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Invited Review

Alternative forms of treatment in inflammatory bowel disease*

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A. HISTORIC REVIEW OF IBD TREATMENT

Ancient Greek Medicine has made the first clinical description of IBD through the words of Hippocrates in his book "about epidemics" dealing with tenesmus and rectosigmoidal bleeding because of rectal ulcerations (Aphorisms, B. VII).[1] In 'modern' western medicine IBD was described either in the form of case reports, initially, or in the form patients cohorts. This started in 1806 with Combe and Sanders in London and was continued with Ambercrombie in 1823, Dalziel in 1931 and B. Crohn in 1932 when he was working at Mount Sinai Hospital.[2] His analytic disease description gave the name of Crohn's to one of the two main forms of the disease.

B. THE PROGRESS OF PHARMACEUTICAL TREATMENT IN IBD

The treatment of IBD passed through many stages of progress the lasted fifty years, starting with sulfasalazine administration in 1942, in Sweden, and continuing with new drugs which characterized the decades when they were initially used: corticosteroids in the 50s', AZA and 6-MP in the 80s', CyA, methotrexate and anti-TNFa monoclonal antibody in the 90s'. In this coming decade the challenge of using molecular and genetic treatment in IBD may one day be a reality. Moreover, recently, new therapies based on new knowledge and traditional treatments (i.e. anti-tuberculosis) are continuously being assessed in laboratories and in clinical trials. Nevertheless, no one to date can claim that they hold the key to the 'gold' IBD treatment.

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C. TARGETS IN IBD TREATMENT

It seems that all efforts to define IBD etiology somehow also determined the targets of IBD treatment. These targets according, to the majority of authors, are, briefly, the following:

a. T-lymphocytes.

b. Cytokines of inflammation (interleukins, TNFa).

c. CD4 and Th cells.

d. Adhesion molecules.

e. Non-specific factors of inflammation and healing.

D. BIOLOGICAL THERAPIES IN IBD

All therapies in IBD using biological products, naturally or synthetically produced, have not yet been a widely accepted and established as routine method of IBD treat-

Abbreviations used in the text:

IBD *= inflammatory bowel disease*
UC *= ulcerative colitis*
CD *= Crohn's disease*
Th cells *= T-helper cells*
AZA *= azathioprine*
6-MP *= 6-mercaptopurine*
TNFa *= tumor necrosis factor alpha*
CyA *= cyclosporine A*
5-ASA *= 5-aminosalycylic acid*
IL *= interleukin*
SCFA *= short chain fatty acids*
IL-ra *= interleukin receptor antagonist*
IFN *= interferon*
Ig *= immunoglobulin*
CSF *= colony stimulating factor*
NF *= nuclear factor*
EPO *= erythropoietin*

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ment. Nevertheless, the following groups of these kinds of therapies seem promising the near future:

a. Natural biological products (whole blood or plasma derived).

b. Recombinant products (cytokine related).

c. Monoclonal antibodies.

d. Nucleic acids and antisense oligonucleotides.

e. Genetic and gene therapies.

E. BASIC TARGETS OF CLINICAL THERAPY IN IBD

There is a continuous re-rating of the basic targets or categories of clinical therapy in IBD due to the daily changing knowledge of cell biology, molecular mechanisms and IBD biochemistry. However the targets of IBD treatment can be summarized as following:

a. Antigen presenting and macrophage activation.

b. CD4 activation and antigen recognition.

c. Th1 and Th2 response and subsequent IL-10 production.

d. Pro-inflammatory cytokine production.

e. Migration, chemotaxis and adhesion.

f. Mechanisms of tissue inflammation and damage.

g. Tissue remodeling and repair mechanisms.

h. Other, insufficiently well determined and assessed targets, such as free radicals (mainly those of oxygen), neuropeptides, growth factors and short chain fatty acids (SCFA).

In the following paragraphs, all these alternative forms of IBD treatment are summarized under but with the awareness that they represent only a small proportion of all proposed methods of alternative IBD treatment.

