


Immunogenicity of Biologics in Chronic Inflammatory Diseases: A Systematic Review

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Abstract

Objectives A systematic review was conducted to explore the immunogenicity of biologic agents across inflammatory diseases and its potential impact on efficacy/safety.

Methods Literature searches were conducted through November 2016 to identify controlled and observational studies of biologics/biosimilars administered for treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA), juvenile idiopathic arthritis (JIA), ankylosing spondylitis

(AS), non-radiographic axial spondyloarthritis (nr-axSpA), psoriasis (Ps), Crohn's disease, and ulcerative colitis.

Results Of >21,000 screened publications, 443 were included. Anti-drug antibody (ADAb) rates varied widely among biologics across diseases (and are not directly comparable because of immunoassay heterogeneity); the highest overall rates were reported with infliximab (0–83%), adalimumab (0–54%), and infliximab biosimilar CT-P13 (21–52%), and the lowest with secukinumab (0–1%), ustekinumab (1–11%), etanercept (0–13%), and golimumab (0–19%). Most ADABs were neutralizing, except those to abatacept and etanercept. ADAb+ versus ADAb– patients had lower rates of clinical response to adalimumab (RA, PsA, JIA, AS, Ps), golimumab (RA), infliximab (RA, PsA, AS, Ps), rituximab (RA), ustekinumab (Ps), and CT-P13 (RA, AS). Higher rates of infusion-related reactions were reported in infliximab- and CT-P13-treated ADAb+ patients. Background immunosuppressives/anti-proliferatives reduced biologic immunogenicity across diseases.

Conclusions Based on reviewed reports, biologic/biosimilar immunogenicity differs among agents, with the highest rates observed with infliximab and adalimumab. As ADAB formation in biologic-/biosimilar-treated patients may increase the risk of lost response, the immunogenicity of these agents is an important (albeit not the only) consideration in the treatment decision-making process.

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Key Points

Across chronic inflammatory disease states, anti-drug antibodies (ADABs) were detected in as many as 50% of patients in studies of adalimumab, infliximab, and the infliximab biosimilar CT-P13, but in lower proportions of patients (<20%) in studies of secukinumab, ustekinumab, etanercept, and golimumab. (Immunogenicity data are not directly comparable among studies because of heterogeneity in immunoassays and other methodological features.)

ADAB formation was associated with reduced clinical efficacy of several biologics/biosimilars, including adalimumab, golimumab, infliximab, rituximab, ustekinumab, and CT-P13, and higher risk of infusion reactions with infliximab and CT-P13.

Because of these potential clinical consequences, the immunogenicity of biologics/biosimilars is an essential (albeit not the only) consideration when clinicians select a therapeutic approach in patients with chronic immune-mediated inflammatory disease.

1 Introduction

Over the past few decades, the introduction and growing use of biologic agents has represented a major advance in the management of inflammatory diseases [1]. These biologic agents include a T cell activation inhibitor/co-stimulation modulator, tumor necrosis factor inhibitor (TNFi) monoclonal antibodies (mAbs) and receptor fusion protein, an anti-CD20 mAb, and anti-interleukin (IL)-17A, IL-6, IL-12/23 mAbs, which have unique protein structures and differing capacities to induce immune responses. Results from randomized controlled trials (RCTs) support the efficacy of biologics across a range of disease states, but a substantial proportion of patients fail to respond or have an inadequate response with initial treatment (primary failure), lose response over time (secondary failure), or develop potentially therapy-limiting adverse events (AEs). The presence of anti-drug antibodies (ADABs) has been identified as an important (albeit not the only) contributor to treatment failure and increased risk of AEs in patients receiving biologic therapy [2–5]. Formation of immune complexes between ADABs and biologics may increase clearance and reduce serum biologic levels and may have a more direct neutralizing effect on product target binding.

Measurement of the immunogenic potential of biologics is challenging, as ADAB detection is technically detailed and standardized criteria for assay sensitivity have not been established [2, 4], which explains in part published discrepancies in ADABs reported for individual agents. Many factors may influence immunogenicity, including product-specific factors (e.g., protein structure), treatment-related factors (e.g., use of concomitant therapies, dosing, continuous or intermittent administration), and patient-related factors (e.g., genetic pre-disposition and underlying disease). Numerous studies of the immunogenicity of individual agents have been conducted, but immunoassay methodologies and study design features, including types [e.g., RCTs, longitudinal observational studies (LOSs)] and duration of treatment, vary widely and thus data interpretation is challenging [5]. Nonetheless, detailed and comprehensive reviews of the published literature on the immunogenicity of all marketed biologic agents across inflammatory disease states are needed to ensure that clinicians remain well informed on this critical issue.

We conducted a systematic literature review (SLR) to examine the immunogenicity of ten approved biologic agents and one approved biosimilar agent across inflammatory diseases. We particularly focused on the reported frequency of ADAB formation; potential effects of ADAB on pharmacokinetics, efficacy, safety, and treatment survival; and factors with a potential impact on the agent's immunogenic potential.

