Optimization of biologics to reduce treatment failure in inflammatory bowel diseases

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Abstract

Moderate to severe inflammatory bowel disease patients can fail to respond to conventional therapy and/or to biologic treatment.

In the era of TNFα antagonists and other non-anti-TNF biologic drugs, it is important to review the literature on biologic treatment failure, which could be defined as primary non-response, secondary loss of response and intolerance.

Therapeutic drug monitoring (TDM), i.e. drug trough level and antidrug antibodies, should enable to determine the mechanisms of treatment failure and to optimize drug efficacy. There is a consensus on reactive TDM at the time of loss of response. Proactive TDM could be of interest during induction and/or maintenance, but randomized controlled trials are required.

Abbreviations used: acute severe ulcerative colitis (ASUC), antidrug antibody (ADA), Azathioprine (AZA), CI (confidence interval), Crohn disease (CD), Day (D), Inflammatory bowel diseases (IBD), Infliximab (IFX), 6-mercaptopurine (6-MP), Primary non-response (PNR), Relative risk (RR), Secondary loss of response (SLR), 6-thioguanine nucleotides (6-TGN), Ulcerative colitis (UC), Ustekinumab (USK), Vedolizumab (VDZ), Week (W)

Key words: Crohn disease; ulcerative colitis; therapeutic drug monitoring; trough level; antidrug antibodies; loss of response; anti-TNFα

Word count: 2215

Introduction

The course of inflammatory bowel diseases (IBD), either Crohn disease (CD) or ulcerative colitis (UC), has changed during the last 2 decades with the use of biologics. However, the management of moderate to severe CD and severe acute UC remains a challenge. It is important to understand the mechanisms of biologic failure in order to personalize appropriately IBD treatments and to improve their effectiveness. Thus, a "prediction, prevention, and therapeutic interventions" approach will become effective.

In this article, we will not develop corticosteroid resistance, immunosuppressive drug metabolism [1], and exclusive enteral nutrition effectiveness [2], but we will focus on TNFα antagonists and other biologics. The introduction of TNFα antagonists was a success, but up to 40% of IBD patients are non-responders [3]. Non-response to anti-TNFα agents can be divided into primary non-response (PNR), secondary loss of response (SLR) and intolerance.

Therapeutic drug monitoring (TDM), i.e. drug and antidrug antibodies (ADA) concentrations, is an important issue [4,5]. Clinical response is positively correlated to anti-TNFα trough levels; adequate trough levels are associated with an increase rate of mucosal healing and a decrease incidence of long-term complications [6-8]. To date, there are differences among scientific societies recommendations of anti-TNFα TDM to assess SLR in order to guide therapeutic change (reactive TDM) [5,9-11] or even PNR [9], but not in quiescent IBD (proactive TDM) [10].

Reduction of primary non-response to TNFα antagonists

The rate of PNR, which is the absence of response during the induction phase, is about 10-40% of IBD patients, while the rate of primary non-remission is about 50-80% [3,12]. These rates vary obviously because different criteria are used to assess disease activity and to define response and remission.

The response to TNFα antagonists differs according to characteristics of patients, of their disease and to drug monitoring. Their efficacy is greater for patients with higher inflammatory syndrome (CRP or even serum TNFα levels) and shorter disease duration at baseline (Table 1). However, the clearance of TNFα antagonists is increased in patients with elevated body weight and low albumin levels [3]. We can hypothesize that these patients should respond to higher induction doses of anti-TNFα drugs in order to reach correct trough levels. Conversely, some patients will not respond to TNFα antagonists because their mechanism of inflammation involves alternative cytokine pathways, like IL-6 or IL-23 [13].

During induction, TNFα antagonists can be used in association with immunomodulator in order to increase efficacy or to reduce immunogenicity [9]. In severe CD with perianal fistula, IFX is preferred to adalimumab; in acute severe UC (ASUC), an accelerated IFX induction regimen is used in the absence of clinical response at D3-D5 [9]. Indeed, anti-TNFα trough levels and tissue concentrations are positively correlated in non-inflammatory area but not in inflammatory ones [14]. Thus a dose escalation could enable to neutralize local TNFα production, in patients with therapeutic trough levels and active disease.

