Inflammatory bowel disease: towards a personalized medicine

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Abstract: The management of inflammatory bowel disease (IBD) has been transformed over the last two decades by the arrival of tumor necrosis factor (TNF) antagonist agents. Recently, alternative drugs have been approved, directed at leukocyte-trafficking molecules (vedolizumab) or other inflammatory cytokines (ustekinumab). New therapeutics are currently being developed in IBD and represent promising targets as they involve other mechanisms of action (JAK molecules, Smad 7 antisense oligonucleotide etc.). Beyond TNF antagonist agents, these alternative drugs are needed for early-stage treatment of patients with aggressive IBD or when the disease is resistant to conventional therapy. Personalized medicine involves the determination of patients with a high risk of progression and complications, and better characterization of patients who may respond preferentially to specific therapies. Indeed, more and more studies aim to identify factors predictive of drug response (corresponding to a specific signaling pathway) that could better manage treatment for patients with IBD. Once treatment has started, disease monitoring is essential and remote patient care could in some circumstances be an attractive option. Telemedicine improves medical adherence and quality of life, and has a positive impact on health outcomes of patients with IBD. This review discusses the current application of personalized medicine to the management of patients with IBD and the advantages and limits of telemedicine in IBD.

Keywords: Crohn's disease, inflammatory bowel disease, personalized medicine, remote patient care, telemedicine, ulcerative colitis

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Introduction

Inflammatory bowel disease (IBD) is caused by a dysregulation of the immune system inducing the production of proinflammatory cytokines and adhesion molecules. Tumor necrosis factor α (TNFα) was identified in the late 1990s as a pro-inflammatory cytokine playing a key role in the inflammatory process in IBD. Beyond aminosalicylates, corticosteroids and immunosuppressive agents (azathioprine, mercaptopurine and methotrexate), the last two decades have been marked by the development of inhibitors of TNF antagonists, which, since the beginning of the 2000s, have revolutionized the management of IBD. A better understanding of the mucosal immune response in IBD has, more recently, led to the development of new drugs directed at inflammatory cytokines and leukocyte-trafficking molecules. Among these, vedolizumab acts by blocking the interaction between an integrin present on the surface of gut-specific lymphocytes and a receptor on the vascular endothelium of the intestinal tract (α4β7 and MAdCAM-1, respectively), and ustekinumab is directed against the common p40 subunit of interleukin (IL)-12 and IL-23. Other promising targets for new therapeutic strategies are currently being developed, such as JAK/STAT signaling pathway inhibitors (tofacitinib, filgotinib, upadacitinib etc.), an integrin inhibitor [β7 integrin inhibitor (etrolizumab)], and a sphingosine 1-phosphate receptor modulator that is a selective small molecule immunomodulatory agonist for G protein-coupled S1P receptor (S1P1), leading to internalization of the S1P1 receptor present on the surface of C-C chemokine receptor type 7 positive lymphocytes and trapping these lymphocytes in lymph nodes. A recent review provides an update on the current status in

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clinical development of these new classes of therapeutics.[1] With the development of multiple new therapies that have different mechanisms of action there is an interest in better characterizing patients and selecting those who may respond preferentially to specific therapies. Indeed, some patients may not respond to a specific therapy (primary nonresponders) or lose the initial response over time (secondary nonresponders). For example, the incidence of primary nonresponse for TNF antagonist therapy varies between clinical trial and clinical practice from 10 to 30%,[2–4] and the annual risk of secondary nonresponse from 13% per patient year for infliximab (IFX)[5] to 20.3% for adalimumab.[6] Thus, to avoid the risk of nonresponse to a drug, it is likely that it would be better to choose the most suitable therapy for each patient at the initiation of the therapy or at loss of response, strengthening the concept of personalized medicine. Indeed, personalized medicine is a relatively new concept that has the potential to optimize efficacy, decrease the risk of adverse drug events, and reduce costs if the treatment is the most suitable therapy for a selected patient. Once treatment has started, personalized medicine also incorporates a personalized support for the patient. A tight and personalized control of disease activity is warranted to prevent long-term complications and improve quality of life (QoL). For example, the development of a telemedicine system for patients with IBD has been shown to improve medical adherence and could be essential in the future for the management of patients with IBD. This review discusses the concept of personalized medicine in IBD in the context of improved quality of clinical practice and targeted-care pathways.

Table 1. Factors predictive of disabling disease and nonresponse to TNF antagonists.

Factors predictive of disabling disease
Extensive disease
Upper gastrointestinal involvement
Smoking
Younger age at diagnosis
Perianal disease
Stricturing or penetrating disease
Factors predictive of primary nonresponse to TNF antagonists
Longer disease duration (>2 years)
Small bowel involvement
Smoking
Normal CRP
Genetic mutations (FAS-L, caspase 9)

CRP, C-reactive protein; TNF, tumor necrosis factor; FAS-L, fatty acid synthase-ligand.