2 Methods

2.1 Data Sources

A comprehensive search strategy was developed to identify relevant RCTs and LOSs from the published literature. Searches of the following databases were conducted for studies published in English through November 2016: MEDLINE[®], MEDLINE in Process and Other Non-Indexed Citations, Embase[®], Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews. Manual searches were conducted of proceedings from the following conferences: the American College of Rheumatology; the European League Against Rheumatism; Advances in Inflammatory Bowel Disease, Crohn's and Colitis; the European Crohn's and Colitis Organisation; European Congress of Immunology; American Academy of Dermatology; European Academy of Dermatology and Venereology; and the International Congress on Spondyloarthropathies. Review articles/editorial reference lists, and previously conducted SLRs were also manually searched. A cross-referencing search was

conducted post hoc to identify relevant studies not captured in the original searches because the incidence/prevalence of ADABs was not included within the studies' abstracts. The cross-referencing search was conducted with an internet search engine (Google Scholar) using mAb-specific immunogenicity terms and manual review of the reference lists of new and existing published studies.

2.2 Study Eligibility and Selection

Eligible studies included RCTs, non-RCTs, and observational studies of patients treated for rheumatoid arthritis (RA), psoriatic arthritis (PsA), juvenile idiopathic arthritis (JIA), axial spondyloarthritis (axSpA), including ankylosing spondylitis (AS) and non-radiographic axSpA (nr-axSpA), psoriasis (Ps), and inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC). Studies of the following approved biologic and biosimilar agents were included: abatacept (ABA), adalimumab (ADA), certolizumab pegol (CZP), etanercept (ETN), golimumab (GLM), infliximab (INF), rituximab (RTX), secukinumab (SEC), tocilizumab (TCZ), ustekinumab (UST), and the INF biosimilar CT-P13 [Supplementary Table 1; see electronic supplementary material (ESM)].

In the first of two rounds of screening, titles and abstracts of publications identified in the literature searches were examined by a single reviewer for eligibility. A second validating reviewer conducted a quality check of 10% of the screened studies; if discrepancies were identified in $\geq 5\%$ of the latter segment of screened studies, the screened studies were to be re-evaluated. Discrepancies were found in 0.6% of the studies. (Authors VS, AB, and SL reviewed all included studies for eligibility.) The complete texts of publications initially identified as eligible were subsequently examined in the second screening round, during which studies that failed to satisfy eligibility criteria were excluded. The validating reviewer inspected 20% of the publications excluded in this second screening and all publications eligible for inclusion. Discrepancies were resolved by a consensus among reviewers.

2.3 Data Extraction

The following categories of information were obtained from the selected studies: (i) publication details/study characteristics; (ii) population characteristics at baseline; and (iii) study outcomes (i.e., pharmacokinetics, safety, efficacy, and treatment survival) and variables assessed. A complete list of the extracted data is shown in Supplementary Table 2 (see ESM).

2.4 Study Quality Assessment

The quality of RCTs identified in the searches was assessed based on specifications from the National Institute for Health and Clinical Excellence single technology appraisal (STA) of manufacturers' submission of evidence [6] and the Jadad [7] scoring tools (Supplementary Table 3; see ESM). The checklist by Downs and Black [8] was used to appraise the quality or risk of bias of non-RCTs and LOSs in full publications (original checklist) and conference proceedings (modified checklist). Studies that received a poor rating on the risk of bias assessments were excluded.

