Impact of immunogenicity on clinical efficacy and toxicity profile of biologic agents used for treatment of inflammatory arthritis in children compared to adults

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Abstract:

The treatment of inflammatory arthritis has been revolutionised by the introduction of biologic treatments. Many biologic agents are currently licensed for use in both paediatric and adult patients with inflammatory arthritis and contribute to improved disease outcomes compared to the pre-biologic era. However, immunogenicity to biologic agents, characterised by an immune reaction leading to the production of anti-drug antibodies (ADA), can negatively impact the therapeutic efficacy of biologic drugs and induce side-effects to treatment. This review explores for the first time the impact of immunogenicity against all licensed biologic treatments.
currently used in inflammatory arthritis across age, and will examine any significant
differences between ADA prevalence, titres and timing of development, as well as ADA impact
on therapeutic drug levels, clinical efficacy and side-effects between paediatric and adult
patients. In addition, this paper will investigate factors associated with differences in
immunogenicity across biologic agents used in inflammatory arthritis, and their potential
therapeutic implications.

Introduction

The discovery and clinical use of biologic treatments in the management of inflammatory
arthritis in children and adults has been associated with significant clinical benefits as well as
advances in understanding the pathogenesis of different types of inflammatory arthritis.
Immunogenicity to biologic treatments is an unwanted immune reaction against a therapeutic
antigen. This immune reaction generates anti-drug-antibodies (ADA), which could counteract
the therapeutic effects of the biologic treatment and, in rare cases, induce adverse reactions (1, 2).

It has become increasingly recognised that biologic treatment duration, mode, rate and route of
administration, and more specifically the type of biologic therapeutic (e.g. monoclonal
antibodies - mAbs versus recombinant fusion proteins) are all factors that influence the risk of
immunogenicity (3). In addition, individual patient factors, such as genetic background (4),
disease type (5), and concomitant use of disease modifying anti-rheumatic drugs (DMARDs)
(6), all contribute differentially to the formation of ADA. Recent research has been focused on
highlighting the genetic risk for developing ADA: e.g. HLA-DRB1*15 was associated with
increased the risk for developing high ADA levels to interferon (IFN)β-1a treatment in multiple
sclerosis, while HLA-DQA1*05 decreased this risk (7), and HLA-DQA1*05 was associated
with increased ADA prevalence across various biologics and autoimmune diseases (8). Other
factors such as smoking and infections are also associated with increased risk (8, 9), whereas
concomitant use of antibiotics and immunosuppressant medication are associated with
decreased immunogenicity risk (8). In addition, the manufacturing process of various biologic
agents, in particular their contamination with low-level host proteins, is a major contributor to
immunogenicity (10).

Therapeutic drug monitoring and immunogenicity testing comprise measurement of trough
drug levels and ADA. The most widely used ADA detection methods are bridging ELISA
(which use labelled therapeutic mAbs) and radioimmunoassay (RIA), while other new methods such as competitive displacement and tandem mass spectrometry have also been proposed (11). Currently, most mAbs on the market are humanised or fully human; however, they still carry immunogenic risk. This could be attributed to anti-idiotype reactivity, which is a common reaction of the immune system to the appearance of any novel antibody (12).

The molecular mechanisms leading to generation of ADA are not completely elucidated and a detailed discussion of immune mechanisms is beyond the scope of this review (for a recent review see (13)). One basis for ADA generation involves the capacity of the human immune system to recognise “non-self”. Since the first therapeutic mAbs of murine origin were developed, further efforts have now been made to improve their performance and decrease their immunogenicity. The continuous advancement in recombinant DNA technologies has led to the development of chimeric (fused human-murine mAbs) and humanised mAbs. Chimeric antibodies were developed by replacing the constant region of murine mAbs with human components and the humanised mAbs are constituted entirely of human sequences, with the exception of the complementarity determining regions (CDRs) of the variable (V) regions which are of mouse-sequence origin. Subsequently, the advanced antibody engineering achieved the production of fully human antibodies where antigen specificity has been selected either in vivo in genetically modified mice or by antibody engineering processes combined with screening (14). Many factors contribute to differences in immunogenicity, from biopharmaceutical properties related to downstream processing and drug formulation (15) to patient individual characteristics, including the antigen burden which correlates with their disease activity (16).

Both ELISAs and RIAs detect only free circulating ADAs; therefore, they can be associated with false negative results in the context of presence of ADA-immune complexes which are detectable only if they exceed in concentration the circulating drug levels (17, 18). In one study, ELISA was more sensitive in detecting ADA when present in high titres than RIA, while in patients with ADA detected by RIA but not by ELISA only the drug levels were significantly associated with treatment response to adalimumab (19). Interestingly, measuring drug levels and drug clearance alone has also been shown to be a reliable predictor for ADA in RA and juvenile idiopathic arthritis (JIA) patients (20)(21). Several studies concluded that although ADA were not independently associated with treatment response, they may be helpful in determining the cause of low drug levels and guide therapeutic decisions (22, 23).
The presence of ADAs may be associated with reduced clinical efficacy through two main mechanisms. ADA that compete with the cytokine binding site (the Fab fragment of the therapeutic agent) have neutralising properties as they block the pharmacological function of the drug. ADA directed against the Fc fragment (more frequently targeting the junction between Fc and Fab) lead to formation of immune complexes associated with enhanced drug clearance may also influence the clinical response to biologic treatment through leading to sub-optimal (sub-therapeutic) drug levels (24). Therefore, based on their specificity ADA can be grouped as neutralising (when they target the antigen binding sites of the therapeutic drug) or non-neutralising (when they recognize epitopes away from the drug binding site, therefore not directly impairing the efficacy of the drug)(3).

Here we review the evidence of impact of ADA against various biologic therapeutics used for treatment of inflammatory arthritis in adults and children as there are no previous reports investigating immunogenicity across age. This review focuses on depicting differences between ADA prevalence, titres and timing of development, as well as impact on therapeutic drug levels, clinical efficacy and side-effects in children compared to adults with inflammatory arthritis. Where data is available, we will also investigate the clinical predictors for ADA development, as well as the influence of additional DMARD therapy on ADA development and biologic drug retention.

Neutralising ADA against mAbs targeting TNF-α were more prevalent than ADA against fusion proteins (etanercept and biosimilars) while the kinetic of ADA generation varied across anti TNF-α agents in adult and paediatric inflammatory arthritis studies

Many studies have reported the presence of ADA against anti-TNF-α inhibitors used to treat different types of inflammatory arthritis including etanercept (fusion protein of the extracellular ligand-binding portion of the human 75KD p75 TNF receptor (TNFR) linked to the Fc portion of human IgG1), adalimumab (fully human mAb), certolizumab (humanised antibody Fab’ fragment), golimumab (human IgG1κ monoclonal antibody) or infliximab (a chimeric mAb) (Table 1). The general observation is that ADA against etanercept have a lower prevalence compared to ADA against adalimumab or infliximab (25). Furthermore, comparative studies show that ADA to human/humanised (adalimumab, certolizumab,
golimumab) and chimeric (infliximab) anti-TNF-α therapeutic mAbs are largely neutralising (26), while the ADA against etanercept are predominantly non-neutralising (27).

