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SYSTEMATIC REVIEW

Comparative Immunogenicity of TNF Inhibitors: Impact on Clinical Efficacy and Tolerability in the Management of Autoimmune Diseases. A Systematic Review and Meta-Analysis

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Abstract

Background Tumor necrosis factor (TNF) inhibitors are a mainstay in the treatment of rheumatoid arthritis (RA), as well as in the management of spondyloarthritis (SpA) and inflammatory bowel diseases (IBD). Unfortunately, a portion of patients taking these drugs require escalating doses within the approved label to achieve response, while others lose response altogether. This may be due to the development of antibodies against TNFi agents.

Objectives Our objective was to examine the immunogenicity of TNF inhibitors (adalimumab, infliximab, etanercept, golimumab, and certolizumab) in RA, SpA, and IBD, and to examine the potential effect of anti-drug antibodies (ADABs) on the loss of clinical response through a systematic literature review and meta-analysis.

Methods We conducted a comprehensive literature search using three databases (PubMed, Web of Science, and the Cochrane library) to identify studies examining the immunogenicity of TNF inhibitors in autoimmune diseases between 1966 and 31 December 2013. Inclusion criteria required that studies be in English, be randomized controlled trials, observational studies, or case reports involving more than five patients, and that the patients be aged 18 years or older. Studies were excluded if they were strictly genetic with no clinical correlate, if the patients had concomitant cancer within 5 years of the study, or if the patients had a renal disease requiring dialysis. Double extraction was followed by a third extraction if needed. Consensus was reached by discussion when disagreements occurred. Random-effect models were generated for the meta-analysis of 68 studies to estimate the odds ratio (OR) of the ADAB effects on TNF inhibitor response. Regression analysis was used to compare among the drugs and diseases.

Results A total of 68 studies (14,651 patients) matched the inclusion/exclusion criteria. Overall, the cumulative incidence of ADABs was 12.7 % [95 % confidence interval (CI) 9.5–16.7]. Of the patients using infliximab, 25.3 % (95 % CI 19.5–32.3) developed ADABs compared with 14.1 % (95 % CI 8.6–22.3) using adalimumab, 6.9 % (95 % CI 3.4–13.5) for certolizumab, 3.8 % (95 % CI 2.1–6.6) for golimumab, and 1.2 % (95 % CI 0.4–3.8) for etanercept. ADABs reduced the odds of clinical response by 67 % overall, although most of the data were derived from articles involving infliximab (nine) and adalimumab (eight). The summary effect for infliximab yielded an estimated OR (with ADABs vs. without) of 0.42 (95 % CI 0.30–0.58); the summary effect for adalimumab yielded an estimated OR (as above) of 0.13 (95 % CI 0.08–0.22); and the OR (as above) for golimumab was 0.42 (95 % CI 0.22–0.81). All figures were statistically significant. ADABS decreased response by 27 % in RA and 18 % in SpA, both of which were statistically significant. However, the effect of ADABS on response was not statistically significant for IBD when we only included the studies that reported the duration of exposure in the regression analysis. The use of concomitant immunosuppressives (methotrexate, 6-mercaptopurine, azathioprine, and others) reduced

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the odds of ADAB formation in all patients by 74 %. The OR for risk with immunosuppressives versus without was 0.26 (95 % CI 0.21–0.32).

Conclusion ADABs developed in 13 % of patients. All five TNF inhibitors were associated with ADABs, but to varying degrees depending on the specific TNF inhibitor and the disease. ADABs are associated with reduced clinical response and an increased incidence of infusion reactions and injection site reactions. Concomitant use of immunosuppressives can reduce ADAB formation.

Key Points

Overall, the positivity of anti-drug antibodies (ADABS) to tumor necrosis factor (TNF) inhibitors occurs in about 13 % of patients but varies greatly, depending on the specific TNF inhibitors and the disease.

ADAB positivity is associated with decreased TNF inhibitor response in rheumatoid arthritis, inflammatory bowel disease, and spondyloarthritis.

Concomitant use of immunosuppressives, notably methotrexate, azathioprine, and 6-mercaptupurine, is effective in reducing TNFi immunogenicity and thus ameliorating the negative clinical effect of the ADABs.

An increased incidence of infusion reactions and injection site reactions was observed in patients who developed ADABs compared with those who did not.

1 Introduction

Tumor necrosis factor (TNF) is a pro-inflammatory cytokine that serves a key role in the pathogenesis of a variety of immunological diseases, such as rheumatoid arthritis (RA), ankylosing spondylitis, psoriasis, Crohn's disease, and ulcerative colitis. TNF is targeted by five biologic agents: infliximab (Remicade®), adalimumab (Humira®), golimumab (Simponi®), certolizumab (Cimzia®), and etanercept (Enbrel®). The use of these agents dramatically improved the outcome of inflammatory diseases; however, they engendered an immune response (immunogenicity). Some studies have indicated that formation of antibodies against these therapeutic agents decreased their efficacy and increased their toxicity, while others found no such effects [1–6]. To help clarify this issue we undertook a systematic literature review and meta-analysis examining the immunogenicity and downstream clinical effects of the five presently available TNF inhibitors in RA, seronegative spondyloarthritis (SpA), and inflammatory bowel diseases (IBDs). In addition, we investigated the data available regarding the management of immunogenicity in these patients.

2 Methods

2.1 Data Sources

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for systematic literature reviews and meta-analyses. A comprehensive literature search using three databases (PubMed, Web of Science, and the Cochrane library) was conducted to identify studies examining the immunogenicity of TNF inhibitors in the designated autoimmune diseases between 1966 and 31 December 2013. A total of 2156 articles were found [see Appendix 1 for the specific Medical Subject Headings (MeSH) terms that were used in the search].

2.2 Eligibility Criteria

Table 1 summarizes the inclusion and exclusion criteria. Studies included only the following illnesses: RA, IBD (the amalgam of Crohn's disease and ulcerative colitis, referred to as IBD throughout) and seronegative SpA (a combination of ankylosing spondylitis and psoriatic arthritis). Inclusion criteria required that studies be reported in English, be randomized controlled trials, observational studies, or case reports involving more than five patients, and that patients be aged 18 years or older. Studies were excluded if they were strictly genetic with no clinical correlate, if the patients had concomitant cancer within 5 years of the study, or if the patients had a renal disease requiring dialysis. Reviews were not included except to examine their bibliographies for potential articles of interest. Double extraction was followed by a third extraction if disagreements existed, and any final disagreements were resolved by consensus.

2.3 Study Selection

Figure 1 depicts disposition of titles, abstracts, and articles to derive the final articles used in the analysis. Of 2156 titles, 2075 were excluded according to exclusion criteria. This left 81 articles to be fully extracted on uniform case report forms. An additional 21 articles were added after reviewing the bibliographies of previous reviews [54].

Table 1 Eligibility criteria for studies included in the systematic literature review

Inclusion criteria
Article features
Article published between 1966 and 31 Dec 2013
Article written in English
Study designed as an observational trial, case report with >5 pts, or a RCT
Study population
Study subjects are human
Study subjects are ≥18 years of age
Study subjects have one of the following autoimmune diseases
Rheumatoid arthritis or its variants
Psoriatic arthritis
Ankylosing spondylitis
Crohn's disease
Ulcerative colitis
Regional ileitis
Exclusion criteria
Article features
Genetic study without clinical correlate
Strictly describes methodology
Study designed as a meta-analysis, review, case report with <5 pts, letter to the editor, or an editorial
Study population
Study subjects had concomitant cancer within <5 years of the study (not including skin cancer)
Study subjects have renal disease requiring dialysis

pts patients, *RCT* randomized controlled trial

During the initial extractions of these 102 articles, further assessment of reliability and relevance to the analysis objectives led to the exclusion of an additional 34 of the 102 articles. Disagreements were discussed and resolved by consensus. The remaining 68 articles were used in the analysis (see Table 2).

