Crohn's Disease: Current state of biological therapy

Doença de Crohn: Estado atual da terapia biológica

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ABSTRACT: The inflammatory bowel diseases (IBD) are defined as nonspecific chronic intestinal inflammations with possible systemic involvement. IBD have unknown etiology. The inflammatory process is complex and heterogeneous, both as to the characterization of the disease that affects the digestive tract, without an intelligible pattern of revelation and balance, and in its different systemic damages when including the extensive and severe extraintestinal symptoms. Aparently, the natural history of the disease is irregular in relation to the offending agent system and the attacked system, both in the intestinal and extraintestinal teguments. Isolated aspects showing irregularity in this balance gives us the notion that IBD, especially Crohn's disease, can be caused by the stimulation of an immune response caused by damaging agents (intestinal bacteria), but mediated by inadequate genetic factors, whose expressions determine different individual susceptibilities. These observations have been shown in genetic studies that emphasize the importance of pathological interaction between host and bacteria subsidized by a genomic region that contains genes producing proteins (NOD2 - nucleotide-binding oligomerization domain containing 2) participating in an enhanced defense response by the tissue. Increased numbers and the activation of these cells in the intestinal mucosa elevate local levels of tumor necrosis factor α (TNF-α), interleukin-1β, interferon-γ, and cytokines of the interleukin-23–Th17 pathway. So, it can be assumed that the susceptibility, which is a result of genetic alterations, is connected to an exaggerated response in the pro-inflammatory phase because of a dysfunction in the intestinal immune system. The identification of tumor necrosis factor (TNF-α) as the active element in the pro-inflammatory inadequate response gave rise to the heightened production of biological substances that could block TNF-α, at different levels, opening a large field of view to new treatment of IBD.

Keywords: Crohn's disease; tumor necrosis factor-alpha; monoclonal antibody.

INTRODUCTION

Inflammatory bowel diseases (IBD) are defined as unspecified chronic inflammation of the digestive tract with skin and articular manifestations of unknown etiology. Concerning this subject, most authors mention proctocolitis and Crohn disease. These are different diseases, whose clinical common aspects are usually abdominal pain, diarrhea, bleeding, anemia and weight loss.

This study focuses on Crohn's disease (CD) and the current state of biological therapy.

CD was first mentioned by Charles Combe and William Saunders, in 1806[1]; they described some observations resulting from necroscopic examinations of specimens in which the lesion was characterized by stenosis, affecting the distal ileum and with colon involvement; in this segment, constriction zones measuring approximately 7 cm each were observed and separated by preserved parts.

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The ileal serosa of the stenosed segment, as well as in the colon, thickened due to the inflammatory process. In 1859, Samuel Wilks[2] observed similar cases. However, Crohn et al. conducted the first well-documented series of the disease in 1932, at Mount Sinai Hospital, in NewYork[1].

CD has been known for more than 200 years, but is still subject of scientific speculations; so far, its etiology has not been clarified.

The inflammatory process is complex and heterogeneous, be it in the characterization of the disease, which compromises the digestive tract and does not follow an intelligible pattern of manifestation and balance, be it in its different systemic expressions[3], when they relate to extensive and severe extraintestinal manifestations[4].

Significant systemic signals and symptoms of CD can be observed when it compromises children (infants or preschoolers). As to these patients, remarkable systemic damage is caused by growth disorders. Also, growth and height deficiency is relevant for children, since it can be the first manifestation of CD[5]. Fever of unknown origin, loss of appetite, pain and weight loss can precede the factors related to more objective manifestations of the disease[5,6].

Relevant extraintestinal changes that are common to CD affect organs and systems simultaneously, with varied degrees of severity[4]. The spectrum of extraintestinal changes demonstrates the unspecified characterization of the disease with etiopathogenic basis connected to the system of origin that is common to other chronic inflammatory diseases; this brings out its condition of systemic disease[4].

Anterior uveitis (iridocyclitis), for instance, is one of the extraintestinal complications of CD, and is also related to a great number of autoimmune and autoinflammatory diseases[7]. In this sense, rheumatic diseases appear (seronegative spondyloarthritis, whose group is characterized by inflammations of one or more joints, big or small, and tendons and muscular-scheletic insertions).

