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REVIEW ARTICLE

Immunogenicity of Therapeutic Antibodies Used for Inflammatory Bowel Disease: Treatment and Clinical Considerations

Ole Haagen Nielsen[1] · Alexander Hammerhøj[1] · Mark Andrew Ainsworth[2] · John Gubatan[3] · Geert D'Haens[4]

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Abstract
The introduction of tumor necrosis factor inhibitors has led to a paradigm shift in the management of inflammatory bowel disease (IBD). The subsequent introduction of both anti-integrins and cytokine blockers has since expanded the biologic armamentarium. However, immunogenicity, defined as the production of anti-drug antibodies (ADAs) to the prescribed biopharmaceutical, means a significant fraction of patients exposed to biologic agents will experience a secondary loss of response to one or more of the drugs. In clinical settings, immunogenicity may be caused by several factors, both patient related (e.g., underlying chronic disease, systemic immune burden, including previous biologic therapy failure, and [epi] genetic background) and treatment related (e.g., dose and administration regimens, drug physical structure, photostability, temperature, and agitation). Here, we outline these elements in detail to enhance biopharmaceutical delivery and therapy for patients with IBD. Moreover, concurrent immunomodulator medication may reduce the risks of ADA generation, especially when using the chimeric drug infliximab. Summarizing the latest developments and knowledge in the field, this review aims to provide strategies to prevent ADA production and information on managing non-responsiveness or loss of response to biologics. Better understanding of the molecular mechanisms underlying the formation of ADAs and the critical factors influencing the immunogenicity of biopharmaceuticals may lead to improved health outcomes in the IBD community that may benefit both the individual patient and society through lower healthcare expenses.

1 Introduction

The use of recombinant therapeutic monoclonal antibodies (i.e., biologics) has transformed the therapy of a wide range of lifelong and debilitating inflammatory disorders, including inflammatory bowel disease (IBD) [1], wherein ulcerative colitis (UC) [2] and Crohn's disease (CD) [3] are the two most predominant entities, followed by microscopic colitis [4]. Thus, the incidence of IBD has been increasing for several decades [5], and IBD is observed in more than 0.7% of the population in some geographical regions [6].

Infliximab is a tumor necrosis factor (TNF)-α, monoclonal, chimeric immunoglobulin G1 (IgG1) antibody and was the first biologic agent approved for the management of IBD [7–9], followed by adalimumab (a human IgG1 monoclonal antibody) [10]. Overall clinical response rates of 60–70% have been documented for both drugs [1]. Despite these drugs having a beneficial primary response against IBD activity, a systematic review and meta-analysis reported that 10.1% and 13.4% of patients treated with infliximab and adalimumab, respectively, experienced an annual loss of response [11], and other studies have shown an increased risk of treatment failure in patients with anti-drug antibody (ADA) formation [12–14]. Subsequently, more biologics have been marketed; however, they all harbor an intrinsic immunogenicity risk, that is, the formation of ADAs that play an important role in the loss of response [15].

This disease places a significant burden on healthcare systems because of its chronicity and need for expensive

✉ Ole Haagen Nielsen
ole.haagen.nielsen@regionh.dk

1 Department of Gastroenterology D112, Herlev Hospital, University of Copenhagen, Borgmester Ib Juuls Vej 1, 2730 Herlev Copenhagen, Denmark

2 Department of Gastroenterology, Odense University Hospital, University of Southern Denmark, Odense, Denmark

3 Department of Gastroenterology & Hepatology, Stanford University School of Medicine, Palo Alto, CA, USA

4 Department of Gastroenterology and Hepatology, Amsterdam University Medical Center, Amsterdam, The Netherlands

Key Points

The introduction of biologics in the treatment of inflammatory bowel disease (IBD) has led to a notable change in basic assumptions of the prognosis of this condition and markedly reduced the need for surgical interventions.

Immunogenicity (i.e., production of anti-drug antibodies to specific biopharmaceuticals) is a major problem in clinical settings and leads to a weakened therapeutic response with potential disease complications.

Several aspects of immunogenicity and the numerous underlying factors are presented, both patient related (age, burden of disease, and genetics) and treatment related (drug physical structure, dose and administration regimens, route of administration, long-term exposure to therapy, photostability, temperature, and agitation).

Related strategies, including coadministration of immunomodulators, may help diminish the risks and help healthcare providers optimize therapy when prescribing biologic therapy in routine clinical situations.

therapies (including biologics) and surgery [16]. In an effort to provide patients with IBD with the most efficient biologic therapy, this review aims to provide clinicians with updated insights into aspects of biologic immunogenicity and their management strategies.

2 Search Strategy and Selection Criteria

We searched MEDLINE and Embase with immunogenicity as the main search term and the following key subsection headings: biologics (infliximab, adalimumab, golimumab, certolizumab, vedolizumab, ustekinumab, risankizumab and mirikizumab) and inflammatory bowel disease (ulcerative colitis and Crohn's disease). In general, the search was focused on publications from the last 10 years up to September 1, 2024, but was expanded retrospectively to include contributions to the literature considered relevant for immunogenicity related to biologics used for the management of IBD.

3 Treatment Failure

The mechanisms of loss of response are broadly divided as follows:

(1) primary non-response (PNR): no clinical effectiveness on response, or remission using well-established disease activity indices of the biological agent within the induction treatment period (e.g., if a TNF inhibitor is used, the inflammatory process may not be governed by TNF but by anti-integrins or interleukin [IL]-12/-23) and

(2) secondary loss of response: an initial beneficial response is observed, but effectiveness is later gradually lost, most often due to immunogenicity [17]).

3.1 Primary Non-Response

According to clinical trials of biopharmaceuticals for controlling IBD, the PNR time frame after initial infusion may vary for each of the available therapeutic antibodies. The induction regimen is usually 6 weeks for infliximab, 2 weeks for adalimumab and golimumab, 4 weeks for certolizumab, 6 weeks for vedolizumab, and 8 weeks for ustekinumab, risankizumab, and mirikizumab. Patients with PNR may have altered pharmacodynamics (i.e., mechanistic failure, such as non-TNF-mediated inflammation) or pharmacokinetics (i.e., rapid clearance of the biopharmaceutical, resulting in low levels of the circulating drug concentration immediately before the next dose ["trough level"]). These phenomena should be considered if recommended dosages have been applied [17, 18]. PNR to TNF inhibitors of up to 30% has been reported in clinical trials [19]. In such cases, dose escalation should be considered to overcome rapid clearance. Alternatively, therapy should be switched to an "out of class" biologic agent if a pharmacokinetic failure is suspected. For example, if a TNF inhibitor was used initially, then an anti-integrin or a cytokine blocker should usually be selected.

