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Immunoassay methods used in clinical studies for the detection of anti-drug antibodies to adalimumab and infliximab

B. Gorovits,* D. J. Baltrukonis,† I. Bhattacharya,‡ M. A. Birchler,§ D. Finco,† D. Sikkema,¶ M. S. Vincent,‡ S. Lula,** L. Marshall†† and T. P. Hickling*
*Pfizer, Andover, MA, USA, †Pfizer, Groton, CT, USA, ‡Pfizer, Cambridge, MA, USA, §GlaxoSmithKline BioPharmaceuticals, Upper Merion, PA, USA, ¶Quanterix Corporation, Lexington, MA, USA, **Envision Pharma Group, London, UK, and ††Pfizer, Collegeville, PA, USA

Summary

We examined the assay formats used to detect anti-drug antibodies (ADA) in clinical studies of the anti-tumour necrosis factor (TNF) monoclonal antibodies adalimumab and infliximab in chronic inflammatory disease and their potential impact on pharmacokinetic and clinical outcomes. Using findings of a recent systematic literature review of the immunogenicity of 11 biological/biosimilar agents, we conducted an ancillary qualitative review of a subset of randomized controlled trials and observational studies of the monoclonal antibodies against anti-TNF factor adalimumab and infliximab. Among studies of adalimumab and infliximab, the immunoassay method used to detect antibodies was reported in 91 of 111 (82%) and 154 of 206 (75%) adalimumab and infliximab studies, respectively. In most adalimumab and infliximab studies, an enzyme-linked immunosorbent assay or radioimmunoassay was used [85 of 91 (93%) and 134 of 154 (87%), respectively]. ADA incidence varied widely among assays and inflammatory diseases (adalimumab, 0–87%; infliximab, 0–79%). Pharmacokinetic and clinical outcomes were only reported for ADA-positive patients in 38 of 91 (42%) and 61 of 154 (40%) adalimumab and infliximab studies, respectively. Regardless of assay format or biological used, ADA formation was associated with lower serum concentrations, reduced efficacy and elevated rates of infusion-related reactions. Consistent with previous recommendations to improve interpretation of immunogenicity data for biologicals, greater consistency in reporting of assay methods and clinical consequences of ADA formation may prove useful. Additional standardization in immunogenicity testing and reporting, application of modern, robust assays that satisfy current regulatory expectations and implementation of international standards for marketed products may help to improve our understanding of the impact of immunogenicity to biologics.

Keywords: adalimumab, anti-drug antibody, anti-tumour necrosis factor monoclonal antibody, immunoassay, infliximab

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Correspondence: T. P. Hickling, Biomedicine Design, Pfizer, 1 Burtt Road, Andover, MA 01810, USA.
E-mail: Timothy.Hickling@pfizer.com

Introduction

Up-regulation of the proinflammatory cytokine tumour necrosis factor (TNF)-α is a common pathogenic mechanism in a wide array of chronic immune-mediated inflammatory diseases [1]. In clinical trials conducted over nearly two decades, biological agents that block inflammatory responses activated by TNF-α have been shown to be clinically effective in treating such diseases. However, a substantial proportion of patients do not achieve a response to anti-TNF therapy, fail to maintain their response after initial improvement and/or develop therapy-limiting adverse events. In patients with chronic inflammatory diseases who receive anti-TNF agents, anti-drug antibodies (ADA) have been associated with loss of response, because of inadequate therapeutic levels caused by increased clearance and/or neutralization of the agent's biological activity and hypersensitivity reactions [2–5]. Given the possible adverse clinical sequelae of treatment-induced ADA formation, evaluation

of ADA and associated outcomes is a critical aspect of patient care in those who receive biological therapy and is required for biological approval by regulatory bodies [6].

Historically, reported ADA prevalence has been inconsistent among studies due, in part, to the various assay formats used to monitor immunogenicity in clinical trials of biologicals in chronic inflammatory diseases [7,8]. Each of the available formats has limitations that can reduce its utility in clinical and research settings and complicate interpretation of findings [9]. Some assays have a poor dynamic range and may generate false-negative results because of interfering interaction with active drug or false-positive results due to other antibodies, such as rheumatoid factor. Although the various immunoassay platforms have been used successfully to detect and quantify ADA in discrete study populations, few studies have directly assessed findings based on the different methods. Important recommendations for immunoassay validation and alignment of terms, definitions and concepts involving biological immunogenicity have been published in the past decade [6,10], but the continuing lack of a unified approach to ADA testing throughout trials prohibits a meaningful comparison of the immunogenicity in studies of the same biological or different biologicals. In the present review, we examined the assay formats used in assessing ADA in patients with chronic inflammatory disease treated with the anti-TNF monoclonal antibodies adalimumab and infliximab, as well as the pharmacokinetic and clinical outcomes reported, to characterize the impact of ADA assessment in clinical studies.

Methods

A systematic literature review (SLR) was conducted previously to evaluate the available data on the immunogenicity of 10 biological agents and one approved biosimilar agent in studies of autoimmune diseases [11]. The search strategy and other methodological aspects of the original SLR, conducted and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12], are presented in detail elsewhere [11] and are summarized briefly below. Using findings of the original SLR, we conducted an ancillary qualitative review focused on immunogenicity assay methods and potential pharmacokinetic and clinical corollaries in a subset of studies of adalimumab and infliximab. For the purposes of this review, the numbers of adalimumab and infliximab studies using each of the different assay types were totalled, the assay timing and cut-points extracted when available and associated outcomes evaluated; no specific assay formats were selected a priori.