1. Therapies targeting in cytokines and immune response

Recently IL-1 and IL-ra (receptor antagonist) have been cloned and synthesized in the laboratory. It is generally accepted that they really represent a precious tool in IBD therapy but their disadvantages are that they must be used parenterically and in relatively high doses. For these reasons, alternative methods of administering those substances are now on their way; the use of soluble IL-1 receptors which bind IL-1 or the production of less antigenic non-proteinic molecules.

IL-2 and IL-2ra (receptor antagonist) still remain of no clinical importance at the moment in IBD. It has been reported that IL-2 deficient mice develop a kind of colitis very similar to UC, while IL-2 administration in 2 patients with CD and Gravitz tumor of the kidney (hypernephroma) resulted in severe CD relapse.[3]

IL-6 and IL-11 are glucoprotein-130 ligands, their use in IBD is to date experimental and their safety and efficacy is restricted to experimental animal studies. IL-8 is reported to be increased in UC, and natural antibodies against IL-8 have been recognized and identified. Clinical trials with therapies based on IL-8 antibody administration are not, so far available. Th2 cell derived IL-10 suppresses Th-1 cells through IFN-γ production. The clinical use of IL-10 is expanding and positive results concerning its efficacy and safety have been suggested.[4]

Inteleukin 11 is an IL-6 family member with a mesenchymal cell origin. Recombinant IL-11 use at a dose of 15/mg/kg/week subcutaneously showed a 37% improved performance in animal studies, while in the same studies placebo succeeded in only 16%. Interleukin 12 enhances Th1 differentiation but its probable therapeutic role is still to be determined. The CDP571 molecule (IgG4 humanized anti-TNFa antibody), when used in CD patients (21 patients, dose of 5mg/kg/day), resulted in statistically significant CDAI reduction. It has been suggested that it is less antigenic than Infliximab, but this statement may also implicate that it may also be less effective. More studies are needed to answer these questions.

Adalimumab is a recombinant monoclonal IgG1 antibody containing only human peptide sequences. Adalimumab binds TNF-α and neutralizes its function by blocking the interaction between TNF and its cell surface receptor. Based on preliminary data, adalimumab may be a safe and effective substitude for infliximab-allergic patients.[5]

Interferons α and β have shown little efficacy in non-controlled clinical trials while IFN-γ seems not to be effective in CD. Growth factors such as G-CSF and GM-CSF are increased in active IBD and their controlled inhibition may be beneficial in some selected cases.

Monoclonal anti-CD4 antibodies have been tested, mainly in CD, on the theoretical basis that HLA II assisted CD4 cells play a major role in antigen presenting and inflammatory process. The CD4 molecules coded as

MAXIGH5 and B-F5 have not been proved efficient in IBD relapsers. The molecule CMT412 is a chimeric monoclonal antibody, which reduces CD4 cells but, unfortunately, in no controlled way, resulting in infections and making its future perspectives for clinical use very questionable.

The BCG vaccine, the use of levamisole, the Bowman-Birk inhibitor (soya derivative) and the I.V. immunoglobulin use have been proposed, but their clinical use was never strongly supported.

Inhibitors of NF-kB transcription seem to be promising in IBD. These inhibitors are proteins or belong to the antisense oligonucleotide family. The NF-kB family is encountering transcription factors that control the expression of several proinflammatory cytokines (IL-1, TNFa), adhesion molecules and acute phase proteins.

The antisense oligonucleotide use in NF-kB 65 inhibition (antagonism) has been suggested to be efficient in experimental models of colitis, surprisingly, in a more successful way than glucocorticoids. In vitro studies have shown that IL-1, IL-6 and TNF-a levels are significantly reduced by NF-Kb inhibition.[6]

2. Therapies targeting the lipidic mediators of inflammation

Increased production of arachidonic acid leading to increased levels of prostaglandins, leukotriens and throboxanes has been reported in IBD. Prostaglandins such as rioprostol, misoprostol, dimethyl PGE2 have already been used in IBD studies, as their cytoprotective role has been shown experimentally. Nevertheless, researchers with UC patients have not been enthusiastic.

