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Bispecific antibodies: The next generation of targeted inflammatory bowel disease therapies

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ABSTRACT

Targeting various disease pathways using monoclonal antibodies (mAbs) has transformed the treatment paradigm for inflammatory bowel disease (IBD), with these agents exhibiting improved efficacy over corticosteroids or immunosuppressive therapies. Antibodies targeting tumor necrosis factor α (TNF-α) were the first approved biologics for IBD, followed by the more recent approval of antibodies targeting the α4β7 integrin heterodimer and ustekinumab, which targets the p40 subunit of interleukin-23. Current efforts are focused on the development of additional biologics targeting these known and other newly discovered pathways. Still significant unmet needs remain, as a large proportion of patients either fail to achieve remission or fail to respond altogether. Both Crohn's disease and ulcerative colitis are complex and heterogeneous diseases with several molecular pathways involved in disease pathophysiology. We propose an additional therapeutic approach to the treatment of IBD, bispecific antibodies (BsAbs), which combine two distinct binding specificities within a single biologic to allow the simultaneous targeting of multiple disease-causing cytokines or pathways. Although primarily used in oncology thus far, the unique combinatorial mechanism of action of BsAbs may provide new therapeutic options for a broad range of clinical applications, including autoimmune and inflammatory diseases. This review will discuss the current status of BsAb development in general and potentially therapeutic application in IBD.

1. Introduction

Crohn's disease and ulcerative colitis, collectively termed inflammatory bowel disease (IBD), are chronic, disabling, intestinal diseases with significant unmet therapeutic need [1]. While conventional immunomodulators (eg, methotrexate and thiopurines [such as azathioprine and 6-mercaptopurine]) modify the immune system in a broad and non-specific manner [2,3], monoclonal antibodies (mAbs) target specific molecules and pathways involved in the inflammatory process, such as tumor necrosis factor α (TNF-α), interleukin-12/23 (p40), interleukin-23 (p19), integrins and integrin-binding proteins (α4, α4β7, β7, and MAdCAM-1) and fractalkine/CX3CL1). Some of these mAbs have already demonstrated improved therapeutic efficacy profiles compared to conventional immunomodulators in treating patients with autoimmune and inflammatory diseases, including IBD [2–13].

Inflammatory bowel disease is a complex and heterogeneous disease; as such, no single therapy has been uniformly efficacious across the entire patient population, with the vast majority of patients unable to achieve clinical remission and many patients losing response over time [14,15]. Combining targeted agents to selectively disrupt multiple biological pathways is a future exploratory direction for the management of IBD, with the ultimate aim of enhancing efficacy. However, combination use of biologic agents clinically presents both practical and commercial challenges. The use of bispecific antibodies (BsAbs) may help overcome some of these issues and provide further mechanisms for differentiation from combination therapy. This review will provide an overview of some of the most relevant targets in IBD as well as mechanisms of action that have been exploited by BsAbs in other autoimmune and inflammatory diseases and oncology. We will also highlight key BsAb molecules in clinical development, with particular emphasis on those with potential therapeutic relevance for the treatment of IBD. Additionally, we will discuss the unique opportunities, challenges, and considerations facing the transition of BsAbs to the clinic.