Personalized medicine in selecting the therapy

Considering the characteristics of the patient and the disease

The last few decades have been marked by major therapeutic advances for the management of IBD. These advances are due to an enhancement of the panel of treatments available and in addition to a better knowledge of the therapeutic strategies for the most active IBD cases or those with some characteristics of aggressive disease that could lead to irreversible damage. The course of the disease is variable, with some patients having much more aggressive disease than others. However, the main difficulty in managing IBD is the early detection of patients with potentially severe disease. It is likely that disease outcome is variable between patients and, although some criteria have been defined as predictors of disabling disease (Table 1), sufficient data are not yet available to allow an accurate prediction of disease severity for a specific patient at the stage of disease diagnosis. Thus, some patients with criteria considered as potentially severe could in fact have a favorable outcome, while the converse is also possible. Some risk factors of complicated Crohn's disease (CD) have been demonstrated to be associated with a poor prognosis, including younger age at diagnosis, extensive disease, upper gastrointestinal involvement, smoking, fistulizing or stricturing phenotype, perianal disease, and the need for corticosteroids.[7–10] For ulcerative colitis (UC), a *post hoc* analysis of the pivotal Active Ulcerative Colitis Trials (ACTs) for the efficacy of IFX demonstrated that the risk of colectomy was associated with a C-reactive protein (CRP) level above 20 mg/liter, the need for corticosteroids at inclusion, the presence of a Mayo score greater than 10, and a recent diagnosis (<3 years).[11] Similarly, in the inflammatory bowel South-Eastern Norway (IBSEN) cohort, four factors were associated with a higher risk of colectomy: extent of disease, age (<40 years), need for systemic steroids, and CRP (⩾30 mg/liter) or erythrocyte sedimentation rate

(⩾30 mm/h) at diagnosis.[12,13] Endoscopic findings can also help to predict disease behavior. In particular, the presence of deep ulcerations in CD has been demonstrated to be predictive of more aggressive disease, with a higher risk of developing penetrating disease.[14] Conversely, in UC, with the arrival of TNF antagonists, the severity of inflammation at initial colonoscopy did not seem to markedly affect the outcome.[15] Biomarkers might also be helpful to identify patients who are at risk of a complicated disease course. In particular, numerous studies have indicated that anti-Saccharomyces cerevisiae antibodies (ASCA) positivity and newly discovered antibodies such as CBir1, Anti-OmpC antibody or anti-I2 in CD are correlated with a higher risk of stricturing, penetrating disease and small bowel resection.[16–18] Similarly, antichitobioside carbohydrate antibody (ACCA), antilaminaribioside carbohydrate antibodies (ALCA), antimannobioside carbohydrate antibodies (AMCA) and gASCA have also been associated with complicated disease and surgery.[19] However, although these biological markers are recognized as indicating a risk of a complicated disease course, they are not routinely assessed.

Beyond the characteristics of the patients and the disease, some situations must be considered as special, and encourage a close monitoring of the disease. In CD, between 70% and 90% of patients will require surgery during their lifetime. Surgery is often considered as a last-resort treatment for CD, in the case of failure of medical treatment or consecutive to a disease complication. In the postoperative course, monitoring of the anastomosis by colonoscopy is recommended to detect an endoscopic relapse and to adapt the treatment. It is likely that the goal of therapeutic management in the postoperative course is to avoid repeat surgery. Some clinical factors have been established as associated with risk of recurrence in this situation: according to the second European evidence-based consensus on the diagnosis and the management of CD, these factors are smoking, penetrating behavior of disease, perianal location, extensive small bowel resection and prior intestinal surgery.[20] In UC, another situation is the risk of pouchitis following ileal pouch anal anastomosis. This risk ranges from 14% to 59% and risk factors include the presence of extraintestinal manifestations, primary sclerosing cholangitis and nonsmoking.[21] These criteria justify special attention in the monitoring of patients.

Over the last two decades a change in the treatment strategy for patients with IBD has come under intense discussion. In 2004, D'Haens and colleagues evaluated the benefit of a top-down strategy (start with a combination of biological therapy and immunosuppressant and de-escalate if possible) compared with the standard step-up management (start with steroids and step up to immunosuppressant and biologics if necessary). These authors demonstrated that clinical remission rates without steroids were similar at week 104 but the mucosal healing rate was higher with the top-down strategy.[22,23] However, if a top-down strategy were recommended for all patients diagnosed with CD, a significant number of patients would be overtreated. In this context, it seems important to well characterize a population at high risk of a damaging disease course that will profit from a highly effective therapy.