In corticosteroid-resistant ASUC, colectomy-free survival was similar with IFX or cyclosporine in association with AZA, 69.1% and 65.1% respectively [15]. Other treatments could be discussed, such as tacrolimus, colectomy… In the future, algorithms based on clinical factors available at diagnosis and 9 colonic micro-RNAs could determine response to steroids, IFX and cyclosporine [16].

Finally, TDM could be useful to identify PNR patients with therapeutic concentrations of anti-TNFα drugs and no ADA, which should be switched to other biologics rather than to a second-line anti-TNFα. PNR should be assessed at least after treatment induction, *i.e.* at W8-W12 for IFX and at W4-W8 for adalimumab [6]. Moreover, early proactive TDM could be useful to reach higher therapeutic thresholds associated with decrease PNR [17,18], and with

short term mucosal healing (W8-14) in UC patients treated with IFX [19,20] or adalimumab [21].

Prevention of secondary loss of response and intolerance to TNFα antagonists

The SLR is defined by the loss of response in patients who initially responded to anti-TNFα drug, and intolerance by the occurrence of unacceptable side effects.

Immunogenicity is a major concern. IBD patients treated with IFX developed ADA at a median time of 1.5 months (range 0.5-31) [22] and ADA > 8 μg/mL were associated with lower IFX concentrations at W4 after the first administration [23]. It is important to consider that drug-sensitive ADA assays do not allow for the detection of ADA in the presence of the drug [3]. Even if immunogenicity detection was increased by drug-tolerant assay, it had no clinical benefit; it should be more important to optimize IFX trough levels [24]. In a real-life IFX study, ADA developed in 23% of patients and ADA > 30 AU/mL were associated with undetectable IFX trough levels [25]. IFX clearance was also increased by previous use of biologics, body weight, and albumin.

Low trough levels of anti-TNFα drugs increase the risk of immunogenicity. ADA formation is decreased by coadministration of immunomodulators.

Therapeutic drug monitoring (TDM) of TNFα antagonists

At the time of SLR, TDM is recommended for anti-TNFα agents [9-11]. However, the level of evidence is low, mainly supported by observational studies [26]. TAILORIX, a double-blind trial of CD patients on IFX and immunosuppressant, did not found differences between clinical, biochemical and/or TDM *vs*. clinical optimization alone on sustained corticosteroid-free clinical remission from W22 to W54 [27]. However, a prospective study found that IFX TDM reduced dose escalations, increased the switch to another anti-TNFα, without loss of efficacy, which was cost-effective [28].

Optimal thresholds vary between studies for achieving mucosal healing because different degrees of sensibility and/or specificity were used (Table 2) [12,29,30]. Coadministration of immunomodulator only increases IFX through level [29], but it decreases the risk of developing ADA to both anti-TNFα [12]. Of note, these thresholds were determined for luminal CD and moderate to severe UC. Response to anti-TNFα was obtained with higher IFX trough levels in CD with perianal fistula [31].

IFX TDM targeting trough level of 3-7 μg/mL resulted in an increase of CD remission rate and a reduction of drug cost [32]. After IFX optimization, TDM did not improve remission after 1 year compared with clinically based dosing, but it significantly reduced the number of patients with undetectable IFX trough level and decreased the need to rescue therapy.

IBD patients failed to respond to an increase in drug dosage or a switch to another anti-TNFα agent if IFX trough level was > 3.8 μg/mL and adalimumab trough level was > 4.5 μg/mL, with 90% specificity. ADA against IFX > 9 μg/mEq and ADA against adalimumab > 4 μg/mEq were 90% specific for failure to dose intensification [33].

Adalimumab trough levels < 4.9 μg/mL were associated with an absence of mucosal healing (88% positive predictive value; 51% negative predictive value) [34]. CD patients with an optimal threshold of 4.8 to 5.9 μg/mL were 2 times more likely to be in remission [35]. Up to 35% of patients developed ADA with negative correlations with trough levels and clinical outcomes; notably, the odd ratio for loss of clinical response in CD patients with ADA was 10.15 (95% CI: 3.9-26.4, $p<0.0001$).