In adults, the rates of ADA formation against infliximab range from 8-62% in rheumatoid arthritis (RA), 15-33% for psoriatic arthritis (PsA) and 6.1-69% for ankylosing spondylitis (AS) (28) (Table 1). ADA against infliximab have also been shown to be associated with lower serum biologic drug concentrations in adult inflammatory arthritis patients (27-35). There is a paucity of studies investigating the timing of development of ADA against various anti-TNF-α agents: evidence suggests that longer exposure to infliximab increases immunogenicity; e.g. ADA against infliximab in adults with RA occurred after the first 10 infusions (23.4 ± 2.4 weeks), while ADA were detected in 25% of JIA patients after 52 weeks and in 37% at 204 weeks (36-38). The dose of biologic agent as well as patients’ age could influence immunogenicity: a higher incidence of ADAs was observed in patients treated with infliximab 3mg/kg (38%), compared to 6 mg/kg (12%) (37), while a significantly higher prevalence of ADA was found in younger children (ADA positive mean age 7.01 years vs. ADA negative 9.88 years, p = 0.003) (39).

The prevalence of ADA against adalimumab has high variability across different types of autoimmune diseases in adults (25, 28, 29, 40-42) and children with JIA (36) (Table 1). The timing of adalimumab ADA development is controversial: in some adult studies ADA prevalence did not increase with treatment duration (43, 44), while in other studies there was a significant increase, with ADA developing between 4.5 months and 12 months of treatment (9, 30, 40, 42, 45, 46). Similarly, studies in JIA showed both trends: a significant increase of ADA with time (36) or no correlation with treatment duration (47), suggesting that ongoing monitoring to establish their clinical relevance and impact on management is required.

Etanercept treatment was associated with a lower ADA rate than infliximab and adalimumab (25) (Table 1), with the vast majority of adult studies reporting no detectable ADA (25, 27-29, 31, 40, 42, 46). This pinpoints that the chemical structure of the anti-TNF-α therapeutic agent (fusion protein versus mAb) is likely to be a key factor in inducing drug immunogenicity. When detected, ADA against etanercept were found to be non-neutralising in both adults and paediatric studies (28, 36). ADA prevalence increased with treatment duration with a corresponding decrease in etanercept drug levels over time in JIA (48, 49).
A highly sensitive ELISA test detected ADA against golimumab in 31.7% of patients with RA, PsA and AS in comparison with standard ELISA which detected ADA only in 4.1% (50), while their prevalence varied across adult studies (Table 1). The impact of ADA on serum golimumab concentrations was consistent in JIA and RA studies, whereby higher ADA titers were associated with lower drug concentrations (28, 51-53). This was generally shown at ADA titres >1:1000 in JIA (51), and in adults, median peak titres ≥100 were associated with undetectable or very low drug levels (59). Interestingly, in another study in PsA, which used a standard assay, the golimumab dose (50mg vs. 100mg) did not appear to affect the ADA rates, which remained low for the whole duration of the study through to week 52 (4.9%) (54).

There are fewer studies investigating the presence of ADA against certolizumab (55, 56), although in both studies, ADA were associated with lower drug levels (Table 2). A more recent study, however, reported that there was no significant correlation between ADA and certolizumab drug levels (r =-0.471, p=0.122). There is evidence that ADA were still detected at higher certolizumab concentrations of >10mg/l (57). The majority of patients with ADA had detectable titres from week 16 onwards and 65% remained ADA positive after one year of follow up (57). There are no studies in paediatric populations.

When anti TNF-α agents have been studied comparatively in adults, there was evidence of increased prevalence of ADA against infliximab compared to adalimumab (25.3% vs 14.1% respectively), as well as between adalimumab and golimumab (14.1% vs 3.8%) (25). Similar trend was found in a meta-analysis of biologic agents in JIA, where the pooled prevalence of ADA against infliximab was 36.6% compared to 21.8% for ADA against adalimumab (36). As mentioned above, the prevalence of ADA against golimumab seems to be higher in children (46.8%) but based on limited evidence (51).

Variable impact of ADA directed against anti TNF-α treatments on clinical efficacy: loss of efficacy to adalimumab and infliximab was consistently found in children and adults who developed ADA

Various studies in RA, PsA, AS provided evidence for an association between the presence of ADA against adalimumab and loss of clinical efficacy or diminished clinical response (23, 28, 29, 40), while other studies found no association (43, 44) (Table 1). The impact of ADA on the
trend of inflammatory markers is not clear; some studies found higher ESR and CRP in patients
who had detectable ADA (27, 29), whereas other studies found no such association (43). In
addition, the presence of both ADA and low adalimumab concentration at 3 months were
together significant predictors of poor response at 12 months (40, 42). However, the risk of
flares following various adalimumab tapering strategies in RA did not seem to be influenced
by the adalimumab serum levels or ADA prevalence (58).

A higher proportion of ADA positive JIA patients treated with adalimumab experienced loss
of response and more clinical relapses than those without ADA (28, 47). In JIA, it was noted
that transient ADA (defined as measurable ADA on up to two consecutive time points which
disappeared on subsequent measurements without having any impact on treatment efficacy of
toxicity) were not associated with diminished response to medication, whereas permanent
ADA did lower treatment response (45).

Most adult rheumatology studies found no detectable ADA against etanercept (27, 30). It has
been suggested that neither etanercept concentrations nor ADA positivity correlated with JIA
activity or remission states (48).

A meta-analysis of 9 studies of infliximab in adult autoimmune diseases found that the presence
of ADA decreased the odds of response by 58% (25). After 52 weeks of treatment with
infliximab, non-responder RA patients were significantly more likely to be ADA positive (34).

Adult RA studies found that ADA against golimumab were associated with a poorer clinical
response (28, 52). ADA positive RA patients (15.2% at 24 weeks) had a worse EULAR
response and higher DAS-28 compared to ADA negative patients (52). However, one study
which utilised a more sensitive method of ADA detection (drug-tolerant enzyme immunoassay,
DT-EIA) in adults, reported no effects of ADA to golimumab on clinical responses at 24 and
52 weeks, across RA, PsA and AS (50). This highlights the importance in sensitivities of assays
used. Studies in children with JIA found that ADA to golimumab did not appear to have impact
on clinical responses (59) (51). Brunner et al., reported that none of the 8 JIA patients found
with high ADA titres >1:1000, experienced flares (51).