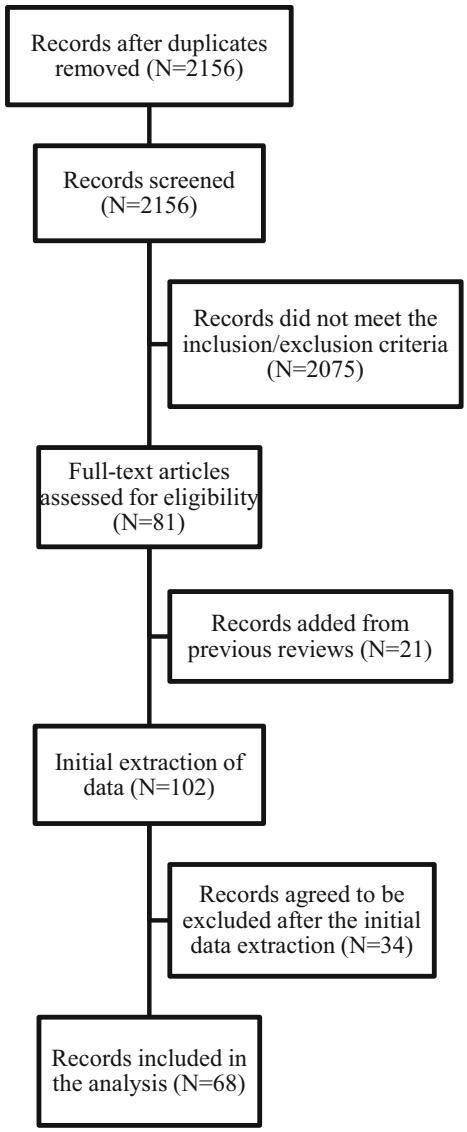

Fig. 1 Disposition of titles, abstracts, and articles to derive the final articles used in the analysis

2.4 Data Extraction and Quality Assessment

Using a standardized case report form, all relevant data were double extracted by sets of two reviewers from six independent reviewers. The following was extracted if available: study design, population demographics, disease activity and severity, TNF inhibitors, percent anti-drug antibodies (ADABs), and their relationship to remission and/or response, detectable drug concentration, concomitant immunosuppressives, and adverse events (AEs). To guard against data entry errors, a third verification was performed by two assessors while data were being entered into the database. For further quality assurance, the included articles were evaluated for quality using a modified version of the Effective Public Health Practice Project (EPHPP) quality assessment tool [84] (see Appendix 2 for definitions).

2.5 Analysis

Random effect models were generated for the meta-analysis of 68 studies to estimate the odds ratios (ORs) of the ADAB effects on TNF inhibitor response.

Data were not normally distributed, so non-parametric statistical tests were used. When cells had zero values, an arbitrary 0.001 value was inserted to allow calculation and was also added to all non-zero values so no effect on statistical results would occur.

To analyze for the effect of 'time on drug' (duration of exposure) and to statistically compare among the TNF

Table 2 Study and baseline patient characteristics

Disease and TNFi	*N* (% female)	Age	Disease duration (years)	MTX %	PRED %	Other IS %	Assay	ADAB %	Study
Inflammatory bowel diseases									
ADAL	225 (55.5)	38.7 ± NA	NA	3.6	19.1	26.2[a]	NA	0.4	Hanauer et al. [71]
ADAL	168 (71.4)	36.3 (27.3–47.1)[b]	10.5 (5.7–17.2)[b]	12.5	24.4	24.4[a]	ELISA	9.2	Karmiris et al. [49]
ADAL	30 (77)	36 (21–73)	NA	13.3	13.3	16.6[a]	RIA	17	West et al. [48]
CZP	331 (53)	37 ± 12	5 (<1–44)	NA	39	38[c]	ELISA	8	Sandborn et al. [44]
CZP	223 (52.9)	36.3 ± 12.6	7.5 ± 8.2	NA	43.5	34.5[c]	NA	3.1	Sandborn et al. [80]
CZP	215 (57)	38 ± 11	7 (<1–33)	NA	35	40[c]	ELISA	8	Schreiber et al. [43]
CZP	210 (48)	38 ± 12	5 (<1–43)	NA	37	41[c]	ELISA	18	Schreiber et al. [43]
IFX	155 (55)	39 (26–50)[b]	NA	10	10	37[a]	NA	22.5	Afif et al. [67]
IFX	33 (48)	37 (21–60)	12 (2–19)[b]	21.2	NA	57.6[a]	RIA	55	Ainsworth et al. [24]
IFX	125 (66)	35 ± NA	NA	2	42	45[a]	ELISA	61	Baert et al. [7]
IFX	62 (58)	33 ± 12[d]	10 ± 7	NA	NA	NA	ELISA	47	Ben-Horin et al. [15]
IFX	338 (49.1)	NA	NA	NA	29.3	50[e]	ELISA	7.3	Colombel et al. [69]
IFX	53 (70)	41.5 (22–72)[f]	NA	9.4	56.6	30.2[e]	ELISA	36	Farrell et al. [12]
IFX	573 (58.3)	NA	NA	4	51	25.3[a]	SEI	15.6	Hanauer et al. [72]
IFX	58 (29)	33.8 (15–55)[f,g]	NA	NA	NA	NA	Novel method	27.6	Imaeda et al. [14]
IFX	121 (35.5)	42.4 ± 14.3	5.9 ± 5.4	NA	57.9	NA	ELISA	8	Lichtenstein et al. [3][h]
IFX	120 (43.3)	40.3 ± 13.3	6.5 ± 5.8	NA	55	NA	ELISA	6	Lichtenstein et al. [3][h]
IFX	122 (41)	41.8 ± 14.9	8.4 ± 8.1	NA	59.8	NA	ELISA	7	Lichtenstein et al. [3][h]
IFX	121 (37.2)	40.5 ± 13.1	6.7 ± 5.3	NA	49.6	NA	ELISA	14	Lichtenstein et al. [3][h]
IFX	193 (NA)	NA	NA	5.7	NA	NA	ELISA	10	Lichtenstein et al. [3][h]
IFX	192 (NA)	NA	NA	3.6	NA	NA	ELISA	7	Lichtenstein et al. [3][h]
IFX	115 (49)	31 (16–72)[g]	7 (0.4–24)	NA	91	23[e]	NA	41	Seow et al. [8]
IFX	106 (55)	NA	NA	6.6	0.9	62.3[e]	RIA	33	Steenholdt et al. [20]
IFX	180 (54)	NA	NA	NA	NA	62[a]	RIA	46	Steenholdt et al. [23]
IFX	108 (49)	37.7 ± NA	11.7 ± NA	NA	59.3	NA	ELISA	2	Targan et al. [82]
IFX	174 (61.5)	39 (18–73)[f]	NA	28.7	NA	37.3[e]	ELISA	55	Vermeire et al. [13]
Rheumatoid arthritis									
ADAL	121 (79)	53 ± 13	12 ± 10	79	34	NA	RIA	17	Bartelds et al. [51]
ADAL	235 (79)	53 ± 12	9 (4–17)[b]	82	34	NA	RIA	20	Bartelds et al. [47]
ADAL	272 (81)	54 ± 12	8 (3–17)[b]	74	34	NA	RIA	28	Bartelds et al. [4]
ADAL	15 (67)	55.9 (34–73)[f]	12.2 (2.5–40)[f]	67	100	NA	ELISA	87	Bender et al. [68]
ADAL	419 (75.9)	56.7 ± NA	11 ± NA	100	NA	NA	ELISA	0.72	Keystone et al. [74]
ADAL	272 (80.5)	53.7 ± NA	NA	NA	NA	NA	RIA	28	Korswagen et al. [76]
ADAL	34 (79)	56 ± 10	NA	41	26	NA	RIA	29	Radstake et al. [6][h]
ADAL	434 (77.4)	53 ± NA	10.8 ± NA	90.8	71.7	NA	ELISA	12	van de Putte et al. [83]
ADAL	99 (79)	54 ± 11	10 (5–17)[b]	68	35	NA	ABT	29	Van Schouwenburg et al. [46]
ADAL	209 (75.1)	55.4 ± NA	12.7 ± NA	100	NA	NA	RIA	0.9	Weinblatt et al. [39]
CZP	126 (72.2)	53 ± 12.3	9.4 ± 7.5	100	NA	NA	NA	5	Choy et al. [40]
CZP	111 (78.4)	52.7 ± 12.7	8.7 ± 8.2	NA	55.9	NA	ELISA	8.1	Fleischmann et al. [41]
CZP	783 (83)	51.9 ± NA	6.1 ± NA	NA	NA	NA	ELISA	6.4	Keystone et al. [45]
CZP	492 (80.9)	52.05 ± NA	6.3 ± NA	100	58.5	NA	NA	5.1	Smolen et al. [42]
ETA	222 (81.1)	53.4 ± 12	9.9 ± 9.1	64.4	45.9	NA	ELISA	5.6	Dore et al. [36]

