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REVIEW

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A review article of inflammatory bowel disease treatment and pharmacogenomics

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Abstract

Inflammatory bowel disease (IBD) involves a variety of conditions, particularly Crohn's disease (CD) and ulcerative colitis (UC). IBD is characterized by chronic inflammatory process of patient's gut. This review aims to summarize the pharmacogenetics of biologics approved for IBD and the correlation with azathioprine-metabolizing enzymes and adverse reactions, therefore highlighting a likely relationship between particular polymorphisms and therapeutic response. Therefore, we reviewed and discussed the activities of TDM protocols which use monoclonal antibodies (mABs) with a particular attention on the integration of other actions aimed to exploit the most effective and safest medications for IBD cases. The pharmacotherapy of IBD (CD and UC) has experienced a great advancement with the advent of mABs which have peculiar pharmacokinetic properties differentiating them from chemical agents, like aminosalicylates, antimetabolites (e.g., azathioprine (AZA), 6-mercaptopurine (6MP)), and methotrexate), and immunosuppressant agents (steroids and cyclosporine). But clinical studies showed that biologicals might have pharmacokinetic variability which can affect the anticipated clinical outcomes, beyond primary resistance phenomena. Thus, therapeutic drug monitoring (TDM) protocols are applied to the doses of medications according to the required serum mABs levels. This aims to maximize the favorable effects of mABs and minimizing the toxicity. But, the presence of particular genetic polymorphisms in patients might determine a different outcome in response to treatment, indicating the heterogeneity of the effectiveness among IBD cases. Indeed, many reports demonstrated significant associations between polymorphisms and response to biologics. In conclusion, the improvement of TNF-, TNFR and IL-1 pharmacogenetics could be the best approach toward a targeted treatment for IBD. Pre-therapy genotyping has to be integrated with IBD therapeutic guidelines, as it is the most suitable approach to choose the most appropriate biologicals for each case. Also, the addition of pharmacodynamic markers (including serum, cellular, or tissue concentrations of TNF-alpha and IL-8) might boost the predictive performance of models and, eventually, control the disease with a significant improvement in quality of life (QOL).

Keywords Pharmacogenetic, Genetic polymorphism, Inflammatory bowel diseases, Crohn's disease, Ulcerative colitis, SNPs, Genotype, Azathioprine, Thiopurine, Biological therapy

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1 Background

Inflammatory bowel disease (IBD), mainly Crohn's disease (CD) and ulcerative colitis (UC), is a significant etiology of chronic gastrointestinal (GI) disease all over the world, with various manifestations and multifactorial nature. Together with marching industrialization, IBD has globalized gradually many epidemiologic studies revealed a stable or reducing incidence in developed countries [1–3]. But, the East has a significant disease burden [3]. Such diseases were initially described by Wilks [4] and Crohn [5], respectively. CD and UC are characterized by remissions and relapses with complex interactions between genes, environmental stimuli, and immune response [6] (Table 1).

UC is an idiopathic inflammatory condition of the colon which results in diffuse friability and superficial erosions on the colonic wall associated with bleeding [7]. It is the most common form of inflammatory bowel disease worldwide. It characteristically involves inflammation restricted to the mucosa and submucosa of the colon. Typically, the disease starts in the rectum and extends proximally in a continuous manner [8].

There is also an association of IBD with the removal of an inflamed appendix. Appendectomy before the age of twenty is associated with a decreased incidence of UC, whereas the opposite is true for CD. In fact, appendectomy has been shown to reduce the risk of developing UC by 69% [9, 10].

CD can involve any part of the gastrointestinal tract. Transmural inflammatory changes can lead to progressive fibrosis with subsequent strictures or perforating disease with abscess formation or fistula. The most common areas of involvement are the small and large bowel, especially the terminal ileum and cecum [11].

CD and UC, the 2 types of IBDs, depend on many therapy classes including aminosalicylates, antimetabolites (i.e., azathioprine (AZA), 6 6-mercaptopurine (6MP), and immunosuppressants (corticosteroids and cyclosporine). Such medications can control IBD manifestations with many systemic toxicities; unfortunately, these treatments failed to control the disease in variable percentages of patients [12].

The commonest type of IBD worldwide is UC, characterized by diffusely friable colon mucosa with superficial erosions and hemorrhage [7]. The early disease appears in patient's rectum and then undergoes proximal proliferation in a continuous manner [13].

IBD is highly prevalent in Northern European and North American countries may be due to a westernized environment and lifestyles; nine to twenty cases are reported among every 100,000 persons per year [14]. UC is more frequent in adult population, while CD is more prevalent in the children [15].

From the other side, appendectomy protects against UC for unknown causes [16], while in some cases, appendectomy following a UC diagnosis was found to actually worsen its course [17]. Appendectomy before 20 years of age was linked to a decreased UC incidence; while the opposite is true for CD, Also, appendectomy has been found to decrease the risk of UC by 69% [9, 10].

A vegetarian diet was found to protect against the UC development [18], signifying that a shift from plant-based diet to process food could enhance UC risk in developing countries [19].

UC is a bi-modal pattern disease as its main peak appears between 15 and 30 years of age, while the second and less severe one happens between 50 and 70 years of age. Many reports indicated that the disease is more common in men, while other reports noted no preference in terms of gender. Also the use of non-steroidal anti-inflammatory drugs (NSAIDs) is correlated with onset or relapse of UC [20].

1.1 Risk factors

Smoking is a crucial risk factor for CD, while stopping of smoking has been described a risk factor for UC. How smoking either causes or provides protection from UC is unclear [21].

Other globally indicated risk factors for UC include factors which influence gut microbiota and, thus, its immunity. They include antibiotics [22], dietary alterations,

Table 1 Approved monoclonal antibodies IFX, ADA, UST, VDZ and golimumab in IBD therapy; IL, interleukin; IV, intravenous; SC, subcutaneous [58]

Biologic treatments	Trade name	Route	Approved use	Mechanism
Infliximab	Remicade Remsima inflectra	IV	CD and UC	TNF antagonist
Adalimumab	Humira	IV	CD and UC	TNF antagonist
Golimumab	Simponi	SC	UC	TNF antagonist
Ustekinumab	Stelara	IV induction SC maintenance	CD	Anti-Il-12 $ 23
Vedolizumab	Entyvio	IV	CD&UC	Anti-integrin

including the extensive utilization of food additives [19, 23], as well as psychiatric comorbidity [24].

It is difficult to understand the complex gut–brain axis; some studies explained the influence of psychiatric comorbidity in UC course to be mediated through the gut microbiota [25].

Appendectomy is a protective factor in UC for unclear reasons [16], yet appendectomy after a UC diagnosis has been shown to actually worsen the disease course [17].

1.2 Management of UC

The goals of treatment of UC are inducing and maintaining remission, improving the QOL, and minimizing the risk of cancer. The choice of treatment depends on the severity and extent of the disease, disease course during follow-up, and patient preferences [15].

1.3 Medical protocol

There are many different classes of medications available for treatment of UC. Sulfasalazine and 5-aminosalicylates (5-ASAs*)* given orally or rectally, or both, are the first-line treatment for UC. They can be used for induction and maintenance of remission. The route of administration depends on the disease extent.

Steroids are used for induction of remission in moderate to severe cases and can be given orally, rectally, or through an intravenous line in both UC and CD [26].

Thiopurines (6-mercaptopurine and azathioprine*)* are effective as steroid-sparing agents; due to the slow onset of action, however, there is limited benefit in using these medications as monotherapy for induction of remission in both UC and CD [27].

