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Biological therapy for pediatric ulcerative colitis

Leczenie biologiczne wrzodziejącego zapalenia jelita grubego u dzieci

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S u m m a r y

Ulcerative colitis is a chronic inflammatory bowel disease of unknown etiology. Actually, the main pathogenic role is attributed to pro-inflammatory cytokines, the major one is Tumour Necrosis Factor alpha (TNF-α). The advances in understanding the pathogenesis of inflammatory bowel disease have led to the introduction of new therapeutic options, biological agents. Till now U.S. Food and Drug Administration (FDA) approved three monoclonal antibodies against TNF-α to treat adults with moderate to severe ulcerative colitis with an inadequate response to conventional therapy, or who are intolerant, or have medical contraindications for such therapy. These are: infliximab, adalimumab and golimumab. Only infliximab has been approved by the agency to treat children, nonetheless adalimumab is also used in treatment of pediatric patients with ulcerative colitis. The purpose of this review is to summarize the current knowledge on the use of biologics in pediatric ulcerative colitis. Currently, this new therapeutic options are the integral part of the pediatric ulcerative colitis treatment algorithm and with time probably will be used more extensively.

S t r e s z c z e n i e

Wrzodziejące zapalenie jelita grubego jest przewlekłą chorobą zapalną jelit o nieznanej etiologii. Obecnie główną rolę w patogenezie przypisuje się cytokinom prozapalnym, główną z nich jest czynnik martwicy nowotworów (TNF-α). Postępy w zrozumieniu patogenezy choroby doprowadziły do wprowadzenia nowych opcji terapeutycznych, mianowicie leków biologicznych. Amerykańska Agencja Żywności i Leków (FDA) do dnia dzisiejszego zarejestrowała trzy przeciwciała monoklonalne skierowane przeciwko TNF-α do leczenia pacjentów dorosłych ze średnio ciężką i ciężką postacią wrzodziejącego zapalenia jelita grubego, którzy niedostatecznie odpowiedzieli na standardowe leczenie lub leczenie jest źle tolerowane bądź istnieją przeciwwskazania do konwencjonalnej terapii. Należą do nich infliximab, adalimumab i golimumab. Jedynie infliximab został zarejestrowany przez agencję do leczenia pacjentów pediatrycznych, pomimo to adalimumab również jest wykorzystywany w terapii u dzieci z wrzodziejącym zapaleniem jelita grubego. Celem poniższej pracy jest podsumowanie aktualnej wiedzy na temat leków biologicznych mających zastosowanie w terapii wrzodziejącego zapalenia jelita grubego u dzieci. Obecnie przeciwciała monoklonalne stanowią integralną część algorytmu leczniczego i prawdopodobnie wraz z czasem coraz częściej będą wykorzystywane w terapii.

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Ulcerative colitis (UC) is an idiopathic chronic disease associated with inflammation in gastrointestinal tract. Genetic, environmental and immunologic factors are considered to take part in the etiology. Actually, the main pathogenic role is attributed to pro-inflammatory cytokines such as TNF-α, IL-1β, IL-8, IL-12. Pediatric UC is characterized by a variable clinical course ranging from mild to severe, unresponsive to conventional therapy. Diarrhea, hemochezia and abdominal pain are the most common signs of the illness, likewise the constipation can be an early symptom (1, 2). In children compared to adult patients the distribution of disease is more extensive, most of them (over 80%) have pancolitis (1, 3). Diagnosis of the disease in the early childhood is associated with more aggressive clinical course, which is often refractory to corticosteroid treatment, requiring intensification of therapy (4-6). **Treatment strategy depends mainly on disease severity. Pediatric UC treatment comprises use of corticosteroids, 5-amionosalicylates 5-ASA (mesalazine, sulfasalazine), immunomodulators: thiopurines (azatioprine AZA, mercaptopurine 6-MP), calcineurin**

inhibitors (ciclosporin, tacrolimus), antibiotics, probiotics and biological agents. Finally, colectomy is always a viable option that must be discussed whenever treatment escalation is considered.