ADA against certolizumab appeared to have an impact on RA clinical response at 3 months,
where the majority of ADA positive patients were non-responders (56), but there was no
independent correlation with the 12 month EULAR response (55), suggesting that there was a
time-dependent relationship. There are no paediatric studies.

A meta-analysis performed on 12 observational prospective cohort studies in adults evaluated
that the development of ADA reduced the anti-TNF response rate (RR) by 68% (RR = 0.32,
95% CI 0.22, 0.48)(60), while in children with JIA, a qualitative analysis found that antibodies
to infliximab and adalimumab were associated with treatment failure (36).

**Additional methotrexate treatment decreased the rate of ADA formation against anti
TNF-α treatments**

Generally, for both adults and children, concomitant DMARD therapy was beneficial and
resulted in a decrease in ADA positivity, but the impact of DMARDs on ADA formation was
not always analysed to enable reliable conclusions (9, 47) (Table 1). Most studies looked at
concomitant methotrexate (MTX) therapy but azathioprine, leflunomide and mycophenolate
have also been shown to be associated with lower ADA prevalence, suggesting that all
DMARDs may be associated with benefits against drug-induced immunogenicity (23, 28, 42)
(31). Unfortunately, none of the studies evaluated comparatively the impact of individual
DMARDs on immunogenicity in inflammatory arthritis because of small numbers of patients
on DMARDs other than MTX, and because some patients were treated with more than one
conventional DMARD. Concomitant use of MTX was associated with lower rates of ADA
against infliximab in RA (28, 31, 32, 40, 61). Moreover, RA patients treated with infliximab
were less likely to develop ADA if they received high biologic doses/induction therapy, or if
they received continuous versus intermittent therapy (28, 30, 32, 61, 62). A RCT of infliximab
plus MTX for the treatment of JIA, found that more patients achieved clinical response in the
ADA negative group (79% vs. 67%) (37).

Similar evidence has been found in children, with studies suggesting a protective effect with
the addition of MTX (36, 45, 59). Interestingly, DMARD use in children was found to be
significantly lower in those who developed permanent ADA to adalimumab (45). It has also
been suggested that MTX reduces immunogenicity against adalimumab in a dose dependent
manner (30, 40), as patients who did not develop ADA were on a higher MTX dose (46).
However, a paediatric study found that there was no difference in ADA rates in JIA patients
with longer exposure to MTX (47).
In adults, concomitant use of MTX was associated with lower incidence of ADA to golimumab (28, 50, 63). A study found that the mean trough golimumab level at 24 weeks was comparable in ADA positive vs. negative patients, with or without concomitant MTX (63).

ADA against infliximab and adalimumab have been associated with side-effects to therapy

In both adults and children, there was no clear consensus on whether ADA have an impact on safety (Table 1). As expected, most reports included a small number of cases experiencing side-effects. Adverse events more frequently mentioned included injection site or infusion reactions, serum sickness and thromboembolic events. Some studies suggested that adverse events occurred more frequently in patients with ADA to adalimumab (28, 29, 62) with others showing no significant differences (27, 44). In paediatric studies, despite limited information available, no association between the presence of ADA and adverse events was reported (36). There was a suggestion of a possible increase in minor upper respiratory tract infections in children with detectable ADA, however, this conclusion was limited by the small sample size (45).

ADA against infliximab have been reported to confer a higher likelihood of adverse drug reactions (25, 28, 30, 32, 35, 40, 62). In a RA study (35), ADA positive patients had an increased risk of adverse drug reactions compared with ADA negative patients over 52 weeks [21 (18%) vs. 7 (7%), P < 0.018] (40). Similarly, JIA infusion reactions to infliximab were more commonly seen in ADA positive patients (58% vs 19%) (37). A retrospective chart review of children with JIA and paediatric inflammatory ocular diseases found that patients with ADA had a 15-fold increased risk of infusion reactions to infliximab compared to patients without ADA (39). This study also found that ADA positive children were significantly younger (mean age 7.01 vs. 9.88 years, p = 0.003).

Limited data were available regarding the impact of immunogenicity against etanercept on safety. Studies across age did not report an association between ADA positivity and adverse events (36, 59). In JIA studies, the proportion of patients with ADA did not differ between responders and non-responders to etanercept (48).
Studies in both paediatric and adult populations did not report an association between ADA and adverse effects to golimumab (51, 52, 59). Similarly, multiple adult studies reported no association between the presence of ADA against certolizumab and adverse effects (55-57); in addition, RA patients who experienced adverse effects did not have ADA (55, 56).

**Immunogenicity to anti TNF-α biosimilars is similar to or lower than that of their originators**

Biosimilars are new biological products which are highly similar to their biological reference drug and have comparable clinical efficacy. At present, the use of biosimilars in JIA is limited, thus the majority of evidence related to their immunogenicity is available from adult studies. Multiple studies have shown similar clinical efficacy and immunogenicity profiles when comparing biosimilars with their reference products (28, 64-72). For example, ADA positive CT-P13 (an infliximab biosimilar) patients showed less clinical improvement (28). ADA against infliximab and adalimumab biosimilars were associated with lower drug concentrations (69)(75). The PLANETRA study found that peak serum CT-P13 concentrations were reduced in the ADA positive group ($C_{\text{max}} = 85.1 \mu g/ml$) compared to the ADA negative subset ($C_{\text{max}} = 96.7 \mu g/ml$) (69). One meta-analysis reported on the pooled response rates (RR) of ADA against anti TNF-α biosimilars compared to their reference product (66). There were no significant differences in ADA formation rates between the infliximab and adalimumab biosimilars and their reference drugs at 24-30 weeks. The etanercept biosimilars showed significantly lower rates of ADA formation compared to the reference product, with a pooled RR = 0.05 at 24-30 weeks (66). A study of etanercept biosimilar GP2015 did not detect any neutralising ADA, and all ADA responses were transient (absent by week 24) (72).

**Clinical relevance of ADA against other biologic agents in adult and paediatric inflammatory arthritis studies**

ADA against abatacept are mainly non-neutralising and do not have significant impact on clinical efficacy unless treatment is temporarily discontinued.
The prevalence of ADA to fusion proteins, such as abatacept (which comprises a Fc region of IgG1 fused to the extracellular domain of CTLA-4) is generally acknowledged to be lower than to therapeutic mAbs. The prevalence of ADA to abatacept ranged from 1-20% in adult studies (28, 30, 41, 73), and from 8.7-23.3% in paediatric studies (36) (Table 2). Younger children with JIA (2-5 years) had a higher prevalence of ADA than older children (6-17 years) (74). One JIA study compared the prevalence of abatacept specific ADA with anti- CTLA-4 specific antibodies and found the latter to be much higher (1.2% vs. 20.7%) (75). In terms of timing of the development of ADA in children, one study found that ADA concentration increased with a longer time of exposure to abatacept (76), whereas another found no increase with continued exposure (77).

