BioDrugs (2020) 34:111–119
https://doi.org/10.1007/s40259-019-00400-2

LEADING ARTICLE

Bispecific Antibodies for Autoimmune and Inflammatory Diseases: Clinical Progress to Date

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Published online: 8 January 2020

Abstract

In autoimmune diseases, a highly complex network comprising diverse cytokines and their receptors on immune cells drives the inflammatory response. A number of therapeutic antibodies targeting these disease-related molecules have been approved for the treatment of autoimmune diseases. Bispecific antibodies (bsAbs), with binding specificity for two different target molecules, have recently been developed for a range of autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and psoriasis, and tested in clinical trials. This review briefly describes the three main categories of bsAb structures developed for autoimmune diseases, including immunoglobulin G (IgG)-like, natural IgG, and tandem antibody fragment formats. The bsAbs developed and evaluated to date mainly target the depletion of T or B cells, the inhibition of T cell differentiation or activation, or the neutralization of proinflammatory cytokines. The clinical evaluation of bsAbs in autoimmune diseases is ongoing, with both successes (phase II trials of obexelimab in systemic lupus erythematosus) and failures (phase II trials of lutikizumab in osteoarthritis and romilkimab in idiopathic pulmonary fibrosis), and this review aims to provide a comprehensive, up-to-date summary of the clinical progress of bsAbs in this therapeutic area. Although many challenges remain, bsAbs offer new therapeutic options in the future direction of autoimmune disease treatments.

Key Points

Antibody recombination technology drives the development of immunoglobulin G (IgG)-like and non-IgG bispecific antibodies (bsAbs) for human autoimmune diseases.

The enhanced therapeutic efficacy of bsAbs is achieved via the crosslinking of two (or more) target cytokines or immune effector cells.

The complexity of the cytokine network and immunogenicity may be barriers to the development of effective bsAbs.

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1 Introduction

Approximately 5–10% of the world's population has autoimmune diseases [1, 2]. In these patients, the excessive activation of immune cells and overexpression of inflammatory cytokines play key roles in the inflammatory process. Antibody drugs have been widely used to treat millions of patients with autoimmune and inflammatory diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), psoriasis, ulcerative colitis (UC), Crohn's disease, and multiple sclerosis [3, 4]. Autoimmune disease control with antibody therapy is highly successful. Antibody drugs target specific molecules and pathways involved in the inflammatory process, such as tumor necrosis factor (TNF)-α, interleukin (IL)-17A, cluster of differentiation (CD)-20, α4-integrin, and so on [5, 6]. Successful treatment with therapeutic antibodies remains challenging, at least partly because inflammatory diseases are complex and heterogeneous. Rates of clinical remission are often relatively low. For example, approximately 20–30% of patients with RA are refractory to anti-TNF therapy or show partial responses [7, 8]. The crosstalk of pro-inflammatory mediators may limit the efficacy of antibody treatment [9]. Diverse antibody engineering approaches have been developed to improve the clinical efficacy of antibody drugs,

such as antibody structure optimization, antigen affinity enhancement, or drug conjugation, and so on [10]. One such important strategy is the generation of bispecific antibodies (bsAbs) that selectively disrupt multiple biological pathways by blocking two interrelated or unrelated antigens, including soluble molecules or cell surface receptors [11, 12]. The use of bsAbs is likely a future exploratory direction for the management of autoimmune diseases. This review focuses on the status and recent clinical progress of bsAbs in autoimmune and inflammatory conditions.

2 Structures of Bispecific Antibodies (bsAbs) for Autoimmune Diseases

As a detailed description of the advances in protein engineering enabling the generation of diverse bsAbs, and the relative advantages and disadvantages of each approach, is beyond the scope of this article, the reader is directed to several recent reviews [12–16].

Immunogenicity was the major problem for early bsAbs generated with chemical conjugation or hybrid hybridomas [13]. With advances in antibody engineering, a large variety of bsAbs with different structures have been developed for autoimmune diseases [12, 14]. The structural formats of bsAbs for the treatment of autoimmune diseases can be divided into three categories (see Fig. 1).