Among these, sacroiliitis and ankylosing spondylitis[8-10] are common for CD, and much more frequent than it is observed in practice, since early changes that cannot always be shown by imaging resources can be asymptomatic, thus going unnoticed[10,11].

Articular manifestations stand out due to pain of varied intensity, according to the extension of the inflammatory process, with the risk to lose mobility or even the articular function[11].

On the other hand, besides the endocrinological changes that have an impact on the immune system[12], there are external integumentary lesions, such as erythema nodosum and pyoderma gangrenosum. Although the cause of erythema nodosum is usually unknown in about 30 to 50% of the time, it can also be connected with a variety of autoimmune diseases, like Crohn's and Behçet, as well as infections caused by streptococcus, tuberculosis, mycoplasmal, diseases related to the Epstein-Barr virus and other herpetic lesions[13].

The pyoderma gangrenosum, which is a neutrophilic dermatosis of unspecific etiology[14-18] and whose necrosis and deep ulcers make the lesion look very unpleasant and painful, is an integumentary disease regarding a dysfunction in the immune system, which has a relation with Crohn's disease[19].

Observing the immunologic response and aiming to understand a bit more about CD in order to explain its etiopathogeny[20,21], there are speculations as to the immune response of the intestine, since is mediation occurs by factors such as: mucus barrier, mucus architecture and integrity, cellular components and their specific functions, and circulating cells of tissue defense.

The balance of intestinal immunity is present at birth; afterwards, it expands with the definition of the intestinal flora until the establishment of the system's homeostasis, that is, a balanced and healthy interaction between host and the luminal microecosystem.

Isolated or connected aspects that demonstrate some irregularity in this balance give us the notion that the IBDs, especially CD, may be caused by the stimulation of an immune response provoked by aggressive agents (intestinal bacteria, for example), but inadequately mediated by genetic factors. Their expressions define different individual susceptibilities[20], which are not only seen in the extension the intestinal mucosa compromise, but also by the dimension and nature of transmural changes. They are also caused by local vascular changes, involved in the inflammatory process; by the manifestations and systemic associations with other immune diseases; by the responses to

clinical conventional treatments; and, finally, by other data that characterize the natural history of the disease and its specificities, for each person[15,16].

These observations have been analyzed in genetic studies that demonstrate the importance of the pathological interaction between host and bacteria[21] – almost exclusively because of the host, rather than the bacteria – subsidized by a genomic region that contains genes that produce proteins (nucleotide oligomerization double-domain protein – NOD2) and participates in the response of tissue defense by signaling the activation of the immune response system; by autophagy genes and by reaction paths with interleukin-23 components competing with T lymphocytes (Th-17)[22-26].

In the NOD2 gene, the protein's role is related to the response of the host defense by signaling the activation of caspase (family of intracellular cysteine endopeptidases that help regulate the inflammation and the apoptosis) and of the system of protein kinase signaling, activated by mitogens (MAP-kinases), a system of intracellular signaling which involves the MAP-kinases cascade – subfamily of enzymes that respond to the extracellular stimulation and regulate the activities of gene expressions, mitosis, differentiation, cellular survival and apoptosis. Usually, the protein codified by the gene NOD2 works as an intracellular sensor of murein, which is a polyssacharide (peptidoglycan) of the cell wall of the bacteria.

The most susceptible association with CD[23,27] was made with changes in the NOD2. Three gene polymorphous that codify the nucleotide oligomerization of the domain 2 of the protein with flaws are known to harm the responses that are sensitive to murein[28,29].

Usually, the secretion of proinflammatory cytokines by the antigen cells that are present in the intestinal wall is minimal, since the invading bacteria are destroyed. This results in the power of defense of the immune system against the elements of the intestinal microecosystem without causing tissue lesion[30]. However, with the aforementioned genetic polymorphism, among other homeostatic changes of the intestinal immune system that occur on patients who have CD, especially that characterized by the higher cellular presence that mediates an ineffective activity against peptidoglycan in the cell wall of the bacteria, it is easy to increase the production of cytokines (such as the tumoral necrosis factor – TNF – and interleukin-1β) and antimicrobial peptides[27, 31]. Thus, there is an exaggerated secretion of proinflammatory cytokines.