Data sources and search terms

In the original SLR [11] the search terms for treatments, including 'adalimumab' and 'infliximab', were used in combination with terms related to study design and disease states, i.e. rheumatoid arthritis (RA), psoriatic arthritis (PsA), juvenile idiopathic arthritis (JIA), axial spondyloarthritis (axSpA), ankylosing spondylitis (AS), non-radiographic axSpA (nr-axSpA), psoriasis (Ps), inflammatory bowel disease (IBD), Crohn's disease (CD) and ulcerative colitis (UC). For the purposes of the present review, because the majority of published studies containing immunogenicity data have been conducted in patients receiving the anti-TNF monoclonal antibodies adalimumab and infliximab, only studies of these biologicals were included for analysis.

Relevant randomized clinical trials (RCTs) and longitudinal observational studies were identified in the literature published in English to November 2016 based on electronic searches of the following databases: MEDLINE®, MEDLINE in Process & Other Non-Indexed Citations, Embase®, Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. Proceedings from major rheumatology, dermatology, gastroenterology and immunology conferences and review papers, editorial reference lists and previously conducted SLRs were searched manually.

Study selection and data extraction

Publication titles and abstracts were screened initially for eligibility by a single reviewer, followed by a quality check of 10% of the screened studies selected randomly by a second validating reviewer. Complete texts of eligible publications were examined in a second screening round, with 20% of excluded publications inspected by the validating reviewer. Information extracted from the selected studies included publication details/study characteristics, baseline demographics, disease characteristics and after-treatment outcomes (i.e. pharmacokinetics, efficacy and safety).

Results

Literature search/screening

Of 1148 total eligible studies included in the original SLR [11], 111 and 206 were identified as adalimumab and infliximab studies, respectively (Fig. 1). Among these, 91 (82%) and 154 (75%) adalimumab and infliximab studies provided a description of the immunogenicity assay method used and were included in this ancillary qualitative review. For adalimumab, a total of nine and 82 RCTs and observational studies, respectively, were included; for infliximab, these totals were 20 and 134.

Immunogenicity assays used, test timing and thresholds for ADA-positive screening

Among the adalimumab and infliximab studies included in this review, the following different testing methods were

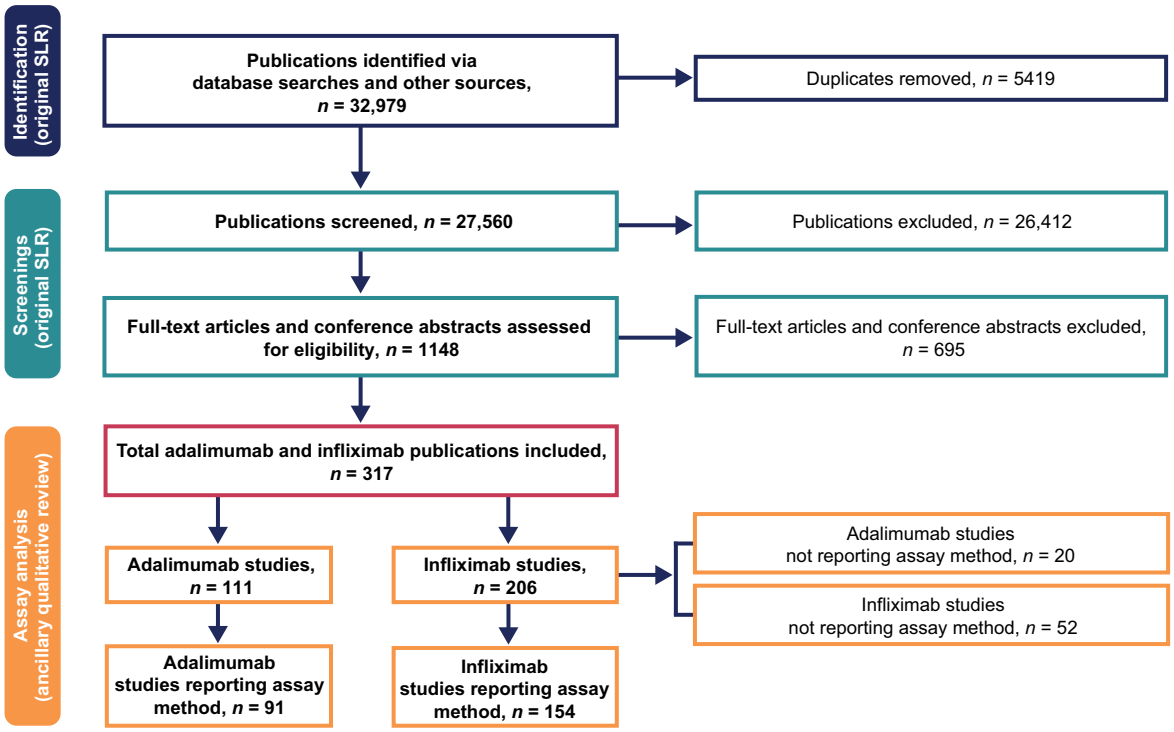

Fig. 1. Flow of publications/studies in the original systematic literature review (SLR) [11] and present ancillary qualitative analysis.