Biologics are genetically engineered medications made from living organisms and their products which interfere with the inflammatory response in patients with colitis. They can be used for induction and maintenance of remission in moderate to severe disease. *Infliximab, adalimumab,* and *golimumab* work through inhibiting the tumor necrosis factor-α. The other recently approved biologic, *vedolizumab,* is a recombinant humanized monoclonal antibody that binds α4β7 integrin and results in gut-selective anti-inflammatory activity. There is an increased risk of infection (including opportunistic infection) and a possibly increased risk of cancer associated with these medications in both of UC and CD [28, 29].

Cyclosporine*,* a T-lymphocyte inhibitor*,* is also a very effective agent for induction of remission in severe cases in hospitalized patients, but unfortunately this medication carries a significant risk of toxicity. Infection, seizures, hypertension, nephrotoxicity, and hyperkalemia are among the severe adverse effects with this medicine [30].

The goal of medical treatment of CD: is induction and maintenance of remission with the least adverse effect from the medications. 5-aminosalicylates (5-ASA) and sulfasalazine: Although oral mesalamine is widely used in practice, the meta-analysis of three large trials with mesalamine has shown a statistically significant but non-clinically relevant difference compared with placebo [31].

Antibiotics: The role of gut bacteria in the pathogenesis of CD has led to the use of antibiotics in mild to moderate cases [32].

Methotrexate can also cause serious adverse events, including but not limited to, bone marrow suppression, hepatotoxicity and cirrhosis, pneumonitis, and pulmonary fibrosis [33].

2 Different therapeutics regimens of IBD

2.1 Thiopurines in IBD treatment

The thiopurines mercaptopurine (MP) and its pro-drug azathioprine (AZA), alone or in combination with other drugs, are commonly used for the maintenance of remission and steroid sparing in patients with IBD. Because of their slow time to clinical response, between 8 and 12 weeks, these agents are not effective for rapid induction of remission. More recently, these immunosuppressants are also employed with biological therapies, as they can reduce the immunogenicity of biologics [34].

Thiopurines themselves are inactive and require intracellular metabolism, catalyzed by multiple enzymes, to the active thioguanine nucleotides (TGN), responsible for causing immunosuppression [35]. MP can be released from AZA both enzymatically by glutathione transferases and spontaneously after reaction with thiols (e.g., glutathione) [36].

Thiopurines have a significant role in CD to maintain remission in steroid-dependent individuals which was confirmed by a meta-analysis of six reports analyzed four hundred and eighty-nine patients [37]. But, thiopurines drugs are not recommended for use for all cases with newly diagnosed CD for maintaining the remission. Early introduction of thiopurines might assist in disease control [38], although the continuation is advised for those receiving thiopurines drugs for long-term maintenance of remission as it was revealed that there was a higher risk of CD recurrence after drug discontinuation [39].

Thiopurine treatment must not be utilized alone to control CD. According to many studies, combination of thiopurine with infliximab (IFX) is suggested for complete remissions in moderate to severe cases that haven't respond to a conventional treatment and have not utilized AZA in early stage [40].

Clinical practice proved that thiopurines failed to achieve maintained remission in many cases, which is recognized as an inadequate response to thiopurine

treatment [41]. No reports do exist about that thiopurines/IFX combination could be beneficial for accomplishing remission, however this combination might help reduce IFX immunity [42].

Both UC patients and CD patients delivered resistance to thiopurines. However, in these patients, it is suggested to shift to biologic treated or using thiopurines/IFX combination [43].

Research by the Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease (SONIC) compared between IFX therapy alone and thiopurines/IFX combination in cases with no response to steroids. This study confirmed that combination treatment showed greater rates of remission at week 26 in comparison to IFX alone [42].

Thiopurines indicated for mild to moderate UC cases that had recurrent relapses with corticosteroids. In a retrospective study, remission rate in those receiving AZA was 58% but improved to 87% following 6 months of dosage [44]. Consequently, those having significant relapse who respond to corticosteroids, cyclosporine, IFX with thiopurines to be utilized to maintain remission [44].

The course duration of AZA does not influence relapse rate after treatment was stopped which was approved in a study of 622 cases having CD and UC, remission rates following 6 months of AZA was 64% in CD and 87% in UC. Following AZA stoppage, the percentage of cases remained in remission was 0.63 after 12 months, 0.44 after 3 years, and 0.35 after 5 years [44].

Long term safety should be taken in consideration when choosing to start AZA in IBD, most observational studies suggested preservative and continuous monitoring due to the risk of non-melanoma tumors and lymphomas during long-term thiopurine therapy [45]. Side effects were recorded in 9.0% (22/245) of cases on thiopurine therapy versus 2.9% (9/311) placebo treatment [46]. We should notice that abnormal therapeutic concentrations of Thioguanine nucleotides (6TGN) can lead to hepatic toxicity, myelosuppression, pancreatitis, or GI intolerance [47] (Fig. 1).

Adverse reaction mainly is dose-dependent as myelosuppression, leukopenia, which appears in about 20% of IBD cases because of Thiopurine methyltransferase gene (TPMT) gene polymorphisms [48], although Thiopurine treatment can also cause myelosuppression, irrespective of TPMT activity which can occur even several months following the start of treatment in individuals with no *TPMT* gene polymorphisms [49].

The main cause of treatment discontinuation is Myelosuppression [50]. Moreover, hepatic toxicity can be also induced by thiopurines, characterized by high transaminases, hepatitis, or hepatic veno-occlusive disease. About

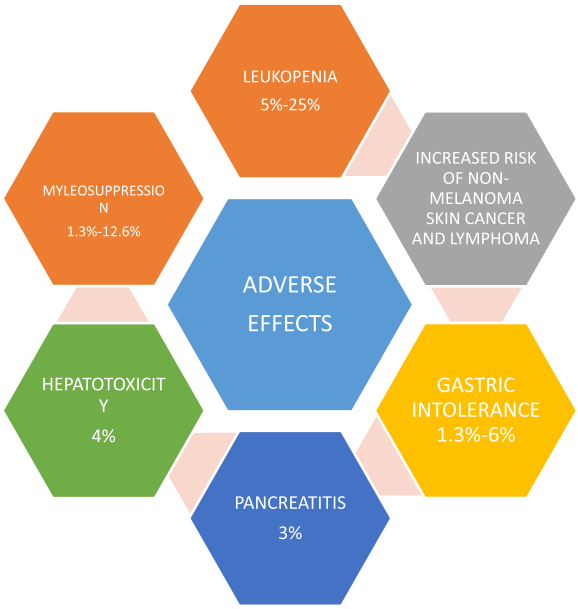

Fig. 1 Side effects of thiopurines in IBD cases (LEUKOPENIA, NON-MELANOMA SKIN CANCER AND LYMPHOMA, pancreatitis, Gastric intolerance, hepatotoxicity, myelosuppression) [47]

5% of those receiving AZA or 6MP suffer from pancreatitis of unknown origin, mostly in the first 30 days of therapy [51].

Furthermore, GI disturbances including nausea, emesis and pain are another side effects which lead to discontinuation [52].

2.2 Monoclonal antibodies used in inflammatory bowel diseases

There is no doubt that the initiation of biologicals with monoclonal antibodies provides significant benefits in UC and CD treatment. They improve the manifestations, inflammation and quality of live (QOL). Furthermore, the magnitude of their benefits has increased which improves understanding of how best to utilize them [12].

TNFα is the main target of the mABs which used in IBD. It promotes cellular proliferation and differentiation as well as the proinflammatory response. We should reserve IFX, adalimumab and golimumab for moderate to severe IBD poorly responding to other treatments. Actually, they can improve disease control, reducing hospitalization and surgery. Unfortunately, patients on such valuable therapies might experience disease relapse [53].

