**Name of journal: World Journal of Gastroenterology**

**ESPS Manuscript NO: 20318**

**Columns: Topic HighlightS**

**2015 Advances in Inflammatory Bowel Disease**

**Current stage in inflammatory bowel disease: What is next?**

Gómez-Gómez GJ *et al.* Current directions in inflammatory bowel disease

Gonzalo Jesús Gómez-Gómez, Ángeles Masedo, Carmen Yela, Maria del Pilar Martínez-Montiel, Begoña Casís

**Gonzalo Jesús Gómez-Gómez, Ángeles Masedo, Carmen Yela, Maria del Pilar Martínez-Montiel, Begoña Casís,** Unidad de Enfermedad Inflamatoria Intestinal, Hospital 12 de Octubre, 28045 Madrid, Spain

**Author contributions**: Gómez-Gómez GJ, Masedo A, Yela C, Martínez-Montiel MP and Casís B analyzed the literature and wrote the manuscript.

**Conflict-of-interest statement:** The authors have no conflict of interest to report.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Correspondence to**: **Dr. Maria del Pilar Martínez Montiel, PhD,** Unidad de Enfermedad Inflamatoria Intestinal, Hospital 12 de Octubre, Av\ Córdoba s/n, 28045 Madrid, Spain. pilarmarmon123@telefonica.net

**Telephone:** +34-91-7792667

**Received:** June 1, 2015

**Peer-review started:** June 2, 2015

**First decision:** June 23, 2015

**Revised:** July 12, 2015

**Accepted:** September 2, 2015

**Article in press:**

**Published online:**

**Abstract**

In recent years, inflammatory bowel disease has experienced an increase in incidence - extending to countries where it was infrequent in the past. As a result, the gap between high and low incidence countries is decreasing. The disease therefore has an important economic impact for the healthcare systems. There have been advances in recent years in pharmacogenetics and clinical pharmacology, with the search for treatment optimization adjusted to the patient profile. At the same time, new drugs aimed at inflammatory targets have been developed that may expand the future treatment options. This review examines the advances in optimizing the existing drug treatment options and the treatment options that are currently under investigation.

**Key words:** Inflammatory bowel disease; Future directions; Pharmacogenetic; Pharmacokinetics; New drugs

**© The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Inflammatory bowel disease (IBD) is a disease with an increasing incidence and prevalence. In recent years there have been changes in the treatment objectives, in the monitoring of IBD, and in the drug treatments for controlling the disorder. This review analyzes the developments referred to pharmacogenetics, clinical pharmacology and the new drug molecules which may expand our treatment options in the future.

Gómez-Gómez gj, Masedo A, Yela C, Martínez-Montiel MP, Casís B. Current stage in inflammatory bowel disease: What is next? *World J Gastroenterol* 2015; In press

**INTRODUCTION**

Inflammatory bowel disease (IBD), Crohn's disease (CD) and ulcerative colitis (UC) are an important public health problem. According to recent studies, the annual incidence of UC varies between 19.2-24.3 cases per 100000 inhabitants in Europe and 6.3 cases per 100000 inhabitants in Asia and the middle East[1]. In the case of CD the estimated incidence is 12.7-20.2 cases per 100000 inhabitants in Europe and the United States *vs* 5 cases per 100000 inhabitants in Asia and the middle East. An increase in the incidence of IBD is currently being seen in areas where the disease was infrequent in the past. As a result, the gap between high‑ and low‑incidence countries is closing[2]. This rising trend runs parallel to technological development, improved living standards, and a greater interest in this disease among physicians[3]. The underlying pathogenesis remains uncertain, though the most widely accepted theory refers to an alteration of the host immune response to the intestinal microbiota in genetically susceptible individuals, triggered by environmental stimuli. None of these alterations alone are able to cause the disease, and the interactions among these four factors cause the pathogenesis to be very complex. In recent decades there have been important advances in reference to each of these factors. Progress in the field of genetics has resulted from the conduction of genome‑wide association studies (GWAS), though they are only able to account for 20%-25% of the cases of IBD[4]. Knowledge of the epigenetic mechanisms could explain the influence of environmental factors and the microbiota upon IBD and the low correlation to concrete genes[5,6]. These developments have opened the door to personalized medicine[7].

Knowledge of the immunological mechanisms involved in the appearance of IBD has led to the development of new biological drugs. The first major advance was represented by the anti‑TNF-α drugs, which have revolutionized the treatment of IBD, since they are able to induce and maintain mucosal healing of the disease[8] this being a key factor for modifying the natural course of the disorder[9,10]. Nevertheless, despite the advances in the treatment of these diseases, one‑third of all patients with CD fail to respond to anti-TNF-α therapy (primary non‑responders), and 10% do not tolerate or do not respond to any of the drugs used to treat CD[11,12]. In the case of UC, the reported colectomy rate reaches 21% after an initial response to anti‑TNF‑α drugs[13]. This has led to the search for new therapeutic targets and further optimization of the existing treatment options. Clinical pharmacology allows us to determine the therapeutic drug concentrations (thiopurine agents and anti-TNF-α drugs), explain their loss of response and the adverse effects. In the coming years we will see personalized medicine in which the treatments will be prescribed according to the risk factors in each individual patient and the probability of achieving response to a given drug substance. At the same time there have been changes in the way in which IBD is monitored, with the adoption of reliable and scantly aggressive techniques such as noninvasive imaging tests, stool markers, breath tests, *etc*.[14], which fall beyond the scope of this review. A description is provided below of the current advances in pharmacogenetics and possible new drug substances.

**PHARMACOGENETICS**

 Personalized medicine seeks to find the ideal drug for each individual patient, at the appropriate dose, and administered *via* the best possible route. This approach allows for increased effectiveness, with the least risk of side effects, and at the lowest possible cost. Physicians try to identify patients with more serious disease, with a view to introducing early and more effective treatment in order to prevent long‑term complications, distinguishing them from those individuals with less severe disease and a more favorable prognosis in which aggressive treatment poses a higher risk of undesired effects. Patient response to drug treatment is dependent upon many factors, including the severity of the disease and genetic and environmental factors.

Pharmacogenetics studies the association between the different polymorphisms of a gene and the variability of response to treatment with a given drug or its toxicity. It has been estimated that polymorphisms can account for 20%-95% of the variability of response to a given drug[15].

A number of drugs are currently available for the treatment of IBD: 5‑aminosalicylates, corticosteroids, immunosuppressors (thiopurine drugs, calcineurinic agents, methotrexate) and biological agents (anti-TNF-α drugs).

**AMINOSALICYLATES**

The aminosalicylates are among the main agents used to treat patients with UC, and their colon cancer chemoprophylactic effect causes them to be used in UC with pancolonic disease involvement. The metabolization of both sulfasalazine and mesalazine is mediated by an enzyme (N-acetyltransferase, NAT). For almost 6 decades the population has been divided into fast and slow acetylators. There are two NAT isoenzymes (NAT1 and NAT2), and different polymorphisms have been described in different ethnic groups[16]. NAT1 metabolizes mesalazine, and no associations to clinical effects have been demonstrated. NAT2 metabolizes salazopyrin derived from sulfasalazine breakdown. As early as 1983 an association was described between NAT2 slow acetylators (which therefore accumulate higher drug levels in blood) and an increased number of side effects. Twenty-five years later, and thanks to our knowledge of single nucleotide polymorphisms (SNPs), it has been possible to confirm the association between NAT2 with a slow acetylator phenotype and dose‑dependent side effects[17]. There are fewer studies on 5-acetylsalicylic acid (5-ASA) than with immunosuppressors and biological drugs, since 5-ASA is only used to reduce side effects that are usually not serious. However, since more prolonged treatment with 5-ASA was proposed due to its chemoprotective effect against colon cancer, the pharmacogenetic studies have become more important.

**GLUCOCORTICOIDS**

Glucocorticoids (GLCs) are used in moderate and severe flare‑ups of IBD, and although they are very effective, 16%-20% of all patients are refractory to GLCs in the Caucasian population, and 28%-36% are corticodependent[18-20]. The GLCs exert their antiinflammatory effect by inhibiting T cell activation and cytokine secretion, following binding of the drug to the intracellular glucocorticoid receptors (GR-alpha), which modify their structural conformation as a result. Three potential mechanisms can cause GLCS treatment to be ineffective: inadequate receptor function; an excess of proinflammatory cytokines, which would reduce affinity between the drug and its intracellular receptor; and a decrease in intracellular corticosteroids secondary to expulsion from the cell[21]. This latter mechanism is dependent upon glycoprotein P-170 (P-gp), which is found in lymphocytes and in the apical membrane of the enterocytes, among other locations. An increase in P‑gp at cell surface level causes drug release into the bloodstream. This protein is encoded by the ABCB1/MDR1 gene of chromosome 7. The expression of this gene is reportedly increased in IBD presenting a greater need for surgery because of a poor response to drug treatment[22]. Different allelic variants (the most widely studied being C3435T and G2677T) are associated to an increased risk of developing extensive UC, though no association to CD has been observed[23]. Studies with larger patient series and stable corticosteroid doses are needed to determine the precise relationship between P-gp and the lack of response to such drugs.

The studies that have explored the different cytokines implicated in corticosteroid response offer contradictory results, and the underlying polymorphisms have not been established[24].

Genetic studies related to the gene (hGR) encoding for the intracellular glucocorticoid receptor have also been carried out. Polymorphism N363S is associated to a good response[25], while polymorphism ER22/23EK is associated to corticosteroid resistance[26]. Knowing the genetic susceptibility of corticosteroid resistant patients would be an important step forward, since it would help avoid important morbidity among patients who stand to derive no benefit from such treatment. None of these pharmacogenetic markers are of use in routine clinical practice.

**THIOPURINE DRUGS**

Thiopurine drugs are used for maintaining remission in patients with moderate to severe IBD. The effects are only observed after three months of administration. Purine metabolization is complex and involves different enzymes; this results in important genetic variability in the efficacy and toxicity of these drug substances (Figure 1).

The thiopurine drugs (TPs) are able to control the disease in 66% of the patients, though an important proportion (10%-25%) must suspend the medication because of serious (leukopenia, pancreatitis, infections or malignancies) or mild side effects (rash, nausea, vomiting, flu syndrome, joint pain). A clear association has been demonstrated between thiopurine methyltransferase (TMPT) deficiency and bone marrow suppression, although this only explains one‑third of the adverse effects. No clear explanation has been found for the rest of the effects. Knowing in advance whether these drugs will be tolerated and the risk of side effects in a given patient may prove useful in daily practice.

***TPMT***

This is the most widely studied enzyme. The identification of genetic mutations before starting treatment with TPs is currently the only pharmacogenetic test performed in IBD.

In 1980, Weinshilboum and Sladeck for the first time described the trimodal distribution of TMPT in Caucasian patients: 90% of the subjects have normal TMPT activity, almost 10% have intermediate activity, and 0.3% have almost zero activity. Posteriorly, over 30 allelic variants have been described, with different distributions depending on the ethnic group considered. The correlation between genotype and phenotype (expressed enzyme activity) is very good in 77%-99% of the cases. The differences can be explained by genetic and epigenetic factors (such as the use of concomitant drugs that inhibit TMPT), the age of the patient and the existence of recent transfusions ‑ since we may be measuring two different enzyme populations: donor and recipient[27,28]. The genetic study of this enzyme allows us to distinguish among homozygous individuals (without enzyme activity) at a high risk of suffering bone marrow suppression; ultra‑fast methylators (high enzyme activity) with high liver toxicity and a low response to treatment; and patients with normal and intermediate enzyme activity, which are the individuals that stand to benefit most from this medication, with a lesser risk of adverse effects. Furthermore, it can guide the choice of dose at which treatment should be started (Table 1).

The association of allopurinol reduces the levels of 6‑methylmercaptopurin (6-MeMp) and increases those of 6‑thioguanine (6TG). Although its mechanism of action is not clear, it has been suggested that the drug inhibits the enzyme xanthine oxidase through competitive inhibition, or reduces the availability of its substrate[29,30]. In daily practice, those patients who require allopurinol and present a normal TPMT genotype (Table 1) should reduce the TP dose to 25% of the normal level. Taking into account that only about one‑third of all cases of bone marrow suppression in patients receiving TPs are explained by genetic disposition and that the origin is therefore multifactorial and will require constant laboratory test monitoring, many authors have questioned whether this strategy is cost‑effective. Nevertheless, most current clinical guides do not recommend genetic study before starting treatment with TPs. On the other hand, such studies are not available in many hospitals; laboratory test monitoring is therefore the safest alternative.

Less scientific evidence is available in relation to the rest of enzymes.

The enzyme xanthine oxidase (XO) is the second most important enzyme in the metabolism of TPs. It is found in many tissues, though its main activity is located in the small bowel and liver. Until a few years ago, it was only known that XO activity varies from one person to another. Discordant variations had been described depending on patient gender or ethnicity[31,32], together with changes induced by environmental factors such as smoking and the diet. In the year 2008, a Japanese group described three polymorphisms of the gene encoding for XO (G514A, A3326C and A3662G) that are associated to the activity of the enzyme ‑ the population being divided into low, normal or high activity[33]. These polymorphisms have not been studied in Caucasians or in patients with IBD. At present we are only able to extrapolate that individuals with low enzyme activity would be at greater risk of suffering adverse effects, while those with high activity would experience treatment failure.

The enzyme inosine triphosphate pyrophosphatase (ITPase) controls the intracellular levels of inosine triphosphate (ITP), transforming it into inosine monophosphate, which acts as a substrate of other enzymes. When the enzyme is deficient, ITP accumulates in the enterocytes. Deficiencies of this enzyme have been known for almost half a century, and have been evaluated in different ethnic groups (with incidences of 5%-7% among Caucasians and African populations, and up to 15% in Asian populations). Five polymorphisms have been described, of which only two are associated to inactivity of the enzyme: C94A, with an activity of between 0% and less than 25% of normal, and I*VS*2+21AC, with an activity of 60% of normal[24].

The studies on IBD show conflicting data regarding their possible relation to side effects (pseudoinfluenza syndrome, rash and pancreatitis) and bone marrow toxicity (Table 2). These studies in general have few patients and an even smaller number of patients with the relevant polymorphisms, and have been carried out in different ethnic groups. Reliable conclusions therefore cannot be drawn. Pseudoinfluenza syndrome causes a large number of patients to abandon the medication. The importance of the genotype of this enzyme in relation to side effects and early treatment suspension is not known.

Until the year 2006, it was believed that the conversion of azathioprine to 6‑mercaptopurine (6‑MP) was not mediated by enzyme action, though Eklund subsequently showed it to be catalyzed by the glutathione‑S‑transferases (GSTs).This author analyzed 14 variants – GST-A1, GST-A2 and GST-M1 being the three with the greatest enzyme activity. All of them are polymorphic. The studies in patients with IBS only allow us to affirm that individuals with low enzyme activity will have low 6‑MP levels and therefore will not respond to the medication, while patients with ultra‑fast activity are at an increased risk of adverse effects due to high 6‑MP levels. If this is confirmed, the clinical application would be evident, since the problem could be overcome by directly prescribing 6‑MP at the correct dose.

Studies have also been made of other enzymes such as inosine monophosphate dehydrogenase, hypoxanthine phosphoribosyltransferase, etc., though without applications at the present time.

Likewise, studies have attempted to determine the relationship between the levels of metabolites (6‑TG and 6MeMP) and the response to treatment or development of adverse effects. Once again, the results have been contradictory, with some studies describing a relationship between activity and the metabolite levels, while others indicate the opposite. A metaanalysis suggests that 6‑TG levels above 260 pmol/8 x 108 imply that the patient has a greater probability of disease remission[47]. Blood 6‑TG levels above 400 pmol/8 x 108 red blood cells increase the risk of bone marrow toxicity[48], and 6‑MeMP levels above 5700 pmol/8 x 108 red blood cells increase the risk of liver toxicity[49,50]. At present, metabolite determination is not available on a generalized basis in clinical practice, and its use is moreover controversial. However, in patients lacking a clinical response, it may help in deciding medication changes (Figures 2 and 3).

**METHOTREXATE**

Methotrexate (MTX) is usually used as an alternative to treatment with TPs in CD both for flare‑ups and as maintenance therapy. Its usefulness in UC is more controversial.

The mechanism of action of MTX in IBD has not been clearly established. The drug is a folic acid antagonist and blocks purine and pyrimidine synthesis. Those tissues characterized by greater cellular regeneration (turnover) show more toxic effects. Consequently, the main adverse effects of MTX are bone marrow suppression, mucositis and gastrointestinal and hepatic alterations. Folic acid supplementing reduces the side effects, though even so up to 30% of all patients have to suspend the medication.

Most pharmacogenetic studies of MTX have focused on patients with hematological tumors and rheumatoid arthritis (RA). In both of these disease conditions the dosage and administration route are very different from those used in IBD; the extrapolation of results is therefore not possible.

Herrlinger has carried out the only study to date in patients with IBD. The mentioned study found that patients with the 1298C allele of the enzyme MTHFR are more susceptible to adverse effects, though these data are in conflict with those recorded in other diseases[51].

