EDITORIAL

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Anti-Tumor Necrosis Factor Alpha Antibodies for Remission Maintenance Therapy in Inflammatory Bowel Disease

Przeciwciała przeciwko czynnikowi martwicy nowotworów α w terapii podtrzymującej remisję w nieswoistych zapaleniach jelit

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Abstract

Inflammatory bowel disease (IBD) comprises chronic inflammatory conditions of the digestive tract including ulcerative colitis, Crohn's disease, and indeterminate colitis. The etiopathogenesis of IBD remains unknown and is probably multifactorial. A key pro-inflammatory cytokine in IBD is tumor necrosis factor α (TNF-α). The goals of the medical treatment of IBD include inducing a clinical response, maintaining clinical remission, mucosal healing, minimizing the use of corticosteroids, improvement of quality of life, and prevention of colorectal cancer. A huge advance in the therapy of inflammatory bowel disease has been the introduction of biological therapies with anti-TNF-α antibodies (infliximab, adalimumab, certolizumab) already administrated in clinical practice (**Adv Clin Exp Med 2010, 19, 2, 143–150**).

Key words: inflammatory bowel disease, ulcerative colitis, Crohn's disease, biological therapy, tumor necrosis factor α, infliximab, adalimumab, certolizumab.

Streszczenie

Nieswoiste zapalenia jelit to przewlekłe choroby przewodu pokarmowego obejmujące wrzodziejące zapalenie jelita grubego, chorobę Leśniowskiego-Crohna i nieokreślone zapalenie jelita grubego. Etiopatogeneza tych chorób pozostaje nieznana i przyjmuje się, że jest wieloczynnikowa. Kluczową cytokiną prozapalną w nieswoistych zapaleniach jelit jest czynnik martwicy nowotworów α (TNF-α). Wśród celów leczenia zachowawczego w nieswoistych zapaleniach jelit są: osiągnięcie odpowiedzi klinicznej (leczenie indukcyjne), podtrzymanie remisji, gojenie błony śluzowej, ograniczenie stosowania glukokortykosteroidów, poprawa jakości życia chorych, prewencja raka jelita grubego. Przełomem w terapii nieswoistych zapaleń jelit stało się wprowadzenie leków biologicznych, z których w praktyce klinicznej stosuje się przeciwciała anty-TNF-α (infliksymab, adalimumab, certolizumab) (**Adv Clin Exp Med 2010, 19, 2, 143–150**).

Słowa kluczowe: nieswoiste zapalenia jelit, wrzodziejące zapalenie jelita grubego, choroba Crohna, terapia biologiczna, czynnik martwicy nowotworów α, infliksymab, adalimumab, certolizumab.

Inflammatory bowel disease (IBD) includes chronic inflammatory conditions of the digestive tract such as ulcerative colitis (UC), Crohn's disease (CD), and indeterminate colitis. The etiological factors of IBD are unclear. Epidemiological studies have shown a stable prevalence of UC and an increasing prevalence of CD [1]. Peak morbidity of UC and CD is observed between 20–40 years and 15–25 years, respectively. Mucosal ulceration, bloody diarrhea, abdominal pain, and phases of flare and remission are characteristic of UC. The symptoms of CD depend on the location of the inflammatory changes in the digestive tract and the disease course (presence of stenoses, fistulas, perianal changes). The diagnostic algorithm in IBD involves laboratory tests, endoscopic and/or radiological examinations, and pathological studies. Many classifications and indices are applied

in the evaluation of patients with IBD, mostly for the purposes of trials. The most commonly used are the Montreal classification and the Crohn's Disease Activity Index (CDAI) together with laboratory markers (mostly C-reactive protein, CRP). As is known, IBD is associated with a worsening of quality of life; therefore QoL has become one of the parameters used in trials evaluating new therapeutic strategies. The contemporary goals of the therapy of inflammatory bowel diseases are inducing a clinical response, maintaining a clinical remission, mucosal healing (chronic inflammation in UC is regarded as probably the most important risk factor for cancer development [2]), minimizing the use of corticosteroids, improvement of quality of life, and prevention of colorectal cancer.

