Review Article

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INFLIXIMAB AND EMERGING BIOLOGICAL TREATMENT FOR PEDIATRIC CROHN'S DISEASE

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Summary

Treatment of Crohn's disease (CD) is complex and based on different drugs. The biological treatments act on different stages of immuno-physiopathological processes of the disease to change the evolution or natural history. The targets of these therapies, most of which are still experimental, and still off label in pediatrics, are highly selective and include proinflammatory cytokines, the CD4 positive T cells, the Th1 and Th2 subgroups and adhesion molecules. At present monoclonal antibodies against TNF-α studied and/or used for Crohn's disease are four: a chimerical one (Infliximab), a 95% humanized one (CDP 571), a humanized and pegylated one (Certolizumab pegol) and finally a fully humanized type (Adalimumab). On the contrary, have been considered TNF-α recombinant receptors (Etanercept and Onercept) that have proven be ineffective for the treatment of active CD. The paediatric Crohn's is an early onset form of disease, that much better takes advantage of biological therapy compared with late onset adulthood forms.

Keywords: proinflammatory cytokines, CD4 positive T cells, TNF-α, monoclonal antibodies

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Introduction

Treatment of Crohn's disease (CD) is complex and based on different drugs. The current approach makes use of antibiotics and aminosalicylates for mild forms, corticosteroids and immunosuppressants (azathioprine, methotrexate) for moderate presentation forms reserving biological drugs for severe ones (1).

In recent years the knowledge concerning the immune mechanisms underlying chronic inflammatory bowel disease (IBD) is significantly improved. In particular, It seems to have different immune pathways underlying the Crohn's disease (CD) and ulcerative colitis. The cytokine pattern expressed by lamina propria lymphocytes of patients with Crohn's disease seems to be a T-helper 1 (Th1) with increased expression of interferon gamma (IFN γ), interleukin 2 (IL-2), IL-12 IL -18and IL-23, which produce an increase in proinflammatory cytokines TNF-α and IL-1 β leading activation of nuclear factor kB (NFkB). On the other hand the immunological pattern of ulcerative colitis appears of Th2 type with increased expression of IL-4, IL-5, IL-6, IL-10 and IL-13. These cytokines and T lymphocytes represent an important target for new biological therapies (2, 3).

The biological treatments act on different stages of immuno-physiopathological processes of the dis-

ease to change the evolution or natural history. The targets of these therapies, most of which are still experimental, and still off label in pediatrics, are highly selective and include proinflammatory cytokines, the CD4 positive T cells, the Th1 and Th2 subgroups and adhesion molecules (4).

The Tumor Necrosis Factor α (TNF-α) is a proinflammatory cytokine that plays many systemic effects and has a central role in the perpetuation of the inflammatory process and in the pathogenesis of tissue damage of the CD (Fig. 1). Many studies have shown that TNF-α can induce a destruction of the intestinal epithelial barrier, the triggering the apoptotic process in villous epithelial cells and the secretion of chemokines from the same intestinal cells. TNF-α activates neutrophils, B lymphocytes and macrophages, it increases production of cytokines of the Th1-type pattern, increases the proliferation and migration of intraepithelial lymphocytes and stimulates the fetal intestine stromal cells to produce metalloproteinase of extracellular matrix, which induce tissue damage. Studies in animal models confirm the central role of TNF-α in maintaining activation of T lymphocytes and in induction of tissue damage. The treatment of animal models of inflammatory bowel disease (IBD) with monoclonal antibodies anti-TNF-α or the inhibition of endogenous synthesis of this cytokine in animals made knock-out for the gene (TNF-α - / -) brings a significant regression of intestinal lesions or the impossibility to their induction (2, 3). On the basis of these observations drugs to block the action or the release of TNF-α in vivo in humans have been developed.

Infliximab and its mechanism of action

At present monoclonal antibodies against TNF-α studied and/or used for Crohn's disease are four: a chimerical one (Infliximab), a 95% humanized one (CDP 571), a humanized and pegylated one (Certolizumab pegol) and finally a fully humanized type (Adalimumab). On the contrary, have been considered TNF-α recombinant receptors (Etanercept and Onercept) that have proven be ineffective for the treatment of active CD (1, 4).