used to assess immunogenicity: enzyme-linked immunosorbent assays (ELISA), radioimmunoassays (RIA), electrochemiluminescent (ECL) immunoassays, homogeneous mobility shift assays (HMSA)/high-performance liquid chromatography (HPLC) and immunological multiparameter chip technology (IMPACT) (Supporting information, Table S1). In the majority of studies, an ELISA or RIA was used to detect ADA [85 of 91 (93%) and 134 of 154 (87%), respectively; Fig. 2]. The specific time-points for serum collection and the assessment of ADA presence at these time-points were reported in 20 of 91 (22%) adalimumab studies and 27 of 154 (18%) infliximab studies. ADA testing was usually conducted immediately before administration of the adalimumab or infliximab dose, at trough serum levels, to minimize drug interference. Reported time-points ranged from 0 to 156 weeks in the adalimumab studies and from 0 to 66 weeks in infliximab studies that provided assay method and time-point data (Supporting information, Table S2). In the majority of studies, testing was conducted at study baseline and at multiple time-points thereafter. In combined adalimumab and infliximab studies in which the timing of immunogenicity testing was reported among disease states, nearly two-thirds of all testing time-points reported were from baseline to 24 weeks [51 of 82 (62%); Fig. 3]. The predetermined thresholds, or cut-points, used to screen for ADA-positive samples were also not stated in all studies.

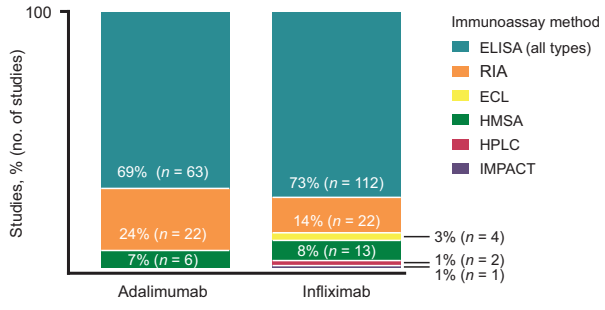

Fig. 2. Summary of immunogenicity assay types used in adalimumab and infliximab studies. Multiple assay methods were used in two adalimumab studies and one infliximab study.

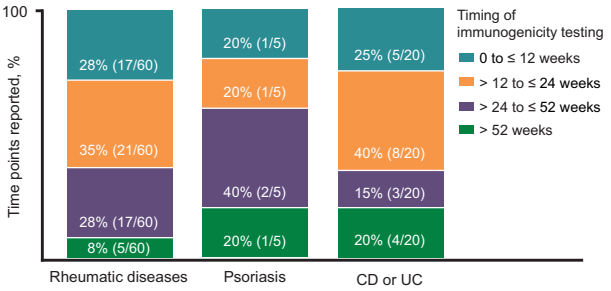

Fig. 3. Summary of time-points for immunogenicity assessment across adalimumab and infliximab studies by disease state. Immunogenicity testing occurred at several time-points in most studies (number of specified time-points reported/number of total reported time-points).

Table 1. Summary of the incidence of ADA detection in adalimumab- and infliximab-treated patients across chronic inflammatory diseases and assay cut-points by immunogenicity assay method

	Adalimumab studies		Infliximab studies	
Immunogenicity assay	ADA-positive patients, % (no. of studies)	Assay cut-points for ADA-positive status	ADA-positive patients, % (no. of studies)	Assay cut-points for ADA-positive status*
ELISA 15,21,24,27,28,34,35,41,45,48,50,52,54,55,58,63,64,66,67,69,74,77,78,80–151	0–40·0 (38)	0·1–35·0 AU/ml; 0·02–4·9 μg/ml; 0·5–20 ng/ml; OD, 0·2–1·0	4·8–79·0 (80)	2–37 AU/ml; 10 ng/ml; 1·7–3·0 μg/ml; OD of 0·27–1·2; OD, 0·25 and 2× pretreatment levels; 2× levels of negative controls; mean ± 2 s.d. levels in normal human serum
Bridging ELISA 16,18,37,38,40,51,59,68,70,71,75,79,152–181	0–54·2 (18)	≤ 1–10 AU/ml; 0·5–20 ng/ml; OD, 0·02; mean ± 6 s.d.	8·8–60·8 (26)	2–50 AU/ml; 5–10 ng/ml; 0·07–≥ 1·7 μg/ml; OD, 0·25 and 2× pretreatment levels; 2× pretreatment levels
Sandwich ELISA [13,169,171]	87 (1)	OD, 0·02	12·5–17·0 (2)	5–8 ng/ml
Acid dissociation ELISA [26,47,182,183]	9·9–35·0 (4)	1·12 μg/ml; 10 ng/ml; OD, 0·14	25·6 (1)	OD, 0·12
RIA 2,4,14,17,19,22,23,28,30,46,53,57,60,62,180,184–205	0–61·5 (22)	10–48 AU/ml; 0·02 μg/ml; or 2× level in ADA$^-$ samples	0–71·4 (22)	4·7–12 AU/ml; > 3% of BL value; or 2× level in ADA$^-$ samples
ECL [32,42,206–208]	–	–	22·5–49·7 (4)	NR
HMSA [25,39,43,44,180,209–226]	4·3–27·0 (6)	1·0–50·0 AU/ml; 0·33 μg/ml	11·1–59·0 (13)	3·1–8·0 AU/ml; 3·1 μg/ml; 3 nM
HPLC [227,228]	–	–	13·6–24·0 (2)	NR
IMPACT [36]	–	–	54·1 (1)	2× pretreatment level

*Cut-points were not reported consistently across all studies; values are provided as available.