The latest advances in understanding the pathogenesis of inflammatory bowel disease have led to the introduction of new therapeutic options, namely biological agents. Currently U.S. Food and Drug Administration (FDA) approved three monoclonal antibodies against pro-inflammatory cytokine Tumour Necrosis Factor alpha (TNF-α) to treat adults with moderate to severe ulcerative colitis. These are: infliximab, adalimumab and golimumab. Only infliximab has been approved by the agency to treat children 6 years and older, however, adalimumab is used out of label in pediatric patients by drawing on data from adults. The aim of this paper is to review the biologics used in the treatment of ulcerative colitis in children.

The first anti-TNF antibody approved for use in adults was infliximab (Remicade, Janssen Biotech). It is a chimeric monoclonal antibody consisting of 3/4 human and 1/4 murine sequences. It binds to both circulating and cell-bound forms of the proinflammatory cytokine TNF-α, thereby neutralizing TNF-α and causing apoptosis of activated lymphocytes (7, 8). Historically, indications for this medication have been extended from treatment of refractory Crohn's disease in adults only to induction and maintenance therapy in luminal and fistulizing Crohn's disease in adults and children, as well as treatment of adults and now (since 2011) children with moderate-to-severe ulcerative colitis unresponsive to conventional treatment (9-11). According to actual ECCO and ESPGHAN evidence-based consensus guidelines about management of pediatric ulcerative colitis infliximab should be considered for treatment of children with persistently active, or steroid-dependent UC, uncontrolled by 5-ASA and thiopurines and may be considered for steroid-refractory (oral or intravenous) disease (12). In Poland, the drug is approved for the treatment of severely active ulcerative colitis in children and adolescents aged 6 to 17 years with an inadequate response to conventional therapies, including corticosteroids and 6-MP or AZA, or who are intolerant, or have medical contraindications for such therapies. The medication is given as an intravenous infusion, the recommended dose is 5 mg/kg (3 induction infusions in scheme 0, 2, 6 weeks, then if patient responded to the treatment subsequent infusions every 8 weeks for maintenance). In some cases, especially when a patient has lost response it is recommended to increase the dosage to 10 mg/kg or to reduce the interval between doses (13). To optimize the treatment it is advisable to measure infliximab level and antibodies to infliximab (14). If there are low levels and negative antibodies, then dose escalation may be indicated. Undetectable infliximab levels in the presence of antibodies may indicate loss of response and the need for dose escalation or switching to a different drug. Normal infliximab level suggests primary nonresponse or an alternative diagnosis as a cause of symptoms.

The definitive evidence for the efficacy of infliximab in adult UC was provided by two randomized, double-blind, placebo-controlled studies the Active Ulcerative Colitis Trials 1 and 2 (ACT 1 and ACT 2) in 2005 (15). In each study, 364 patients were randomized to receive either infliximab (5 or 10 mg/kg intravenously) or placebo at weeks 0, 2, and 6, then every 8 weeks for a total of 46 weeks in ACT 1 or 22 weeks in ACT 2. At week 8 in ACT 1, 69.4% of patients in the group receiving infliximab 5 mg/kg and 61.5% of patients in the group receiving 10 mg of infliximab had had a clinical response, as compared with 37.2 percent of patients in the placebo group and in ACT 2 64.5% of patients in the group receiving lower dose of infliximab and 69.2% of patients in the group receiving higher dose of medication had had a clinical response, as compared with 29.3% of patients in the placebo group. Furthermore, in the infliximab group more patients sustained this clinical response, demonstrated mucosal healing, and had greater decreases in their median daily corticosteroid dose. The pooled data analysis of two studies also showed improvement in the quality of life of patients treated with infliximab, reduction in the number of hospitalizations due to ulcerative colitis and the number of surgical procedures. Colectomy was performed in 11.6% of patients treated with infliximab at a lower dose, in 7.4% of patients who received the drug in higher doses and in patients receiving placebo in 14.8% of cases. A systematic review of seven randomized controlled trials (RCTs) published in 2006 also evaluating the efficacy of infliximab concluded that it was effective for inducing clinical remission, clinical response, promoting mucosal healing, and reducing the need for colectomy in the short term in patients with moderate to severe UC refractory to corticosteroids and/or immunomodulators (16). Gisbert et al. one year later in 2007 performed a systematic review and meta-analysis on the efficacy and tolerance of infliximab in ulcerative colitis. Only randomized clinical trials comparing the efficacy of infliximab vs. placebo or steroids in patients with UC were included. According to that analysis infliximab is more effective than placebo, with an NNT from 3 to 5, for the treatment of moderate-to-severe UC, achieving clinical remission in 40% of the patients at approximately 9 months of follow-up (17).