The first is a group of immunoglobulin G (IgG)-like bsAbs comprising one IgG antibody backbone and two coupled antibody fragments or cytokines: IgG-like bsAbs are usually tetravalent to provide crosslinking of targets that enhances binding avidity. The representative IgG-like structures include IgG-single-chain variable fragments (scFvs) and dual variable domain (DVD)-Igs, which are tetravalent through the fusion of two scFvs to an IgG. Fragment crystallizable (Fc)-mediated heterodimerization is usually achieved with quadroma technology or the knobs-into-holes method [15].

The second is a group of natural IgG bsAbs that maintain the natural structure of an IgG molecule. Natural IgG bsAbs are bivalent for binding two antigens by its two fragment antigen binding (Fab) arms. The major advantage of the natural architecture of an IgG is its ability to avoid non-native issues associated with the bsAb.

The third is a group of tandem antibody fragments that are linked with two individual antibody fragments without Fc regions [16]. These formats include tandem Fvs (tascFvs) that are dimers of scFvs, diabodies (Dbs) that consist of two crossed-over scFvs, dual-affinity re-targeting (DART) (single-chain Dbs [scDbs]) that are diabodies containing an inter-Fv disulfide [12].

Each of these formats has its own unique merits. For example, the Fc regions of IgG-like and natural IgG bsAbs may lead to an increased half-life. However, high production yields and good stability are challenging for large IgG-like bsAbs. Nonhuman portions introduced in IgG-like bsAbs potentially result in unfavorable pharmacokinetics in humans. The production of tandem antibody fragments is relatively stable and feasible.

3 Bispecific Antibodies in Preclinical and Clinical Phases of Immune Diseases

Several bsAbs have been studied in preclinical or clinical trials under a number of autoimmune and inflammatory conditions. At least 12 bsAbs for autoimmune indications are advancing in clinical trials, the details of which are described in this section and summarized in Table 1. Their structures are also outlined in Fig. 1. Some reports of clinical trials remain as conference abstracts at this stage and fully published, peer-reviewed data are awaited.

3.1 Clinical Phases

3.1.1 Lutikizumab (ABT-981)

Lutikizumab is a fully human DVD-Ig bsAb developed by Abbvie for the treatment of osteoarthritis (OA). In a mouse model, it reduced OA progression by neutralizing IL-1α and IL-1β. In a phase I study in knee OA (NCT01668511), the tolerability of lutikizumab was satisfactory and pharmacodynamic effects were as expected [17]. The proportions of adverse events (AEs) and serious AEs (SAEs) were proportional between the placebo and lutikizumab groups. In two individual phase II studies (NCT02384538; NCT02087904) in patients with either erosive hand OA or knee OA-associated synovitis [18–20], lutikizumab significantly decreased serum IL-1α/IL-1β levels and blood neutrophils. Its pharmacokinetics were consistent with those in phase I studies. However, in a double-blind placebo-controlled randomized study of 350 patients, lutikizumab did not improve pain or inflammation compared with placebo. The differences in pain reduction were not significant between the lutikizumab and placebo groups. These published data suggest that IL-1 blockade does not effectively suppress inflammation in most patients with knee OA or associated synovitis.

3.1.2 APVO210

APVO210 is an IgG-like bispecific molecule being developed by Aptevo; it comprises an anti-CD86 antibody fused with a monomeric IL-10. APVO210 is designed to selectively induce IL-10R signaling in CD86+ antigen-presenting cells (APCs) but not activate resting lymphocytes [21]. These activated APCs may promote antigen-specific