**ANTI TNF‑α DRUGS**

Infliximab (IFX) is a chimeric IgG1 monoclonal antibody (Ab) targeted to TNF‑α. It is used for induction and maintenance in patients with moderate to severe flare‑ups of IBD. IFX is a very useful drug that has been shown to produce mucosal healing and reduce the number of flare‑ups, hospital admissions and surgeries. A number of clinical factors indicative of a good response have been described, such as the start of patient treatment at a young age, colonic location of the disease, and associated immunosuppressor therapy. It seems that a shorter duration of the disease, non‑smoking, and elevated C‑reactive protein levels at the start of therapy also favor a good response[52,53]. Even so, 25% of all patients are primary non‑responders, and 20%-30% lose response over time (secondary non‑responders). Most of these latter cases are a consequence of the production of antibodies against IFX[11-13]. Furthermore, the drug is expensive and has potentially serious side effects. IFX has been an important subject of pharmacogenetic studies.

Table 3 summarizes the genetic studies made with IFX in patients with IBD. Studies have been carried out related to the genes that encode for TNF‑α, the TNF‑α receptor, genes regulating the expression of TNF‑α (NOD2/CARD2), apoptotic mechanisms, and other proinflammatory cytokines. To date it has not been possible to demonstrate an association between response to the drug and a concrete gene. There are two main problems in this sense: on one hand, many studies fail to reach statistically significant results because of the small number of patients involved, and on the other hand the studies are not always comparable, since different response criteria are used (C‑reactive protein, CDAI score, Harvey‑Bradshaw index), patients with different degrees of disease activity are included, and different doses are administered.

Perhaps in the near future knowledge of the genotype of TNF‑α and its receptor may help us identify non‑responders to anti‑TNF‑α therapy.

***Pharmacokinetics in ibd***

Knowledge of the pharmacokinetics of a drug is very important for adjusting the dose required to guarantee therapeutic concentrations, since many factors are able to influence drug concentration in blood. In clinical practice, the determination of blood drug levels has been used to monitor treatments with drug substances that have a narrow therapeutic margin or window. In IBD, such monitoring has been applied to cyclosporine A and tacrolimus, and in recent years it has become particularly important in the management of anti‑TNF‑α drugs.

The differences in the administration route, degradation and clearance of anti‑TNF‑α modify their concentration in blood, and this in turn conditions the treatment response. In this regard, achieving adequate blood drug levels is correlated to clinical and endoscopic remission of the disease[70,71]. When the anti‑TNF‑α drug is administered *via* the intravenous route (IFX), the maximum blood drug concentration is reached immediately after infusion, with few differences among patients. However, when the anti‑TNF‑α drug is administered *via* the subcutaneous route (ADA, golimumab, certolizumab), the maximum concentration is reached after approximately 10 d, and the bioavailability ranges between 50%-100%[72,73].

The clearance of anti‑TNF‑α drugs from blood is complex and multifactorial. Among the variables associated to increased drug clearance, mention must be made of those that depend upon or reflect the severity of the disease (hypoalbuminemia, decreased hemoglobin levels, C‑reactive protein elevation, TNF‑α, leukocytosis, and increased IFX intestinal losses), demographic parameters (increased body mass, male gender and age under 40 years) and immunogenicity (the development of antibodies against the drug)[74]. The concomitant use of immunosuppressors (TPs drugs and MTX) is associated to a decrease in immunogenicity and higher anti‑TNF‑α drug levels.

Up to 40% of all patients that respond to anti‑TNF‑α drug treatment will require one or more dose adjustments in order to maintain treatment efficacy. After one year of treatment, only one‑third of all responders maintain efficacy[75].

The need for dose adjustment of these drugs may occur at two timepoints during treatment: at the start (primary failure) or during the maintenance phase (secondary failure).

Primary failure or a primary lack of response refers to the absence of improvement of the signs and symptoms of the disease that leads to treatment suspension during the induction phase[76]. The timepoint at which this primary lack of response is assessed varies among the different studies. In patients treated with IFX, as in the ACCENT I trial[77], assessment was made two weeks after the first IFX infusion. In contrast, assessment in the ACCENT II trial was made 10‑14 wk after induction[78]. In studies including patients treated with ADA, the response was assessed in week 4 in the CLASSIC I trial[79] and in week 6 in the CLASIC II trial[80]. In the different published studies, the lack of primary response to treatment rate with anti‑TNF‑α drugs varied from 10%-40%, and was found to be higher in UC than in CD. Lack of response was noted particularly in severe presentations of UC. This observation could be explained by increased drug clearance as a result of a greater inflammatory intestinal surface[76].

Secondary failure or secondary lack of response is defined as failure occurring in the course of treatment in those patients that have responded to induction therapy, and is observed in approximately 13% of the patients treated with IFX[81] and in 10%-24% of those treated with ADA[82]. Failure is more frequent in the first year of therapy.

Tables 4 and 5 describe the risk factors associated to primary and secondary failure[11,83].

In secondary failure, the most widely investigated factor is the development of antidrug antibodies (ADAs), for when a loss of treatment response occurs, and once the possible existence of intercurrent processes and lack of adherence to therapy have been discarded, the patient requires does adjustment or a switch to some other molecule. In this context it is very useful to know the blood drug levels and whether or not ADAs have developed.

The development of ADAs is conditioned by the patient immune condition, and is much more common in intermittent treatments (over 60% of the cases) than in maintenance therapy (10%-20%). Furthermore, it has been seen that those patients having developed ADAs and who remain a long time without treatment exhibit slow clearance of these antibodies[84].

Many studies have been carried out to determine when and how to determine these antibody titers with a view to performing the necessary adjustments and for defining the interval during which therapeutic blood drug levels are present. In routine clinical practice, if this is not possible, dose adjustment is made empirically, shortening the interval between doses or switching to another molecule when loss of response occurs or an immune‑mediated reaction is observed. Three different methods can be used to determine the drug levels.

The most widely used option is the ELISA technique, which can also be used to determine the ADAs titers, though this requires the anti‑TNF‑α drug to be undetectable in blood, since otherwise it binds to the antibodies to form immune complexes that are not detected.

Radioimmunoassay (RIA) is similar to ELISA, though its use is limited since it involves the use of a radioactive reagent. Furthermore, and in the same way as ELISA, it cannot detect the presence of ADAs if there are detectable drug levels in blood.

Another method for determining the drug and antibody is variable mobility testing, which allows the detection of ADAs (against IFX and ADA) in the presence of drug in blood.

The determination of anti‑TNF‑α drug levels is performed immediately before administration of the next dose, and ADAs are only detected when the drug levels are undetectable ‑ since the most widely used technique in clinical practice is the ELISA test, which can complicate interpretation of the results if detectable drug levels are present in blood.

Different studies have correlated the development of ADAs to an increased risk of infusion reactions and increased drug clearance from blood[85]. However, not all studies have established correlations to loss of response. In this regard, a systematic review published by Chaparro[86] found no differences between maintenance or loss of response according to whether ADAs develop or not, while the metaanalysis conducted by Kavinderjit found patients who develop ADAs to have a three‑fold greater risk of loss of treatment response than patients who do not develop such antibodies[87].

Although there is great variability among studies in defining the minimum effective concentration of anti‑TNF‑α drugs, the determination of drug levels has been correlated to improved disease control, and to clinical and endoscopic remission. This is important in designing treatment algorithms[70]. To date, the management approach in clinical practice has depended on the drug values and on the presence or absence of ADAs (see Table 6).

Current studies are evaluating the role of routine anti‑TNF‑α drug level measurements in blood during therapy, as is done with other drug substances, in order to facilitate better dose adjustment[85]. However, the different studies contemplate different cutoff values in defining the therapeutic range. Studies are therefore needed to determine the adequate therapeutic interval or window.

***Future treatments***

The biological drugs currently authorized for the treatment of IBD are monoclonal antibodies targeted to TNF‑α (IFX, ADA, certolizumab and golimumab) and monoclonal antibodies targeted to the leukocyte integrins (natalizumab, approved by the United States FDA for refractory CD; and vedolizumab, approved by the EMA and the FDA).

A number of lines of research have been developed with the aim of blocking the inflammatory process at different levels, and in the coming years new drugs will be introduced that will contribute to expand the current therapeutic options.

The drug options that are presently in the most advanced stages of development are analyzed below.

**INTERLEUKINS**

Interleukins (ILs) are soluble inflammatory response messenger (signaling) molecules. Their role in IBD has been clearly established, and research in this field has been particularly wide‑ranging and advanced[88].

***Anti‑IL‑12/23 drugs***

**Ustekinumab:** this is the drug with the most advanced results to date. Ustekinumab is a fully humanized IgG1κ anti‑IL‑12/23 monoclonal antibody. It specifically binds to the p40 protein subunit shared by both of the mentioned ILs. Binding prevents the mentioned subunit from interacting with the IL‑12Rβ1 receptor protein, which is expressed on the surface of immune cells ‑ thereby inhibiting innate and adaptive immune response stimulation. In an inflammatory environment, naive CD4+ T cells are induced to IFN‑γ producing Th1 cells by the action of IL‑12, and to Th17 cells by the action of IL‑23. The Th17 cells in turn are responsible for the production of proinflammatory cytokines such as IL‑17, IL‑17F, IL‑6 and TNF‑α[89,90]. Blocking this pathway has been successfully employed in animal models[91,92], and both ILs play a key role in the inflammatory processes of CD[90,93,94].

The results of a first double‑blind and placebo (PB)‑controlled phase II clinical trial were published in 2008[95]. This was a study with a complicated design that included two patient populations. In population 1 the results referred to the primary endpoint were discouraging, with a clinical response rate in week 8 of 49% in the group of patients treated with ustekinumab *vs* 40% in the PB group (*p =* 0.34). However, in a subgroup of 49 patients previously treated with IFX, statistical significance *vs* PB was reached, with a response rate of 59% and 26%, respectively (*p =* 0.05), in week 8. In population 2 the clinical response rate with ustekinumab in week 8 was 43% in the subcutaneous treatment group and 54% in the intravenous treatment group. Failure of the study to confirm the primary endpoint was attributed to the high percentage response observed in the PB group. No serious adverse events were detected in week 8, and the recorded problems were moreover similar to those seen in the PB group. The end conclusion was favorable regarding the capacity of the active drug to elicit a clinical response in the induction phase.

The CERTIFI trial was published in 2012[96]. This was a randomized, double‑blind, PB‑controlled phase IIa study on the efficacy of ustekinumab in patients with moderate to severe CD refractory to IFX. A total of 526 patients resistant to treatment (50% of the subjects having received at least 2 anti‑TNF‑α drugs) were randomized to four intravenous induction treatment arms (1, 3 or 6 mg/kg of ustekinumab) and a PB arm. The 145 patients responding to ustekinumab in week 6 were randomized to subcutaneous maintenance therapy in weeks 8 and 16 with PB *vs* ustekinumab 90 mg. The primary endpoint was the clinical response rate in week 6 ‑ the recorded percentages being 36.6%, 34.1% and 39.7% (1, 3 or 6 mg/kg of ustekinumab) *vs* 23.5% in the PB arm. Only the 6 mg dose reached statistical significance *vs* PB. In the maintenance phase, 41.7% of the patients treated with ustekinumab showed clinical remission *vs* 27.4% of the patients in the PB arm (*p =* 0.03), and the clinical response rate was 69.5% *vs* 42.5%, respectively (*p <* 0.001). The safety profile was found to be similar to that of other biological drugs.

The publication of the results of three phase III clinical trials is currently pending. The first of these studies (UNITI‑1)[97] is a randomized, double‑blind trial designed to evaluate the efficacy and safety of induction with ustekinumab in patients with moderate to severe CD who have failed or are intolerant to anti‑TNF‑α therapy. The primary endpoint is clinical response in week 6, while the secondary endpoints are remission and clinical response in week 8. A total of 769 patients have been randomized to three arms: (1) intravenous PB; (2) ustekinumab 130 mg i.v.; and (3) ustekinumab 6 mg/kg i.v. as a single dose. The study ended in July 2013. The second study (UNITI‑2)[98] has the same design as the first, though the included patients are naive to biological drugs and show failure or intolerance to immunosuppressors or corticosteroids. This study ended in October 2014 and includes a total of 642 patients. Lastly, the IM‑UNITI[99] trial is also a randomized, double‑blind, PB‑controlled, parallel group multicenter study. This trial was designed to determine efficacy in the maintenance phase of CD and is currently in the recruitment stage. The study plans to include 1310 patients from the two previously mentioned trials, with conclusion in November 2018.

# There are two other anti‑IL12/23 molecules: briakinumab (ABT‑874), which likewise targets the p40 subunit, and apilimod mesylate, which is a small molecule administered *via* the oral route that inhibits the transcription of IL‑12 and IL‑23. The initial results with both molecules have not been significant[100,101].

***Anti‑IL‑6 drugs***

Interleukin‑6 is a proinflammatory cytokine produced by different types of cells. It participates in a series of processes including T lymphocyte activation and immunoglobulin secretion through the differentiation of B cells into plasma cells[102,103]. Iinterleukin‑6 exerts its action *via* membrane or soluble receptors[104]. In healthy individuals, the IL‑6 levels are low and are seen to increase in the context of immune processes[102]. This cytokine is increased in CD in the same way as its soluble receptor, and a correlation is moreover observed with the C‑reactive protein concentrations[105,106].

Tocilizumab is an IgG1 monoclonal antibody indicated in RA. It binds specifically to the soluble and membrane receptors of IL‑6. In CD we have the results of a study that randomized 36 patients with active CD to two treatment arms (8 mg/kg i.v. every 2 wk or every 4 wk) *vs* PB[107]. The clinical response rate in the group administered tocilizumab every two weeks was 80% *vs* 31% in the PB arm, though only 20% achieved clinical remission. The drug was well tolerated, though studies in RA have evidenced neutropenia, altered liver biochemical parameters and hyperlipidemia. In this regard, dyslipidemia might prove to be a safety problem of the drug over the long term[108].

Two phase II studies are in course involving two monoclonal antibodies (BMS‑945429, formerly ALD518, and PF‑04236921) targeted to IL‑6, though results are not yet available, since patient recruitment has ended only recently[109,110].

***Other anti‑interleukin drugs***

Interleukin‑2 is another molecule that plays a key role in T cell activation and proliferation.

Basiliximab and daclizumab are monoclonal antibodies targeted to CD25, which is the alpha‑chain of the IL‑2 receptor. Both drugs are used for the prevention of renal graft rejection. Initial studies with basiliximab documented clinical remission in 8 out of 10 patients with UC refractory to corticosteroid therapy[111], and a later study recorded a remission rate of up to 65%, though without a control group[112]. In the case of daclizumab we have a comparative study *vs* PB in which the efficacy results were not good[113].

Interleukin‑13 is produced by naive T cells and activates NK cells, which in turn synthesize IL‑13. Interleukin‑13 has been shown to play a key role in the pathogenesis of UC[114,115].

Two phase II trials (IMA‑648 [arunkinzumab] and CAT‑345 [tralokinumab]) published in 2014 randomized the patients to the antibody[116,117] at different doses in the case of the first study) or PB. Neither study recorded differences in terms of treatment response or clinical remission. Both studies documented a tendency towards lower activity index scores, and the safety profile was favorable. A third phase II study in patients with perianal CD has been designed to evaluate the efficacy and safety of another antibody targeted to IL‑13 (QAX576)*vs* IFX as comparator drug[118]. Ten patients have been included, and the trial is pending results after the end of the recruitment phase.

Vidofludimusis an immunosuppressor that inhibits the release of IL‑17 and IFN‑γ (by interfering with the JAK/STAT pathway and NF‑kB), which moreover blocks the enzyme dihydroorotate dehydrogenase (DHODH). This is a small molecule administered *via* the oral route. The results of the ENTRANCE study, a non‑controlled multicenter trial, were published in 2013[119]. This study evaluated 34 patients with corticosteroid‑dependent IBD (CD and UC) treated with vidofludimus 35 mg/d p.o. during 12 wk. The primary endpoint was clinical remission without corticosteroids in week 12, and was reached by 56% of the patients with CD and 50% of those with UC. The drug was well tolerated, and no serious adverse events were reported ‑ though additional studies with larger patient series are needed.

Other targets currently under investigation are antibodies against IL‑17 (AMG 827), with a study that has been closed due to worsening of the patients[120], IL‑18 (GSK1070806)[121] and IL‑21(PF‑05230900)[122] ‑ since these interleukins have also been implicated in the pathogenesis of IBD[123-125].

***Antiinflammatory interleukins***

Lastly, studies have been made referred to the administration of antiinflammatory interleukins such as IL‑10, IL‑11 and IFN‑β, though the results have not been encouraging[126-130].

**CHEMOKINE ANTAGONISTS**

Chemokines are small cytokines that are able to induce chemotaxis by interacting with the chemokine transmembrane receptors bound to protein G[131,132]. Their ligand is CCL25, which in the intestine is fundamentally expressed by the luminal epithelial cells[133]. In IBD, and especially in CD, high levels of CCL25 and of T lymphocytes expressing CCR9 have been detected[134].

***Vercirnon***

 CCX‑282B (vercirnon) is a molecule administered *via* the oral route that acts as a CCR9 receptor antagonist, and which has been suggested to be able to reduce lymphocyte trafficking towards the intestine[135]. The data derived from the PROTECT‑1 multicenter trial were published in 2013[136]. This was a double‑blind multicenter study randomizing 436 patients with CD to three vercirnon treatment groups (250 mg/d p.o., 250 mg twice daily p.o., 500 mg/d p.o.) *vs* PB over an induction phase lasting 12 wk. Subsequently, in the case of clinical response, the patients were again randomized to vercirnon (250 mg twice daily p.o.) *vs* PB until week 36. The results were not statistically significant, though in week 8 a tendency towards greater efficacy in terms of clinical response was observed in the group administered 500 mg/d *vs* PB (49% *vs* 60% with OR = 1.53, *p =* 0.111). In week 52 significance was reached in terms of the percentage of patients in remission (47% *vs* 31% with OR = 2.01, *p =* 0.12). The safety profile was found to be favorable, with similar serious and non‑serious adverse events rates in both groups.

