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# Antidrug antibodies in psoriasis: a systematic review*

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## Summary

Antidrug antibodies (ADAs) against biological agents may be clinically significant and potentially alter a biological drug's treatment efficacy. This systematic review aims to (i) determine the prevalence of ADAs against infliximab, etanercept, adalimumab and ustekinumab in patients with psoriasis; (ii) ascertain whether ADAs are associated with changes in drug efficacy; and (iii) explore the use of concomitant methotrexate to prevent ADA formation. Through a systematic search using Medline and Embase from 29 January 1950 to 29 March 2013, we identified 25 studies that met the inclusion criteria. Of 7969 patients with psoriasis, 950 tested positive for ADAs. Antibodies against infliximab, etanercept, adalimumab and ustekinumab were reported in 5·4–43·6%, 0–18·3%, 6–45% and 3·8–6% of patients, respectively. Anti-infliximab antibodies were associated with lower serum infliximab concentrations in three studies, and decreased treatment response in five studies. ADAs against etanercept were non-neutralizing and not associated with any apparent effects on clinical response. Antiadalimumab antibodies were associated with lower serum adalimumab concentrations in three of five studies, and reduced clinical efficacy in four studies. Two of six studies reported that antiustekinumab antibodies were associated with lower Psoriasis Area and Severity Index responses, and three ustekinumab studies noted that most of these antibodies were neutralizing. Although the use of concomitant methotrexate with biological agents to prevent ADA formation in other immune-mediated diseases is promising, their use in psoriasis is sparse. ADA development remains a challenge with biological therapies and therefore should be considered in patients with psoriasis who experience diminished treatment response.

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### What's already known about this topic?

- Antidrug antibodies have been shown to form in patients with psoriasis receiving infliximab, etanercept, adalimumab or ustekinumab.
- Certain antidrug antibodies have been noted to influence treatment efficacy.

### What does this study add?

- This is among the first reviews to examine the available scientific evidence on the prevalence of antidrug antibodies against biological agents, their impact on treatment efficacy, and the utility of concomitant methotrexate to prevent antidrug antibody formation in patients with psoriasis.

Psoriasis is an immune-mediated disease characterized by well-demarcated patches and plaques on the skin; it is associated with psoriatic arthritis and other comorbidities.[1,2] Although the pathogenesis of psoriasis is poorly understood, upregulation of T-helper (Th)1 and Th17 pathways resulting in increased levels of tumour necrosis factor (TNF)-α and interleukin (IL)-23 has been implicated.[3–5] Through the growing understanding of the pathogenesis of psoriasis, treatments have evolved from topical agents to biological therapies including fusion proteins and monoclonal antibodies.

Monoclonal antibodies are categorized as murine, chimeric, humanized or fully human. Murine antibodies induce antidrug

antibodies (ADAs) against the murine variable and constant domains, limiting their therapeutic effectiveness due to significant immunogenicity.[6] Chimeric antibodies are composed of human constant domains and murine variable domains, suggesting less immunogenicity compared with murine antibodies.[7,8] Humanized antibodies contain murine sequences only in the antigen-binding sites. Fully human antibodies are synthesized with fully human sequences and are therefore theoretically less immunogenic.[9]

Infliximab, etanercept, adalimumab and ustekinumab are approved by the US Food and Drug Administration for treatment of moderate-to-severe psoriasis.[10–13] Infliximab, a chimeric IgG1κ antibody, binds to soluble and membrane-bound TNF-α.[14] Etanercept, a fully human fusion protein composed of two p75 TNF receptors fused to a single IgG1 Fc subunit, binds to both TNF-α and TNF-β, but with less affinity for TNF-α than infliximab. Adalimumab is a fully human IgG1κ antibody that targets both soluble and membrane-bound TNF-α.[15] Ustekinumab, another fully human IgG1κ antibody, binds the common p40 subunit of IL-12 and IL-23.[16]

The clinical significance of ADAs needs to be thoroughly explored, as studies suggest that they may be associated with decreased drug efficacy.[17–19] We conducted a systematic review to (i) determine the incidence of ADA formation against infliximab, etanercept, adalimumab and ustekinumab in psoriasis; (ii) ascertain whether ADAs are associated with changes in drug efficacy in psoriasis; and (iii) determine whether concomitant methotrexate prevents ADA formation in the psoriasis population.

## Materials and methods

### Data sources and study selection

We performed a systematic search using the Medline and Embase databases from 29 January 1950 to 29 March 2013 with the following search query: (infliximab OR etanercept OR adalimumab OR ustekinumab) AND psoriasis AND clinical trial[ptyp] AND English[lang]. The initial search yielded 484 unique references, which were combined with six hand-searched references identified from the references of relevant articles, resulting in 490 references (Fig. 1).[20,21] For any studies involving the same patient cohort, we selected the latest primary article with the longest follow-up period.