Therefore, for patients with IBD and risk factors of complicated disease, the European Crohn's and Colitis Organization (ECCO) consensus recommends a highly effective therapy early in the course of the disease and the possible combining of therapeutics. The SONIC study demonstrated that a combination of IFX/immunosuppressor was more effective than IFX or immunosuppressor alone, both to achieve corticosteroid-free remission (56.8%, 44.4% and 30.0%, respectively) and mucosal healing (43.9%, 30.1% and 16.5%, respectively).[24] Indeed, the aim of a highly effective treatment early in the course of the disease by combining therapies is to offer the possibility to modify the disease course and then to avoid the risk of complications, hospitalizations and surgery.[25,26] The recent REACT study demonstrated that an early combined immunosuppression (ECI) was more effective than conventional management for controlling the risk of major adverse outcomes in CD, represented by surgery, hospital admission or serious disease-related complications (27.7% and 35.1%, respectively, $p = 0.0003$).[27] However, although the baseline characteristics of the patients were well balanced in both groups, most of the patients included had longstanding disease and prior intestinal resection. The findings of this study should thus be confirmed in patients who are newly diagnosed or have a shorter disease duration. Furthermore, in this study, the primary outcome, the proportion of patients in corticosteroid-free remission at 12 months, was not superior in the ECI group compared with the conventional management group (66% *versus* 61.9%; $p = 0.52$).

Considering the choice of drug

The last two decades have been marked by the arrival of TNF antagonist agents and more recently other therapeutic drugs targeting different pathways of inflammation. Beyond the inhibition of TNFα (anti-TNF agents), other treatments that have been approved for CD include a drug targeting IL-12/23 (ustekinumab) and another for CD and UC that blocks the α4β7 integrin present on the surface of gut-specific lymphocytes and the MAdCAM-1 receptor on the vascular endothelium (vedolizumab). More recently, the JAK/STAT signaling pathways represent another promising target, given that a large number of cytokines operate by activating JAK signaling during the inflammatory response. These new therapeutic options are of great value since they allow the envisaging of different sequences of therapy in the case of failure of one treatment. For example, in spite of the clinical efficacy of anti-TNF agents, around 10–30% of patients do not respond to the first biological therapy but could be responders to another therapeutic class. The question then arises, which molecules should be used as a first-line therapy in the future? Although all the immunosuppressive therapies that are currently approved for the treatment of CD are effective and could theoretically be used, it will be crucial to consider the right drug in appropriately selecting the initial therapy; that is, in determining predictive factors of response to targeted therapy. In the case of disease with aggressive factors, the treatment should be highly effective in order to avoid a delay that would allow the potential development of intestinal damage with irreversible consequences (perianal disease, extensive small bowel inflammation). In this case, it is likely that a drug with a certitude of efficacy will be the most suitable therapy.

In this context of personalized medicine, it is important to point out that some clinical trials are becoming more and more selective in their patient inclusion with respect to disease characteristics. For example, Gilead has just launched two phase II trials to evaluate filgotinib in the treatment of perianal fistulizing CD [ClinicalTrials.gov identifier: NCT03077412] and CD limited to the small bowel only [ClinicalTrials.gov identifier: NCT03046056]. In the future, with the results of such studies where the selection criteria have been tightened, the choice of drug could be made depending on disease location or disease behavior, strengthening the concept of personalized medicine.

In this context of personalized medicine, many studies have investigated predictive factors of therapeutic efficacy in comparing responders and nonresponders after the initiation of the therapy. Thus, a number of individual patient characteristics have been evaluated for an association with a response to TNF antagonist agents. Studies have demonstrated that young age, isolated CD colitis, and elevated CRP levels at the initiation of therapy are variables favoring a short-term response to IFX.[28,29] Conversely, smokers were less likely to respond than nonsmokers[30,31] and those with a disease duration longer than 2 years were less likely to respond than those with a shorter disease duration.[32] Genetic markers have also been evaluated to predict response to IFX but no gene has been found to be sufficiently relevant for use in clinical practice (Table 1).[33–35]

Other studies have evaluated some predictive factors of therapeutic efficacy at baseline (before the initiation of the therapy), demonstrating that gene expression profile, molecular imaging, and the microbiome could be of interest for this concept. Again, predictive factors of TNF antagonist agent response have been the most studied.

Thus, gene expression profiles could be of interest for response to IFX. In the study by Arjis and colleagues, the gene expression profiles from 37 patients with active CD (19 Crohn's colitis and 18 Crohn's ileitis) were compared before and after first IFX treatment. In Crohn's colitis, a top-five gene set (TNFAIP6, S100A8, IL11, G0S2, S100A9) was demonstrated to completely discriminate responders and nonresponders, with a 100% accurate predictive gene signature. Conversely, this study failed to identify a predictive gene set for Crohn's ileitis.[36] The same analysis was performed by the same authors for UC, showing that the top five differentially expressed genes between two cohorts of responders and nonresponders (osteoprotegerin, stanniocalcin-1, prostaglandin-endoperoxide synthase 2, IL-13 receptor α2, IL-11) could separate the two groups with 95% sensitivity and 85% specificity.[37] Similarly, Toedter and colleagues demonstrated that in UC, unlike responders, nonresponders did not show significantly modulated gene expression before and after IFX therapy, especially for the T_{H1}, T_{H2} and T_{H17} pathways.[38] However, although these studies allow a better understanding of the mechanisms of response and resistance to TNFα antagonist therapy, gene expression

profiling of patients with IBD is not yet used in clinical practice to differentiate response to IFX.