Similar to etanercept, abatacept generated ADA which bind to the Fc fragment (hinge region) and have no neutralising activity (28). Non-neutralising ADA decreased the circulating levels of abatacept by enhancing drug clearance in adults (30, 41). In children, ADA were also found to be non-neutralising but were not found to be associated with low abatacept concentrations (75, 76).

No loss of efficacy due to ADA against abatacept was found in JIA studies (36, 75-77), while in contrast, in adults with RA, intermittent treatment discontinuation led to higher incidence of immunogenicity and loss of clinical response (73). It was observed that adult patients who discontinued the treatment temporarily had a higher ADA rates than those on continuous treatment (7.4% vs 2.6% respectively) (30). Similarly, ADA were more frequent in children with JIA who interrupted treatment and had abatacept concentration below therapeutic levels, suggesting that higher treatment doses may be beneficial against immunogenicity (75).

Some adult studies suggested that intravenous therapy was associated with less immunogenicity than subcutaneous administration (28),(78), while other studies found no difference (30). In JIA, no difference was found between the two routes of administration (36).

In RA, concomitant MTX therapy did not significantly affect immunogenicity (73). In paediatric studies the impact of MTX has not been studied (36). Reassuringly, ADA against abatacept were not associated with increased risk for injection site reactions, hypersensitivity or any other safety concerns (36, 73, 75, 76), even when patients have been followed up to 7 years (77).
ADA against B cell targeted therapies are dose-dependent and have impact on clinical
efficacy and risk of adverse reactions

Rituximab is a chimeric mAb against CD20. There have been no paediatric studies
investigating the relevance of ADA against rituximab. However, ADA against rituximab have
been reported in 0-21% of adult RA patients (28). Additionally, ADA have been found to be
associated with a reduced treatment response and higher rates of treatment serious adverse
events (28, 79). Lower serum rituximab concentrations have been reported in ADA positive
patients compared to ADA negative patients in RA (80). Moreover, the use of higher rituximab
doses and induction therapy have been associated with a decreased incidence of ADAs in RA
(28).

A meta-analysis reported that the pooled RR of ADA formation for rituximab biosimilars was
0.86 at week 24-28 (67). Of note, the pooled RR of neutralising ADA formation at the same
time point was 1.16. Neutralising ADA were also of a very low incidence at week 72 in the
rituximab biosimilar CT-P10 (68). Multiple studies have demonstrated a similar side effect
profile for biosimilars, as higher rates of infusion-related reactions were present in ADA-
positive patients compared to ADA-negative patients (28, 64, 65, 70, 71) (Table 2).

Neutralising ADA against tocilizumab have no clear impact on clinical efficacy and
potential on side-effects in adults, while there is a trend for clinical impact in children

Tocilizumab is a humanized mAb against the interleukin-6 receptor (IL-6R). Several studies
have reported low ADA rates in RA patients (28) (81, 82). ADA positivity has been recorded
in 1.5% and 1.2% of RA patients receiving intravenous and subcutaneous tocilizumab
respectively, with a high proportion of these being neutralising ADA (83) (Table 2). The rate
of ADA formation has not been seen to significantly differ in tocilizumab monotherapy versus
combination therapy with conventional synthetic DMARDs (83). No correlation has been
found between ADA rates and adverse events or a reduced treatment efficacy in adults (41,
83). Similarly, low levels of ADA to tocilizumab have been reported in JIA patients, with a
pooled prevalence of 2.3% across four studies (36). However, neutralising antibodies against
tocilizumab in JIA have indeed been shown to correlate with treatment failure, as well as with
infusion and hypersensitivity reactions (36, 84). Yokota et al. (84) found that out of five JIA
patients treated with tocilizumab who developed ADA, four (80%) withdrew from the study due to infusion reactions.

**ADA to sarilumab seem to have limited impact on clinical efficacy and no impact on adverse events**

Sarilumab is human recombinant mAb that blocks both the soluble and membrane-bound IL-6 receptor, similarly to tocilizumab, but with a higher affinity. Currently there are no studies of immunogenicity in paediatric populations. The presence of ADA did not appear to affect clinical efficacy in various trials (85-87). The MONARCH trial demonstrated that only 2.7% of RA patients had persistent ADA, however, no neutralising ADA were detected (85). It has been suggested that ADA against sarilumab are in majority of cases transient (88). Xu et al. described a trend towards higher apparent linear clearance of sarilumab when ADA were present (89). In addition, patients with persistent ADA had a lower mean drug levels compared to ADA negative patients. At a dose of 150mg, treatment-emergent ADA incidence was 24.6% compared to 18.2% at a higher dose of 200mg. Of those who had persistent ADA, the incidence of neutralising ADA was also higher in the group receiving 150mg sarilumab compared to 200mg (10.8% and 3.0% respectively) (86). Multiple studies have shown that ADA positivity was not associated with a higher incidence of adverse effects (85) (86, 87). Hypersensitivity reactions occurring during treatment were reported in 8.0% of ADA-negative patients and in 3.1% of ADA-positive patients (87).

**Neutralising ADA against IL12/23 blockade have low prevalence but possible impact on clinical efficacy in inflammatory arthritis**

Ustekinumab is a human immunoglobulin G1κ monoclonal antibody against common sub-unit p40 of IL-12 and IL-23. The prevalence of ADA was 8-11% in psoriatic arthritis adult patients treated with ustekinumab (28). Moreover, a study evaluating the efficacy of subcutaneous ustekinumab in the treatment of RA reported that 7/123 (5.7%) of patients had ADA, while 4/123 (3.3%) had neutralising ADA (90). In this study, serum concentrations of ustekinumab were generally lower in ADA positive patients (90) (Table 2). There is evidence that neutralising ADA against ustekinumab were associated with lower drug levels and loss of clinical efficacy in psoriasis and Crohn’s disease (91, 92), suggesting overall that they may
have similar impact in inflammatory arthritis. The relevance of ustekinumab immunogenicity is yet to be studied in children.

Very low prevalence of ADA against IL-17 blockade has been reported and no impact on side-effects or clinical efficacy

Secukinumab is a mAb targeting IL17A. The treatment is not licensed for children. In a recent systematic review, the prevalence of ADA against secukinumab was 0-1% (28). A study evaluated the prevalence of ADA at 52 weeks in patients with psoriasis, PsA and AS treated with secukinumab and found it to be <1%; ADA were not associated with loss of efficacy, changes in drug levels or adverse events (93).

