Standard and innovative therapy of inflammatory bowel diseases

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ABSTRACT

During last years, treatment of IBD evolved from a non-specific suppression of the mucosal immunological response to a more specific intervention in the immunocascade. While corticosteroids and aminosalicylates remain the mainstay of treatment, more potent immunosuppressors like azathioprine, methotrexate and cyclosporine are used in corticodependent or resistant patients. Safety profiles of these drugs become better established. The successful introduction of biological therapies such as a chimeric monoclonal antibody against TNFα, opened a new field of research and possibilities. New humanized agents interfering at several levels in the production of cytokines are in development. Moreover, other pathways are focused like signal transduction, adhesion of cells to tissue, modulation of tissue architecture, bacterial flora …. Challenges for the next future remain the development of more effective and safe drugs, the identification of target populations for every drug , the study of the influence of biological therapies on natural history of the disease and finally the definite cure of the patient. An updated review from current and future treatment modalities is given.

Introduction

Crohn's disease and ulcerative colitis are chronic inflammatory bowel diseases (IBD) resulting from the interaction between genetic susceptibility factors and microenvironment. The result is an inappropriate immunologic response leading to mucosal self-destruction. There is clear evidence for activation of intestinal lymphocytes, macrophages and other cells of the immune system leading to an upregulated immune response. The antigenic trigger is unknown but is most likely a common, non-pathogenic microbial agent within the intestine against which patients mount an immune response. Genetic determinants (ex. NOD2/CARD gene mutations and others) are responsible for the inability to mount an appropriate response against bacterial lipopolysaccharides resulting in an inappropriate and prolonged inflammation.

Treatment is focused on the suppression of this immunocascade. During last years a clear evolution is observed from a non-specific suppression of different pathways to a more and more specific intervention in the inflammatory reaction by the introduction of monoclonal antibodies and other biological factors. Although the exact role of these different molecules in the treatment and the natural evolution of the disease remains to be elucidated, this research is extremely existing and promising. The ultimate goal of therapy is to interrupt definitely the cascade and to cure the patient from his/her disease.

Actual therapeutic modalities in naive patients

The universal mainstay of treatment in active disease remains conventional corticosteroids (daily dose of 40 – 80 mg prednisolone or 10 mg/kg body weight) inducing remission in 65 – 85% of the patients. However, their use falls more and more in discredit because of the important side effects.

Although some effects are rather esthetic and more or less reversible (moon face - acne - striae) others are clinically more important and sometimes irreversible (osteoporosis - adrenal suppression - diabetes). Active Crohn's disease is already known to be associated with osteopenia in 25-30% of the patients at the time of diagnosis. Additional use of corticosteroids may aggravate this bone loss (1).

An alternative for conventional corticosteroids is the use of a new topically active corticosteroid budesonide (Entocort - Budenofalk) (9 mg per day). These preparations have a high affinity for the mucosal corticoidsteroid receptor associated with an important first-

pass metabolism in the liver. They can be presented to the mucosa in an oral slow-release form or in a topical form. It has been shown that 50% to 70% of budesonide controlled ileal release is absorbed in terminal ileum and ascending colon and can induce remission in 53% of the patients (2). The major advantage is the local effect, associated with an important reduction in systemic side-effects.

The role of aminosalicylates in the induction of remission is more controversial. Although some effects were demonstrated in Crohn patients (3, 4), results are not dramatic and drugs are only advisable in very mild forms. In contrast, in ulcerative colitis there is good evidence that aminosalicylates are very effective in mild to moderate disease. Mesalazine administered orally and/or topically in doses ranging between 2 and 4 g per day induces remission in 60% of patients after 4 to 8 weeks of therapy (5). Complications are rare.

Considerable efforts and research have been centered on the maintenance of remission. Meta-analyses support the role of aminosalicylates. These drugs suppress the inflammation by several mechanisms such as inhibition of prostaglandins, leukotrienes, PAF production, cytokine production such as IFNγ - IL1β - IL2r, inhibition of NFkB activation, scavenger of oxygen free radicals. In ulcerative colitis, several randomised trials demonstrated a beneficial effect of mesalazine in the maintenance of remission (6). However, the optimal dose and formulation remain unknown. In contrast, the effects of 5-ASA preparations are not impressive in Crohn's disease (7). The major advantage of 5-ASA preparations is the very low toxicity.

Conventional systemic corticosteroids in the setting of maintenance therapy for Crohn's disease do not appear to reduce the risk of relapse over a 24 month period of follow-up according to a meta-analysis published in Cochrane review 2001. Only four studies were eligible for inclusion. The odds ratios for relapse on active treatment were respectively 0.71 - 0.82 and 0.72 at 6 - 12 and 24 months (8). Studies with budesonide have neither shown any difference in relapse rate at 12 months compared with placebo but may prolong the duration of remission after succesful short term treatment (9,10).