3 Results

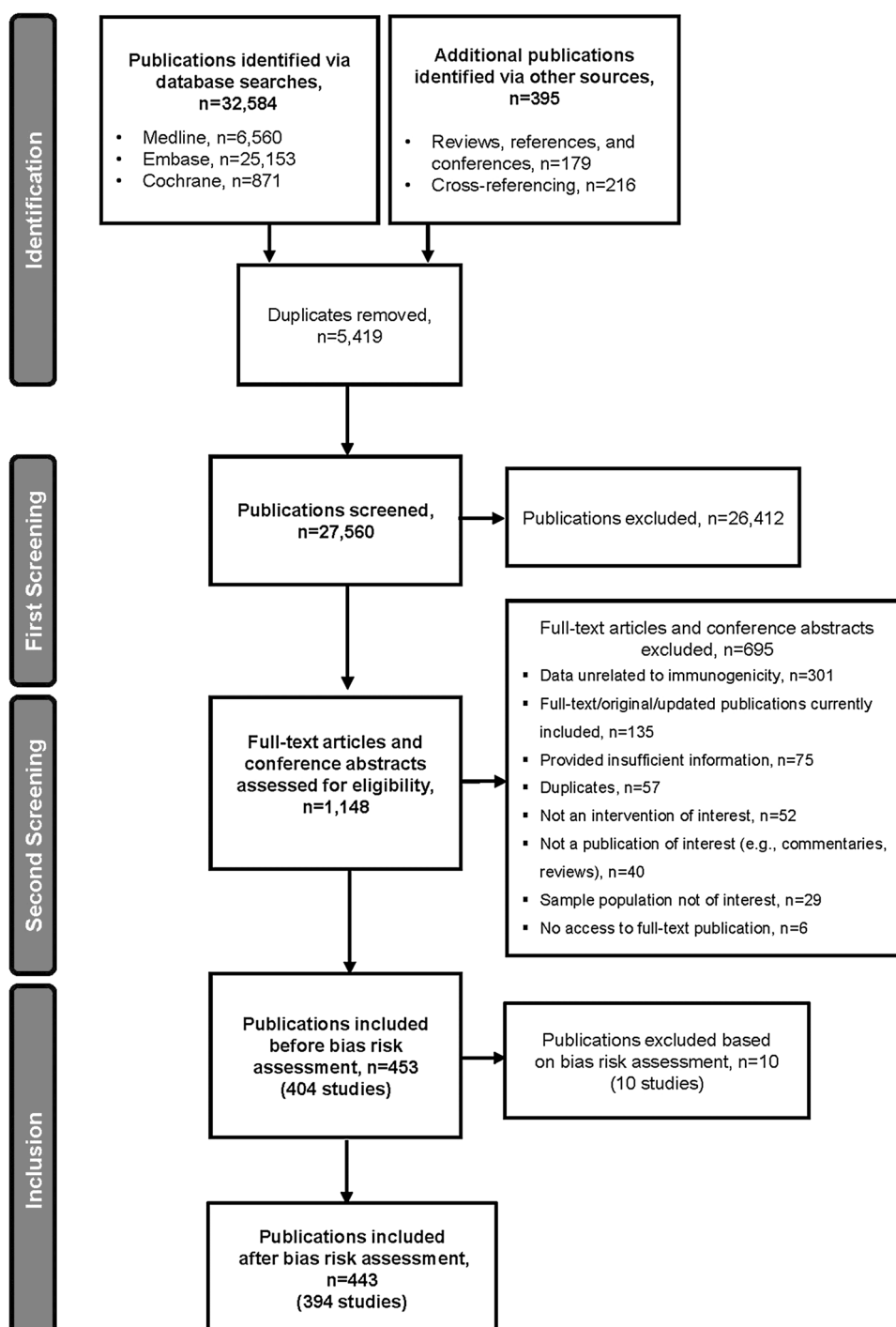
3.1 Literature Search/Screening

A total of 32,584 publications were initially identified in the literature; 27,560 were reviewed in the first screening, and 1148 in the second screening (Fig. 1). After 10 publications (10 studies) were excluded due to risk of bias (based on the Downs and Black checklist [8]) [9–18], 443 publications (394 studies) were included in the review. Due to the earlier introduction of ADA, ETN, and INF, these biologics had the greatest overall number of publications and studies included in the review (Supplementary Fig. 1; see ESM). The ratio of RCTs to non-RCTs and observational studies varied widely among the biologic/biosimilar agents. A broad range of disease states, study durations, and immunoassay methods were found among the biologic/biosimilar studies (Tables 1, 2). The timing of ADAB testing was often not reported; however, in most studies that provided this information, testing was conducted at study baseline and at multiple time points thereafter (frequently coinciding with visits scheduled for efficacy and safety assessment). Considerable variability is also seen in the demographic and disease characteristics at baseline of patients when assessed by individual diseases (studies, $n = 293$; Supplementary Table 4; see ESM).

3.2 Anti-Drug Antibody (ADAB) Formation

The proportions of patients who developed treatment-induced ADABs varied widely across biologic/biosimilar agents (Table 3). Data are represented as a range of ADABs observed across studies and diseases included in the review. Comparisons of immunogenicity across agents should be conducted with caution due to fundamental differences in their molecular structure, number of studies reporting ADABs for individual agents, disease states

Fig. 1 Flow of publications/studies through the search and screening process



included, and study designs and assay methods. Agents associated with the highest overall rates of ADA formation were INF (0–83%), ADA (0–54%), and the INF biosimilar CT-P13 (21–52%), whereas those with the lowest were SEC (0–1%), UST (1–11%), ETN (0–13%), and GLM (0–19%). The incidence of ADA formation appeared to vary considerably across assay methods used and inflammatory disease states.