Ixekizumab is a humanized mAb which targets IL17A used for the treatment of plaque psoriasis, PsA and AS. The prevalence of ADA was 5.3% (94) and 9% (95) in adult patients with psoriasis and PsA, and they occurred within the first 12 weeks of treatment (95). ADA were found to be non-neutralising and did not correlate with the rate of adverse reactions (Table 2). Patients with psoriasis or PsA who developed ADA against ixekizumab had low and constant titres, which did not significantly impact clinical response. No data in children are available.

ADA against IL-1 blockade do not have significant impact on clinical efficacy or side-effects

Anakinra is a recombinant a human IL-1 recombinant receptor antagonist initially trialled in RA, where it has been associated with a prevalence of ADA ranging from 50.1 to 70.9% (96, 97). Similar to other recombinant proteins, only a small proportion of ADA were neutralising (25/1240, 1.9%) (96) (Table 2). Of these 25 RA patients, 13 (52%) reported disease progression; however, no relationships were found between neutralising antibody status and the occurrence of severe allergic reactions, malignancies, opportunistic infections, or serious infections (96). One study assessing the efficacy of anakinra in patients with JIA found that the prevalence of ADA increased from 75% at 12 weeks to 82% at 12 months (98). At 12 weeks, all 4/64 (6%) of patients who had neutralising antibodies to anakinra were non-responders to treatment (98). However, non-neutralising antibodies to anakinra were not
associated with a reduced response to treatment (98). There have been no studies analysing the
association between ADA to anakinra and adverse events in JIA.

Canakinumab is a fully human mAb against anti-IL1-β used in systemic-onset JIA (soJIA).
Studies in children with systemic JIA found a prevalence of ADA against canakinumab of
3.1% (6/196) (99), and 8% (100), and ADA had no neutralising capacity and did not affect the
drug levels or the rate of side-effects.

Rilonacept is a fully human dimeric fusion protein that acts as a soluble decoy receptor which
blocks IL-1β. An RCT in soJIA did not find an association between ADA positivity and clinical
response (101). This trial found that 54.2% (13/24) of patients developed ADA during the 23-
month period of open label treatment (following a 4-week double blind treatment phase). There
was no correlation between ADA positivity and plasma levels of rilonacept (101). Although
the sample size was small, this study noted that the patients who developed ≥3 injection site
reactions were all ADA positive, thus suggesting that there is an association between ADA and
adverse effects.

Conclusion:

Immunogenicity to biologic treatment has been investigated in various types of inflammatory
arthritis in children and adults. The overall impression is that immunogenicity to biologics used
in rheumatology was not particularly confounded by clinical indication or significantly affected
by patients’ age (Table 3). However, a direct comparison between the studies evaluated by this
report is not possible, because of the high study heterogeneity, low number of studies
investigating less commonly used biologic treatments and high variability between the methods
of ADA detection and time-points of ADA measurements, study design and concomitant MTX
therapy.

As there are some differences between the biologic agents approved for use in paediatric versus
adult rheumatic diseases, in some cases there were no data available to enable comparisons
between the two populations (e.g. certolizumab, sarilumab, secukinumab, ustekinumab and
ixekinumab have no studies in children, while rilonacept and canakinumab are not commonly
used in adults). The discrepancy found between the rate of ADA against golimumab is not easy
to interpret, because they have been investigated only in one study in JIA.

This literature review provided evidence for variable prevalence of ADA depending on the
study methodology, sample size, time-points for sample evaluation, concomitant DMARD
therapy as well as laboratory assays used for ADA detection. Overall, the highest ADA
prevalence was found in patients treated with mAbs against TNF-α and recombinant human
IL-1 receptor antagonist (anakinra), although the impact of ADA on clinical efficacy was
clearly influenced by their neutralising properties and impact on drug levels. In contrast to
immunogenicity to IL-1 blockade, which had minimal or no impact on clinical efficacy as the
proportion of neutralising ADA was very low, ADA against adalimumab, infliximab,
certolizumab, and to a certain extent golimumab had a significant impact on clinical efficacy.
As a consequence, the choice of biologic therapeutic agent in a certain patient influences their
immunogenicity monitoring strategy.

All mAbs against TNF-α (and their biosimilars) were associated with higher prevalence of
ADA than etanercept (a fusion protein) and this is probably explained by the structure of the
biologic agent as well as frequency of administration, which in the case of etanercept ensures
a more constant serum drug levels. It is recognized that anti-idiotypic ADA against therapeutic
mAbs usually target the drug binding site as this does not belong to the patient immunoglobulin
repertoire, therefore these ADA have neutralising properties with impact of drug efficacy and
they are clinically relevant (62). The detection of neutralising ADA in certain patients should
be monitored and correlated with clinical response and drug levels to guide further therapeutic
decisions (102). Neutralising ADA have been found in patients treated with adalimumab,
infliximab, certolizumab pegol, and golimumab, as well as tocilizumab, ustekinumab and
secukinumab.

By contrast, in the case of fusion proteins which comprise a naturally occurring receptor fused
with the constant region of human Ig, the immunogenicity process is primarily triggered by the
recognition of the fusion part of the molecule with no direct impact on the drug binding site.
Overall these therapeutic agents were associated with less immunogenicity, although
neutralising ADA against fusion proteins have also been described with both etanercept and
abatacept (103, 104), suggesting that their monitoring could be relevant in selected categories
of patients, especially if the treatment has been discontinued temporarily.
Despite the potential side-effects associated with the presence of ADA overall, irrespective of their neutralising properties, detection of ADA does not preclude loss of clinical response as long as it does not reduce the serum concentration of the biologic agent below the therapeutic threshold (62), therefore monitoring of ADA without drug levels has no clinical relevance.

High ADA concentration correlated with lower drug levels and impact on clinical efficacy when patients of all ages were treated with adalimumab, infliximab, golimumab, certolizumab, rituximab, abatacept, anakinra, canakinumab, and possibly ustekinumab, while the presence of ADA had less impact on clinical efficacy in adult patients treated with IL-6 and IL-17 blockage and children treated with rilonacept (IL-1β decoy receptor). Patients with higher ADA titers and lower or not/detectable drug levels are probably at risk of losing clinical efficacy and need to be monitored more closely.

It is clinically important to take into consideration the fact that not all detectable neutralising ADA had impact on clinical outcomes (e.g. tocilizumab ADA lowered treatment response in children with JIA but less in adults with RA). Neutralising ADA were more commonly found in patients treated with mAbs compared to fusion proteins; however, not all ADA against mAbs had neutralising properties or impact on clinical efficacy (e.g. ADA against ixekizumab were predominantly non-neutralising and did not influence clinical response).

The timing of developing ADA varied according to the type of biologic treatment and patients’ age. Patients developed ADA against adalimumab earlier in their disease course, while ADA in children with JIA treated with abatacept increased with longer time exposure to the drug. Although data from paediatric studies are scarce overall, studies found that younger age in children with JIA was associated with a higher prevalence of ADA as well as side-effects to certain biologics, suggesting that caution in monitoring younger patients is advisable.