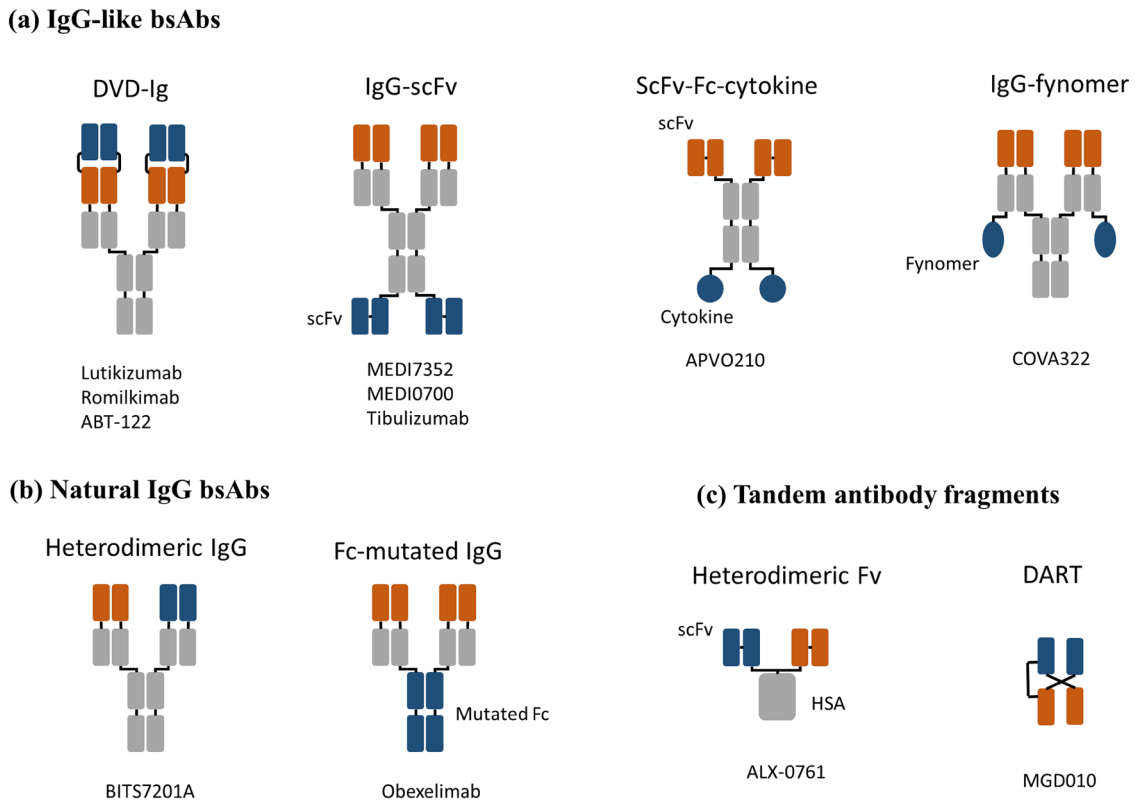

Fig. 1 Structure of bispecific antibodies in clinical studies for autoimmune diseases. **a** IgG-like bsAbs that are composed of one IgG antibody and two coupled antibody fragments, cytokines or antibody similar; **b** natural IgG bsAbs that maintain the natural structure of an antibody IgG molecule; **c** tandem antibody fragments composed of two antibody fragments and a carrier; and DART, which are diabodies containing an inter-Fv disulfide. *bsAbs* bispecific antibodies, *DART* dual-affinity re-targeting, *DVD* dual variable domain, *Fv* variable fragment, *IgG* immunoglobulin G, *scFv* single-chain variable fragment

T-regulatory type 1 (Tr1) cells to subsequently suppress immune responses in patients with UC. A phase I study (NCT03768219) is being conducted to evaluate the safety, tolerability, and pharmacodynamics of APVO210 in healthy subjects. Although the T-lymphocyte response is induced, several key T-cell cytokines associated with SAEs remain low. Preliminary data show that APVO210 does not cause drug-related AEs or have any dose-limiting toxicities [22]. However, Aptevo decided to discontinue the development of APVO210 in October, 2019.

3.1.3 Obexelimab (XmAb5871)

Obexelimab is a natural IgG bsAb that consists of an antibody variable domain targeting CD19 and an inhibitory Fc domain targeting FcγRIIb on B cells [23]. B lymphocytes play a major role in the pathogenesis of autoimmune diseases by targeting surface receptors on T cells. Obexelimab is used to treat SLE and IgG4-related diseases (IgG4-RDs) by suppressing innate and adaptive B-cell activation pathways. A phase I bioavailability study (NCT02867098) in healthy volunteers who received intravenous or subcutaneous obexelimab was completed in 2017. No drug-related SAEs were reported. Only 33% of patients experienced treatment-emergent ADAs. Obexelimab inhibits B-cell function without destroying these immune cells. A phase II study in SLE (NCT02725515) was completed in 2018 and reported that obexelimab was well-tolerated and that the infection rate was lower than those reported in other SLE trials [24]. Transient AEs and infusion-related gastrointestinal side effects were observed at rates similar to those with placebo. Improvement lasted to day 225 in 42% (21/50) of patients receiving obexelimab compared with 28.6% (12/42) of those receiving placebo. Xencor is preparing to initiate a phase III trial. In another phase II trial (NCT02725476), obexelimab showed a promising treatment effect in patients with IgG4-RD [25]. Six of six patients with major salivary or lacrimal gland enlargement demonstrated improvement after receiving obexelimab. Clinical trial results have been reported as conference abstracts thus far, and fully published, peer-reviewed data are awaited.