Table 2 continued

Disease and TNFi	*N* (% female)	Age	Disease duration (years)	MTX %	PRED %	Other IS %	Assay	ADAB %	Study
ETA	292 (82)	52.8 ± 12.7	8 (3–16)[b]	76	28	NA	ELISA, RIA, IgG4-ABT	0	Jamnitski et al. [37]
ETA	367 (79)	52.6 (20–87)[f]	8.7 (0–51)[f]	52.3	NA	NA	ELISA	3	Keystone et al. [75]
GOL	159 (84.3)	48.2 ± 12.85	4.1 ± 5.6	0	63.5	3.8[c]	ELISA	13.5	Emery et al. [32][h]
GOL	318 (81.8)	50.6 ± 11.58	3.6 ± 5.86	100	67.6	3.5[c]	ELISA	2.8	Emery et al. [32][h]
GOL	137 (77.4)	54 (46–64)[b]	8.2 (3.4–13.9)[b]	100	NA	NA	ELISA	6.5	Kay et al. [31]
GOL	444 (80.6)	NA	NA	78	68.9	NA	ELISA	2.1	Keystone et al. [29]
GOL	643 (80.4)	49.6 ± NA	8.1 ± NA	60	87.1	7[c]	ELISA	7	Kremer et al. [25]
GOL	461 (79.6)	NA	NA	66.2	NA	NA	ELISA	3	Smolen et al. [30]
GOL	308 (81.8)	52.3 ± 11.4	8.9 ± 8.5	NA	NA	NA	ELISA	3.5	Takeuchi et al. [81]
GOL	173 (87.3)	50.2 ± 11.1	8.4 ± 7.7	100	NA	NA	ELISA	0	Tanaka et al. [34]
GOL	463 (NA)	NA	NA	100	NA	NA	ELISA	3	Weinblatt et al. [35]
GOL	33 (75.8)	55.1 ± 13	8.9 ± 8.3	NA	NA	NA	ELISA	6.25	Zhuang et al. [33][h]
GOL	16 (75)	57.3 ± 9.9	10.3 ± 8	68.8	NA	NA	ELISA	0	Zhuang et al. [33][h]
IFX	49 (81.6)	55.2 ± 10.9	9.1 ± 7.4	100	85.7	0	ELISA	42.2	Abe et al. [17][h]
IFX	51 (78.4)	56.8 ± 10.5	7.1 ± 5.1	100	92.2	0	ELISA	32.6	Abe et al. [17][h]
IFX	106 (70)	57 ± 13	11 ± 8.7	63	76	6.6[e]	RIA	44	Bendtzen et al. [10]
IFX	17 (NA)	NA (28–65)	NA (1–30)	52.9	70.6	NA	DA-ELISA	41.2	Ducourau et al. [70]
IFX	64 (77)	NA	13.8 ± NA	81	47	NA	ELISA	12.5	Finckh et al. [18]
IFX	51 (70.6)	55.9 ± NA	15.3 ± NA	94.1	27.5	NA	ELISA	39	Haraoui et al. [73]
IFX	87 (73.6)	52.6 ± NA	10.4 ± NA	NA	51.7	NA	ELISA	17.4	Maini et al. [77]
IFX	85 (81)	53.8 ± 14.2	NA	81	74	NA	ELISA	32.9	Pascual-Salcedo et al. [79]
IFX	35 (86)	57 ± 10	NA	100	29	NA	RIA	51	Radstake et al. [6][h]
IFX	18 (78)	53 ± 14	11 ± 7.1	83	28	6[e]	RIA	22	van den Bemt et al. [21][h]
IFX	147 (69)	58 ± 12	11 ± 7	67	NA	NA	NA	33	van der Maas et al. [22]
IFX	15 (80)	54 (28–75)	10.4 (2.8–21.4)	100	73.3	NA	NA	26.7	Westhovens et al. [9][h]
IFX	21 (81)	NA (37–74)	NA (0.8–34.1)	100	52.4	NA	NA	5	Westhovens et al. [9][h]
IFX	7 (71.4)	55 (40–68)	6 (2.7–22.1)	100	71.4	NA	NA	42.9	Westhovens et al. [9][h]
IFX	51 (82)	56 ± 13	12 ± 9	86	0	5.9[e]	RIA	43	Wolbink et al. [11]
IFX	304 (84.2)	50 (21–74)	NA	100	NA	NA	ECLI	48.2	Yoo et al. [2]
Spondyloarthritis									
ADAL	35 (24)	43 ± 12	9 (3.5–16.5)[b]	0	NA	NA	RIA	31	de Vries et al. [50]
ADAL	22 (36)	43.3 (21–61)[f]	6.3 (1–18)	55	NA	NA	RIA	14	van Kuijk et al. [52]
ETA	53 (60)	41 ± 11	NA	NA	NA	NA	RIA	0	de Vries et al. [5]
ETA	101 (43)	47.6 ± NA	9 ± NA	42	19	NA	ELISA	0	Mease et al. [38]
GOL	278 (28.1)	38 (29–46)[b]	5.2 (1.5–12.3)[b]	20.5	15.8	NA	ELISA	4.1	Inman et al. [26]
GOL	292 (40)	46.95 ± NA	7.45 ± NA	48	16	NA	ELISA	4.6	Kavanaugh et al. [27]
GOL	405 (39.8)	47 ± NA	7.5 ± NA	47.9	NA	NA	NA	4.9	Kavanaugh et al. [28]
IFX	38 (32)	40 ± 10	NA	0	8	16[c]	RIA	29	de Vries et al. [19]
IFX	91 (NA)	NA (14–76)[g]	NA (0–24)	27.5	15.4	NA	DA-ELISA	15.4	Ducourau et al. [70]
IFX	125 (17.6)	38 (18–66)	NA	NA	NA	NA	ECLI	22.5	Park et al. [78]

Table 2 continued

Disease and TNFi	*N* (% female)	Age	Disease duration (years)	MTX %	PRED %	Other IS %	Assay	ADAB %	Study
IFX	94 (44)	50 ± 11	NA	38	41.8	NA	ELISA	25.5	Plasencia et al. [16]

Results are given as mean ± SD or median (range) unless otherwise indicated

ABT antigen-binding test, *ADAB* anti-drug antibodies, *ADAL* adalimumab, *CZP* certolizumab, *DA* double-antigen ELISA, *ECLI* electrochemiluminescent immunoassay, *ELISA* enzyme-linked immunosorbent assay, *ETA* etanercept, *GOL* golimumab, *IBD* inflammatory bowel disease, *INF* infliximab, *IQR* interquartile range, *IS* immunosuppression, *MTX* methotrexate, *N* number, *NA* not available, *PRED* prednisone, *RA* rheumatoid arthritis, *RIA* radioimmunoassay, *SD* standard deviation, *SEI* sandwich enzyme immunoassay, *SpA* spondyloarthritis, *TNFi* tumor necrosis factor inhibitor

[a] The IS is azathioprine and/or 6-mercaptupurine

[b] Median (IQR)

[c] These studies did not specify the type of the IS

[d] Median ± SD

[e] The IS is azathioprine

[f] Mean (range)

[g] Although they included patients aged less than 18 years, we decided to include these studies because the median for the age is more than 18 years

[h] These studies had multiple arms based on the medication and the dose that participants received and, therefore, each arm was analyzed separately

inhibitors and between diseases, we conducted a linear regression analysis for each of the following: the effect of ADABs on response, the effect of immunosuppression on ADAB positivity, and the effect of ADABs on infusion reactions. Duration of exposure was available in 60 studies overall: IBD 14 of 20 studies; RA 36 of 38 studies; and SpA 11 of 11 studies (one study was counted twice as it concerned two different diseases). To maintain data completeness, regressions were carried out only in the 60 studies in which duration of exposure was available. A sensitivity analysis including all studies showed no differences, except for the IBD studies where one of 16 analyses changed from a non-significant effect of ADABs on TNF inhibitor response to a significant effect. Given the number of analyses, we judged this to be a statistical effect only and without clinical significance. The dependent variables were response, ADAB positivity, and infusion reactions. The independent variables were duration of exposure, medication or disease (as appropriate), and ADAB by medication (or disease) interactions. Results are expressed as ORs with 95 % confidence intervals (CIs) with p values for each OR.