Actual trend is the early use of thiopurine analogues (azathioprine and 6-mercaptopurine) as maintenance therapy in patients with tendency to steroid-dependence. These purine analogues inhibit ribonucleotide synthesis competitively and maintain remission in 64% of patients with quiescent Crohn's disease and 87% of patients with ulcerative colitis (11). This efficacy is reasonably well sustained over 5 years. General recommended daily doses are 2 - 2.5 mg/kg of AZA or 1 - 1.5 mg/kg 6-MP. Allergic side effects including pancreatitis, hepatitis, fever and rash occur in about 5% of the patients. Neutropenia and thrombocytopenia can occur in 2 to 4% of patients even after long-term requiring checking of blood counts at regular intervals. Recent studies suggest that the level of active drug metabolites rather than the actual 6-MP/AZA doses is associated with a therapeutic effect. AZA and 6-MP are both inactive pro-drugs undergoing different metabolic transformations resulting in the formation of several active metabolites: 6-thioguanine nucleotides (6-TGN) and 6-methylmercaptopurine ribonucleotides (6-MMPR).

Recent studies have shown that the red blood cell 6-TGN level is significantly associated with clinical remission. Optimal response seems associated with levels > 235 pmol/8 x 10^8 (12). However accumulation of 6-thioguanine seems also related to complications like bone marrow suppression. Moreover it has been demonstrated that dose-escalation of 6-MP/AZA does not always result in the attainment of optimal 6-TGN production and clinical response but rather results in the production of the potentially hepato- and hematotoxic 6-MMPR metabolites identifying a subgroup of patients resistant to these drugs (13). Interaction with other drugs can also be important. Inhibition of xanthine oxidase pathway by allopurinol can lead to an accumulation of 6-MP and its active metabolites. Finally, catabolism of 6-MP by thiopurine methyltransferase enzyme (TPMT) is subject to interindividual variations and may also influence TGN levels.

An open label pilot study suggested a beneficial effect of 6-thioguanine self in treatment of CD resistant or intolerant to 6 MP therapy but wait for larger controlled trials (14).

On long-term increased risk of non-Hodgkin lymphoma has been a concern. Recently, Lewis *et al.* (15) showed in a decision-analytic model that AZA increases quality-adjusted life for most patients principally youngest patients, and that the risk for non-Hodgkin lymphoma must increase to nearly 10-fold in order to reduce the overall quality-adjusted life expectancy.

Mycophenolate mofetil (2 g per day) is another non-competitive inhibitor of guanosin nucleotide synthesis and may be considered as an alternative immunosuppressive therapy in CD patients who do not tolerate azathioprine although its efficacy was only demonstrated in open trials (16) and not confirmed in a randomised trial (17).

Therapeutic modalities in cortico-resistent and corticodependent patients

The efficacy of the antifolate antimetabolite methotrexate in the treatment of active Crohn's disease was demonstrated by Feagan *et al.* in 1995 (18) in a placebo controlled trial using a dose of 25 mg IM/ week. Significantly more methotrexate treated patients were able to withdrawn steroids and enter remission compared to placebo (39% versus 19% - $p = 0.025$). Recently, the same group demonstrated in a multicenter, placebo-controlled trial an advantage of methotrexate in low dose (15 mg/ week) as maintenance therapy. In this 7-center study 76 chronically active Crohn patients were included, all of whom had already achieved successful steroid-free remissions on 16-24 weeks of methotrexate 25 mg IM per week. Half of the placebo-treated patients had already relapsed at 22 weeks, while less than half of methotrexate treated patients relapsed during the 40 week study. By the end of the study, at week 40 remission rates with methotrexate and placebo were respectively 65% and

39% (p = 0.04). Fewer patients in the methotrexate group required prednisolone for relapse (19). Further support for the maintenance values of methotrexate appears from an uncontrolled French study following patients over a 3 years period (20). Side effects include skin rash,leucopenia, thrombocytopenia and a very rare but irreversible allergic pneumonitis. Methotrexate-induced hepatotoxicity has been extensively investigated in patients with psoriasis and rheumatoid arthritis, but seems much less frequent in IBD (21).

Immunomodulators like cyclosporin A and tacrolimus (FK506) bind to extracellular receptors capable to inhibit the function of calcineurine. This results in a blockade of genes involved in the process of T cel activation like IL-2. In ulcerative colitis, efficacy of intravenous cyclosporine in doses of 4 mg/kg per day has clearly been demonstrated in steroid-refractory patients (22). Uncontrolled data suggest a similar role for steroid refractory CD patients. However, a meta-analysis of 4 randomized controlled trials failed to show a therapeutic value in CD (23). Cyclosporine has no role in the maintenance therapy.