We applied the inclusion criteria to the 490 identified references. The inclusion criteria were having at least 15 patients in the study, documenting serial skin assessments of psoriasis severity, and reporting ADAs in patients with psoriasis receiving biological agents (infliximab, etanercept, adalimumab or ustekinumab). Two authors (A.W.A. and B.T.S.) independently read the abstracts of the 490 articles and excluded 352 articles based on the selection criteria. The two authors then reviewed the full text of the remaining 138 articles and identified 25 that met the inclusion criteria. To measure study quality, we used the five-point Jadad scale for reporting randomized controlled trials (RCTs), and a six-point scale, which was previously described and adopted from a proposal by Stroup *et al.*, for reporting observational studies.[22–24] The Jadad scale has values of 0 or 1 assigned to the mention of randomization,

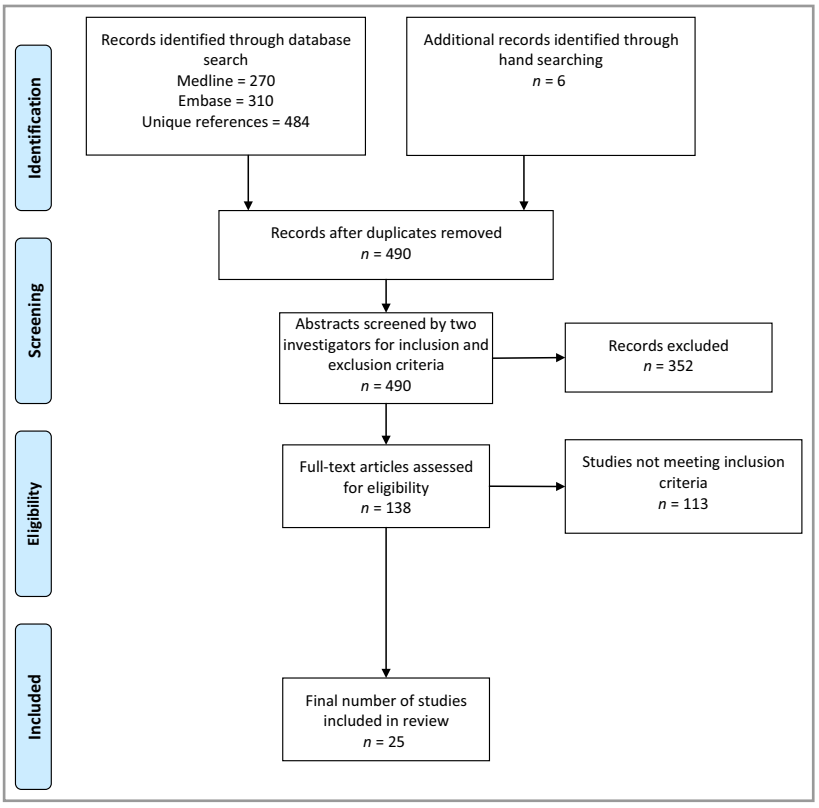


**Fig 1.** Selection process for study inclusion in the systematic review.

appropriateness of randomization method, mention of blinding, appropriateness of blinding method, and accounting of all patients.[23] RCTs with a score of 0–3 were categorized as lower quality and studies with a score of 4–5 were categorized as higher quality. The observational study six-point scale has values 0 or 1 assigned to study design, assessment of exposure, assessment of outcome, control for confounding, evidence of bias and assessment of psoriasis severity. Observational studies with a score of 0–3 were categorized as lower quality, and studies with a score of 4–6 were categorized as higher quality.[22] The ratings measure the study quality for the primary end points such as treatment efficacy, rather than antibody formation, for most of the studies examined herein.

### Data extraction

Two reviewers extracted data independently from each of the 25 articles, with discrepancies resolved by discussion (Tables 1–4). The data collected for each study included (i) study identification including year of publication; (ii) biological drug evaluated; (iii) study design; (iv) prevalence of ADAs; (v) testing modality; (vi) testing period; (vii) whether samples were drawn during trough drug levels; (viii) relationship of ADAs to psoriasis severity; (ix) methotrexate use and its relationship to ADA formation; and (x) neutralizing status of the ADAs.

ADA prevalence was determined with respect to the total number of patients tested in each study, rather than the total number of patients in the study, in order to reduce the underestimation of ADA formation. Although not all patients in the studies were tested for various reasons, this approach remained the most precise and structured interpretation of ADA prevalence for comparison with other studies. A few studies had partial information regarding the total number of patients undergoing ADA testing. Some studies reported the ADA status as inconclusive or indeterminate when both the antibody and biological drug were present, while other studies reported the ADA status dichotomously as positive or negative. If the study authors could not be contacted, we inferred the number of patients testing negative for ADAs based on the data of the total study population tested and the number of patients testing positive for ADAs.[11,25–28]

## Results

We identified 25 studies with 7969 patients with psoriasis who had laboratory tests to determine ADA status, and 950 patients tested positive for ADAs.