Table 1 Bispecific antibodies in clinical trials for autoimmune diseases

Name	Targets	Developer	Format	Indication	Trial	Phase	Efficacy and safety	References
IgG-like bsAbs								
Lutikizumab (ABT-981)	IL-1α × IL-1β	Abbvie	DVD-Ig	OA	NCT02384538, NCT02087904	II	No significant improvements compared with placebo; similar AEs and SAEs between placebo and lutikizumab	[17–19]
APVO210	CD86 × IL10-R	Aptevo	scFv-Fc-cytokine	UC, PS	NCT03768219	I	No drug-related AEs, dose-limiting toxicities, ADAs observed	[21]
MEDI7352	NGF × TNFα	AstraZeneca	IgG-scFv	Painful OA	NCT02508155	I	Not reported	
MEDI0700 (AM 570)	BAFF × B7RP-1	Amgen/AstraZeneca	IgG-scFv	RA	NCT02618967	I	No drug-related SAEs or fatal AEs	[35, 36]
				SLE	NCT03156023	I	Not reported	
Tibulizumab (LY3090106)	BAFF × IL-17	Eli Lilly	IgG-scFv	RA	NCT01925157	I	Discontinued	[30]
				Sjögren's syndrome	NCT02614716	I	Not reported	
Romilkimab (SAR156597)	IL-4 × IL-13	Sanofi	DVD-Ig	IPF	NCT02345070	II	Discontinued; no significant improvements vs. placebo; similar AEs between placebo and SAR156597	[31, 32]
				Systemic sclerosis	NCT02921971	II	Good safety and tolerability; significant improvement vs. placebo	
ABT-122	TNFα × IL-17A	AbbVie	DVD-Ig	PsA	NCT02349451	II	Efficacy of ABT-122 superior to placebo and no clearly differentiated efficacy between ABT-122 and adalimumab over 12 weeks; similar AEs between ABT-122 and adalimumab; low serious AEs	[40–42]
				RA	NCT02141997			
COVA322	TNFα × IL-17A	Covagen	IgG-fynomer	PS	NCT02243787	I/II	Good tolerability in cynomolgus monkeys	[27, 29]
Natural IgG bsAbs								
BITS7201A	IL-13 × IL-17A	Roche	Heterodimeric IgG	Asthma	NCT02748642	1	Good safety and tolerability; ADA formation	[26]
Obexelimab (XmAb5871)	CD19 × CD32b	Xencor	Fc-mutated IgG	SLE	NCT02725515	II	Good tolerability; transient AEs and infusion-related GI side effects; no drug-related AEs. Significant improvement vs. placebo	[23–25]
					IgG4-RD NCT02725476 2		Obvious improvement in index assessment of the disease within 2 weeks; no drug-related SAEs; treatment-emergent ADAs; improvement in six of six patients with major salivary or lacrimal gland enlargement	
Tandem antibody fragments								
ALX-0761 (M-1095)	IL-17A × IL-17F	Merck	Heterodimeric Fv	PS	NCT02156466	I	Good tolerability, mild or moderate AEs, ADA formation	[33, 34]
MGD010 (PRY 3279)	CD32B × CD79B	MacroGeneics	DART	AD	NCT02376036, NCT03955666	I	Acceptable safety and good pharmacodynamic activity, no SAEs	[37–39]

AD autoimmune disorders, *ADA* antidrug antibody, *AE* adverse event, *BAFF* B-cell activating factor, *bsAbs* bispecific antibodies, *CD* cluster of differentiation, *DART* dual-affinity re-targeting, *DVD* dual variable domain, *Fc* Fragment crystallizable, *GI* gastrointestinal, *IgG* immunoglobulin G, *IgG4-RD* IgG4-related diseases, *IL* interleukin, *IPF* idiopathic pulmonary fibrosis, *NGF* nerve growth factor, *OA* osteoarthritis, *PS* psoriasis, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis, *SAE* serious AE, *scFv* single-chain variable fragments, *SLE* systemic lupus erythematosus, *TNF* tumor necrosis factor, *UC* ulcerative colitis