Eicosanoid inhibitors (COX inhibitors, LTB4 inhibitor) and thromboxane inhibitors, TXA2, TXB2 (ridogrel, picotamide) acting at the level of production or antagonism may be useful. Fish oil and SCFA use p.o or enema is reported to enhance eicosipentanoic acid metabolism of the cell membrane into the less toxic LTB5.5-lipoxygenase inhibitors (FLAP, MK-591, Zileuton) and have also been tested for IBD therapy.

Zileuton has shown marginally positive results in one study but its use inhibits 5-ASA action; consequently their concomitant use is contraindicated. Complement activation inhibitors (K67) have not proved efficacious in UC, while PAF inhibitors such as SR27471A are well tolerated but unfortunately of no clinical use in active UC under mesalazine treatment. Arachidonic acid inhibitors (chloroquine) have been tried for Th cell inhibition but proved unsuccessful in ulcerative colitis patients.[3]

3. Nicotine and IBD

Theoretically nicotine induces mucous production and enhances TNF and IL-2 inhibition. In every-day clinical practice nicotine has not proved useful despite the fact that the reverse correlation between UC and smoking has already been shown in many studies. Many forms of nicotine, for local and systemic administration, have been used with marginal profit but severe side effects. Practically the hot point about nicotine use in IBD is the right advice to smokers and non-smokers with IBD.[3]

4. Therapies against antigen targets

Metronidazole, antituberculous therapy and many other antibiotics have been proposed but to date none of them has been proved to induce short-term or longitudinal disease remission. Probiotics have been proposed these last years as the information about the role of enteric microflora is sufficient to propose probable changing mechanisms in the intestinal microflora. For instance, E. coli (Nissle 1917) has been reported to induce IBD remission. However, the true impact of this enteric microflora change still remains unknown and we should always have in mind that all studies using probiotics against placebo are difficult and sometimes unethical to perform.[4]

5. Newer and older immunosuppressive agents

ACTH is considered equal to corticosteroids but, firstly, it should be administered intramuscularly and, secondly, the activation of the angrogen-alatocorticoid axis is not avoided as result of whole adrenal gland activation.

Mycophenolate mofetil (MMF) inhibits purine synthesis in lymphocytes through reversible inhibition of the IMP dehydrogenase. In doses of 500 mgx2 or 15mg/kg/d (divided in 2 doses) MMF has been proved useful in CD by minimizing the requirements for corticosteroids.

Thalidomide has been suggested to have antiangiogenetic and anti-TNF properties. It has been suggested as useful in CD, but its teratogenic side effects should never been overlooked.

Cyclosporine in doses of 5mg/kg/d p.os for a 3-18 month period has ambiguous results according to many controlled studies. Intravenous use of CyA in doses of 4 mg/kg/d has proved of use in fistulizing CD in non-controlled trials.It has been proposed that every responder to intravenous CyA should continue the same drug P.O. CyA enemas have been suggested in left colitis, and CyA micropellets have shown satisfactory pharmacokinetic stability but not established clinical efficacy. In conclu-

sion, CyA is indicated according to the existing studies, in small bowel CD, fistulizing, esophageal and gastroduodenal CD and with care in steroid resistant fulminant attacks of UC.

Disease relapses after CyA discontinuation is common and, at the moment, it is advisable to administer CyA for a long period of time with the concomitant use of another immunosuppresant agent. CyA side-effects have been reported in up to 27% of IBD patients and include paresthesias, renal failure, opportunistic infections and anaphylaxis.