### Anti-infliximab antibodies

Ten studies documented the prevalence of anti-infliximab antibodies (AIAs). Four were RCTs, four were prospective cohort studies and two were retrospective studies.[13,26,29–36] AIAs were reported in 5·4–43·6% of patients (Table 1). Four studies used enzyme-linked immunosorbent assays (ELISAs) to detect AIAs, and six studies tested for AIAs at drug trough levels.[26,29,31,32,34,36] Three studies reported an association between AIAs and lower serum infliximab concentrations.[31,34,36] Five studies noted an association between AIAs and decreased clinical improvement.[13,26,29,32,33] In the study of Reich *et al.*, of those patients achieving a 75% improvement in Psoriasis Area and Severity Index (PASI 75 response) at week 10, 81% (106/131) of AIA-negative patients and 39% (20/51) of AIA-positive patients maintained this response through week 50.[13] Krathen *et al.* noted that 92% (11/12) of AIA-positive patients did not maintain a 'clear' or 'almost clear' assessment on the Physician's Global Assessment scale during 1 year of infliximab therapy.[33] Adişen *et al.* reported that 33% of patients (five of 15) tested AIA-positive from the fifth to the thirteenth infliximab infusion.[29] The mean PASI scores in AIA-negative and AIA-positive patients were 5·3 and 10, respectively ($P = 0{\cdot}02$).[29] Torii *et al.* found that 20% of patients (10/50) tested AIA-positive.[36] At 8 weeks postinfliximab infusion, AIA-negative and AIA-inconclusive patients had serum infliximab levels $> 0{\cdot}1$ μg mL$^{-1}$, whereas AIA-positive patients had undetectable levels ($< 0{\cdot}1$ μg mL$^{-1}$).[36] The PASI 75 response rates were 96% (22/23) in patients with serum infliximab concentrations of 1–10 μg mL$^{-1}$, 71% (five out of seven) in patients with serum infliximab concentrations of 0·1–1 μg mL$^{-1}$, and 60% (six out of 10) in patients with serum infliximab concentrations $< 0{\cdot}1$ μg mL$^{-1}$ (P-value not specified).[36] Hoffmann *et al.* reported AIAs in 21% of patients (six out of 29).[32] The authors noted worsening skin or joint symptoms in 13% of AIA-negative patients (three out of 23) and four of six AIA-positive patients.[32] Takahashi *et al.* reported AIAs in 30% of patients (six out of 20) at 48 weeks.[34] The authors reported 48-week mean serum trough infliximab concentrations of 4·12 μg mL$^{-1}$ in 14 ADA-negative patients and 1·21 μg mL$^{-1}$ in six ADA-positive patients ($P < 0{\cdot}01$).[34] No articles reported the neutralizing status of AIAs.

Three infliximab studies reported data on the relationship of methotrexate with ADA incidence.[29,32,33] Krathen *et al.* detected AIAs in 10/66 patients (15%) without concomitant methotrexate and in two of seven patients receiving a mean methotrexate dose of 7·5 mg per week.[33] Adişen *et al.* found that an unspecified number of the five AIA-positive patients became AIA negative after 8 weeks of methotrexate 5–15 mg per week.[29] Hoffman *et al.* reported AIAs in five of 22 patients (23%) without concomitant methotrexate and in one of seven patients treated with an unspecified methotrexate dose.[32]

### Antietanercept antibodies

Six studies measured antietanercept antibodies (AEAs) in patients with psoriasis. Four were RCTs and two were prospective cohort studies.[11,25,37–40] The prevalence of AEAs ranged from 0% to 18·3% (Table 2). Five studies detected AEA status with ELISA, and one study documented collecting serum samples while simultaneously collecting the serum drug trough samples. Leonardi *et al.* reported that the percentages of AEA-negative patients with a PASI 75 response at weeks 48