TNF-α

TNF-α is the key pro-inflammatory cytokine in Crohn's disease. TNF-α is produced by innate immune cells such as macrophages, monocytes, and differentiated T cells. The pro-inflammatory properties of this multifunctional cytokine are associated with the increased production of IL-1β and IL-6, initiation of acute-phase responses, and inhibition of apoptosis [3]. The etiology of IBD remains unknown, but CD and UC are considered immune diseases of T helper 1 (Th 1) and T helper 2 (Th 2) type lymphocytes, respectively. TNF-α, together with other proinflammatory cytokines (interleukin-2, interferon-γ), is produced by Th 1 lymphocytes. An increased concentration of TNF-α was found in blood, lamina propria, and stool of patients with IBD [4, 5].

Anti-TNF-α Antibodies

The results of studies that provided new insights into the pathogenesis of IBD and the role of TNF-α led to the development of biological therapies that target this key molecule. Three anti-TNF-α agents are currently available in clinical practice: infliximab, adalimumab, and certolizumab. Infliximab was the first anti-TNF agent approved by the FDA for the treatment of Crohn's disease in 1998. Infliximab is a mouse-human chimeric monoclonal antibody administrated intravenously. Adalimumab is fully human antibody that patients receive subcutaneously. Certolizumab pegol is a pegylated Fab` fragment of a humanized anti-TNF-α monoclonal antibody administrated subcutaneously.

Trials and Meta-Analyses of Trials with Anti-TNF-α for IBD

It is well documented that infliximab induces clinical remission in patients with moderate to severe active CD. Additionally, it is effective in decreasing corticosteroid requirements and fistula closure. The ACCENT I study (A Crohn's disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen) was designed to assess the efficacy and safety of infliximab in patients with CD. Five hundred seventy-three patients with active CD (CDAI>220) received intravenously an infusion of infliximab at week 0 and after evaluation of response at week 2 they were randomized to three regimens: placebo (episodic treatment), infliximab 5 mg/kg at weeks 0, 2, and 6 and then every 8 weeks until week 46 (5-mg/kg scheduled maintenance), or infliximab 5 mg/kg at weeks 2 and 6 followed by 10 mg/kg every 8 weeks until week 46 (10-mg/kg scheduled maintenance). Patients who responded to the initial dose of infliximab and received infliximab every 8 weeks maintained the response longer [6]. Additionally, scheduled infliximab therapy was more effective than episodic treatment in healing mucosal lesions. An interesting finding in this study was the lack of a strong relationship between mucosal healing and clinical remission [7].

The effectiveness of infliximab in induction and maintenance therapy in adults with moderate-to-severe ulcerative colitis was evaluated in two randomized trials: the ACT 1 (364 patients) and ACT 2 (364 patients) (Active Ulcerative Colitis Trials 1 and 2). Patients received infliximab intravenously (5 or 10 mg per kilogram of body weight) at weeks 0, 2, and 6 and then every 8 weeks through week 46 in ACT 1 and through week 22 in ACT 2. In both studies, the rates of clinical response at weeks 8, 30, and 54 were higher in the patients treated with infliximab than in the placebo groups. Moreover, in both studies mucosal healing at weeks 8, 30, and 54 was found significantly more often in the patients receiving infliximab. The frequency of adverse events, including infections, did not differ between the infliximab and placebo groups [8].

The effectiveness of adalimumab in the induction therapy for CD was shown in the CLASSIC I trial (Clinical Assessment of Adalimumab Safety and Efficacy Studied as an Induction Therapy in Crohn's Disease) [9]. The efficacy and safety of subcutaneously administrated adalimumab for the maintenance treatment of CD was evaluated in the CLASSIC II trial [10]. Adalimumab was effective in the maintenance of remission for over one year.