More recently, other studies have suggested that molecular imaging could be predictive of TNF antagonist agent efficacy. Molecular imaging is represented by single photon emission computed tomography (SPECT) and positron emission tomography (PET). These have mainly been evaluated to detect active disease in IBD.[39] However, Van den Brande and colleagues also tested whether the ability of rapid anti-TNF-induced apoptosis in the gut could predict the efficacy of anti-TNF treatment in IBD. In this study, (99 m)Technetium (Tc)-annexin V SPECT was performed in murine models and in 14 patients with CD; after IFX infusion, colonic (99 m)Tc-annexin V significantly increased in patients responding to therapy compared with nonresponders (mean increase of 98.7% in colonic uptake of marker in responders *versus* 15.2% in nonresponders, $p = 0.03$).[40] Molecular imaging has also been tested with topical fluorescent antibodies in order to predict response to the introduction of IFX in IBD.[41] Patients with high numbers of membrane-bound TNF immune cells detected by topical antibody administration showed significantly higher short-term response rates (92%) at week 12 upon subsequent anti-TNF therapy compared with patients with low cell counts (15%): the high membrane-bound TNF (mTNF) group had a significantly lower Crohn's disease activity index (CDAI) score than the low mTNF group at week 12 (92 *versus* 249; $p = 0.02$), a significant reduction in steroid use ($p = 0.04$), and a sustained remission ($p = 0.04$). Sensitivity and specificity for the prediction were 92% and 85%, respectively. This *in vivo* molecular imaging thus has the potential to individualize specific therapies based on molecular-level analysis.

Similarly, some studies are evaluating the effects of anti-integrin therapies at a molecular level. A recent study aimed to identify the immunophenotype, cytokine production and cytokine responsiveness of lymphocyte subpopulations that do *versus* do not bind vedolizumab in the peripheral blood of patients with CD, and demonstrated that circulating integrin $\alpha4\beta7^+$ lymphocytes targeted by vedolizumab had a proinflammatory phenotype. In the randomized, controlled, phase II trial of another anti-integrin therapy, etrolizumab, a humanized monoclonal antibody that selectively binds the β7 subunit of the heterodimeric integrins α4β7 and αEβ7, the presence of baseline colonic αE expression detected by flow cytometry assays improved response to the drug. Indeed, in this study etrolizumab reduced αE^+ cell association with the intestinal epithelium, suggesting that $\alpha E\beta7^+$ lymphocytes contribute to the physiopathology of UC.[42] In a concept of personalized medicine it is then interesting to consider that therapeutic antibody targets like ustekinumab, anti-integrin or anti-JAK could be tested at a molecular level to determine the best pathway of inflammation to treat for a patient needing a targeted therapy.

The gut microbiome has also been evaluated to predict outcome and therapeutic response in IBD. Over the last decade, increasing numbers of studies have highlighted the role of the gut microbiome in IBD. These microbial studies have determined the normal composition of the gut microbiome and its perturbations in the setting of IBD. In particular, the most well defined change that has been noted in patients with CD is the reduced abundance of *Firmicutes* compared with controls, especially *Faecalibacterium prausnitzii*. Several trials have studied the role of pro- and prebiotics, antibiotics and fecal transplantation in CD treatment. However, few studies have analyzed the role of the microbiome to predict the course of IBD. A subanalysis of the prospective STORI study, which aimed to identify predictive factors of clinical relapse after IFX discontinuation, evaluated the gut microbiota composition of 33 patients with CD and 29 control subjects. A low level of *F. prausnitzii* ($p = 0.014$) and a low level of *Bacteroides* ($p = 0.030$) predicted relapse independently of high CRP level ($p = 0.0001$).[43] In another longitudinal prospective cohort of 19 patients with newly diagnosed IBD, Shaw and colleagues demonstrated that patients with IBD had dysbiosis compared with controls and analysis of the microbiome at baseline could potentially be used to predict a response in treatment-naive patients. The authors found differences in specific gut microbiome genera between responders and nonresponders, including in particular, *Akkermansia*.[44] Similarly, Ananthakrishnan and colleagues conducted a prospective study with 42 patients with CD and 43 patients with UC initiating anti-integrin therapy (vedolizumab). Among 31 patients with CD achieving week 14 remission, community α diversity at baseline was significantly higher, and *Roseburia inulinivorans* and a *Burkholderiales* species were two more abundant species. However, this did not achieve statistical significance in UC. The authors supposed that a

more diverse microbiome composition at baseline may reflect prevalent microbes or metabolites with an anti-inflammatory effect on colonic inflammation and a less disrupted mucosal barrier, leading to a greater treatment response. The findings of this study strengthen the concept that the gut microbiome plays a role of initiation and propagation of luminal inflammation, and can be regulated by biological therapy. In demonstrating the association between baseline gut microbiome composition and clinical remission, the authors suggested incorporating both clinical and microbiome data in predicting clinical remission.[45]

Personalized medicine in the monitoring therapy

Monitoring of remission in patients with IBD

Over the last decade, many strategic studies on the use of IBD therapy have been carried out, particularly for TNF antagonist agents. In these studies, the therapeutic strategy has been completely changed. Indeed, with the arrival of TNF antagonist agents, the goal of the treatment is to obtain a deep remission for patients with IBD and to avoid the risk of disease complications in the long term, represented by the bowel damage related to inflammation both in CD and UC. Deep remission leads to a better QoL, lower need for hospitalization and surgery, and lower rate of colorectal cancer. Beyond the absence of symptoms of disease activity, parameters of remission for assessing the response to treatment are becoming essential.