**Table 1** Anti-infliximab antibodies (AIAs) in psoriasis

| Study | Study design | Antidrug antibody prevalence | Testing period | Testing modality | Collected at trough | Relation to clinical efficacy | Methotrexate use | Quality rating (Jadad scale)[a] | Quality rating (observational studies)[b] |
|---|---|---|---|---|---|---|---|---|---|
| Gottlieb 2004[30] | RCT | 23·3% (38/163) | To week 26 | ELISA | Not reported | Not specified | Not used | 5 | – |
| Reich 2005[13] | RCT | 26·5% (70/264) | At weeks 0, 46, 66 | Not reported | Not reported | Of PASI 75 responders at week 10, 81% (106) of AIA-negative, 96% (22) of AIA-inconclusive and 39% (20) of AIA-positive patients maintained a PASI 75 response at week 50 (P-value not reported) | Not used | 5 | – |
| Krathen 2006[33] | Retrospective study | 16% (12/73)[c] | At or beyond month 12, only those who lost response were tested | Not reported | Not reported | 92% (11/12) of AIA-positive patients had loss of efficacy in < 1 year | Two of seven patients on methotrexate at 5–7·5 mg per week developed AIAs | – | 4 |
| Menter 2007[26] | RCT | 43·6% (237/543)[c] | At weeks 0, 30, 50 and 66 | Not reported | Yes | AIA-positive patients were less likely to maintain response through week 50 than AIA-negative patients (no. patients and P-value not specified) | Not used | 5 | – |
| Adişen 2010[29] | Prospective cohort study | 33% (5/15) | To 84 weeks | ELISA | Yes | Mean PASI scores in AIA-negative and AIA-positive patients were 5·3 and 10, respectively (P = 0·02) | An unspecified number of AIA-positive patients tested negative for AIAs after 8 weeks of methotrexate 5–15 mg per week | – | 6 |

**Table 1** (continued)

| Study | Study design | Antidrug antibody prevalence | Testing period | Testing modality | Collected at trough | Relation to clinical efficacy | Methotrexate use | Quality rating (Jadad scale)[a] | Quality rating (observational studies)[b] |
|---|---|---|---|---|---|---|---|---|---|
| Torii 2010[36] | RCT | 20% (10/50) | To week 78 | Not reported | Yes | 8 weeks postinfliximab infusion, AIA-negative and AIA-inconclusive patients had serum infliximab levels > 0·1 μg $mL^{-1}$; AIA-positive patients had undetectable levels (< 0·1 μg $mL^{-1}$). At week 62, PASI 75 response rates were 96% (22/23) in patients with serum infliximab 1–10 μg $mL^{-1}$, 71% (5/7) for 0·1–1 μg $mL^{-1}$ and 60% (6/10) for < 0·1 μg $mL^{-1}$ (P-value not specified) | Not used | 4 | – |
| Hoffmann 2011[32] | Retrospective case–control study | 21% (6/29) | After a median of 11 infusions (range 3–21) | ELISA | Yes | Four of six AIA-positive patients had worsening of skin or joint symptoms vs. 13% (3/23) of AIA-negative patients (P-value not specified) | One of seven patients on an unspecified dose of methotrexate had AIAs | – | 6 |
| Torii 2011[35] | Prospective cohort study | 30% (19/64) | To week 54 | Not reported | Not reported | Not specified | Four of 64 patients received methotrexate, but AIA status was not reported | – | 5 |
| Gottlieb 2012[31] | Prospective cohort study | 5·4% (9/168) | At week 22 | Not reported | Yes | Serum infliximab trough concentrations at week 22 were undetectable in an unspecified number of AIA-positive patients (P-value not specified) | Eight patients received methotrexate at doses < 25 mg per week. No report on the relationship of methotrexate to AIAs | – | 6 |

**Table 1** (continued)

| Study | Study design | Antidrug antibody prevalence | Testing period | Testing modality | Collected at trough | Relation to clinical efficacy | Methotrexate use | Quality rating (Jadad scale)[a] | Quality rating (observational studies)[b] |
|---|---|---|---|---|---|---|---|---|---|
| Takahashi 2013[34] | Prospective cohort study | 30% (6/20) | At week 48 | ELISA | Yes | AIA-positive patients had lower serum trough infliximab concentrations than AIA-negative patients ($P < 0{\cdot}01$) | Not used | – | 5 |

RCT, randomized controlled trial; ELISA, enzyme-linked immunosorbent assay; PASI, Psoriasis Area and Severity Index. [a]Studies with a score of 0–3 are categorized as lower quality and 4–5, higher quality. [b]Studies with a score of 0–3 are categorized as lower quality and 4–6, higher quality. [c]Denominator calculated based on the percentage and numerator given.

and 72 were 52% and 49%, respectively.[39] Those who tested AEA-positive had comparable response rates to etanercept with those testing negative. Specifically, 52% and 49% of patients who tested negative for AEAs achieved a PASI 75 response at weeks 48 and 72, respectively; 54% and 57% of patients testing AEA-positive three or more times achieved a PASI 75 response at weeks 48 and 72, respectively.[39] Tyring *et al.* reported PASI 75 responses of 64% and 60% in AEA-negative and AEA-positive patients, respectively, at week 12.[25] Three studies found no apparent difference in safety or efficacy between AEA-negative and AEA-positive patients.[11,37,38] All AEAs were reported as non-neutralizing. Concomitant methotrexate was not used in the six studies.