ADA = anti-drug antibody; AU = arbitrary units; BL = baseline; ECL = electrochemiluminescent; HMSA = homogeneous mobility shift assay; HPLC = high performance liquid chromatography; IMPACT = immunological multi-parameter chip technology; NR = not reported; OD = optical density; s.d. = standard deviation.

Although standardized cut-points have been used increasingly in recent studies, overall the cut-points were inconsistent between studies (Table 1).

Frequency of ADA immune responses

The proportions of ADA-positive patients varied widely in adalimumab and infliximab studies among inflammatory diseases and assay methods and over years (Table 1, Fig. 4; Supporting information, Table S3). The widest ranges of ADA detection rates were observed in studies in which ELISA formats (adalimumab, 0–87%; infliximab, 5–79%) or RIA (0–62%, 0–71%) were used, whereas narrower ranges were seen in studies in which newer platforms were employed (e.g. HMSA, 4–27% and 11–59%, respectively). However, ELISA or RIA formats were used in a broader range of disease populations and in many more studies than HMSA; these factors, as well as other possible confounders, such as differences in study design, patient characteristics, and concomitant immunosuppressive therapies, may account for the greater variability in ADA rates observed with these older platforms.

Inconsistency in the frequency of immune response was also observed when assessing individual inflammatory disease states and categories of inflammatory disease among most assays used (Supporting information, Table S3). In adalimumab studies, the highest ADA incidences were reported in an RA study using a sandwich ELISA (87%) [13] and an AS study using RIA (62%) [14]. In infliximab studies, the highest immunogenicity rates were observed in AS studies using RIA (71%) [14] and CD or UC studies using ELISA (79%) [15]. As shown in Fig. 4, variable immunogenicity rates are also evident among years in adalimumab and infliximab studies, regardless of inflammatory disease or assay type. Overall, higher immunogenicity rates have been reported in recent years.

Impact of ADA immune response

Pharmacokinetic and/or clinical outcomes (efficacy and/or safety) in ADA-positive patients were reported in 42 and 40% of adalimumab and infliximab studies, respectively. In 15 of 38 (39%) adalimumab studies [16–30] and 18 of 62 (29%) infliximab studies [19,24,27,28,31–44], ADA-positive patients had lower serum concentrations of the biological than ADA-negative patients. The association between biological serum concentrations and ADA formation was evident in inflammatory disease states and