Until now, the cause of failure is unknown, but possible risk factors represented by individual are alterations in pharmacokinetic and pharmacodynamics properties or immunogenicity, so dose optimization for every patient in therapeutic drug monitoring (TDM) protocols is suggested to be valuable (Table 2). Newly mABs target

Table 2 Monoclonal antibody dosing regimen and dose flexibility

Subcutaneous [12]. BIOLOGIC	Induction regimen	Maintenance dose	Maintenance interval	Escalation
Infliximab	5 mg at week 0	5 mg/kg	Q8	10 mg/kgQ8 OR 5 mg/kg Q4
Adalimumab	160 mg at week 0 80 mg at week 2	40 mg	Q2	80 mg Q2 Or 40 mg weekly
Golimumab	200 mg at week 0 100 mg at week 2	50 mg if > 80 kg 100 mg if > 80 kg	Q4	IF < 80 KG Increase to 100 mg From week 6 (if > 80 kg, N/A)
Vedolizumab	300 mg at weeks 0, 2, & 6	300 mg	Q8	Q4 (Additional Week 10 dose in CD)
Ustekinumab	Week 0.iv: < 55 kg 260 mg 55–85 kg 390 mg > 85 kg 520 mg	90 mg SC	Q12 OR Q8	Q8

CD Crohn's disease, *IV* intravenous; *N/A* not applicable; SC [62]

extra-cellular proteins which have a role in IBD onset and maintenance [54].

2.3 Infliximab (IFX)

The structure of a recombinant monoclonal antibody of IgG1 kappa subclass is 25% murine and 75% human sequences. Infliximab has a variable murine Fab′region connected to human Immunoglobulin G1 (IgG1) constant region by bisulfide bonds [55] (Table 1).

There is evidence from clinical trials involving cases with Rheumatoid arthritis (RA), psoriatic arthritis, or ankylosing spondylitis that blocking the drug's efficacy due to the existence of antibodies against the anti-tumor necrosis factor (anti-TNF-α) molecule. These results reveal the development of a fully human anti-TNF-α molecule to prevent the immunogenic effects and antibodies' production which might drug's efficacy and safety in trials with CD patients, noting that IFX has a cytotoxic and apoptotic like action [56].

Furthermore, the potentiality to induce immune genicity can be done by all exogenous proteins, while fully human proteins could be non-immunogenic at all (Table 1).

2.4 Adalimumab (ADA)

This is a fully humanized recombinant monoclonal antibody with direct TNF-α inhibitory effect, cytotoxicity and apoptosis. It is structured basically of human-derived variable regions and a human IgG: j constant region [56]. ADA lower circulatory Interleukins (IL-6) and acute phase proteins, like C-Reactive protein (CRP). It is shown that ADA-stimulating apoptosis through reverse signaling in blood monocytes, leukemia cells, and lamina propria T-lymphocytes [56] also has the ability to promote the proliferation of antibodies in many cases [57].

Several clinical trials have confirmed that the generation of antibodies against ADA is less frequently than that for IFX. Clinical study revealed that 9.2% of CD cases that have lower trough serum IFX values developed ADA antibodies. Moreover, three clinical studies indicated that 5% only of ADA-treated rheumatoid arthritis patients developed ADA-neutralizing antibodies [57] (Table 1).

2.5 Vedolizumab (VDZ)

VDZ prevents the migration of alpha-4 beta-7 integrin molecules that expressed on gut-specific lymphocytes into the GI parenchyma and the consequent inflammatory response. Although all biologics have a systemic immunosuppressive effect, VDZ is unique in its gut-selective mechanism of action [58].

The largest cohort to date which has been performed by US VICTORY consortium (Vedolizumab health outcomes in IBD) established that among 212 CD cases, the rate of clinical remissions at one year was 35% [59]. Moreover, such rate must be taken in the consideration of the high previous anti-TNF inhibitor exposure rate (90%) [60] (Table 1).

The reduced response rates in observational studies are due to relatively increased rates of prior anti-TNF utilization confirmed that the rates in the phase III GEMINI trials of VDZ (48% in GEMINI I and 62% in GEMINI II) are a marker of the complexity of patients observed in practice. Also, high prior anti-TNF exposure was revealed in several other 'real-world' cohort studies [61] (Table 1).

2.6 Ustekinumab (UST)

UST is a recently NICE-approved monoclonal antibody for CD treatment. It binds to IL-12 and IL-23 and prevents activation of antigen presenting cells and their differentiation into Th1 and Th17 lymphocytes

[62]. Consequently, the inflammatory cascade which involves the formation and secretion of many cytokines (e.g., *interferon (*IFN-γ), IL2, IL10, IL22 and TNF-α) is decreased [58].

Anti-TNF-refractory cases that initiated therapy as long ago as 2011 found to response with 39% and 60% at 3 and 6 months, respectively, in the real-world CD Canadian cohort ($n=167$) with remission rates of 15% and 25% [62]. Such figures might be utilized in patient's counseling in terms of possibility of benefit and certainly are optimistic, even in the face of anti-TNF non-response [63] (Table 1).

2.7 Golimumab

Fully human monoclonal IgG1 antibody developed by Janssen Biotech, Inc. Golimumab is utilized for moderate to severe UC in adults not responding to conventional treatment such as steroids and 6-MP or AZA, or have intolerance to or contraindications for these drugs. Increased serum and tissue concentrations of TNF-α have been implicated in the pathophysiologic process of many chronic inflammatory disorders such as CD and UC [64]. It was demonstrated that cytokines, chemokines, and growth factors have significant roles in the pathophysiologic process of IBD. Golimumab, like other anti-TNF agents, acts by direct binding to the soluble and transmembrane precursor forms. But preclinical studies demonstrated that golimumab has a greater binding affinity compared with IFX or adalimumab for the soluble and transmembrane TNF-α. To prevent TNF-α binding to its receptors, golimumab suppresses the biological activity of TNF-α [65].

There are 2 TNF-α receptors (TNFR1 and TNFR2), and their activation by TNF-α triggers an intracellular signaling cascade, leading to release of cytokines, cellular proliferation, and apoptosis. TNFR1 activation induces nuclear factor-κB (NFKB), which undergoes translocation to nucleus to activate the transcription of many pro-inflammatory cytokines including IL-8, IL-1, IL-6, COX-2, and TNF-α [66] (Table 1).

2.8 Positioning of monoclonal antibodies

The choice of first-line biological treatment according to the mechanism of action is very critical. Head-to-head randomized control trial data show the benefit of a certain approach over other approaches. However, these data cannot predict the response of individual patients to each medication [67].

Many factors are incorporated in the choice of biological drugs, like the high prevalence of extraintestinal manifestations or perianal disease (where anti-TNF is favored), additionally if there are comorbidities like predisposition to or history of cancer or infections (where VDZ is favored). Furthermore, the choice of suitable biological treatment must take in the consideration if it is being administered as monotherapy or in combination with an immunomodulatory [68].

Additional factors including patient's preference and administration route must be also taken in consideration. In general, most active CD cases start with TNF antagonists as their first monoclonal; this class has been found to have high effectiveness in recent clinical practice. They are highly beneficial in extraintestinal manifestations and perianal disease with applying TDM to optimize their effect drug [68].

From the other side, patient who responds well to one TNF antagonist, however has a pharmacokinetic loss of response will benefit from another anti-TNF drug [68] and in cases of failure of the first-line therapy, a switch out of class is then recommended. Positioning of first-line therapy in UC is less clear except with VDZ which demonstrate adequate tolerance, strong mucosal healing data [69], the longevity of effect [70] and minor immunogenicity [71].