3.2 Secondary Loss of Response

Available data have shown annual secondary loss of response rates to TNF inhibitors of 9.6–20.9% per patient-year [20], and a systematic review and meta-analysis found broadly similar risks of secondary loss of response to infliximab and adalimumab for CD [21]. Pooled incidences of annual secondary loss of response in IBD have been reported in up to 47.9% of patients receiving vedolizumab, including those for whom TNF therapy has failed [22], and in up to 21.0% of those receiving ustekinumab (CD only) [23]. Secondary loss of response may be related to the low levels of drug, which in turn may be caused by antibody-induced or antibody-independent increased clearance. However, an insufficient response may also occur in spite of sufficient drug levels, presumably due to inflammatory pathways that are not blocked by the specific drug. Patients with low drug levels without antibodies benefit from increased doses of the same drug, whereas patients

with low levels due to antibodies should change treatment to a drug either of the same class (as antibodies to one specific drug of a class rarely cross-react with other drugs of the same class) or of another class. Patients with sufficient drug levels (and no ADAs) are unlikely to respond to another drug of the same class and should be switched to a drug of another class. Data have shown that increasing the dose of a biologic agent or adding immunosuppressive co-medication may overcome ADAs [24]. Measuring drug levels and ADAs to determine the most likely mechanism behind failure before deciding on the next step (i.e., a reactive therapeutic drug monitoring [TDM] approach) have been shown to be cost-effective strategies in clinical settings [25, 26].

Secondary loss of response, based on trough levels and ADAs (see Section 4), is attributed to several reasons. Often, the initially prescribed biopharmaceutical causes an adaptive immune response, leading to the production of neutralizing ADAs against the specific biologic [27]. ADAs are particularly associated with negative therapeutic outcomes [12]. A meta-analysis in patients with IBD identified that both the risk of losing therapeutic response and the frequency of adverse events were higher in patients with ADAs to infliximab than in those without detectable ADAs [12]. Nonetheless, although a gradually impaired therapeutic response is prevalent in clinical settings, the prevalence of ADAs is generally low, indicating that other factors may be associated with the clinical effectiveness of biologics in IBD [19, 28–31]. One such factor is low trough drug levels (defined as the serum concentration immediately before the next infusion/injection) [31–33]. In this context, there is growing evidence that exposure to high drug induction concentrations may prevent the development of ADAs [34, 35]. This phenomenon is termed "high zone tolerance" and occurs when large doses of a medication (typically two to four times higher than recommended and usually without toxic effects) suppress immunological responses [36]. Nevertheless, immunogenicity may be influenced by structural drug properties, that is, alternations in the tertiary structure, including protein folding, chimeric versus humanized monoclonal antibodies, and therapeutic antibodies directed at cell surface membranes, which have a higher rate of immunogenicity than those against soluble factors [37–39]. In this context, other factors, including treatment characteristics (such as mode of administration, dose regimen, or concomitant medication with immunomodulators) and patient characteristics (including gene susceptibility, e.g., carriage of human leukocyte antigen [HLA]-DQA1*05 risk variant for infliximab [40, 41]), may also be important for immunogenicity.

4 Therapeutic Drug Monitoring

4.1 Trough Concentrations

The amount of the prescribed biologic drug may correlate with the therapeutic effect. Optimal drug trough levels throughout induction and maintenance therapy seem to be a critical determinant of both immunogenicity and a prolonged efficacy of a biopharmaceutical (Table 1). Numerous investigations into drug levels versus treatment response have concluded that patients who respond well to therapy generally have higher drug levels than those who do not [26, 42].

Given the wide range of differences in the pharmacokinetics of current biologics and the natural course of IBD, a customized therapeutic strategy with TDM, combined with patient characteristics, for example, the pharmacokinetics of the drug, may enable more efficient application of biologic drugs [43]. Thus, TDM is an important tool for clinical decision-making because it helps identify patients who may benefit from higher dosing and/or shorter intervals between dosing or a second TNF inhibitor versus a non-TNF inhibitor for subsequent treatment [31, 33]. Thus, TDM, including trough levels of specific biologics and ADA concentrations, might assist in optimizing treatment decisions, taking both immunogenicity and high-dose immune unresponsiveness into account [31]. Accordingly, to reduce the risk of secondary loss of response due to ADA formation, proposed therapeutic trough concentrations for biologics (infliximab [44], adalimumab [45], certolizumab [46], golimumab [47], vedolizumab [48], ustekinumab [49, 50]) should be kept at a certain minimum level during maintenance treatment (Table 1). However, large-scale data are not yet available for the two recently introduced biologics, risankizumab [51] and mirikizumab [52].

It should be noted that, although TDM for intravenously administered drugs is usually based on the measurement of drug trough levels, the timing of measurement of the drug level is less clearly defined when using TDM for subcutaneously administered drugs [53, 54]. Total exposure as measured by area under the concentration–time curve may be just as predictive of outcome as trough level.

4.2 Anti-Drug Antibodies

All biologics used for IBD may trigger an immune response generating ADAs against the drug (Fig. 1), especially chimeric antibody structures. Such ADAs may reduce the efficacy of the biologic agent by altering the clearance pathway through various steps. The ADAs can be "neutralizing," wherein they directly block and interfere with the drug's ability to bind its target [58]. Alternatively, they can be "non-neutralizing," wherein they recognize other epitopes

Table 1 Proposed minimum thresholds of trough levels for various biologics used for maintenance management of inflammatory bowel disease (with upper concentrations for some)

Drug name	Drug trough threshold (μg/mL)	References
Infliximab	> 5–10 (for CD fistulas, probably > 10)	[44, 46]
Adalimumab	> 8–12	[45, 46]
Certolizumab	> 32–36	[46, 55]
Golimumab	> 3–7	[47, 56]
Vedolizumab	> 11–15	[46, 48]
Ustekinumab	≥ 4	[46, 49, 50, 57]

Exact trough level thresholds are unknown

CD Crohn's disease

on the drug without affecting its binding capacity, causing the formation of complexes that enhance the biologic's clearance from circulation and also induce adverse events due to immunological reactions [59, 60]. A prospective trial of the temporal evolution of ADAs in individuals with IBD treated with infliximab determined ADAs to be most often developed during the first few months of therapy [61]. However, the molecular processes underlying the formation of ADAs are not completely understood. This includes areas such as epitope characterization of biologics, variability of patient-specific influence of the immune system, an interplay between the innate and humoral immune system, and mechanisms involved in T-cell recognition and self-tolerance. This notwithstanding, an immune response might not always be important in clinical settings. However, an impaired clinical response or occurrence of side effects will typically occur only among patients with elevated or persistent ADA levels [62, 63].