***BMS‑936557***

In relation to UC, a parallel line of research is based on interferon gamma‑induced protein 10 (IP‑10, also known as CXCL10). This protein is secreted by monocytes, endothelial cells and fibroblasts in response to stimulation by IFN‑γ[137]. The importance of the protein is that it is implicated in chemotaxis and interaction phenomena with T cells through the CXCR3 receptor[138]. Inhibition of this pathway could incline the Th1 response towards a Th2 response[139]. In patients with UC, CXCL10 is over‑expressed in plasma and colon tissue[140], and in animal studies it has shown a reasonable efficacy profile warranting the start of evaluations in humans[141]. BMS‑936557 (MDX‑1100) is a monoclonal antibody targeted to protein IP‑10. Its safety profile has been evaluated in phase I studies[142], and based on the evidence obtained in patients with RA[143], a specific double‑blind multicenter trial on active UC has been started[144]. This phase II trial randomized 109 patients to PB or four doses of 10 mg/kg i.v. of BMS‑936557 every two weeks. The primary endpoint (clinical response on day 57) was better among the patients that had received the antibody, though statistical significance was not reached (52.7% *vs* 35.2%, *p =* 0.083). Nevertheless, the results were statistically significant in the group of subjects with the highest titers in blood (87.5% *vs* 37%, *p <* 0.001). The number of infections was greater in the active treatment group (12.7%) compared with PB (5.8%), and drug suspension because of adverse events proved necessary in 3.6% of the cases. At present, we are in wait of the publication of the results of another two phase II trials randomizing patients to different doses of the molecule *vs* PB in application to moderate or severe CD[145] or UC[146].

***Other chemokine antagonists***

There are other lines of research involving chemokines in autoimmune diseases, such as the binding of CXCL10 to its CXC3 receptor[147], which has been shown to result in a reduction of its concentrations in patients with CD, in parallel to reduction in the C‑reactive protein levels[148]. On the other hand, it has been reported that patients with UC show serum and tissues elevations of exotaxin‑1, a chemokine that would act by recruiting eosinophils at intestinal level.

Bertilizumab is a humanized IgG4 monoclonal antibody that blocks exotaxin‑1 activity[149]. A phase II study involving 42 patients with moderate or severe UC is planned, with the aim of assessing the efficacy and safety of the drug[150].

**ENDOGENOUS ANTI‑TNF: TNF‑Kinoid**

Another line of investigation involves the generation of anti‑TNF‑α polyclonal antibodies through active immunotherapy. This strategy is based on the use of a TNF‑α derivative as vaccine. The compound is known as TNK‑kinoid (TNF‑K), and while biologically inactive, it can interrupt B cell tolerance of their own cytokines ‑ resulting in the production of high titers of antibodies[151]. A first phase I/II study was presented on occasion of the Digestive Disease Week in 2011[152], involving 21 patients with moderate to severe CD assigned to different doses on an open‑label basis. The safety profile was found to be favorable, with no serious adverse events and the generation of antibodies in 81% of the cases. Clinical remission in week 12 was achieved by 50% of the patients. The results of a second randomized phase II study were published in 2012, involving patients with moderate to severe CD and loss of response or with intolerance to conventional anti‑TNF‑α drug therapy. The trial included 68 patients randomized *vs* PB into two cross‑over treatment arms with intramuscular doses of 180 µg on days 0, 7, 28, 84, 91 and 112, with switching of the active drug to PB in the fifth dose, and of PB to the active drug in the third dose in the control group. The safety data were again favorable in this case, with only one serious adverse event related to worsening of CD, though the efficacy results were not reported[153].

**JANUS KINASE ANTAGONISTS**

The Janus kinases (JAKs) are a group of proteins corresponding to enzymes associated to cytokine receptors. They form part of a complex system of signal transmission from outside the cell towards the nucleus, activating transcription of the genes that intervene in important cell processes such as growth, differentiation, proliferation or migration. The process begins when the membrane receptor is stimulated by a chemical messenger such as for example a cytokine. This receptor activates Janus kinase, which undergoes auto‑phosphorylation and in turn phosphorylates the STAT protein. The latter protein then binds to another phosphorylated STAT protein (i.e., it undergoes dimerization) and is translocated to the cell nucleus where DNA transcription factors are activated. This system, known as JAK/STAT system[154], has been implicated in the pathogenesis of different diseases[155,156], including specifically IBD[157].

***Tofacitinib***

This is a small molecule administered *via* the oral route that selectively inhibits JAK1 and JAK3, affecting the signaling pathways of cytokines such as IL‑2, 4, 7, 9, 15 and 21[158,159]. Blocking these pathways could suppress the activation and proliferation of lymphocytes while maintaining T cell regulatory function[159,160]. In the year 2002, the United States FDA approved the drug for the treatment of RA. In the case of IBD the initial data are not encouraging in reference to CD as regards disease response or remission ‑ though the drug is associated to a significant decrease in biomarkers (C‑reactive protein and calprotectin)[161]. In reference to UC, the results of a randomized, double‑blind phase II trial involving four treatment doses (0.5, 3, 10 or 15 mg/d p.o.) or PB in 194 patients with moderate to severe UC were published[162]. The primary endpoint was clinical response in week 8. In the high dose groups (10 and 15 mg, respectively), the clinical response was greater than in the PB series ‑ statistical significance being reached with the 15 mg dose (61% and 78% *vs* 42%, *p =* 0.10 and *p <* 0.001). Clinical remission reached statistical significance *vs* PB with both doses (48% and 41% *vs* 10%, *p <* 0.001). A subsequent sub‑analysis demonstrated improvement in patient quality of life[163]. Further studies involving larger patient samples are needed to confirm the efficacy and safety of the drug.

***Inhibition of IL‑13***

In this line of research, studies have been made of the inhibition of the mentioned pathway with monoclonal antibodies targeted to IL‑13, which is responsible for activating the JAK/STAT pathway[164]. The studies are cited in the section on interleukin antagonist drugs.

**ANTIADHESION MOLECULES**

Adhesion molecules constitute one of the most advanced lines of research in IBD. Adhesion molecules are transmembrane receptors with three domains (intracellular, transmembrane and extracellular) that induce cellular changes following stimulation by external molecules. These molecules include the integrins and lymphocyte homing receptors.

***Natalizumab***

This was the first drug to be investigated, and consists of an IgG4 monoclonal antibody targeted to integrin subunit α4. Natalizumab initially showed favorable results in CD[165,166], though the risk of progressive multifocal leukoencephalopathy (PML) secondary to reactivation of the JC virus has limited its use[167,168]. Natalizumab acts by blocking the interaction of α4 β7 with mucosal vascular addressin cell adhesion molecule‑1 (MadCAM‑1) and the interaction of α4 β1 with vascular cell adhesion molecule‑1 (VCAM‑1), which is critical to lymphocyte trafficking towards the central nervous system ‑ thereby giving rise to the risk of JC virus reactivation[169].

***Vedolizumab***

This is another IgG1 monoclonal antibody that binds to integrin α4 β7, preventing it from binding to its specific intestinal ligand, MadCAM‑1. T lymphocyte migration towards the inflamed intestinal areas is inhibited as a result. In contrast to natalizumab, it does not bind to integrins α4β1 and αEβ7, and does not antagonize the interaction of integrin α4 with VCAM‑1. At present, and based on the results of clinical trials[170,171], vedolizumab has been approved by both the FDA and the EMA for the treatment of patients with moderate to severe CD or UC who fail to respond to conventional treatment or therapy with anti‑TNF‑α drugs.

***AMG 181***

AMG81 is another humanized IgG2 monoclonal antibody likewise targeted to integrin α4β7[172]. Early‑stage studies warrant the safety, pharmacological and tolerability profile of the drug. AMG 181 is currently being investigated in the context of two randomized, PB‑controlled trials in application to both CD[173] and UC[174]. More evidence will be obtained in the coming years.

***AJM300***

This is a small molecule administered *via* the oral route that inhibits the α4 receptor. It is known to inhibit the binding of integrin α4β1/α4β7 ‑ expressing cells to VCAM‑1/MAdCAM‑1, and has demonstrated its efficacy in the prevention of colitis in animal studies[175]. The results of a double‑blind multicenter phase IIa trial were published in 2012[176]. The study involved the randomization of 102 patients with active moderate UC to receiveAJM 300 at a dose of 960 mg or PB three times daily for 8 weeks. The primary endpoint was the clinical response rate in week 8, which was found to be 62.7% *vs* 25.5% in the AJM300 group and PB group, respectively (OR = 5.35; *p =* 0.0002). The secondary endpoints (clinical remission and mucosal healing in week 8) were also favorable to the study molecule (23.5% *vs* 3.9% with OR = 7.81; *p =* 0.0099 and 58.8% *vs* 29.4% with OR = 4.65; *p =* 0.0014). No serious adverse events (progressive multifocal leukoencephalopathy) were documented over the short term.

***Etrolizumab***

This is a humanized monoclonal antibody targeted to the B7 subunit present in integrins α4β7 and αEβ7. The results of a double‑blind multicenter phase II trial were published in 2013[177]. The study involved the randomization of 124 patients with refractory moderate to severe UC to etrolizumab in two treatment arms (100 mg monthly s.c. or 300 mg monthly s.c plus a loading dose of 420 mg s.c. between weeks 0 and 2) or PB. The primary endpoint was the clinical remission rate in week 10, with significant results in both active treatment arms *vs* PB (20.5% and 10.3% *vs* 0%; *p =* 0.004 and *p =* 0.049). In the subgroup of patients naive to anti‑TNF‑α drug treatment, the differences obtained with the 100 mg dose were even greater (43.8% *vs* 0%; *p =* 0.007). The adverse event rates were similar in all three groups.

***MECA‑367 and PF‑00547,659***

The pharmacological properties of two monoclonal antibodies (MECA‑367 and PF‑00547,659) targeted to MAdCAM, with inhibition of binding of the latter to integrin α4β7 were presented in 2009[178], though subsequent data are only available for PF‑00547,659. In 2011 a double‑blind study randomized 80 patients with active UC to different single or multiple s.c. or i.v. doses of PF‑00547,659 *vs* PB. Good efficacy *vs* PB was recorded, with endoscopic improvement of the lesions, a good safety and tolerability profile, and no immunogenicity. This year has seen publication of the results of the TURANDOT trial[179], a double‑blind, PB‑controlled multicenter efficacy and safety study in 357 patients with moderate to severe UC randomized to PB or to doses of the antibody (7.5, 22.5, 75 or 225 mg every 4 wk for three doses). The primary endpoint was the remission rate in week 12, and the secondary endpoints were the response rate and mucosal healing rate in week 12. Remission and mucosal healing were significantly greater in the 22.5 mg and 75 mg dose groups *vs* PB, while response was significantly greater for the 22.5 mg and 225 mg groups *vs* PB. The safety profile remained favorable.

**OTHER LINES OF RESEARCH**

***Laquinimod***

Laquinimod is a molecule administered *via* the oral route, with great bioavailability, and with purported regulatory activity upon antigen‑presenting cells (APCs) and T lymphocytes[180,181]. A phase II trial randomizing 180 patients to different doses of active treatment *vs* PB has reported results inversely proportional to the increase in dose as regards percentage response or remission[182]. Specifically, the lowest dose (0.5 mg) elicited a clinical response in 55.2% of the patients treated with the active drug *vs* in 31.7% of the patients administered PB, with respective remission rates of 48.3% *vs* 15.9% in week 8.

***Masitinib***

Gastrointestinal mast cells are usually found beneath the epithelial surfaces and are able to release cytokines, chemokines, prostaglandins, histamine and heparin. The proliferation of these cells is seen to increase at intestinal mucosal and submucosal level in CD[183,184]. Masitinib is a selective tyrosine kinase inhibitor that targets c‑kit receptor (expressed by mast cells), but also platelet‑derived growth factor receptor‑α/β, lymphocyte‑specific kinase, Lck/Yes‑related protein, fibroblast growth factor receptor 3 and the focal adhesion kinase activation pathway[185]. A phase IIb/III phase is currently underway with this molecule, with the planned inclusion of 450 patients with CD[186].

***Visiluzimab, rituximab and abatacept***

Attempts have been made to invert the natural inflammation process in which T cell proliferation *vs* apoptosis is observed. Visiluzimab(a humanized monoclonal antibody against T cell receptor CD3) and rituximab (a chimeric monoclonal antibody targeted to B cell receptor CD20) have been evaluated in IBD, where they have shown an unfavorable safety profile[187-192]. Abatacept is a recombinant protein that blocks T cell co‑stimulation by the antigen‑presenting cells (APCs). Its use has been approved for RA, though the results referred to IBD have been disappointing[193,194].

***Morgensen***

Immunosuppressive cytokine transforming growth factor (TGF)–β1 is a secreted cytokine with growth, proliferation, differentiation and apoptotic functions. It has been attributed with immune regulating functions depending on the cell upon which it acts and the environment in which it is found. Diminished TGF–β1 activity has been reported in CD. This is due to the binding of an intracellular protein called SMAD 7 to the TGF–β1 receptor[195]. A molecule known as Morgensen (GED301) was presented in 2001. This is an antisense oligonucleotide that hybridizes to the human *SMAD7* messenger RNA (mRNA) and facilitates RNase H–mediated RNA degradation through a classic antisense mechanism. Its release is pH‑dependent; accordingly, it is released in the ileum and right colon[195]. Favorable safety results from a phase I study in 15 patients with CD were published in 2012[196]. Recently, a phase II trial has evaluated 166 patients with active CD assigned to three active drug treatment groups *vs* PB[197]. The clinical remission rates associated to the two highest drug doses were 55% and 65% *vs* 10% for PB (*p =* 0.001), while the clinical response rates were 58% and 72% *vs* 18% (*p =* 0.04). The total and serious adverse event rates were similar, with no reported neoplasms.

***RPC1063 and GLPG0974***

Lastly, the results of two randomized, double‑blind, PB controlled trials were presented on occasion of the ECCO meeting in 2015, involving two new molecules: RPC1063 and GLPG0974.

RPC1063 is a molecule administered *via* the oral route with selectivity for sphingosine 1‑phosphate (S1P) 1 and 5 receptor modulator. The study included 197 patients with moderate or severe UC administered 0.5 mg or 1 mg of the active drug *vs* PB, once daily[198]. The primary endpoint (the proportion of subjects in remission in week 8) reached statistical significance in the highest dose group (16.4% *vs* 6.2%; *p =* 0.0482). The adverse events profiles were comparable between groups, with approximately 31% of the patients experiencing a treatment emergent adverse event.

GLPG0974 is a selective free fatty acid receptor antagonist. Binding of the fatty acids to their receptor would induce neutrophil activation and migration. The results have been assessed in 45 patients with mild to moderate UC treated with GLPG0974 during four weeks (200 mg/12 h p.o. *vs* PB)[199]. A decrease in calprotectin levels and of myeloperoxidase‑positive cells was recorded, though no differences were observed in terms of response, clinical remission or mucosal healing. The safety and tolerability profile was favorable.

***Stem cells***

Different stem cell therapies have been used in CD and UC. Stem cell therapy involves the use of autologous hematopoietic stem cell transplantation in CD, mesenchymal stem cells administered systemically or locally in perianal fistulas, and other cell treatments where experience is more limited, such as regulatory T cells and dendritic cells. We refer readers to two recent reviews carried out by our group in this field[200,201].

***Herbal remedies***

Studies have been made that specifically compare treatment with herbal remedies *vs* PB or even conventional therapy, though there are discrepancies in the results due to the lack of homogeneity among the different studies. The findings in terms of safety are favorable, and the predictable costs are lower than in the case of conventional treatment. We recommend a recent systematic review, which affords a more detailed analysis of this subject[202] (see Table 7). Among the different herbal remedies employed, special mention must be made of *Andorgraphis paniculata* extract, known as HMPL‑004, and which has been found to reduce TNF, IL‑1β, IFN‑γ and IL‑22 in the development of experimental colitis[203].

***Fecal transplant***

It is a therapeutic alternative in gastrointestinal processes such as Clostridium difficile-infection, metabolic syndrome, constipation, pouchitis, irritable bowel syndrome and IBD[204]. In IBD effectiveness appears to be related to the stability of the colonization of donated bacteria[205]. The experience in CD is limited to 6 patients accumulated[206,207]. In UC there are data of up to 106 patients[205,207-211]. The study with more patients included 62 cases with UC, referring clinical improvement in 92% and clinical remission in 68%. In the rest of studies the results have not been as favourable as the forementioned studies, with clinical remission ranging from 0% to 30% and clinical response from 0% to 70%. The relative small number of patients evaluated so far, does not allow to establish firmly conclusions, but it stresses theimportance of the microbiota in the pathogenesis of IBD.

**CONCLUSION**

At present there are a large number of on-going studies in various stages of research on new molecules for the treatment of IBD. An analysis of mucosal
healing is needed in order to evaluate the impact of the therapy. In this way it is expected to change the course of IBD. Among the different alternatives the pathway of the anti-adhesion molecules and interleukin drugs are a real anti-TNF-α alternative treatment.