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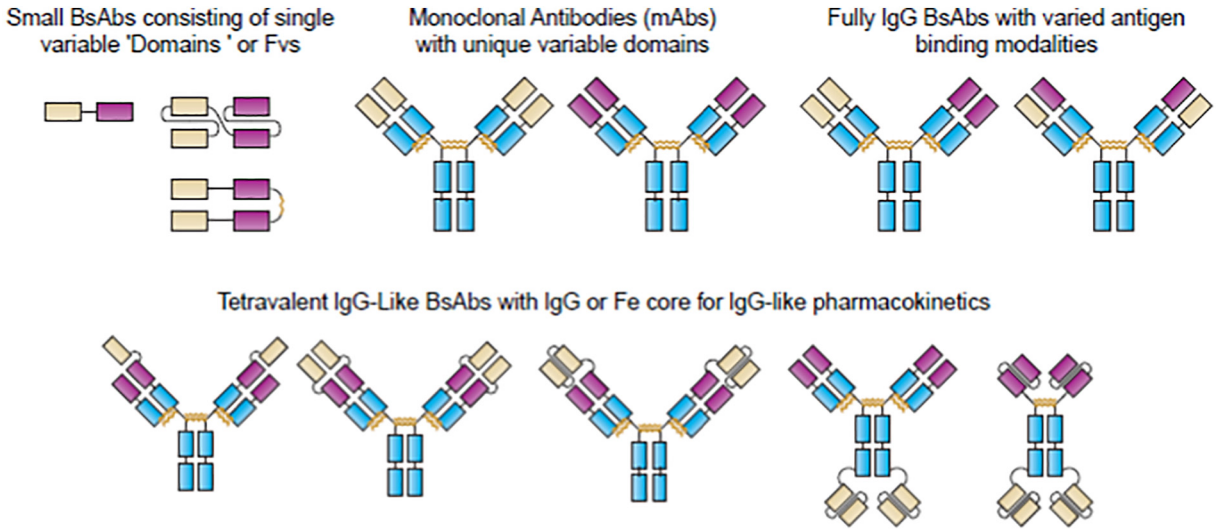

Fig. 1. Schematic diagram of relevant bispecific antibody structures [33].

2. What is a bispecific antibody?

Bispecific antibodies are unique antibody formats that typically recognize two different target antigens from different proteins [16,17]. Early predecessors of modern-day BsAbs were developed in the 1980s. First-generation BsAbs were developed using chemical conjugation methods or quadroma technology, involving somatic hybridization of two antibody-secreting hybridoma cells [16,17]. However, these approaches were limited by immunogenicity or the complexity of their manufacture [18,19]. Recently, there has been a resurgence in BsAb development, aided in part by innovative advancements in BsAb platforms facilitated by novel molecular, structural, and computational biology techniques. As such, many novel formats (around 100) are now available (Fig. 1; reviewed in [17,18,20–22] and more than 50 different BsAbs are currently in various stages of clinical development across a number of therapeutic indications, including oncology, autoimmune/inflammatory diseases (Fig. 2), infectious diseases, and cardiovascular disease.

Broadly, BsAbs may be divided into three major structural classes: (1) antibody fragments, which lack an Fc domain (eg, diabodies and tandem single-chain variable fragments [scFvs]) [16,23,24]; (2) antibody fragments or alternative scaffold proteins fused to an antibody, antibody Fc region, or human serum albumin, to enhance their pharmacokinetic (PK) properties and/or valency (eg, dual variable-domain immunoglobulins [DVD-Igs] and IgG-scFvs) [16,21,25,26]; and, more recently, (3) fully IgG BsAbs that maintain the architecture of native IgGs, which may help avoid non-native issues associated with antibody fragments [17,22,27–32]. Each of these formats has its own unique advantages. For example, the Fc fusion BsAbs provide tetravalency, which may be important for potency and crosslinking (described below in Section 3.2) [33]. Fully IgG BsAbs are typically able to engage antigens with a single arm, which has benefits that will be described in greater detail later. Fully IgG BsAbs also mimic naturally occurring IgG4 BsAbs in humans, which result from 'Fab-arm exchange', and thus have biological precedence [22,34]. Several engineered BsAbs are in clinical development for the treatment of a number of autoimmune and inflammatory conditions (Fig. 2).

3. Bispecific antibodies: How do they work?

Targeting of two (or more) validated pathways to enhance therapeutic efficacy represents an attractive and logical application of BsAbs in IBD. Moreover, the unique ability of BsAbs to serve as bridging molecules between distinct therapeutic targets provides novel means to expand their use. Therapeutic strategies utilized by rationally designed BsAbs include the selective targeting of specific immune cell types, co-localization and cross-linking of cell surface receptors to induce novel signaling, or the redirection of the immune system to target pathogenic cell types [16,35] (Fig. 3).