3 Results

3.1 Percent Anti-Drug Antibody (ADAB)

A total of 14,651 patients from 68 studies were examined (8766 RA, 4351 IBD, and 1534 SpA) (see Table 2). Trial durations were from 2 to 156.4 weeks, with a median of 26 weeks and a mean of 37.8 weeks. All doses of TNF inhibitors used were within the approved registered dose. Overall, the cumulative incidence of ADABs was 12.7 % (95 % CI 9.5–16.7).

Of the extracted articles, 38 were randomized controlled trials and 30 were observational studies. According to EPHPP criteria, 32 articles were of good quality, 26 of moderate quality, and ten of poor quality. This needs to be taken into consideration when reviewing the strength of the conclusions. The highest percentage of ADABs was detected in patients receiving infliximab [25.3 % (95 % CI 19.5–32.2)] compared with 14.1 % (95 % CI 8.6–22.3) of those receiving adalimumab, 6.9 % (95 % CI 3.4–13.5) for certolizumab, 3.8 % (95 % CI 2.1–6.6) for golimumab, and 1.2 % (95 % CI 0.4–3.8) for etanercept (see Fig. 2; Table 3).

Our study showed statistically significant differences in percentage of ADABs between infliximab and each of adalimumab ($p = 0.029$), certolizumab ($p < 0.001$), golimumab ($p < 0.001$), and etanercept ($p < 0.001$), with more ADABs for infliximab in each case. Likewise, a statistically higher percentage of ADABs was observed with adalimumab than each of golimumab ($p < 0.001$) and etanercept ($p < 0.001$). On the other hand, no statistically significant difference was observed between percentage of ADABs against adalimumab and certolizumab ($p = 0.092$), which could be because the number of published studies on certolizumab was low.

The cumulative incidence of ADABs in IBD was 15.8 % (95 % CI 9.6–24.7), most of whom were receiving infliximab (14 of 20 trials) compared with 12.1 % in RA

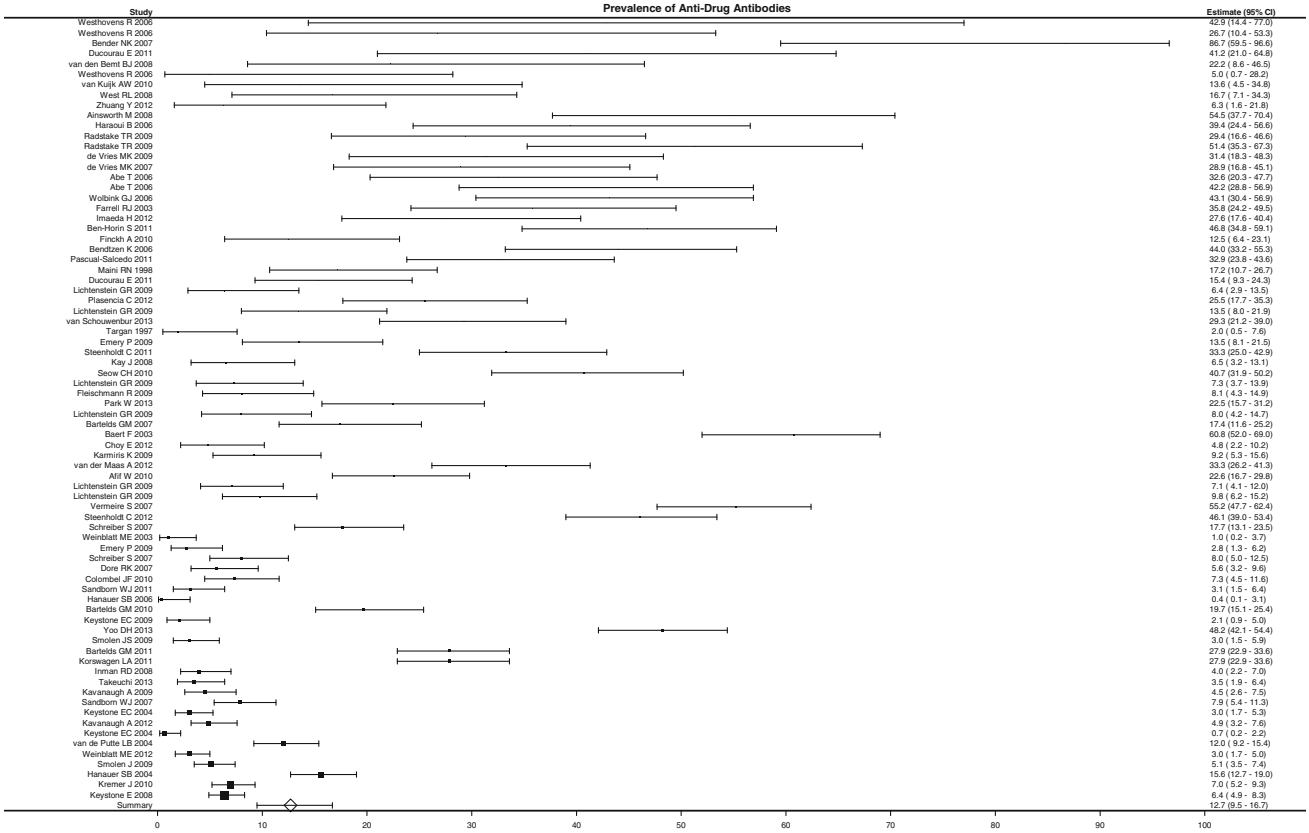

Fig. 2 The prevalence of ADAB in each of the studies; the cumulative incidence of ADABs was 12.7 % (95 % CI 9.5–16.7). *CI* confidence interval

(95 % CI 8.1–17.6) and 8.9 % in SpA (95 % CI 3.8–19.2) (Table 3).

3.2 Clinical Response

Figure 3 and Table 4 show that ADABs reduced the odds of clinical response by 67 % overall, although most of the data derived from articles on infliximab (nine) and adalimumab (eight), while golimumab added only four articles. To be clear, this indicates a 67 % likelihood of some reduction of TNF inhibitor response, not that the reduction of response was 67 %. Using a random-effects model, the summary effect of ADABs to infliximab decreased the odds of response by 58 %, they decreased the odds of response to adalimumab by 87 %, and odds of response to golimumab by 58 % (Table 4, column 4); all these estimates are statistically significant. This showed that for infliximab, adalimumab, and golimumab, response was compromised by ADABs. Three of the five etanercept studies documented ADAB effect on the drug response. All three had essentially no ADABs after etanercept exposure as measured by the assays used, so no effect of having ADABs on the response could be calculated. Likewise one of the five golimumab studies that reported the effect of ADAB positivity on golimumab response had no ADABs after golimumab exposure and was not included in the analysis of ADAB effect on the drug response. Only one of the seven certolizumab studies reported the effect of ADABs on the certolizumab response, so no judgment regarding ADAB effect on the drug response could be made.