In the literature there is a lot of single center reports evaluating clinical response to infliximab in children (18-25). The principal study that establish efficacy of this monoclonal antibody in pediatric UC was REACH trials by Hyams et al. (26). 60 patients, 6-17 years old, with moderately to severely active UC received an induction treatment of infliximab 5 mg/kg at weeks 0, 2, and 6. At week 8, patients who achieved clinical response were randomized equally to receive infliximab in the same dose every 8 weeks or every 12 week. Efficacy results in this study were generally similar to those achieved by adult patients with moderately to severely active UC in the ACT 1 and ACT 2 trials. Infliximab induced a response at week 8 in

73.3% of investigated children, clinical remission was achieved in 33.3% (using PUCAI score) and mucosal healing in 68.3% of patients. In week 54 the proportion of patients with clinical remission was 38% (8/21) in the group with maintenance therapy once every eight weeks, and 18% (4/22) in the group receiving infliximab every 12 weeks. In 2010 Hyams et al. published the results of another multicenter cohort study aimed to determine the outcome after treatment with infliximab in pediatric UC. Corticosteroid-free inactive disease was observed in 38 and 21% of patients at 12 and 24 months, respectively. By 24 months, 61% of patients had avoided colectomy. The results of analysis carried out in 2011 by Turner et al. provide further evidences of the effectiveness of infliximab in pediatric UC. Six studies of infliximab in refractory severe pediatric UC enrolled at least five children were included to the study. The pooled short-term success rate (in most cases meaning discharge without the need for colectomy) was 75% (95% CI: 67-83%) with a pooled 1-year response of 64% (95% CI: 56-72%) (27).

Adalimumab (Humira, Abbott Laboratories) is a fully human monoclonal antibody that may be less immunogenic than infliximab. The mechanism of action is based on both the neutralization of TNF-alpha bioactivity and the induction of apoptosis of TNF-expressing mononuclear cells. It is given as a subcutaneous injection. In adults a standard induction dose is 160 mg, followed by 80 mg after 2 weeks. Maintenance doses are then scheduled at 40 mg every other week (EOW) (28). Based on data for adults and case studies in children the loading dose of adalimumab in treatment of pediatric ulcerative colitis is 100 mg/m^2 to 160 mg/m^2, then 50-80 mg/m^2 after 2 weeks and then every other week 25-40 mg/m^2, in some cases individualization of dosage may be necessary (29).