There is good evidence that higher doses of rituximab and infliximab, as well as more regular administration (as in the case of etanercept) were associated with lower ADA prevalence, suggesting that medication discontinuation and tapering biologic treatment doses could have impact on clinical efficacy. Monitoring patients’ compliance and taking into consideration their dosing regimen, route and frequency of biologic medication administration are important aspects of immunogenicity risk assessment. Increasing treatment dose as well as switching to
IV formulations can lower the ADA and restore treatment response, therefore these are useful therapeutic strategies to address the clinical impact of drug-induced immunogenicity.

In addition, the large variability of ADA levels against biologic agents detected in various adult and pediatric studies of inflammatory arthritis is very likely influenced by the sensitivity of the assay used, concomitant MTX dose, time point of sample collection, as well as patients’ characteristics (genetic background, smoking, age). The overall impact of ADA on drug efficacy, as well as therapeutic drug monitoring are particularly relevant in guiding future therapeutic strategies of tapering biologic treatments in inflammatory arthritis patients (102, 105), although further research related to their impact on clinical decision making is required (16, 58).

Based on data available in the literature, concomitant treatment with MTX to address the risk of immunogenicity is recommended in patients treated with abatacept, infliximab, golimumab, while in the case of treatment with etanercept, abatacept and tocilizumab the impact of additional MTX is not significant.

We propose a potential strategy for drug immunogenicity monitoring for improved clinical benefit (Figure 1). The main clinical instances when ADA and drug levels should be monitored is loss of clinical efficacy, monotherapy with biologic agents recommended to be prescribed in addition to MTX, clinical reasons for frequent dose intermittent discontinuation, in patients who tapered biologics (especially administered subcutaneously), patients who develop infusion/injection reactions and other side-effects to therapy. Further research especially focused on patient individual risk to develop immunogenicity to biologics is required to enable personalized therapy selection.

Acknowledgments: ECJ and CC are supported by NIHR UCLH Biomedical Research Centre grants (BRC772/III/EJ/101350 and BRC525/III/CC/191350). LC is supported by UCL & Birkbeck MRC Doctoral Training Programme. This work was performed within the Centre for Adolescent Rheumatology Versus Arthritis at UCL UCLH and GOSH supported by grants from Versus Arthritis (21593 and 20164), GOSCC, and the NIHR-Biomedical Research Centres at both GOSH and UCLH. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.
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| Author et al., year [ref] | Country | Type of study (including meta-analyses) | Number of patients treated with a certain biologic | Type of inflammatory arthritis | Disease duration | Prevalence of ADA | Impact of additional DMARD therapy on ADA prevalence | Impact on clinical efficacy | Impact on side-effects to biologic therapy |
|--------------------------|---------|----------------------------------------|-----------------------------------------------|-----------------|-----------------|-----------------|-------------------------------------------------|-----------------------------|---------------------------------|
| Strand et al., 2017 [28] | Systematic review | RA N= 1282 PsA N= 59 JIA N= 23 AS = 204 | RA (35-64) PsA (43-55) JIA (3-14.2) AS (30-48) | RA: 1-34 PsA: 5-21 JIA: 1-5 AS: 4-15 | RA 0-51%; PsA 0-54% JIA 6-33%; AS 8-39% Concomitant use of MTX, AZA, leflunomide or MMF was associated with lower rates of ADA in RA, JIA, AS | ADA was associated with less improvement of disease activity for RA, PsA and AS. A higher proportion of ADA+ve JIA patients experienced loss of response than ADA-ve patients (no P value reported). | Adverse events occurred more frequently in ADA+ve patients compared to ADA-ve (27% vs 15%, no P value reported) |
| Doeleman et al., 2019 [39] | Systematic review and meta-analysis | N= 355 | JIA 10.5 | 3.45 | Pooled prevalence of 21.5% (95% CI = 14.1 – 29.8) Addition of MTX reduced the risk of ADA development by 67% (RR 0.33) | Increased median disease activity score in patients with ADA was found (no P value reported) | No association with adverse events generally was found, but in patients with JIA-associated uveitis, ADA were associated with a significantly higher severity of uveitis (no P value reported). |
| Marino et al., 2018 [47] | Italy Prospective observational study | N=27 | JIA Age at inclusion 9.5±3.32 ADA+ve 11.15 ± 3.11 | 4.79± 3.04 | Overall prevalence 37% 31% vs. 45% in MTX+ve vs. MTX-ve groups. No impact of MTX treatment duration on ADA development was found -22.9 months | ADA+ve patients experienced more relapses, P<0.017. 30% of ADA+ve patients were in clinical remission, | No infusion reactions or side effects were found |
| Study | Location | Study Design | N | RA | SpA | ADA-ve Rate | ADA+ve Rate | ADA-ve vs. ADA+ve | Conclusion |
|-------|----------|--------------|---|----|-----|-------------|-------------|------------------|------------|
| Maid et al., 2018 [29] | Argentina | Cross-sectional study | 52 | 56.5 (13.3) | 36.5% | 36% of MTX+ve patients and 38% of MTX-ve patients tested positive for ADA | ADA-ve patients had a tendency towards better clinical outcomes than those who were ADA+ve – 39.4% of ADA-ve patients achieved an HAQ-DI score <0.5, compared to only 31.6% of ADA+ve patients (comparative statistics were not performed) | Injection site reactions were reported by 6.3% in the ADA-ve group and 4.3% in the ADA+ve group (no p-value reported) (combined data for adalimumab, infliximab and etanercept) |
| Balsa et al., 2018 [31] | Spain | Cross-sectional, observational study | 217 | RA = 56.3 (12.1) | 25.5% | RA: 25.5%; SpA: 32.7% | 82.5% ADA+ve patients had no detectable drug levels in the serum. Only one ADA+ve patient reported drug concentrations within the normal range. No p-value reported. | Data not available |
| Quistrebert et al., 2019 [9] | Europe | European retrospective multi-cohort analysis | 240 | RA = 50.3 | 19.2% | 96.6% of patients were MTX+ve, but study was not powered to analyse the effects | ADA positivity was significantly associated with a lower probability of a good clinical response based on 278 clinical observations from 215 patients (hazard ratio = 0.58, 95% CI 0.39–0.86) | Data not available |
| Verstegen et al., 2020 [62] | Systematic review | JIA | 103 | Data not available | 6.7%-37% | Concomitant treatment with MTX showed a protective effect against ADA development for ADA to adalimumab were associated to impaired clinical outcome (no comparative statistics performed) | Data not available |
| Skrabl-Baumgartner et al., 2019 [45] | Austria Prospective observational study | JIA | JIA data not available | Duration of JIA-associated uveitis 3.5±3.5 | 45% (including permanent and transient ADA) Concomitant use of DMARDs significantly lower in group with permanent ADA+ve (2/7) vs ADA-ve (10/11) – p<0.05 | 7/8 who had a loss of response had permanent ADA. Transient ADA were not associated with a diminished response (no comparative statistics performed) | No severe adverse reactions were found. |
|----------------------------------|----------------------------------------|-----|------------------------|------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------|-----------------------------------------------|
| Moots et al., 2017 [27]         | Multinational non-interventional study | RA  | Symptom duration 9.3±8.43 | RA 31.2% | Significant differences between patients with and without detectable ADA were observed in ESR (p=0.008) and CRP (p=0.0011). When data for all three TNF inhibitors were pooled, a greater proportion of patients without detectable ADA (226/484; 46.7%) than those with detectable ADA (29/94; 30.9%) were in remission (p=0.0046). | No differences in safety outcomes were reported |