Within the next few years the developments referred to pharmacogenetics, clinical pharmacology, the use of indexes that try to classify patients by defining profiles of severity and the new drug molecules will allow us to tailor treatments.

**REFERENCES**

1 **Molodecky NA**, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, Benchimol EI, Panaccione R, Ghosh S, Barkema HW, Kaplan GG. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* 2012; **142**: 46-54.e42; quiz e30 [PMID: 22001864 DOI: 10.1053/j.gastro.2011.10.001]

2 **Burisch J**, Pedersen N, Čuković-Čavka S, Brinar M, Kaimakliotis I, Duricova D, Shonová O, Vind I, Avnstrøm S, Thorsgaard N, Andersen V, Krabbe S, Dahlerup JF, Salupere R, Nielsen KR, Olsen J, Manninen P, Collin P, Tsianos EV, Katsanos KH, Ladefoged K, Lakatos L, Björnsson E, Ragnarsson G, Bailey Y, Odes S, Schwartz D, Martinato M, Lupinacci G, Milla M, De Padova A, D'Incà R, Beltrami M, Kupcinskas L, Kiudelis G, Turcan S, Tighineanu O, Mihu I, Magro F, Barros LF, Goldis A, Lazar D, Belousova E, Nikulina I, Hernandez V, Martinez-Ares D, Almer S, Zhulina Y, Halfvarson J, Arebi N, Sebastian S, Lakatos PL, Langholz E, Munkholm P; for the EpiCom-group. East-West gradient in the incidence of inflammatory bowel disease in Europe: the ECCO-EpiCom inception cohort. *Gut* 2014; **63**: 588-597 [PMID: 23604131 DOI: 10.1136/gutjnl-2013-304636]

3 **Lakatos PL**. Environmental factors affecting inflammatory bowel disease: have we made progress? *Dig Dis* 2009; **27**: 215-225 [PMID: 19786744 DOI: 10.1159/000228553]

4 **Knights D**, Lassen KG, Xavier RJ. Advances in inflammatory bowel disease pathogenesis: linking host genetics and the microbiome. *Gut* 2013; **62**: 1505-1510 [PMID: 24037875 DOI: 10.1136/gutjnl-2012-303954]

5 **Kalla R**, Ventham NT, Kennedy NA, Quintana JF, Nimmo ER, Buck AH, Satsangi J. MicroRNAs: new players in IBD. *Gut* 2015; **64**: 504-517 [PMID: 25475103 DOI: 10.1136/gutjnl-2014-307891]

6 **Zuk O**, Hechter E, Sunyaev SR, Lander ES. The mystery of missing heritability: Genetic interactions create phantom heritability. *Proc Natl Acad Sci USA* 2012; **109**: 1193-1198 [PMID: 22223662 DOI: 10.1073/pnas.1119675109]

7 **Patel KK**, Babyatsky MW. Medical education: a key partner in realizing personalized medicine in gastroenterology. *Gastroenterology* 2008; **134**: 656-661 [PMID: 18325381 DOI: 10.1053/j.gastro.2008.01.064]

8 **Cohen LB**, Nanau RM, Delzor F, Neuman MG. Biologic therapies in inflammatory bowel disease. *Transl Res* 2014; **163**: 533-556 [PMID: 24467968 DOI: 10.1016/j.trsl.2014.01.002]

9 **Laharie D**, Filippi J, Roblin X, Nancey S, Chevaux JB, Hébuterne X, Flourié B, Capdepont M, Peyrin-Biroulet L. Impact of mucosal healing on long-term outcomes in ulcerative colitis treated with infliximab: a multicenter experience. *Aliment Pharmacol Ther* 2013; **37**: 998-1004 [PMID: 23521659 DOI: 10.1111/apt.12289]

10 **Papi C**, Aratari A. Mucosal healing as a treatment for IBD? *Expert Rev Gastroenterol Hepatol* 2014; **8**: 457-459 [PMID: 24654957 DOI: 10.1586/17474124.2014.902302]

11 **Kopylov U**, Ben- Horin S, Seidman E. Therapeutic drug monitoring in inflammatory bowel disease. *Ann Gastroenterol* 2014; **27**: 304-312 [PMID: 25331715]

12 **Ben-Horin S**, Kopylov U, Chowers Y. Optimizing anti-TNF treatments in inflammatory bowel disease. *Autoimmun Rev* 2014; **13**: 24-30 [PMID: 23792214 DOI: 10.1016/j.autrev.2013.06.002]

13 **Ferrante M**, Vermeire S, Fidder H, Schnitzler F, Noman M, Van Assche G, De Hertogh G, Hoffman I, D'Hoore A, Van Steen K, Geboes K, Penninckx F, Rutgeerts P. Long-term outcome after infliximab for refractory ulcerative colitis. *J Crohns Colitis* 2008; **2**: 219-225 [PMID: 21172214 DOI: 10.1016/j.crohns.2008.03.004]

14 **Nancey S**, Roblin X. [Non-invasive follow up of patients with inflammatory bowel diseases]. *Rev Prat* 2014; **64**: 1256-1261 [PMID: 25638865]

15 **Evans WE**, McLeod HL. Pharmacogenomics--drug disposition, drug targets, and side effects. *N Engl J Med* 2003; **348**: 538-549 [PMID: 12571262 DOI: 10.1056/NEJMra020526]

16 **Sim E**, Lack N, Wang CJ, Long H, Westwood I, Fullam E, Kawamura A. Arylamine N-acetyltransferases: structural and functional implications of polymorphisms. *Toxicology* 2008; **254**: 170-183 [PMID: 18852012 DOI: 10.1016/j.tox.2008.08.022]

17 **Chen M**, Xia B, Chen B, Guo Q, Li J, Ye M, Hu Z. N-acetyltransferase 2 slow acetylator genotype associated with adverse effects of sulphasalazine in the treatment of inflammatory bowel disease. *Can J Gastroenterol* 2007; **21**: 155-158 [PMID: 17377643]

18 **Faubion WA**, Loftus EV, Harmsen WS, Zinsmeister AR, Sandborn WJ. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. *Gastroenterology* 2001; **121**: 255-260 [PMID: 11487534 DOI: 10.1053/gast.2001.26279]

19 **Munkholm P**, Langholz E, Davidsen M, Binder V. Frequency of glucocorticoid resistance and dependency in Crohn's disease. *Gut* 1994; **35**: 360-362 [PMID: 8150347 DOI: 10.1136/gut.35.3.360]

20 **Reinisch W**, Gasché C, Wyatt J, Moser G, Lochs H, Vogelsang H, Gangl A. Steroid dependency in Crohn's disease. *Lancet* 1995; **345**: 859 [PMID: 7898245 DOI: 10.1016/S0140-6736(95)92995-9]

21 **Farrell RJ**, Kelleher D. Glucocorticoid resistance in inflammatory bowel disease. *J Endocrinol* 2003; **178**: 339-346 [PMID: 12967327 DOI: 10.1677/joe.0.1780339]

22 **Farrell RJ**, Murphy A, Long A, Donnelly S, Cherikuri A, O'Toole D, Mahmud N, Keeling PW, Weir DG, Kelleher D. High multidrug resistance (P-glycoprotein 170) expression in inflammatory bowel disease patients who fail medical therapy. *Gastroenterology* 2000; **118**: 279-288 [PMID: 10648456 DOI: 10.1016/S0016-5085(00)70210-1]

23 **Onnie CM**, Fisher SA, Pattni R, Sanderson J, Forbes A, Lewis CM, Mathew CG. Associations of allelic variants of the multidrug resistance gene (ABCB1 or MDR1) and inflammatory bowel disease and their effects on disease behavior: a case-control and meta-analysis study. *Inflamm Bowel Dis* 2006; **12**: 263-271 [PMID: 16633048 DOI: 10.1097/01.MIB.0000209791.98866.ba]

24 **Smith MA**, Marinaki AM, Sanderson JD. Pharmacogenomics in the treatment of inflammatory bowel disease. *Pharmacogenomics* 2010; **11**: 421-437 [PMID: 20235796 DOI: 10.2217/pgs.10.4]

25 **De Iudicibus S**, Stocco G, Martelossi S, Drigo I, Norbedo S, Lionetti P, Pozzi E, Barabino A, Decorti G, Bartoli F, Ventura A. Association of BclI polymorphism of the glucocorticoid receptor gene locus with response to glucocorticoids in inflammatory bowel disease. *Gut* 2007; **56**: 1319-1320 [PMID: 17698869 DOI: 10.1136/gut.2006.116160]

26 **van Rossum EF**, Koper JW, Huizenga NA, Uitterlinden AG, Janssen JA, Brinkmann AO, Grobbee DE, de Jong FH, van Duyn CM, Pols HA, Lamberts SW. A polymorphism in the glucocorticoid receptor gene, which decreases sensitivity to glucocorticoids in vivo, is associated with low insulin and cholesterol levels. *Diabetes* 2002; **51**: 3128-3134 [PMID: 12351458 DOI: 10.2337/diabetes.51.10.3128]

27 **Derijks LJ**, Wong DR. Pharmacogenetics of thiopurines in inflammatory bowel disease. *Curr Pharm Des* 2010; **16**: 145-154 [PMID: 20205660 DOI: 10.2174/138161210790112773]

28 **Van Asseldonk DP**, de Boer NK, Peters GJ, Veldkamp AI, Mulder CJ, Van Bodegraven AA. On therapeutic drug monitoring of thiopurines in inflammatory bowel disease; pharmacology, pharmacogenomics, drug intolerance and clinical relevance. *Curr Drug Metab* 2009; **10**: 981-997 [PMID: 20214590 DOI: 10.2174/138920009790711887]

29 **Priest VL**, Begg EJ, Gardiner SJ, Frampton CM, Gearry RB, Barclay ML, Clark DW, Hansen P. Pharmacoeconomic analyses of azathioprine, methotrexate and prospective pharmacogenetic testing for the management of inflammatory bowel disease. *Pharmacoeconomics* 2006; **24**: 767-781 [PMID: 16898847 DOI: 10.2165/00019053-200624080-00004]

30 **Winter J**, Walker A, Shapiro D, Gaffney D, Spooner RJ, Mills PR. Cost-effectiveness of thiopurine methyltransferase genotype screening in patients about to commence azathioprine therapy for treatment of inflammatory bowel disease. *Aliment Pharmacol Ther* 2004; **20**: 593-599 [PMID: 15352906 DOI: 10.1111/j.1365-2036.2004.02124.x]

31 **Guerciolini R**, Szumlanski C, Weinshilboum RM. Human liver xanthine oxidase: nature and extent of individual variation. *Clin Pharmacol Ther* 1991; **50**: 663-672 [PMID: 1752110 DOI: 10.1038/clpt.1991.205]

32 **Relling MV**, Lin JS, Ayers GD, Evans WE. Racial and gender differences in N-acetyltransferase, xanthine oxidase, and CYP1A2 activities. *Clin Pharmacol Ther* 1992; **52**: 643-658 [PMID: 1458773 DOI: 10.1038/clpt.1992.203]

33 **Kudo M**, Moteki T, Sasaki T, Konno Y, Ujiie S, Onose A, Mizugaki M, Ishikawa M, Hiratsuka M. Functional characterization of human xanthine oxidase allelic variants. *Pharmacogenet Genomics* 2008; **18**: 243-251 [PMID: 18300946 DOI: 10.1097/FPC.0b013e3282f55e2e]

34 **Marinaki AM**, Ansari A, Duley JA, Arenas M, Sumi S, Lewis CM, Shobowale-Bakre el-M, Escuredo E, Fairbanks LD, Sanderson JD. Adverse drug reactions to azathioprine therapy are associated with polymorphism in the gene encoding inosine triphosphate pyrophosphatase (ITPase). *Pharmacogenetics* 2004; **14**: 181-187 [PMID: 15167706 DOI: 10.1097/00008571-200403000-00006]

35 **Allorge D**, Hamdan R, Broly F, Libersa C, Colombel JF. ITPA genotyping test does not improve detection of Crohn's disease patients at risk of azathioprine/6-mercaptopurine induced myelosuppression. *Gut* 2005; **54**: 565 [PMID: 15753546 DOI: 10.1136/gut.2004.055947]

36 **Gearry RB**, Roberts RL, Barclay ML, Kennedy MA. Lack of association between the ITPA 94C& gt; A polymorphism and adverse effects from azathioprine. *Pharmacogenetics* 2004; **14**: 779-781 [PMID: 15564886 DOI: 10.1097/00008571-200411000-00010]

37 **De Ridder L**, Van Dieren JM, Van Deventer HJ, Stokkers PC, Van der Woude JC, Van Vuuren AJ, Benninga MA, Escher JC, Hommes DW. Pharmacogenetics of thiopurine therapy in paediatric IBD patients. *Aliment Pharmacol Ther* 2006; **23**: 1137-1141 [PMID: 16611274 DOI: 10.1111/j.1365-2036.2006.02853.x]

38 **Hindorf U**, Lindqvist M, Peterson C, Söderkvist P, Ström M, Hjortswang H, Pousette A, Almer S. Pharmacogenetics during standardised initiation of thiopurine treatment in inflammatory bowel disease. *Gut* 2006; **55**: 1423-1431 [PMID: 16543290 DOI: 10.1136/gut.2005.074930]

39 **von Ahsen N**, Armstrong VW, Behrens C, von Tirpitz C, Stallmach A, Herfarth H, Stein J, Bias P, Adler G, Shipkova M, Oellerich M, Kruis W, Reinshagen M, Schütz E. Association of inosine triphosphatase 94C& gt; A and thiopurine S-methyltransferase deficiency with adverse events and study drop-outs under azathioprine therapy in a prospective Crohn disease study. *Clin Chem* 2005; **51**: 2282-2288 [PMID: 16214825 DOI: 10.1373/clinchem.2005.057158]

40 **Ansari A**, Arenas M, Greenfield SM, Morris D, Lindsay J, Gilshenan K, Smith M, Lewis C, Marinaki A, Duley J, Sanderson J. Prospective evaluation of the pharmacogenetics of azathioprine in the treatment of inflammatory bowel disease. *Aliment Pharmacol Ther* 2008; **28**: 973-983 [PMID: 18616518 DOI: 10.1111/j.1365-2036.2008.03788.x]

41 **van Dieren JM**, van Vuuren AJ, Kusters JG, Nieuwenhuis EE, Kuipers EJ, van der Woude CJ. ITPA genotyping is not predictive for the development of side effects in AZA treated inflammatory bowel disease patients. *Gut* 2005; **54**: 1664 [PMID: 16227370]

42 **Zelinkova Z**, Derijks LJ, Stokkers PC, Vogels EW, van Kampen AH, Curvers WL, Cohn D, van Deventer SJ, Hommes DW. Inosine triphosphate pyrophosphatase and thiopurine s-methyltransferase genotypes relationship to azathioprine-induced myelosuppression. *Clin Gastroenterol Hepatol* 2006; **4**: 44-49 [PMID: 16431304 DOI: 10.1016/j.cgh.2005.10.019]

43 **Uchiyama K**, Nakamura M, Kubota T, Yamane T, Fujise K, Tajiri H. Thiopurine S-methyltransferase and inosine triphosphate pyrophosphohydrolase genes in Japanese patients with inflammatory bowel disease in whom adverse drug reactions were induced by azathioprine/6-mercaptopurine treatment. *J Gastroenterol* 2009; **44**: 197-203 [PMID: 19214663 DOI: 10.1007/s00535-008-2307-1]

44 **Shipkova M**, Franz J, Abe M, Klett C, Wieland E, Andus T. Association between adverse effects under azathioprine therapy and inosine triphosphate pyrophosphatase activity in patients with chronic inflammatory bowel disease. *Ther Drug Monit* 2011; **33**: 321-328 [PMID: 21544018 DOI: 10.1097/FTD.0b013e31821a7c34]

Is Analyse...