The disease in which the drugs were used affected the influence of ADABs in all the three examined diseases/disease groupings (RA, IBD, and SpA) ($p < 0.001$). However, when the analysis was conducted on all the studies by disease, this changed to statistically insignificant for IBD. After examining only articles that included duration of exposure, when we included only those articles reporting the duration of exposure in the regression analysis [OR 1.16 (95 % CI 0.66–2.13), $p = 0.612$], ADABs decreased the odds of TNF inhibitor response in SpA by 18 % [OR = 0.18 (95 % CI 0.09–0.37), $p < 0.001$) and in RA by 27 % [OR 0.27 (95 % CI 0.20–0.36), $p < 0.001$].

The use of concomitant immunosuppressives (methotrexate, 6-mercaptopurine, azathioprine, and others, but mostly methotrexate) reduced the odds of ADAB formation in all patients by 74 %. The OR for risk with immunosuppressives versus without was 0.26 (95 % CI 0.21–0.32, $p < 0.001$).

Data were insufficient to analyze the effect of individual immunosuppressives on clinical response (Fig. 4; Table 5).

Table 3 Percentage of anti-drug antibody by disease and drug

Disease/disease grouping/drug	No. of studies	% ADAB	95 % CI	Drug/disease/disease grouping
Overall	68	12.7	9.5–16.7	IFX, ADAL, ETA, CZP, GOL, IBD, RA, SpA
IBD	20	15.8	9.6–24.7	IFX, ADAL, CZP
RA	38	12.1	8.1–17.6	IFX, ADAL, ETA, CZP, GOL
SpA	11	8.9	3.8–19.2	IFX, ADAL, ETA, GOL
IFX	30	25.3	19.5–32.3	IBD, RA, SpA
ADAL	15	14.1	8.6–22.3	IBD, RA, SpA
CZP	7	6.9	3.4–13.5	RA, IBD
GOL	12	3.8	2.1–6.6	RA, SpA
ETA	5	1.2	0.4–3.8	RA, SpA

ADAB anti-drug antibodies, *ADAL* adalimumab, *CI* confidence interval, *CZP* certolizumab, *ETA* etanercept, *GOL* golimumab, *IBD* inflammatory bowel disease, *INF* infliximab, *RA* rheumatoid arthritis, *SpA* spondyloarthritis

Of importance, immunosuppression had a distinct effect on ADAB formation in all examined diseases. They decreased the odds of ADABs by 92 % [OR 0.08 (95 % CI 0.03–0.21)] in SpA, 71 % [OR 0.29 (95 % CI 0.22–0.38)] in RA, and 73 % [OR 0.27 (95 % CI 0.19–0.37)] in IBD. This indicates that the use of concomitant immunosuppressives with TNF inhibitors might abrogate the negative clinical effects of ADABs on response, although this is shown only indirectly and is thus speculative.

3.3 Adverse Events

ADAB formation increased the odds of developing infusion reactions and injection site reactions compared with those who were ADAB negative [OR 3.25 (95 % CI 2.35–4.51)].

Duration of exposure to ADABs was accounted for in the regression analysis and was not statistically significant in any of the analyses.

4 Discussion

Our systematic literature review and meta-analysis included 68 articles, 38 randomized controlled trials, and 30 observational studies, representing the most thorough systematic literature review and meta-analysis to date. Our data extend and improve on previous data, particularly as we had more data to examine all five TNF inhibitors, and we examined three diseases/disease groupings (RA, SpA, and IBD). We were able to conduct a full systematic literature review and meta-analysis, following PRISMA guidelines and the EPHPP quality assessment guidelines. This assured transparency, uniformity, and an evaluation of article credibility. A previous systematic literature review and meta-analysis analyzed 17 articles but examined only adalimumab and infliximab [53]. Another literature review [54] included non-rheumatic conditions, e.g., psoriasis, and was not a meta-analysis.

4.1 Cumulative Incidence of ADABs

Our study documented the variable occurrence of immunogenicity, including differences among drugs and diseases. We showed that infliximab was the most immunogenic (25.3 %), followed by adalimumab (14.1 %), certolizumab (6.9 %), golimumab (3.8 %), and etanercept (1.2 %). In reviews that were not systematic literature reviews or meta-analyses, Vincent et al. [54] reported results that support our findings in his 'clinical perspectives' article of the five TNF inhibitors, their % ADABs, and some clinical associations.

4.2 ADABs and Decreased Clinical Response

We showed an association between the occurrence of ADABs and decreased clinical response. Overall, ADABs reduced the odds of clinical response by 67 %; most of the data derived from articles involving infliximab (nine) and adalimumab (eight), and only four articles involved golimumab. ADABs decreased the odds of response to adalimumab by 87 %, to infliximab by 58 %, and to golimumab by 58 %. ADAB data were too limited to test for etanercept or certolizumab. Alawadhi et al. [57] supported data on ankylosing spondylitis and RA, but they did not examine IBD. As in our article, they found neutralizing ADABs were associated with a reduced likelihood of achieving a clinical remission; in addition, they related ADABs to decreased drug survival, increased instances of dose escalation, and adverse events.

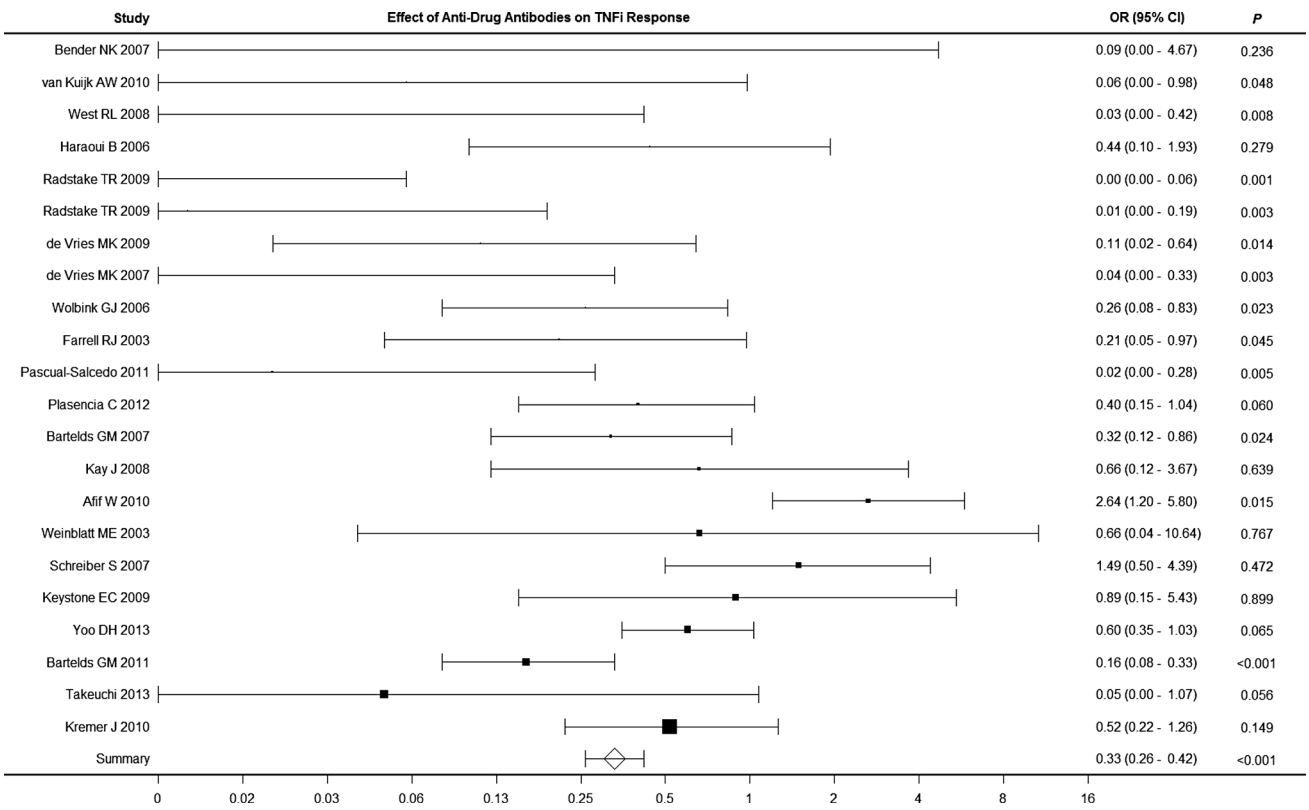

Fig. 3 Effect of ADAB on clinical response to TNF inhibitors. Overall, ADAB reduced the odds of clinical response by 67 %. *CI* confidence interval, *TNFi* tumor necrosis factor inhibitor