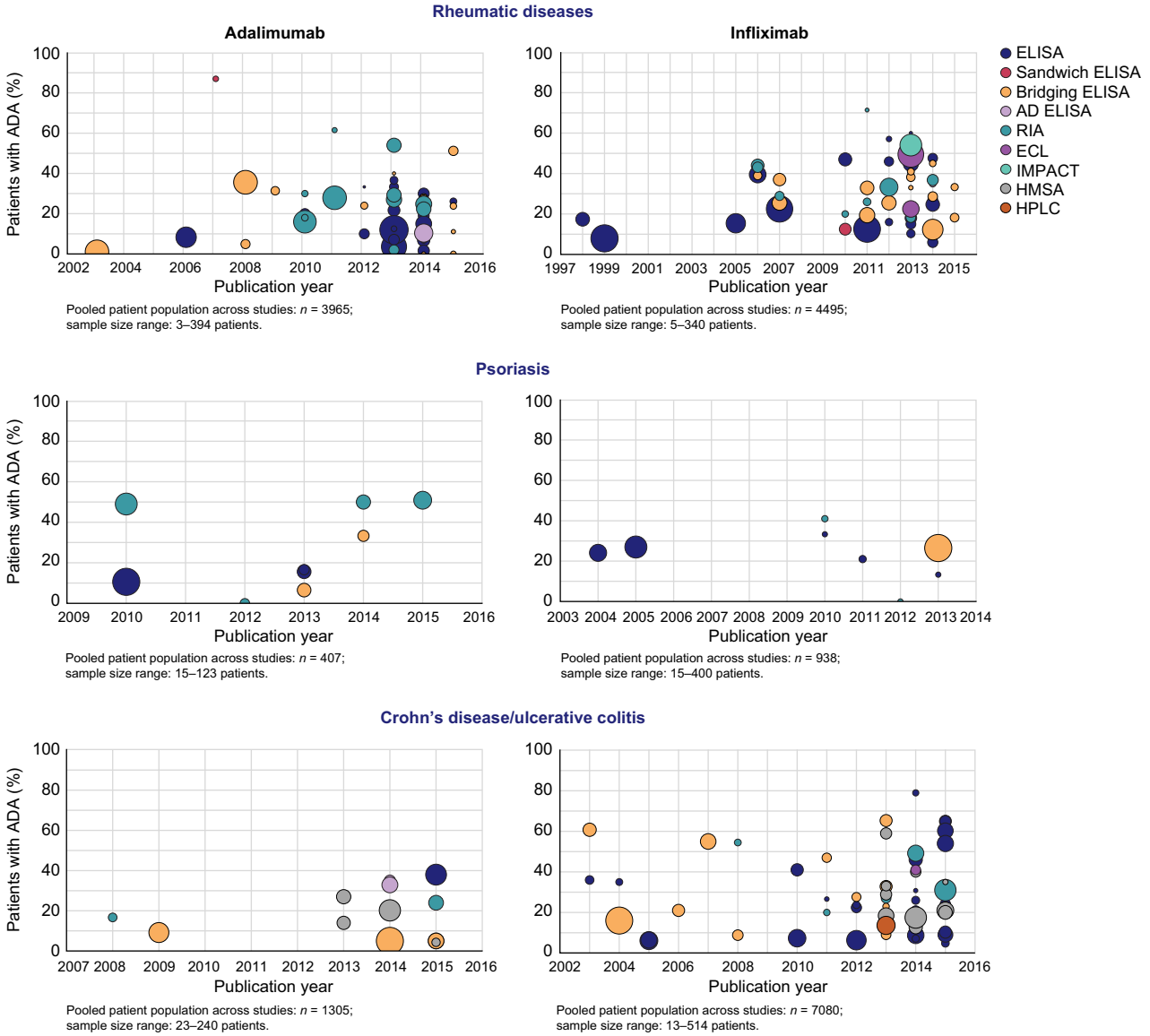

Fig. 4. Proportions of anti-drug antibody (ADA)-positive patients treated with adalimumab or infliximab by inflammatory disease state, assay method and publication year. Bubble size denotes the number of patients assessed for ADA.

immunoassay formats. Differences in serum concentrations between ADA-positive and -negative patients were found to be statistically significant in nine of 38 (24%) adalimumab studies [18,20–22,24,25,27,28,30] and 12 of 62 (19%) infliximab studies [24,27,28,35–39,41–44]. For example, in an observational cohort study of 115 patients with AS who received adalimumab, after 24 weeks of treatment serum levels of the biological were significantly higher in ADA-negative patients than in ADA-positive patients [12·7 mg/l (interquartile range = 8·2–18·0) *versus* 1·2 mg/l (0·0–2·0); $P < 0{\cdot}001$] [22]. Similarly, in a prospective cohort study conducted in 327 patients with Crohn's disease, mean [standard deviation (s.d.)] trough infliximab levels were 7·4 (11·9) μg/ml and 1·6 (3·6) μg/ml at week 8 in patients who were ADA-negative and ADA-positive, respectively [39]. In addition, at this time-point a significantly higher proportion of ADA-negative patients had therapeutic infliximab trough levels (defined as $\geq$ 3 μg/ml) compared with ADA-positive patients (76 *versus* 14%; $P < 0{\cdot}001$).

In many of the included studies in which the type of immunoassay was identified and pharmacokinetic or clinical outcomes evaluated, the presence of ADA was associated with decreased efficacy [20 of 38 (53%) adalimumab studies and 26 of 62 (42%) infliximab studies; Tables 2 and 3]. In adalimumab studies conducted in patients with RA using several different assay formats, ADA-positive patients had significantly less improvement in clinical symptoms with treatment [45,46], were significantly more likely to

Table 2. Summary of efficacy outcomes in ADA-positive and -negative patients treated with adalimumab

Adalimumab reference	Study design (no. of patients)	Assay format (cut-point)	Study outcomes (time-point)	ADA-positive patients no. (%)*	ADA-negative patients no. (%)*	*P*-value
RA						
Villalba *et al.* 2013 [45]	Prospective cohort study ($n = 69$)	ELISA (NR)	Adalimumab and infliximab: Δ in DAS28: (52 weeks)	0·94	1·63	0·045
			(104 weeks)	0·72	1·83	0·021
			(156 weeks)	0·44	2·02	< 0·0001
Avdeeva *et al.* 2014 [48]	Prospective cohort study ($n = 25$)	ELISA (NR)	No DAS28 response (24 weeks)	NR (100)	NR (11)	< 0·05
Miyasaka *et al.* 2008 [16]	RCT ($n = 275$)	Bridging ELISA (LLOD: 0·5 ng/ml)	ACR20 response (24 weeks)			
			Overall	23 (23·5)	85 (48·0)	–
			20 mg	5 (14·3)	20 (38·5)	
			40 mg	10 (27·5)	29 (56·9)	
			80 mg	8 (34·8)	36 (56·3)	
Chen *et al.* 2015 [18]	Prospective cohort study ($n = 36$)	Bridging ELISA (12 AU/ml)	Poor EULAR response			
			(26 weeks)	6 (75)	0 (0)	< 0·001
			(52 weeks)	7 (70)	3 (11·5)	< 0·001
			DAS28 LDA (52 weeks)	1 (10)	10 (38·5)	0·127
Bartelds *et al.* 2011 [17]	Prospective cohort study ($n = 272$)	RIA (12 AU/ml)	DAS28 remission	3 (4)	67 (34)	< 0·001
Korswagen *et al.* 2011 [49]			DAS28 LDA	10 (24)	95 (48)	< 0·001
Radstake *et al.* 2009 [229]	Prospective cohort study ($n = NR$)	RIA (NR)	EULAR non-response (26 weeks)	NR (100)	0 (0)	–
Van Schouwenburg *et al.* 2013 [190]	Prospective cohort study ($n = 99$)	RIA (12 AU/ml)	DAS28 remission			–
			(50 weeks)	0 (0)	12 (28)	
			(100 weeks)	0 (0)	14 (31·6)	
			(150 weeks)	0 (0)	16 (36·1)	
Jani *et al.* 2014 [46]	Prospective cohort study ($n = 125$)	RIA (12 AU/ml)	Change in DAS28 (52 weeks)	2·4	3·4	0·022
Jani *et al.* 2015 [230]			EULAR response, regression coefficient (52 weeks)	−1·03		0·037
PsA						
Van Kuljk *et al.* 2010 [189]	Prospective cohort study ($n = 22$)	RIA (12 AU/ml)	EULAR good response			
			(12 weeks)	2 (67)	8 (42)	
			(52 weeks)	1 (33)	7 (37)	–
JIA						
Skrabl-Baumgartner *et al.* 2015 [21]	Prospective cohort study ($n = 23$)	ELISA (0·1 AU/ml)	Loss of response	5 (83)	1 (6)	–
AS						
Davis *et al.* 2006 [54]	RCT ($n = 204$)	ELISA (NR)	ASAS20 response	NR (69)	NR (76)	–
Ps						
Asahina *et al.* 2010 [55]	RCT ($n = 123$)	ELISA (NR)	PASI50 response	5 (39)	NR (87)	< 0·001
			PASI75 response	3 (23)	NR (73)	< 0·001
			PASI90 response	0 (0)	NR (52)	< 0·001