3.1.4 MEDI7352

AstraZeneca is developing an IgG-like bsAb targeting a nerve growth factor and TNFα for the treatment of painful OA. TNFα is a potent inducer of the inflammatory response in the development of the innate immune response. Blockade of TNF signal pathways reduces the production of a range of proinflammatory cytokines. This bsAb is currently being tested in a phase I study (NCT02508155) in subjects with painful OA of the knee. This study is expected to be completed in March, 2020. Meanwhile, the efficacy and safety of MEDI7352 is being evaluated in one individual phase II study (NCT03755934) in patients with painful diabetic neuropathy. The trial is expected to be completed in 2021. No clinical reports have yet been released.

3.1.5 BITS7201A (RG7990)

BITS7201A is a natural IgG bsAb that binds and neutralizes IL-13 and IL-17. Roche conducted a phase I trial (NCT02748642) in healthy volunteers and participants with mild atopic asthma in 2016 [26]. BITS7201A showed good safety and tolerability but a high incidence of ADA formation.

3.1.6 COVA322

COVA322 is an IgG-like bispecific FynomAb that consists of an antibody binding to TNFα and IL-17A [27]. FynomAb, developed by Covagen, is a fusion of a Fynomer molecule to an IgG backbone [28]. Fynomers, small binding proteins (7 kDa) derived from the SH3 domain of Fyn kinase, showed no cross-reactivity to tissues and no indication of causing cytokine-release syndrome. In cynomolgus monkeys, COVA322 was well-tolerated in single- and repeat-dose toxicity studies [29]. Covagen completed a phase I/II trial (NCT02243787) in subjects with stable chronic moderate-to-severe plaque psoriasis in 2015. The peer-reviewed development data are awaited.

3.1.7 Tibulizumab (LY3090106)

LY3090106 is an IgG-like bsAb developed by Eli Lilly to target B-cell activating factor (BAFF) and IL-17 [30]. It was designed to prevent abnormal B-cell activation and proliferation in RA, SLE, and primary Sjögren's syndrome. In cynomolgus monkeys, LY3090106 was well-tolerated without indication of an ADA response. B-cell development and survival were suppressed without destroying these immune cells. To evaluate the safety and side effects of LY3090106, Eli Lilly completed three phase I studies in healthy volunteers and subjects with RA in 2015 (NCT01925157), in subjects with Sjögren's syndrome in 2018 (NCT02614716), and in healthy Caucasian and Japanese subjects in 2019 (NCT03736772). No recent reports have been released, but the study in RA was discontinued.

3.1.8 Romilkimab (SAR156597)

SAR156597 is a DVD-Ig bsAb developed by Sanofi to target IL-4 and IL-13. Sanofi completed a phase II trial (NCT02345070) of SAR156597 in idiopathic pulmonary fibrosis (IPF) in 2017. However, SAR156597 failed to demonstrate significant improvement compared with placebo in the treatment of IPF [31], and these studies were discontinued. Meanwhile, Sanofi evaluated the efficacy and safety of SAR156597 in a phase I trial in diffuse systemic sclerosis in 2019. Results were released as an abstract at the 2019 American College of Rheumatology (ACR) annual meeting [32]. SAR156597 was well-tolerated, with no major safety concerns. Patients who received SAR156597 experienced statistically significant reductions in disease symptoms compared with those receiving placebo.

3.1.9 ALX-0761 (M-1095)

ALX-0761 is a small-size bsAb comprising two variable domain heavy-chain (VHH domains) targeting IL-17A and IL-17F and a human serum albumin. The preclinical results were published as an abstract at the 2013 ACR annual meeting [33]. In a cynomolgus monkey collagen-induced arthritis model, ALX-0761 significantly relieved disease symptoms by neutralizing both IL-17A and IL-17F. In a completed phase I trial in psoriasis (NCT02156466) in 2015 [34], ALX-0761 exhibited a good safety profile with dose-dependent improvements. Merck conducted a phase II multiple-ascending-dose trial of ALX-0761 in patients with psoriasis (NCT02156466) in 2015, but no reports have been released.