Tacrolimus (FK 506) is a macrolidic antibiotic with properties similar to CyA. FK 506 at doses of 0.15-0.25 mg/kg/d is considered useful but the problem of maintaining stable levels in the blood stream still remains unsolved.[7]

6. Neuro-hormono-immunologic approach in IBD therapy

Somatostatin (vapreotidel) has been proposed in IBD therapy as natural somatostatin synthesis in bowel epithelium of CD patients is decreased. Despite all experimental studies a multicenter clinical trial has shown efficacy only in reducing abdominal pain. Several neurohormaonal substances have been proposed as alternative therapies in IBD. These substances include VIP, substance P, and bombesin, but did not prove satisfactory in inducing disease remission. The antisense oligonucleotides represent a synchronous and experimentally well-documented therapeutic alternative in IBD. The down regulation of ICAM-1 in steroid-dependent CD patients was promising enough compared to placebo.

Local anesthetic use in UC represents a new and promising therapeutic area. The use of lidocaine (subcutaneously, intrarectally) is considered to be a satisfactory alternative therapy in UC, mainly in left UC. The mechanism of lidocaine action is still unknown but the inhibition of adrenergic neurons or neuropeptides is strongly suggested. Systemic absorption of administered anesthetics in UC does not seem to imply any danger, as serum levels are safely low. For the UC treatment lidocaine gel 2% in a 20-100 ml enema twice a day is proposed with satisfactory results. Another promising anesthetic is ropivacaine in a dose of 200mgx2/d for two weeks, but there is a lack of studies to suggest its further routine use.[3-4]

7. Adhesion and chemotaxis inhibitors

The adhesion molecule ICAM-1 and adhesion inhibitors is a current topic waiting its turn to enter the list of alternative treatments of IBD. The ISIS-2302 molecule is the first paradigm of antisense oligonucleotide use in the GI tract. This molecule is included in the ICAM translation procedure and promotes the accumulation of monocytes and granulocytes in the inflamed tissues.

Restricted numbers of studies with placebo are in favour of ISIS-2302 (17% vs 90%). The anti-a4-antibody (humanized) showed efficacy in a very small number of studies in UC and CD and needs further investigation.[6]

8. Non-specific inhibitors of inflammation and tissue damage

Free radical scavengers are a familiar mechanisms in the theoretical support in IBD treatment strategy. The use of free radical scavengers, including superoxide dismutase, vitamin E, iron cooper and zinc, chelic molecules have resulted in questionable benefit according to current studies.

PNM elastase, the active oxygen molecule (ROM) and nitric oxide radicals (LNAME, LNMMA) represent a well-organized group of stressors for the intestinal epithelium.

Furthermore, allopurinol is considered as an antioxidant factor because it inhibits the xanthino-oxidase pathway to produce ROM. Allopurinol use has been suggested in pouchitis. Nevertheless, to date 5-ASA still remains the best antioxidant substance ever used in IBD.[3,4,6]

9. Factors of remodelling and repair

Several factors of remodelling and repair have been suggested, such as trefoil proteins, mucin, peptidic growth factors (EGF, TGF-2, VEG, TGFa, KGF), but all studies have been performed in experimental models of colitis.[6]

10. 'Strange' and 'anti-conformistic' treatments in IBD

As the causal factor or factors of IBD still remain unknown, several 'strange' treatments have been tried which apparently do not agree with the western medical way of thinking or seem to ignore the theoretical background of IBD. These kinds of treatments also include currently used drugs such as clonidine, which was proved satisfactory in UC, probably due to its central nervous system action or bowel motility regulation. Of course, nicotine and smoking habits in UC is also a 'strange' therapy included in this group.

The citrate/subsalicylate bismuth enema has been reported to be equivalent to mesalazine enema. Classic or low molecular weight heparin has been reported to

enhance polymorphonuclear cell chemotaxis and tissue repair. Studies in UC have clearly shown that heparin has a 'strange' positive action in active UC which is suggested to result from microthrombosis inhibition in bowel epithelium or from the up-regulation of the intestinal apoptotic mechanisms. The positive therapeutic role of coagulation factor FXIII (Fibrogammin P) in UC, the hyperbaric oxygen use in perianal CD, the leukapheresis or plasmapheresis in acute UC are suggested alternative treatments needing larger controlled studies with IBD patients.[4,7]