3.1. Targeting multiple receptors to selectively impact specific cell types

Bispecific antibodies can be designed to simultaneously interact with two cell membrane-associated receptors specific to a cell type(s). This capability may be exploited to selectively modify signaling in pathogenic immune cell types, such as IL-23R$^+$/IL-1R$^+$ T cells and innate lymphoid cells associated with IBD [36]. By preferentially binding cells that express two target proteins, BsAbs may be tuned to achieve greater selectivity for the desired target cell type and/or activity [17,35]. This approach has been used in the development of MGD010, a dual-affinity–retargeting (DART®) BsAb that dampens B-cell activation with potential for treating autoimmune or inflammatory diseases [37]. MGD010-mediated crosslinking of CD32B with CD79 places the inhibitory receptor, FcγRIIB, in close proximity to the B-cell receptor, resulting in downregulation of B-cell receptor–induced signaling [37–39]. This could potentially be used to treat B-cell-related autoimmune diseases through disabling of autoimmune antibody production.

3.2. Novel signaling through receptor co-localization and hyper-crosslinking of immune receptors

Another novel function of BsAbs that may be harnessed in the treatment of IBD relates to their ability to crosslink immune receptors to either enhance signaling or replicate the aggregation of targets that occurs during immune regulation [16]. For example, BsAbs or bispecific fusion proteins have been designed to bring regulatory receptors directly to immune signaling complexes to influence immune cell signaling or differentiation [37]. Bispecific moieties specifically targeting CD32B (FcgRIIB) and CD79B activating receptor-signaling complex have been shown to enable the CD32B ITIM signaling components to dampen immune activation of the B-cell receptor complex, which could potentially treat lupus or other B cell-centric AI diseases [37]. Another BsAb targeting CD32B and the IgE receptor was shown to reduce degranulation of mast cells or basophils that occurs during allergic responses [40]. In a similar approach, a LAG3xCD80wa bispecific fusion protein colocalized CTLA-4 to the TCR complex, which steered naïve T cells to differentiate into regulatory T cells (Treg) [41]. This bi-

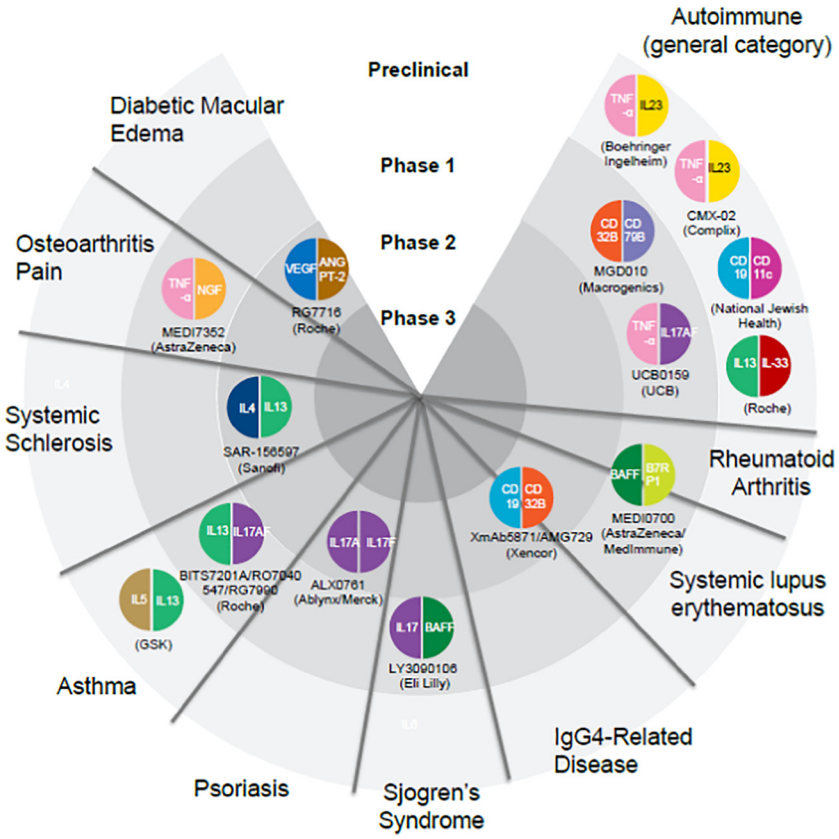

Fig. 2. Bispecific antibodies currently in preclinical or early-phase trials for autoimmune and inflammatory conditions.

functional protein was capable of protecting non-obese diabetic mice from developing autoimmune-mediated Type I diabetes [42]. Similar bispecific approaches could be explored for regulating inflammatory cell pathogenesis in IBD.