As of 2008 adalimumab has been approved by the U.S. Food and Drug Administration for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, moderate to severe chronic psoriasis and juvenile idiopathic arthritis. After the publication of the results of the two randomized, placebo-controlled, double-blind trials (ULTRA 1 and ULTRA 2) (30, 31) adalimumab was approved by FDA for use in adult patients with moderate-to-severe active ulcerative colitis who were nonresponders or intolerant to standard therapy. The aim of the UTRA 1 trial was to assess the efficacy of adalimumab (ADA) for the induction of clinical remission in anti-TNF naïve adult ambulatory patients with moderately to severely active ulcerative colitis. Finally, after amendment of the original study protocol, 390 patients were randomised to subcutaneous treatment with ADA 160/80 (160 mg at week 0, 80 mg at week 2, 40 mg at weeks 4 and 6), ADA 80/40 (80 mg at week 0, 40 mg at weeks 2, 4 and 6) or placebo. At week 8, 18.5% of patients in the ADA 160/80 group and 10.0% in the ADA 80/40 group were in remission, compared with 9.2% in the placebo group. Efficacy of induction treatment, long-term remission and maintenance with adalimumab was evaluated in a study ULTRA 2. Data of 494 adult patients with moderately severe to severe UC were analyzed. Patients were stratified based on prior exposure to TNF-α antagonists and randomly assigned to groups given adalimumab 160 mg at week 0, 80 mg at week 2, and then 40 mg every other week or placebo. Primary end points were remission at weeks 8 and 52. In the 8th week of treatment clinical remission was obtained in 16.5% of patients (9.3% for placebo) and at week 52 of 17.3% (8.5% for placebo). It is noteworthy that among patients with prior exposure to TNF-α antagonists rate of remission at week 8 was lower than in anti-TNF-α naïve patients, respectively 21.3 vs 9.2%, corresponding values week 52 were 22 vs 10.2%.

Multiple evidence from open-label and retrospective studies on adalimumab in ulcerative colitis patients, have been available for several years (32-35). In this year McDermott et al. published the results of a prospective single-center study evaluating the efficacy of adalimumab maintenance therapy. The study included 23 people, most of which (87%) were previously treated with infliximab. As many as 70% of cases it was necessary to discontinue the drug. Mean duration of therapy was 23 months. Treatment failure was not associated with age, gender, extent of disease, smoking, or the amount of inflammatory markers (CRP). The percentage of patients whose therapy was ineffective at 6, 12 and 24 months of treatment was respectively 50, 65 and 72% (36). Taken together, the current evidence indicates that adalimumab is effective for the treatment of patients with different types of ulcerative colitis, including biologically naïve and difficult-to-treat patients (37-39). Unfortunately, pediatric data are restricted primarily to retrospective studies of off-label use in ulcerative colitis (40, 41).

The most recent biological agent, registered by the FDA in 2013 to treat adults with moderate to severe ulcerative colitis is golimumab (Simponi, Janssen Biotech). It is a human monoclonal antibody, administered subcutaneously, forming stable complexes with a high affinity to both the soluble and transmembrane form of human tumor necrosis factor alpha (TNF-α), preventing the binding of TNF-α to its receptors. Efficacy was confirmed in moderate to severe UC in adult patients. In phase 3 of the trial, rates of clinical response at week 6 were 51.8 and 55.0% among patients given 200 mg/100 mg and 400 mg/200 mg golimumab, respectively vs 29.7% among those given placebo. Authors concluded that treatment with subcutaneous golimumab induces clinical response, remission, and mucosal healing, and increases quality of life in larger percentages of patients with active UC than placebo (42, 43). At present, there is no data on its use in children, but because of fact that the clinical course of disease in pediatric patients is often severe unresponsive to standard therapy, we can expect that in the near future children's gastroenterologists will reach for this drug too.

In the treatment of inflammatory bowel disease (IBD) one more TNF-α inhibitor is used, certolizumab (Cimizia, UCB Pharma SA). The formulation is administered subcutaneously, and because of the process of pegylation, drug has a longer half-life in comparison with other anti-TNF antibodies. The recommended dose is 400 mg for three consecutive injections for induction, followed by a maintenance dose once a month. Data in adults indicate the effectiveness of the drug comparable to other antibodies, there is no research on pediatric patients (44-46). It seems that lack of data about the use of this drug in ulcerative colitis results from the fact that there are already three other TNF-α blockers of proven efficacy.