Typically, the initial response of B cells results in the production of IgM isotype antibodies, which are generally of low affinity and broad specificity. With repeated exposure to the same antigen, B cells undergo class switching, leading to the production of a different range of antibodies (IgG, IgE, and/or IgA) depending on the specific antigen and the surrounding cytokine environment [62]. This is followed by affinity maturation, where somatic hypermutation of immunoglobulin genes occurs [64]. During this process, follicular helper T cells select B-cell progeny with the highest affinity for the antigen, promoting their survival and clonal expansion and the production of high-affinity antibodies [65]. Although ADAs that result in a loss of response are typically IgG1 or IgG4, emerging evidence suggests that a single individual may develop a diverse array of clonally distinct ADAs, each targeting different epitopes [66]. Additionally, other immunoglobulin isotypes beyond IgG may play a role in ADA-induced infusion reactions. For instance, in a study of patients experiencing infliximab-induced infusion reactions, several patients had IgE or IgM ADAs [67].

In contrast to the proposed thresholds for the drug trough levels presented in Table 1, the ADA levels that could trigger a therapeutic intervention remain unknown. However, in routine clinical situations, testing for ADAs is most often conducted in patients who have lost therapeutic response, based on a more pronounced activity of their IBD [33].

4.2.1 Tests for Measuring Anti-Drug Antibodies

Multiple assays with different characteristics and sensitivities are available for measuring ADAs, but no single assay is used consistently, which is the reason for inconsistent correlations between ADAs and clinical consequences [68, 69]. Two methods currently exist: drug-sensitive assays only detect ADAs when serum drug levels are below clinically relevant concentrations (i.e., limited ADA detection in the presence of the specific biologic agent); drug-tolerant assays measure ADA levels even in the presence of high drug levels, and sensitivity is maintained in the presence of the biopharmaceutical in the serum, causing (when available in equivalent concentrations to ADAs) the formation of immune complexes [70].

In the clinical context, it is also important to evaluate the existence of neutralizing antibodies that may interfere with the drug and clinical activity because some individuals may exhibit low levels of ADAs but an elevated neutralization index. One method to detect neutralizing ADAs in patient serum is a functional ADA cell-based bio-immunoassay, which quantifies TNF-α antagonist activity by assessing both drug activity and neutralizing ADA levels [71]. In sera with low ADA levels, such an assay may detect neutralizing ADAs even before clinical loss of response to the specific biologic is observed, allowing prediction of a clinical loss of response. However, these assays require an active cell line, complicating their clinical implementation. Nonetheless, a quantitative bio-immunoassay to quantify ADAs against TNF-α inhibitors has been adapted to evaluate the in vitro neutralizing abilities of ADAs [72].

As drug-sensitive assays have historically been the primary means of observing robust correlations between immunogenicity and clinical consequences, clinical judgments derived from drug-tolerant assays need to be carefully evaluated [73]. Nonetheless, most assays used in European and American clinical studies (i.e., radioimmunoassay, reporter-gene assay, enzyme-linked immunosorbent assay [ELISA], and homogenous mobility shift assay) have shown acceptable correlations with each other (r = 0.91–0.97) [68].