11. Growth factors and other hormonal factors

The subcutaneous administration of GH with concomitant use of a high quality proteinic diet resulted in a statistically significant CDAI reduction when compared to placebo. This reduction was translated into reduction of recorded bowel movements, abdominal pain, and generally improved health status in 19 patients with moderate to severe CD, in a recent pilot study. In this study corticosteroid use was minimized as result of the GH use. Growth hormone's most important reported side effects were edema and headache, while the exact amount of each dose, the number of doses, the long term results and the duration of therapy has not yet been determined. No long-term studies of GH in children with IBD have so far been published. Testosterone may be of use in children with IBD who are sexually retarded. Therapy with testosterone should be performed in a well-controlled way and with monthly doses for a period of 3-6 months. Serum IGF-I levels are decreased in IBD and its use may be of benefit as the results with experimental models of colitis were satisfactory.[3,4]

12. Erythropoietin

The administration of EPO in IBD patients in doses of 150-450 MU/week has been strongly supported by many case reports and a few studies. This humanized synthetic drug represents a valuable solution in IBD patients with anemia during disease relapse or remission phase. EPO mechanisms of action, except that of erythropoiesis, have been insufficiently clarified. It has an important role as a growth factor promoting bowel epithelium repair but also in improving chronic disease anemia, being also a pre and post-bowel surgery complementary treatment. EPO cost-effectiveness assessment of its use, patient quality of life and the official establishment of indications for IBD therapy are points which really need further analysis and consensus for general approval.[4]

13. Neurobiology of stress and IBD

Not much information is available on changes in the autonomous nervous system in IBD. Experimental studies show that moderate stress enhances bowel response to chemically induced inflammation (CD4+ lymphocyte response). Moreover it has been shown that stress increases the levels of myelohyperoxidase and bowel mucosa permeability with mechanisms not well documented. One of the most studied mechanisms is probably the sympathetic/parasympathetic regulation of the bowel immune system in chronic colitis. This response includes mucous production, immune response and intestinal permeability.[8]

14. Psychotherapy and psychiatry in IBD

The role of psychotherapy in IBD is considered to be important. Psychotherapy in chronic non-fatal diseases such as IBD may be used with patients individually or in group sessions. One of its main targets is the release of stress, while secondary targets are the remission of disease symptoms and of all intestinal and extraintestinal manifestations. A well-trained psychiatrist, experienced in IBD can also contribute to information, support and patient's self-confidence, helping him/her to participate again in the routine, social, every-day events, work and leisure. Moreover psychiatry may help the patient to understand better the real need for continuous treatment, follow-up, and conformity to all instructions given by his gastroenterologist.[8]

15. Sports and IBD

Moderate sport activity in IBD may result in a tremendously positive impact on the patient's perception of good health status. Exercise also helps to prevents steroid-induced osteoporosis and fracture risk in all steroid dependent patients, mainly the older ones.

16. Alternative medicine

In USA many IBD patients (27%) seek for alternative methods of treatment for their bowel disease.These methods generally represent a combination of mind and body treatment, but results of such therapies have never been reported in a well-documented way. In Greece the exact number of IBD patients visiting alternative doctors is unknown. In North-West Greece, in a random sample of 70 IBD patients, only 3 had visited an alternative doctor or been followed-up for a short period of time with alternative drugs. In the same cohort 8 other patients changed their treating gastroenterologist for another one.

All the above mentioned numbers of patients impls that IBD patients generally trust their treating gastroenterologists. In addition to this statement, no specific contribution of alternative medicine in inducing disease remission has ever been reported in international journals or forums of the traditional Western or alternative medicine. Consequently, it seems that until proved the contrary, alternative doctors may probably offer only higher quality of care due to the growthy increased time dedicated to each patient, at each appointment.

17. Greek traditional Medicine in IBD

Traditional Greek medicine has contributed in inflammatory bowel diseases, the same as or similar to IBD, as already reported in Hippocrates traditional remedies; grapes, honey, thyme, pomegranate, ivy, root of wild vine and many others. In North-West Greece traditional Hippocratic medicine for treating bowel inflammation has continued through centuries in villages, where people still use all the above remedies and report satisfactory, results.