46 **Zabala-Fernández W**, Barreiro-de Acosta M, Echarri A, Carpio D, Lorenzo A, Castro J, Martínez-Ares D, Pereira S, Martin-Granizo I, Corton M, Carracedo A, Barros F. A pharmacogenetics study of TPMT and ITPA genes detects a relationship with side effects and clinical response in patients with inflammatory bowel disease receiving Azathioprine. *J Gastrointestin Liver Dis* 2011; **20**: 247-253 [PMID: 21961091]

47 **Osterman MT**, Kundu R, Lichtenstein GR, Lewis JD. Association of 6-thioguanine nucleotide levels and inflammatory bowel disease activity: a meta-analysis. *Gastroenterology* 2006; **130**: 1047-1053 [PMID: 16618398 DOI: 10.1053/j.gastro.2006.01.046]

48 **Hindorf U**, Lindqvist M, Hildebrand H, Fagerberg U, Almer S. Adverse events leading to modification of therapy in a large cohort of patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2006; **24**: 331-342 [PMID: 16842460 DOI: 10.1111/j.1365-2036.2006.02977.x]

49 **Cuffari C**, Théorêt Y, Latour S, Seidman G. 6-Mercaptopurine metabolism in Crohn's disease: correlation with efficacy and toxicity. *Gut* 1996; **39**: 401-406 [PMID: 8949645 DOI: 10.1136/gut.39.3.401]

50 **Dubinsky MC**, Lamothe S, Yang HY, Targan SR, Sinnett D, Théorêt Y, Seidman EG. Pharmacogenomics and metabolite measurement for 6-mercaptopurine therapy in inflammatory bowel disease. *Gastroenterology* 2000; **118**: 705-713 [PMID: 10734022 DOI: 10.1016/S0016-5085(00)70140-5]

51 **Herrlinger KR**, Cummings JR, Barnardo MC, Schwab M, Ahmad T, Jewell DP. The pharmacogenetics of methotrexate in inflammatory bowel disease. *Pharmacogenet Genomics* 2005; **15**: 705-711 [PMID: 16141796 DOI: 10.1097/01.fpc.0000172242.19675.33]

52 **Vermeire S**, Louis E, Carbonez A, Van Assche G, Noman M, Belaiche J, De Vos M, Van Gossum A, Pescatore P, Fiasse R, Pelckmans P, Reynaert H, D'Haens G, Rutgeerts P. Demographic and clinical parameters influencing the short-term outcome of anti-tumor necrosis factor (infliximab) treatment in Crohn's disease. *Am J Gastroenterol* 2002; **97**: 2357-2363 [PMID: 12358256 DOI: 10.1111/j.1572-0241.2002.05991.x]

53 **Parsi MA**, Achkar JP, Richardson S, Katz J, Hammel JP, Lashner BA, Brzezinski A. Predictors of response to infliximab in patients with Crohn's disease. *Gastroenterology* 2002; **123**: 707-713 [PMID: 12198696 DOI: 10.1053/gast.2002.35390]

54 **Taylor KD**, Plevy SE, Yang H, Landers CJ, Barry MJ, Rotter JI, Targan SR. ANCA pattern and LTA haplotype relationship to clinical responses to anti-TNF antibody treatment in Crohn's disease. *Gastroenterology* 2001; **120**: 1347-1355 [PMID: 11313304 DOI: 10.1053/gast.2001.23966]

55 **Louis E**, Vermeire S, Rutgeerts P, De Vos M, Van Gossum A, Pescatore P, Fiasse R, Pelckmans P, Reynaert H, D'Haens G, Malaise M, Belaiche J. A positive response to infliximab in Crohn disease: association with a higher systemic inflammation before treatment but not with -308 TNF gene polymorphism. *Scand J Gastroenterol* 2002; **37**: 818-824 [PMID: 12190096 DOI: 10.1080/713786515]

56 **Mascheretti S**, Hampe J, Kühbacher T, Herfarth H, Krawczak M, Fölsch UR, Schreiber S. Pharmacogenetic investigation of the TNF/TNF-receptor system in patients with chronic active Crohn's disease treated with infliximab. *Pharmacogenomics J* 2002; **2**: 127-136 [PMID: 12049175 DOI: 10.1038/sj.tpj.6500091]

57 **Mascheretti S**, Hampe J, Croucher PJ, Nikolaus S, Andus T, Schubert S, Olson A, Bao W, Fölsch UR, Schreiber S. Response to infliximab treatment in Crohn's disease is not associated with mutations in the CARD15 (NOD2) gene: an analysis in 534 patients from two multicenter, prospective GCP-level trials. *Pharmacogenetics* 2002; **12**: 509-515 [PMID: 12360101 DOI: 10.1097/00008571-200210000-00002]

58 **Vermeire S**, Louis E, Rutgeerts P, De Vos M, Van Gossum A, Belaiche J, Pescatore P, Fiasse R, Pelckmans P, Vlietinck R, Merlin F, Zouali H, Thomas G, Colombel JF, Hugot JP. NOD2/CARD15 does not influence response to infliximab in Crohn's disease. *Gastroenterology* 2002; **123**: 106-111 [PMID: 12105838 DOI: 10.1053/gast.2002.34172]

59 **Pierik M**, Vermeire S, Steen KV, Joossens S, Claessens G, Vlietinck R, Rutgeerts P. Tumour necrosis factor-alpha receptor 1 and 2 polymorphisms in inflammatory bowel disease and their association with response to infliximab. *Aliment Pharmacol Ther* 2004; **20**: 303-310 [PMID: 15274667 DOI: 10.1111/j.1365-2036.2004.01946.x]

60 **Matsukura H**, Ikeda S, Yoshimura N, Takazoe M, Muramatsu M. Genetic polymorphisms of tumour necrosis factor receptor superfamily 1A and 1B affect responses to infliximab in Japanese patients with Crohn's disease. *Aliment Pharmacol Ther* 2008; **27**: 765-770 [PMID: 18248655 DOI: 10.1111/j.1365-2036.2008.03630.x]

61 **Louis E**, El Ghoul Z, Vermeire S, Dall'Ozzo S, Rutgeerts P, Paintaud G, Belaiche J, De Vos M, Van Gossum A, Colombel JF, Watier H. Association between polymorphism in IgG Fc receptor IIIa coding gene and biological response to infliximab in Crohn's disease. *Aliment Pharmacol Ther* 2004; **19**: 511-519 [PMID: 14987319 DOI: 10.1111/j.1365-2036.2004.01871.x]

Is Analyse...

63 **Hlavaty T**, Pierik M, Henckaerts L, Ferrante M, Joossens S, van Schuerbeek N, Noman M, Rutgeerts P, Vermeire S. Polymorphisms in apoptosis genes predict response to infliximab therapy in luminal and fistulizing Crohn's disease. *Aliment Pharmacol Ther* 2005; **22**: 613-626 [PMID: 16181301 DOI: 10.1111/j.1365-2036.2005.02635.x]

64 **Hlavaty T**, Ferrante M, Henckaerts L, Pierik M, Rutgeerts P, Vermeire S. Predictive model for the outcome of infliximab therapy in Crohn's disease based on apoptotic pharmacogenetic index and clinical predictors. *Inflamm Bowel Dis* 2007; **13**: 372-379 [PMID: 17206723 DOI: 10.1002/ibd.20024]

65 **Willot S**, Vermeire S, Ohresser M, Rutgeerts P, Paintaud G, Belaiche J, De Vos M, Van Gossum A, Franchimont D, Colombel JF, Watier H, Louis E. No association between C-reactive protein gene polymorphisms and decrease of C-reactive protein serum concentration after infliximab treatment in Crohn's disease. *Pharmacogenet Genomics* 2006; **16**: 37-42 [PMID: 16344720 DOI: 10.1097/01.fpc.0000182776.57437.d8]

66 **Dideberg V**, Louis E, Farnir F, Bertoli S, Vermeire S, Rutgeerts P, De Vos M, Van Gossum A, Belaiche J, Bours V. Lymphotoxin alpha gene in Crohn's disease patients: absence of implication in the response to infliximab in a large cohort study. *Pharmacogenet Genomics* 2006; **16**: 369-373 [PMID: 16609369 DOI: 10.1097/01.fpc.0000204993.91806.b1]

67 **Dideberg V**, Théâtre E, Farnir F, Vermeire S, Rutgeerts P, De Vos M, Belaiche J, Franchimont D, Van Gossum A, Louis E, Bours V. The TNF/ADAM 17 system: implication of an ADAM 17 haplotype in the clinical response to infliximab in Crohn's disease. *Pharmacogenet Genomics* 2006; **16**: 727-734 [PMID: 17001292 DOI: 10.1097/01.fpc.0000230117.26581.a4]

68 **Jürgens M**, Laubender RP, Hartl F, Weidinger M, Seiderer J, Wagner J, Wetzke M, Beigel F, Pfennig S, Stallhofer J, Schnitzler F, Tillack C, Lohse P, Göke B, Glas J, Ochsenkühn T, Brand S. Disease activity, ANCA, and IL23R genotype status determine early response to infliximab in patients with ulcerative colitis. *Am J Gastroenterol* 2010; **105**: 1811-1819 [PMID: 20197757 DOI: 10.1038/ajg.2010.95]

69 **Dubinsky MC**, Mei L, Friedman M, Dhere T, Haritunians T, Hakonarson H, Kim C, Glessner J, Targan SR, McGovern DP, Taylor KD, Rotter JI. Genome wide association (GWA) predictors of anti-TNFalpha therapeutic responsiveness in pediatric inflammatory bowel disease. *Inflamm Bowel Dis* 2010; **16**: 1357-1366 [PMID: 20014019 DOI: 10.1002/ibd.21174]

70 **Colombel JF**, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D'Haens G, Diamond RH, Broussard DL, Tang KL, van der Woude CJ, Rutgeerts P. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010; **362**: 1383-1395 [PMID: 20393175 DOI: 10.1056]

71 **Mazor Y**, Almog R, Kopylov U, Ben Hur D, Blatt A, Dahan A, Waterman M, Ben-Horin S, Chowers Y. Adalimumab drug and antibody levels as predictors of clinical and laboratory response in patients with Crohn's disease. *Aliment Pharmacol Ther* 2014; **40**: 620-628 [PMID: 25039584 DOI: 10.1111/apt.12869]

72 **Vaughn BP**, Martinez-Vazquez M, Patwardhan VR, Moss AC, Sandborn WJ, Cheifetz AS. Proactive therapeutic concentration monitoring of infliximab may improve outcomes for patients with inflammatory bowel disease: results from a pilot observational study. *Inflamm Bowel Dis* 2014; **20**: 1996-2003 [PMID: 25192499 DOI: 10.1987/MIB.0000000000000156]

73 **Lobo ED**, Hansen RJ, Balthasar JP. Antibody pharmacokinetics and pharmacodynamics. *J Pharm Sci* 2004; **93**: 2645-2668 [PMID: 15389672 DOI: 10.1002/jps.20178]

74 **Colombel JF**, Feagan BG, Sandborn WJ, Van Assche G, Robinson AM. Therapeutic drug monitoring of biologics for inflammatory bowel disease. *Inflamm Bowel Dis* 2012; **18**: 349-358 [PMID: 22021134 DOI: 10.1002/ibd.21831]

75 **Ben-Horin S**, Chowers Y. Review article: loss of response to anti-TNF treatments in Crohn's disease. *Aliment Pharmacol Ther* 2011; **33**: 987-995 [PMID: 21366636 DOI: 10.1111]

76 **Papamichael K**, Gils A, Rutgeerts P, Levesque BG, Vermeire S, Sandborn WJ, Vande Casteele N. Role for therapeutic drug monitoring during induction therapy with TNF antagonists in IBD: evolution in the definition and management of primary nonresponse. *Inflamm Bowel Dis* 2015; **21**: 182-197 [PMID: 25222660 DOI: 10.1097/MIB.0000000000000202]

77 **Hanauer SB**, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Rutgeerts P. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002; **359**: 1541-1549 [PMID: 12047962 DOI: 10.1016/S0140-6736(02)08512-4]

78 **Sands BE**, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, Kamm MA, Korzenik JR, Lashner BA, Onken JE, Rachmilewitz D, Rutgeerts P, Wild G, Wolf DC, Marsters PA, Travers SB, Blank MA, van Deventer SJ. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004; **350**: 876-885 [PMID: 14985485 DOI: 10.1056/NEJMoa030815]

79 **Hanauer SB**, Sandborn WJ, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh D, Panaccione R, Wolf D, Pollack P. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology* 2006; **130**: 323-33; quiz 591 [PMID: 16472588 DOI: 10.1053/j.gastro.2005.11.030]

80 **Sandborn WJ**, Hanauer SB, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh DG, Panaccione R, Wolf D, Kent JD, Bittle B, Li J, Pollack PF. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. *Gut* 2007; **56**: 1232-1239 [PMID: 17299059 DOI: 10.1136/gut.2006.106781]

81 **Gisbert JP**, Panés J. Loss of response and requirement of infliximab dose intensification in Crohn's disease: a review. *Am J Gastroenterol* 2009; **104**: 760-767 [PMID: 19174781 DOI: 10.1038/ajg.2008.88]

82 **Peters CP**, Eshuis EJ, Toxopeüs FM, Hellemons ME, Jansen JM, D'Haens GR, Fockens P, Stokkers PC, Tuynman HA, van Bodegraven AA, Ponsioen CY. Adalimumab for Crohn's disease: long-term sustained benefit in a population-based cohort of 438 patients. *J Crohns Colitis* 2014; **8**: 866-875 [PMID: 24491515 DOI: 10.1016/j.crohns.2014.01.012]

83 **Yanai H**, Hanauer SB. Assessing response and loss of response to biological therapies in IBD. *Am J Gastroenterol* 2011; **106**: 685-698 [PMID: 21427713 DOI: 10.1038/ajg.2011.103]

84 **Moss AC**. Optimizing the use of biological therapy in patients with inflammatory bowel disease. *Gastroenterol Rep (Oxf)* 2015; **3**: 63-68 [PMID: 25567472 DOI: 10.1093/gastro/gou087]

85 **Warman A**, Straathof JW, Derijks LJ. Therapeutic drug monitoring of infliximab in inflammatory bowel disease patients in a teaching hospital setting: results of a prospective cohort study. *Eur J Gastroenterol Hepatol* 2015; **27**: 242-248 [PMID: 25569569 DOI: 10.1097/MEG.0000000000000279]

86 **Chaparro M**, Guerra I, Muñoz-Linares P, Gisbert JP. Systematic review: antibodies and anti-TNF-α levels in inflammatory bowel disease. *Aliment Pharmacol Ther* 2012; **35**: 971-986 [PMID: 22443153 DOI: 10.1111/j.1365-2036.2012.05057.x]

87 **Nanda KS**, Cheifetz AS, Moss AC. Impact of antibodies to infliximab on clinical outcomes and serum infliximab levels in patients with inflammatory bowel disease (IBD): a meta-analysis. *Am J Gastroenterol* 2013; **108**: 40-7; quiz 48 [PMID: 23147525 DOI: 10.1038/ajg.2012.363]

88 **McLean MH**, Neurath MF, Durum SK. Targeting interleukins for the treatment of inflammatory bowel disease-what lies beyond anti-TNF therapy? *Inflamm Bowel Dis* 2014; **20**: 389-397 [PMID: 24356385 DOI: 10.1097/01.MIB.0000437616.37000.41]

89 **Parrello T**, Monteleone G, Cucchiara S, Monteleone I, Sebkova L, Doldo P, Luzza F, Pallone F. Up-regulation of the IL-12 receptor beta 2 chain in Crohn's disease. *J Immunol* 2000; **165**: 7234-7239 [PMID: 11120856 DOI: 10.4049/jimmunol.165.12.7234]

90 **Iwakura Y**, Ishigame H. The IL-23/IL-17 axis in inflammation. *J Clin Invest* 2006; **116**: 1218-1222 [PMID: 16670765 DOI: 10.1172/JCI28508]

91 **Neurath MF**, Fuss I, Kelsall BL, Stüber E, Strober W. Antibodies to interleukin 12 abrogate established experimental colitis in mice. *J Exp Med* 1995; **182**: 1281-1290 [PMID: 7595199 DOI: 10.1084/jem.182.5.1281]

92 **Elson CO**, Cong Y, Weaver CT, Schoeb TR, McClanahan TK, Fick RB, Kastelein RA. Monoclonal anti-interleukin 23 reverses active colitis in a T cell-mediated model in mice. *Gastroenterology* 2007; **132**: 2359-2370 [PMID: 17570211 DOI: 10.1053/j.gastro.2007.03.104]

93 **Duerr RH**, Taylor KD, Brant SR, Rioux JD, Silverberg MS, Daly MJ, Steinhart AH, Abraham C, Regueiro M, Griffiths A, Dassopoulos T, Bitton A, Yang H, Targan S, Datta LW, Kistner EO, Schumm LP, Lee AT, Gregersen PK, Barmada MM, Rotter JI, Nicolae DL, Cho JH. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. *Science* 2006; **314**: 1461-1463 [PMID: 17068223 DOI: 10.1126/science.1135245]

94 **Kastelein RA**, Hunter CA, Cua DJ. Discovery and biology of IL-23 and IL-27: related but functionally distinct regulators of inflammation. *Annu Rev Immunol* 2007; **25**: 221-242 [PMID: 17291186 DOI: 10.1146/annurev.immunol.22.012703.104758]

95 **Sandborn WJ**, Feagan BG, Fedorak RN, Scherl E, Fleisher MR, Katz S, Johanns J, Blank M, Rutgeerts P; Ustekinumab Crohn's Disease Study Group. A randomized trial of Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease. *Gastroenterology* 2008; **135**: 1130-1141 [PMID: 18706417 DOI: 10.1053/j.gastro.2008.07.014]

96 **Sandborn WJ**, Gasink C, Gao LL, Blank MA, Johanns J, Guzzo C, Sands BE, Hanauer SB, Targan S, Rutgeerts P, Ghosh S, de Villiers WJ, Panaccione R, Greenberg G, Schreiber S, Lichtiger S, Feagan BG. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. *N Engl J Med* 2012; **367**: 1519-1528 [PMID: 23075178 DOI: 10.1056/NEJMoa1203572]

97 A Study to Evaluate the Safety and Efficacy of Ustekinumab in Patients With Moderately to Severely Active Crohn's Disease Who Have Failed or Are Intolerant to Tumor Necrosis Factor (TNF) Antagonist Therapy (UNITI-1). 2015. Available from: URL: https: //clinicaltrials.gov/ct2/show/results/NCT01369329

98 Available from: URL: https: //clinicaltrials.gov/ct2/show/NCT01369342?term=ustekinumabcrohn&rank=2se

99 Available from: URL: https: //clinicaltrials.gov/ct2/show/NCT01369355?term=ustekinumab crohn&rank=1

100 **Panaccione R**, Sandborn WJ, Gordon GL, Lee SD, Safdi A, Sedghi S, Feagan BG, Hanauer S, Reinisch W, Valentine JF, Huang B, Carcereri R. Briakinumab for treatment of Crohn's disease: results of a randomized trial. *Inflamm Bowel Dis* 2015; **21**: 1329-1340 [PMID: 25989338 DOI: 10.1097/MIB.0000000000000366]