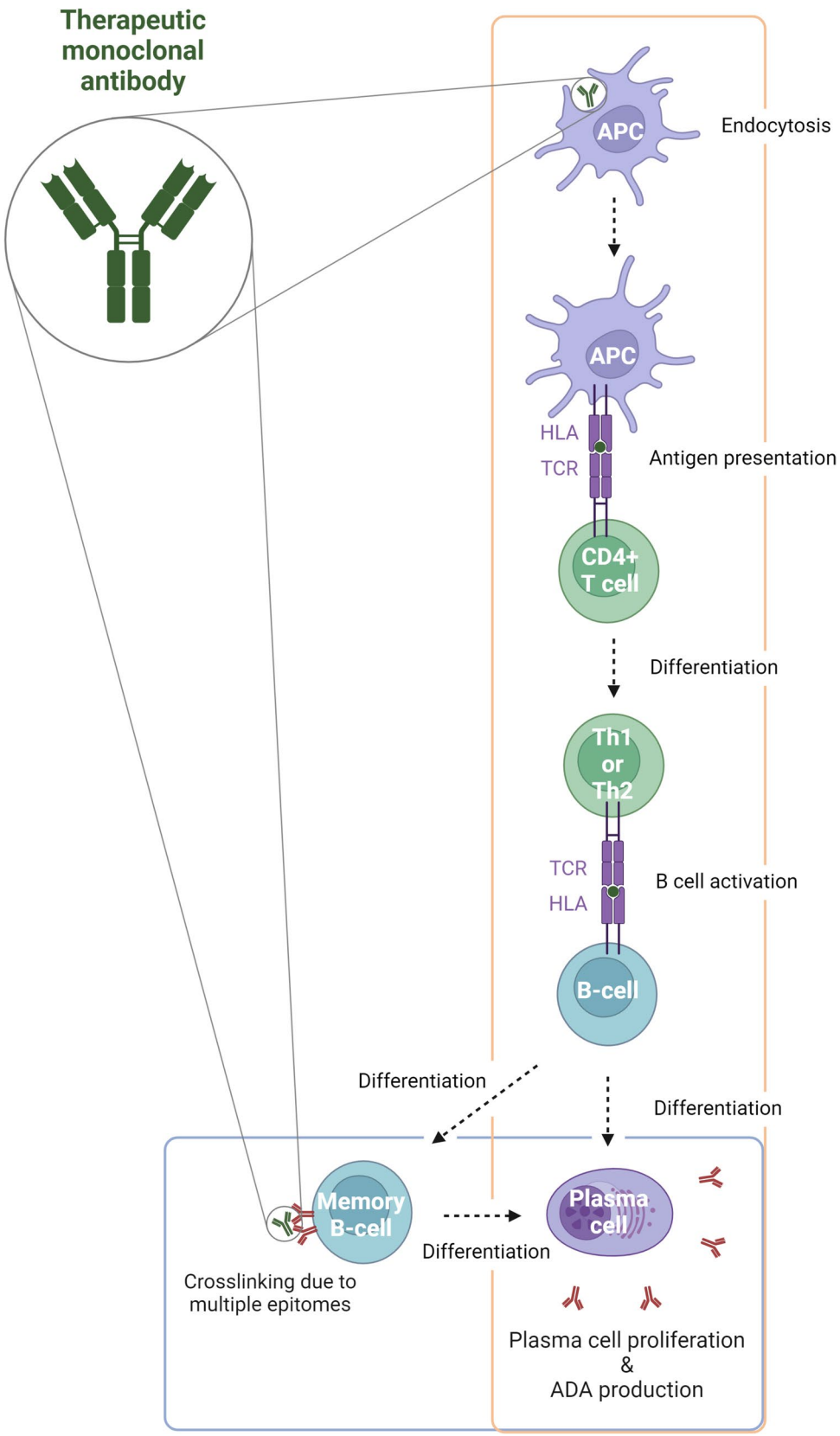

Fig. 1 Intercellular pathway of antibody formation. Anti-drug antibodies (ADAs) can be produced through two different pathways: a T-cell-dependent pathway (orange) or a T-cell-independent pathway (blue) that relies on B-cell activation. In the T-cell dependent pathway, therapeutic monoclonal antibodies (mAbs) carrying epitopes are detected as foreign substances by antigen-presenting cells (APCs), such as dendritic cells, macrophages, or B cells. The mAbs are internalized, processed, and presented to T cells via the interaction between the human leukocyte antigen (HLA) system and T-cell receptors (TCRs). The specific immune response that occurs depends on the cytokine environment during this interaction. ADAs are generated in the T-cell-dependent pathway when T cells differentiate into either a type-1 or -2 T-helper cell (Th1/2) phenotype. Through subsequent interactions with B cells, Th cells stimulate the proliferation of plasma cells that secrete ADAs. Th1 tends to promote the production of ADAs of the immunoglobulin G1(IgG1) and IgG2 isotypes, whereas a Th2 response primarily promotes ADAs of the IgG4 isotype. In contrast, the T-cell independent pathway involves mAbs with multiple epitopes that cross-link B-cell receptors (BCRs), directly stimulating B cells to differentiate into plasma cells that produce ADAs. Impurities and aggregates in mAbs can increase the number of adjacent epitopes, which may shift the immune response toward a T-cell-independent pathway through B-cell crosslinking.

4.2.2 Drug Clearance

As target-mediated drug disposal causes the clearance rate to be non-linear at lower concentrations, ADA development is associated with an accelerated clearance of the biologic agent used to control IBD [74]. This leads to a reduction in the circulating levels of the drug available to dampen inflammation. In this context, the calculation of drug clearance, an important pharmacokinetic parameter [75], is another critical determinant of therapeutic outcomes (compared with circulating ADA concentrations alone) in the efforts to secure sufficient circulating levels of the biopharmaceutical to ameliorate the inflammatory burden of IBD [76]. Thus, several variables, including sex, body weight, ADAs, low albumin, high C-reactive protein, and high fecal calprotectin, are independently associated with increased drug clearance, leading to lower drug levels [46, 74].

4.2.3 Impaired Clinical Response to Biologics Due to Anti-Drug Antibodies

Meta-analyses have shown that ADAs in the circulation of patients treated with biologics have a negative impact on clinical response [12, 77]. However, several studies of the clinical relevance of ADAs have been based on drug-sensitive assays, implying that only free ADAs (i.e., not bound in immune complexes with the drug) were detected. These studies reported a strong association between ADAs and loss of response [12, 78, 79]. Nevertheless, this association was much weaker in subsequent studies using drug-tolerant assays where ADA detection was independent of drug concentrations [80–82]. The concentration of the biological agent should be high enough to achieve clinical remission because the effects of circulating ADAs rely on the quantity of biopharmaceuticals neutralized by ADAs and the concentration of the free drug. Therefore, assessing serum drug levels is crucial for correctly interpreting any clinical impact of the formation of ADAs. Thus, low ADA levels against a TNF inhibitor may be overcome by dose escalation or, in the case of infliximab or adalimumab, the addition of an immunomodulator [83]. In contrast, high ADA concentrations against a specific TNF inhibitor may require a switch to another TNF antagonist or an alternative drug class.

To maintain a therapeutic response in patients, some clinicians have initiated the use of "treat-to-target" drug levels, which involve modifying the dosage to reach a certain trough level of the prescribed biological (a concept better known as proactive TDM). This is because the impact of ADAs is more pronounced with low trough levels of the biopharmaceutical used [84]. Although proactive TDM is generally not recommended, keeping drug levels above a certain level by measuring drug levels and adjusting the dose accordingly may help prevent the development of antibodies and theoretically improve outcomes. In this context, the randomized controlled NOR-DRUM B study demonstrated that proactive TDM improved outcomes in terms of avoiding a disease flare [85].

4.2.4 Adverse Events Due to Anti-Drug Antibodies

Apart from a potential to lower pharmacologically active drug levels and a subsequent loss of efficacy, ADAs may more rarely be linked to adverse effects [12]. Most ADA-related adverse events associated with TNF inhibitors, especially with infliximab, are infusion reactions. These are reported to be more than doubled in ADA-positive patients [12].

However, the substantial variances in analytical tests to measure ADAs against biologics have hindered the comparison of the true levels of ADAs in various biological studies in IBD [12]. Moreover, infusion reactions may vary from simple symptoms (redness, itching, and fever) to more severe reactions, including anaphylaxis and cardiovascular collapse [86, 87]. These phenomena have been proposed to be IgE mediated since some resemble type 1 allergic reactions. Nonetheless, one study reported that only 11% of patients with acute infusion reactions had detectable IgE ADAs and that most of those reactions were IgG mediated [88]. Moreover, in patients rechallenged with biologics after a drug holiday, a delayed hypersensitivity reaction comprising one or more of myalgia or arthralgia, fever, rash, itchiness/urticaria, edemas of lips/face, fatigue, and headache has been reported to occur up to 14 days following administration of a biopharmaceutical [89].