It has to be noted that this is a significantly moving field and that the next wave of biologicals and small molecules (e.g., tofacitinib and ozanimod) will add further complexity. In cases of failure of therapy or the patients does not respond to TNF-α antagonists, we should shift to another anti-TNF-α agent. Many studies declared that antibodies formed against a particular anti-TNF-α agent are specific and do not influence the bioavailability of another TNF-α antagonist, although in the studies in patients with rheumatoid arthritis, the risk of developing antibodies against certain TNF-α antagonist is greater among those who developed antibodies against a preceding TNF-α antagonist [71].

3 Combination therapy of thiopurines and IFX for IBD patients

Clinical practice and studies demonstrated that combined IFX and thiopurine therapy has more efficacy in the induction of remissions in CD and UC as compared with monotherapy of each agent, these results could be clarified by the concept of diminished risk of immunogenicity accompanied with lower anti-IFX antibodies. Moreover, such effect is a result of a higher drug availability and consequently an enhanced clinical response [72].

Half of patients lose the effect of IFX maintenance therapy, this can be caused by formation of antibodies against IFX [anti-IFX Abs] leading to minimized or absent circulating levels of active drug [73]. Continued IFX therapy in the existence of anti-IFX Abs can also be reflected to severe hypersensitivity reactions [74]. Patients who promoted anti-IFX Abs are prone to later develop

anti-adalimumab Abs, leading to repeat loss of response. Thus, it is pertinent to find ways to minimize the risk of anti-IFX Ab formation. These studies have convincingly shown that combination therapy with IFX and thiopurines is more effective than monotherapy with either agent in immunosuppressor-naïve IBD patients [75].

Thiopurines have to initiated as soon as rapid as anti-IFX generation was observed to start at 18 days post-initiation of therapy which leads to the construction of their use [76].

Combination therapy is accompanied with many side effects, graded from infections to malignancy. Data about the safety of combination therapy come predominantly from drug registration trials, dedicated trials on combination therapy, as well as registries. Cases on combination therapy had a higher incidence of infection. From the other side, CD cases on immunosuppressant showed a greater risk of cancers while those administering IFX combined with immunosuppressive agents had a greater incidence of infection [77].

Doses of immunosuppressive agents must be reduced as compared with monotherapy in cases that started therapy with IFX for about a year, but cases that discontinued biologic therapy appear better to continue AZA [37].

3.1 Combined therapy versus monotherapy

Combination of TNF antagonist and immunosuppressants has been found to decrease the risk of antibodies production among CD cases; the magnitude of decrease is augmented when anti-TNF agents are given after a scheduled strategy [78–81]; this indicated that the rate of antibodies' production in refractory CD cases receiving IFX episodically was significantly lower than patients administering concomitant immunosuppressive agents in comparison to patients not on such agents respectively [79].

Vermeire and co-workers have confirmed such results in their study measuring the efficacy of immunosuppressive agents in preventing antibodies' formation in IFX-treated CD patients in an on-demand schedule. AZA or methotrexate also caused a more reduced incidence of antibodies in comparison to those not o immunosuppressants [80].

Hanauer et al. confirmed that the risk of immunogenicity can be reduced by concomitant usage of immunosuppressives in cases administering IFX in a scheduled approach comparing with patients receiving IFX monotherapy [81].

The SONIC trial investigated rates of antibodies formation in CD cases that were naive to immunosuppressive and TNF antagonist which, randomized to receive AZA or IFX or their combination, revealed that the antibodies production was considerably lower in patients taking the combination treatment than in those on IFX alone [42].

Feagan and colleagues also found that the combination of methotrexate and IFX in CD cases significantly decreased the rate of antibodies production (4% in cases administering combination therapy versus 20.4% in those administering infliximab alone—following a scheduled regimen) [82].

Similarly, to infliximab, ADA could also stimulate the production of antibodies this risk is also diminished when mAbs are administered together with immunosuppressants following a scheduled maintenance strategy [83, 84]. Furthermore, UC patients on combination therapy of AZA immunosuppressant with IFX showed reduced antibodies production and increases IFX trough levels [82, 85, 86].

Regarding efficacy, it is clear that the combined therapy of IFX and AZA has more effectiveness compared with either drug monotherapy for inducing clinical remission and mucosal healing in CD and UC [42, 82]; this high effectiveness is because of lower rates of antibodies production and greater IFX drug concentrations in cases administered combination regimen [82].

3.2 Personalized medicine in IBD

The TDM protocols along with pharmacogenetic analyses are with added benefits in following therapeutic effects of mABs and protecting individuals from toxic effects; such endpoints might be combined with indicators of clinical effectiveness and tolerability (for example: age, severity, and extension) or inflammatory biomarkers (FCP and CRP) to enhance the predictive value of the phenotypic and/or gene signature [87].

Weak treatment efficacy may be associated with antibodies in patients' plasma, whereas their formation might be variable between TNFα antagonists, ranging from $\leq$ 2.3% for UST [88, 89], up to 25.3% for IFX [90], ADA (14.1%), certolizumab (6.9%), and golimumab (3.8%). Moreover, modulation of serum antibodies formation can be achieved by simultaneous intake of other medications, including AZA and methotrexate. Actually, the IFX-AZA combination was linked to a decreased incidence of antibodies (0.9% versus 14.6%) and high trough concentration (C min) values of mAB than the sole IFX [91].

The combinations of IFX-thiopurines or ADA-methotrexate are superior to bringing antibodies to non-detectable concentrations in 77% of cases that had high immunogenicity and poor response [92].

Methotrexate in pediatric population significantly decreased IFX clearance and likely reduce the antibodies production; this may be due to the fact that formation of antibodies depends on the schedule mAB approach

[93]. The development of adverse drug reactions (ADAs) is greater following an occasional intake of mABs rather than a regular approach [42, 93]. Furthermore, the genotype at human leukocyte antigen (HLA-DQA1*05) locus can predict the immunogenicity against IFX [94].

4 Pharmacogenes in inflammatory bowel diseases

4.1 Genetic factors

Many patients have a positive family history of IBD. This was revealed in about 10% to 25% of patients in Western countries however was significantly lower (less than 5%) in Asian countries [95]. A study reported that concordance rates in monozygotic twins with IBD were 35% and 16% for CD and UC, respectively, signifying genetic background [96]. Genome-wide association studies (GWAS) recognized 163 loci [97]. Another study found that Autophagy Related 16 Like 1 (ATG16L1) and tumor necrosis factor super family 15 (TNFSF15) were linked to CD [98]. In general, such genetic variants explain approximately 13.6% of CD and 7.5% UC patients [97].

Patients with IBD usually necessitate therapy all over the life, and the availability of pharmacological therapy is limited to certain medications such as aminosalicylate, corticosteroids, immunosuppressant agents, biologicals and antibiotic agents, while thiopurines drug is an established second-line medications to maintain remission [13, 99].

Thiopurines are considered the 1st choice immunomodulating agents for treating IBD. They are used for managing inflammatory UC, CD and chronic inflammatory GI diseases [99].

Thiopurines is well tolerated by most IBD patients; approximately one-third of patients have their medications modified or stopped because of several side effects [47, 78]. Newer pharmacologic treatments, such as monoclonal antibodies (mABs) with their targeted activity against inflammation and their tolerability in mABs represent a new era for intense research [78].

Progress in genetic-testing technology allowed the evolution of studies to more densely map the genome through association studies containing many hundreds of thousands of markers known as single nucleotide polymorphisms (SNPs). Multiple studies with large patient numbers using genome-wide association studies (GWAS) followed to identify IBD susceptibility loci [100–105]. Despite the large numbers in each of these individual studies, it has been the resultant meta-analyses which have really aided in the identification of a larger number of IBD susceptibility loci [106, 107].