In the context of personalized medicine, therapeutic goals have been proposed by a group of IBD experts, the International Organization for the Study of IBD (IOIBD) group. The aim of this consensus was to define the role of several parameters of remission in the management of the disease and to suggest a target to reach for a patient with IBD. In CD, the targets proposed by the group of experts were represented by clinical remission, defined in the patient-reported outcome as resolution of abdominal pain and diarrhea/altered bowel habit due to the disease activity; endoscopic remission or 'mucosal healing' defined as resolution of ulceration at ileocolonoscopy or resolution of findings of inflammation on cross-sectional imaging in patients who cannot be adequately assessed with ileocolonoscopy. In UC, the targets proposed by the group of experts were clinical remission, defined as resolution of rectal bleeding and diarrhea/altered bowel habit (related to the disease activity), and endoscopic remission (mucosal healing), defined as a Mayo endoscopic subscore of 0 or 1. However, these targets should be considered as an aid in the management of our patients and it is likely that the response to an induction therapy is extremely variable between patients.

Therefore, it is likely that the management of patients with IBD is currently focused on more objective rather than subjective parameters, such as normalization of laboratory evidence of inflammation [CRP, fecal calprotectin (FC) etc.], mucosal healing, histologic healing and normalization/stabilization of imaging.

Biologic remission. Biologic parameters are widely available and relatively inexpensive to evaluate, and allow regular monitoring of patients with IBD. Louis and colleagues found that after induction therapy with a TNF antagonist, the response rate to IFX was significantly higher in patients with an elevated (>5 mg/liter) compared with normal (<5 mg/liter) CRP value before treatment (76% *versus* 46%; $p = 0.004$).[29] Other studies have demonstrated that early normalization of CRP level is correlated with a sustained long-term response ($p < 0.001$),[46] without the need for therapeutic adjustment.[47] Similarly, studies have evaluated the interest of FC measurement to predict IBD outcome in clinical practice. Molander and colleagues demonstrated that normalization of FC (<100 μg/g) after induction therapy with TNF antagonist was predictive of sustained clinical remission after 12 months compared with an elevated postinduction FC level (88% *versus* 38%; $p < 0.0001$).[48] Additionally, for patients with IBD in remission, elevated FC is a predictor of relapse during follow up[49] or before anti-TNF discontinuation.[50] However, it is likely that these biologic parameters should be considered merely as helpful for management of the disease, but an abnormality of one of them alone should not lead to a therapeutic modification.

Endoscopic remission. In contrast to corticosteroids,[51] azathioprine is capable of inducing and maintaining mucosal healing in CD, but this effect may take months to be achieved and appears to be modest (only 16.5% of patients at week 26 in the SONIC trial).[24] However, interestingly, D'Haens and colleagues demonstrated that successful azathioprine therapy defined by clinical remission was often accompanied by complete mucosal healing

(in the colon in 70% of patients and in the ileum in 54% of patients).[52] In patients with CD, methotrexate seems to have less efficacy to induce mucosal healing than azathioprine or TNF antagonists.[53] In randomized clinical trials, the effect of TNF antagonists on mucosal healing in CD has mostly been studied as a secondary endpoint (except for the EXTEND study for CD, which used complete mucosal healing as a primary endpoint). In this study (EXTEND) and in an ACCENT 1 substudy, mucosal healing was achieved in 24% of patients at 52 weeks who received adalimumab[54] and 50% of patients at 54 weeks who received scheduled IFX, respectively.[55] However, the mucosal healing may be merely partial and Schnitzler and colleagues demonstrated that mucosal healing induced by IFX treatment, even when partial, was also associated with an improved long-term outcome of the disease.[56] Thus, it seems essential to achieve at least an endoscopic improvement with the induction therapy.

In contrast to CD, many studies have demonstrated that mesalazine is capable of promoting mucosal healing in UC, with variability in rates due to the design of the studies (up to 80%).[57–59] It is important to note that the Mayo score of 1 was included in the definition of mucosal healing in these studies, which includes mild erythema and friability. Similarly, azathioprine is capable of inducing mucosal healing in up to half of patients with UC treated for at least 6 months, which can be maintained over time.[60,61] Ardizone and colleagues demonstrated that, compared with mesalamine, azathioprine is significantly more effective in inducing clinical and endoscopic remission.[62] In the ACT, ULTRA-2 and PURSUIT studies, mucosal healing (defined as Mayo endoscopic subscore of 0 or 1) was also significantly achieved in about 46%, 25% and 42% for IFX, adalimumab and golimumab, respectively, at 1 year (*versus* 18%, 15% and 27% for placebo, respectively).[63–65] However, a recent study evaluated the risk of relapse according to the degree of mucosal healing (i.e. Mayo 0 *versus* Mayo 1), showing that patients with an endoscopic Mayo score of 1 had a higher risk of relapse than those with a score of 0 (9.4% *versus* 36.6% of relapse at 6 months, respectively, $p < 0.001$).[66] This result highlights the prognostic importance of mucosal healing in UC, although this target is sometimes difficult to achieve.