Moreover, treatment with adalimumab was associated with quality-of-life improvement and had a steroid-sparing effect.

The CHARM trial (Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance) was designed to evaluate the efficacy and safety of adalimumab [11]. After induction therapy the patients were randomized (n = 778) to double-blind placebo treatment with placebo, adalimumab 40 mg every other week, or adalimumab 40 mg weekly through week 56. Both adalimumab strategies were more effective than placebo in maintaining remission. Moreover, adalimumab was well tolerated. The authors concluded that adalimumab is an effective maintenance therapy in patients with moderate to severe CD who have responded to induction therapy with adalimumab. Patients receiving adalimumab had better quality of life compared with those who received placebo. Additionally, complete fistula closure occurred more often in patients receiving adalimumab. Another observation of great clinical significance is that the patients were in clinical remission also after the discontinuation of corticosteroids.

Adalimumab-treated patients of the CHARM trial were enrolled in the open-label extension trial ADHERE (Additional Long-Term Dosing With HUMIRA to Evaluate Sustained Remission and Efficacy in CD). The results of this trial showed that adalimumab is effective in the maintenance therapy of CD for 3 years. Additionally, the study demonstrated that the adalimumab-treated patients who were in remission at the end of CHARM maintained remission for an additional 2 years [12]. Moreover, the steroid-sparring effect of adalimumab demonstrated in CHARM was also sustained; 27% and 28% of the patients receiving steroids at CHARM baseline and randomized to adalimumab were in steroid-free remission at 2 and 3 years after the CHARM baseline [13]. Feagan et al. studied the influence of adalimumab treatment on the risk of both all-cause and CD-related hospitalization and surgery. Results of the comparison of CHARM patients receiving placebo and adalimumab demonstrated that patients receiving adalimumab had a lower one-year risk of hospitalization and surgery than patients receiving placebo [14]. Data from the CHARM and ADHERE trials were additionally analyzed for the evaluation of the number and the risk of CD-related hospitalization. The numbers of hospitalizations per patient-year were year 1: 0.16 (73/458), year 2: 0.12 (36/373), and year 3: 0.08 (20/262). Weibull model analysis of hospitalization rates demonstrated that the risk of hospitalization decreased over time, which, as the authors highlighted in the conclusion, is related with lower healthcare costs for patients treated with adalimumab [15]. Furthermore, the impact of long-term therapy with adalimumab on the quality of life (QoL) of patients enrolled in the CHARM and ADHERE trials was evaluated. QoL was measured with the Inflammatory Bowel Disease Questionnaire (IBDQ), Short Form 36 Survey (SF-36), Physical (PCS), and Mental (MCS) Component Summaries. QoL not only improved in patients who received adalimumab in the CHARM trial (both regimens: 40 mg every other week and 40 mg weekly), but also for three years of adalimumab maintenance therapy [16]. Also, patients with fistulizing CD demonstrated significant and sustained improvement in QoL measures [17]. However, it needs to be underlined that ADHERE is an ongoing study and the analyses are based on preliminary results.

The efficacy of certolizumab pegol was evaluated in a group of 662 patients with moderate-to-severe CD. Patients were randomized to receive certolizumab pegol (400 mg subcutaneously) or placebo at weeks 0, 2, and 4 and then every 4 weeks. Although treatment with certolizumab resulted in a modest improvement in response, there was no improvement in remission rate [18]. The PRECISE 2 trial (Pegylated Antibody Fragment Evaluation in Crohn's disease: Safety and Efficacy) evaluated the safety and efficacy of certolizumab pegol for maintenance therapy in moderate-to-severe CD. Patients who responded to the induction therapy (400 mg subcutaneously) maintained the remission more often at week 26 when they received certolizumab than placebo [19].