## Antiadalimumab antibodies

Five studies reported antiadalimumab antibodies (AAAs) in patients with psoriasis.[12,27,34,40,41] Two studies were RCTs and three were prospective cohort studies. These studies described incidence rates of AAAs from 6% to 45% (Table 3). Three studies utilized ELISA to detect AAAs,[27,34,40] and one study used radioimmunoassay (RIA).[41] Three of the studies reported collecting samples immediately prior to administration of the next drug dose.[27,34,41] Takahashi *et al.* and Lecluse *et al.* reported higher intravascular adalimumab concentrations in AAA-negative patients than in AAA-positive patients.[34,41] Four of the five studies reported decreased drug efficacy with AAA positivity.[12,34,40,41] Menter *et al.* reported AAAs in 8·8% of patients (73/825).[12] Of the patients who achieved a PASI 75 response by week 33, 27·9% (65/233) of AAA-negative patients and 42·8% of AAA-positive patients lost clinical response (PASI < 50) by week 52.[12] Asahina *et al.* documented AAAs in 10·6% of patients (13/123).[27] At week 16, 72·7% of AAA-negative patients achieved at least a PASI 75 response, compared with 23·1% of AAA-positive patients ($P < 0{\cdot}001$).[27] Lecluse *et al.* reported week-24 median adalimumab trough concentrations of 9·6, 1·3 and 0·0 mg $L^{-1}$ in AAA-negative, AAA-positive low-titre and AAA-positive high-titre patients, respectively ($P < 0{\cdot}001$).[41] At week 24, the PASI 75 response rate decreased as AAA titres increased. The authors documented that a PASI 75 response was achieved by 56% of patients (nine out of 16) without antidrug antibodies, one of six patients with a low titre of AAAs, and none of the seven patients with a high titre of AAAs ($P < 0{\cdot}001$).[41] Takahashi *et al.* measured mean trough adalimumab concentrations of 7·27 μg $mL^{-1}$ in 28 AAA-negative patients vs. 2·77 μg $mL^{-1}$ in five AAA-positive patients at week 48 ($P < 0{\cdot}01$).[34] No articles reported the neutralizing status of the AAAs. Lecluse *et al.* found AAAs in 50% of patients (13/26) not on methotrexate and in none of three patients receiving concomitant methotrexate at a mean dose of 12 mg per week.[41]

## Antiustekinumab antibodies

Six studies reporting antiustekinumab antibodies (AUAs) were examined. Five were RCTs and one was a prospective cohort

**Table 2** Antietanercept antibodies (AEAs) in psoriasis

| Study | Study design | Antidrug antibody prevalence | Testing period | Testing modality | Collected at trough | Relation to clinical efficacy | Methotrexate use | Quality rating (Jadad scale)[a] | Quality rating (observational studies)[b] |
|---|---|---|---|---|---|---|---|---|---|
| Leonardi 2003[11] | RCT | Eight patients positive; negative patients not specified | At week 24 | ELISA | Not reported | No apparent difference (*P*-value not specified) | Not used | 4 | – |
| Papp 2005[37] | RCT | 2·7% (15/549) | At weeks 12, 24 or early termination | ELISA | Not reported | No apparent difference (*P*-value not specified) | Not used | 5 | – |
| Gordon 2006[38] | RCT | 4·7% (14/297) | Up to at least 60 weeks | ELISA | Not reported | No apparent difference (*P*-value not specified) | Not used | 5 | – |
| Tyring 2007[25] | RCT | 18·3% (111/606)[c] | By 96 weeks | ELISA | Not reported | No apparent alteration in PASI response | Not used | 5 | – |
| Leonardi 2010[39] | Prospective cohort study | 15·2% (130/857) | By 72 weeks | Not reported | Not reported | PASI 75 response at weeks 48 (52%) and 72 (49%) in AEA-negative patients vs. 52% and 48% of patients testing AEA-positive 1–2 times and 54% and 57% of patients testing positive ≥ 3 times, respectively (*P*-value not specified) | Not used | – | 4 |
| Mahil 2013[40] | Prospective cohort study | 0% (0/25) | Not specified | ELISA | Not reported | No AEAs reported | Not used | – | 5 |

RCT, randomized controlled trial; ELISA, enzyme-linked immunosorbent assay; PASI, Psoriasis Area and Severity Index. [a]Studies with a score of 0–3 are categorized as lower quality and 4–5, higher quality. [b]Studies with a score of 0–3 are categorized as lower quality and 4–6, higher quality. [c]Denominator calculated based on the percentage and numerator given.