Among the anti-TNF-α of biological derivation the most studied and used is a monoclonal antibody known as Infliximab, which binds both the soluble TNF-α and the TNF-α bound on the surface of mononuclear phagocytes. The Infliximab

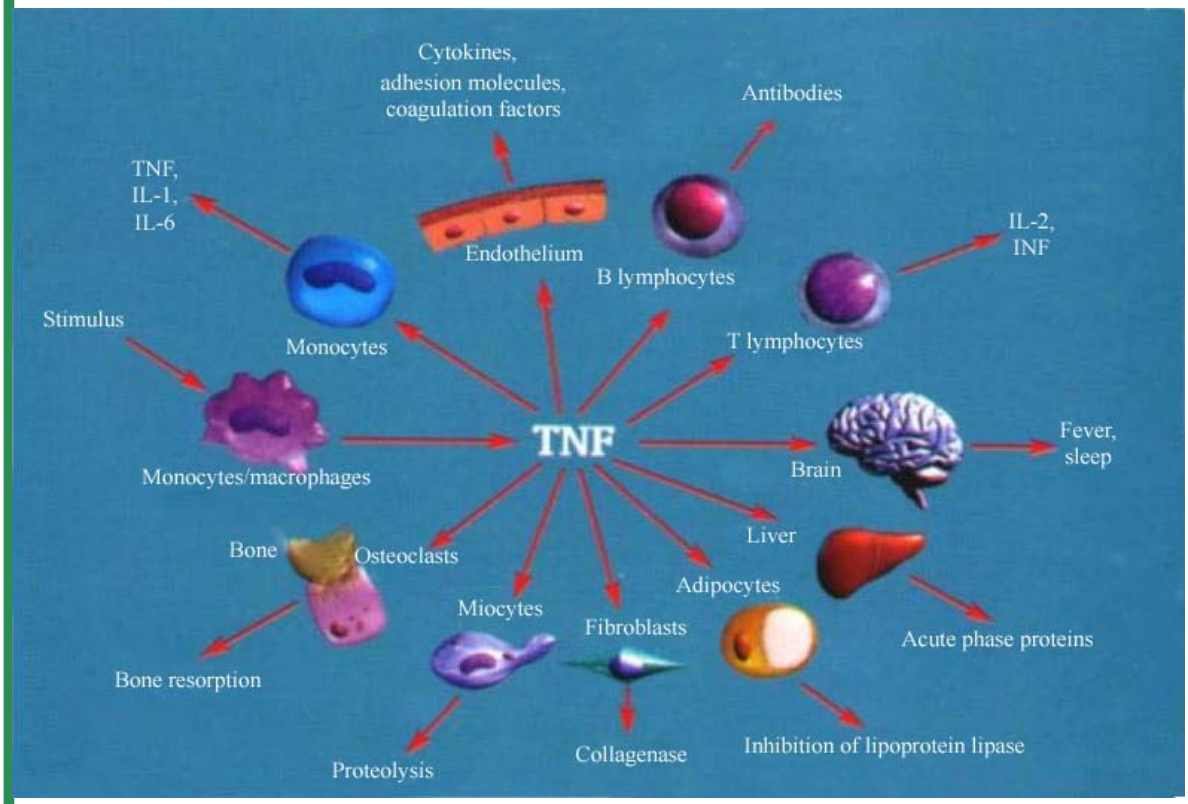

Fig. 1: Biological activity of TNF-alpha (adapted from Ref. 21).

action is secondary to the break of cells that secrete TNF-α. The bond between the antibody (IgG1) anti TNF-α and the TNF-α expressed on the membrane of the cells that secrete it will in fact induce break of them, through a mechanism of antibody-dependent or complement-dependent cytotoxicity. Less important appears to be the block of the TNF-α already released by mononuclear phagocytes (5).

Infliximab is used in the treatment of severe and or fistulizing Crohn's disease in active phase, or in patients with lacking response to adequate treatment with corticosteroids and/or immunosuppressants (6). It is a chimerical antibody (IgG1 75% human and 25% murine) with molecular weight of 149,000 Dalton, produced by genetic engineering.