101 **Sands BE**, Jacobson EW, Sylwestrowicz T, Younes Z, Dryden G, Fedorak R, Greenbloom S. Randomized, double-blind, placebo-controlled trial of the oral interleukin-12/23 inhibitor apilimod mesylate for treatment of active Crohn's disease. *Inflamm Bowel Dis* 2010; **16**: 1209-1218 [PMID: 19918967 DOI: 10.1002/ibd.21159]

102 **Melton L**, Coombs A. Actemra poised to launch IL-6 inhibitors. *Nat Biotechnol* 2008; **26**: 957-959 [PMID: 18779787 DOI: 10.1038/nbt0908-957]

103 **Kishimoto T**. The biology of interleukin-6. *Blood* 1989; **74**: 1-10 [PMID: 2473791]

104 **Jones SA**, Horiuchi S, Topley N, Yamamoto N, Fuller GM. The soluble interleukin 6 receptor: mechanisms of production and implications in disease. *FASEB J* 2001; **15**: 43-58 [PMID: 11149892 DOI: 10.1096/fj.99-1003rev]

105 **Mitsuyama K**, Toyonaga A, Sasaki E, Ishida O, Ikeda H, Tsuruta O, Harada K, Tateishi H, Nishiyama T, Tanikawa K. Soluble interleukin-6 receptors in inflammatory bowel disease: relation to circulating interleukin-6. *Gut* 1995; **36**: 45-49 [PMID: 7890234 DOI: 10.1136/gut.36.1.45]

106 **Hosokawa T**, Kusugami K, Ina K, Ando T, Shinoda M, Imada A, Ohsuga M, Sakai T, Matsuura T, Ito K, Kaneshiro K. Interleukin-6 and soluble interleukin-6 receptor in the colonic mucosa of inflammatory bowel disease. *J Gastroenterol Hepatol* 1999; **14**: 987-996 [PMID: 10530495 DOI: 10.1046/j.1440-1746.1999.01989.x]

107 **Ito H**, Takazoe M, Fukuda Y, Hibi T, Kusugami K, Andoh A, Matsumoto T, Yamamura T, Azuma J, Nishimoto N, Yoshizaki K, Shimoyama T, Kishimoto T. A pilot randomized trial of a human anti-interleukin-6 receptor monoclonal antibody in active Crohn's disease. *Gastroenterology* 2004; **126**: 989-96; discussion 947 [PMID: 15057738 DOI: 10.1053/j.gastro.2004.01.012]

108 **Nishimoto N**, Ito K, Takagi N. Safety and efficacy profiles of tocilizumab monotherapy in Japanese patients with rheumatoid arthritis: meta-analysis of six initial trials and five long-term extensions. *Mod Rheumatol* 2010; **20**: 222-232 [PMID: 20221663 DOI: 10.1007/s10165-010-0279-5]

109 Available from: URL: http: //www.clinicaltrials.gov/ct2/show/study/NCT01545050?show\_locs=Y

110 Available from: URL: https: //www.clinicaltrials.gov/ct2/show/NCT01287897?term=PF-04236921&rank=4

111 **Creed TJ**, Norman MR, Probert CS, Harvey RF, Shaw IS, Smithson J, Anderson J, Moorghen M, Gupta J, Shepherd NA, Dayan CM, Hearing SD. Basiliximab (anti-CD25) in combination with steroids may be an effective new treatment for steroid-resistant ulcerative colitis. *Aliment Pharmacol Ther* 2003; **18**: 65-75 [PMID: 12848627 DOI: 10.1046/j.1365-2036.2003.01639.x]

112 **Creed TJ**, Probert CS, Norman MN, Moorghen M, Shepherd NA, Hearing SD, Dayan CM; BASBUC INVESTIGATORS. Basiliximab for the treatment of steroid-resistant ulcerative colitis: further experience in moderate and severe disease. *Aliment Pharmacol Ther* 2006; **23**: 1435-1442 [PMID: 16669958 DOI: 10.1111/j.1365-2036.2006.02904.x]

113 **Van Assche G**, Sandborn WJ, Feagan BG, Salzberg BA, Silvers D, Monroe PS, Pandak WM, Anderson FH, Valentine JF, Wild GE, Geenen DJ, Sprague R, Targan SR, Rutgeerts P, Vexler V, Young D, Shames RS. Daclizumab, a humanised monoclonal antibody to the interleukin 2 receptor (CD25), for the treatment of moderately to severely active ulcerative colitis: a randomised, double blind, placebo controlled, dose ranging trial. *Gut* 2006; **55**: 1568-1574 [PMID: 16603634 DOI: 10.1136/gut.2005.089854]

114 **Heller F**, Florian P, Bojarski C, Richter J, Christ M, Hillenbrand B, Mankertz J, Gitter AH, Bürgel N, Fromm M, Zeitz M, Fuss I, Strober W, Schulzke JD. Interleukin-13 is the key effector Th2 cytokine in ulcerative colitis that affects epithelial tight junctions, apoptosis, and cell restitution. *Gastroenterology* 2005; **129**: 550-564 [PMID: 16083712 DOI: 10.1053/j.gastro.2005.05.002]

115 **Danese S**. IBD: of mice and men-shedding new light on IL-13 activity in IBD. *Nat Rev Gastroenterol Hepatol* 2011; **8**: 128-129 [PMID: 21304479 DOI: 10.1038/nrgastro.2011.17]

116 **Reinisch W**, Panés J, Khurana S, Toth G, Hua F, Comer GM, Hinz M, Page K, O'Toole M, Moorehead TM, Zhu H, Sun Y, Cataldi F. Anrukinzumab, an anti-interleukin 13 monoclonal antibody, in active UC: efficacy and safety from a phase IIa randomised multicentre study. *Gut* 2015; **64**: 894-900 [PMID: 25567115 DOI: 10.1136/gutjnl-2014-308337]

117 **Danese S**, Rudziński J, Brandt W, Dupas JL, Peyrin-Biroulet L, Bouhnik Y, Kleczkowski D, Uebel P, Lukas M, Knutsson M, Erlandsson F, Hansen MB, Keshav S. Tralokinumab for moderate-to-severe UC: a randomised, double-blind, placebo-controlled, phase IIa study. *Gut* 2015; **64**: 243-249 [PMID: 25304132 DOI: 10.1136/gutjnl-2014-308004]

118 Available from: URL: https: //www.clinicaltrials.gov/ct2/show/study/NCT01355614?term=qax576&rank=9

119 **Herrlinger KR**, Diculescu M, Fellermann K, Hartmann H, Howaldt S, Nikolov R, Petrov A, Reindl W, Otte JM, Stoynov S, Strauch U, Sturm A, Voiosu R, Ammendola A, Dietrich B, Hentsch B, Stange EF. Efficacy, safety and tolerability of vidofludimus in patients with inflammatory bowel disease: the ENTRANCE study. *J Crohns Colitis* 2013; **7**: 636-643 [PMID: 23078909 DOI: 10.1016/j.crohns.2012.09.016]

120 **Targan S**, Feagan B, Vermeire S, Panaccione R, Melmed G, Blosch C, Newmark R, Zhang N, . A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Efficacy of AMG 827 in Subjects With Moderate to Severe Crohn's Disease. *Gastroenterology* 2012; **143**: e26 [DOI: 10.1053/j.gastro.2012.07.084]

121 Available from: URL: https: //clinicaltrials.gov/ct2/show/NCT01035645?term=gsk1070806&rank=2

122 Available from: URL: https: //clinicaltrials.gov/ct2/results?term=PF-05230900 &Search=Search

123 **Pallone F**, Fina D, Caruso R, Monteleone G. Role of IL-21 in inflammatory bowel disease. *Expert Rev Clin Immunol* 2010; **6**: 537-541 [PMID: 20594126]

124 **Rovedatti L**, Kudo T, Biancheri P, Sarra M, Knowles CH, Rampton DS, Corazza GR, Monteleone G, Di Sabatino A, Macdonald TT. Differential regulation of interleukin 17 and interferon gamma production in inflammatory bowel disease. *Gut* 2009; **58**: 1629-1636 [PMID: 19740775 DOI: 10.1136/gut.2009.182170]

125 **Ludwiczek O**, Kaser A, Novick D, Dinarello CA, Rubinstein M, Tilg H. Elevated systemic levels of free interleukin-18 (IL-18) in patients with Crohn's disease. *Eur Cytokine Netw* ; **16**: 27-33 [PMID: 15809203]

126 **Fedorak RN**, Gangl A, Elson CO, Rutgeerts P, Schreiber S, Wild G, Hanauer SB, Kilian A, Cohard M, LeBeaut A, Feagan B. Recombinant human interleukin 10 in the treatment of patients with mild to moderately active Crohn's disease. The Interleukin 10 Inflammatory Bowel Disease Cooperative Study Group. *Gastroenterology* 2000; **119**: 1473-1482 [PMID: 11113068 DOI: 10.1053/gast.2000.20229]

127 **Schreiber S**, Fedorak RN, Nielsen OH, Wild G, Williams CN, Nikolaus S, Jacyna M, Lashner BA, Gangl A, Rutgeerts P, Isaacs K, van Deventer SJ, Koningsberger JC, Cohard M, LeBeaut A, Hanauer SB. Safety and efficacy of recombinant human interleukin 10 in chronic active Crohn's disease. Crohn's Disease IL-10 Cooperative Study Group. *Gastroenterology* 2000; **119**: 1461-1472 [PMID: 11113067 DOI: 10.1053/gast.2000.20196]

128 **Colombel JF**, Rutgeerts P, Malchow H, Jacyna M, Nielsen OH, Rask-Madsen J, Van Deventer S, Ferguson A, Desreumaux P, Forbes A, Geboes K, Melani L, Cohard M. Interleukin 10 (Tenovil) in the prevention of postoperative recurrence of Crohn's disease. *Gut* 2001; **49**: 42-46 [PMID: 11413109 DOI: 10.1136/gut.49.1.42]

129 **Herrlinger KR**, Witthoeft T, Raedler A, Bokemeyer B, Krummenerl T, Schulzke JD, Boerner N, Kueppers B, Emmrich J, Mescheder A, Schwertschlag U, Shapiro M, Stange EF. Randomized, double blind controlled trial of subcutaneous recombinant human interleukin-11 versus prednisolone in active Crohn's disease. *Am J Gastroenterol* 2006; **101**: 793-797 [PMID: 16635225]

130 **Pena Rossi C**, Hanauer SB, Tomasevic R, Hunter JO, Shafran I, Graffner H. Interferon beta-1a for the maintenance of remission in patients with Crohn's disease: results of a phase II dose-finding study. *BMC Gastroenterol* 2009; **9**: 22 [PMID: 19302707 DOI: 10.1186/1471-230X-9-22]

131 **Charo IF**, Ransohoff RM. The many roles of chemokines and chemokine receptors in inflammation. *N Engl J Med* 2006; **354**: 610-621 [PMID: 16467548 DOI: 10.1056/NEJMra052723]

132 **Zabel BA**, Agace WW, Campbell JJ, Heath HM, Parent D, Roberts AI, Ebert EC, Kassam N, Qin S, Zovko M, LaRosa GJ, Yang LL, Soler D, Butcher EC, Ponath PD, Parker CM, Andrew DP. Human G protein-coupled receptor GPR-9-6/CC chemokine receptor 9 is selectively expressed on intestinal homing T lymphocytes, mucosal lymphocytes, and thymocytes and is required for thymus-expressed chemokine-mediated chemotaxis. *J Exp Med* 1999; **190**: 1241-1256 [PMID: 10544196 DOI: 10.1084/jem.190.9.1241]

133 **Kunkel EJ**, Campbell JJ, Haraldsen G, Pan J, Boisvert J, Roberts AI, Ebert EC, Vierra MA, Goodman SB, Genovese MC, Wardlaw AJ, Greenberg HB, Parker CM, Butcher EC, Andrew DP, Agace WW. Lymphocyte CC chemokine receptor 9 and epithelial thymus-expressed chemokine (TECK) expression distinguish the small intestinal immune compartment: Epithelial expression of tissue-specific chemokines as an organizing principle in regional immunity. *J Exp Med* 2000; **192**: 761-768 [PMID: 10974041 DOI: 10.1084/jem.192.5.761]

134 **Papadakis KA**, Prehn J, Moreno ST, Cheng L, Kouroumalis EA, Deem R, Breaverman T, Ponath PD, Andrew DP, Green PH, Hodge MR, Binder SW, Targan SR. CCR9-positive lymphocytes and thymus-expressed chemokine distinguish small bowel from colonic Crohn's disease. *Gastroenterology* 2001; **121**: 246-254 [PMID: 11487533 DOI: 10.1053/gast.2001.27154]

135 **Walters MJ**, Wang Y, Lai N, Baumgart T, Zhao BN, Dairaghi DJ, Bekker P, Ertl LS, Penfold ME, Jaen JC, Keshav S, Wendt E, Pennell A, Ungashe S, Wei Z, Wright JJ, Schall TJ. Characterization of CCX282-B, an orally bioavailable antagonist of the CCR9 chemokine receptor, for treatment of inflammatory bowel disease. *J Pharmacol Exp Ther* 2010; **335**: 61-69 [PMID: 20660125 DOI: 10.1124/jpet.110.169714]

136 **Keshav S**, Vaňásek T, Niv Y, Petryka R, Howaldt S, Bafutto M, Rácz I, Hetzel D, Nielsen OH, Vermeire S, Reinisch W, Karlén P, Schreiber S, Schall TJ, Bekker P. A randomized controlled trial of the efficacy and safety of CCX282-B, an orally-administered blocker of chemokine receptor CCR9, for patients with Crohn's disease. *PLoS One* 2013; **8**: e60094 [PMID: 23527300 DOI: 10.1371/journal.pone.0060094]

137 **Luster AD**, Unkeless JC, Ravetch JV. Gamma-interferon transcriptionally regulates an early-response gene containing homology to platelet proteins. *Nature* ; **315**: 672-676 [PMID: 3925348 DOI: 10.1038/315672a0]

138 **Dufour JH**, Dziejman M, Liu MT, Leung JH, Lane TE, Luster AD. IFN-gamma-inducible protein 10 (IP-10; CXCL10)-deficient mice reveal a role for IP-10 in effector T cell generation and trafficking. *J Immunol* 2002; **168**: 3195-3204 [PMID: 11907072 DOI: 10.4049/jimmunol.168.7.3195]

139 **Romagnani P**, Maggi L, Mazzinghi B, Cosmi L, Lasagni L, Liotta F, Lazzeri E, Angeli R, Rotondi M, Filì L, Parronchi P, Serio M, Maggi E, Romagnani S, Annunziato F. CXCR3-mediated opposite effects of CXCL10 and CXCL4 on TH1 or TH2 cytokine production. *J Allergy Clin Immunol* 2005; **116**: 1372-1379 [PMID: 16337473 DOI: 10.1016/j.jaci.2005.09.035]

140 **Torres J**, Danese S, Colombel JF. New therapeutic avenues in ulcerative colitis: thinking out of the box. *Gut* 2013; **62**: 1642-1652 [PMID: 24104885 DOI: 10.1136/gutjnl-2012-303959]

141 **Sasaki S**, Yoneyama H, Suzuki K, Suriki H, Aiba T, Watanabe S, Kawauchi Y, Kawachi H, Shimizu F, Matsushima K, Asakura H, Narumi S. Blockade of CXCL10 protects mice from acute colitis and enhances crypt cell survival. *Eur J Immunol* 2002; **32**: 3197-3205 [PMID: 12555665 DOI: 10.1002/1521-4141(200211)32:11<3197::AID-IMMU3197>3.0.CO;2-1]

142 **Hardi R**, Mayer L, Targan SR, Yellin M, Cardarelli P, Das K. A phase 1 open-label, single-dose, dose-escalation study of MDX-1100, a high-affinity, neutralizing, fully human Igg1(kappa) anti-CXCL10 (Ip10) monoclonal antibody, in ulcerative colitis. *Gastroenterology* 2008; **134**: A99–A100 [DOI: 10.1016/S0016-5085(08)60466-7]

143 **Yellin M**, Paliienko I, Balanescu A, Ter-Vartanian S, Tseluyko V, Xu LA, Tao X, Cardarelli PM, Leblanc H, Nichol G, Ancuta C, Chirieac R, Luo A. A phase II, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of MDX-1100, a fully human anti-CXCL10 monoclonal antibody, in combination with methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum* 2012; **64**: 1730-1739 [PMID: 22147649 DOI: 10.1002/art.34330]

144 **Mayer L**, Sandborn WJ, Stepanov Y, Geboes K, Hardi R, Yellin M, Tao X, Xu LA, Salter-Cid L, Gujrathi S, Aranda R, Luo AY. Anti-IP-10 antibody (BMS-936557) for ulcerative colitis: a phase II randomised study. *Gut* 2014; **63**: 442-450 [PMID: 23461895 DOI: 10.1136/gutjnl-2012-303424]