This process involving the contribution of the NOD2 gene polymorphism to the intestinal inflammation observed at CD is complex and not completely understood[27] – there are over 30 genomic locus involved in the genetics of CD[33,34]. However, the general idea is that the active stage of the inflammatory process is characterized by the lamina propria of the mucosa with defense cells (neutrophils, macrophages, dendritic cells and T-killer leukocytes), without the presence of an increased invasion of microbes. Under these conditions, the susceptibility caused by gene changes may be connected to an exaggerated response in the proinflammatory phase, as a result of a dysfunction in the intestinal immune system[21].

BIOLOGICAL THERAPY

The biological therapy, which is under analysis in this study, will result in the biological response modifiers of the intestine, with special attention to the blockage of specific cytokines that modulate the inflammatory process at the existence of genetic pleomorphism[21,27,35].

Genetic aspects involving CD have been known since the past century, usually due to epidemiological studies addressed to etiological and pathogenetic factors[36-40]. However, the genetic perspective was only established after the first gene related to CD was described[41], and successfully confirmed[42-44].

The pathogenesis of CD and its genetic link is partly subsidized by the complicated interaction between immune, innate and adaptive cells, involving the vascular blood and the lymphatic intestinal systems, as well as local tissue immunity. There is the participation of cytokines and genetically controlled modulators, which provides more or less balance as to the tolerance of the organism to the intestinal "microbiota", expressed by proinflammatory responses, which may be inadequate[21,35,45,46].

The observations of these inadequate responses and of proper genetic studies led to the acknowledgement of the association between CD and NOD2 gene polymorphism, as aforementioned. This gene is relatively common among CD patients coming from Eu-

rope, is absent among Asians and rare among African American people with the disease[26,27,29,47].

Estimates show that approximately 30% of the patients with CD coming from Europe have at least one of the three NOD polymorphism genes. Those who carry the polymorphism gene are more prone to presenting ileal disease, with a complication related to stenosis and the need for surgical resection, when compared to those who do not carry it[31]; heterozygotes have increased risk of CD (factor 1.75 to 4), while homozygotes have a much higher risk (factor 11 to 27)[30]. However, the NODS polymorphism gene alone is not sufficient to cause CD, which demonstrate the complex aspects of the multifactorial disease, that is yet to be fully understood[21,48].

In the process of proinflammatory activity, among the different cytokines that are produced, the tumoral necrosis factor stands out (TNF-α), which is a model of proinflammatory cytokine with multiple effects on the innate and adaptive immune system cells, as well as on the vascular endothelium of microcirculation[49,50]. The tumoral necrosis factor stimulates the stage of acute inflammation, as well as apoptosis. It also increases the production of cytokines and the cytokines of small peptides; it increases the secretion of elastase and collagenase; it increases the properties of molecular adhesion to the vascular endothelium; and promotes the accumulation of leukocytes in the tissue[51]. These multiple actions define the pleiotropic feature of TNF- α, turning it into a specific target for the treatment of intestinal bowel disease[50].

The interpretation of this fact, which is not only related to CD, but also to other autoimmune inflammatory diseases, led to the conduction of research plans with the objective to create substances that should be completely produced by the host, and at the same time able to block the unwanted actions of active proteins that impact the proinflammatory stage. However, it should present low specificity for the invading antigen with harmful effects for the host.

Current information taken from studies concerning the association of genetics with the clinical aspects and the results of animal experiments about the inflammatory bowel phenomenon have gathered elements to interpret that the etiopathogenesis of CD may be at least partly dependent on a innate genetic error, which promotes the unbalance of the intestinal immune system.

The disorder that appears during the proinflammatory stage expresses itself by the exaggerated production of cytokines (TNF and interleukin-1β) and antimicrobial peptides[27,52]. Among these cytokines, TNF-α has been considered as the key element49,51,53,54, thus becoming the target for the development of new therapy strategies for CD[55-59].