Currently, anti-TNF-α antibodies are the integral part of the pediatric ulcerative colitis treatment algorithm. It is known that they are effective to induce remission in about 2/3 of cases, of which some patients will lost a response with time, therefore, new methods of therapy with a different mechanism of action are searched (47, 48). Such new drugs during the clinical trials are verdolizumab and ertolizumab. Verdolizumab is a monoclonal antibody directed against α4β7. At present, the role of verdolizumab in the treatment of UC is unknown, but the results of clinical trials in adult patients with ulcerative colitis are promising. The drug was effective in those who have not responded to standard treatment with corticosteroids and in who failed anti-TNF-α therapy (49-51). Ertolizumab is a monoclonal antibody directed selectively against subunit β7 and is currently under phase II studies (52).

The use of biologics in pediatric IBD has transformed treatment outcomes and quality of life in many children. At present in Poland only two biologic agents are used in therapy in pediatric ulcerative colitis: infliximab and adalimumab. Infliximab is presently the first-line biological agent, adalimumab should only be used in those who lost response or were intolerant of infliximab.

BIBLIOGRAPHY

1. Sawczenko A, Sandhu BK: Presenting feature of inflammatory bowel disease in Great Britan and Ireland. Arch Dis Child 2003; 88(11): 995-1000.
2. Hyams J, Davis P, Lerer T et al.: Clinical outcome of ulcerative proctitis in children. J Pediatr Gastroenterol Nutr 1997; 25(2): 149-152.
3. Van Limbergen J, Russel RK, Drummond E et al.: Definition of phenotypic characteristics of childhood – onset inflammatory bowel disease. Gastroenterology 2008; 135: 1114-1122.
4. Griffiths AM: Specificities of inflammatory bowel disease in childhood. Best Pract Res Clin Gastroenterol 2004; 18: 509-523.
5. Goodhand J, Dawson R, Hefferon M et al.: Inflammatory bowel disease in young people: the case for transitional clinics. Inflamm Bowel Dis 2010; 16: 947-952.
6. Uchida K, Araki T, Toiyama Y et al.: Preoperative steroid-related complications in Japanese pediatric patients with ulcerative colitis. Dis Colon Rectum 2006; 49(1): 74-79.
7. Caviglia R, Boskoski I, Cicala M: Maintenance treatment with infliximab for the management of Crohn's disease in adults. Biologics 2009; 3: 39-49.
8. Papa A, Mocci G, Bonizzi M et al.: Use of infliximab in particular clinical settings: management based on current evidence. Am J Gastroenterol 2009; 104(6): 1575-1586.
9. Turner D, Mack D, Leleiko N et al.: Severe pediatric ulcerative colitis: a prospective multicenter study of outcomes and predictors of response. Gastroenterology 2010; 138: 2282-2291.
10. Mahadevan U, Cucchiara S, Hyams JS et al.: The London Position Statement of the World Congress of Gastroenterology on biological therapy for IBD with the European Crohn's and Colitis Organisation: pregnancy and pediatrics. Am J Gastroenterol 2011; 106: 214-223.
11. Lichtenstein GR, Abreu MT, Cohen R, Tremaine W: American Gastroenterological Association Institute medical position statement on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. Gastroenterology 2006; 130: 935-939.
12. Turner D, Levine A, Escher JC et al.: Management of Pediatric Ulcerative Colitis: Joint ECCO and ESPGHAN Evidence-based Consensus Guidelines JPGN 2012; 55: 340-361.
13. Chaparro M, Guerra I, Munoz-Linares P et al.: Systematic review: antibodies and anti-TNF-alpha levels in inflammatory bowel disease. Aliment Pharmacol Ther 2012; 35: 971-986.