3.3. Redirected T-cell targeting of pathogenic cell types

One of the most well-known applications of BsAbs has been the redirection of effector cells (such as T cells, natural killer cells, or monocytes/neutrophils) to destroy malignant tumor cells [43]. This approach enables antigen-expressing cells to be depleted at target receptor levels significantly lower than those required for antibody-

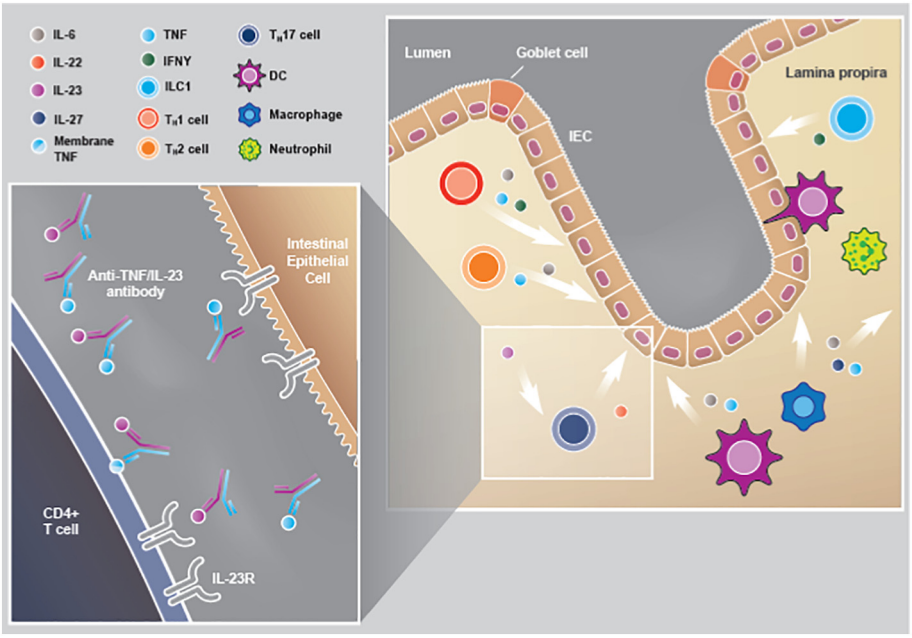

Fig. 3. Sample BsAb mechanisms in IBD. [69].

dependent, or complement-dependent, cellular cytotoxicity [44]. The first wave of bispecifics designed for this purpose were either hybrid hybridomas or antibody fragments for oncology including Blincyto®, which redirects T cells through CD3 binding to kill CD19-expressing target cells and is approved for treating refractory acute lymphoblastic leukemia (ALL) and shows potential for treatment of non-Hodgkin lymphoma (NHL) [45] [46]. Next-generation BsAbs have been described, including fully IgG BsAbs that redirect T cells to kill $CD20^+$ B cells [47,48]. These BsAbs deplete circulating $CD20^+$ B cells with exceptional potency and to a greater extent than the anti-CD20 monoclonal antibody, rituximab, in spleen and lymphoid tissues [47,48]. A similar approach could be explored in IBD, by targeting certain immune cell types with pathogenic relevance [3,36]. However, this approach is not without safety concerns. Low-level antigen expression on vital tissues may result in target-mediated toxicity. Further, cytokine-release syndrome, a potentially life-threatening condition involving high-level immune activation, has been observed following administration of T cell-engaging BsAbs in the oncology setting [49]. The complete depletion of particular immune cell subsets may also make patients more susceptible to serious infection or malignancies. The risk-benefit ratio associated with ablation of certain cell types may not be readily extrapolated to conditions outside oncology. Therefore, effector cell-redirected therapies may only be appropriate for patients with severe IBD, refractory to all other treatment options.

4. Bispecific antibodies: Preclinical and clinical experience

Preclinical and clinical studies have demonstrated that the simultaneous blockade of two or more cytokine targets using a combination of mAbs can achieve superior efficacy compared with individual mAbs alone [50,51].

4.1. Preclinical studies

In a TNF transgenic arthritis model, blockade of both TNF and IL-1 using a combination of infliximab and anakinra displayed synergistic activity and provided superior inhibition of synovial inflammation, bone erosion, and cartilage damage when compared with either mAb alone [51]. These results corresponded with near-complete remission of disease [51].