Coadministration of immunomodulators was associated with higher trough levels and lower antibodies to IFX, at least during the first 6 months of treatment [6].

Reactive TDM is used in clinical practice to optimize anti-TNFα treatment at the time of loss of response (Figure 1) [36], and therapeutic thresholds are proposed by scientific societies (Table 2) [10,11]. However, proactive TDM could be recommended in the future to improve

treatment success and patients' outcomes [37]. Indeed, a large retrospective study found that during IFX maintenance proactive TDM was more effective than reactive TDM to reduce treatment failure, but also CD-related surgery, hospitalization, ADA, and serious infusion reactions [38]. They reported 5% of serious infusion reactions, mainly in patients with ADA (70%). Treatment failure was also reduced by proactive adalimumab TDM *vs.* standard of care (reactive TDM or empiric dose escalation) [39]. In CD children, proactive adalimumab TDM increased corticosteroid-free remission compared to reactive TDM [40].

Vedolizumab

Vedolizumab (VDZ) is an $\alpha_4\beta_7$ integrin antibody, blocking lymphocyte infiltration into intestinal mucosa. The delay of VDZ efficacy (300 mg at W0 and W2) is longer in CD than in UC patients; only ≈15% of CD but 47.1% of UC patients were in clinical remission at W6; the rate increased to ≈42-45% at W52 in UC patients and to ≈36-39% in CD patients [41-43]. Only 4% of patients developed VDZ antibodies. VDZ is effective for induction and maintenance of remission in CD and UC. Meanwhile, anti-TNFα naïve CD patients could achieve clinical remission earlier than anti-TNFα failure ones (31.4% at W6 compared to 26.6% at W10) [43]. Finally, 48.9% of anti-TNFα CD naïve and 27.7% of anti-TNFα failure patients were still in clinical remission with VDZ at W52 [44].

VDZ was more effective to reach clinical, biologic or endoscopic response at W14 (UC) and W22 (CD) if patients had higher trough levels during induction (>30 and > 24 µg/mL at W2 and W6 respectively) and maintenance therapy (>14 µg/mL up to W30) (Table 2) [45]. Higher CRP, lower albumin, and lower hemoglobin levels, as well as higher BMI, at treatment initiation, were predictive factors of lower VDZ trough levels (Table 1) [45].

Pharmacokinetics of VDZ was similar between UC and CD, with a half-life of 25 days. VDZ clearance was increased by albumin concentrations < 3.2 g/dL, and was positively correlated

with body weight; however, prior anti-TNFα use, concomitant immunomodulator medication, and disease activity had no clinically relevant impact [46].

Other studies also found that higher trough levels during induction were associated with clinical or endoscopic outcomes [47-50]. Immunogenicity does not seem to be an important issue with low prevalence of transient antibodies [41,43,48,51-53] and without need for drug optimization [41,51]. Meanwhile, PNR patients had lower VDZ trough levels than patients with SLR (20.3 *vs.* 30.7 µg/mL), which was not significant [54]. Patients with low VDZ trough levels could benefit from an increase of dose or frequency [50]. Similar findings were obtained during maintenance [53,55]. VDZ efficacy could be more important in UC than in CD [52,55]. In a meta-analysis, VDZ trough levels were only associated with favorable clinical outcomes in UC, with a threshold of ≥ 18.5-20.8 µg/mL at W6 and ≥ 9-12.6 µg/mL during maintenance [52]. **Ustekinumab**

Ustekinumab (USK) is a biologic targeting the p40 subunit of IL-12 and IL-23.

USK, 90 mg subcutaneously at W0, W4, and W12, and every 8 weeks, was effective in refractory CD patients: clinical response (46%) and remission (35%), endoscopic response (76%) and remission (24%) [56]. A 270 mg booster was delivered at W8 if there was no or limited clinical response.