The risk of adverse events is influenced by several parameters, such as the form and size of TNF inhibitor–ADA complexes [90]. When a therapeutic antibody is attached to a TNF inhibitor, these complexes are typically dimers [90]. However, under some circumstances, such as high concentrations of both drug and ADAs, larger complexes (e.g., hexamers) have been identified in the sera of patients with antibodies to infliximab, and this observation may depend on the ADA titer versus the drug:ADA ratio [90, 91]. The size of large complexes may contribute to complement cascade activation by multimerization with ADAs forming ring-shaped complexes. Here, the antigen-recognizing regions face inward, and the Fc tails point outward. Nevertheless, if large complexes are created, the Fc tails come closer to one another, which allows both the binding of C1q but also the

activation of the complement cascade [91] (Fig. 2). However, the paucity of severe infusion-related effects may be attributed to the infrequency of the formation of such large complexes [91].

4.2.5 Resumption of Biologic Therapy

If a patient has been treated sufficiently for a while but later gets flaring IBD, available data have shown that resumption with a TNF inhibitor is possible even if ADAs persist. The STORI trial reported a clinical response among 98% of patients after an infliximab drug holiday of a median of 16 months, including patients with ADAs [92]. Moreover, in women with IBD who, because of pregnancy, previously often discontinued infliximab around week 28 [93], no problems were observed when this drug was restarted after delivery [94]. Further, more than half of patients with CD for whom infliximab or adalimumab successively failed experienced clinical effectiveness when infliximab was reintroduced after a period off treatment [95]. In contrast, the absence of a reaction following the first dose after resuming anti-TNF therapy does not rule out subsequent reactions. The highest risk, of up to 25%, of an infusion reaction has been reported at the second dose after resuming a TNF inhibitor [96].

For patients with ADAs to a specific biopharmaceutical, a slow infusion protocol and premedication with glucocorticoids may be a precautionary measure before resumption of, for example infliximab, to reduce potential risks of allergic manifestations caused by T-cell responses to monoclonal antibody drugs and to induce immune system tolerance, despite weak evidence [97].

5 Factors Associated with Immunogenicity Development

The immunogenic potential of biologics used for IBD may be influenced by several covariates of both patient- and treatment-related factors (Fig. 3), including disease burden, the structure and composition of specific therapeutic antibodies, their route of administration and co-medication, longer disease duration, and higher baseline disease activity. For instance, patients with an activated immune system are more susceptible to developing ADAs than are healthy controls or immunosuppressed patients [98–100]. Several studies have also indicated that patients who previously developed ADAs toward a biologic agent are more susceptible to developing ADAs against any subsequent biologic agents, even if not cross-reactive, which is probably a genetically determined phenomenon [101–103]. For instance, a case–control study comprising 7400 patients with IBD who were switched from infliximab or adalimumab to either vedolizumab or ustekinumab identified a significantly higher risk of developing ADAs to vedolizumab than to ustekinumab. Among those who were ADA positive versus ADA negative before the therapy switch [102], the risk of developing ADAs was lower with ustekinumab than with vedolizumab [102, 104].

5.1 Patient-Related Factors

Patient-related factors may influence the formation of ADAs and may comprise both the type and the burden of disease and genetics [41, 105]. Knowledge of specific patient-related factors of importance for an enhanced possibility of immunogenicity may assist in developing more

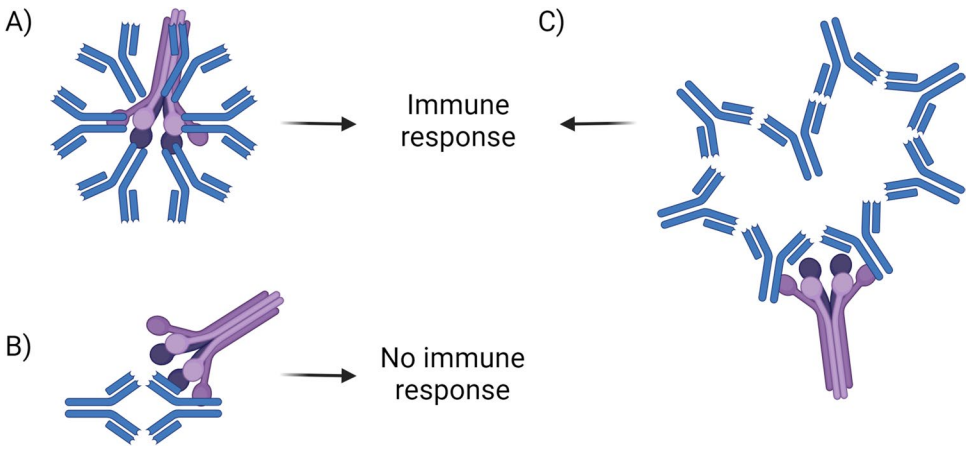

Fig. 2 Antibody complexes. **A** "Typical" target of the complement component 1 (C1) complex: a complex of antibodies with the Fc tails pointing inward and thus in close proximity to each other. **B** Anti-drug antibodies (ADAs) often form small complexes with the Fc tails pointing outward. As such, C1 cannot bind to multiple Fc tails and facilitate the immune response. **C** However, if the ADA complexes are sufficiently large, the outward-pointing Fc tails may come close enough for C1 to bind and initiate an immune response, enabling further ADA production.

Fig. 3 Potential risk factors for formation of anti-drug antibodies (ADAs). Several known risk factors, both patient- (yellow) and drug- and treatment-related (purple), may contribute to the collective risk of ADA formation upon biologic therapy. *mAbs* monoclonal antibodies.

efficient therapeutic strategies. However, why some patients develop ADAs and others with a similar disorder and on the same biopharmaceutical will not remains unclear. It has been hypothesized that this discrepancy might be associated with differences in the basic immunological pathways involved in the pathogenesis of the disease [29]. It has also been suggested that the immunological process responsible for the production of ADAs is dependent on T cells, making HLA variations of significant importance [106]. Nonetheless, the overall immunogenicity rates of the chimeric drug, infliximab, as both monotherapy and concomitant therapy in UC and CD is higher than those for the other biologics used [14, 62, 107].

5.1.1 Age

The exclusion of older adults from most clinical trials has led to insufficient effectiveness data within populations. A multicenter study evaluated the effectiveness of infliximab in an IBD population aged ≥ 65 years compared with those aged < 65 years and found no significant differences in infliximab exposure and endoscopic remission rates [108]. Thus, infliximab exposure for patients without preexisting hepatitis B, latent tuberculosis, demyelinating disease, and moderate-to-severe heart failure is not recognized as a risk factor for any safety events [108], including infections, even at supratherapeutic levels. Hence, the influence of patient age per se as a risk factor for the development of ADAs is considered negligible.