145 Available from: URL: https: //clinicaltrials.gov/ct2/show/NCT01466374?term=BMS-936557&rank=1

146 Available from: URL: https: //clinicaltrials.gov/ct2/show/record/NCT01294410?term=BMS-936557&rank=2&show\_locs=Y

147 **Antonelli A**, Ferrari SM, Giuggioli D, Ferrannini E, Ferri C, Fallahi P. Chemokine (C-X-C motif) ligand (CXCL)10 in autoimmune diseases. *Autoimmun Rev* 2014; **13**: 272-280 [PMID: 24189283 DOI: 10.1016/j.autrev.2013.10.010]

148 **Grip O**, Janciauskiene S. Atorvastatin reduces plasma levels of chemokine (CXCL10) in patients with Crohn's disease. *PLoS One* 2009; **4**: e5263 [PMID: 19421322 DOI: 10.1371/journal.pone.0005263]

149 **Coburn LA**, Horst SN, Chaturvedi R, Brown CT, Allaman MM, Scull BP, Singh K, Piazuelo MB, Chitnavis MV, Hodges ME, Rosen MJ, Williams CS, Slaughter JC, Beaulieu DB, Schwartz DA, Wilson KT. High-throughput multi-analyte Luminex profiling implicates eotaxin-1 in ulcerative colitis. *PLoS One* 2013; **8**: e82300 [PMID: 24367513 DOI: 10.1371/journal.pone.0082300]

150 Available from: URL: https: //www.clinicaltrials.gov/ct2/show/record/NCT01671956?term=bertilimumab&rank=1

151 **Zagury D**, Le Buanec H, Bizzini B, Burny A, Lewis G, Gallo RC. Active versus passive anti-cytokine antibody therapy against cytokine-associated chronic diseases. *Cytokine Growth Factor Rev* 2003; **14**: 123-137 [PMID: 12651224 DOI: 10.1016/S1359-6101(03)00004-2]

152 Vandepapeliere P, Malan F, Rogler G, van der Bijl A, Kruger F. Safety, Immunogenicity and Clinical Phase I-II Results of TNFa-Kinoid Immunotherapeutic in Crohn’s Disease Patients. *Gastroenterology* 2011: **140** Suppl 1: S123 [DOI: 10.1016/S0016-5085(11)60501-5]

153 Dewit O, Hebuterne X, Dupas J, Howaldt S, Bures J, Schreiber S, Pace A, Klaus J, Bouhnik Y, Reinshagen M, ALlez M, Hoffmann P, D´Haens G, Van Bondegraven A, Stimac D, Goetz M, Kahi S, Vandepapeliere P, Colombel JF, Rutgers P, Vermiere S. Results of a phase II, randomized, double blind, controlled trial of the efficacy of active therapeutic immunization with TNFKinoid in patients with moderate to severe Crohn’s disease with secondary resistance to TNFα antagonist. *Gastroenterology* 2012: **142**: S567-S568 [DOI: 10.1016/S0016-5085(12)62179-9]

154 **Aaronson DS**, Horvath CM. A road map for those who don't know JAK-STAT. *Science* 2002; **296**: 1653-1655 [PMID: 12040185 DOI: 10.1126/science.1071545]

155 **Seavey MM**, Dobrzanski P. The many faces of Janus kinase. *Biochem Pharmacol* 2012; **83**: 1136-1145 [PMID: 22209716 DOI: 10.1016/j.bcp.2011.12.024]

156 **O'Shea JJ**, Plenge R. JAK and STAT signaling molecules in immunoregulation and immune-mediated disease. *Immunity* 2012; **36**: 542-550 [PMID: 22520847 DOI: 10.1016/j.immuni.2012.03.014]

157 **Ghoreschi K**, Jesson MI, Li X, Lee JL, Ghosh S, Alsup JW, Warner JD, Tanaka M, Steward-Tharp SM, Gadina M, Thomas CJ, Minnerly JC, Storer CE, LaBranche TP, Radi ZA, Dowty ME, Head RD, Meyer DM, Kishore N, O'Shea JJ. Modulation of innate and adaptive immune responses by tofacitinib (CP-690,550). *J Immunol* 2011; **186**: 4234-4243 [PMID: 21383241 DOI: 10.4049/jimmunol.1003668]

158 **Flanagan ME**, Blumenkopf TA, Brissette WH, Brown MF, Casavant JM, Shang-Poa C, Doty JL, Elliott EA, Fisher MB, Hines M, Kent C, Kudlacz EM, Lillie BM, Magnuson KS, McCurdy SP, Munchhof MJ, Perry BD, Sawyer PS, Strelevitz TJ, Subramanyam C, Sun J, Whipple DA, Changelian PS. Discovery of CP-690,550: a potent and selective Janus kinase (JAK) inhibitor for the treatment of autoimmune diseases and organ transplant rejection. *J Med Chem* 2010; **53**: 8468-8484 [PMID: 21105711 DOI: 10.1021/jm1004286]

159 **Changelian PS**, Moshinsky D, Kuhn CF, Flanagan ME, Munchhof MJ, Harris TM, Whipple DA, Doty JL, Sun J, Kent CR, Magnuson KS, Perregaux DG, Sawyer PS, Kudlacz EM. The specificity of JAK3 kinase inhibitors. *Blood* 2008; **111**: 2155-2157 [PMID: 18094329 DOI: 10.1182/blood-2007-09-115030]

160 **Sewgobind VD**, Quaedackers ME, van der Laan LJ, Kraaijeveld R, Korevaar SS, Chan G, Weimar W, Baan CC. The Jak inhibitor CP-690,550 preserves the function of CD4CD25FoxP3 regulatory T cells and inhibits effector T cells. *Am J Transplant* 2010; **10**: 1785-1795 [PMID: 20626385 DOI: 10.1111/j.1600-6143.2010.03200.x]

161 **Sandborn WJ**, Ghosh S, Panes J, Vranic I, Spanton Ch, Niezychowski W. Phase 2 randomized study of CP-690,550, an oral janus kinase inhibitor, in active Crohn’s disease. *Gastroenterology* 2011; **140**: S110 [DOI: 10.1016/S0016-5085(11)60445-9]

162 **Sandborn WJ**, Ghosh S, Panes J, Vranic I, Su C, Rousell S, Niezychowski W; Study A3921063 Investigators. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. *N Engl J Med* 2012; **367**: 616-624 [PMID: 22894574 DOI: 10.1056/NEJMoa1112168]

163 **Panés J**, Su C, Bushmakin AG, Cappelleri JC, Mamolo C, Healey P. Randomized trial of tofacitinib in active ulcerative colitis: analysis of efficacy based on patient-reported outcomes. *BMC Gastroenterol* 2015; **15**: 14 [PMID: 25651782 DOI: 10.1186/s12876-015-0239-9]

164 **Mannon P**, Reinisch W. Interleukin 13 and its role in gut defence and inflammation. *Gut* 2012; **61**: 1765-1773 [PMID: 22942239 DOI: 10.1136/gutjnl-2012-303461]

165 **Sandborn WJ**, Colombel JF, Enns R, FEagan B, Hanauer S, Lawrance I, Panaccione R, Sander M, Schreiber S, Targan S, Van Deventer S, Goldblun R, Despain D, Hogge G, Rutgeerts P. Natalizumab induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2015; **372**: 2074 [PMID: 25992761 DOI: 10.1056/NEJMx140055]

166 **Targan SR**, Feagan BG, Fedorak RN, Lashner BA, Panaccione R, Present DH, Spehlmann ME, Rutgeerts PJ, Tulassay Z, Volfova M, Wolf DC, Hernandez C, Bornstein J, Sandborn WJ. Natalizumab for the treatment of active Crohn's disease: results of the ENCORE Trial. *Gastroenterology* 2007; **132**: 1672-1683 [PMID: 17484865 DOI: 10.1053/j.gastro.2007.03.024]

167 **Kleinschmidt-DeMasters BK**, Tyler KL. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis. *N Engl J Med* 2005; **353**: 369-374 [PMID: 15947079 DOI: 10.1056/NEJMoa051782]

168 **Van Assche G**, Van Ranst M, Sciot R, Dubois B, Vermeire S, Noman M, Verbeeck J, Geboes K, Robberecht W, Rutgeerts P. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. *N Engl J Med* 2005; **353**: 362-368 [PMID: 15947080 DOI: 10.1056/NEJMoa051586]

169 **Lobatón T**, Vermeire S, Van Assche G, Rutgeerts P. Review article: anti-adhesion therapies for inflammatory bowel disease. *Aliment Pharmacol Ther* 2014; **39**: 579-594 [PMID: 24479980 DOI: 10.1111/apt.12639]

170 **Feagan BG**, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, Van Assche G, Axler J, Kim HJ, Danese S, Fox I, Milch C, Sankoh S, Wyant T, Xu J, Parikh A. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2013; **369**: 699-710 [PMID: 23964932 DOI: 10.1056/NEJMoa1215734]

171 **Sandborn WJ**, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, Lukas M, Fedorak RN, Lee S, Bressler B, Fox I, Rosario M, Sankoh S, Xu J, Stephens K, Milch C, Parikh A. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2013; **369**: 711-721 [PMID: 23964933 DOI: 10.1056/NEJMoa1215739]

172 **Pan WJ**, Köck K, Rees WA, Sullivan BA, Evangelista CM, Yen M, Andrews JM, Radford-Smith GL, Prince PJ, Reynhardt KO, Doherty DR, Patel SK, Krill CD, Zhou K, Shen J, Smith LE, Gow JM, Lee J, Treacy AM, Yu Z, Platt VM, Borie DC. Clinical pharmacology of AMG 181, a gut-specific human anti-α4β7 monoclonal antibody, for treating inflammatory bowel diseases. *Br J Clin Pharmacol* 2014; **78**: 1315-1333 [PMID: 24803302 DOI: 10.1111/bcp.12418]

173 Available at: URL: https: //clinicaltrials.gov/ct2/show/NCT01696396?term=amg181&rank=3

174 Available at: URL: https: //clinicaltrials.gov/ct2/show/NCT01694485?term=amg181&rank=4

175 **Sugiura T**, Kageyama S, Andou A, Miyazawa T, Ejima C, Nakayama A, Dohi T, Eda H. Oral treatment with a novel small molecule alpha 4 integrin antagonist, AJM300, prevents the development of experimental colitis in mice. *J Crohns Colitis* 2013; **7**: e533-e542 [PMID: 23623333 DOI: 10.1016/j.crohns.2013.03.014]

176 **Watanabe M**, Yoshimura N, Motoya S, Tominaga K, Iwakiri R, Watanebe K, Hibi T. AJM300, an Oral α4 Integrin Antagonist, for Active Ulcerative Colitis: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 2A Study. *Gastroenterology* 2013; **146**; S82

177 **Vermeire S**, O’Byrne S, Williams M, Mansfield J, Feagan B, Panés J, Baumgart D, Schreiber S, Dotan I, Sandbron W, Keir M, Luca D, Rutgeers P. Differentiation between etrolizumab (rhuMAb beta7) and placebo in the Eucalyptus phase II randomized double-blind placebo-controlled induction study to evaluate efficacy and safety in patients with refractory moderate-to-severely active ulcerative colitis. *Gastroenterology* 2013; **144**: S-36 [DOI: 10.1016/S0016-5085(13)60130-4]

178 **Pullen N**, Molloy E, Carter D, Syntin P, Clemo F, Finco-Kent D, Reagan W, Zhao S, Kawabata T, Sreckovic S. Pharmacological characterization of PF-00547659, an anti-human MAdCAM monoclonal antibody. *Br J Pharmacol* 2009; **157**: 281-293 [PMID: 19366349 DOI: 10.1111/j.1476-5381.2009.00137.x]

179 **Vermeire S**, Sandborn W, Danese S, Hebuterne X, Salzberg B, Klopocka M, Tarabar D, Vanasek T, Gregus M, Hellstern P, Kim J-S, M. Sparrow M, Gorelick KJ, Ahmad A, Hassan-Zahraee M, Pradhan V, Cataldi F, Reinisch W. TURANDOT: a randomized, multicenter double-blind, placebo-controlled study of the safety and efficacy of Anti-MAdCAM Antibody PF-00547659 (PF) in patients with moderate to severe Ulcerative Colitis (UC). *J Crohns Colitis* 2015; Suppl 1: S13

180 **Brück W**, Wegner C. Insight into the mechanism of laquinimod action. *J Neurol Sci* 2011; **306**: 173-179 [PMID: 21429524 DOI: 10.1016/j.jns.2011.02.019]

181 **Yang JS**, Xu LY, Xiao BG, Hedlund G, Link H. Laquinimod (ABR-215062) suppresses the development of experimental autoimmune encephalomyelitis, modulates the Th1/Th2 balance and induces the Th3 cytokine TGF-beta in Lewis rats. *J Neuroimmunol* 2004; **156**: 3-9 [PMID: 15465591 DOI: 10.1016/j.jneuroim.2004.02.016]

182 **D’haens G**, Colombel J, Sandborn W, Rutgeerts P, Feagan B. Safety and efficacy of laquinimod in inducing clinical and biochemical improvement in active Crohn’s disease: results of an exploratory trial. *Gastroenterology* 2013; **144**: S21 [DOI: 10.1016/S0016-5085(13)60070-0]

183 **He SH**. Key role of mast cells and their major secretory products in inflammatory bowel disease. *World J Gastroenterol* 2004; **10**: 309-318 [PMID: 14760748]

184 **Beunk L**, Verwoerd A, van Overveld FJ, Rijkers GT. Role of mast cells in mucosal diseases: current concepts and strategies for treatment. *Expert Rev Clin Immunol* 2013; **9**: 53-63 [PMID: 23256764 DOI: 10.1586/eci.12.82]

185 **D'allard D**, Gay J, Descarpentries C, Frisan E, Adam K, Verdier F, Floquet C, Dubreuil P, Lacombe C, Fontenay M, Mayeux P, Kosmider O. Tyrosine kinase inhibitors induce down-regulation of c-Kit by targeting the ATP pocket. *PLoS One* 2013; **8**: e60961 [PMID: 23637779 DOI: 10.1371/journal.pone.0060961]

186 Available at: URL: https: //www.clinicaltrialsregister.eu/ctr-search/search?query=masitinib and crohn

187 **Baumgart DC**, Targan SR, Dignass AU, Mayer L, van Assche G, Hommes DW, Hanauer SB, Mahadevan U, Reinisch W, Plevy SE, Salzberg BA, Buchman AL, Mechkov GM, Krastev ZA, Lowder JN, Frankel MB, Sandborn WJ. Prospective randomized open-label multicenter phase I/II dose escalation trial of visilizumab (HuM291) in severe steroid-refractory ulcerative colitis. *Inflamm Bowel Dis* 2010; **16**: 620-629 [PMID: 19714757 DOI: 10.1002/ibd.21084]

188 **Baumgart DC**, Lowder JN, Targan SR, Sandborn WJ, Frankel MB. Transient cytokine-induced liver injury following administration of the humanized anti-CD3 antibody visilizumab (HuM291) in Crohn's disease. *Am J Gastroenterol* 2009; **104**: 868-876 [PMID: 19240707 DOI: 10.1038/ajg.2008.138]

189 **Blombery P**, Prince HM, Levinson M, Pianko S, Maxwell E, Bhathal P. Rituximab-induced immunodysregulatory ileocolitis in a patient with follicular lymphoma. *J Clin Oncol* 2011; **29**: e110-e112 [PMID: 21098319 DOI: 10.1200/JCO.2010.31.8899]

190 **El Fassi D**, Nielsen CH, Kjeldsen J, Clemmensen O, Hegedüs L. Ulcerative colitis following B lymphocyte depletion with rituximab in a patient with Graves' disease. *Gut* 2008; **57**: 714-715 [PMID: 18408106 DOI: 10.1136/gut.2007.138305]

191 **Ardelean DS**, Gonska T, Wires S, Cutz E, Griffiths A, Harvey E, Tse SM, Benseler SM. Severe ulcerative colitis after rituximab therapy. *Pediatrics* 2010; **126**: e243-e246 [PMID: 20566611 DOI: 10.1542/peds.2009-3395]

192 **Goetz M**, Atreya R, Ghalibafian M, Galle PR, Neurath MF. Exacerbation of ulcerative colitis after rituximab salvage therapy. *Inflamm Bowel Dis* 2007; **13**: 1365-1368 [PMID: 17604367 DOI: 10.1002/ibd.20215]

193 **Hanauer SB**, Sandborn WJ, Sands BE, Rutgeers P, Panaccione R, Bressler B, Whiteside M, Swanink R, Aranda R, Luo A. A randomized placebo-controlled trial of abatacept for moderately-to-severely active Crohn’s disease (CD). *Gastroenterology* 2010; **138**: S-86 [DOI: 10.1016/S0016-5085(10)60394-0]

194 **Sandborn WJ**, Colombel JF, Sands BE, Rutgeerts P, Targan SR, Panaccione R, Bressler B, Geboes K, Schreiber S, Aranda R, Gujrathi S, Luo A, Peng Y, Salter-Cid L, Hanauer SB. Abatacept for Crohn's disease and ulcerative colitis. *Gastroenterology* 2012; **143**: 62-69.e4 [PMID: 22504093 DOI: 10.1053/j.gastro.2012.04.010]

195 **Monteleone G**, Kumberova A, Croft NM, McKenzie C, Steer HW, MacDonald TT. Blocking Smad7 restores TGF-beta1 signaling in chronic inflammatory bowel disease. *J Clin Invest* 2001; **108**: 601-609 [PMID: 11518734 DOI: 10.1172/JCI12821]

