Intestinal inflammation during IBD is linked to an inappropriate host immune response to intestinal flora. The investigation and analysis of the mechanisms causing this uncontrolled intestinal inflammation have resulted in the development of targeted therapies. Recent discoveries in genetics, the regulation of immune responses and anomalies in intestinal flora have shown just how complex these diseases are and raised many questions. Genetic susceptibility to IBD has now been clearly established, in particular by concordance studies in twins. The identification of NOD2 as the susceptibility gene for Crohn’s disease supports the hypothesis of an overactive immune response to microbiota. Indeed, this innate immune receptor, expressed in the intestinal epithelium, recognizes bacterial motifs. However, the mechanisms leading to loss of function of NOD2 and the uncontrolled intestinal inflammation observed during Crohn’s disease, are still under debate. In particular it contributes to deficient production of defensins by Paneth cells in the intestinal crypts [1]. These deficiencies in the primary defense mechanisms could favor the persistence of bacteria in the crypts and stimulate an overactive immune response. Since the discovery of the role of the NOD2 gene, more than 30 susceptibility genes have been identified or confirmed in the last three years using Genome-wide association studies [2]. These studies have not changed the importance of NOD2, but have opened new avenues of research, such as autophagia. Even if the biological function in intestinal inflammation of each of these genes has not been completely clarified, many of them are involved in the immune response to bacterial flora, and are expressed in the intestinal epithelium.

The environmental factors causing IBD are difficult to study because some of them may play a role before the onset of clinical signs of the disease [3]. Numerous epidemiological studies have been published, often with contradictory results, giving the impression of a series of unconvincing theoretical voguees. Numerous theories and hypotheses have been proposed, but are mainly observations without substantial support. Only tobacco and previous appendectomy play a clear role, but even then, the mechanism of action is not well understood.

Research on specific infectious agents in Crohn’s disease has not been particularly successful to date [4]. Atypical mycobacteria have become a popular topic in scientific publications as identification techniques have improved, but they are usually disproved by newer studies. The recent publication of a new Australian therapeutic trial showing negative results, and the positive action of anti-TNF antibodies suggest that they do not play a role in the disease. The amazing work of Arlette Darfeuille-Michaud’s group has shown the presence of an abnormal strain of Escherichia coli with adherent and invasive properties in ileal Crohn’s disease. The mechanisms of adhesion of this bacterial strain have been elucidated, but there is still a way to go before it can be proven that these bacteria really play a role in triggering the disease and the development of lesions. Another French team recently showed that there was a deficit in Faecalibacterium prausnitzii, a bacteria with anti-inflammatory properties. All these studies on the intestinal flora give hope that targeted probiotic treatments can be developed to modify the intestinal flora and the immune response. But, in fact, long and even short term therapeutic progress will be probably made in IBD thanks to expanding knowledge in the immunopathology of these diseases. After the spectacular success of anti-TNF antibodies, other avenues of research have emerged with more or less successful attempts at developing novel therapeutics [5]. Today, two approaches
seem promising. Adhesion molecule inhibitors, in particular anti-α4 (natalizumab) and anti-αvβ7 (MLN02) antibodies, have been shown to be effective in Crohn’s disease and ulcerative colitis. The development of natalizumab has been blocked by rare reports of progressive, multifocal leuкоencephalopathy. There have been no reports of this type with MLN02, but only initial, limited studies are available for the moment. Research on IL12/IL23 is also interesting. IL12 is essential for the activation of Th1 pathways while IL23 is involved in the activation of T lymphocytes producing IL17 (called Th17). These TH17 lymphocytes seem to play an important role in Crohn’s disease and studies in murine intestinal inflammation models show the predominant role of the Th17 response compared to the Th1 response. Two monoclonal antibodies directed against the sub-unit p40, common to IL12 and IL23 have been tested with promising results in phase 2 clinical trials in Crohn’s disease. While waiting for new treatments, we must try to use existing tools as effectively as possible [6]. Existing guidelines for the management of chronic IBD, which were recently updated by the the European Crohn’s and Colitis Organisation (ECCO) statement suggest taking a careful, progressive approach in ascending steps. This so-called step-up strategy makes it possible not to overtreat patients who have a relatively benign disease progression, and prevents having to give them treatments that are not without risk. The disadvantage is that patients with more aggressive disease progression are not given the most effective treatments, or at least this is delayed thus exposing them to a greater risk of irreversible lesions and complications. New strategies have been proposed based on these observations and all include early use of immunomodulators especially in Crohn’s disease. Thus, the early administration of azathioprine has been studied in children [7] and is under study in adults in the RAPID trial conducted by the GETAID. This management strategy is already in practice for certain indications, such as pediatric forms of the disease where an attempt is made to limit the use of corticosteroids to protect normal growth, in complicated forms of the disease where an attempt is made to limit the use of corticosteroids or in certain extensive forms where surgery would result in significant sequellae. The early use of anti-TNF antibodies is more controversial. Two strategies were compared in a recent study called “Step-up/Top Down” [8]. The classic Step-up strategy included the administration of corticosteroids, then in case of relapse, azathioprine while infliximab was used in case of failure. In the other arm of the study, the Top Down approach was used with a treatment including three perfusions of infliximab and azathioprine; additional perfusions of infliximab were proposed in case of relapse, and corticosteroids as a “last resort”. This study was not completely convincing: indeed, at one year the percentage of patients in remission without corticosteroids was similar in the two study arms. Nevertheless, remission without corticosteroids was obtained faster in the Top Down arm. Moreover, during a two year follow-up, a high percentage of patients were found to have endoscopic healing of lesions. Longer term follow-up showed fewer relapses and complications in these patients. Other strategies could be imagined such as the early administration of anti-TNF antibodies in monotherapy. However, the SONIC study recently showed that azathioprine and infliximab were more effective than monotherapy. For the moment, Top Down strategies can be used in selected patients with a risk of rapidly progressive severe disease. Among the different factors studied to try to determine these populations, selection criteria could include the presence of anoperineal lesions, young age, and the early need for corticosteroids. Although these criteria can be helpful in making decisions they are not discriminant enough to be used systematically. One question with the Top Down strategy is also to decide when to reduce treatment once the patient has been stabilized. Different approaches have been suggested such as stopping classic immunosuppressants when a combination was initially used. This was studied in the IMID study and showed no benefit to continuing immunosuppressants in patients who were stabilised after six months of treatment with combination immunosuppressants and infliximab [9]. Nevertheless, a gradual reduction in the dose of infliximab was observed, suggesting that there was greater immunisation in the group that had discontinued immunosuppressants. The other strategy is to stop infliximab while continuing immunosuppressants. This was tested in the STORI study which was recently presented by GETAID. This study clearly confirmed that “deep remission” of the disease characterized by a stable clinical remission, the absence of biological signs of inflammation and endoscopic healing of lesions, could be obtained. This new aim could become part of clinical practice in the near future. An interesting strategy would be to rapidly modify treatment when this goal is not met. Nevertheless, it must still be shown that this “Rapidly-adjusted step up” approach really modifies long term disease progression without too much risk for the patients.

Conflict of interest:

Mathieu Allez carried out clinical trials as co-investigator for Abbott and UCB. He gave advisory services to UCB. He attended conferences organized by Schering-Plough, Abbott and UCB as contributor. Marc Lemman has not declared any conflict of interest.

References