14. AfifW, Loftus EV Jr, Faubion WA et al.: Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. Am J Gastroenterol 2010; 105: 1133-1139.
15. Rutgeerts P, Sandborn WJ, Feagan BG et al.: Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005; 353: 2462-2476.
16. Lawson MM, Thomas AG, Akobeng AK: Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis. Cochrane Database Syst Rev 2006; CD005112.
17. Gisbert JP, González-Lama Y, Maté J: Systematic review: Infliximab therapy in ulcerative colitis. Aliment Pharmacol Ther 2007 Jan 1; 25(1): 19-37.
18. Mamula P, Markowitz JE, Brown KA et al.: Infliximab as a novel therapy for pediatric ulcerative colitis. J Pediatr Gastroenterol Nutr 2002; 34(3): 307-311.
19. Mamula P, Markowitz JE, Cohen LJ et al.: Infliximab in pediatric ulcerative colitis: two-year follow-up. J Pediatr Gastroenterol Nutr 2004; 38(3): 298-301.
20. Russell GH, Katz AJ: Infliximab is effective in acute but not chronic childhood ulcerative colitis. J Pediatr Gastroenterol Nutr 2004; 39(2): 166-170.
21. Eidelwein AP, Cuffari C, Abadom V, Oliva-Hemker M: Infliximab efficacy in pediatric ulcerative colitis. Inflamm Bowel Dis 2005; 11(3): 213-218.
22. Fanjiang G, Russell GH, Katz AJ: Short- and long-term response to and weaning from infliximab therapy in pediatric ulcerative colitis. J Pediatr Gastroenterol Nutr 2007; 44(3): 312-317.
23. Cucchiara S, Romeo E, Viola F et al.: Infliximab for pediatric ulcerative colitis: a retrospective Italian multicenter study. Dig Liver Dis 2008; 40 (suppl. 2): S260-S264.
24. McGinnis JK, Murray KF: Infliximab for ulcerative colitis in children and adolescents. J Clin Gastroenterol 2008; 42(8): 875-879.
25. Tiemi J, Komati S, Sdepanian VL: Effectiveness of infliximab in Brazilian children and adolescents with Crohn disease and ulcerative colitis according to clinical manifestations, activity indices of inflammatory bowel disease, and corticosteroid use. J Pediatr Gastroenterol Nutr 2010; 50(6): 628-633.
26. Hyams J, Damaraju L, Blank M et al.: Induction and maintenance therapy with infliximab for children with moderate to severe ulcerative colitis. Clin Gastroenterol Hepatol 2012; 10: 391-399.
27. Turner D, Griffiths AM: Acute severe ulcerative colitis in children: a systematic review. Inflamm Bowel Dis 2011; 17: 440-449.
28. HUMIRA (adalimumab) subcutaneous injection (product monograph). IL: Abbott Laboratories, Ltd, North Chicago 2012.
29. Burness CB, Keating GM: Adalimumab: A Review of Its Use in the Treatment of Patients with Ulcerative Colitis. BioDrugs 2013 Apr 12.
30. Reinisch W, Sandborn WJ, Hommes DW et al.: Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut 2011; 60: 780-787.
31. Sandborn WJ, van Assche G, Reinisch W et al.: Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2012 Feb; 142(2): 257-265.e1-3. doi: 10.1053/j.gastro.2011.10.032. Epub 2011 Nov 4.
32. Afif W, Leighton JA, Hanauer SB et al.: Open-label study of adalimumab in patients with ulcerative colitis including those with prior loss of response or intolerance to infliximab. Inflamm Bowel Dis 2009; 15(9): 1302-1307.
33. Hudis N, Rajca B, Polyak S et al.: The outcome of active ulcerative colitis treated with adalimumab. Gastroenterology 2009; 136 (5 suppl. 1): A661.
34. Gies N, Kroeker KI, Wong K, Fedorak RN: Treatment of ulcerative colitis with adalimumab or infliximab: long-term follow-up of a single-centre cohort. Aliment Pharmacol Ther 2010; 32(4): 522-528.