196 **Monteleone G**, Fantini MC, Onali S, Zorzi F, Sancesario G, Bernardini S, Calabrese E, Viti F, Monteleone I, Biancone L, Pallone F. Phase I clinical trial of Smad7 knockdown using antisense oligonucleotide in patients with active Crohn's disease. *Mol Ther* 2012; **20**: 870-876 [PMID: 22252452 DOI: 10.1038/mt.2011.290]

197 **Monteleone G**, Neurath MF, Ardizzone S, Di Sabatino A, Fantini MC, Castiglione F, Scribano ML, Armuzzi A, Caprioli F, Sturniolo GC, Rogai F, Vecchi M, Atreya R, Bossa F, Onali S, Fichera M, Corazza GR, Biancone L, Savarino V, Pica R, Orlando A, Pallone F. Mongersen, an oral SMAD7 antisense oligonucleotide, and Crohn's disease. *N Engl J Med* 2015; **372**: 1104-1113 [PMID: 25785968 DOI: 10.1056/NEJMoa1407250]

198 **Sandborn W**, Feagan B, Wolf D, D'Haens G, Vermeire S, Hanauer S, Ghosh S, Smith H, Cravets M, Frohna P, Gujrathi S, Olson A. OP024. A randomized, double-blind, placebo-controlled induction trial of an oral S1P receptor modulator (RPC1063) in moderate to severe Ulcerative Colitis: Results of the TOUCHSTONE study. *J Crohns Colitis* 2015; Suppl 1: S15

199 **Vermeire S**, Kojecky V, Knoflicek V, Reinisch W, Van Kaem T, Namour F, Beetens J, Vanhoutte F. DOP030. GLPG0974, an FFA2 antagonist, in ulcerative colitis: efficacy and safety in a multicenter proof-of-concept study. *J Crohns Colitis* 2015; Suppl 1: S39

200 **Martínez-Montiel Mdel P**, Gómez-Gómez GJ, Flores AI. Therapy with stem cells in inflammatory bowel disease. *World J Gastroenterol* 2014; **20**: 1211-1227 [PMID: 24574796 DOI: 10.3748/wjg.v20.i5.1211]

201 **Flores AI**, Gómez-Gómez GJ, Masedo-González Á, Martínez-Montiel MP. Stem cell therapy in inflammatory bowel disease: A promising therapeutic strategy? *World J Stem Cells* 2015; **7**: 343-351 [PMID: 25815119 DOI: 10.4252/wjsc.v7.i2.343]

202 **Ng SC**, Lam YT, Tsoi KK, Chan FK, Sung JJ, Wu JC. Systematic review: the efficacy of herbal therapy in inflammatory bowel disease. *Aliment Pharmacol Ther* 2013; **38**: 854-863 [PMID: 23981095 DOI: 10.1111/apt.12464]

203 **Michelsen KS**, Wong MH, Ko B, Thomas LS, Dhall D, Targan SR. HMPL-004 (Andrographis paniculata extract) prevents development of murine colitis by inhibiting T-cell proliferation and TH1/TH17 responses. *Inflamm Bowel Dis* 2013; **19**: 151-164 [PMID: 23292349 DOI: 10.1002/ibd.22983]

204 **Rossen NG**, MacDonald JK, de Vries EM, D'Haens GR, de Vos WM, Zoetendal EG, Ponsioen CY. Fecal microbiota transplantation as novel therapy in gastroenterology: A systematic review. *World J Gastroenterol* 2015; **21**: 5359-5371 [PMID: 25954111 DOI: 10.3748/wjg.v21.i17.5359]

205 **Angelberger S**, Reinisch W, Makristathis A, Lichtenberger C, Dejaco C, Papay P, Novacek G, Trauner M, Loy A, Berry D. Temporal bacterial community dynamics vary among ulcerative colitis patients after fecal microbiota transplantation. *Am J Gastroenterol* 2013; **108**: 1620-1630 [PMID: 24060759 DOI: 10.1038/ajg.2013.257]

206 **Vermeire S**, Joossens M, Verbeke K, Hildebrand F, Machiels K, Van den Broeck K, Van Assche G, Paul J. Rutgeerts, Jeroen Raes23. Pilot Study on the Safety and Efficacy of Faecal Microbiota Transplantation in Refractory Crohn. *Gastroenterology* 2012; **142** Suppl 5: S360 [DOI: 10.1016/S0016-5085(12)61356-0]

207 **Greenberg A**, Aroniadis O, Shelton C, Brandt LJ. Long-term followup study of fecal microbiota transplantation (FMT) for Inflammatory Bowel Disease (IBD). ACG Annu Sci Meet Abstr 2013; San Diego, EEUU. P1629

208 **Borody TJ**, Warren EF, Leis S, Surace R, Ashman O. Treatment of ulcerative colitis using fecal bacteriotherapy. *J Clin Gastroenterol* 2003; **37**: 42-47 [PMID: 12811208 DOI: 10.1097/00004836-200307]

209 **Kunde S**, Pham A, Bonczyk S, Crumb T, Duba M, Conrad H, Cloney D, Kugathasan S. Safety, tolerability, and clinical response after fecal transplantation in children and young adults with ulcerative colitis. *J Pediatr Gastroenterol Nutr* 2013; **56**: 597-601 [PMID: 23542823 DOI: 10.1097/MPG.0b013e318292fa0d]

210 **Kump PK**, Gröchenig HP, Lackner S, Trajanoski S, Reicht G, Hoffmann KM, Deutschmann A, Wenzl HH, Petritsch W, Krejs GJ, Gorkiewicz G, Högenauer C. Alteration of intestinal dysbiosis by fecal microbiota transplantation does not induce remission in patients with chronic active ulcerative colitis. *Inflamm Bowel Dis* 2013; **19**: 2155-2165 [PMID: 23899544 DOI: 10.1097/MIB.0b013e31829ea325]

211 **Kump PK**, Gröchenig HP, Spindelböck W, Gorkiewicz G, Wenzl H, Petritsch W, Reicht G. Preliminary clinical results of repeatedly fecal microbiota transplantation (FMT) in chronic active ulcerative colitis. *United* *European Gastroenterol J* 2013; **1** Suppl 1: A57 [DOI: 10.1177/2050640613502899]

**P-Reviewer:** Lakatos PL, Marie JC **S-Editor:** Ma YJ **L-Editor:** **E-Editor:**

**Table 1 azatioprine treatment basis of individuals thiopurine methyltransferase status**

|  |  |  |
| --- | --- | --- |
| **TMPT genotype** | **TPMT fenotype (activity) (pmol/mgHb)** | **Treatment dosis****(mg/kg)** |
| Homozygous | < 10 | Avoid or consider 0.1-0.2 |
| Heterozygous | 10-24 | 1-1.5 |
| Wild type (Normal) | 25-35 | 2-2.5 |
| Wild type (High) | > 35 | 0.5 + 100 mg Allopurinol |

TMPT: thiopurine methyltransferase.

**Table 2 Genetic association studies of adverse events secondary to azathioprine in inflammatory bowel disease patients**

|  |  |  |  |
| --- | --- | --- | --- |
| **study (year)** | **nº patients** | **conclusion** | **ref** |
| Mariniki *et al* (2004) | 130 | Significant association with flu-illness, rash and pancreatitis.No association with mielotoxicity | [34] |
| Allorge *et al* (2005) | 72 | No association with flu-illness, rash, pancreatitis or mielotoxicity | [35] |
| Gearry *et al*(2004) | 147 | No association with flu-illness, rash and pancreatitis | [36] |
| De Ridder *et al* (2006) | 72 | No association with side effects | [37] |
| Hindorf *et al*(2006) | 60 | No association with side effects | [38] |
| Von Ahsen *et al* (2005) | 71 | Early withdrawal of therapy but not association with specific adverse events | [39] |
| Ansari *et al* (2008) | 202 | Association with flu-like symptoms but not withdrawal of therapy | [40] |
| Van Dieren *et al* (2005) | 109 | Not associated with an increased risk for the development of leucopenia and other side effects. | [41] |
| Zelinkova *et al* (2006) | 262 | Increased risk of leucopenia | [42] |
| Uchiyama *et al* (2009) | 16 | Increase risk of mielotoxicity (leucopenia) | [43] |
| Shipkova *et al* (2011) | 160 | Increase risk of mielotoxicity | [44] |
| Kim *et al* (2010) | 248 | No association with leucopenia | [45] |
| Zabala-Fernandez *et al* (2011) | 232 | Significant association with artralgia | [46] |

|  |
| --- |
| **Table 3 Genetic association studies of infliximab response in inflammatory bowel disease patients** |
| **study (year)** | **patients****recruited** | **response****criteria** | **genes****investigated** | **conclusion** | **ref** |
| **Taylor *et al*****(2001)** | 75 | CDAI | Polymorphims TNF/LTA region | Homozygosity for the LTA1-1-1-1 haplotype may identify subgroups with poorer response | 54 |
| **Louise *et al* (2002)** | 226 | CDAI | TNFA | No association with treatment outcome | 55 |
| **Mascheretti *et al* (2002)** | 90444 | CDAI | TNF and TNFR polymorphism | 196Arg homozygotes had poorer clinical response than 196Metheterozygotes and homozygotes (*P =* 0.036).No predictive treatment outcome | 56 |
| **Mascheretti *et al* (2002)** | 534 | CDAI | CARD15/NOD2 | A strong relation to susceptibility to CD but not association with treatment outcome | 57 |
| **Vermeire *et al* (2002)** | 245 | CDAI | CARD15/NOD2 | Not predictive of treatment outcome | 58 |
| **Pierik *et al* (2004)** | 166 | CDAI | TNF/TNFR | Biological response to infliximab was lower in patients carrying *TNFR1*-36G. | 59 |
| **Matsukura *et al* (2008)** | 80 | HBI | TNFRSF1ATNFRSF1B | 28% of G allele heterozygotes and homozygotes respondedcompared to 73% of A allele homozygotes (*P =* 0.04)5% of patients with AT haplotype responded compared to 20%–40% of patients with other haplotypes (*P =* 0.01) | 60 |
| **Louise *et al* (2004)** | 200 | CDAI | FcɣRIIIa | Positive (V/V genotype) association with good treatment outcome | 61 |
| **Urcelay *et al* (2005)** | 40 | CDAI | IBD5(5q31) | Polymorphims TT is associated with negative response | 62 |
| **Hlavaty *et al* (2005)** | 287 | CDAI | FASL/CASP9 | Positive association | 63 |
| **Hlavaty *et al* (2007)** | 287 | CDAI | FASL | Negative association (stadistical model) | 64 |
| **Willot *et al* (2006)** | 189 | CRP | CRP | Polymorphims evaluated are not associated with treatment outcome | 65 |
| **Dideverg V *et al* (2006)** | 214 | CDAI | TNF/LTA region | No association |  66 |
| **Dideverg V *et al* (2006)** | 186 | CDAI and CRP | ADAM17 | Minor allele homozygotes for each SNP associated with clinicalresponse (*P <* 0.002) |  67 |
| **Jürgens *et al* (2010)** | 90 | CAI | IL-23RIL-2/IL-21 | Homozygous carriers of IBDrisk-increasing *IL-23R* variants more likely to respond to infliximab than homozygous carriers of IBD risk-decreasing *IL-23R* variants (*p =* 0.001). | 68 |
| **Dubinski *et al* (2010)** | 94 | HBI and Partial Mayo score | rs2241880 2q37/*ATG16L1*rs21889625q31rs6908425 6p22/*CDKAL1*rs762421 21q22/*ICOSLG*rs2395185 6p21/*HLA-DAQ1*rs2836878 21q22/*BRWD1* | Six known susceptibility lociassociated with primary nonresponse(*p <* 0.05). Only the 21q22.2/*BRWDI*loci remained significant in thepredictive model | 69 |

Aailable from: URL: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4419078/>

**Table 4 Risk factors associated to primary failure**

|  |  |
| --- | --- |
| **Crohn's disease** | **Ulcerative colitis** |
| * Duration of the disease > 2 yr
* Smoking
* Extensive small bowel involvement
* Low C‑reactive protein levels
* Genetic mutations or polymorphisms of the apoptosis and caspase 6 genes and locus IBD 5
 | * Old age
* Anti‑neutrophil cytoplasmic (ANC) antibodies
* Negative antibodies against *Saccharomyces cerevisiae*
* Previous exposure to anti‑TNF‑α drugs
 |

IBD: inflammatory bowel disease.

**Table 5 Risk factors associated to secondary failure or loss of response**

* Individual differences in bioavailability and pharmacokinetics
* Symptoms not due to inflammatory bowel disease
* Lack of adherence to therapy
* Drug loss in stools
* Intermittent treatments
* Non‑inflammatory symptoms
* Structuring disease pattern
* Smoking
* Development of antibodies

**Table 6 Treatment algorithm according to antidrug antibodies and drug levels**

|  |  |  |
| --- | --- | --- |
| **Anti‑TNF‑α drug levels** | **Antibodies** | **Action** |
| **Low** | Negative | Increase dose |
| **Low** | Positive | Switch drug  |
| **High** | Not determined | Switch to a drug with a different mechanism of action |

**Table 7 Treatment with herbal remedies**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Author** | ***n*** | **Producto** | **Comparador** | **Indicación**  | **Remisión/response herbal *vs* PB or drug (%)** |
| Langmead | 44 | Aloe vera | Placebo | Induction remission CU | 30 *vs* 7 |
| Ben-Arye | 23 | Triticum aestivum | Placebo | Induction remission CU | 91 *vs* 42 |
| Khan | 14 | Bovine colostrum enema | Placebo | Induction remission CU |  |
| Sandborn | 224 | HMPL-004 | Placebo | Induction remission CU | 38/60 *vs* 25/40 |
| Fukunaga | 30 | Xilei-san suppository | Placebo | Induction remission CU | 46 *vs* 0 |
| Zhang | 35 | XIlei-san enema | Enema dexametasona | Induction remission CU |  |
| Tang | 120 | HMPL-004 | Mesalazina | Induction remission CU | 21 *vs* 16 |
| Gupta | 30 | Boswellia serrata | Sulfasalazina | Induction remission CU | 70 *vs* 40 |
| Cheng | 153 | Jian Pi Ling tablet | SulfasalazinaPlacebo | Induction remission CU | 53 *vs* 28/19 |
| Wang | 106 | Kui Jie Quing enemas | SulfasalazinaPrednisolona | Induction remission CU | 72 *vs* 9 |
| Cheng | 118 | Yukui tang ablets | PrednisolonoaNeomicinaVitamina B | Induction remission CU | 33 *vs* 17 |
| Fernández Bañares | 105 | Plantago ovata sedes | Mesalazine | Maintenance remission CU | 60 *vs* 65 |
| Hanai | 89 | Curcumin | Placebo | Maintenance remission CU | 95 *vs* 79 |
| Greenfield | 43 | Oenothera biennis | Evening primrose oil and olive oil | Maintenance remission CU |  |
| Omer | 40 | Artemisia absinthium | Placebo | Treatment and prevention recurrence EC | 65 *vs* 0 |
| Krebs | 20 | Artemisia absinthium | Placebo | Treatment and prevention recurrence EC | 80 *vs* 20 |
| Gerhardt | 102 | Boswellia serrata extract | Mesalazine | Treatment and prevention recurrence EC | 36 *vs* 31 |
| Ren | 20 | Tripterygium wilfordii | Placebo | Treatment and prevention recurrence EC |  |
| Holtmeier | 108 | Boswellia serrata extract | Placebo | Treatment and prevention recurrence EC | 60 *vs* 55 |
| Tao | 45 | Tripterygium wilfordii | Mesalazine | Treatment and prevention recurrence EC | 68 *vs* 61 |
| Liao | 39 | Tripterygium wilfordii | Sulphasalazine | Treatment and prevention recurrence EC | 94 *vs* 75 |

Adapted from Ng *et al*[202].



**Figure 1 Metabolism of azatioprine and 6-mercaptopurine.** AZA: Azathioprine; 6-MP: 6- mercaptopurine; 6-MeMP: 6- Methylmercaptopurine; 6-TU: 6-thiouric acid; 8-OH 6MP: 8-hydroxymercaptopurine; 6Me-tIMP: 6-methyl thioinosine monophosphate; 6-tIMP: 6-thioinosine monophosphate; 6-TIDP: 6-thioinosine diphosphate; 6-TITP: 6-thioinosine triphosphate; 6-MeTITP: 6-methylthioinosine triphosphate; tXMP: Thioxanthine monophosphate tGMP: thioguanine monophosphate; tGDP: Thioguanine diphosphate; tGTP: Thioguanine triphosphate; Me-tGMP: Methylthioguanine monophosphate; Deoxy-tGTP: Deoxythioguanine triphosphate; GST: Glutathione S-transferasa; TPMT: Thipurine methyltransferase; XDH: Xanthine dehydrogenase; AO: Aldehyde oxidase; HGPRT: Hypoxanthine guanine phosphoribosyltransferase; IMPDH: Inopine monophosphate dehydrogenase; GMPS: Guanosine monophosphate synthetase; PK: Phosphokinase; rPK: Reductase phosphokinase.

~~~~

**Figure 2 Algorithm of treatment for non responders patients to thiopurine drugs.** AZA: Azathioprine; 6-MP: 6-mercaptopurine; 6-TG: 6-thioguanine; 6-MeMp: 6-methyl mercaptopurine.



**Figure 3 True and false determination of antibodies according to drug levels.**