Monoclonal antibodies

In 1901, Paul Ehrlich and Johan Morgenroth used the term "self-toxic horror" to express their "concern for the destruction that an autoimmune reaction could cause in relation to the inflammatory response, which is so necessary to protect the organism".

The formation of tissue autotoxin, result of the defense process, however, could be a real threat to the living being[60]. Such concept became the basis for future knowledge regarding autoimmune diseases, the systemic inflammatory reaction and multiple organ failure.

As to IBD, the importance of TNF-α and its pleiotropic aspects for the triggering of tissue changes and the emerging challenge related to the idea of specific agonist block, connected to knowledge regarding immunotherapy (the discovery of the antibody structure and the development of hybridoma) and the subsequent production of monoclonal antibodies, led to the first intention to create the proteins "originating from different genes and species" (*chimeric* proteins* = obtained by means of genetic modifications, linking factors from two species, for example: mouse-human). Thus, as a monoclonal antibody, it is possible to oppose to the action of TNF-α.

The terms chimeric and "humanized" – referring to monoclonal antibodies – are used to express the combination of sources coming from human and mouse DNA in the process of recombination, which leads to the formation of the antibody[61].

Infliximab

The first monoclonal antibody to be therapeutically used for autoimmune human diseases that interested CD therapy was infliximab, which was first administrated for the treatment of rheumatoid arthritis[62,63].

Created in the 1990s, infliximab is a monoclonal antibody (IgC1) of human nature (constant region – 75%) and murine (variable region – 25%), which binds to human TNF (TNF-α) and neutralizes its biological action. Originally, the antibody was believed to obstruct the link between the cytokine and its natural receptor[64,65]. However, the observation that another blocker, called *etanercept* – which is not a monoclonal antibody, but blocks the action of TNF-α by binding with the receptor without producing any biological effect over CD, or causing a situation that is worse than the placebo[66] –, led to other speculations about the pharmacological action of infliximab. As a result, it was demonstrated that the action of the monoclonal antibody is extended to the lymphocytes of the peripheral blood and to the lamina propria T-lymphocytes, inducing both to apoptosis[66-68].

The first relevant studies were published by the end of the 1990s[55-58,69], with promising results as to the action of infliximab on CD, specially the fistulizing effect involving multicentric cooperation.

Along the past ten years, more than 50 publications addressed to the treatment of IBD, including CD in its different forms, prove the positive results of the long and medium term therapy with the chimeric monoclonal antibody, including for infants[70-78].

The first promising responses for 61% of the treated patients *versus* 17% on placebo come from double prospective study (placebo-medicine) conducted with more than 100 patients with CD refractory to the conventional treatment, with high levels of disease activity, using different doses of infliximab (5, 10 and 20 mg/kg). Clinical responses were registered on week 2, similar to the 70-point drop in CD activity index (CDAI). Besides this answer, this stage also demonstrated clinical remission in 27% of the treated patients, against 8% in the placebo group[55]. Non-controlled studies conducted in a short period to compare clinical results with population studies were developed afterwards[79,80].

In Italy, the experience was registered in a project with 63 patients; some had refractory CD (31 patients) and others had fistulizing CD (32 patients). In order to assess the results, clinical remission for the group with refractory CD, analyzed on week 0, 2 and 6, was defined by the authors as CDAI≤150, and clinical response was determined with a 70-point drop or more in the initial score. For the group with fistulizing CD, the complete response was defined as the fistula closure observed in the evaluation performed on week 10, or as the partial response in situations in which the number, size and drainage of the fistulae decreased on the same week[79]. In this study, clinical response on week 2 was observed in 42.5% of the patients with refractory CD, while clinical remission was observed in 31.3% of the patients. More precise data were noticed on week 10, with clinical response in 80.6% and remission in 71% of the patients. Among patients with fistulizing CD, 47% presented full responses, 25% had partial responses and 28% showed no responses whatsoever until the end of the treatment. Side effects were present in 16% of the patients, and were interpreted by the authors as a result of the immunomodulator therapy used as adjuvant[79].