3.3 Neutralizing and Non-Neutralizing ADABs

Neutralizing ADABs have been reported with biologic/biosimilar agents, including ADA [19, 20], CZP [21, 22], GLM [23–27], TCZ [28, 29], and CT-P13 [30, 31], albeit very infrequently with the fusion proteins ABA and ETN [2, 3, 32–34]. ADABs against TNFi mAbs target idiotypes within or close to the epitope-binding

Table 1 Summary of agents and disease states evaluated in included publications

Biologic/biosimilar	No. of publications ^a		Disease state						
	No. of agents evaluated ^b								
	Single	Multiple	RA	AS, axSpA, SpA	PsA	JIA	Ps	CD, UC	
ABA (<i>n</i> = 10)	10	0	8	0	0	2	0	0	
ADA (<i>n</i> = 133)	68	65	55	27	19	6	13	36	
CZP (<i>n</i> = 22)	22	0	11	1	0	0	1	9	
ETN (<i>n</i> = 61)	14	47	42	17	11	2	6	0	
GLM (<i>n</i> = 36)	34	2	21	7	2	0	0	7	
INF (<i>n</i> = 220)	148	72	73	36	16	3	16	107	
RTX (<i>n</i> = 12)	7	5	12	0	0	0	0	0	
SEC (<i>n</i> = 11)	11	0	0	2	2	0	7	0	
TCZ (<i>n</i> = 22)	22	0	19	0	0	3	0	0	
UST (<i>n</i> = 15)	14	1	0	0	2	0	11	2	
CT-P13 (<i>n</i> = 13)	2	11	7	4	1	0	1	4	

^a Numbers represent all publications that report findings for the specified biologic/biosimilar and for the specified disease state

^b Numbers of publications of studies in which a single biologic/biosimilar or multiple biologics/biosimilars were evaluated

ABA abatacept, ADA adalimumab, ADAb anti-drug antibody, AS ankylosing spondylitis, axSpA axial spondyloarthritis, CD Crohn’s disease, CT-P13 INF biosimilar CT-P13, CZP certolizumab pegol, ETN etanercept, GLM golimumab, INF infliximab, JIA juvenile idiopathic arthritis, Ps psoriasis, PsA psoriatic arthritis, RA rheumatoid arthritis, RTX rituximab, SEC secukinumab, SpA spondyloarthritis, TCZ tocilizumab, UC ulcerative colitis, UST ustekinumab

Table 2 Summary of study duration and immunoassay methods used in included publications

Biologic/biosimilar	Number of publications							
	Study duration (week)			Immunoassay method				
	≤24	>24	NR	ELISA	ECL	RIA	Other	NR
ABA (<i>n</i> = 10)	2	6	2	5	4			2
ADA (<i>n</i> = 133)	21	47	65	65		28	13	27
CZP (<i>n</i> = 22)	8	12	2	13		2		7
ETN (<i>n</i> = 61)	11	26	24	34	1	10		16
GLM (<i>n</i> = 36)	9	24	3	26		1		9
INF (<i>n</i> = 220)	19	82	119	111	13	31	21	44
RTX (<i>n</i> = 12)	7	4	1	6	1			5
SEC (<i>n</i> = 11)	4	7		3	3		2	3
TCZ (<i>n</i> = 22)	4	14	4	13				9
UST (<i>n</i> = 15)		12	3	7	1	1		6
CT-P13 (<i>n</i> = 13)		12	1	3	9			1

ABA abatacept, ADA adalimumab, CT-P13 INF biosimilar CT-P13, CZP certolizumab pegol, ECL electrochemiluminescent immunoassay, ELISA enzyme-linked immunosorbent assay, ETN etanercept, GLM golimumab, INF infliximab, NR not reported, RIA radioimmunoassay, RTX rituximab, SEC secukinumab, TCZ tocilizumab, UST ustekinumab

portions in the Fab regions of the mAbs and prevent their binding to TNF [35, 36]. Anti-idiotypic ADAbs are clinically important as they can directly diminish therapeutic activity by interfering with the agent’s ability to execute its therapeutic mode of action. In addition, both

neutralizing and non-neutralizing antibodies can impact clinical responses to biologics/biosimilars by forming immune complexes that may influence their pharmacokinetics (i.e., increased clearance) and lowering serum concentrations [35].

Table 3 Summary of ADAb formation rates for individual biologic/biosimilar by chronic inflammatory disease

Biologic	Frequency of ADAb formation, % (no. of studies ^a)							
	RA	PsA	JIA	AS	Ps	CD	UC	Range
ABA	2–20 (7)		2–11 (2)					2–20 (9)
ADA	0–51 (33)	0–54 (8)	6–33 (6)	8–39 (9)	0–51 (12)	0–35 (13)	3–5 (3)	0–54 (80)
CZP	2.8–37 (7)				21 (1)	3–25 (6)		3–37 (14)
ETN	0–13 (25)	0 (3)	0–6 (2)	0 (4)	2–5 (5)			0–13 (37)
GLM	2–10 (11)	6 (1)		0–6.4 (2)			0–19 (8)	0–19 (22)
INF	8–62 (48)	15–33 (3)	26–42 (2)	6.1–69 (10)	0–41 (12)	3–83 (29)	6–46 (10)	0–83 (110)
RTX	0–21 (8)							0–21 (8)
SEC		0–0.1 (3)		0–0.3 (3)	0–1 (8)			0–1 (14)
TCZ	0–16 (14)		1–8 (3)					0–16 (17)
UST		8–11 (3)			4–8.6 (10)	0–1 (2)		1–11 (15)
CT-P13	26–52 (2)			27 (1)		21 (1)	24 (1)	21–52 (5)

