration of adalimumab resulted effective in the maintenance of remission or response, potential steroid sparing effects, and improved quality of life over one year in CD including patients naive to biologic therapy and patients who failed infliximab. Adalimumab was well-tolerated, and the safety profile was consistent with prior studies in CD. Data from both CLASSIC II and CHARM trials support the use of maintenance dosing regimen of adalimumab for patients with moderately to severely active CD[16,17]. Moreover, adalimumab demonstrated statistically significant and clinically meaningful effects on fistula closure.

Certolizumab Pegol

PRECISE I and PRECISE II assess the efficacy of Certolizumab pegol in the induction and maintenance of response and remission in patients with active CD. These data support also the tolerability of this anti-TNF agent[18].

Beyond Antagonists of TNF

Therapeutic perspectives in IBD have been deeply changed over recent years and other inflammatory targets were discovered.

Natalizumab, a humanized monoclonal antibody against α4 integrin, inhibits leukocyte adhesion and migration into inflamed tissue. Induction therapy with natalizumab for Crohn's disease resulted in small, not significant improvements in response and remission rates. Nevertheless, the benefit of natalizumab will need to be weighed against the risk of serious adverse events, including progressive multifocal leukoencephalopathy[19].

IL-12 is a cytokine composed of 2 subunits (p40 and p35) that induces Th1 differentiation and production of other cytokines (IFNγ and TNFα). IL-23 is a cytokine composed of 2 subunits (p40 and p19) that induces Th17 differentiation and production of cytokines such as IL-17, IL-6 and TNFα. Polymorphisms of IL-23R gene have been associated to IBD susceptibility. Ustekinumab, a fully human IgG1 monoclonal antibody to the IL-12/23 shared p40 subunit, and ABT-874/J695, a recombinant human full-length IgG1 antibody genetically modified to recognize interleukin-12/23 p40 subunit, will play an important role in the future treatment of IBD. Phase II/III clinical trial are ongoing as regards both drugs[20].

Tocilizumab, a humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody, approved for treatment of severe rheumatoid arthritis, is currently investigated for potential use in the treatment of other IL-6 related disorders including CD[21].

Safety Data of Biological Agents for IBD: do they Increase Cancer Risk?

Although the use of TNF-antagonist led to treatment advantages for IBD patients by offering a more targeted anti-inflammatory therapy, there is concern that it might increase the risk of non-Hodgkin's lymphoma (NHL).

In clinical trials of infliximab for all indications, patients treated with infliximab had a higher incidence rate of lymphoma (0.11 cases per

100 person-years) than patients treated with placebo (0 cases). After commercial release, an increasing number of lymphomas were reported and the standardized incidence ratio (SIR) for lymphoma in patients treated with infliximab has been estimated ≅ 4[22]. In a large single-center experience in IBD to date, (over 500 consecutive patients receiving infliximab treatment for CD followed for a median of 17 months), eighty-six percent of patients were taking concomitant immunosuppressive therapy (11% methotrexate-MTX and 75% azathioprine-AZA). Two patients developed lymphoma (0.4%)[23]. In a population-based cohort study from Sweden, 212 IBD patients who received therapy with infliximab were followed for a 28-month period. The Authors reported the development of NHL in 3 patients (1.4%), all of whom had CD, and 1 of whom was on concomitant AZA[24]. Rare cases of the very aggressive hepatosplenic T-cell lymphoma have been reported in adolescent and young adult patients with CD treated with anti TNFα agents on concomitant treatment with azathioprine or 6-mercaptopurine.

Analyses of lymphoma risk in patients receiving biologic agents directed against TNFα are confounded by concomitant use of immunosuppressive agents in most of these patients. Nevertheless, there may be a small but real risk of lymphoma associated with these therapies.

Conclusions

Biologic TNFα blockage is an effective option for many patients whose disease is inadequately controlled by conventional treatment. Overall the benefit-risk for biologic TNFα blockage appears favourable but long-term evaluation and monitoring of rare adverse events must continue. Future research will clarify if biological therapies of IBD could play a role also in the prevention of inflammation associated colorectal dysplasia and cancer.

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