USK was more effective intravenously than placebo to obtain a response in CD patients. The delay of response was longer after TNFα antagonist failure than immunomodulators/corticosteroids failure: ≈34% *vs.* ≈52-55% at W6, and 53.1% (90 mg subcutaneously every 8 weeks) and 48.8% (90 mg subcutaneously every 12 weeks) at W44, respectively. USK was effective to induce an early response, from the 3rd week, and remission [57]. Clinical remission was significantly higher if USK trough levels were > 3.3 µg/mL at W8 and > 0.8-1.4 µg/mL during maintenance; trough levels were inversely correlated with CRP levels and were not associated with immunomodulator use [58]. Another study found

that the optimal threshold of USK trough level associated with an endoscopic response was 4.5 μg/mL after W26; no patients developed ADA [59]. Immunomodulators did not affect USK trough levels and immunogenicity [58].

Therapeutic drug interventions

A 2015 meta-analysis evaluated the efficacy of a second-line anti-TNFα drug. In CD, 32 studies switched IFX to adalimumab, 4 infliximab to certolizumab and 1 adalimumab to IFX. The remission and response rates were higher when the first one was withdrawn for intolerance (61% and 72%), SLR (45% and 62%), or PNR (30% and 53%) respectively [60]. All UC studies switched IFX to adalimumab; 6 over 8 reported remission rates from 0 to 50% [60]. In IBD patients with immune-mediated LOR to a first optimized anti-TNFα drug, coadministration of AZA with anti-TNFα drug was associated with favorable outcomes by 2 years [61]. These results are in contrast with a study described above [33].

Another meta-analysis evaluated the response to a second-line non-TNFα biologic according to the reason for first-line anti-TNFα discontinuation [7]. PNR, SLR, and intolerance were reported in a median of 43.1%, 64.7%, and 35.4% respectively. Patients with PNR were 24% (RR 0.76 [0.61-0.96]) and 27% (RR 0.73 [0.56-0.97]) less likely to achieve remission with second-line biologics than patients with intolerance and SLR respectively. In PNR patients in comparison to SLR patients, difference was found with USK (RR 0.53 [0.39-0.71]), but not with VDZ, in achieving remission [7].

Conclusion and perspectives

It should be useful for IBD patients to know predictive factors of response and to assess their response to biologics using clinical, biochemical, endoscopic endpoints and performing therapeutic drug monitoring. Therefore, our knowledge of biologic use, as well as new approaches in moderate to severe IBD will improve, and we will reach a more personalized treatment.

Moreover, a better management of the disease should come from the development of new treatments targeting the impaired intestinal barrier including the gut microbiota (fecal microbiota transplantation, phages, pre- or probiotic, and/or the use of a Crohn disease exclusion diet [62]) and permeability (inhibiting the activity of myosin light chain kinase (MLCK), the over-expression of Claudin-2 and the mechanisms involved in cell death).

Figure 1. Algorithm using therapeutic drug monitoring for management of anti-TNFα loss of response

Abbreviations: ADA, antidrug antibodies; IBD, inflammatory bowel diseases

Figure 2. Alternative therapeutics for IBD targeting impaired intestinal barrier function.

On the left part, there is a schematic view of the intestinal epithelial cells and the lumen compartment with impairment found in IBD, e.g. paracellular permeability and microbiota dysbiosis. On the right side, we detailed the box corresponding to the tight junction area and the targets of new drugs/approaches, which are the microbiota (1) by fecal microbiota transplantation, probiotics, exclusion diet, and the intestinal epithelial cell proteins (claudin 2 (2) and MLCK (3).

Abbreviations: MLCK, myosin light chain kinase, ZO, zonula occludens

Table 1. Relation between predictive factors and efficacy of biologics

Factor	**TNFα antagonists [3,6,12,29,30,35]**	**Vedolizumab [45,46]**	**Ustekinumab [7,47,58]**
High inflammatory syndrome (CRP)	increase	decrease	decrease
Shorter disease duration	increase		
Elevated body weight	decrease	decrease	
Current smoking	decrease		
Low albumin levels	decrease	decrease	
Low hemoglobin levels		decrease	
Prior anti-TNF use		No effect	Decrease (more in PNR than in SLR)
Disease activity		No effect	
Immunomodulator coadministration	Increases IFX trough levels; Decreases ADA formation (IFX and adalimumab)	No effect	No effect