**Table 3** Antiadalimumab antibodies (AAAs) in psoriasis

| Study | Study design | Antidrug antibody prevalence | Testing period | Testing modality | Collected at trough | Relation to clinical efficacy | Methotrexate use | Quality rating (Jadad scale)[a] | Quality rating (observational studies)[b] |
|---|---|---|---|---|---|---|---|---|---|
| Menter 2008[12] | RCT | 8·8% (73/825) | Once or more during 52 weeks and at day 70 | Not reported | Not reported | Three of seven AAA-positive patients and 65 (27·9%) of 233 AAA-negative patients lost adequate response | Not used | 5 | – |
| Lecluse 2010[41] | Prospective cohort study | 45% (13/29) | At weeks 12 and 24 | RIA | Yes | At week 24, median adalimumab trough concentrations in AAA-negative, AAA-positive low-titre and AAA-positive high-titre patients were 9·6, 1·3 and 0·0 mg $L^{-1}$, respectively; ns. patients with PASI 50 response were 81% (13/16), 50% (3/6) and 0% (0/7) and PASI 75 response 56% (9/16), 17% (1/6) and 0% (0/7), respectively ($P < 0·001$) | None of 3 patients on methotrexate (mean dose 12 mg per week) developed AAAs | – | 5 |
| Asahina 2010[27] | RCT | 10·6% (13/123)[c] | At weeks 0, 16 and 24; follow-up visits | ELISA | Yes | PASI 50, 75 and 90 responses in AAA-negative vs. AAA-positive patients were 87·3%, 72·7% and 51·8% vs. 38·5%, 23·1% and 0%, respectively ($P < 0·001$) | Not used | 5 | – |
| Takahashi 2013[34] | Prospective cohort study | 16% (5/32) | At week 48 | ELISA | Yes | Mean trough adalimumab levels in AAA-negative and AAA-positive patients were 7·27 and 2·77 μg $mL^{-1}$, respectively ($P < 0·01$) | Not used | – | 5 |
| Mahil 2013[40] | Prospective cohort study | 6% (2/31) | Not specified | ELISA | Not reported | None of the 23 patients with PASI 75 response by 6 months had AAAs. Two of eight patients without PASI 50 response by 6 months were AAA-positive | Not used | – | 5 |

RCT, randomized controlled trial; ELISA, enzyme-linked immunosorbent assay; RIA, radioimmunoassay; PASI, Psoriasis Area and Severity Index. [a]Studies with a score of 0–3 are categorized as lower quality and 4–5, higher quality. [b]Studies with a score of 0–3 are categorized as lower quality and 4–6, higher quality. [c]Denominator calculated based on the percentage and numerator given.

**Table 4** Antiustekinumab (AUAs) antibodies in psoriasis

| Study | Study design | Antidrug antibody prevalence | Testing period | Testing modality | Collected at trough | Relation to clinical efficacy | Neutralizing status | Quality rating (Jadad scale)[a] | Quality rating (observational studies)[b] |
|---|---|---|---|---|---|---|---|---|---|
| Kauffman 2004[16] | Prospective cohort study | 6% (1/18) | At week 16 | ELISA | Not reported | Not specified | AUAs were neutralizing | – | 5 |
| Krueger 2007[42] | RCT | 4·1% (12/293) | To 52 weeks | ELISA | Excess drug removed prior to testing | Not specified | Not specified | 5 | – |
| Papp 2008[43] | RCT | 5·4% (65/1202) | To week 52 | ELISA | Not reported | AUAs were present in 2·0% (12/589) and 12·7% (20/158) of PASI 75 and PASI 50 responders, respectively (P-value not reported) | Most AUAs were neutralizing | 5 | – |
| Griffiths 2010[44] | RCT | 3·8% (32/835) | By week 64 | Not reported | Not reported | Not specified | Not specified | 4 | – |
| Tsai 2011[28] | RCT | 4·4% (5/113)[c] | At week 36 | Not reported | Not reported | At week 28, PASI 75 responses in AUA-negative and AUA-positive patients were 74·5% (79/106) and 60% (3/5), respectively (P-value not reported) | Not specified | 5 | – |
| Kimball 2013[10] | RCT | 5·2% (39/746) | To week 264 | ELISA | Excess drug removed prior to testing | No affect on clinical response. At the week-244 assessment, 4·3% (6/140) of patients lost response in the absence of AUAs and without a decrease in serum ustekinumab (P-value not reported) | 64% of AUAs were neutralizing | 5 | – |

RCT, randomized controlled trial; ELISA, enzyme-linked immunosorbent assay; PASI, Psoriasis Area and Severity Index. [a]Studies with a score of 0–3 are categorized as lower quality and 4–5, higher quality. [b]Studies with a score of 0–3 are categorized as lower quality and 4–6, higher quality. [c]Denominator calculated based on the percentage and numerator given.