Chimerical antibodies (Fig. 2) consist of a human constant region (C) and a murine part of the variable region (V), since the variable regions contain the specific domains to bind the antigen (TNF-alpha) (6, 7).

The recombinant DNA technology has provided an alternative and successful method to reduce the immunogenicity of murine monoclonal antibodies used initially. The first method used to reduce the antigenicity was to make chimerical genes that codify proteins in which the variable regions of murine antibodies are fused with the constant regions of a human one: the chimerical antibody keeps specificity of binding but look more like a natural human antibody.

It is noted that the chimerical antibodies:

- They are significantly less immunogens
- They have a prolonged serum half-life
- They allow the activation of various functions mediated by the Fc region first of all the complement one (7, 8).

The Infliximab binds to soluble and transmembrane form of TNF-α with high affinity, blocking interaction with its receptors, neutralizing the biological activity of TNF-α itself (8, 9).

Used in clinic for the first time in 1993, was evaluated in a series of controlled clinical trial in patients with Rheumatoid Arthritis and Crohn's disease.

At present the use of the Infliximab is suitable in two particular situations:

In patients in which the symptoms do not respond to treatment with steroid (steroid-resistant), or which need to take continuous high doses of steroid to control symptoms (steroid-dependent). In both these cases Infliximab is usually recommended if the immunosuppressant drugs (azathio-prine, 6-mercaptopurine, methotrexate) are not used for any of the following reasons:

- because they have been used without benefit
- because the patient does not tolerate these drugs
- because the disease is so much severe that you can not wait for these drugs begin to work.

In patients with fistulas or severe perianal lesions and/or where other forms of therapy have not proved effective.

Moreover, it is pioneering the use of Infliximab also in severe ulcerative colitis (Act 1, Act 2) (10).

The two ACCENT trials showed that Infliximab induces endoscopic healing and reduces the need for surgery and hospitalization (11, 12).

Infliximab is contraindicated in patients with serious infections such as sepsis, abscesses, tuberculosis and opportunistic infections. Recently, it has been reported that Infliximab may promote endogenous reactivation of tuberculosis. The absolute risk of get tuberculosis is still very low: about 76,000 patients treated with Infliximab in the U.S. in 18 cases were reported this disease (13).

Infliximab's administration

Infliximab should not be administered to patients with hypersensitivity to it, neither to other murine proteins nor any of the excipients. Infliximab is administered by

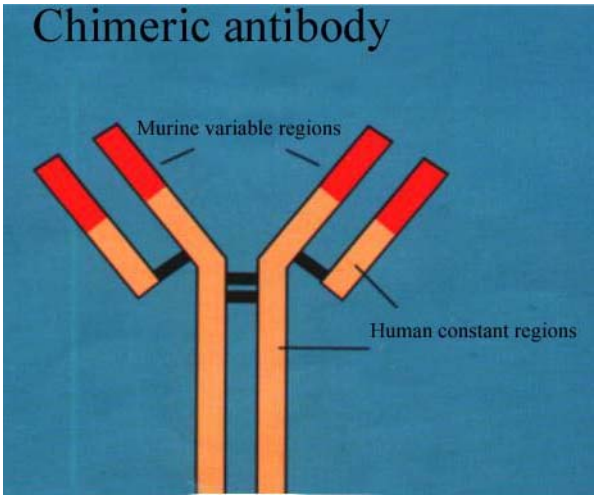

Fig.2: Monoclonal chimeric human/murine antibody (adapted from Ref. 22).