While BsAbs have not yet reached the clinic for patients with IBD, a number of promising molecules are in development. For example, bispecific molecules targeting TNF and IL-23 are in preclinical development for the treatment of IBD and other autoimmune/inflammatory diseases [52,53]. In a CD40-induced colitis model, a murine BsAb targeting IL-23 showed synergistic efficacy relative to antibodies against TNF and IL-23 alone [52,53]. A TNF/IL-23 BsAb would represent one of the first examples of a BsAb targeting two validated pathways with validated efficacy in IBD. AZ17 is a BsAb that was in preclinical development and had theoretical potential for IBD as it neutralized both IL-23 and IL-6 [2,54,55]. The preclinical efficacy of AZ17 was demonstrated in a xenograft mouse model of psoriasis, in which this BsAb prevented IL-23–induced ear inflammation and significantly improved the clinical and histological signs of psoriasis compared with controls [55].

4.2. Clinical studies

The potential utility of targeting multiple cytokines or pathways has been evaluated in clinical studies of combinations of biologics in inflammatory diseases. In a phase 2 study of patients with active Crohn's disease not achieving remission with the TNF inhibitor infliximab, the addition of the antibody natalizumab, which targets α4 integrins, to infliximab therapy led to a greater reduction in the Crohn's Disease Activity Index than infliximab alone [50]. Further, a higher proportion of patients receiving natalizumab and infliximab (46%) achieved clinical remission at any time during the study than did patients receiving infliximab alone (41%) [50].

There have been several clinical studies in rheumatoid arthritis that examined the efficacy and safety of a combination of biologics relative to the corresponding individual agents. In a phase 2 study of patients receiving combination therapy with etanercept and abatacept for active rheumatoid arthritis, combination antibody therapy showed improvement in some clinical end points and patient-reported outcomes relative to etanercept alone [56]. However, a higher incidence of serious infections was reported in the combination arm [56]. Similarly, a study combining etanercept and anakinra in patients with active rheumatoid arthritis who had previously failed methotrexate therapy reported higher rates of serious infections relative to etanercept alone [57]. Generally, combination therapy improves outcomes for the targeted indication, but can pose additional safety risks not seen with biologics administered individually. Concomitant administration of existing biologics may be limited to doses defined for the individual therapy. Exploratory dose-ranging studies for a BsAb could define a dose or doses that achieve the benefits of combination targeting, having a good benefit-risk ratio.

Bispecific antibodies to treat autoimmune and inflammatory diseases are advancing in the clinic (Fig. 2). The first two BsAbs approved by the FDA were not for autoimmune indications: (1) blinatumomab, which targets CD3/CD19, for the treatment of Philadelphia chromosome–negative relapsed or refractory acute lymphoblastic leukemia and (2) emicizumab, which targets Factor IX/Factor X, for the treatment of hemophilia A. However, several BsAbs for autoimmune indications are under clinical evaluation. For instance, a BsAb targeting CD19 and CD32B has reached the clinic, having completed a trial in IgG4-Related Disease [NCT02725476,ClinicalTrials.gov] (Fig. 2). Additionally, LY3090106, a BsAb targeting B-cell activating factor (BAFF) and IL-17, is under development for immunological indications such as Sjogren's Syndrome [NCT02614716,ClinicalTrials.gov]. Numerous other BsAbs and their potential autoimmune and inflammatory disease indications are listed in Fig. 2.

The results mentioned highlight some potential for benefit via the simultaneous targeting of multiple pathways. BsAbs provide an opportunity to deliver a single therapy capable of targeting multiple pathways, with the potential for efficacy that is additive or even synergistic relative to targeting each individual pathway. Administration of a combination of biologics at the doses defined for individual therapies has in some instances been associated with an unfavorable benefit-risk ratio. It is not known whether bispecifics will alleviate this issue with careful dose-finding to define an appropriate safe and efficacious dose during development. Limited data currently exist regarding the safety of BsAb molecules and their observed profile in the oncology setting may not be generalizable to autoimmune and inflammatory disease indications. Nevertheless, the ability of BsAb molecules to block key immune pathways in IBD means that they could theoretically suppress multiple critical elements of the normal immune response. As has been the case for currently approved biologics, large and adequately powered studies will be required to define the safety profile and risk-benefit ratio of BsAbs.