3.1.10 MEDI0700 (AMG570)

AMG570 is an IgG-like bispecific antibody-peptide2 conjugate developed by Amgen and AstraZeneca that targets BAFF and B7-related protein-1 (B7RP-1) for the treatment of SLE and RA [35]. The preclinical and clinical results were published as an abstract at the 2018 ACR annual meeting [36]. In mouse collagen-induced arthritis and lupus models, AMG570 significantly relieved disease symptoms. Amgen completed a phase I trial in healthy subjects in 2018 (NCT02618967). AMG570 was well-tolerated, and pharmacodynamic activity was good in a single-ascending-dose study. No drug-related SAEs or fatal AEs were observed. Another phase I study (NCT03156023) is evaluating the

safety and tolerability of multiple doses of AMG570 in subjects with RA; completion is expected in 2020.

3.1.11 MGD010 (PRV 3279)

MGD010 is a small-size bsAb with a DART structure owned by MacroGenics company. It was designed to simultaneously ligate the inhibitory molecule CD32B (FcγRIIb) with the B-cell receptor component CD79B on B cells [37]. This novel approach leads to signal suppression in activated B cells without B-cell depletion. A phase I study (NCT02376036) of MGD010 in healthy volunteers was completed in 2017. MGD010 demonstrated acceptable safety and good pharmacodynamic activity [38, 39]. Completion of a phase Ib study (NCT03955666) in healthy subjects was expected in late 2019, but no further reports have been released.

3.1.12 ABT-122

ABT-122 is a DVD-Ig bsAb that specifically neutralizes both human TNFα and IL-17A. AbbVie completed two individual phase II trials in subjects with active psoriatic arthritis (NCT02349451) and RA (NCT02141997) who had inadequate response to methotrexate in 2015 and 2016 [40, 41]. In both studies, the safety of ABT-122 compared with placebo was satisfactory. No serious infections or systemic hypersensitivity reactions were observed. Although the efficacy of ABT-122 was better than that with placebo over 12 weeks, no clearly differentiated efficacy between ABT-122 and the anti-TNFα adalimumab was observed. In another long-term extension study in RA or psoriatic arthritis, ABT-122 demonstrated acceptable tolerability and maintenance of efficacy over 36 weeks [42]. The incidence of SAEs and serious infections was relatively low.

3.2 Preclinical Phases

A number of promising bsAbs have not yet reached the clinic but are in development via targeting different molecules. Several IgG-like bsAbs targeting TNF and IL-17 are in preclinical development for the treatment of RA [43, 44]. Data for these products have shown that blockade of TNF and IL-17 inhibited the development of inflammation and cartilage destruction in arthritic mice. An in vivo model of arthritis showed that simultaneous targeting of TNF and angiopoietin 2 (Ang2) with a bsAb was more efficacious than monotherapies with TNF and Ang2 [45]. A bispecific fusion molecule of an anti-IL-6R antibody and TNFR2 efficiently suppressed the proliferation and migration of fibroblast-like synoviocytes from patients with RA [46]. Another bsAb targeting IL-1β and IL-17A exhibited promising efficacy in RA [47]. In a mouse model, a bsAb targeting IL-6R and IL-17A also showed synergistic efficacy in modulating the in vivo inflammatory response [48]. Several bsAbs targeting IL-17A and IL-23 have been generated to neutralize the bioactivities of both cytokines [49]. A fully humanized IgG-like bsAb targeting CXCR3/CCR6 was used to decrease chemotaxis and/or specific depletion of proinflammatory T-cell subsets [50]. A bsAb combining an anti-TNF nanobody and an anti-F4/80 scFv (a surface molecule abundant on myeloid cells) could significantly limit the production of TNFα by immune cells [51].