^a Studies of patients with multiple chronic inflammatory diseases are included for each disease state

ABA abatacept, ADA adalimumab, ADAb anti-drug antibody, AS ankylosing spondylitis, CD Crohn's disease, CT-P13 INF biosimilar CT-P13, CZP certolizumab pegol, ETN etanercept, GLM golimumab, INF infliximab, JIA juvenile idiopathic arthritis, Ps psoriasis, PsA psoriatic arthritis, RA rheumatoid arthritis, RTX rituximab, SEC secukinumab, TCZ tocilizumab, UC ulcerative colitis, UST ustekinumab

3.4 Impact of ADABs

3.4.1 Pharmacokinetics

In published studies of ADA [37–69], CZP [70–80], GLM [81], INF [1, 2, 36, 45, 46, 54, 57, 58, 60, 61, 63, 64, 67, 82–117], RTX [118], UST [119, 120], and CT-P13 [2, 30, 82–85, 121, 122], ADAb-positive patients were reported to have lower serum biologic concentrations than ADAb-negative patients. Differences in serum biologic concentrations between ADAb-positive and -negative patients were found to be statistically significant in studies of ADA [42–44, 47–50, 53–55, 57, 58, 61] and INF [54, 57, 58, 61, 87–91, 97, 98, 105, 107, 111, 113, 114] across chronic inflammatory diseases. In the Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate, a 12-month observational prospective cohort study, ADABs against ADA were detected in 31 of 160 (19%) ADA-treated patients and were significantly associated with lower ADA concentrations ($r_s = -0.51$; $p < 0.0001$) [44]. In a prospective cohort study of PsA, Vogelzang et al. reported that 23 of 103 (22%) patients had detectable ADABs against ADA after 52 weeks and ADA concentrations were significantly lower after 28 and 52 weeks in ADAB-positive versus -negative patients (week 28: 1.3 vs 8.7 mg/L, $p < 0.001$; week 52: 0.9 vs 9.4 mg/L, $p = 0.0001$) [47, 48]. Significantly lower serum ADA concentrations have also been observed in patients with and without detectable ADABs in prospective cohort studies of JIA [ADAb-positive, 6 of 23 (26%), ADA serum

concentrations, 1.6 vs 14.1 mg/L, $p = 0.006$] [49]; AS [31 of 115 (27%), 1.2 vs 12.7 mg/L, $p < 0.001$] [50]; Ps [27 of 53 (51%), 0.8 vs 4.8 mg/L, $p < 0.001$] [53]; and CD [5 of 23 (22%), 7.5 vs 9.5 mg/L, $p = 0.002$] [55].

Similarly, in a prospective cohort study of INF in patients with rheumatic diseases (RA, axSpA, PsA, and others), ADABs were detected in 12 of 24 (50%) of patients, with significantly lower serum INF levels observed in patients who developed ADABs versus those who did not (0.004 vs 3.8 mg/L, $p = 0.002$) [58]. In a study of similar design conducted in patients with Ps, 6 of 20 (30%) INF-treated patients developed ADABs and serum INF levels were significantly lower in ADAB-positive patients (1.2 vs 4.1 $\mu\text{g/L}$, $p < 0.01$) [54]. In the largest of several prospective cohort studies with significant and consistent findings in CD or UC, Levesque et al. found that 57 of 326 (18%) patients had antibodies against INF and that a lower proportion of ADAB-positive patients had therapeutic INF concentrations compared with ADAB-negative patients after 8 weeks of treatment (14% vs 76%, $p < 0.001$) [98].

3.4.2 Clinical Efficacy

A consistent association between development of ADAB positivity and efficacy has been reported in studies of several biologic/biosimilar agents (Supplementary Table 5; see ESM). Specifically, in RA, patients with ADABs against ADA [19, 37–39, 41–44, 123–128], GLM [24, 81, 129], INF [2, 82–86, 90, 116, 124, 125, 128, 130–134],

RTX [118, 135, 136], and CT-P13 [2, 82–85] showed less improvement in disease activity and were less likely to achieve clinical responses. Less robust evidence of such a relationship has been reported in studies of CZP [80] and ETN [137]. In ADA-treated patients with JIA, higher proportions of ADAb-positive patients experienced a loss of response than those without antibodies [49]. Similarly, responses were lower in ADAb-positive patients receiving ADA and INF in studies of PsA [138–141], AS [58, 126, 142–145], and Ps [51–53, 146–149]; in patients receiving UST in Ps [120, 150]; and those receiving CT-P13 in AS [30, 121, 122]. In several studies of CD and UC, clinical response/remission rates were found to be lower in patients with antibodies than in those without when treated with ADA [151], CZP [152], and INF [153–156].