The greatest breakthrough in the treatment of Crohn's disease was the introduction monoclonal antibodies directed to the tumor necrosis factor (TNFα). This cytokine is a pro-inflammatory cytokine produced by activated macrophages, lymphocytes and natural killer cells. It has numerous biologic activities in inflammation, proliferation and differentiation. Infliximab, a chimeric IgG1 monoclonal antibody against TNFα, is the first drug used in the daily clinical practice. A single infusion in therapy refractory Crohn patients, resulted in a clinical response rate of 65% and remission rate of 33% at week 4 compared to respectively 17% and 4% in placebo treated patients (24). Not only symptom improvement but also mucosal healing was shown (25).

Actually, multiple studies have been published confirming this dramatic effect in both active luminal disease and fistulizing disease (26). The actual recommended dose is 5 mg/kg used as single infusion in luminal disease and 3 infusions in fistulizing disease. The mean duration of response is 8 - 12 weeks. In a effort to assess maintenance of remission, Rutgeerts *et al.* (27) reported the results of a randomised double-blind multicenter, placebo controlled trial of repeated infusions of infliximab every 8 weeks. Although an individual study patient who received a single dose of infliximab had a 20% chance of maintaining remission at week 44, differences between retreatment arm and placebo arm were statistically significant for remission and trended towards significance for clinical response.

These findings were confirmed in a large muticenter randomised international trial (ACCENT I) showing that maintenance therapy with infliximab is superior to a single dose with respect to clinical response and remission rates. Retreatment every 8 weeks prolongs remissions in patients with moderate to severe Crohn's disease and is associated with a steroid sparing effect (28).

The introduction of anti-TNF in the clinical practice was the start of a revival of older therapeutic drugs. Thalidomide has an innate but weak TNFα inhibitory capacity and was proved efficacious in open trials with steroid dependent patients (29-30) (used dose: 50-300 mg/day). A significant response was noted at 4 weeks in 58% of the patients associated with a significant reduction in use of corticosteroids. Thalidomide was well tolerated despite mild cases of drowsiness, neuropathy, dermatitis and oedema.

Emerging therapies

Emerging therapies are more and more focused on specific targets in the immunological pathways associated with the intestinal inflammation. Many new drugs have been studied during recent years but the majority of published trials were not designed to assess efficacy of these therapies but evaluated primarily safety and tolerability. Larger more powerful trials are actually ongoing to establish a possible clinical efficacy.

A. Cytokines

The increased secretion of proinflammatory cytokines appears to play a central role in the initiation and the perpetuation of the inflammation. Therefore, a reduction of the production of TNFα and IL-12 remains the primary goal of treatment. However, the restoration of the balans between pro- and anti-inflammatory cytokines by the use of IL-10 and IL-11 is another therapeutic alternative.

TNFa reducing drugs

- Etanercept is a genetically engineered fusion protein consisting of 2 identical chains of the recombinant human TNFreceptor-p75 monomer fused with Fc-domain of human Ig, binding and inactivating soluble and membrane-bound TNF. In a recent double-blind placebo-controlled trial including 43 patients with moderate to severe Crohn's disease, treatment with 25 mg Etanercept subcutaneously twice weekly was safe but not effective in inducing clinical response at week 4 (31). Higher doses or more frequent dosing may be required to achieve a clinical effect.
- Humanised monoclonal antibodies against TNFα (CDP571 - CDP870) have the potential advantage above Infliximab to avoid the development of neutralising antibodies responsible for delayed hypersensitivity and a progressive decrease in drug effect. Two trials with CDP571 showed efficacy and safety (32,33). Results with CDP870 will be provided in the near future.
- p55 tumor necrosis factor binding protein-1 (onercept) has been demonstrated to be a safe and well tolerated molecule suitable for clinical studies in Crohn patients (34).

Other cellular pathways as potential targets in the inhibition of TNF production:

- inhibition of transcription factors (NFkB). A recent study including a systemic administration of an antisense p65NFkB molecule evoked dramatic side effects and seems not suitable for clinical use.
- Inhibition of mitogen activated protein kinases (MAPKs). These signal-transducing enzymes regulate cellular processes like gene expression

and cell proliferation. A small open study with CNI-1493, inhibiting the phosphorylation of JNK, demonstrated a significant clinical benefit and a rapid endoscopic ulcer healing (35).
- Inhibition of matrix metalloproteinase (MMP) responsible for TNFα mediated tissue injury. A potential pathway is the use of marimastat with documented beneficial effects in TNBS rats. Moreover MMP inhibitors prevent the release of mature TNFα from its precursor in leukocytes.

Anti–IL12
IL-12 modulates T-cells to Th1 phenotype and stimulates IFNγ production by fully differentiated T cells. Abundant populations of IL12 producing macrophages were found in lamina propria of Crohn patients. In animal models, such as colitis in IL10$^{-/-}$ mice, anti-IL-12 demonstrated a beneficial effect on the initiation of the colitis but had no role in late colitis. No data are available in man.