Histologic remission. For the experts of the IOIBD group, in patients with UC, histological remission and biologic markers of remission are considered as an adjunctive target.[67] However, histologic healing also seems to be of prognostic importance. Indeed, Riley and colleagues demonstrated that 52% of patients with an acute inflammatory cell infiltrate relapsed compared with 25% of relapses in the absence of such infiltrate ($p = 0.02$). Relapse rates were higher in the presence of crypt abscesses, mucin depletion and breaches in the surface epithelium.[68] Other studies would be essential to determine precisely the role of histologic remission in UC.

Therapeutic drug monitoring in the induction and maintenance therapy

To optimize the use of drugs, pharmacokinetic measurements of TNF antagonists are being more frequently employed in the management of IBD in the induction and maintenance phases. Some studies have evaluated the role of trough levels (TLs) and antidrug antibody (ADA) concentrations for anti-TNF agents. A significant correlation between anti-TNF pharmacokinetic concentrations and clinical response is suggested; indeed, patients can have factors known to be associated with higher clearance of the drug, that is, low albumin level, high body weight and inflammatory burden (with high concentration of CRP and specific fecal markers). In 2006, Maser and colleagues confirmed the link between pharmacokinetics and clinical outcome by demonstrating that in patients with CD treated with scheduled maintenance infusions, the rate of clinical remission was higher for those with detectable IFX levels than for patients in whom TLs were undetectable (82% *versus* 6%; $p < 0.001$).[69] In the same way, for UC, Seow and colleagues reported that detectable levels of IFX at week 54 after IFX initiation were associated with higher rates of clinical remission (69% *versus* 15%; $p < 0.001$) and endoscopic improvement (76% *versus* 28%; $p < 0.001$).[70]

Role of therapeutic drug monitoring in assessing a response to a drug. In the CLASSIC I trial, Chui and colleagues demonstrated that adalimumab concentrations were higher in patients with CD who achieved clinical remission compared with nonresponders at week 4 (8.1 *versus* 5.05 μg/ml, $p < 0.05$).[71] In UC, in the pivotal ULTRA 2 trial, median trough serum adalimumab concentrations were also higher in patients who achieved remission at week 8 and week 52 (11.4 ± 5.15

Table 2. Therapeutic adjustment algorithm in the case of loss of response to IFX; adapted from Bendtzen and colleagues.[76]

Loss of clinical response		Antidrug antibody	
		Negative	**High concentration**
Trough level	Low concentration	Dose intensification	Switch to another TNF antagonist or add IS
	Normal concentration	Switch to another therapeutic class	Switch to another therapeutic class

IFX, infliximab; TNF, tumor necrosis factor; IS, immunosuppressors.

and 10.8 ± 7.45, respectively) compared with patients who did not achieve remission (8.49 ± 4.35 and 6.18 ± 4.22, respectively).[64] In the PURSUIT studies for golimumab, it is interesting that, based on receiver operating characteristic curve analysis, a serum golimumab concentration of 2.5 μg/ml minimum at week 6 seemed to be an adequate concentration for induction of clinical response.[72]

Additionally, studies have attempted to identify anti-TNF TL cutoffs that can predict a favorable clinical outcome after IFX initiation. In CD, Cornillie and colleagues, in a *post hoc* analysis of the pivotal ACCENT 1 trial, demonstrated that a serum IFX TL of at least 3.5 μg/ml at week 14 post IFX induction in association with a minimum of 60% CRP decrease was significantly associated with a durable sustained response.[73] In the same way, Bortlik and colleagues showed that a serum IFX TL greater than 3 μg/ml at week 14 or 22 was associated with a decreased risk of treatment failure during a median follow up of 2 years (hazard ratio 0.34; 95% confidence interval 0.16–0.75).[74] Although the cutoff differed between studies (according to the TNF antagonist agent and the definition of the time of clinical remission), a minimum of 3 μg/ml for IFX and 5 μg/ml for adalimumab is recognized to be considered as beneficial during maintenance therapy.[3,75]

Pharmacokinetic parameters could be helpful to guide therapeutic decisions, in particular in two separate situations: managing the loss of response to the drug, and considering drug withdrawal for patients with disease in remission.