Peyrin-Biroulet et al. conducted a meta-analysis of placebo-controlled trials (fourteen trials with luminal CD, n = 3995, and ten trials with fistulizing CD, n = 776) to evaluate the effectiveness and safety of anti-TNF therapy of Crohn's disease. The authors concluded that infliximab, adalimumab, and certolizumab are effective in luminal CD. Although anti-TNF therapy was not associated with an increased risk of death, malignancy, or serious infection among 5356 patients in 15 studies, the authors suggested a longer duration of follow-up and a larger number of patients for a better assessment of the safety of anti-TNF agents in CD [20].

Guidelines

With the introduction of biological therapies, the problem of a treatment algorithm in Crohn's disease raised. There is an ongoing discussion if the medical therapy for CD should be step-up (classic therapeutic strategy) or top-down (early introduction of biological therapy and immuno-

modulators) therapy [21]. Rutgeerts et al. underlined that due to the safety risk, the place of biological therapies in treatment algorithms must be defined carefully [22].

European Crohn's and Colitis Organization (ECCO) Consensuses

First European evidence-based consensus on the diagnosis and management of CD was published in 2006 [23]. An up-dated consensus published in 2010 presents the treatment strategy of CD based on the newest study results [24]. The part of the consensus dedicated to maintenance therapy cities the results of studies aimed at evaluating the epidemiology of relapse and factors predicting relapse (age ≤ 25 years, interval more than six months since the previous flare, time greater than the years since the first symptoms of the disease, and of treatment). 5-ASA and corticosteroids are not recommended for maintenance therapy of CD. Budesonide, although it may delay the relapse, is not effective at maintaining remission for 12 months. Azathioprine at a dose of 2.0–2.5 mg/kg/d and methotrexate (intramuscularly, 15 mg/week) are effective in maintaining remission of CD. The ECCO consensus demonstrates evidence for the effectiveness of infliximab, adalimumab, and certolizumab in maintaining remission of luminal CD in patients who responded to induction therapy. The European evidence-based consensus on the diagnosis and management of ulcerative colitis was published in 2008. The ECCO consensus defines the goals of maintenance therapy (steroid-free remission, clinically and endoscopically defined) and factors which determinate the choice of maintenance therapy (e.g. disease extent, disease course, cancer prevention). The guidelines underline that all patients require maintenance therapy. 5-ASA preparations at a minimal dose of 1 g per day have a basic place in the therapy. Azathioprine and mercaptopurine are recommended in the certain situations, for example intolerance to 5-ASA and steroid dependence. The ECCO consensus presents the results of ACT1 and ACT2 studies and includes the statement that a patient responding to infliximab is recommended for maintenance therapy. Short-term combination (6 months) of infliximab with an immunosuppressant is recommended in order to decrease immunogenicity. The duration of combined treatment should be consider carefully due to the safety problems. Other than infliximab, biological therapies have not been evaluated for maintenance therapy in ulcerative colitis. Additionally, data on the duration of treatment with azathioprine and infliximab are missing [25].

American College of Gastroenterology Practice Guidelines

The American College of Gastroenterology (ACG) guidelines "Management of Crohn's Disease in adults" were published in 2009. Analogous to the ECCO consensus, sulfasalazine, mesalamine, and conventional corticosteroids are not recommended in the maintenance therapy of CD after inductive medical therapy. The ACG guidelines share the same statement about budezonid. The authors of these guidelines point out that azathioprine/6-mercaptopurine and methotrexate are effective after inductive therapy with corticosteroids. However, the possible side effects of azathioprine need to be monitored. The new approach to the maintenance therapy in CD is related to the demonstration that infliximab, adalimumab, and certolizumab pegol can maintain remission. Moreover, infliximab is more effective than azathioprine in patients [26].