These works have culminated in the publication of a meta-analysis of GWAS and the identification of 163 IBD susceptibility loci, 30 of which are classified as CD-specific and 23 as UC-specific [107]. Subsequent studies have increased this number to 206 known IBD susceptibility genes [108, 109]. Advancing the understanding of genetic determinants of IBD has been a recent multinational immunochip study which suggested that there may in fact be three genetically distinct sub-phenotypes of IBD: ileal CD, colonic CD and ulcerative colitis [110].

Examples include defects in the innate immune system, in the genes regulating autophagy and in the IL 23 signaling. Such discoveries have provided a further understanding of etiologic mechanisms in IBD and have led to the development of novel therapies. However, GWA studies have yet to account for the heritability estimates of IBD suggested in twin studies. This is known as missing heritability and it highlights some of the flaws of GWA studies in identifying causal genetic variants for diseases which are both phenotypically as well as genetically complex [111, 112].

Cohorts are heterogeneous and the SNP coverage in GWA studies can be incomplete. The variable role of environmental risk factors cannot be fully accounted for in studies. Large datasets have been combined in meta-analyses in order to adequately power studies to identify IBD susceptibility loci. Many of the alleles identified in these studies are relatively common, with MAF > 5% (minor allele frequency) and with low effect sizes. Therefore, it is felt that IBD is multi-factorial requiring multiple genetic risk factors combined with environmental exposures. An increasing genetic burden of the aforementioned 163 IBD susceptibility genes has been associated with earlier onset of disease in CD [113].

One exception to this has been the identification of a number of monogenic disorders associated with very early onset IBD [114]. For example, IL-10 receptor mutations result in a severe, early onset colitis, which has been successfully treated by bone marrow transplant [115, 116]. However, the differing phenotype and treatment of these monogenic disorders suggest they may be a different entity to more conventional IBD [117].

Enzyme activity assessment is considered a useful predicting method at the phenotype and genotype levels for pre-drug practice responses. In 1980, the first report to measure TPMT activity in human was conducted on 298 Caucasians. Investigators reported that 11.1% had intermediate activity, 89.6% had high activity, and 0.3% had no activity. The findings were liked to an autosomal codominant inheritance of a pair of alleles for low and high TPMT activities and were a big deal in pharmacogenetic science [118].

4.2 TPMT gene

Pre-therapy detection of TPMT activity might be valuable to predict thiopurines toxicities. But, evidence of their values remains unknown. For instance, cases with

TPMT activity less than 30.5 EU/mL are more expected to respond to thiopurines drugs compared with cases with greater activity [118]. Other reports failed to report such association [119]. A high percentage of adults with myelosuppression effects showed a normal TPMT genotype, indicating the inaccuracy between the genotype and phenotype of TPMT [120].

Genetic variability causes a reduced TPMT enzymatic activity and therefore affects the increased formation of the metabolite 6TGN. Accordingly, the Bone marrow becomes disrupted with a reduction in the production of leukocytes [121]. Many studies enrolling IBD patients and patients with other autoimmune disorders demonstrated the significance of applying a deeper analysis of genotyped cases [122, 123].

Valuable data exists in clinical research about the pharmacogenetics of thiopurines and personalized medicine aims at predicting the impact of treatment in advance by examining genetic signatures and thus adjust the drug and doses. For thiopurines, the complex biotransformation pathway of azathioprine and 6-mercaptopurine is implicated and the association between TPMT gene alleles and the metabolism rate was significant and was approved by the FDA as the first main pharmacogenetic biomarker [37].

Targeted loci in IBD can be recognized and the value of various genomic markers like functional polymorphisms in the relevant genes which encode for the response to TNF treatment among IBD cases has been assessed [124, 125]. As anti-TNF mAbs target TNF, functional polymorphisms for TNF and TNF-receptor superfamily are a valuable region for research [124–126].

Research at the level of cytokine pathways polymorphisms in (IL-1B, IL-6, IFN-gamma, TNFRSF1A, NLRP3, IL1RN, IL-18, and JAK2) and NFkB pathway (TLR2, TLR4 and NFKBIA) found a close association with response to TNF antagonists among IBD cases [125, 127].

The development of genomic-relevant antibodies in IBD cases has been recently identified. Degenhardti and co-workers demonstrated that the anti-GP2 IgA and IgG antibodies were linked to CD and had a great discriminatory capacity for CD vs. UC [128].

New era of a genomic association with antibody expression is developed; it can recognize various loci linked to concentrations of anti-GP2 isoform beta IgG and IgA, several of which are responsible loci for IBD susceptibility, although their importance in assessing the effectiveness of TNF antagonists in CD vs UC has not been evaluated [128].

Genotyping sensitivity considerably ranges among cases having intermediate and poor enzymatic activity. From the other side, polymorphisms have been found to have a central role in thiopurines' toxicity [129].

In addition, numerous enzymes that involved in thiopurine biotransformation and their variable activities offer a clue for the measurement of serum metabolites which reflect the drug metabolism and distribution and facilitate the determination of the optimum dose of medications for each patient to prevent side effects and toxicities [130] (Fig. 2).

4.3 NUDT15 gene

In the case of the reduced activity of TPMT and Nudix Hydrolase 15 (NUDT15), the Clinical Pharmacogenetics Implementation Consortium recommends decreasing azathioprine, 6-mercaptopurine, or 6TG doses, or introducing a non-thiopurine immunosuppressive agent to improve the efficacy of thiopurine treatment and resolve their cytotoxicity, taking in the consideration the balance between effectiveness and cytotoxicity with proper monitoring [131].

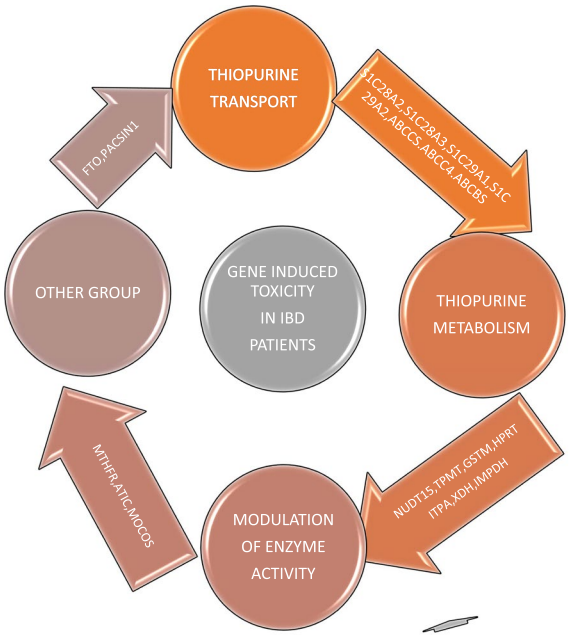

Fig. 2 Potential genes causing cytotoxicity in IBD patient. Explanation of Abbreviations: 28-member soluble SLC28A2 transporter family 2, The 28-member soluble SLC28A3 transporter family 3, The soluble SLC29A1 transporter family 29 members 1, *SLC29A2* Solute 29 Vector family member 2, *ABCC5* ATP binding tape subclass C 28 member 5, *ABCC4* ATP subclass C binding strand member 4, *ABCB5* ATP Subclass B Member 5 binding tape, *NUDT15* nudix hydrolase 15, *TPMT* Thiopurine S-methyltransferase, *GSTM* glutathione S-transferase mu, *HPRT* hypoxanthine phosphoribosyltransferase, *ITPA* inosine triphosphatase, *XDH* xanthine dehydrogenase, *IMPDHA* inosine-5′-monophosphate dehydrogenase, *MTHFR* methylenetetrahydrofolate reductase, *ATIC-5* aminoimidazole-4-carboxamide ribonucleotide formyltransferase; dioxygenase dependent on FTO-alpha ketoglutarate, *MOCOS* molybdenum sulfate cofactor, *PACSINI* protein kinase C and a casein kinase substrate in neurons 1

The involved genes in thiopurine metabolism include TMPT, Inosine Triphosphatase gene (ITPA), hypoxanthine phosphoribosyltransferase 1(HPRT), GSTM1, Xanthine dehydrogenase (XDH), Guanine Monophosphate Synthase (GMPS), and NUDT15 [132]. But, the impacts of TPMT and NUDT15 on thiopurines effects and toxicity have been reported. So, it is recommended to adjust the initial dosages of azathioprine, 6-mercaptopurine, and 6TG in accordance to TPMT and NUDT15 genotypes, and to detect the polymorphism among IBD cases [131].