IL-10
IL-10 inhibits activated Th1 cells and effector functions of activated macrophages and monocytes. Although the use of anti-inflammatory cytokines is very attractive, clinical studies are inconclusive. In an open study including steroid-refractory patients, daily subcutaneously administrated IL-10 was safe, well-tolerated and possibly effective (36). Another study including steroid-naïve patients showed similar results (37). However, a prospective multicentric double-blind placebo controlled study including 329 refractory CD patients failed to demonstrate a clinical effect. Clinical improvement occurred in 46% of IL-10 treated patients and 27% of placebo treated patients (38).
A very interesting approach is the use of genetic manipulated bacterial strains like lactoccus lactis producing IL-10 and providing a local mucosal delivery of the cytokine. A therapeutic and preventive effect was demonstrated in an animal model of colitis with mices treated with dextran sulfate sodium (39).

IL-11
Il-11 is a mesenchymally derived cytokine with pleiotropic activities such as inhition of TNFα – IL1β – IL12 – IL6 and NO production by activated macrophages. A randomized controlled trial of recombinant human IL-11 in 148 patients with active Crohn's disease not receiving steroids has demonstrate a clinical efficacy and very good safety profile. Weekly subcutaneous administration of rhuIL-11 was associated with a trend toward decreased mean per cent change in CDAI and a significant greater rate of remission (36.7% versus 16.3% with placebo at week 6) (40).

B. Blocking leukocyte trafficking
A second possible therapeutic pathway is the inhibiton of cell traffic between blood circulation and mucosal tissue by interference with specific adhesion molecules.

Intracellular adhesion molecule 1 (ICAM-1)
ICAM-1 is a transmembrane glycoprotein expressed on vascular endothelial cells, monocytes, macrophages, keratinocytes and a subset of B and T cells. It's major function is the facilitation of the leucocyte emigration in response to inflammatory stimuli. ISIS 2302 is a antisense oligonucleotide inhibiting cytokine induced ICAM-1 expression and successfully used in a small controlled trial with steroid treated patients. It has an effect in the induction and preservation of the remission beneath a steroid sparing effect (41). This clinical effect was not confirmed in a recent large multicenter placebo controlled trial including 75 steroid refractory patients (42). Only 2 treated patients and no placebo-treated patients were in steroid-free remission at week 14. A third trial including 300 patients also failed to establish significance for the induction of a steroid-free remission at week 14 (43).

Integrins
Integrins are glycoproteins widely expressed on leukocytes and important mediators of leukocyte migration across vascular endothelium in intestinal mucosa. The α4 integrins usually exist in combination with β1 or β7 subunits and interact with endothelial ligands VCAM-1 and mucosal addressin cellular adhesion molecule (MAdCAM-1). In a recent randomised placebo controlled trial, a single infusion of 3 mg/kg recombinant humanized monoclonal antibody to α4 integrin (natalizumab – Antegren) administrated to 30 patients with moderately active Crohn's disease was well tolerated and efficacious although difference in efficacy was not statistical significant (39% remission at week 2 versus 8% in placebo-treated group) (44). Results of a large multicenter randomised placebo controlled trial including 248 patients were presented in abstract form ,confirmed these results and will be published soon.

C. Pro- and pre-biotics
Gut bacteria directly contribute to energy salvage and metabolic support of the local mucosa. Bacterial products may initiate or aggravate mucosal inflammation. In IBD increased levels of mucosa-associated bacteriae were reported (45-46). It remains unsolved whether this includes novel adhesive bacteria species or primary mucosal disorder impairing the adhesion of a diversity of bacterial species.
Manipulation of enteric microflora by diet and microbial competition forms the basis of emerging pre- and probiotic therapies (47). In a study including 32 patients, a combination of mesalazine and Saccharomyces was more efficient to sustain remission in CD at 6 months than mesalazine alone. These preliminary results warrant additional larger controlled trials but are encouraging (48).

Conclusions
With the advent of biological therapies, the management of IBD has dramatically changed during last years. In the next future an acceleration in the introduction of new agents can be expected. Many trials are necessary to define the efficacy and safety of these agents. Economic constraints will force to target specific therapies to specific patients by the identification of specific

genotypes and phenotypes associated with optimum drug response. Actual biological agents are focused on the induction of remission of disease mostly in patients with active Crohn's disease, unresponsive to or dependent of corticosteroids.

No study evaluated the effect of treatment on the natural evolution of the disease. It remains unsolved whether it is recommendable to start very early in the course of the disease with aggressive immunosuppressive therapy or not.

Long-term maintenance of symptom-free periods or definitively cure of the disease remains a vision for the future.

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