3.4.3 Safety/Tolerability

The presence of ADABs may also be associated with biologic/biosimilar safety and tolerability, with the most extensive evidence derived from studies of INF. In INF study publications, infusion-related reactions occurred in higher proportions of ADAb-positive versus -negative patients across several disease states, including RA [86, 90, 145, 157], JIA [158, 159], AS [144, 160, 161], Ps [162], and CD [154, 163–165], or UC [89, 111, 166, 167]. In a large retrospective cohort study conducted in patients with RA, Krintel et al. observed a significantly increased risk of discontinuation due to adverse drug reactions in patients who developed anti-INF antibodies compared with those who did not develop ADABs after 6 weeks of treatment [hazard ratio (HR) 5.1; $p < 0.0001$] and 14 weeks of treatment (HR 3.3; $p = 0.0009$) [90]. In the PLANETRA (Programme eValuating the Autoimmune disease iNvEstigational drug cT-p13 in RA) RCT, higher rates of infusion-related reactions were observed in ADAb-positive patients versus ADAb-negative patients in groups receiving the biosimilar CT-P13 (87% vs 8%) and INF (81% vs 10%) [83].

In a prospective cohort study in RA, AS, and PsA, AEs occurred more frequently in ADAb-positive patients than in ADAb-negative patients treated with ADA (27% vs 15%) [168]. In an RCT of ADA in patients with Ps, greater proportions of ADAb-positive versus -negative patients reportedly had infectious AEs (54% vs 48%), injection site reactions (23% vs 16%), and hepatic-related AEs (39% vs 30%) [146]. Numerically higher rates of treatment-emergent AEs (89% vs 68%) and serious AEs (22% vs 16%) were reported in patients with RA who developed anti-RTX ADABs compared with those who did not [135, 136]. Studies of other biologics have not included findings on the effects of immunogenicity on safety/tolerability.

3.4.4 Treatment Survival

The relationship between treatment survival and immunogenicity of biologic/biosimilar agents has not been well studied, with little or no evidence available from study publications for most biologics. However, in RCTs of INF in patients with RA and/or axSpA, treatment survival times were found to be shorter in ADAb-positive patients [91, 131, 145]. Pascual-Salcedo et al. reported a significant difference in treatment survival (4.2 vs 8.9 years; $p = 0.0006$) in a cohort of RA patients with and without ADABs against INF [131].

3.5 Factors Associated with Immunogenicity

3.5.1 Structure/Target Molecule

The protein structures of biologic/biosimilar agents, which are not identical to endogenous immunoglobulins, are capable of inducing immune responses and formation of ADABs. Basic differences in the molecular structures of these agents (Fig. 2) may help explain differences in immunogenicity rates between agents. For example, rates of ADAb formation are higher with chimeric TNFi mAbs (e.g., INF) compared with some fully human TNFi mAbs (e.g., GLM) and fusion proteins (e.g., ETN) (Table 3). Interestingly, a marked difference has been reported in the immunogenic potential of GLM and ADA: GLM is fully humanized by homologous recombination with an immunogenicity rate of up to 10%; ADA is developed by phage substitution, with ADABs directed against the epitope binding region and an immunogenicity rate of up to 54%. The receptor fusion proteins ABA and ETN both exhibit immunogenicity to the linker portion between soluble receptor and Fc portion, which may explain in part the low frequency of ADAb formation and lack of neutralizing activity.

The immunogenic potential of some biologic/biosimilar agents may also be related to the target molecule. For example, the low incidence of ADABs observed with TCZ may be explained in part by the fact that IL-6 is necessary for the antibody response or that the assay sensitivity is low in the presence of circulating drug levels.

3.5.2 Immune Complex Formation

Formation of immune complexes between biologics/biosimilars and the target protein may also be an important factor determining immunogenic potential [2]. The size of these immune complexes appears to vary by therapeutic agent, as the fusion protein ETN forms small complexes (≤ 300 kDa), generally with only one of three trimers of TNF α , and monoclonal antibodies ADA and INF are able