Table 4 Likelihood of reduction of clinical response to tumor necrosis factor inhibitors caused by the presence of anti-drug antibodies

Disease/disease grouping/drug	No. of studies	OR	LRCR[a]	95 % CI	Drug/disease/disease grouping
Overall	21	0.33	67	0.26–0.42	IFX, ADAL, ETA, CZP, GOL, IBD, RA, SpA
IBD	4	1.16	−16	0.66–2.03	IFX, ADAL, CZP
RA	13	0.27	73	0.20–0.36	IFX, ADAL, ETA, GOL
SpA	4	0.18	82	0.09–0.37	IFX, DAL, ETA
IFX	9[b]	0.42	58	0.30–0.58	IBD, RA, SpA
ADAL	8[b]	0.13	87	0.08–0.22	IBD, RA, SpA
ETA	0[c]	NA	NA	NA	RA, SpA
CZP[d]	1	1.49	−49	0.50–4.39	IBD
GOL	4[c]	0.42	58	0.22–0.81	RA

ADAB anti-drug antibodies, *ADAL* adalimumab, *CI* confidence interval, *CZP* certolizumab, *ETA* etanercept, *GOL* golimumab, *IBD* inflammatory bowel disease, *INF* infliximab, *LRCR* likelihood of reduced clinical response, *OR* odds ratio, *RA* rheumatoid arthritis, *SpA* spondyloarthritis, TNFi tumor necrosis factor inhibitor

[a] $\text{LRCR} = (1 - \text{OR}) \times 100$

[b] One study was calculated twice as it was on IFX and ADAL

[c] All three ETA studies and one of the five GOL studies that documented the effect of ADAB on the TNFi response, were not included in the analysis of the effect of ADAB positivity on the drug response as they had no ADAB after the drug exposure

[d] Effect of the ADAB towards CZP on the response was judged insufficient to make a judgment regarding ADAB effect on the drug response

4.3 Decreasing ADABs using Immunosuppressives

Our meta-analysis shows that the use of concomitant immunosuppressive drugs could ameliorate ADABs. It reduces the odds of ADAB formation by 74 % overall. Of the 68 studies included in the meta-analysis, 41 addressed the issue of concomitant immunosuppressives, primarily regarding methotrexate, 6-mercaptopurine, and azathioprine

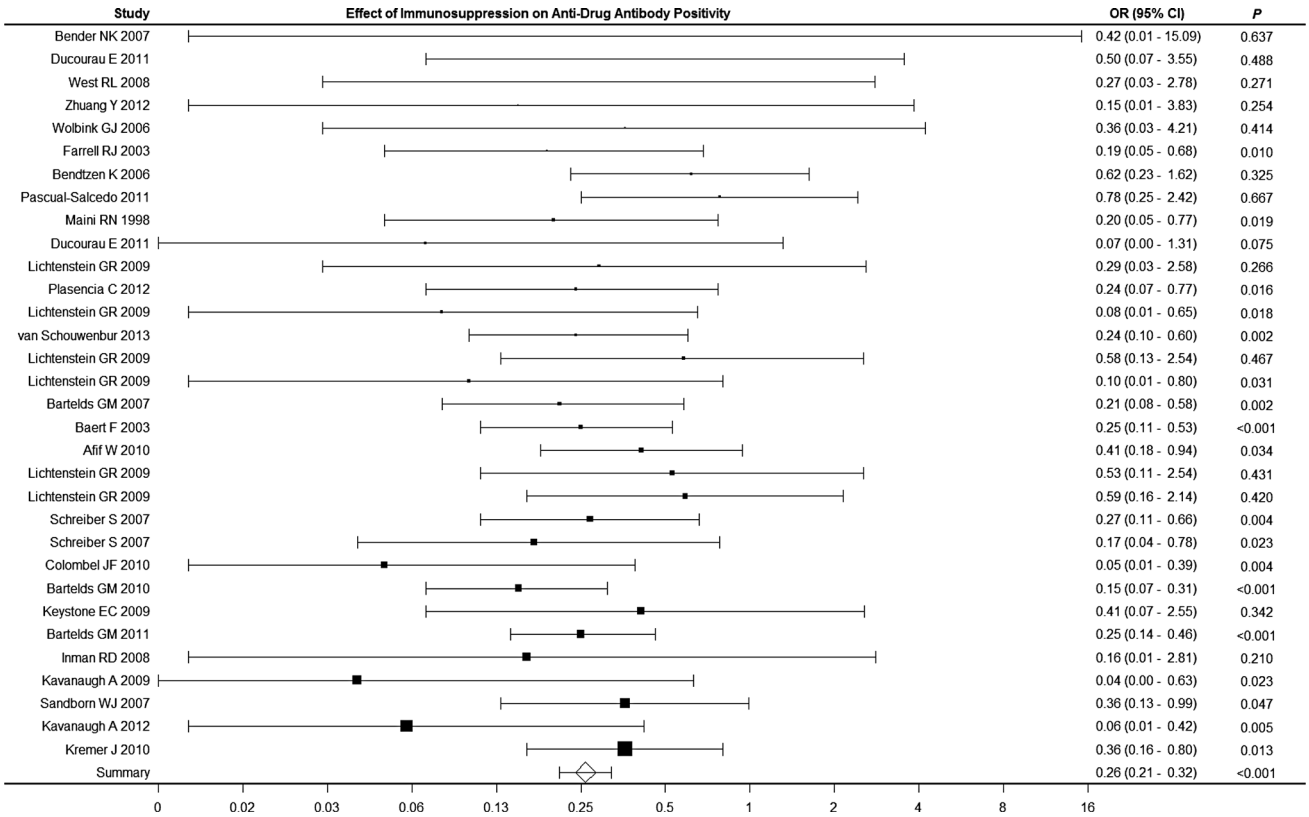

Fig. 4 Effect of immunosuppressives (IS) on ADAB; according to our data, overall, IS reduced the odds of ADAB formation by 74 %. *CI* confidence interval

Table 5 Likelihood of reduction of developing anti-drug antibodies when using immunosuppression

Disease/disease grouping	No. of studies	OR	LRDA[a]	95 % CI	Drug
Overall	36	0.26	74	0.21–0.32	IFX, ADAL, ETA, CZP, GOL
IBD	8	0.27	73	0.19–0.37	IFX, ADAL, CZP
RA[b]	23	0.29	71	0.22–0.38	IFX, ADAL, ETA, CZP, GOL
SpA[b]	5	0.08	92	0.03–0.21	IFX, ADAL, ETA, GOL

ADAB anti-drug antibodies, *ADAL* adalimumab, *CI* confidence interval, *CZP* certolizumab, *ETA* etanercept, *GOL* golimumab, *IBD* inflammatory bowel disease, *INF* infliximab, *OR* odds ratio, *RA* rheumatoid arthritis, *SpA* spondyloarthritis

[a] $\text{LRDA} = (1 - \text{OR}) \times 100$

[b] No-one in the study samples of two studies (one on RA and one on SpA) was using immunosuppressants; therefore, they were not included in the analysis of the effect of IS on ADAB development

treatment [3, 7, 10–13, 51]. Many studies support these data, although there is some uncertainty [22, 23, 60].