In Hungary, the results of a multicentric experience involving 363 patients for 6 years in a geographically extensive and long-lasting study were reported. The group had patients with refractory CD (31.4%), patients with fistulizing CD (53.7%), steroid-dependent CD patients (7.2%) and patients with both situations – refractory and fistulizing CD (4.4%)[80].

In the global scenario, response to therapy was 86.2%. The most significant positive results were observed in patients who had been recently diagnosed, and among those who have had concomitant immunomodulator therapy. Adverse effects were allergic reactions (9.4%), late hypersensitivity (4.7%), infection (4.4%) and malignant neoplasm (0.8%). These results were considered as good, but there was the suggestion of the concomitant effect of immunodepression[80].

As for infants, infliximab was also tested as to safety and effectiveness. The project Pediatric Inflammatory Bowel Disease Collaborative Research Group Registry, that aims to evaluate the long-term therapy, included 729 children in a multicentric study (approximate age of 16 years)[75]. Patients who had infliximab – a group of 202 children – presented clinical history and diagnosis of the disease for a period that ranged from 1 year, one to two years, and older than two years (62, 23 and 15%, respectively). Immunomodulators and steroids were used as an adjuvant therapy among children who needed a prolonged treatment. Treatment with infliximab lasted less than one year, up to three years, and children remained with the inactive disease,

without other medications or surgical treatment[75]. Despite the exciting benefits[75,81], and before the top down approach to the treatment with infliximab[81,82] is established, the case reports that explain the effects of remission caused by the monoclonal antibody should be emphasized, especially regarding infants. That is why it is important to review the duration and the meaning of benefic effects in this population, especially by observing that prolonged use was followed by "loss of response", with limited duration of the effect, since 50% of the patients lose the benefits after five years under maintenance treatment. This forces the doses to be adjusted so the prior levels of therapy effectiveness could be reached, thus substantially increasing the time of submission to the medicine. Besides this lack of efficiency, such exposure for patients who initially needed continuous infusions and adjustments for a longer period increases the chances of unwanted side effects, thus leading to the search for new therapy strategies for the infants with CD[83].

Similar aspects have been observed in the adult population: 25 to 40% of the patients who presented clinical responses to early therapy stopped responding effectively to the medication. In this case, they needed to have their doses and intervals readjusted; sometimes, the medication needed to be discontinued for a significant number of patients because it completely lost its efficiency, or due to side effects[76,84-86].

This sudden loss of action is probably related to the high concentration of antibodies against infliximab[87,88] in a patient who used staggered doses of monoclonal antibody for an efficient therapy response, probably induced by the murine fraction of infliximab[89-91].

Adalimumab

Adalimumab (ADA) – result of a joint research (BASF Bioresearch Corporation and Cambridge Antibody Technology) that initiated din 1993[92] – is a monoclonal antibody, just like infliximab, type IgG1, but its composition is 100% human. It is the third substance directed to TNF after infliximab and *etanercept*, and the second monoclonal developed for humans with the goal to act the same as the first, but with the likely advantage not to cause the unwanted effects of reaction to hypersensitivity[93,94]. Thus, it is useful to treat CD in a patient who is "resistant" to infliximab[59]. The posology is simple, and the application is subcutaneous, which facilitates its use. The recommendation for CD, especially in the most complicated cases, is 160 mg as the induction dose on the first day, followed by 80 mg on the 14th and 40 mg on the 28th day. The history of this new antibody begins with the publication of clinical trials concerning the action on rheumatoid arthritis, in 1999[92]. In 2002, ADA was approved by FDA to treat rheumatoid arthritis and, in 2007-2008, it was subsidized by the studies of Hanauer et al.[95] and Sandborn et al.[96], respectively. It did not only prove its efficiency and safety to induce the remission of the disease in patients who have not used a monoclonal antibody[95], but also tested its action as to maintenance of response[96], including in patients who had been treated with infliximab[97]; it also demonstrated balance as to prolonged use[98].

These results gave new directions for the treatment of CD, especially due to the "purity" of ADA and by the growing number of patients for whom the failed response to infliximab showed something similar to what had been observed with other drugs used to treat CD.