Table 2. *Continued*

Adalimumab reference	Study design (no. of patients)	Assay format (cut-point)	Study outcomes (time-point)	ADA-positive patients no. (%)*	ADA-negative patients no. (%)*	*P*-value
Mostafa *et al.* 2016 [58]	RCT ($n = 1212$)	ELISA (0·5 ng/ml)	PASI75 response (16 weeks)	5 (11)	562 (76)	–
Mahil *et al.* 2013 [59]	Prospective cohort study ($n = 31$)	Bridging ELISA (10 ng/ml)	PASI75 response	0 (0)	23 (79)	–
			PASI50 non-response	2 (100)	6 (21)	
Lecluse *et al.* 2010 [23]	Prospective cohort study	RIA (12 AU/ml)	PASI good response (24 weeks)	1 (8)	9 (56)	–
Menting *et al.* 2014 [56]	[$n = 29$ (24 weeks)]		PASI moderate response (24 weeks)	2 (15)	4 (25)	
	[$n = 80$ (52 weeks)]		PASI good response (52 weeks)	5 (13)	27 (66)	
			PASI moderate response (52 weeks)	6 (15)	7 (17)	
Chui *et al.* 2015 [57] *CD*	Retrospective cohort study ($n = 53$)	RIA (12 AU/ml)	Response	12 (44)	23 (89)	–
West *et al.* 2008 [60]	Retrospective cohort study ($n = 25$)	RIA (12 AU/ml)	Response	1 (20)	NR (90)	–

*Number of patients with specified outcome unless noted otherwise.

ACR20 = American College of Rheumatology 20% improvement criteria; ADA = anti-drug antibody; AS = ankylosing spondylitis; ASAS20 = Assessment of SpondyloArthritis International Society criteria 20; DAS28 = Disease Activity Score 28 score; ELISA = enzyme-linked immunosorbent assay; EULAR = European League Against Rheumatism; JIA = juvenile idiopathic arthritis; LDA = low disease activity; LLOD = lower limit of detection; PASI = Psoriasis Area and Severity Index; Ps = psoriasis; NR = not reported; RA = rheumatoid arthritis; RCT = randomized clinical trial; RIA = radioimmunoassay.

have poor response or treatment failure [18,47,48] and were significantly less likely to achieve clinical remission or low disease activity [17,49] compared with ADA-negative patients. Similar results were observed in infliximab studies in RA regardless of immunoassay type [4,32,36,45,50–53]. Although the relationship between immunogenicity and efficacy was evaluated in a greater number of RA studies than studies of other conditions, diminished efficacy was also seen in ADA-positive patients who received adalimumab in JIA [21], AS [54], Ps [23,55–59] and CD [60], and infliximab in PsA [61], AS [62], Ps [63], CD [64] and UC [65,66].

Immunogenicity was also associated with biological safety and tolerability, independent of the immunoassay format used to detect ADA, although fewer studies reported on this relationship [two of 38 (5%) adalimumab studies and 19 of 62 (31%) infliximab studies] than on biological efficacy. In an adalimumab study conducted in patients with RA, AS or PsA, adverse events were more common in patients with ADA than in those without ADA [67]. In a Ps study, infections, hepatic-related adverse events and injection-site reactions were reported more frequently in adalimumab-treated patients with ADA than in those without ADA [55]. In infliximab studies, increased rates of infusion-related reactions with infliximab were observed in ADA-positive *versus* -negative patients throughout inflammatory disease states, including RA [32,34,36,68,69], JIA [70,71], AS [62,72,73], Ps [74], CD [64,75–77] and UC [43,78–80].

Discussion

Based on our review of 111 adalimumab and 206 infliximab studies, a substantial proportion of patients who receive the anti-TNF monoclonal antibodies adalimumab and infliximab to treat chronic inflammatory disease develop ADA. In a number of these studies, the presence of ADA has been shown to correlate with altered drug clearance and reduced serum levels, contribute to loss of response and increase the risk of hypersensitivity reactions in some patients. Therefore, clinicians, patients, researchers and regulators share a particular interest in the immunogenicity profile of these biological agents.