The tolerance, efficacy and risk associated with thiopurine toxicity also described in the term of polymorphisms [132]. The cytotoxicity of thiopurine treatment is dependent upon the existence of TPMT *3A allele in Caucasians. Simultaneously, in Latin and Asian races, it is the allele c.719A>G. Clinical trials including 219 participating IBD cases showed a difference between Caucasian and Asian races [133, 134].

NUDT15 gene is a critical gene for AZA-associated leukopenia in Chinese cases, c.415C>T (rs116855232) polymorphism. The C/T genotype was found in 44 cases, 16 of them administered azathioprine, and 50% had significant leukopenia. Homozygotes C/C were linked to a 17.2% likelihood of depletion of leukocytes and subsequent inflammation [135]. NUDT15 causes a deactivation of 6TG triphosphate by hydrolysis to monophosphate [135].

Decreased activity and the accumulation of toxic metabolites in DNA may be related to polymorphism p.R139C and alleles T/T and C/T [136]. It was reported that TPMT gene is responsible for leukopenia and myelotoxicity among European cases [137]. TPMT gene polymorphisms were associated with hepatic dysfunction in 10% of cases having a deficiency in a functional allele and 21% of heterozygotes being treated for inflammatory disorders [123, 138].

A total of 107 European IBD cases with the following missense variants in NUDT15 gene were considered significant: p. Gly17_Val18del, p. Val18_Val19insGlyVal, p. Arg139Cys, c.3G>C, c.217delA [139]. The new c.3G>C allele resulted in a loss of the start codon, whereas c.217delA influenced the reading frameshift. Signs of anemia and leukopenia were also detected in all patients who underwent sequencing for a non-functional TPMT allele [123].

NUDT15 gene polymorphism was found in 13% of persons, and in 6%, 2 variants of genes and significant liver toxicity were detected [123].

Choi et al. 2022 examined 131 cases with IBD, sequencing of additional 34 genes were included other than NUDT15 and TPMT. Two 5-Aminoimidazole-4-Carboxamide Ribonucleotide Formyltransferase/IMP Cyclohydrolase (ATIC) gene polymorphisms were significant ($p < 0.05$). Polymorphism rs3821353 accounted for the intracellular concentration of 6TGN, whereas polymorphism rs16853834 and rs11706052 Inosine Monophosphate Dehydrogenase 2 (IMPDH2) gene were associated with the ratio of 6TGN and the administrated dose of thiopurines. The activity of ITPA rs6139036 was clearly related to the concentration of 6-methylmercaptopurine nucleotide (6MMPN) metabolite and the maintenance dose of the medication were associated with [140].

4.4 ITPA gene

The same result from last analysis was shown for polymorphism rs8362 of ITPA gene [141]. In IBD children and in the group having other autoimmune diseases, the decreased in ITPA activity strongly related to 6MMP accumulation [142, 143].

In Asians, c.400G>A polymorphism of the alpha-ketoglutarate dependent dioxygenase gene alpha-ketoglutarate-dependent dioxygenase (FTO) was linked to a 65% reduction in its enzymatic activity with significant leukopenia [144]. This gene might be regulated by the genetic variant rs16952570. Higher WBCs were detected in cases with C/C FTO genotypes in comparison with T/T homozygous 30 days following initiating thiopurines therapy [145].

4.5 HLA gene

Additionally, polymorphisms in encoding several other genes including HLA-DQA1*05 have also been confirmed to be linked to response to TNF antagonists [94]. The polymorphism rs2647087 of HLA gene is correlated with pancreatitis among patients administering thiopurines treatment. In the non-functional C/C homozygotes, the inflammation risk was 14.6%, A/C heterozygote 4.3%, while wild-type A/A 0.5% [146].

In a study that revised 15 GWAS, it was documented that 110 IBD loci were shared between UC and CD while 30 loci were specific for CD and 23 loci were specific for CD [97]. Moreover, a recently published GWAS involving 1240 biological naïve cases reported a significant relationship between HLADQA1* 05 locus and the enhanced rate of immunogenicity and the production of antibodies against IFX and adalimumab, although the usage of the biologicals alone or combined with other medications did not influence such correlation [94].

In another report on 252 IBD cases, the variant HLA-DQA1*05 was linked to a significant increase in the risk for antibodies against IFX (HR _ 7.29) with no effect of age, sex, weight, and immunomodulatory [147].

The initial clinical studies investigating the effect of Molybdenum Cofactor Sulfurase (MOCOS) gene on the

metabolic pathways of thiopurines revealed its significant role in enzymatic regulation of Aldehyde Oxidase 1 (AOX1) and XDH. But more investigations should be conducted to completely indicate the role of MOCOS gene on cytotoxic effects. This study also examined children with IBD indicated that GMPS gene significantly underlines tolerance to the medication utilized. The mechanism of cytotoxicity was achieved by an attachment of the phosphate residue to 6-TIMP converting it to 6TGN [129].

The effect of transporters in IBD is not completely declared yet. Polymorphism rs8180093 of ATP-binding cassette sub-family G member 5 (ABCC5) gene causes resistance to mercaptopurine and affected the occurrence of leukopenia among IBD cases where solute carrier family (SLC29) and SLC28 genes regulate thiopurines' uptake, transport and accumulation of cytotoxic metabolites [140]. In fact, such impact was demonstrated in those with ALL receiving thiopurines drugs. More studies are necessary for investigating the association of their polymorphisms with the cytotoxicity of thiopurine drugs among IBD cases [141].

4.6 FCGR3A gene

In addition, the polymorphism in Fc portion of immunoglobulin G (FCGR)3A gene was an indicator of therapeutic response among CD cases. Of note, Bank and colleagues who examined 587 CD and 458 UC cases, replicated the genetic signature in a following study [148]. The updated signature demonstrated 10 polymorphisms involved in nuclear factor-κB (NFκB-), TNFα-, and cytokines' signaling. Also, cases that had risk signatures for TNFα-driven inflammation had a higher likelihood of experiencing benefits from TNFα antagonist. An additional cohort also confirmed such results in 103 IBD cases [149].

Of note, the wild-type variant of polymorphism rs396991 (V158F) in FCGR3A gene was associated with the production of antibodies and decreased IFX levels. Generally, the studies demonstrated the necessity for investigating several factors to acquire genetic signatures with adequate predictive/prognostic value [12].

In 2016, a meta-analysis study conducted to investigate the relation between polymorphisms in TLR2, TLR4, TLR9, TNFRSF1A, IFNγ, IL-6, and IL-1β genes and therapy response among IBD cases [148].

Genetic markers might also combine with clinical or laboratory data. One cohort revealed a significant association between polymorphism rs1143634 in IL1β gene, the greater cytokines' levels at baseline, and decreased response in 29 CD and 18 UC cases, based on the clinical remission of IFX at week 14 [150]. Also, polymorphism rs2228273 in Zinc finger protein 133 (ZNF133) was a predictor of reduced response to IFX after the initial administration [151].