5.1.2 Inflammatory Burden of the Disease

Immunogenicity may be impacted by the immunological effects of a chronic inflammatory disorder and the systemic inflammatory burden of the disease because the degree of host immune system activation or inhibition may influence the development of ADAs. For instance, inflammatory signals from inflamed organs such as the intestine may cause B lymphocytes to produce IgGs against biologic-derived antigens with greater potency [109]. In addition, hyperactivation of the innate and adaptive immune response is considered crucial for immunogenicity in IBD [110, 111]. Therefore, patients with low serum albumin or increased levels of C-reactive protein in the circulation, which in IBD are

considered indirect indicators of a substantial inflammatory burden, have been linked to a higher clearance of infliximab from the serum [112].

5.1.3 Genetics

Genetics has been identified as a significant patient-related component for the occurrence of biologic immunogenicity, due to either immune response polymorphisms to foreign antibodies or a lack of tolerance to proteins without genetic information. Thus, polymorphisms in immunoglobulins, cytokines, and HLA may affect the risk of ADA production in IBD. Several studies have reported that the HLADQA1*05 genotype in IBD is correlated with ADA formation and the loss of response to infliximab and adalimumab [40, 41, 113–117] but not ustekinumab [118]. The HLADQA1*05 genotype has also been associated with a greater extent of colonic inflammation at diagnosis in children with UC [119]. Therefore, ADA development in patients with IBD may result from variations in the early course of the disease rather than from an isolated reaction to drug exposure. In a previous meta-analysis, HLA-DQA1*05 carriage was associated with immunogenicity to TNF inhibitors in IBD, but the certainty of the evidence was low [120]. IgG1 allotypes do not seem to increase the risks of inducing ADAs in response to infliximab or adalimumab [90, 121]. Moreover, IL-10 gene polymorphisms are associated with ADA formation against adalimumab [122]. Taken together, these observations suggest the existence of a different source of the immunogenicity trigger, rather than a specific HLA allele or IgG1 polymorphism.

5.2 Drug- and Treatment-Related Factors

The ability of different biologics, including biosimilars, to elicit an immune response may vary according to how they are delivered and structured [123, 124]. Understanding the role of improper handling of biologics when administered at infusion centers or in patients' homes is crucial because mismanaging biopharmaceuticals may cause protein aggregation, potentially triggering immunogenicity [124]. Such stresses include exposure to light, temperature alterations (including freeze–thawing), and agitation, all of which may lead to protein aggregate development [125]. Aggregates of proteins can trigger an immune response against both foreign and self-proteins, ranging in size from oligomers to smaller molecules [125]. Biopharmaceutical protein particles or aggregates, even in minute levels, have the potential to elicit an immune response (especially higher-molecular-weight aggregates), which may react with the protein's original structure [125].

Notably, no data have suggested safety issues of clinical relevance regarding the development of immunogenicity when comparing biosimilars and originators for IBD [126–128]. For example, a longitudinal, observational study with an individual patient follow-up of 80 weeks reported that switching from originator infliximab to a biosimilar did not influence clinical disease activity, C-reactive protein levels, or changes in the pharmacological profile or immunogenicity [129]. However, whether switching back and forth between the originator and a biosimilar may increase the risk of immunogenicity or alterations in pharmacokinetics remains unknown [130]. Finally, a relatively large prospective study has shown an association between prolonged infusion intervals and ADAs to infliximab [100].

5.2.1 Physical Structure of Biologics

The degree of "humanization" of the four TNF inhibitors used in IBD is a confounder of the observed differences in ADA rates [131]. Originally, it was believed that the immunogenicity of biologics could be avoided by engineering humanized or "fully" human antibodies. However, the development of ADAs when subcutaneous "human" adalimumab administration is maintained has been reported to be as high as 27% in clinical practice [83]. As seen from Table 2, a chimeric antibody such as infliximab poses the highest risk of ADA development compared with that of human antibodies (adalimumab and golimumab) or humanized antibodies (certolizumab pegol with an increased proportion of human amino acid sequences). However, the human/humanized structure does not completely eliminate immunogenicity risks [132]. Furthermore, translational changes in the protein structure, such as pegylation, have been thought to decrease immunogenicity via protection of immunogenic epitopes and prevention of aggregation of proteins [133]. Nonetheless, certolizumab pegol is still associated with immunogenicity (Table 2), as pegylation alone may lead to the development of antibodies against its polyethylene glycol moiety, causing enhanced clearance and reduced efficacy [134]. Finally, no significant differences in immunogenicity have been observed for biosimilars sharing immunodominant epitopes with the originator [126, 127, 135].

5.2.2 Dose and Administration Regimens

Higher introductory doses of infliximab have been suggested to induce immune tolerance in rheumatology [136], and this observation has been corroborated by studies in IBD [137]. This phenomenon may occur because increasing doses of infliximab may result in increased free drug concentrations versus the drug concentrations neutralized by ADAs. Furthermore, augmented doses of infliximab may speed up the clearance of ADAs because of the development of complexes [138]. A gradual loss of response to biologic therapy observed in several patients has guided clinicians

to escalation of doses of the biologic agent (i.e., the "dose-creep" phenomenon) [139]. Moreover, a correlation between ADA formation (and the need for increasing drug doses or increased frequency of infusion reactions [140]) and loss of response has also been identified [28].

In the initial clinical infliximab studies in IBD, dosing was episodic, with single rather than scheduled infusions [141]. Nonetheless, based on clinical experience and the ACCENT trial [8], treatment regimens were rapidly changed to scheduled regimens because of their higher effectiveness, trough levels, and lower risk of ADA development [142–144]. Moreover, previous use of the same or structurally related biological agent was identified as increasing the chance of ADA development [99, 145].

Even in individuals who develop ADAs against a biological agent, a natural decline over time may occur. For example, a study revealed that one-quarter of patients on infliximab maintenance therapy may have transient ADAs only. It was also reported that these patients only seldom discontinued biologic therapy compared with the cohort of patients with persistent ADAs [146].

In cases of secondary loss of response, pure dose intensification of a TNF inhibitor seems inferior for clinical outcomes compared with dose intensification combined with a concomitant immunomodulator [147]. However, in cases of non-immunogenic loss of response (i.e., without ADAs detected), infliximab dose escalation to a serum trough concentration >9 mg/L may be beneficial without concomitant immune suppression [148].