Role of therapeutic drug monitoring optimization in case of loss of response. It is well known that, despite a well conducted treatment with anti-TNF agents, some patients may lose clinical remission over time. Two meta-analyses found a loss of response in 37% and 18.2% for IFX and adalimumab, respectively, with annual risk calculated to be 13% and 24.4% per patient year, respectively.[5,6] In this situation, measurement of TLs and ADA is an essential component in determining the most suitable therapy, alongside optimization of the therapy with an increased dose of the drug, association with a concomitant immunomodulatory drug, or a switch to another therapeutic class. Bendtzen and colleagues have designed an algorithm that may prove useful in dealing with these complexities (although this is not yet validated in clinical studies).[76] In particular, in this algorithm (Table 2), for patients exhibiting a low drug concentration without antibodies against the drug, an increase in the dose is advised in theory. Patients exhibiting a low drug concentration due to a high level of ADAs can, in theory, benefit from changing to another TNF antagonist treatment against which the patient has not yet developed antibodies. Finally, in the algorithm, for patients with a high drug concentration, a switch to another therapeutic class should be considered. For patients developing secondary failure to IFX, Paul and colleagues demonstrated that after IFX dose intensification, increase in IFX TLs at week 8 (with a Δ IFX TL > 0.5 μg/ml) was associated with mucosal healing in both CD and UC.[77]

Role of therapeutic drug monitoring for drug de-escalation or drug withdrawal. In the TAXIT trial, Vande Casteele and colleagues demonstrated the interest of pharmacokinetic measurements, in particular for patients exhibiting high TLs. The authors implemented a drug de-escalation in patients with CD with clinical remission and high TLs (>7 μg/ml) by one of two means: reduction of the dose to 5 mg/kg (if previously on 10 mg/kg) or extension of the interval between two infusions, each time by 2 weeks (to a maximum interval of

12 weeks). Of 72 patients with TLs greater than 7 μg/ml, 93% achieved a normal range after dose reduction without affecting clinical outcome.[78] Pharmacokinetic parameters may also be useful for patients with CD in clinical remission for whom a withdrawal of anti-TNF is considered. The STORI study aimed to identify predictive factors of clinical relapse after IFX discontinuation in patients with nonactive CD. This study demonstrated that relapse occurred in 50% of these patients within 18 months of IFX withdrawal, and the presence of clinical, biological and endoscopic criteria of remission prior to anti-TNF discontinuation predicted a relapse-free survival over time. TL measurement was performed prior to IFX cessation and revealed for the first time that TLs above 4.5 μg/ml were predictive of relapse.[50] The fact that patients with higher TLs at the time of IFX discontinuation were more prone to relapse suggests that these patients probably require continued anti-TNF administration to maintain an adequate drug concentration and therefore clinical remission. Similarly, Ben Horin and colleagues compared the duration of relapse-free survival in patients with IBD in remission who discontinued IFX or adalimumab in the presence or absence of detectable levels of the drug. Forty-eight patients were included (30 CD, 18 UC) and followed up with a median time of 12 months. After anti-TNF cessation, relapse occurred in 80% of patients with measurable drug levels compared with 32% of patients with undetectable drug levels (OR 8.4, $p = 0.002$). Although the number of patients in the study is low, and about one-third of them had relapsing disease in the first year, this suggests that the finding of an undetectable anti-TNF drug level in a patient with stable, long-term, deep remission may identify a subset of patients whose clinical remission is no longer dependent on anti-TNF treatment, which may then be stopped.[79]

Role of therapeutic drug monitoring for preemptive optimization of the drug. With the arrival of TNF antagonist pharmacokinetic measurement, the proactive measurement of TLs even for patients with IBD in clinical remission has been developed, with the primary objective of maintaining optimal anti-TNF concentrations, and consequently reducing costs and the risk of adverse events. Comparative observational studies evaluating the role of routine, proactive therapeutic drug monitoring (TDM) for achieving remission are very scarce.

A recent randomized, controlled study, TAILORIX [ClinicalTrials.gov identifier: NCT01442025], aimed to compare the management of patients with IBD according to pharmacological and clinical criteria *versus* clinical criteria alone. The authors hypothesized that prospective TDM would lead to higher remission rates compared with pure symptom-based dose adaptations. The primary endpoint of this trial was sustained steroid-free clinical remission from week 22 to week 54 and absence of ulceration after 1 year.

Of the 122 patients included in this study, the primary endpoint was attained in 47% in group 1 [dose intensification of IFX in (maximally two) steps of 2.5 mg/kg based on clinical symptoms and pharmacologic analysis], 38% in group 2 (dose intensification of IFX from 5 to 10 mg/kg based on the same criteria) and 40% in group 3 (IFX dose increase to 10 mg/kg based on clinical symptoms alone). The authors concluded that proactive, TL-based dose intensification was not superior to dose intensification based on symptoms alone.[80] However, due to the design of the study, comparison between the three groups remains difficult and the conclusions should be considered carefully. Conversely, in a recent retrospective study, Papamichael and colleagues compared patients with IBD receiving proactive drug monitoring (titrated to a target concentration) *versus* reactive monitoring (titration performed after loss of response). In this study, proactive monitoring was associated with better clinical outcomes (greater drug durability, less surgery or hospitalization, and lower risk of immunogenicity to IFX).[81]