The results of the treatment with ADA were beneficial for 60% of the patients for an average period of 2 years, not only favoring those who had been under monoclonal antibody, but also for those who were using it for the first time. However, after a while and with the growing number of patients included in the studies, for a relevant number of people (28%)[99] the antibody also lost its effect due to immunological intolerance[99,100]. The population involved had twice as many patients who had received anti-TNF in relation to those who were being treated for the first time (22 *versus* 8% per patient per year of treatment). For those patients who presented with the extraintestinal manifestation of CD, the risk of losing efficiency is even higher[101].

In spite of that, the initially surprising results have been interpreted as a rich and suggestive experience – for example, in the infant population – that can guide the "early introduction of the monoclonal antibody with the hope to change the natural course of CD in this population"[81,82,102], thus inducing the idea of "top-down" therapy. On the other hand, an interesting point observed in investigations that comprise groups on drugs and placebo groups, even if the difference among them is not mathematically defined, is that the positive results in the placebo group are not negligible. In the study about the induction of remis-

sion using ADA, it was observed that, among the 301 patients who completed the investigation – 159 in the group on drugs and 166 in the placebo group –, 21% of those who had drugs and 7% of those who were in the placebo group presented clinical remission on week 4. When the result was assessed by the CD activity index (CDAI)[103] for 70 points, comparison values between group on drugs and placebo group were 52 and 34%, respectively. In both circumstances, the differences were statistically confirmed[97].

It is a known fact that remission in CD can be spontaneous. If we could remove these values spontaneously generated in the treated group, the difference between groups would certainly not be 14.2% for clinical remission, nor 17.8% for the points given by CDAI.

The loss of response and the need to intensify the dose involve medical and economic interests that may cause unwanted repercussions for the patients.

With the profile of a substance that is able to cause the remission of CD both in patients who had not been treated with a monoclonal antibody and in those who were victims of infliximab[95,104], ADA was used with the expectation that the results could be superior to those observed with infliximab, especially concerning prolonged use and no loss of activity. This is because other effects, whose frequencies may range from 1 to 26% (1, 11 and 26%, including dose adjustment, temporary discontinuation and permanent withdrawal, respectively), are sometimes negligible, but of variable severity, such as mere allergic reactions (cutaneous rash, pruritus, difficulty breathing, constrictive chest pain, although, under some circumstances, they may be severe[105-107] and fatal[108], which requires a criterious selection of patients[110]).

The loss of response that corresponds to 18.2% means 20.3% of risk per patient a year. The average number of patients who needed to reinforce the dose among primary users was 37%, with a risk of 24.8% per patient/year. Considering the ones who primarily presented good response to ADA and those who did not respond well, the mean percentage of patients who needed to progressively increase their dose was 21.4%, with annual risk of 24.4% per patient/year. On the other hand, the group who required reinforcement recovered the response in 71.4% of the cases, and showed remission in 40%[111]. The same study that showed these data demonstrated the possibility to predict loss of response or the need for the staggered increase of the dose, especially concerning the following factors: male, smokers, family history of IBD, disease restricted to the colon, extraintestinal manifestations, induction with a 40/80 mg dose, long term condition, prior use of monoclonal antibody (infliximab), no good response[111,112]. Actually, one out of five patients experiments loss of response and needs a dose reinforcement[111].

Relevant aspects resulting from these facts have recently been approached by Dretzk et al.111 in a systematic review about the benefit-cost involving two monoclonal antibodies, with emphasis for the following conclusions: a. "therapy with adalimumab and infliximab may be beneficial in comparison with the conventional treatment, when the results are measured at induction and maintenance"; b. for induction both have benefits that compensate for the cost when compared to the conventional treatment applied on severe CD; the same is true for ADA in relation to moderate CD, but not for infliximab; c. based on this review, "none of the two drugs is profitable as a maintenance therapy, be it for severe or moderate CD".

CONCLUSION

The new formal knowledge about etiopathogeny of CD, especially when it depends on genetic changes and the relation between the proinflammatory activity of TNF-α in the mechanism of tissue lesions, enabled the development of monoclonal antibodies, which were profusely used due to the belief that it would be possible to change the natural history of the disease. This way, the dream to offer an unprecedented benefit-cost treatment could come true. However, the association between CD and NOD2 polymorphism gene is variable among populations, being relatively common among patients with CD from Europe, but is absent among Asians, and rare among African Americans with the disease[26,27,29,47]. This gives CD a multifactorial etiologic character, with or without the genetic implication.