18. Etiologic or symptomatic therapeutic strategy in IBD?

There is no doubt that the unknown IBD etiology obscures every effort for a disease-efficient treating stategy. Many editorials written by IBD experts ponder whether, for all these years, we have been treating the tree or the forest behind IBD. What we have learned in these 100 years about IBD has probably not been sufficiently meta-analyzed. Consequently, several questions a rise, such as, whether the disease is one or more, whether it changes through the years, whether there is a real racial or genetic background, and whether all drugs used have changed the natural history, clinical symptoms and disease outcome.

19. Prevention-Education-Support in IBD

These three parameters are considered extremely important for every therapy in IBD, including the alternative ones. These parameters deal with secondary IBD prevention strategy, which includes early recognition of IBD complications, continuous patient information and psychological support, family and partner advice. It is also important to clarify from the first moment of disease diagnosis all issues relating to sexual performance, ability and possibility for fertility and potential childbirth. The role of social support and welfare mechanisms is important for the patient and his environment. Continuous support and information about insurance, official approval of new drugs, endoscopy and other facilities is of sine-qua-non for every newly diagnosed IBD patient. Moreover, it is very important that every region has its own IBD medical team, which can assist IBD patients with any problem.

20. The need for individualization of IBD therapy-the individualized response to drugs in IBD

Many authors still wonder whether IBD is one or more diseases. In addition, it is difficult to predict the factor or factors that influence response to treatment and disease outcome in each patient. It is also common practice that many extraintestinal manifestations request bowel symptoms remission and not other than the bowel organ therapy. Some drugs are useful in IBD acute attacks but completely useless or contraindicated in longitudinal phase of IBD therapy when remission is achieved and vice versa.

21. Overview of the basic principals of IBD therapeutics

The current and future targets of IBD therapy are probably the following:

1. Complete disease remission and symptom relief.
2. Satisfactory quality of life even in relapse phase.
3. Complete mental and social health.

As synopsis, the basic principals of IBD therapeutics are:

1. Analytic information about the disease -discussion with patients and family about all worries and concerns.
2. Explanation of the drugs administered and their side-effects.
3. Continuous scientific support and follow up pre and post-surgery.

22. The real need for a medical team in IBD therapy

IBD needs a multisystemic approach because it has a continuous psychological and organic impact. For this reason, every well-equipped hospital needs an IBD working team consisting of a gastroenterologist, a surgeon, a psychiatrist, an ophthalmologist, a dermatologist, a dietician, a stoma therapist, a nurse and a social care provider. This team must work in a cooperative way in order to assure quality of care and efficacy of the health system for patients.[9,10]

23. New treatment protocols in IBD

There is a variety of phase II and phase III protocols for IBD therapy and we should all be skeptical. Patients' organizations, when existing, should have say in these trials, in order to express their feelings about but also to help every trial to end with success and validity. Patients' rights for information and health should never be neglected. The need for a supervising working team, apart of course, from existing official organizations, dealing with all IBD protocols is a real need in Greece. No one center, unless qualified, should carry out an IBD treating protocol, because that will confuse rather than help science and IBD patients.

24. Therapy in IBD = A roulette that never wins?

Every gastroenterologist's dream is to find IBD etiology and win the Nobel Prize. Until that happens, hopefully, a mathematic model in order to win this IBD therapeutic challenge should be reviewed as following if we want to win this "roulette game" of IBD therapy:

- we must bet on every appearing drug or combination of effective drugs
- we must find disease etiology or any co-existing triggering factors
- we may hope that the disease will, one day, automatically disappear
- we must construct models of combined risk factors (genetic+environmental) and test them in a prospective way with patient-control (case control) studies. Finally, we should continue living and practicing medicine with the hope that one day something new and important will arises and shed light on the dark side of the moon were IBD therapy still lies today.

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