Proactive TDM is probably very interesting in the context of de-escalation of IFX dose in patients with IBD in clinical and endoscopic remission and with supratherapeutic levels of IFX. In a prospective study including 20 patients with CD, Paul and colleagues proposed in such cases a progressive de-escalation of IFX, reducing the dose by 1 mg/kg at each 8-weekly infusion. The de-escalation was stopped when an IFX TL of 3–7 μg/ml was reached. The IFX TL was achieved in this range in 18 patients (90%) without relapse. None of the patients had a TL below 3 μg/ml after de-escalation. Most of the patients achieved the targeted TLs at an IFX dose of 7 mg/kg.[82]

Proactive TDM should also be of interest for patients with IBD and an abnormal profile of pharmacokinetics. Indeed, some patients can

have undetectable TLs associated with high or sustained antibodies. In these patients, in the case of loss of response, some studies have reported that adding an immunomodulator can be interesting.[83,84] Indeed, with this strategy, half of these patients showed normalized IFX pharmacokinetics at 6 months and had a clinical response.

Telemedicine in IBD

Telemedicine is represented by several applications of telemonitoring, teleconsulting and teleeducation. It is likely that the extent of use of mobile phones and the internet have helped the development of telemedicine programs, with respect to both telemonitoring (symptoms, side effects, medications, weight etc.) and tele-education. Telemedicine has been used successfully in chronic pathologies such as diabetes, asthma, congestive heart failure and IBD. It is useful in IBD because, given the unpredictable nature of the disease, flares can occur at any time, with the need for continuous medication to improve/maintain health.[85–87] Telemedicine studies have focused on techniques to improve outpatient management (out of the provider office). Until now, in the case of disease flare, first management has often been initiated *via* a phone call, but in some cases, this could be avoided. Indeed, previous UC studies demonstrated that some patients were able to initiate treatment following a treatment plan, leading to fewer office visits or hospitalizations than controls. In these studies, telemedicine was well accepted by patients and had a positive impact on health outcomes. Moreover, QoL was maintained without evidence of anxiety about the program.[88,89]

Some remote-care models have been used for better management of patients with IBD. For example in Spain the Crohn colitis care unit (UACC), a care program using a remote communication system, proved its efficacy by demonstrating a decrease in the ratio of hospitalized/UACC-registered patients between the start and end of a study period.[90] The aim of these remote-care applications is to improve medical adherence and QoL of patients with IBD, which must be higher than with a standard clinical follow up. This is achieved through a better understanding of the disease by the patient, and better communication between patients and healthcare providers. Moreover, these remote-care models have the advantage of reducing direct and indirect costs incurred from transport, loss of working hours, and so on, which contributes to public savings.

Figure 1. Limits of telemedicine. Do physicians have enough time to apply the telemedicine program alone? What is the limit of self management by patients in the case of an emergency? How should the payment of this time-consuming activity be considered?

It is likely that, in the future, for the development of these programs, gastroenterologists will be helped by other IBD specialists. Indeed, due to their high workload, gastroenterologists could be helped by IBD nurse specialists. In this context, in a recent study the telemedicine program, myIBDcoach, has been developed with IBD nurse specialists and dietitians,[91,92] and has been compared with standard follow up. In myIBDcoach the telemedicine tool monitors many parameters, including disease activity, medication side effects, QoL, asthenia, stress and work participation. Although no differences were observed in disease flare, corticosteroid use or emergency visits between the two study groups, patients using myIBDcoach reported higher medication adherence rates ($p < 0.001$), better QoL and similar self-efficacy scores compared with controls. Moreover, patients graded the system with a mean of 7.8/10, and 93% of patients recommended the program to other patients.

Telemedicine has some advantages, but also limits (Figure 1). Primary limits of telemedicine concern the limits of self management by a patient and the absence of a physical examination in the case of an emergency request, with the risk of losing information. Another limit of the telemedicine applications is the confidentiality of the

personal information of patients. Indeed, telemedicine includes the liabilities of the health professional and the duty to maintain the privacy of patient records. All personal information that can circulate on the internet needs to be managed on safe servers in these programs. Another limit is the issue of funding/reimbursement for remote care provided using a telemedicine service. It would be useful if telemedicine practitioners could work with insurance companies, with the objective to develop the service for patients. In the United States, telemedicine is progressing towards expanded reimbursement for telemedicine services and this can be from private sources. An evaluation found that 81% of practitioners who received private payment reported no difficulty in reimbursement with telemedicine services compared with traditional face-to-face consultations.[93] Conversely, without reimbursement, we cannot expect to see a widespread adoption of telemedicine services.

In conclusion, with the arrival of new drugs, personalized medicine is emerging and will become a requirement in the management of patients with IBD. The most suitable therapy should be dispensed early in the course of the disease, especially for patients exhibiting characteristics of aggressive disease. In addition to the progress of therapeutics in IBD, some studies are currently being evaluated for predictive factors of response to these drugs to better manage IBD. The best control of IBD in the context of personalized medicine will progress more and more through an implication of the patients *via* the development of telemedicine, which will encourage patients towards better adhesion to their management program.

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