These facts could involve data to explain the more or less efficient action of the monoclonals. For now, the most effective procedure involving the biological therapy should meet some criteria that should be at least defined to choose the candidates for treatment with monoclonal antibodies.

So, the National Institute for Health and Clinical Excellence (UK) brings about some items whose interest and relevance enable to transcript six of them[114]:

1. Infliximab and adalimumab are recommended for adult patients who have severe CD and do not respond to conventional therapy (including steroids and immunosuppressors), or for those who do not tolerate medicines or present factors that contraindicate the use of conventional therapy. Infliximab or adalimumab should be in accordance with a treatment plan in which the administration will be continued until there is no response, or 12 months after the beginning, or less, if there is any problems;
2. Treatment should be initiated with cheaper drugs, considering the cost of administration, the necessary doses and the price per dose;
3. Infliximab was released to treat fistulizing CD after not responding to conventional treatment (including antibiotics, surgical drainage and immunosuppressors) and was planned for a definite time of 12 months, or earlier, if the treatment fails;
4. The treatment with adalimumab or infliximab should only continue if it becomes clear that the disease is active by clinical symptoms, biological markers, endoscopic tests, if necessary;
5. For its purpose, CD is considered severe when the general health status is significantly compromised, associated with one or more symptoms, such as: weight loss, fever, severe and frequent abdominal pain (3-4 times or more per day), daily diarrhea, regardless of presenting extraintestinal manifestations or fistula. This definition corresponds to CDAI[103] of 300, or a Harvey-Bradshaw index lower than 8-9;
6. Treatment with infliximab or adalimumab should be administered and assessed by doctors who have experience with TNF-α inhibitors and with the treatment of patients with CD.

RESUMO: As doenças intestinais inflamatórias (DII), definidas como inflamação crônica inespecífica dos intestinos, com eventual comprometimento sistêmico, são de etiologia desconhecida. O processo inflamatório é complexo e heterogêneo, tanto na caracterização da doença que atinge o trato digestório, onde não obedece a um padrão inteligível de revelação e de equilíbrio, como em seus variados danos sistêmicos, quando englobam os extensos e graves sintomas extraintestinais. Tudo indica que, na história natural da doença, há uma notável irregularidade entre agente agressor e sistema agredido, tanto a nível intestinal, como nos tegumentos extraintestinais. Aspectos isolados ou de conjunto que denotam irregularidade nesse equilíbrio dão-nos a noção de que as DII, sobretudo a doença de Crohn, podem ser originadas pela estimulação de uma resposta imune, provocada por agentes agressores (bactérias intestinais, por exemplo), mas mediadas de forma inadequada por fatores genéticos, cujas expressões determinam diferentes susceptibilidades individuais. Essas observações têm sido realçadas em estudos genéticos, que destacam a importância da interação patológica entre hospedeiro e bactéria, subsidiados por uma região genômica que contém genes produtores de proteínas (proteína de dois domínios de oligomerização de nucleotídeos - NOD2), com participação na resposta de defesa tecidual pela sinalização da ativação do sistema de resposta imune; por genes autofágicos e por vias de reações com componentes de interleucinas-23 com a concorrência de linfócitos-T (Th-17). Nessas condições, o que pode ser suposto é que a susceptibilidade, que decorre de alterações gênicas, esteja ligada a uma exagerada resposta na fase pró-inflamatória, decorrente de uma disfunção do sistema imune intestinal. A identificação do fator de necrose tumoral (TNF-α) como o elemento ativo na resposta pró-inflamatória inadequada e exacerbada ensejou a produção de substâncias biológicas que fossem capazes de bloquear o TNF-α, em diferentes níveis, abrindo um campo grande de perspectiva para novo tipo de tratamento das DII.

Palavras-chave: doença de Crohn; fator de necrose tumoral alfa; anticorpo monoclonal.

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