Surprisingly, in the clinical studies of adalimumab and infliximab included in this review, the specific assay format used to test immunogenicity was not reported in approximately one-quarter to one-fifth of studies. In studies in which assay format is specified, variations in the formats, including type of assay and cut-points used, hamper interpretation of study findings and cross-study comparisons. We found that immunogenicity rates varied widely among inflammatory disease states and immunoassay formats and over years. Nonetheless, our findings support a high prevalence of ADA in adalimumab- and infliximab-treated patients, even if they do not answer important questions

Table 3. Summary of efficacy outcomes in ADA-positive and -negative patients treated with infliximab by inflammatory disease state and immunogenicity assay method

Infliximab reference	Study design (no. of patients)	Assay format (cut-point)	Study outcomes (time-point)	ADA-positive patients no. (%)*	ADA-negative patients no. (%)*	*P*-value
RA						
Lukina *et al.* 2012 [50]	Prospective cohort study ($n = 20$)	ELISA (NR)	EULAR good response	2/7 (28·6)	5/13 (38·5)	0·035
			EULAR moderate response	2/7 (28·6)	8/13 (61·5)	
Villalba *et al.* 2013 [45]	Prospective cohort study ($n = 69$)	ELISA (NR)	Adalimumab and infliximab: Δ in DAS28: (52 weeks)	0·94	1·63	0·045
			(104 weeks)	0·72	1·83	0·021
			(156 weeks)	0·44	2·02	< 0·0001
Valor *et al.* 2015 [52]	Prospective cohort study ($n = 60$)	ELISA (37 AU/ml)	DAS28 < 3·2 (LDA)	1/36 (2·8)		0·005
			DAS28 ≥ 3·2	7/24 (29·2)		
Pascual-Salcedo *et al.* 2011 [51]	Retrospective cohort study ($n = 85$)	Bridging ELISA [50 AU/ml (mean +6 s.d.)]	EULAR good response (26 weeks)	1/28 (3·6)	8/57 (14·0)	–
			(52 weeks)	0/28 (0·0)	14/57 (24·6)	
			(> 208 weeks)	2/28 (7·1)	16/57 (28·1)	
Fleischmann *et al.* 2014 [172]	Single-arm study ($n = 195$)	Bridging ELISA (NR)	EULAR response (10 weeks)	6 (35·3)	84 (60·4)	–
			(26 weeks)	7 (41·2)	95 (68·3)	
Wolbink *et al.* 2006 [4]	Prospective cohort study ($n = 51$)	RIA (12 AU/ml)	EULAR response	8/22 (36·4)	20/29 (69·0)	0·04
Radstake *et al.* 2009 [229]	Prospective cohort study ($n = $ NR)	RIA (NR)	EULAR good response (26 weeks)	1 (7·0)	15 (93·0)	–
			EULAR moderate response (26 weeks)	NR (50·0)	NR (50·0)	
Ishikawa *et al.* 2016 [53]	Prospective cohort study ($n = 57$)	RIA (NR)	DAS28 LDA or remission (24 weeks)	3 (18·8)	27 (77·1)	0·0001
Yoo *et al.* 2013 [32,231,232] Yoo *et al.* 2014 [233]	RCT ($n = 304$)	ECL (NR)	ACR20 response (30 weeks)	78 (64·5)	97 (75·2)	–
			(54 weeks)	NR (48·1)	NR (67·2)	
			ACR50 response (30 weeks)	41 (33·9)	61 (47·3)	
			ACR70 response (30 weeks)	16 (13·2)	29 (22·5)	
			EULAR-CRP response (30 weeks)	99 (82·50)	117 (91·41)	
Choe *et al.* 2016 [234]	RCT ($n = 293$)	ECL (NR)	ACR20 response (30 weeks)	79 (59·4)	94 (71·2)	–
			ACR50 response (30 weeks)	42 (31·6)	57 (43·2)	
			ACR70 response (30 weeks)	23 (17·3)	27 (20·5)	
			DAS28 LDA (30 weeks)	31 (23·3)	37 (28·0)	
			DAS28 remission (30 weeks)	17 (12·8)	25 (18·9)	
Krintel *et al.* 2013 [36]	Retrospective cohort study ($n = 218$)	IMPACT (0·27 ng/ml)	DAS28 response	27 (34)	37 (44)	–
			EULAR good response	15 (15)	17 (22)	
			EULAR moderate response	43 (44)	25 (33)	
PsA						
Kavanaugh *et al.* 2007 [61] Antoni *et al.* 2005 [110]	RCT ($n = 173$)	ELISA (NR)	ACR improvement	NR (22)	NR (33)	–