5. Therapeutic and regulatory challenges with bispecific antibodies

5.1. Immunogenicity and fixed stoichiometry

Progress in protein engineering has resulted in the creation of humanized (~90% human) and fully human (100%) antibodies, which are typically associated with less immunogenicity than chimeric (~70% human) antibodies such as infliximab [58,59]. While fragment-based and non-native formats may compound the risk of immunogenicity compared to more native-like IgG architecture, all protein drugs have the potential to spur production of anti-drug antibodies, particularly

with extended use [29,60]. Patients with autoimmune and inflammatory diseases, regardless of prior exposure to biologics, have been shown to produce autoantibodies, which may cross-react with therapeutic antibodies [29]. Also of potential concern, large immune complexes that result from bispecific target engagement could induce 'danger signals' that induce immunogenicity. However, continued clinical and preclinical experience should provide more clarity.

Another potential limitation of BsAbs relates to their fixed stoichiometry, which prohibits flexible dose adjustment of each component antibody according to patient needs [12,21]. As such, dosing considerations for BsAbs may differ from those for traditional antibodies, with the primary objective being determination of a safe and efficacious dose that may exploit the additive or potentially synergistic effects of targeting dual pathways, rather than the optimal targeting of individual pathways. However, innovative engineering of the affinity and avidity of the BsAb towards each of its targets may enable the matching of dosing regimens for each target.

5.2. Regulatory and technical challenges

The development of mAbs over the past two decades has provided considerable insight into the regulatory requirements for antibody-based therapeutics [61]. From a regulatory perspective, the development of BsAbs is, in principle, the same as for any mAb with regards to characterization, quality, efficacy, and safety [62,63]. However, owing to their complex and heterogeneous nature, they also present a unique set of challenges. For example, preclinical toxicity testing may prove problematic because both targets need to be present in the animal model [61,62]. For some bispecific constructs, large-scale production under Good Manufacturing Practice conditions may still be difficult and stability may be an issue [17,35]. While there are challenges, progress is being made to enable Good Manufacturing Practices in BsAb production [64]. Bispecific antibodies possess inherently more complex mechanisms than traditional mAb therapeutics, including the potential for larger and/or more complex immune complexes, induction of cell-cell interactions, and incorporation of the liabilities of both targets. It is therefore anticipated that the relative efficacy and safety of a molecule at various doses will be closely scrutinized by regulatory authorities, with firm justification required to support dose selection. Notwithstanding these challenges, the development of BsAbs in oncology has benefited from the recognition by regulatory agencies that bispecific moieties are not separate entities, unlike combination drugs, which require demonstration of efficacy and safety for each individual component prior to their demonstration in combination [65] [66].

6. Discussion and future directions

Inflammatory bowel disease is an extremely heterogeneous disease; although all patients exhibit inflammation, their history, disease phenotype, and response to treatment vary dramatically [67]. Bispecific antibodies represent the next generation of therapeutic antibodies and provide clinicians with the opportunity to implement sophisticated targeting strategies with the aim of achieving greater therapeutic efficacy than existing biologics for the treatment of IBD. This may be achieved through: (1) the enhanced or simultaneous blockade of target cytokines or pathways; (2) selective targeting of specific cell types; (3) novel signaling via receptor colocalization or hyper-crosslinking; or (4) destruction of pathogenic cell types via T-cell redirection.

It is envisioned that BsAbs may offer new options for personalized therapy in IBD, based on a patient's own unique immune signature. Though the use of BsAbs in autoimmune and inflammatory diseases is still in its infancy, recent advances in their engineering have enabled more robust and, in some cases, more IgG-like molecules for development. Two BsAbs have already entered the market, with a rich and diversified pipeline of more than 50 molecules in various stages of clinical development [68]. While issues surrounding cost are yet to be defined, a single therapeutic agent that can perform the work of two mAbs may offer advantages from this perspective [65]. Although many challenges remain, BsAbs have promising clinical applications and are expected to feature prominently in the future of IBD treatment.

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