35. Taxonera C, Estellés J, Fernández-Blanco I et al.: Adalimumab induction and maintenance therapy for patients with ulcerative colitis previously treated with infliximab. Aliment Pharmacol Ther 2011; 33(3): 340-348.
36. McDermott E, Murphy S, Keegan D et al.: Efficacy of Adalimumab as a long term maintenance therapy in ulcerative colitis. J Crohns Colitis 2013 Mar; 7(2): 150-153.
37. Feagan BG, Sandborn WJ, Lazar A et al.: Adalimumab Therapy is Associated with Reduced Risk of Hospitalization in Patients with Ulcerative Colitis. Gastroenterology 2013 Sep 22. pii: S0016-5085(13)01360-7.
38. Italian Group for the Study of Inflammatory Bowel Disease: Adalimumab in active ulcerative colitis: A "real-life" observational study. Dig Liver Dis 2013 Sep; 45(9): 738-743.
39. Armuzzi A, Pugliese D, Nardone OM et al.: Management of difficult-to-treat patients with ulcerative colitis: focus on adalimumab. Drug Des Devel Ther 2013 Apr 8; 7: 289-296.
40. Russell RK, Wilson ML, Loganathan S et al.: A British Society of Paediatric Gastroenterology, Hepatology and Nutrition survey of the effectiveness and safety of adalimumab in children with inflammatory bowel disease. Aliment Pharmacol Ther 2011; 33: 946-953.
41. Noe JD, Pfefferkorn M: Short-term response to adalimumab in childhood inflammatory bowel disease. Inflamm Bowel Dis 2008; 14(12): 1683-1687.
42. Sandborn WJ, Feagan BG, Marano C et al.: Subcutaneous Golimumab Induces Clinical Response and Remission in Patients with Moderate-To-Severe Ulcerative Colitis. Gastroenterology 2013 Jun 1. pii: S0016-5085(13)00846-9.
43. Danese S: IBD: Golimumab in ulcerative colitis: a "ménage à trois" of drugs. Nat Rev Gastroenterol Hepatol 2013 Sep; 10(9): 511-512.
44. Bousvaros A: Use of immunomodulators and biologic therapies in children with inflammatory bowel disease. Expert Rev Clin Immunol 2010; 6(4): 659-666.
45. Bradley GM, Oliva-Hemker M: Pediatric ulcerative colitis: current Treatment approaches including role of infliximab. Biologics: Targets and Therapy 2012; 6: 125-134.
46. de Bie CI, Escher JC, de Ridder L: Antitumor necrosis factor treatment for pediatric inflammatory bowel disease. Inflamm Bowel Dis 2012 May; 18(5): 985-1002. doi: 10.1002/ibd.21871. Epub 2011 Sep 20.
47. Dignass A, Lindsay JO, Sturm A et al.: Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. J Crohns Colitis 2012; 6(10): 991-1030.
48. Danese S: New therapies for inflammatory bowel disease: from the bench to the bedside. Gut 2012; 61(6): 918-932.
49. Parikh A, Leach T, Xu J, Feagan B: P235. Long-term clinical experience with vedolizumab (VDZ) in patients with mild to moderate ulcerative colitis (UC). J Crohns Colitis 2012; 6 (suppl. 1): S103.
50. Feagan B, Rutgeerts P, Sands J et al.: 943b Induction therapy for ulcerative colitis: results of GEMINI I, a randomised placebo-controlled, double-blind, multicentre phase 3 trial. Gastroenterology 2012; 142(5): S160-S161.
51. Rutgeerts PJ: Vedolizumab induction therapy for ulcerative colitis: results of GEMINI I, a randomized, placebo-controlled, double-blind, multicentre phase 3 trial. Gut 2012; 2012 (suppl. 3): A65.
52. Rutgeerts PJ, Fedorak RN, Hommes DW et al.: A randomised phase I study of etrolizumab (rhuMAb β7) in moderate to severe ulcerative colitis. Gut 2012 Jun 20. (Epub ahead of print).

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