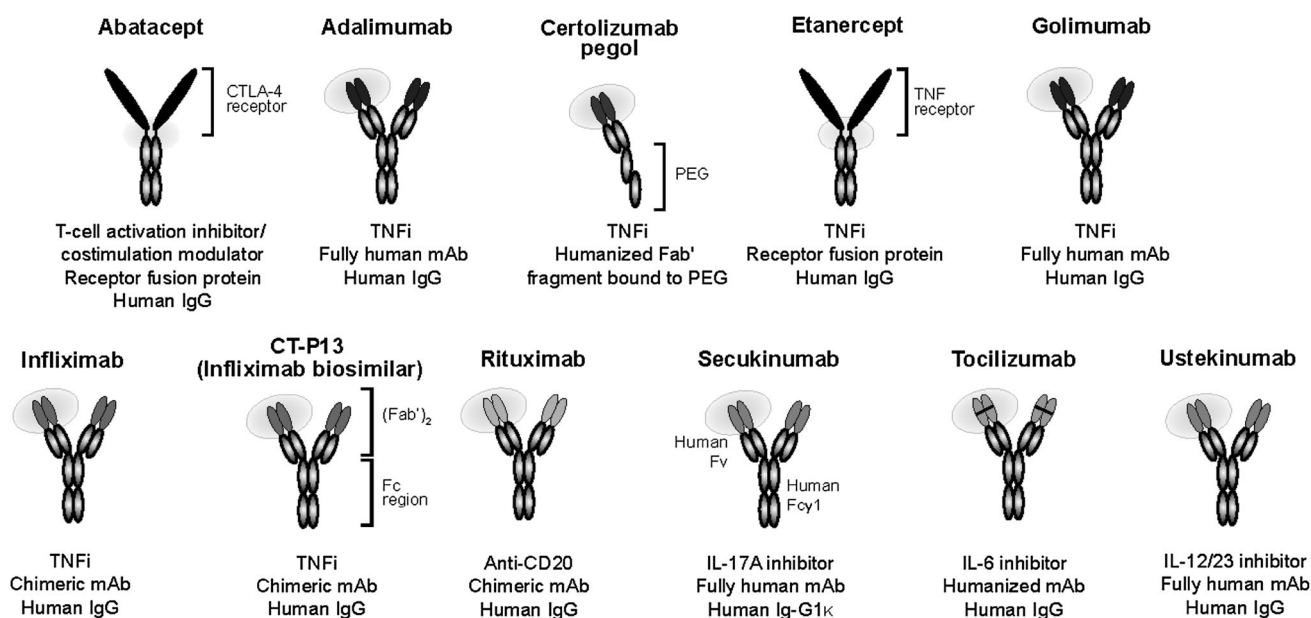


Fig. 2 Immunogenic portions of molecular structures of biologic/biosimilar agents. *IgG* immunoglobulin G, *IL* interleukin, *mAb* monoclonal antibody, *PEG* polyethylene glycol, *TNFi* tumor necrosis factor- α inhibitor

to bind two trimers to form larger complexes (~ 4000 kDa and 14,000 kDa, respectively) [101]. Large immune complexes are taken up earlier by antigen-presenting cells and are cleared from the system more rapidly, potentially resulting in greater immunogenicity [2].

3.5.3 Background Therapy

Evidence from many studies of biologic agents across disease states indicate that background immunosuppressive/anti-proliferative therapy reduces immunogenicity. As expected based on these agents' immunosuppressive mechanism, concomitant use of methotrexate, azathioprine, leflunomide, or mycophenolate is associated with lower rates of ADABs against ADA in RA, JIA, AS, axSpA, and CD [38–40, 49, 143, 151, 169–173]; CZP in RA and CD [3, 62, 70–75, 78]; GLM in RA, PsA, AS, and UC [129, 174–182]; INF in RA, Ps, CD, and UC [91, 110, 111, 113, 114, 145, 153, 163, 165–167, 172, 183–195]; TCZ in RA [29]; and UST in PsA [119]. Differences in the benefit of methotrexate versus other immunosuppressives/anti-proliferatives in terms of immunogenicity were not evident from the literature.

3.5.4 Biologic Dose/Regimen

High biologic doses and induction therapy were also associated with decreased incidence of ADABs in some published trials, including trials of ADA in RA and CD [37, 196–199]; CZP in RA and CD [70–75, 77]; INF in RA and CD [157, 163, 183, 186, 200]; and RTX in RA [201].

Patients who received continuous versus intermittent therapy with ADA, CZP, and INF were less likely to develop ADABs [33, 53, 72–74, 202]. In addition, intravenous therapy is associated with less immunogenicity than subcutaneous administration of ABA [173] and GLM [174].

3.5.5 Other

Several reports in the literature also indicate that patients who previously developed ADABs against a biologic agent are more likely to develop ADABs with subsequent agents, although none are cross-reactive [41, 56, 59, 119, 203–205]. Other factors, including sex, comorbid conditions, and ethnicity, may also influence immunogenicity but insufficient evidence was available for evaluation.