study.[10,16,28,42–44] The prevalence of AUAs ranged from 3·8% to 6% (Table 4). Four studies described AUA detection by ELISA, but no studies designated whether samples were collected at trough drug levels. However, two studies reported washing sera of the drug prior to testing samples for AUAs.[10,42] Two studies demonstrated an association between AUAs and lower PASI response.[28,43] Papp *et al.* reported AUAs in 5·4% (65/1202) of patients and documented that most of the AUAs (proportion not specified) were neutralizing.[43] The authors also noted that 12·7% (20/158) of PASI 50 responders were AUA-positive, compared with 2·0% (12/589) of PASI 75 responders, suggesting a trend for decreased treatment response with AUA formation (P-value not reported).[43] Tsai *et al.* reported AUAs in 4·4% of patients (five out of 113).[28] At week 28, 79 (74·5%) of 106 AUA-negative patients achieved a PASI 75 response vs. three of five AUA-positive patients.[28] Concomitant methotrexate was not used in these studies.

## Discussion

This is among the first systematic reviews on the prevalence of ADAs, their relationship to clinical response, and the effect of concomitant methotrexate therapy in psoriasis. Based on the studies reviewed herein, we found great variability in the rate of ADA detection in psoriasis, and this was also observed in other systemic inflammatory diseases such as rheumatoid arthritis (RA), Crohn disease (CD) and ankylosing spondylitis (AS) (Table 5). It is believed that treatment- and patient-related factors including genetics, pharmacokinetics, disease type and drug dosing intervals may contribute to ADA formation. ADAs have been correlated with patients who had higher baseline disease activity, longer disease duration, more severe disease and increased C-reactive protein.[17]

Additional variables that may have contributed to the wide range of detection include the use of different ADA detection assays and timing of serum sample collection in relation to drug administration. ELISA and RIA are two commonly used assays for serum ADA detection. Although specific, ELISA is prone to false negatives because it does not detect IgG4. It also requires both Fab arms of the antibody to be bound to the assay for detection, leading to drug interference if ADAs are bound in immune complexes with the biological agent.[45] The RIA detects more clinically relevant antibodies but has been associated with false positive results.[17,46] A majority of the studies utilized ELISA to detect ADAs, and these assays may be limited by the presence of the drug in the serum samples.[46] ADA development and detection are likely influenced by multiple factors. Further studies are needed to understand better their pathophysiology along with improvement in methods for optimal ADA detection.

Although ADAs were detected at variable rates among different diseases, their effects on treatment response have been shown to be relatively analogous among these diseases.[18,47,48] ADAs have been described as neutralizing or non-neutralizing. Neutralizing antibodies are thought to interfere with the biological agent's binding activity, leading to subsequent diminished clinical response; non-neutralizing antibodies do not interfere with drug–target binding and have no effect on treatment response.[9,49] AIA positivity has been associated with lower serum infliximab concentrations and diminished clinical response in psoriasis, as well as in RA, CD and AS.[26,31,35,36,48,50] No studies of patients with psoriasis, or patients with RA or AS receiving etanercept, have shown any clear association between AEAs and reduced treatment efficacy.[11,25,37–39,47,51,52] Among patients with psoriasis treated with adalimumab, AAA development was associated with lower serum adalimumab levels and lower PASI 75 responses.[12,27,34,40,41] Studies of patients with RA have also described lower serum adalimumab levels and significantly fewer treatment responders associated with AAAs.[47,53,54] For example, Bartelds *et al.* documented median adalimumab concentrations of 1·2 and 11·0 mg $L^{-1}$ in AAA-positive and AAA-negative patients, respectively ($P < 0·001$).[53] The authors also reported that 4% of AAA-positive patients (three out of 76) vs. 34% (67/196) of AAA-negative patients sustained disease remission at week 28 ($P = 0·001$).[53] The effects of AUAs on serum ustekinumab levels and treatment response are unclear. Researchers have reported that some AUAs were neutralizing and suggested an association with diminished response.[10,16,28,42,43] Their impact on the treatment of other immune-mediated diseases was not reported.[55,56] The results herein suggest that ADAs against certain biological agents may modify serum drug levels and influence treatment efficacy.

Different theories have been proposed to explain the clinical effects of ADAs. Structural components of biological agents have been proposed as causes of immunogenicity. Infliximab contains murine components at the drug target's binding sites, likely inducing an antigenic reaction specific to them.[9] In contrast, the binding sites of etanercept are naturally occurring type II (p75) receptors, suggesting immunogenicity against other portions that do not compromise etanercept's therapeutic activity.[9] One study reported that the antiadalimumab response *in vitro* was specifically confined to the TNF-α binding region of adalimumab, leading to functional neutralization of the drug.[49] Another study speculated that ADAs may form immune complexes with the drug, subsequently accelerating drug and ADA clearance given the shorter half-lives of immune complexes compared with free-standing antibodies.[57] The mechanisms behind the neutralizing consequences of ADAs are not clearly understood, but their effects on treatment response are clinically significant.