Goss et al. [64], in their abstract, showed that higher methotrexate doses from the beginning are associated with a lower incidence of ADAB formation against adalimumab in a dose-responsive manner, with 10 mg/week giving an approximate maximum effect. In addition Burmester et al. [65] showed increased response to adalimumab with higher doses of methotrexate, up to 10 mg/week in RA patients.

Other immunomodulators such as leflunomide, cyclosporine, azathioprine, etc. are apparently used (personal communication), but no published data regarding these are applicable to ADABs.

4.4 Decreasing ADABs with Immunosuppressives Maintains Clinical Response

Using immunosuppressives in all three diseases decreased ADABs. Since ADABs decreased clinical response, particularly in SpA and RA, it is tempting to connect these. Thus some immunosuppressants decreased ADABs and some ADABs decreased clinical response. Decreasing ADAB

formation may help maintain response to TNF inhibitors and would generally encourage the use of these drugs when starting TNF inhibitors in SpA, RA, and, perhaps, IBD. We do not have sufficient data to compare specific immunosuppressives nor to examine dose effects of immunosuppressives on ADABs. Further research in these areas is justified.

4.5 ADABs and Infusion Reactions/Injection Site Reactions

Our study shows a difference in the incidence of infusion reactions and injection site reactions in those who developed ADABs compared with those who did not, with more reactions among those with ADABs [OR 3.25 (95 % CI 2.35–4.51)]. The data are supported by several individual clinical trials that found a higher incidence of infusion reactions and injection site reactions among those with ADABs [15, 16, 70, 72, 79].

4.6 Other Factors Affecting ADABs: Effects of Methodology on Results

Atzeni et al [56]. and many others supported the importance of multiple factors that could affect immunogenicity, including disease activity, dose, dose schedule, route of administration, and concomitant medications, including immunosuppressives and genetics [7, 9, 10, 13, 14, 16, 17, 22, 33, 50, 51, 61–63].

Van Schouwenburg et al. [55] pointed out that the methodology used to detect ADABs can effect apparent immunogenicity. The article by Emi Aikawa et al. [59] pointed out that different methodologies contribute to the variability of the results, also apparent in our study. For example, we found that ADABs occurred in 0–87 % of patients and was reported as decreasing clinical response in 0–100 [5, 6, 34, 81]. Some of this variability is clearly affected by methodology. Two of the most frequently used techniques were ELISA (enzyme-linked immunosorbent assay) and the radioimmunoassay [14, 68]. False-negative results occur with the ELISA technique. For example, because the light kappa infliximab chains occupy the binding sites of the anti-infliximab antibodies, the infliximab may interfere with the ELISA capture by the immobilized infliximab. The detection phase can similarly be affected [14]. Radioimmunoassays are more accurate but still subject to interference by drug–anti-drug complexes [59]. Immunoaffinity chromatography and the pH-shift anti-idiotype antigen-binding test are more accurate than ELISA, and their increasing use will be helpful in the future [14, 55]. Unfortunately, these improved techniques were used in only a few of the studies [14, 46, 55].

All biological drugs induced immunogenicity but to different degrees [51, 61, 62]. Part of this variation can be explained by the structural differences among TNF inhibitors. Our data analysis found a statistically significant difference between the incidence of ADABs against infliximab versus adalimumab ($p = 0.03$) As expected, ADABs to adalimumab (14.1 %) are lower than to infliximab (25.3 %), adalimumab is fully human, and infliximab is chimeric. On the other hand, the difference between the immunogenicity of adalimumab (14.1 %) and golimumab (3.8 %) was statistically significant ($p < 0.001$), although both are totally human immunoglobulin (Ig)-Gs [33, 51]. It may be that the number of exposed epitopes in the variable region determines immunogenicity to some extent.

In our systematic literature review, ADABs were found as early as 2 weeks, but they also developed as late as 3 years after the initiation of treatment [4, 16, 23, 36, 48, 71]. The route of administration was apparently a factor that could influence the immune response [9, 16, 33, 51], with more immunogenicity after repeated intramuscular than repeated subcutaneous administration [9].

Fluctuating levels of TNF inhibitors in the body may be another factor that initiates antibodies to TNF inhibitors [5, 13, 17, 22, 51]. This may partially explain the higher percentage of ADABs formed to infliximab, which is given less frequently than etanercept [5]. The use of higher doses of TNF inhibitors can be less immunogenic than low doses of the drug; the mechanism of this effect may be due to the induction of immunotolerance after higher doses [11, 16, 47, 51], although this mechanism is not fully established. Other possible explanations are that giving more TNF inhibitors may lower ADAB levels because TNF inhibitor clearance is enhanced while formation is unchanged or that multimers (various number of combined molecules) are formed that are not measured, giving the impression that ADAB levels are lower.

4.7 Other Factors Affecting ADABs: Genetics

Some patients seem to be more susceptible to initiating an immune response to TNF inhibitors than others; this is perhaps related to human leukocyte antigen (HLA) types or other polymorphisms. Again, the genetic factors governing immunogenicity are not known [50, 60, 63].

4.8 Suggestions to Manage ADABs

The following suggestions regarding the management of ADABs arise from a total of 24 articles (see Table 6), which suggested five main strategies to manage ADABs. The first strategy is to increase the TNF inhibitor dose, although this is somewhat controversial. The rational is that increasing doses will saturate the ADAB sites, allowing non-bound drug to remain active [10–12, 24, 30, 51, 67, 70, 79]. This rational is not universally accepted because the

Table 6 Recommendations to modify the effect of anti-drug antibodies

Suggestions	References
Dose adjustment (increase dose/increase frequency)	[10–12, 20, 24, 51, 67, 70, 79]
Switch to another TNFi with a different chemical structure	[11, 24, 30, 47, 66, 67, 79]
Concomitant use of immunosuppressive drug	[4, 7, 10, 12, 13, 17, 23, 29, 32, 43, 47, 58, 67, 72, 73, 79]
Induction doses followed by maintenance and scheduled rather than episodic treatment based on clinical response	[13, 17, 58, 72, 73]
Measuring TNFi and ADAB levels	[10, 20, 67]

ADAB anti-drug antibodies, *TNFi* tumor necrosis factor inhibitor

doses required may be higher than those presently recommended by regulatory agencies, and higher doses may increase the possibility of adverse events. Our review would not ascertain the effect of such a strategy, as all drug doses in the article were within registered doses. A second strategy is to switch to another TNF inhibitor with a different chemical structure [11, 24, 30, 47, 66, 67, 79]. While this is inherently logical because the specific immune response is abrogated, the actual fact is that the active epitopes may be similar and illicit a similar and rapid ADAB response. The third method is to administer an immunosuppressive drug with the biologic from beginning of treatment [4, 7, 10, 12, 13, 17, 23, 29, 32, 43, 47, 58, 67, 72, 73, 79]. In our opinion, the third approach, suppressing the appearance of ADABs, may be particularly appropriate, although the necessary dose of these concomitant medications is not known. A fourth strategy involves induction doses followed by maintenance [17, 72] and giving TNF inhibitors on a scheduled regimen rather than as episodic treatment [13, 58, 73]. A fifth suggested approach, suggested in three articles, involved using a treatment algorithm based on the response, TNF inhibitor level, and the ADAB status of the patient [10, 20, 67]. This last approach may be appropriate when methods to measure TNF inhibitor and ADABs become readily available.

4.9 Limitations

This meta-analysis represents the most thorough review of immunogenicity to TNF inhibitors in RA, IBD, and SpA. However, it does have some limitations. First, it unavoidably includes only published studies, thus perhaps missing data or results not available from the medical literature. Second, the studies were heterogeneous in design, used variable amounts of concomitant drugs and immunosuppressives, utilized different measurement techniques, and employed variable sampling strategies, which contributed to the variability of the results. We realize that such variability makes a meta-analysis less reliable and implies a uniformity that could be misleading. This is true of many meta-analysis. Nevertheless, this review and analysis shares the breadth of the literature available to the reader and, by pointing out the literature limitations, can allow the reader to judge for themselves while being able to examine the totality of the data to date. Finally, we cannot guarantee that all patients were unique, and some patients might have been part of more than one study.