4 Immunogenicity Challenges of bsAbs for Autoimmune Diseases

A strong scientific rationale often supports the engagement of two targets in therapeutic strategies for specific autoimmune diseases. Immunogenicity leads to many challenges in developing effective bsAbs and limits their use in chronic inflammatory and autoimmune diseases [52]. Immunogenicity is typically assessed by the presence of ADAs. The incidence of ADAs has been evaluated in patients receiving treatment with bsAbs [53]. Formation of ADAs varies among bsAbs. Generally, the structure and non-native sequences of bsAbs may lead to ADA formation. Multiple other factors, including the properties of either the bsAbs (impurities, administration route, dose) or the patients (disease stage, patient characteristics), may influence immunogenicity [54]. Several approaches have been proposed to manage the immunogenicity of antibody drugs in patients. The incidence of ADA formation is associated with B-cell activation. Treatment with B-cell-depleting agents before and during treatment appears to have a low risk of immunogenicity. Alternatively, immunogenicity may be prevented by removal of B-cell epitopes from bsAb sequences, leading to a decrease in B-cell activation [55]. Meanwhile, immunogenicity may be reduced by implanting regulatory T-cell epitopes into a bsAb sequence, which induces tolerance in a patient's immune system [56]. Premedication with immunosuppressive agents is believed to effectively control ADA reactions to bsAbs in some patients with autoimmune diseases [57]. The optimization of appropriate dosing regimens and administration schedules may decrease the risk of inducing ADA formation in patients.

5 Conclusions and Perspectives

To date, two bsAbs, blinatumomab (CD19 × CD3) and emicizumab (Factor IX/Factor X), have been approved to treat oncological and hematological diseases [12]. Although bsAbs for autoimmune diseases remain in the early stages of development, significant advances have been made in

the treatment of RA, UC, SLE, asthma, psoriasis, and other autoimmune diseases. These existing and developing agents may offer new options for personalized therapy. Customized bsAbs can be further considered based on the characteristics of the immune system in specific patients. At least 12 bsAbs have been evaluated in clinical trials. Their protein structures are diverse, from small antibody fragments (DART, heterodimeric Fv) to large IgG-like formats (DVD-Ig, IgG-scFv, heterodimeric IgG, and so on). The IgG-like formats predominate (10 of 12 bsAbs). Each of these formats has its own pros and cons. Some IgG-like formats (such as scFv-IgG) do not achieve the long half-life of IgGs, although Fc regions are retained in the structure [58]. The implanted non-human portions (such as artificial linkers) in IgG-like bsAbs seem to influence their pharmacokinetics. In autoimmune diseases, immunological synapses in autoimmunity are formed through interactions between naive T cells and APCs or B lymphocytes. The therapeutic actions of bsAbs mainly involve preventing immunological synapses, either through targeting the surface markers of immune cells (four bsAbs) or neutralizing inflammatory cytokines (eight bsAbs). These targets focus on surface receptors on B cells (CD19, FcγRIIb, BAFF, B7RP-1, CD32B, CD79B) or APCs (CD86), as well as proinflammatory T-cell regulators (IL-1, IL-4, TNFα, IL-13, IL-17).

However, inflammatory diseases are extremely heterogeneous and complex. Multiple factors, such as patient history and disease phenotype, can affect a patient's response to treatment. Because the interface of the immune network is sophisticated and indistinct, human clinical trials should be carefully and seriously initiated. The anti-CD28 antibody TGN1412 is an example of a failed therapy as it induced an unpredicted cytokine storm and other side effects [59]. Lessons from recent clinical treatments of autoimmune diseases indicate that not all bsAbs work as expected. Two recent clinical reports have shown that lutikizumab, a bsAb against IL-1-α/β, did not improve painful syndromes in patients with either knee or hand OA compared with placebo, even though IL-1-α/β levels were effectively suppressed [18, 19, 60]. These clinical observations suggest that we may need to further develop our understanding of the pathological role of inflammatory targets in autoimmune diseases. Clinical data from these bsAbs, regardless of whether clinical outcomes were met, are therefore of value in advancing our knowledge.

In conclusion, bsAbs are emerging as therapeutic options for the treatment of autoimmune and inflammatory diseases because these molecules can offer sophisticated targeting strategies in the complex inflammatory network. These novel bispecific molecules represent the next generation of therapeutic antibodies that may enhance treatment beyond monotherapy.

Acknowledgements The author acknowledges support from The Science and Technology Development Fund, Macau SAR (File no. FDCT/131/2016/A3, FDCT/0015/2018/A1), the Multi-Year Research Grant (file no. MYRG2019-00069-FHS), Start-up Research Grant (file no.SRG2016-00082-FHS), the intramural research program of the Faculty of Health Sciences, University of Macau, and National Key Research and Development Project of the Ministry of Science and Technology of China (2019YFA09004400).

Compliance with Ethical Standards

Funding No funding was received for this review.

Conflict of interest Qi Zhao has no conflicts of interest that are directly relevant to the content of this article.

Ethical approval Not required.

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