Microarrays, GWAS, as well as next-generation sequencing platforms have recently been employed in pharmacogenetics which enables screening for multiple genetic markers simultaneously [152]. Additionally, genetic markers were used in combination with clinical and laboratory data to achieve highly-performant productivity [153]. For example, a recent study including 231 UC Caucasians reported 2 genetic signatures of 8 and 12 single nucleotide polymorphisms (SNPs) linked to primary non-response (PNS) and duration of response (DR) to TNF-α antagonists, respectively [154].

It is important to mention that genetic risk scores of primary non-response (PNS) and DR had no associations with IFX concentrations or antibodies' development, so the correlations of such SNPs might be through another mechanism than pharmacokinetics or antibodies' development [12].

Another research assessed whether the gene signature developed for IFX would also be a predictor for mucosal healing in UC cases, clinical response, and remission following golimumab administration [155]. The results showed that genetic signature was predominantly drug-specific as it failed in identifying cases that achieved remissions or responses following golimumab administration. This study also assessed the likely diagnostic factor for TNFα antagonists [156]. Furthermore, in 474 IBD European cases, rs116724455 in TNFS4/18 and rs2228416 in PLIN2 were predictors for treatment effectiveness [157].

In the context of genetic polymorphism and drug efficacy, a study from Spain reported a significant relationship between 5 polymorphisms in TNF-α or NFκB pathways and serum levels of IFX (rs5030728 in TLR4 and rs11465996 in LY96) and adalimumab (rs1816702 in TLR2, rs2569190 in CD14, and rs3397 in TNFRS1B) in children with IBD [158]. However, dissimilar regimens and patients' number in subgroups are considered weak points for those associations [159].

Finally, biomarkers might have an important role in distinguishing pediatrics—from adult-onset IBD. For instance, GWAS has shown SNP differences in the polygenic architecture between pediatrics and adult-onset IBD, which could be the valuable genetic markers to examine the role and significance of accumulated rare and detrimental variants in involved pediatric—and adult-onset [125].

5 Discussion

Taking into account the necessity for using thiopurines for IBD patients and the challenge of personalized medicine, thus conduction of more pharmacogenetic studies

and metabolite monitoring appears natural and obvious [37, 160].

The era of anti-TNF mAbs give promising treatment for better outcome of the disease, even so, responding to these therapies failed in high percentage of patients but the optimization of the treatment will lead to improvement. Patients who loss of response could be managed by monitoring plasma drug levels and ADAs (immunogenicity) [161].

Kinetics of mAbs is a persistent need to indicate patient's response, characteristics of the disease and many factors related to patients affect the PK of mAbs. Assessment of variables that affect configuration of mAbs could help recognizing patients that taking greater doses due to the fastest clearance of the drug. Unlikely, studies merged such variables into a single PK model in aimed population have not been completed yet. From the other side, increasing numbers of mAbs treatment of IBD make the monitoring of efficient dosing and factors influencing PK and PD of mAbs very critical steps so the success of these drugs will be established. Combined clinical, imaging, and PK studies must lead to worth advances in how to customize drug dosage and monitoring therapeutic response. Lately guiding individual dosage by PK algorithms is safer, effective and cheaper [162].

Systematic demonstrated a trend toward a higher adherence to adalimumab than to IFX, showing that self-administration of adalimumab does not impair adherence to TNF antagonists in CD cases. Higher adherence rates to adalimumab might be partially elucidated by the fact that only CD patients were treated with this biologic, while IFX was prescribed for cases with CD and UC. But, differences in methods and study design between studies do not permit a direct comparison between both agents. Also, only 13 studies were included and most of them were retrospective, while four studies were available only as an abstract. Lastly, many studies included a mixed population (rheumatoid arthritis, psoriasis, and IBD), and no data were provided according to disease type [163–165].

Regarding expecting response, pharmacogenomics tests may give clue before starting the biologic treatments [157]. In fact, realizing how much risk of UD and CD incubate could be done by expectable biomarkers of response to mABs called germinal genetic variants [166]. It's valuable that we notice that forecasting progress by a gene signature instead of a single genetic locus [167].

Designing the drug treatment for each IBD cases means selecting an effective approach which can be changed immediately if there is a poor response or after toxicities appear. Furthermore, some causes may continue to improve treatment on an individual basis, besides, chronic regime of combined drugs, its narrow therapeutic index, and the gradual disease exacerbation [168].

For thiopurines, methotrexate, aminosalicylates, and immunosuppressants, the mentioned strategy is also beneficial both in adults and children especially when the protocols of TDM needs chromatographic ways that can be exhausted and need experts as in case of thiopurines. Furthermore, predicting the impact of combined treatment regimens could be analyzed by pharmacogenomic, that are advantageous as second-line therapy [169] for instance, German study defined genetic passport which covered multiple loci (TPMT, NUDT15, HLA-DQA1*02:01-HLA-DRB1*07:01, and HLA-DQA1*05) related to thiopurines toxicity and anti-TNFα mABs [170].

Pharmacogenomic signature would work with clinical risk factors (i.e., prior treatment with TNF-α antagonists) [171], moreover it will help in decreasing the coast, improve health-care systems (QOL) [172]. But exciting of rare variant alleles will decline the curve [173], taking into consideration that genotyping and phenotyping are beneficial in monitoring failure and adverse reactions during treatment [174].

Conversely, since the body comprises more microbes than cells, the microbiome is of great interest in research. Therefore, significant research about microbiota interaction on the effect of thiopurines' therapy is expected for IBD cases. Effenberger et al. supported this hypothesis, and described an in silico metabolic prediction analysis for those treated with AZA or TNF antagonists. Authors evaluated the impact of microbiota on remission state and demonstrated that the predicted butyrate production showed significant improvement in those with remissions [37].

Such results suggested an association between microbiota and the efficacy of immunosuppressants for IBD patients. Whether the composition of microbiota in human body might also have a role in the cytotoxic effects of thiopurines is still questioned [37].

6 Future genetic markers

Perspectives in the future many genetic markers are linked to anti-TNF therapeutic response in IBD and, commonly, interpretation of genetic information in a meaningful manner might be challenging [65]. The significance of various genomic markers has been assessed, mainly markers that might affect anti-TNF therapeutic response, finding that not only polymorphisms of TNF and TNFR have a role to therapeutic response after pharmacotherapy, but also polymorphisms of cytokines and immunological pathways. In spite of the fact that they cannot be fully considered predictive markers as they require validation, these markers are not altered with

time and many of them are promising in clinical practice. Thus, relationship between SNPs and response to biologicals in IBD was assessed in many pharmacogenetic studies, reporting a relationship between some SNPs and response to biologics [148].

Genetic polymorphisms linked to therapy outcome in IBD cases receiving biologicals have been assessed to discover a possible pharmacogenetic approach for predictive value. So far, no recommendations do exist about the search for genetic polymorphisms incorporated in the pathogenetic process of IBD as part of therapeutic optimization [124].

In particular, polymorphisms of TNF and TNFR genes, were linked to inadequate response, in addition to the rs1799724, rs767455, rs1061624 and rs976881. In contrast, other polymorphisms in such genes were linked to a good response, for example rs361525 and rs3397. The majority of polymorphisms in innate immunity genes showed no association with therapeutic response; but, TLR4 rs5030728, rs1554973, IL-1_ rs4848306 and IL-17 rs766748 polymorphisms were linked to a good response, whereas IL-1_ rs1143634 was associated with a worse response. Furthermore, we reported that FasL rs763110, Caspase-9 rs4645983 and ATG16L1 rs10210302 polymorphisms were linked to with a good response, but ATG16L1 rs2241880 polymorphism was correlated to a worse response [175].