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Appendix 1

("Arthritis, Rheumatoid"[MeSH Terms] OR (Rheumatoid [all fields] AND arthriti* [all fields]) OR "caplan syndrome" [all fields] OR ("felty syndrome" [all fields] OR "felty's syndrome" [all fields]) OR ("adult" [all fields] AND ("still disease" [all fields] OR "still's disease" [all fields])) OR "Crohn Disease"[MeSH Terms] OR (crohn [all fields] OR crohn's [all fields]) OR ((colitis [all fields] OR enteritis [all fields] OR ileitis [all fields]) AND (regional [all fields] OR granulomatous [all fields])) OR ((regional [all fields] OR terminal [all fields]) AND ileitis [all fields]) OR ("Spondylitis, Ankylosing"[Mesh] OR "ankylosing spondylitis" [all fields] OR "Bechterew Disease" [all fields] OR "Marie Struempell Disease" [all fields] OR "Marie Strumpell Disease" [all fields]) OR ("Arthritis, Psoriatic"[Mesh] OR "psoriatic arthritis"[all fields] OR (psoriasis [all fields] AND arthritis [all fields])) OR ("Colitis, Ulcerative"[Mesh] OR (ulcerative [all fields] AND colitis [all fields]))) AND ((cimzia [all fields] OR certolizumabpegol [all fields] OR cdp870[All Fields] OR certolizumabpegol [Supplementary Concept]) OR (enbrel [all fields] OR etanercept [all fields] OR TNFR-Fc fusion protein [All Fields] OR TNFR-Fc fusion protein [Supplementary Concept]) OR (humira [all fields] OR adalimumab [all fields] OR adalimumab [Supplementary Concept]) OR (remicade [all fields] OR infliximab [all fields] OR infliximab [Supplementary Concept] OR mab ca2 [All Fields] OR monoclonal antibody ca2[All Fields]) OR (simponi [all fields] OR golimumab [all fields] OR golimumab [Supplementary Concept] OR cnto-148[All Fields])) AND (immunogenic* [all fields] OR "antibody formation" [all fields] OR Antibody Formation [MeSH terms] OR "response failure" [all fields] OR bioavailability OR biological availability OR "Biological Availability"[MeSH Terms] OR "drug tolerance"[all fields] OR Drug Tolerance [MeSH Terms] OR "treatment outcome" [all fields] OR Treatment Outcome [MeSH Terms]) AND (("Randomized Controlled Trial" [ptyp] OR "Controlled Clinical Trial" [ptyp] OR "Multicenter Study" [ptyp] OR "randomized"[tiab] OR "randomised"[tiab] OR "placebo"[tiab] OR "randomly"[tiab] OR "trial"[tiab] OR "randomized controlled trials as topic"[MeSH Terms]OR "random allocation"[MeSH Terms] OR "double-blind method"[MeSH Terms] OR "double-blind"[text word] OR "single-blind method"[MeSH Terms] OR "single-blind" [text word] NOT ("Meta-Analysis" [ptyp]OR "Review" [ptyp] OR "Letter" [ptyp] OR "Editorial" [ptyp])) AND ("1966/01/01"[PDat] : "2012/12/1"[PDat] AND English[lang]) NOT (animals[mh] NOT human[mh])).

Appendix 2: Quality Assessment Tool for Quantitative Studies

QUALITY ASSESSMENT TOOL FOR QUANTITATIVE STUDIES

COMPONENT RATINGS

A) SELECTION BIAS

(Q1) Are the individuals selected to participate in the study likely to be representative of the target population?
1. Very likely 2. Somewhat likely 3. Not likely 4. Can't tell

(Q2) What percentage of selected individuals agreed to participate?
1. 80 - 100% agreement 2. 60 – 79% agreement 3. less than 60% agreement 4. Not applicable 5. Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

B) STUDY DESIGN

Indicate the study design
1. Randomized controlled trial 2. Controlled clinical trial
3. Cohort analytic (two group pre + post) 4. Case-control
5. Cohort (one group pre + post (before and after)) 6. Interrupted time series
7. Other specify _____ 8. Can't tell

Was the study described as randomized? If NO, go to Component C.
No Yes
If Yes, was the method of randomization described? (See dictionary)
No Yes
If Yes, was the method appropriate? (See dictionary)
No Yes

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

C) CONFOUNDERS

(Q1) Were there important differences between groups prior to the intervention?
1. Yes 2. No 3. Can't tell

The following are examples of confounders:
1. Race 2. Sex 3. Marital status/family
4. Age 5. SES (income or class) 6. Education
7. Health status 8. Pre-intervention score on outcome measure

(Q2) If yes, indicate the percentage of relevant confounder s that were controlled (either in the design (e.g. stratification, matching) or analysis)?
1. 80 – 100% (most) 2. 60 – 79% (some) 3. Less than 60% (few or none) 4. Can't Tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

D) BLINDING

(Q1) Was (were) the outcome assessor(s) aware of the intervention or exposure status of participants?
1. Yes 2. No 3. Can't tell

(Q2) Were the study participants aware of the research question?
1. Yes 2. No 3. Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

E) DATA COLLECTION METHODS

(Q1) Were data collection tools shown to be valid?
1. Yes 2. No 3. Can't tell

(Q2) Were data collection tools shown to be reliable?
1. Yes 2. No 3. Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

F) WITHDRAWALS AND DROP-OUTS

(Q1) Were withdrawals and drop-outs reported in terms of numbers and/or reasons per group?
1. Yes 2. No 3. Can't tell 4 Not Applicable (i.e. one time surveys or interviews)

(Q2) Indicate the percentage of participants completing the study. (If the percentage differs by groups, record the lowest).
1. 80 -100% 2. 60 - 79% 3. less than 60% 4. Can't tell 5. Not Applicable (i.e. Retrospective case-control)

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

G) INTERVENTION INTEGRITY

(Q1) What percentage of participants received the allocated intervention or exposure of interest?
1. 80 -100% 2. 60 - 79% 3. less than 60% 4. Can't tell

(Q2) Was the consistency of the intervention measured?
1. Yes 2. No 3. Can't tell

(Q3) Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?
4. Yes 5. No 6. Can't tell

H) ANALYSES

(Q1) Indicate the unit of allocation (circle one)
community organization/institution practice/office individual

(Q2) Indicate the unit of analysis (circle one)
community organization/institution practice/office individual

(Q3) Are the statistical methods appropriate for the study design?
1. Yes 2. No 3. Can't tell

(Q4) Is the analysis performed by intervention allocation status (i.e. intention to treat) rather than the actual intervention received?
1. Yes 2. No 3. Can't tell

GLOBAL RATING

COMPONENT RATINGS

Please transcribe the information from the gray boxes on pages 1-4 onto this page. See dictionary on how to rate this section.

A	SELECTION BIAS	STRONG	MODERATE	WEAK	
		1	2	3	
B	STUDY DESIGN	STRONG	MODERATE	WEAK	
		1	2	3	
C	CONFOUNDERS	STRONG	MODERATE	WEAK	
		1	2	3	
D	BLINDING	STRONG	MODERATE	WEAK	
		1	2	3	
E	DATA COLLECTION METHOD	STRONG	MODERATE	WEAK	
		1	2	3	
F	WITHDRAWALS AND DROPOUTS	STRONG	MODERATE	WEAK	
		1	2	3	Not Applicable

GLOBAL RATING FOR THIS PAPER (circle one):
1 STRONG (no WEAK ratings)
2 MODERATE (one WEAK rating)

3 WEAK (two or more WEAK ratings)

With both reviewers discussing the ratings:

Is there a discrepancy between the two reviewers with respect to the component (A-F) ratings?
No Yes
If yes, indicate the reason for the discrepancy
1 Oversight
2 Differences in interpretation of criteria
3 Differences in interpretation of study

Final decision of both reviewers (circle one):

1. STRONG	2. MODERATE	3. WEAK

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