**Infliximab and biosimilars**

| Strand et al., 2017 [28] | Systematic review | RA (35-64) PsA (43-55) JIA (3-14.2) AS (30-48) | RA: 1-34 PsA: 5-21 JIA: 1-5 AS: 4-15 | RA 8-62%; PsA 15-33%; JIA 26-42%; AS 6.1-6.9%; Concomitant use of MTX, A2A, leflunomide or MMF is associated with lower rates of ADA in RA | ADA+ve patients showed less improvement in disease activity and were less likely to achieve clinical responses (RA, PsA, AS) - (no comparative statistics performed) | Increased risk of treatment discontinuation due to adverse events and higher rates of infusion reactions were reported in ADA+ve patients (no comparative statistics performed) |
| Authors, Year | Country/Study Design | RA Study & SpA Study | RA & SpA Data | ADA Data | Clinical Outcomes | Notes |
|---------------|----------------------|----------------------|---------------|-----------|------------------|-------|
| Maid et al., 2018 [29] | Argentina | Cross-sectional study | N=13 | RA 55.5 (10.6) | 13.1±8.5 | 30.8% 22.2% of MTX+ve and 50% of MTX-ve patients had ADA | ADA-ve patients had a tendency towards better clinical outcomes than those who were ADA+ve – no comparative statistics were performed due to low numbers. |
| Balsa et al., 2018 [31] | Spain | Cross-sectional, observational study | N=188 | RA and SpA RA = 56.3 (12.1) SpA = 47.9 (11.5) | RA = 13.9 ± 8.7 SpA = 12.5 ± 10.2 | RA: 21.1%; SpA: 31.3% No significant difference between the two patient groups (p=0.114) Concomitant use of DMARDs associated with lower ADA – ADA-ve 29/130 (22.3%) vs 22/58 ADA+ve (37.9%); P = 0.021 | 78.4% ADA positive patients had no detectable drug in the serum. Only one ADA+ve patient reported drug concentrations within the normal range. No p-value reported. |
| Quistrebert et al., 2019 [9] | European retrospective multi-cohort analysis | N=126 | RA 50.6 | 2.65 | RA 29.4% ADA were detected more frequently in infliximab-treated patients (29.4%) than in adalimumab-treated patients (19.2%). | ADA positivity was significantly associated with a lower probability of a good clinical response based on 149 clinical observations from 125 patients (hazard ratio = 0.61, 95% CI 0.32–0.76) |
| Ruperto et al., 2007 [36] | Multicentre RCT | N=122 | JIA 11.2 | 3.9 | 25.5% | Infusion reactions were observed in 58% of ADA+ve patients compared to 19% of ADA-patients. Serious infusion reactions additionally occurred in 20% of ADA+ve patients, |

Injection site reactions were reported by 6.3% in the ADA-ve and 4.3% in the ADA+ve group (no p-value reported.) (combined data for adalimumab, infliximab and etanercept)
| Study | Design | Patient Group | Infusion-Related Reactions | ADA+ve Patients | Comparison |
|-------|--------|---------------|---------------------------|----------------|------------|
| Ruperto et al., 2010 [37] | Multicentre open-label extension study N= 78 | JIA | Data not available | 37% (+32% inconclusive) | Data not available |
| | | | | | 32% patients had ≥1 infusion-related reaction, with a higher occurrence amongst patients who were ADA+ve (15/26 [58%] ADA+ve patients had infusion-related reactions). No comparative statistics performed |
| Moots et al., 2017 [27] | Multicentre noninterventional study N=196 | RA | 60.7±13.01 | Symptom duration 10.0±10.11 | RA 17.4% |
| | | | | | 95/184 (51.6%) were in low disease activity, of which 14/32 (43.8%) had detectable ADA and 81/152 (53.3%) had no detectable ADA (P = 0.3387). Significant differences between patients with and without detectable ADA were observed in ESR (p<0.0001) and CRP (p=0.0001). No significant correlation between adverse events and ADA was found. |

**Etanercept and biosimilars**

| Study | Design | Patient Group | RA % | PsA % | JIA % | AS % | RA % | PsA % | JIA % | AS % |
|-------|--------|---------------|------|-------|-------|------|------|-------|-------|------|
| Strand et al., 2017 [28] | Systematic review RA N=589 PsA, JIA, AS N = not available | RA (35-64) PsA (43-55) JIA (3-14.2) AS (30-48) | RA: 1-34 PsA: 5-21 JIA: 1-5 AS: 4-15 | RA 0-13%; PsA 0% JIA 0-6%; AS 0% | Data not available | Data not available |
Balsa et al., 2018 [31]  Spain  Cross-sectional, observational study  N= 165  RA and SpA  RA = 56.3 (12.1)  SpA = 47.9 (11.5)  RA = 13.9 ± 8.7  SpA = 12.5 ± 10.2  RA: 0%; SpA: 0%  Data not available  Data not available

Doeleman et al., 2019 [39]  Systematic review and meta-analysis  N= 268  JIA  11.8  4.7  Pooled prevalence 8.5% (95% CI = 0.5 – 23.2)  No reported association between treatment failure and the presence of non-neutralizing ADA  No association between adverse events and ADA was observed

Maid et al., 2018 [29]  Argentina  Cross-sectional study  N=54  RA  54.5 (13.6)  12.5±10.1  0%  Data not available  Data not available

Bader-Meunier et al., 2019 [48]  France  Prospective multi-centre study  N=126  JIA  10.5 (2-17)  4.62 (0.16-16.3)  15.7% at baseline 33% after 366 (302-712) days of treatment  ADA levels not significantly different between responders and non-responders (7.22±3.60 vs. 6.47±3.98ng/ml), No significant difference with concomitant MTX. p-values < 0.05 were considered significant.  No severe adverse events occurred.