5.2.3 Route of Administration

Subcutaneous administration is less invasive and faster than intravenous administration of biologics and allows for self-administration in home settings [149], reducing the healthcare burden by reducing visits to infusion centers [150].

A systematic review determined that the risk of immunogenicity was comparable between subcutaneous or intravenous infliximab and vedolizumab administration [151], and the route of administration did not affect clinical effectiveness [152–154]. Given that maintenance therapy with some biologics (infliximab, vedolizumab, mirikizumab, and risankizumab) is preceded by intravenous induction regimens, a phase III study of infliximab suggested, depending on pharmacokinetic/pharmacodynamic simulations at week 10, introducing subcutaneous maintenance therapy 4 weeks after finishing intravenous induction therapy in an effort to minimize low plasma levels and thereby the risk of immunogenicity [155]. In this context, another study argued that immunogenicity-mediated treatment failure is reduced after subcutaneous therapy, which may also facilitate concomitant immunomodulator withdrawal for infliximab or even abolish the need for immunosuppression at all [156]. However, subcutaneous administration may result in more efficient antigen presentation because of differences in subpopulations of dendritic cells involved in first encounters. Dermal dendritic cells may instigate a proinflammatory response because these cells are positioned to encounter pathogens [157].

Table 2 Frequency of pooled anti-drug antibody (ADA) formation reported in patients with inflammatory bowel disease (a meta-analysis of 68 studies with 5850 patients [12])

Drug	Pooled ADA rates (%)
Infliximab	28
Adalimumab	8
Certolizumab pegol	11
Golimumab	4
Vedolizumab	8
Ustekinumab	6

The pooled rates reported in the table are not factual because of differences in both the specific assays applied and the timepoints of measurements in each of the studies included in the meta-analysis

5.2.4 Long-term Exposure to Biologic Therapy

Although ADAs often develop early in treatment, neutralization of the biologic may also appear later during treatment [158], and a longer exposure to infliximab or adalimumab seems to correlate with an increased risk for development of ADAs [116, 159]. ADAs formed during long-term exposure to biologics (e.g., adalimumab) are primarily of the IgG4 isotype [160], which is generally thought to be less harmful than other IgG isotypes because of its low affinity for Fcγ receptors and a tendency to form small complexes, limiting its ability to trigger an immune response [161]. However, lower functional drug levels and impaired clinical remission rates have still been observed in patients receiving adalimumab [162].

5.2.5 Photostability

Proteins exposed to light are vulnerable to oxidative degradation, and oxidized and aggregated proteins may trigger an immune response [163]. Therefore, biologics exposed to indoor lighting may produce harmful effects, leading to an increase of particles and protein aggregation [164]. Thus, precautions are warranted to reduce needless exposure of biologics to light.

5.2.6 Temperature

When biologics in aqueous solutions are subjected to a temperature outside the advised storage temperature range of 2–8 °C, they may aggregate. This problem may arise if the biopharmaceutical is either "warmed up" before use or transported as pre-filled syringes in a heated vehicle. Thus, biologics become immunogenic if vials are kept at ambient temperature [165]. A survey revealed that patients who self-administered a TNF inhibitor frequently stored their medications incorrectly and outside of the recommended range for more than a week before use [166].

Keeping an insulated container at a storage temperature when shipping or transporting is challenging without the use of ice mats/packs. Moreover, unintentional freezing of biological agents may occur during storage in a normal refrigerator since temperatures may vary according to where the drug is stored and over time. Consequently, in both outpatient clinics and the homes of patients, close attention needs to be paid to the manufacturer's instructions regarding the indicated temperature range for storing biopharmaceuticals, as mechanical stresses induced by the freeze–thaw process are anticipated to play a crucial role in destabilizing biologics [167].

5.2.7 Agitation

It is important to avoid agitating/shaking solutions when reconstituting biologics before administration. Biopharmaceuticals are more likely to agglomerate when they encounter hydrophobic interfaces, such as liquid–surface or air–liquid interfaces, which can lead to particle formation and aggregation [168]. Moreover, during agitation, bubble entrainment may cause pieces of the dehydrated protein formulation to become stuck in or close to air bubbles, impairing their ability to rehydrate. It is also imperative to use the precise vehicle solution prescribed by the manufacturer because combining a therapeutic protein product with an inappropriate vehicle solution could result in particles and aggregates. As such, preventing aggregate-induced immunogenicity—which may be a significant risk factor for decreased efficacy—requires that both patients and clinical personnel receive adequate education on how to handle biopharmaceuticals [169].

6 Concomitant Therapy with Immunomodulators to Prevent Anti-Drug Antibodies

A systematic review and meta-analysis showed that concomitant therapy with a biologic and immunomodulators against IBD, for example, thiopurines (i.e., azathioprine and 6-mercaptopurine) or methotrexate, may reduce ADAs against several biologics [170]. However, although the protective effect of combination treatment is of clinical relevance for biologics with high immunogenic potential only (e.g., infliximab for IBD) [12, 170], the risks with concomitant use of immunomodulators (linked with a wide range of adverse events [171, 172]) and non-chimeric biologics have not been justified in clinical trials for this indication [12, 173]. Immunomodulators may reduce immunogenicity and ADA formation by inducing T-cell apoptosis and inhibiting complex formation between T cells and antigen-presenting cells [24, 174, 175], thereby interrupting the cascade leading to ADA production by B cells (thiopurines) [171, 176]. They may also achieve effectiveness by inhibiting dihydrofolate reductase—leading to reduced purine and pyrimidine synthesis—and 5-aminoimidazole-4-carboxyamide ribonucleotide, reducing the expression of several inflammatory mediators (methotrexate) [176]. In IBD, immunomodulators are mainly indicated for up to 12 months of infliximab therapy [83, 177]. However, because they may have negative side effects, their use needs to be carefully considered in the light of the patient's overall treatment plan and a customized risk–benefit analysis [173, 178, 179]. Withdrawal of an immunomodulator after a minimum of 6 months of therapy has not been observed to increase loss of response to therapy with infliximab for up to 2 years post-cessation [180].