intravenous infusion.
These infusions should last no less than 2-3 hours and should be carried out under medical and/or nursing staff supervision. For this reason, it is recommended that patients undergoing infliximab administration must be hospitalised.
The first infusion (week 0), at a dose of 5 mg/kg, is followed by two more treatments at 2 and 6 weeks. These first three infusions should obtain, in responding patients, remission of symptoms. Later infusions are performed every 8 weeks at a dose of 5 mg/kg (according to the ACCENT 1 study). It is recommended that infliximab infusion follow the administration of an antihistamine (chlorpheniramine at a dose of 10 mg i.m. and/or e.v.) to reduce the probability of occurrence of IgE-mediated collateral effects (11).
Patients intolerant to, or who have suspended for any reason the therapy with methotrexate or other non-corticosteroid immunosuppressants (azathioprine 6-mercaptopurine) before or during treatment with Infliximab have a greater risk of developing antibodies against the monoclonal antibody (ATI). In a significant number of patients with Crohn's disease retreated with Infliximab, after a period of 2-4 years without treatment, was observed a delayed hypersensitivity reaction (14, 15). The maximum length of time for which you can continue with these infusions has not yet been established.
The simultaneous intake of immunosuppressants is recommended even in cases where these drugs had previously proven ineffective, as it was shown that they can reduce both the risk of collateral immunological effects, and the risk that the effectiveness of Infliximab may decrease over time for the production of antibodies to-Infliximab (1, 15).
On the other hand, up to date, with the report of 8 cases of hepatosplenic lymphoma, in paediatric patients treated concomitantly with Infliximab and azathioprine, it tends to avoid this association, continuing the only biological therapy every 8 weeks as ACCENT 1 scheme for the maintenance of clinical remission (10, 11).
In some centres biological therapy is continued for several years, but we must consider whether this is really convenient. In particular, it remains to be determined which is the long term tolerability of the drug and to examine whether the effectiveness of the drug is not reduced by the continuation of his administration.
It is demonstrated by studies conducted by a research team of Italian paediatric gastroenterologists (16), that the response to the Infliximab is better in early stages of disease. If these data will find confirmation Infliximab could be a particularly useful weapon in the management of paediatric Crohn's disease.
Infliximab also seems to be useful in the treatment of some complications of extra-intestinal IBD, that are rare but often difficult to treat with other drugs, such as ankylosing spondylitis, nodosum erythema and pyoderma gangrenosum (6, 15).

Other emerging biological treatments
Treatment with chimerical monoclonal antibody anti-TNF-α (Infliximab) was however associated with the induction of some collateral effects, such reactions in the course of infusion and delayed hypersensitivity, resulting also in anti-chimerical human antibodies (ATI) and in anti-DNA ds antibodies, which in some cases led to loss of response to biologic drug and to the development of erythematosus systemic lupus respectively. For this reason a monoclonal humanized anti-TNF-α antibody was developed. In deed CDP 571, consists of a chimera composed of human residues for 95% and murine residue for 5%. The CDP 571 was studied in 3 randomized controlled trials. At a dose of 10 mg/kg was effective in obtaining a clinical remission (54% vs 27% in patients treated with placebo) and in reducing the steroid treatment (zero in 44% of treated vs 22% for placebo), even if in reprocessing every 8 or 12 weeks it was not superior to placebo. The aim of this new molecule is mainly the reduced immunogenicity, however specific antibodies were observed in more than 5% of cases. So the CDP 571 has shown benefits in the short term as induction therapy but it was not sufficient to maintain a long-term effect. CDP 571 has not demonstrated the ability to wean patients with CD from steroid therapy, but was better tolerated in patients who had shown an allergic reaction to Infliximab infusion.
These results suggest that CDP 571 is a safe drug, but not as effective as Inflixi-

mab in CD (17).
With a similar strategy has been developed the Etanercept, a fusion recombinant human protein consisting of two identical portions of the soluble receptor for TNF-α (p75) linked to the Fc fragment of a monoclonal IgG1. The drug, administered subcutaneously, is effective in the treatment of Rheumatoid Arthritis, while the results of some studies conducted in patients with active CD give evidence to the inefficacy of the drug (18).
Adalimumab is a monoclonal antibody anti-TNF-α, it consists of a fully humanized immunoglobulin IgG1 that is effective as Infliximab in the treatment of patients with Rheumatoid Arthritis. In vitro studies have revealed that this antibody has the same effect of the Infliximab in inducing apoptosis in monocytes. Since this molecule has not been set up with mouse peptide sequence, it is expected to be more tolerated than Infliximab. Two uncontrolled pilot studies with Adalimumab in patients with CD who had not responded or had developed intolerance to Infliximab showed that the subcutaneous administration is well tolerated, suggesting the clinical benefit of it. In an international multicenter double-blind and placebo-controlled study (GAIN), some patients with active CD who received Adalimumab at dose of 160 mg sc at week 0 and 80 mg at week 2 the rate of clinical remission was significantly greater than in the placebo group (36% vs 12%). From these results, it follows that Adalimumab may be effective in the treatment of CD and that could be a valuable therapeutic alternative for patients non-responders or who are intolerant to Infliximab (19).
The Certolizumab pegol is a humanized monoclonal molecule anti-TNF-α of Fc portion of immunoglobulin, linked to two molecules of polyethylene glycol, which can be administered subcutaneously. It seems to be another anti-TNF-α agent effective in the treatment of active Crohn's disease. It remains to define its role relative to other therapeutic goals, such as healing of fistulas, healing of endoscopic lesions and the efficacy in patients refractory to the Infliximab (20).
The Thalidomide, a drug that can inhibit the synthesis of TNF-α in vitro, shows efficacy in refractory active CD, although severe collateral effects and teratogenicity restrict its use.
Emerging biological treatments should replace the Infliximab, which by its chimerical nature has a high antigenicity, with the risk of adverse reactions during the infusion and the loss of its effectiveness in the long run (1, 4).
Although these drugs are not still widely used, the next future probabily belongs to them.

