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

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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

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
used to assess immunogenicity: enzyme-linked immuno-
sorbent assays (ELISA), radioimmunoassays (RIA), electro-
chemiluminescent (ECL) immunoassays, homogeneous
mobility shift assays (HMSA)/high-performance liquid
chromatography (HPLC) and immunological multi-
parameter chip technology (IMPACT) (Supporting infor-
mation, 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%) adali-
mumab studies and 27 of 154 (18%) infliximab studies.
ADA testing was usually conducted immediately before
administration of the adalimumab or infliximab dose, at
through 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 mul-
tiple 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 predeter-
mined 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.
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...
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 (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 ≥ 3 μg/ml) compared with ADA-positive patients (76 versus 14%; \( P < 0.001 \)).

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
| Adalimumab reference | Study design | Assay format | 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] | Prospective cohort study (n = 125) | RIA (12 AU/ml) | DAS28 remission (26 weeks) | NR (100) | 0 (0) | – |
| Radstake et al. 2009 [229] | Prospective cohort study (n = NR) | RIA (NR) | EULAR non-response (26 weeks) | – | – | – |
| Van Schouwenburg et al. 2013 [190] | Prospective cohort study (n = 99) | RIA (12 AU/ml) | DAS28 remission | 0 (0) | 12 (28) | – |
| | | | | (50 weeks) | 0 (0) | 14 (31.6) | – |
| | | | | (100 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] | Prospective cohort study (n = 99) | RIA (12 AU/ml) | EULAR response, regression coefficient (52 weeks) | −1.03 | 3.4 | 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 |
| Study design               | Assay format       | ADA-positive patients no. (%) | ADA-negative patients no. (%) | Study outcomes (time-point) |
|---------------------------|---------------------|------------------------------|------------------------------|----------------------------|
|                           |                     | (no. of patients)            | (cut-point)                  | Adalimumab reference      |
|                           |                     |                              |                              |                            |
|                           |                     | 5 (11)                       |                              |                            |
|                           |                     | 0 (0)                        |                              |                            |
|                           |                     | 562 (76)                     |                              |                            |
|                           |                     | 23 (79)                      |                              |                            |
|                           |                     | 621 (76)                     |                              |                            |
|                           |                     | 27 (66)                      |                              |                            |
|                           |                     | 12 (44)                      |                              |                            |
|                           |                     | 23 (89)                      |                              |                            |
|                           |                     | 1 (20)                       |                              |                            |
|                           |                     | NR (90)                      |                              |                            |

**Table 2. Continued**

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
| 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 |
| Villalba et al. 2013 [45] | Prospective cohort study (n = 69) | ELISA (NR) | Adalimumab and infliximab: Δ in DAS28: (52 weeks) (104 weeks) 0.72 | 1.83 | 0.021 |
| Valor et al. 2015 [52] | Prospective cohort study (n = 60) | ELISA (37 AU/ml) | EULAR moderate response 8/13 (61-5) | 0.045 |
| Pascual-Sakedo et al. 2011 [51] | Retrospective cohort study (n = 85) | Bridging ELISA [50 AU/ml (mean + 6 s.d.)] | EULAR good response (26 weeks) (52 weeks) (128 weeks) (208 weeks) 14/57 (24-6) | 0.005 |
| Fleischmann et al. 2014 [172] | Single-arm study (n = 195) | Bridging ELISA (NR) | EULAR response (10 weeks) 6 (35-3) | 84 (60-4) | – |
| 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) (26 weeks) 1 (7-0) | 15 (93-0) | – |
| Ishikawa et al. 2016 [53] | Prospective cohort study (n = 57) | RIA (NR) | EULAR moderate response (26 weeks) NR (50-0) | NR (50-0) | – |
| Yoo et al. 2013 [32,231,232] | RCT (n = 304) | ECL (NR) | ACR20 response (30 weeks) (54 weeks) (ACR50 response (30 weeks) (ACR70 response (30 weeks) 78 (64-5) | 97 (75-2) | – |
| Choe et al. 2016 [234] | RCT (n = 293) | ECL (NR) | EULAR-CRP response (30 weeks) 99 (82-30) | 117 (91-41) | – |
| Krintel et al. 2013 [36] | Retrospective cohort study (n = 218) | IMPACT (0-27 ng/ml) | EULAR response 27 (34) | 37 (44) | – |
| PsA                 |                             |                         |                             |                               |                               |         |
| Kavanaugh et al. 2007 [61] | RCT (n = 173) | ELISA (NR) | ACR improvement NR (22) | NR (33) | – |
| Antoni et al. 2005 [110] |                             |                         |                             |                               |                               |         |
| 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                  | Prospective cohort study (n = 38) | RIA [12 AU/ml (mean +/− s.d.)] | ASAS20 response (24 weeks) | 2 (29) | 22 (71) | – |
| Park et al. 2013 [206,235] | RCT/LTE (n = 125) | ECL (NR) | ASAS40 response (30 weeks) | 10 (40) | 45 (45) | – |
| De Vries et al. 2007 [62] | Prospective cohort study (n = 38) | ELISA (OD, 0-25 and 2× pretreatment levels) | PASI75 response (10–50 weeks) | 20 (39) | 106 (81) | – |
| CD                  | Prospective cohort study (n = 53) | ELISA (1.69 μg/ml) | Continuous response | 0 (0) | 21 (62) | – |
| 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) | – |
| 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) | – |
| 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                  | RCT [n = 229 (ACT I)] | ELISA (NR) | Mayo response (I) | 3 (21-4) | 3 (8-3) | – |
| Rutgeerts et al. 2005 [135] | RCT [n = 188 (ACT II)] | ELISA (NR) | 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 |
| 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; LLLOD = 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 immunemediated 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.

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