Table 3. *Continued*

Infliximab reference	Study design (no. of patients)	Assay format (cut-point)	Study outcomes (time-point)	ADA-positive patients no. (%)*	ADA-negative patients no. (%)*	*P*-value
AS						
De Vries *et al.* 2007 [62]	Prospective cohort study ($n = 38$)	RIA [12 AU/ml (mean +6 s.d.)]	ASAS20 response (24 weeks)	2 (29)	22 (71)	–
			(54 weeks)	1 (9)	20 (74)	
Park *et al.* 2013 [206,235] Park *et al.* 2014 [236]	RCT/LTE ($n = 125$)	ECL (NR)	ASAS40 response (30 weeks)	10 (40)	45 (45)	–
Ps						
Reich *et al.* 2005 [63]	RCT ($n = 264$)	ELISA (OD, 0·25 and 2× pretreatment levels)	PASI75 response (10–50 weeks)	20 (39)	106 (81)	–
CD						
Farrell *et al.* 2003 [64]	Prospective cohort study ($n = 53$)	ELISA (1·69 μg/ml)	Continuous response	0 (0)	21 (62)	–
			Partial response	2 (11)	6 (18)	
			Non-response	6 (32)	3 (9)	
Sands *et al.* 2004 [77]	RCT ($n = 258$)	ELISA (NR)	CDAI response	14 (32)	25 (31)	–
Colombel *et al.* 2010 [117]	RCT/LTE ($n = 219$)	ELISA (NR)	Steroid-free remission (26 weeks)	9 (56)	12 (67)	–
			(50 weeks)	8 (57)	12 (71)	
Hanauer *et al.* 2004 [75]	RCT ($n = 514$)	Bridging ELISA (OD, 0·25 and 2× pretreatment levels)	CDAI improvement (54 weeks)	6 (67)	25 (59)	–
			CDAI remission	3 (33)	16 (36)	
Maser *et al.* 2006 [176]	Prospective cohort study ($n = 105$)	Bridging ELISA (1·69 μg/ml)	Endoscopic improvement	NR (25)	NR (7)	0·43
UC						
Rutgeerts *et al.* 2005 [135]	RCT [$n = 229$ (ACT I)] [$n = 188$ (ACT II)]	ELISA (NR)	Mayo response (I)	3 (21·4)	3 (8·3)	–
			Mayo response (II)	11 (58)	45 (57)	
Seow *et al.* 2010 [66]	Prospective cohort study ($n = 108$)	ELISA (NR)	Mayo response	6 (14)	4 (18)	0·95
			Endoscopic improvement	11 (25)	8 (35)	0·61
			Colectomy	23 (52)	13 (59)	0·78
Brandse *et al.* 2015 [65]	Prospective cohort study ($n = 20$)	HMSA (NR)	Mayo response	1 (14)	10 (50)	–

*Number of patients with specified outcome unless noted otherwise.

ACR20 = American College of Rheumatology 20% improvement criteria; ACT = Active Ulcerative Colitis Trial; ADA = anti-drug antibody; AS = ankylosing spondylitis; ASAS20 = Assessment of SpondyloArthritis International Society criteria 20; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CRP = C-reactive protein; DAS28 = Disease Activity Score 28 score; ECL = electrochemiluminescent; ELISA = enzyme-linked immunosorbent assay; EULAR = European League Against Rheumatism; HMSA = homogenous mobility shift assay; IMPACT = immunological multi-parameter chip technology; JIA = juvenile idiopathic arthritis; LDA = low disease activity; LLOD = lower limit of detection; LTE = long-term extension; OD = optical density; PASI = Psoriasis Area and Severity Index; Ps = psoriasis; PsA = psoriatic arthritis; NR = not reported; RA = rheumatoid arthritis; RCT = randomized clinical trial; RIA = radioimmunoassay; s.d. = standard deviation; UC = ulcerative colitis.

about which patients are at risk of developing ADA and losing response to their biological therapy.

To this point, fewer than half the studies included in this review of adalimumab and infliximab reported findings, either positive or negative, related to the pharmacokinetics, efficacy or safety of treatment in patients who did or did not develop an immune response. We hesitate to draw pointed conclusions about the impact of ADA on clinical outcomes because of the aforementioned lack of assay standardization as well as other differences in methodology, therapeutic response measures and patient characteristics. However, in the studies that presented such findings, independent of immunoassay format, investigators consistently reported decreased serum adalimumab and infliximab concentrations in patients with ADA, reduced efficacy and increased rates of infusion-related reactions in ADA-positive patients.

Based on our review of the literature, we determined that individual studies generally provide 'high-level' data on immunogenicity, often with very little detail. On close inspection, multiple confounding factors were uncovered, including the lack of standard terms, standard assays and standardized interpretation (including cut-points). Although some progress has been apparent in recent years, inspired in large part by recommendations for precise immunogenicity-related definitions of terms and concepts and assay method validation proposed by expert working groups in this field [6,10], a lack of standardization and consistency in assay methodology and reporting may hinder this area of research. Several actions may prove to be useful in improving the reliability and interpretation of immunogenicity data for biological agents, including adoption of modern assays that may be more robust with less drug interference, more consistent reporting of the immunogenicity assay methods used and analysis of the potential clinical consequences of ADA formation in published biological studies. Standardization in immunogenicity testing and reporting, as suggested nearly a decade ago by Shankar *et al.* [6], as well as disease activity measures, may help to advance our understanding of the impact of immunogenicity to biologicals in patients with chronic immune-mediated inflammatory diseases.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1. Summary of the characteristics of assay methods used to detect anti-drug antibody (ADA) in biological clinical trials.
Table S2. Time-points for immunogenicity testing in adalimumab and infliximab studies.
Table S3. Summary of the incidence of ADA detection in (**a**) adalimumab- and (**b**) infliximab-treated patients by chronic inflammatory disease and immunogenicity assay method.