Also, the role of polymorphism which interfere with the biological therapy that targets IL-12 and IL-23 has been evaluated despite only one study linked PTPN2 rs7234029 polymorphism to poor response to Ustekinumab. Nonetheless, environmental factors including nutritional factors, lifestyle, and other medications which might interact with genetic susceptibility were not taken into consideration [176].

Furthermore, the monitorization time, differences among populations, genetic heterogeneity as well as gene–gene interaction were not considered. Similarly, some statistical errors might have affected the results. Also, the included studies in the systematic review were heterogenous for many characteristics (ethnicity, biologicals administered, IBD type), a likely bias could be ascribed. Besides, only published studies were retrieved, while preprint servers, another registries/results database were not included [177].

The potentially overlapping data were ruled out; however, some overlapping data were missed or non-overlapping data might have unintentionally ruled out. Furthermore, the degree of disease activity in patients might have been different among studies, consequently this might have introduced other biases. Also, we could not rule out that correlations were not reported due to low statistical power in many studies included in the review. Nonetheless, the systematic review has strengths: we assessed a large number of polymorphisms which could alter the effectiveness of biologicals approved for IBD, offering a wide pharmacogenetic overview of current biologic therapy used to treat IBD. Furthermore, all the filtered genes which were considered, having a biologic effect, allowed a logical version of the observed effects [124].

The study highlights correlations between therapy response and specific alleles based on a robust biologic or clinical effect. To conclude, improving TNF, TNFR and IL-1 pharmacogenetics could be the most appropriate approach toward a targeted treatment for IBD, even if bias like ethnicity and different types of biologic drugs utilized must be considered. Pre-therapy genetic testing must be combined with clinical IBD therapeutic guidelines, because it is the most appropriate way to choose the most suitable biologic agent for each subject. Lastly, clinical implementation of pre-therapy genotyping can be achieved through investigating the role of target genes that can interfere with the action of other biological agents apart from anti-TNF-_ agents to recognize genetic variants of higher predictive performance [178].

7 Conclusion

Lastly, taking into consideration the constant necessity for using thiopurines drugs to treat IBD and the challenge of personalized medicine, extensive pharmacogenetic studies and metabolites' monitoring are needed.

Large prospective studies are necessary for comparing standard care with pharmacogenetics and metabolites' monitoring to confirm the role of these new investigations.

Pharmacogenomic studies on the association between the new monoclonal antibody drugs and various genetic polymorphisms are insufficient. Moreover, factors involved in immunity and inflammation are very diverse, and there is currently no clear direction for personalized medicine, Therefore, further research is essential, and this will increase the safety and efficacy of the newly developed monoclonal antibody drugs, enabling more complete precision medicine.

The safety of providing purine drugs for IBD treated has been an issue of significant argument for several years. The current knowledge supports the selection of thiopurine drugs for pregnant females with IBD. In other words, the safety concerns of these drugs are real but also uncommon.

Monitoring thiopurine metabolites and enzymatic activity allow personalized dosing in IBD cases that started therapy and what is our knowledge of pharmacogenetic biomarkers as predictors prior to therapy, such questions will be discussed in this review.

Thiopurine effectiveness and toxicity are linked to the relative levels of metabolites. Genetic polymorphisms in metabolizing enzymes result in a large inter-individual variability in drug response and risk of toxicity. TPMT is one of the first pharmacogenetic tests to be incorporated in clinical practice. It is recommended before commencing thiopurines to prevent potentially myelosuppression. TPMT enzyme activity might be valuable for determination of the starting dose.

6-TGN and 6-MMP monitoring is beneficial in determination of the cause of non-response to thiopurines and 6-TGN monitoring might help decrease the risk of Myelosuppression.

Furthermore, predictive pharmacogenetic screening has more effectiveness because of extending the TPMT gene analysis to NUDT15, and thiopurine benefit are more than its risks in most of individuals, even during pregnancy. Adjustment of thiopurine doses via measuring their metabolites is routinely recommended and is better that weight-based dose.

It is worth to know also the relations between acute cytotoxicity and concurrent incidence of TPMT and NUDT15 gene polymorphisms [179]. Finally, all genes involved in increasing thiopurines toxicity in IBD patients are still unspecific. A lot of correlations require verification and functional studies in genome-wide research. However, expecting thiopurines side effects in IBD cases prior to treatment induction can be done by pharmacogenetics.

Abbreviations

GI	Gastrointestinal
IBD	Inflammatory bowel disease
NSAIDs	Non-steroidal anti-inflammatory drugs
TNFSF15	Tumor necrosis factor super family 15
ATG16L1	Autophagy related 16 like 1
SONIC	Study of Biologic and Immunomodulator Naive Patients in Crohn's disease
QOL	Quality of life
RA	Rheumatoid arthritis
IgG1	Immunoglobulin G1
ADRs	Adverse drug reactions
PGx	Pharmacogenetics
AZA	Azathioprine
IFX	Infliximab
ADA	Adalimumab
UST	Ustekinumab
IL	Interleukins
VDZ	Vedolizumab
IFN	*Interferon*
NFKB	Nuclear factor-κB
COX-2	Cyclooxygenase-2
NUDT15	Enzyme Nudix Hydrolase 15
FCP	Fecal calprotectin
NUDT15	Nudix Hydrolase 15 gene
C min	Trough concentration
TPMT	Thiopurine methyltransferase gene
HPRT	Hypoxanthine phosphoribosyltransferase 1
NLRP3	Family pyrin domain containing 3
XDH	Xanthine dehydrogenase
(ITPA)	Inosine triphosphatase gene
JAK2	Janus Kinase 2
GMPS	Guanine monophosphate synthase
ATIC	5-Aminoimidazole-4-Carboxamide Ribonucleotide Formyltransferase/IMP Cyclohydrolase
GSTM1	Glutathione S-Transferase Mu 1
IMPDH2	Inosine Monophosphate Dehydrogenase 2
6MMPN	6-Methylmercaptopurine nucleotide
FTO	Alpha-ketoglutarate-dependent dioxygenase
ABCC5	ATP-binding cassette sub-family G member 5
MOCOS	Molybdenum cofactor sulfurase
SLC	Solute carrier family
AOX1	Aldehyde Oxidase 1
FCGR	Fc portion of immunoglobulin G
PLIN2	Perilipin 2
ZNF133	Zinc finger protein 133
CBC	Complete blood count
GWAS	Genome-wide association studies
PNS	Primary non-response
HLA	Human leukocyte antigen
DR	Duration of response
TLR	Toll-like receptor 4
CRP	C-reactive protein
LY96	Lymphocyte antigen 96
ESR	Erythrocyte sedimentation rate
CD	Crohn's disease
UC	Ulcerative colitis
SCCAI	Simple Colitis Clinical Activity Index
PUCAI	The Paediatric Ulcerative Colitis Activity Index
UCDAI	The Mayo Clinic Score and Ulcerative Colitis Disease Activity Index
JAK	Janus kinase
6-MP	6-Mercaptopurine
6-TGNs	Thioguanine nucleotides
DPWG	Dutch Pharmacogenetics Working Group
CPIC	Clinical Pharmacogenetics Implementation Consortium
6-TITP	6-Thioinosine triphosphate
SNPs	Single nucleotide polymorphisms
PK	Pharmacokinetics
PD	Pharmacodynamic
TNF	Anti-tumor necrosis factor
SNPs	The single nucleotide polymorphisms

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Availability of data and materials
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Declarations

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Not applicable.

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Competing interests
The authors declare that they have no competing interests.

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