Conclusion

In conclusion, biological drugs have a great potential in improving the treatment of IBD. However, their role in long-term therapy is not clear; In particular their cost are high and most of them require parenteral administration. Adalimumab is likely designed to will be the most used one in the next years for its fully humanization and for the easy way of administration replacing its forefather Infliximab.
The paediatric Crohn's is an early onset form of disease, that much better takes advantage of biological therapy compared with late onset adulthood forms (1). In the future, the biggest challenge will be related to the ability to detect indicators of response and reliable markers of disease in order to be able to individualize therapy for the patient, in order to administer the drug or the combination of drugs that has the highest probability to be effective for the specific phase and the specific type of disease.

References

1. Travis SPL, Stange EF, Lémann M, Öresland T, Chowers Y, Forbes A, D'Haens G, Kitis G, Cortot A, Prantera C, Marteau P, Colombel JF, Gionchetti P, Bouhnik Y, Tiret E, Kroesen J, Starlinger M, Mortensen NJ: European evidence based consensus on the diagnosis and management of Crohn's disease: current management. Gut 2006; 55(Suppl. 1):i16-i35
2. Plevy SE, Landers CJ, Prehn J, Carramanzana NM, Deem RL, Shealy D, Targan SR: A role of TNF-α and mucosal Th1 cytokines in the pathogenesis of Crohn's disease. J Immunol 1997; 159:6276-6282.
3. Schreiber S, Campieri M, Colombel JF, van Deventer SJ, Feagan B, Fedorak R, Forbes A, Gassull M, Gendre JP, van Hogezand RA, Lofberg R, Modigliani R, Pallone F, Petritsch W, Prantera C, Rampton D, Seibold F, Vatn M, Zeitz M, Rutgeerts P: Use of antitumour necrosis factor agents