Table 2. Different thresholds of anti-TNFα and vedolizumab trough levels

	Infliximab [12,29,30,32]	**Adalimumab [12,29,34,35]**	**Vedolizumab [45,54]**
Low threshold	< 3 µg/mL	< 4.9 µg/mL	< 20.3 µg/mL
Therapeutic threshold	> 3.4 µg/mL [30] > 5 µg/mL [29] > 7 µg/mL [12]	> 7.1 µg/mL [29] > 7.2 µg/mL [30] > 12 µg/mL [12]	> 30 µg/mL (W2) > 24 µg/mL (W6) > 14 µg/mL (maintenance)
High threshold	8 µg/mL [29]	12 µg/mL [29]	
Scientific societies recommendations	3-8 µg/mL [11] ≥ 5 µg/mL [10]	5-12 µg/mL [11] ≥ 7.5 µg/mL [10]	

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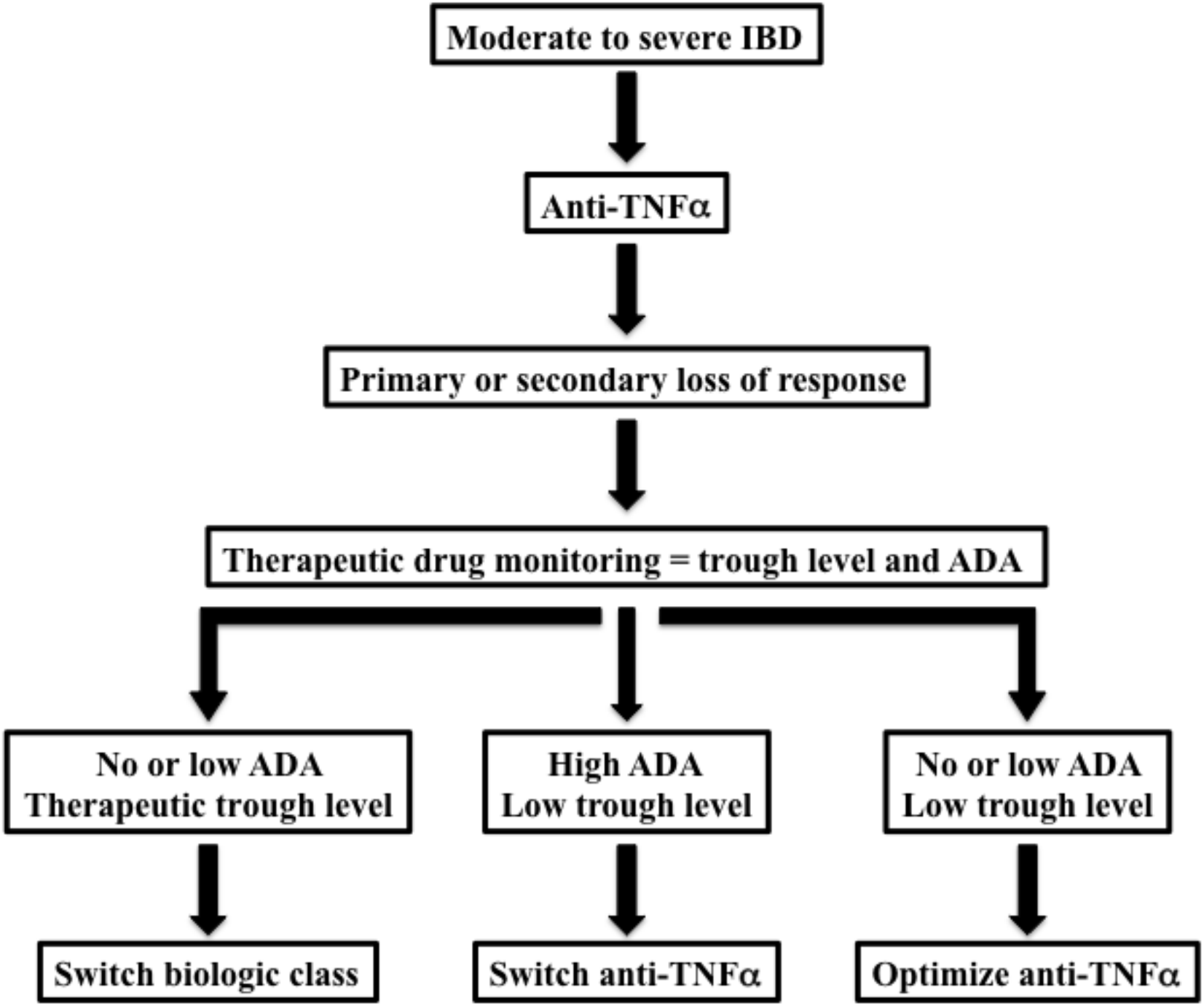
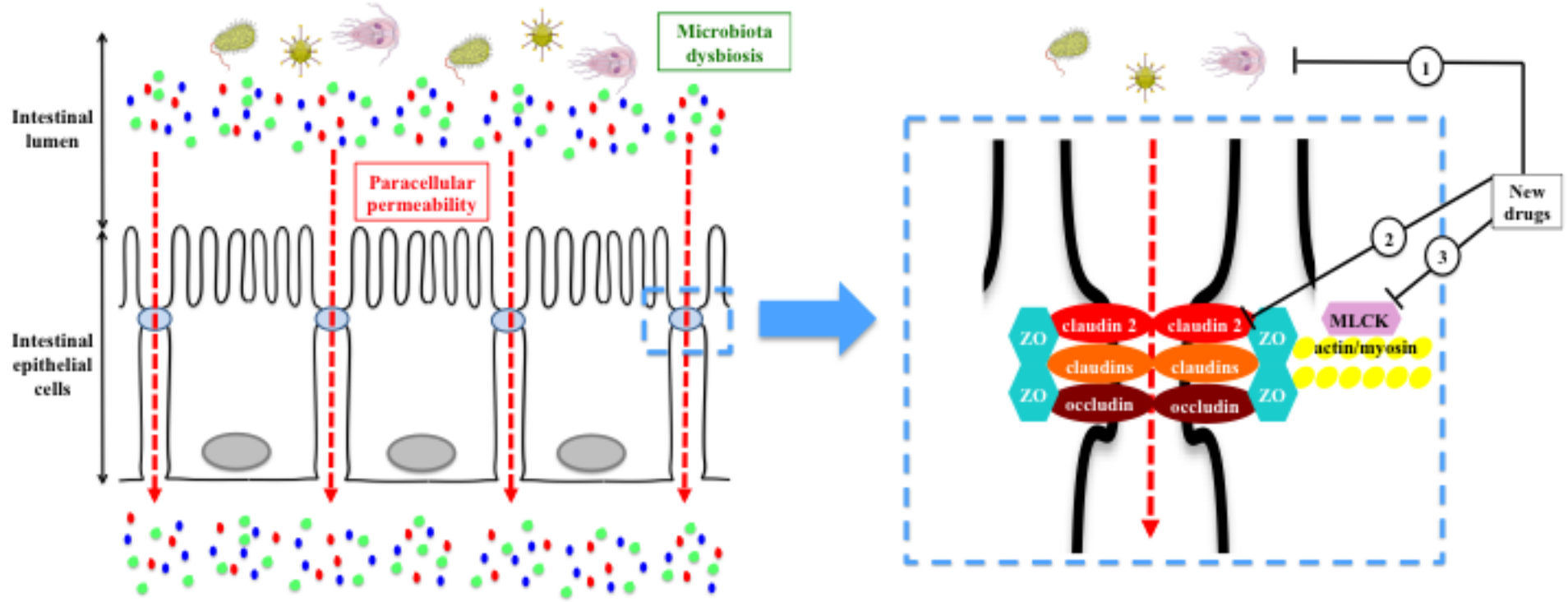

Moderate to severe IBD
Anti-TNFα
Primary or secondary loss of response
Therapeutic drug monitoring = trough level and ADA
No or low ADA
Therapeutic trough level
High ADA
Low trough level
No or low ADA
Low trough level
Switch biologic class
Switch anti-TNFα
Optimize anti-TNFα


Microbiota dysbiosis
Intestinal lumen
Paracellular permeability
Intestinal epithelial cells
1
New drugs
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