4 Discussion

In the RCTs and LOSs included in this review, ADABs were detected in as many as one-half of patients treated with commonly used TNFi mAbs, and in a lower proportion of patients receiving other biologics. Across chronic inflammatory disease states, immunogenicity rates were highest ($>50\%$) in studies of ADA, INF, and the INF biosimilar CT-P13, and lowest ($<20\%$) in studies of SEC, GLM, ETN, and UST, but considerable variability in immunogenicity was seen between studies of the same and different agents. Differences between ADAB assays, including differences in assay interference by circulating serum biologic levels, and timing of ADAB testing, as well

as differences in study design may have contributed to the observed fluctuations. The majority of older detection methods, such as enzyme-linked immunosorbent assays, are affected by ‘drug interference’; as a result, ADAb levels may only be detected when they exceed biologic serum levels. Differences in sample collection timing and protocols between studies also can influence the results reported. Finally, other factors, such as study population characteristics, use of concomitant medications, and treatment modalities may also play a role. We noted that ADAb rates reported in the literature may differ from those reported in the agents’ summary of product characteristics and product labeling, likely due to the use of different assays that are frequently proprietary and unpublished (Supplementary Table 6; see ESM).

The persistent presence of ADABs decreases biologic activity via interference with epitope bindings and/or formation of immune complexes, which results in lower serum levels of the biologic and consequently possible loss of clinical response. Based on our literature search, we found the most extensive evidence of a link between ADAb formation and biologic pharmacokinetics in studies of the anti-TNF mAbs ADA and INF across several inflammatory diseases. Monitoring of ADABs and biologic concentrations may provide essential information to clinicians that can potentially improve treatment management decisions as well as outcomes and reduce risks and costs. Interestingly, such assessment is not currently routine in rheumatology clinical practice, but heightened awareness of the immunogenic potential of biologics and the putative clinical consequences has been achieved among gastroenterologists who treat IBD [110, 206, 207]. Further research into immunogenicity, potential benefits of ADAb monitoring, and clinically validated, standardized ADAb assays are required to support this management approach in the future.

The impact of ADABs against biologic/biosimilar agents on pharmacokinetics is just one consideration in their overall immunogenicity profile. The literature supports an association between ADAb formation and diminished clinical efficacy of several biologics/biosimilars, with the strongest evidence again reported in study publications of ADA and INF across disease states. Immunogenicity also has the potential to increase the frequency of AEs, particularly infusion site reactions with INF and the INF biosimilar CT-P13. Receptor fusion proteins ABA and ETN are not associated with neutralizing ADABs, and little or no evidence is found in clinical studies of immunogenicity-related efficacy or safety/tolerability effects with these agents. It should be noted, however, that although no neutralizing activity was detected with the TNFi fusion protein lenercept, ADABs were found to bind to the Fc portion of the molecule [208], occasionally resulting in

serum sickness. The latter finding suggests that generalizations should be avoided with respect to immunogenicity potential, and biologics need to be characterized on a case-by-case basis. Use of background therapy, high biologic doses and/or induction regimens, and continuous versus intermittent treatment have been shown to reduce ADAb formation with biologics. Importantly, previous detection of ADABs also appears to be associated with a higher incidence of immunogenicity with subsequently administered biologics.

Several limitations should be considered when evaluating the findings of this SLR. The review is only as informative as the reports published in the literature. More robust data are available for agents that have been marketed for longer periods; less data have been published for newer agents. The diversity of study type and design, patient populations, sample size and detection methods pose a major challenge in formulating conclusions based on this review. In particular, assay standardization and cross-laboratory validation is greatly needed. Findings may not reflect the true incidence of immunogenicity or the frequency/magnitude of its associated outcomes. When levels of the biologic/biosimilar exceed those of ADABs, assays with drug interference underestimate the true prevalence of immunogenicity (‘hidden immunogenicity’). Additional studies using a similar design and methodology are necessary to better define immunogenicity and associated outcomes. In addition, rates of ADAb formation reported in sponsored trials may differ substantially from those in real-world settings. Despite these acknowledged limitations, the majority of publications reported similar findings on the presence of ADABs and their possible consequences in the chronic inflammatory diseases investigated.

5 Conclusions

In conclusion, based on data from reviewed reports, as many as 50% of patients receiving ADA, INF, and the INF biosimilar CT-P13 develop ADABs. Factors such as the molecular structure, concomitant use of methotrexate or other immunosuppressive/anti-proliferative agents, dose and regimen of the biologic/biosimilar administered, history of ADAb development with previous biologic treatment, and patient sex, ethnicity, and comorbid conditions may influence the immunogenic potential of the agents. In the published literature, ADAb positivity has been consistently linked to diminished clinical improvement and loss of response with several biologic/biosimilar agents, including ADA, GLM, INF, RTX, and CT-P13, but direct causation has not been established and other processes may play a role. Although of less importance, some evidence

suggests an elevated risk of hypersensitivity reactions in ADAb-positive patients, particularly with INF. Because of these potential clinical consequences, the immunogenicity of biologics/biosimilars is a vital (albeit not the only) consideration when selecting therapy, dose, and dosing regimen, and use of background immunosuppressive/anti-proliferative agents in patients with chronic immune-mediated inflammatory disease.

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Compliance with Ethical Standards

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