6.1 Combination Therapy of IBD with Thiopurines or Methotrexate and Specific Biologics

6.1.1 Infliximab

Patients randomized to infliximab (a 75% human and 25% murine chimeric antibody) monotherapy did not achieve the same beneficial clinical outcomes as those receiving infliximab and a thiopurine combined, according to the SONIC and SUCCESS trials (Table 3) [178, 181]. In patients with IBD, the standard dose for infliximab induction and maintenance therapy is 5 mg/kg; however, if a patient experiences no response, the dose may be increased to 10 mg/kg [182]. The overall ADA prevalence in clinical trials has been reported to be approximately the same regardless of whether patients received infliximab 5 or 10 mg/kg (6.7 vs. 4.4% in ACCENT 1 and 1.7 vs. 5.5% in ACT-1, respectively) [9, 183].

An early clinical trial in CD reported a longer duration of response (71 vs. 35 days, $p < 0.001$) to be independently related with ADA concentrations < 8 µg/mL or infliximab trough level concentrations ≥ 12 µg/mL [140]. Moreover, week 4 drug concentrations ≥ 12 µg/ mL were more often associated with combined azathioprine immunosuppression [140]. In line with these results, another study reported that patients receiving infliximab alone significantly more

frequently (15%) developed ADAs than those receiving concomitant azathioprine and infliximab (1%) [178]. Compared with monotherapy, concurrent azathioprine administration was linked to increased infliximab trough drug concentrations at week 30 (3.5 and 1.6 µg/mL, respectively; $p < 0.001$) [178]. Moreover, methotrexate may improve the pharmacokinetics of infliximab in both CD and UC (Table 3) [170], even though this drug by itself is not confirmed to be effective for the management of UC [184].

6.1.2 Adalimumab

Data regarding combined therapy with adalimumab (fully human antibody) and immunomodulators are conflicting, with limited evidence supporting this strategy [173]. For example, the DIAMOND study in immunosuppressant-naïve patients with CD found no superiority at week 26 for the combination of adalimumab with azathioprine versus adalimumab monotherapy in inducing clinical remission [185]. Moreover, a systematic review and meta-analysis found no benefit of adalimumab combined with an immunomodulator versus monotherapy with adalimumab in the clinical course of CD [186]. Regarding methotrexate, a recent small clinical study with 55 patients diagnosed with CD suggested that triple combination therapy including vedolizumab may improve endoscopic remission rates, but no pharmacokinetic data were revealed [187]. Adalimumab is used in a flat dosing regimen. However, development of ADAs and loss of response over time may be increased by week 4 after serum adalimumab concentrations reduce below 5 µg/mL, calling for intensified dosing, for example, reduced dose intervals [188].

Table 3 Effectiveness of combined immunomodulator therapy with thiopurines (i.e., azathioprine or mercaptopurine) or methotrexate and the various biological agents used for the management of inflammatory bowel disease

Drug name	Thiopurines	Methotrexate
Infliximab	+	+
Adalimumab	–	? (see Sect. 6.1.2.)
Golimumab	–	No data
Certolizumab	–	–
Vedolizumab	–	–
Ustekinumab	–	–
Risankizumab/mirikizumab	No data	No data

+ indicates beneficial effect observed, – indicates no beneficial effect observed compared with biological monotherapy

6.1.3 Golimumab

The development of ADAs against golimumab (fully human antibody) with flat dosing may negatively affect clinical efficacy [189]. However, a sub-analysis of the PURSUIT-M trial (where 31.2% of patients with UC received concomitant thiopurine compared with golimumab monotherapy) showed no effectiveness differences [190]. No subsequent studies for this drug have supported combination treatment against ADAs [173].

6.1.4 Certolizumab Pegol

Certolizumab pegol, a humanized antibody, is also used in a flat dosing regimen, and the development of ADAs has frequently been reported. In one study, ADAs were detected in 28% of patients with CD who received certolizumab [55]. However, no available data have supported combination treatment with an immunomodulator and certolizumab against ADA development [173].

6.1.5 Vedolizumab

Although a retrospective study reported that vedolizumab (humanized antibody) in combination with an immunosuppressor was associated with better clinical outcomes in patients with CD [191], a subsequent prospective multicenter study on combination therapy with an immunomodulator did not find benefits in augmenting pharmacokinetics or influencing immunogenicity [170]. Thus, no available data support combination treatment with thiopurines and vedolizumab [173] or with methotrexate [170].

For vedolizumab (initial intravenous flat dosing with the possibility of subsequent subcutaneous dosing), the GEMINI studies showed that the proportion of ADA-positive individuals with or without concurrent immunosuppressive medication use was similar (3% and 4%, respectively) [192, 193]. However, the true sensitization rate was underestimated in these studies because of the use of a drug-sensitive ELISA. Notably, the percentage of patients with ADAs in the GEMINI trial increased from 2% to 22% upon re-treatment after interrupted treatment [82]. Furthermore, in patients assigned to vedolizumab re-treatment, fewer patients with concomitant immunomodulator use were ADA positive (11%) relative to those on vedolizumab monotherapy (27%) [82].

6.1.6 Ustekinumab

Ustekinumab (a fully human antibody to the p40 subunit of IL-12/-23), whose dosing regimen is initially weight based followed by flat dose maintenance therapy, may also lead

to ADA development, although the risk is reportedly low [194]. However, most ADAs detected have been transient and non-neutralizing [49]. In a prospective study on IBD, combination therapy of ustekinumab with a thiopurine or methotrexate did not influence the pharmacokinetics [170], and no available data support concomitant ustekinumab treatment with an immunomodulator [170, 173].

6.1.7 Risankizumab and Mirikizumab

For the two latest additions of biologics used for management of IBD, risankizumab and mirikizumab (both humanized antibodies with high affinity to the p23 subunit of IL-23) [52, 195, 196], no data are available at this stage to support combination therapy with an immunomodulator.

7 Future Perspectives for Mitigation Strategies

The robust safety, efficacy levels, and reasonable cost of biologics, especially with price reductions since the introduction of biosimilars, have led to their place as pivotal treatments for IBD, and several also offer effective management of various extraintestinal manifestations related to IBD [197]. As highlighted, the issue of immunogenicity toward therapeutic biologics used to manage IBD is complex. However, better knowledge regarding the molecular mechanisms behind the formation of ADAs and the key variables affecting the immunogenicity of the biopharmaceuticals may result in improved health outcomes in the IBD community [198].

This review outlines several strategies that can be considered in the efforts to optimize IBD treatment and minimize immunogenicity at different levels of the "drug-to-patient" journey, including optimizing trough levels and/or doses, adding immunomodulators to initial infliximab maintenance therapy for IBD [199], and avoiding stresses that may induce protein aggregation, among others. These endeavors aim to provide the most efficient treatment of IBD using biologics under clinical settings.

Declarations

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