**Table 5** Antidrug antibody formation in other systemic inflammatory diseases

| | Rheumatoid arthritis | Crohn disease | Ankylosing spondylitis |
|---|---|---|---|
| Infliximab[47,59,62] | 12–43% | 6–73% | 3·0–29·0% |
| Etanercept[18,47,62,63] | 3–5·6% | – | 0% |
| Adalimumab[47,62,64] | 1–17% | 2·6–20·0% | 31% |
| Ustekinumab[56] | – | 0·7% | – |

To prevent potentially decreased response due to ADAs, studies have investigated the use of concomitant methotrexate to optimize treatment response. Among patients with psoriasis, concomitant methotrexate therapy with infliximab or adalimumab has been limited, although the findings suggest favourable results. Methotrexate incorporation into infliximab or adalimumab treatment of RA or CD has been more extensively studied. In a cohort of 101 patients with RA, Maini *et al.* showed that AIAs developed respectively in 15%, 7% or 0% of patients receiving infliximab at 1, 3 or 10 mg $kg^{-1}$ doses, as well as methotrexate 7·5 mg per week.[58] In CD, one study noted AIA incidences of 44% (22/50) in patients receiving concomitant methotrexate vs. 73% in patients receiving infliximab monotherapy.[59] With respect to adalimumab therapy, Weinblatt *et al.* reported that < 1% of patients (two of 209) with RA on both adalimumab and methotrexate developed AAAs.[60] Additionally, one study reported that 84% (84/100) of AAA-negative patients received concomitant methotrexate vs. 52% (11/21) of AAA-positive patients, indicating a decreased prevalence of immunogenicity against adalimumab with concomitant immunosuppressive agents ($P = 0{\cdot}003$).[53] Methotrexate use has not been shown to alter the safety profile of biological treatments in studies with rheumatology patients.[45] Concomitant methotrexate in psoriasis is limited, but its use with biological agents in other inflammatory diseases is seen optimistically.

Although concomitant methotrexate has been associated with less ADA formation in patients receiving infliximab or adalimumab, the mechanism behind this effect has not been elucidated. Studies have proposed that methotrexate acts through a synergistic or anti-immunological effect based on the magnitude of clinical response relative to monotherapy.[45,59,61] The methotrexate concentration administered to patients varied among different studies. Methotrexate coadministration of up to 25 mg weekly with biological agents is commonly used in RA, which may influence the prevalence of ADA formation in RA studies. In CD, supplementary methotrexate use is less defined, and the drug is generally administered on a short-term basis. There are no clear guidelines for prescribing or dosing concomitant immunomodulators.[45] Further studies are needed to determine the optimal concomitant methotrexate dose and duration to reduce ADA formation while minimizing methotrexate toxicity. Data on methotrexate coadministration in RA and CD provide a relevant background for investigating its use with biologics for moderate-to-severe psoriasis. Methods to prevent or counteract ADA development will become increasingly crucial as the use of biological agents for psoriasis continues to grow.

The results of this systematic review need to be interpreted in the context of the primary studies. Inclusion and exclusion criteria may have excluded certain studies, potentially resulting in selection bias that may contribute to differing views on the topics addressed herein. Also, a majority of studies detected ADAs as a secondary end point, and most studies were not powered to detect significant differences among ADA-positive patients. ADA testing in patients who withdrew prematurely from studies and the timing of serum sample collection were variably reported among the studies. Additionally, ADA testing at different intervals and after receiving varying numbers of treatment infusions may influence the ADA prevalence documented in these studies. These factors subsequently lead to possible underestimation of the true prevalence, as those who were not tested may have been ADA positive. Despite these limitations, a majority of studies reported similar conclusions on ADA formation against each biological agent and their respective impacts on treatment efficacy.

In summary, biological agents have been reported to have a favourable benefit–risk ratio in clinical trials. Their use in moderate-to-severe psoriasis will continue to grow, and ADA development will remain a challenge. This is among the first systematic reviews that have examined the incidence of ADA formation and its subsequent effect on therapeutic response to infliximab, etanercept, adalimumab and ustekinumab in patients with psoriasis. Based on the studies reviewed herein, ADAs have been linked to decreased treatment efficacy with infliximab and adalimumab but not with etanercept. The effect of AUAs on treatment response is yet to be determined. Although studies of other inflammatory diseases have reported promising results with concomitant methotrexate use to prevent ADA formation, the dearth of studies examining its use in patients with psoriasis suggests a need for further investigation to determine its utility in this population. Optimizing treatment response remains the primary objective of biological therapies in psoriasis. Therefore, ADAs should be considered an important contributing factor in patients with diminished clinical response to biological agents.

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