Polish Recommendations

Polish recommendations on the management of IBD patients were published in 2007. Maintenance therapy in ulcerative colitis includes sulfasalazine (2–3 g daily) or 5-aminosalicylic acid. A small percentage of patients may require the administration of immunosuppressive agents (azathioprine, 6-mercaptopurine). A possible positive effect of probiotics is also presented. The medical treatment of CD is more complex. Currently, steroids are the most commonly used anti-inflammatory agent in the active disease. Although slow tapering of the dose over 2–3 months is recommended, about 25% of patients are steroid dependent and require continuous steroid therapy. Sulfasalazine and 5-aminosalicylic acid can be effective in flare prevention in some cases, especially after small bowel resection. The introduction of immunosuppressive medications is indicated in patients with fistula, severe perianal disease, and steroid dependence. A steroid-dependent patient can also be treated with methotrexate. The recommendations also demonstrate the new therapeutic approach to CD with the biological therapies. Indications for infliximab treatment in CD are induction therapy in moderate and severe active disease not responding to conventional treatment, maintenance therapy in patients who

responded to induction therapy with infliximab, and induction and maintenance treatment in patients with fistula resistant to conventional treatment. The recommendations also shortly describe the results of clinical trials with adalimumab (the CLASSIC I, CLASSIC II, and CHARM trials) and underline the good safety profile of this agent and the small percentage of patients developing antibodies against it [27].

Safety of Anti-TNF-α in IBD

The safety profiles of the anti-TNF-α agents need to be always considered before the introduction of this therapy. The following side effects are associated with anti-TNF-α therapy: infections, antibody formation, infusion reactions, autoimmunity, malignancies, demyelization, abnormal liver function tests, cardiac abnormalities, and skin eruptions [28, 29]. The risk of serious infection in the TREAT Registry in patients receiving infliximab (prospective observational multicenter long-term registry of North American patients with CD, n = 6290, 3179 infliximab treated) was related to concomitant use of prednisone and disease severity. The mortality rates did not differ between patients treated with infliximab and those who were not [30]. An analysis of the patients of the ACCENT I, ACCENT II, ACT 1, and ACT 2 trials (n = 1383) receiving infliximab maintenance therapy showed that the infection and serious infection rate did not differ when concomitant immunomodulators were administrated [31]. As opportunistic infections may be a new problem in IBD patients receiving immunomodulators, The European Crohn's and Colitis Organisation published guidelines in 2009. The ECCO consensus on opportunistic infections in IBD patients recommends before the introduction of immunomodulators:

- a detailed interview (history of bacterial, fungal, and viral infections (varicella zoster virus, herpes simplex virus, hepatitis B virus), risk of tuberculosis, history of travel);
- a physical examination (signs of active infections);
- laboratory tests (e.g. neutrophil and lymphocyte cell count, hepatitis B virus serology);
- screening for tuberculosis;
- consideration of vaccination.

Based on data showing that a significant part of IBD patients will receive immunomodulators, the consensus suggests considering a vaccination program at the diagnosis of inflammatory bowel disease [32].

There is also ongoing discussion on the relation between anti-TNF-α therapy and the risk of lymphoma. Siegel et al. demonstrated the results of a meta-analysis evaluating the risk of non-Hodgkin lymphoma (NHL) in adult CD patients treated with anti-TNF agents. The rate of NHL among patients receiving anti-TNF was compared with that of patients treated with immunomodulators and with a population-based registry. The study included 21,178 patient-years of follow-up. Although the risk of NHL was significantly higher among the patients treated with anti-TNF agents or immunomodulators compared with the expected rate from the database (6.1 vs. 1.9 vs. 4.0 per 10,000 patient-years, respectively), the authors concluded that the absolute rate of NHL was low [33].

In the SONIC clinical trial, azathioprine together with infliximab was more effective than azathioprine or infliximab as monotherapy. Simultaneously, all treatment regimens had similar safety profiles [34].

Conclusions

Three anti-TNF-α agents are now approved for the treatment of Crohn's disease: infliximab, adalimumab, and certolizumab. Although comparative trials of these agents are missing, it seems that they are equally effective in luminal and fistulizing CD and infliximab is effective in ulcerative colitis. They also share similar safety profiles, but differ in their mode of administration [35].

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