in inflammatory bowel disease. European guidelines for 2001-2003. Int J Colorectal Dis 2001; 16:1-11.
4. Sostegni R, Pera A, Daperno M, Rocca R: I farmaci biologici nella terapia delle malattie infiammatorie croniche intestinali. Recenti progressi in medicina Gennaio 2008; Vol. 99, N. 1, Pagg. 10-18
5. Targan SR, Hanauer SB, Van Deventer SJ, Mayer L, Present DH, Braakman T: A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor α for Crohn's disease. N Engl J Med 1997; 337: 1029-1035
6. Blam ME, Stein RB, Lichtenstein GR: Integrating anti-tumor necrosis factor therapy in inflammatory bowel disease: current and future perspectives. Am J Gastroenterol 2001; 96:1977-1997
7. Brekke OH and Sandlie I: Therapeutic antibodies for human disease at the dawn of the twenty-first century. Nat Rev Drug Discov 2003; 2:52-62.
8. Eigler A, Sinha B, Hartmann G, Endres S: Taming TNF: strategies to restrain this proinflammatory cytokine. Immunol Today 1997; 18:487-492.
9. Saeed SA, Crandall WV: Managing Crohn disease in children and adolescents: focus on tumor necrosis factor antagonists. Paediatr Drugs 2008; 10(1):31-8.
10. Sands BE, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, Kamm MA, Korzenik JR, Lashner BA, Onken JE, Rachmilewitz D, Rutgeerts P, Wild G, Wolf DC, Marsters PA, Travers SB, Blank MA, van Deventer SJ: Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med 2004; 350:876-885
11. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Rutgeerts P, ACCENT I Study Group Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 2002; 359:1541-1549.
12. Sands B, Van Deventer S, Bernstein C: Long-term treatment of fistulizing Crohn's disease: Response to infliximab in the ACCENT II trial through 54 weeks. Gastroenterology, 2002; 122: A81.
13. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, Siegel JN, Braun MM: Tuberculosis Associated with Infliximab, a Tumor Necrosis Factor α–Neutralizing Agent. N Engl J Med 2001; 345:1098-1104.
14. Heuschkel R, Salvestrini C, Beattie RM, Hidebrand H, Walters T, Griffiths A: Guidelines for the management of growth failure in childhood inflammatory bowel disease. Inflamm Bowel Dis 2008; 14:839-849.
15.Veres G, Baldassano RN, Mamula P: Infliximab therapy for pediatric Crohn's disease. Expert Opin Biol Ther 2007; 7:1869-1880.
16. Lionetti P, Bronzini F, Salvestrini C, Bascietto C, Canani RB, Dé Angelis GL, Guariso G, Martelossi S, Papadatou B, Barabino A: Response to Infliximab is related to disease duration in paediatric Crohn's disease. Aliment Pharmacol Ther 2003; 18:425-431.
17. Sandborn WJ, Feagan BG, Hanauer SB: An engineered human antibody to TNF-α (CDP571) for active Crohn's Disease: a randomized double-blind placebocontrolled trial. Gastroenterology 2001; 120:1330-1338.
18. Sandborn WJ, Hanauer SB, Katz S, Safdi M, Wolf DG,. Baerg RD: Etanercept for active Crohn's disease: a randomized, double- blind, placebo-controlled trial. Gastroenterology 2001; 121:1088-1094.
19. Sandborn WJ, Hanauer SB, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh DG: Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut 2007; 56:1232- 1239.
20. Sandborn WJ, Feagan BG, Stoinov S, Honiball PJ, Rutgeerts P, Mason D, Bloomfield R, Schreiber S: PRECISE 1 Study Investigators. Certolizumab pegol for the treatment of Crohn's disease. N Engl J Med 2007; 357:228-238.
21. Della Corte G, Lucarelli G: La terapia delle malattie reumatiche nel terzo millennio. Rassegna trimestrale 2000; Anno 19° - Numero Unico.
22. Knight DM, Trinh H: Construction and initial characterization of a mouse-human chimeric anti-TNF antibody. Mol Immunol. 1993; 30:1443–1453

INFLIXIMAB E TERAPIE BIOLOGICHE EMERGENTI PER LA MALATTIA DI CROHN IN ETÀ PEDIATRICA

La terapia della malattia di Crohn (MC) è complessa e si basa su farmaci diversi. I farmaci biologici intervengono sulle diverse tappe dei processi immuno-fisiopatologici della malattia nel tentativo di modificarne l'evoluzione o la storia naturale. I bersagli di queste terapie, la maggior parte delle quali ancora sperimentali, sono estremamente selettivi e comprendono le citochine proinfiammatorie, le cellule T CD4 positive, i sottogruppi Th1 e Th2 e le molecole di adesione. Al momento attuale gli anticorpi monoclonali contro il TNF-α studiati e/o utilizzati per la malattia di Crohn sono quattro: uno chimerico (Infliximab), uno umanizzato al 95% (CDP 571), uno umanizzato e peghilato (Certolizumab pegol) ed uno totalmente umano (Adalimumab). Al contrario, sono stati valutati recettori del TNF-α ricombinanti (Etanercept e Onercept) che si sono dimostrati inefficaci per il trattamento della MC attiva. Il Crohn ad insorgenza pediatrica è per definizione una malattia recente, che assai meglio si avvantaggia della terapia biologica a paragone di forme esordite tardivamente nell'età adulta.

Keywords: Citochine pro-infiammatorie, linfociti T $CD4^+$, TNF-α, anticorpi monoclonali

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