Moots et al., 2017 [27]  Multicentre non-interventional study  N=200  RA  56.5±13.37  Symptom duration 0.8±10.67  0%  No patients developed ADA on ETN.  Data not available

Constantin et al., 2016 [49]  Multicentre prospective open-label study  JIA  8.6± 4.6  ERA 14.5± 1.6  JPsA 14.5±2.0  JIA  31.6±31.7 months  ERA  JIA - 18.3%, ERA- 23.7%, JPsA 20.5%, combined - 20.7%  No significant changes in effectiveness in patients who were ADA+ve was found  No safety concerns in patients who were ADA+ve were reported
| Study | Design | N | Disease Duration | ADA Status | Comments |
|-------|--------|---|-----------------|------------|----------|
| Strand et al., 2017 [28] | Systematic review | RA N=358 PsA, JIA and AS N = not available | RA (35-64) PsA (43-55) JIA (3-14.2) AS (30-48) RA: 1-34 PsA: 5-21 JIA: 1-5 AS: 4-15 | RA: 2.8-37%; PsA: 5-21 JIA: 1-5 AS: 4-15 | Concomitant use of MTX, AZA, leflunomide or MMF was associated with lower rates of ADA in RA, PsA and AS |
| Brunner et al., 2018 [51] | Multicentre withdrawal RCT | JIA | Disease duration not available | ADA: 2.8-37% | ADA+ve RA patients showed less improvement in disease activity and were less likely to achieve clinical responses (no comparative statistics performed) |
| Leu et al., 2019 [50] | Samples from 3 RCTs | RA PsA AS | Data not available | RA: 24.9% PsA: 39.9% AS: 30.3% | No effect of ADA on clinical response was found |
| Kneepkens et al., 2014 [53] | The Netherlands Prospective observational cohort study | RA | Data not available | 8.1% | 3 patients out of 37 (8.1%) were ADA+ve at 52 weeks and all 3 discontinued golimumab prematurely due to inefficacy |

**Golimumab**

- **Strand et al., 2017 [28]**
  - RA N=358 PsA, JIA and AS N = not available
  - RA: 1-34 PsA: 5-21 JIA: 1-5 AS: 4-15
  - ADA: 2.8-37%
  - Concomitant use of MTX, AZA, leflunomide or MMF was associated with lower rates of ADA in RA, PsA and AS

**Certolizumab**

- **Strand et al., 2017 [28]**
  - RA N=358 PsA, JIA and AS N = not available
  - RA: 1-34 PsA: 5-21 JIA: 1-5 AS: 4-15
  - ADA: 2.8-37%
  - Concomitant use of MTX, AZA, leflunomide or MMF was associated with lower rates of ADA in RA, PsA and AS

**Data not available**
| Study Reference | Study Location | Study Design | Study Population | ADA Prevalence | ADA+ve vs ADA-ve | Correlation | Other Findings |
|-----------------|----------------|--------------|------------------|----------------|----------------|-------------|---------------|
| Gehin et al., 2019 [56] | Norway | Longitudinal observational study | RA, AS, PsA and other inflammatory joint disease N=116 | Prevalence 6.1% (19/310 patients: 6 AS, 5 RA, 4 PsA and 4 other IJD) Among RA patients, 80% of ADA+ve patients had concomitant synthetic DMARDs (mostly MTX) vs. 73% of ADA- patients. 9% ADA+ve patients were responders at 3 months vs. 55% of ADA- patients No p-value reported | Data not available | 8 patients experienced one or more injection-site reactions, all of which were ADA- at 3 months. |
| Jani et al., 2017 [55] | The Netherlands | Prospective observation cohort study | RA N=115 | No correlation between ADA+ve and EULAR response was found (p = 0.18) | Data not available |

**Table 1** - Impact of ADA on disease outcomes in children and adults with inflammatory arthritis treated with anti TNF-α agents.

Legend: ADA- antidrug antibodies; AS – ankylosing spondylitis; AZT – azathioprine; ERA - enthesitis-related arthritis; EULAR- European League Against Rheumatism; JIA- juvenile idiopathic arthritis, JPsA – juvenile psoriatic arthritis; MMF- mycophenolate mofetil; MTX- methotrexate; N – number of patients treated with a certain biologic included in the study/systematic review; RA- rheumatoid arthritis, RCT – randomised control trial; PsA- psoriatic arthritis; +ve – positive; -ve - negative
| Author et al., year [ref] | Country | Type of study | Type of inflammatory arthritis N (F:M) Age (mean+/ SD) | Disease duration | Prevalence of ADA Impact of additional DMARD therapy on ADA prevalence | Impact on clinical efficacy | Impact on side-effects |
|--------------------------|---------|---------------|------------------------------------------------------|------------------|---------------------------------------------------------------|-----------------------------|------------------------|
| Strand et al., 2017 [28] | Systematic review | RA Patient demographics n/a | Data not available | 0-21% | Patients with ADAs vs RTX showed less improvement in disease activity and were less likely to achieve clinical responses in RA patients. No comparative statistics/meta-analysis performed. | Higher rates of Tx emergent adverse events (89% vs 68%) were reported in patients with RA who develop anti-RTX ADAs compared to those who did not |
| Thurlings et al., 2010 [80] | The Netherlands Open-label cohort study | RA N=58 (F:M = 44:14) | Data not available | Data not available | Response to treatment and re-treatment measured by decrease in DAS28 and EULAR response was similar in ADA-positive and ADA-negative patients: p=0.87 and p=0.32 for the responses at 24 weeks after courses 1 and 2, respectively | Data not available |
| Combier et al., 2020 [79] | France Retrospective cohort study | RA N=124 (F:M=97:27) Age (mean = 62; range 22-89) Other ARDS (including pSS, SLE, myositis) N=75 | RA 13 years (1-60) Other ARDS 10 years (1-28) | RA 2.4% Other ARDS 14.7% | No data available on ADA impact on clinical efficacy 14.29% were tested because of loss of efficacy, and 78.6% were tested because of adverse reactions. No comparative statistics performed. | 78.57% of ADA+ve patients (48/62 tested) with RA and other ARDs had infusion reactions to second or subsequent RTX cycles |
| Study Authors, Date | Study Design | JIA Patients | RA Patients | Other Details |
|--------------------|--------------|--------------|-------------|---------------|
| Strand et al., 2017 [28] | Systematic review | JIA: 1-5 | RA: 1-54 | Suggested that IV therapy associated with less immunogenicity than SC |
| Doeleman et al., 2019 [39] | Systematic review and meta-analysis | JIA: 1-5 | RA: 1-54 | Data not available |
| Hara et al., 2019 [76] | Japan Open label, multicentre single arm study | JIA: 1-5 | RA: 1-54 | No association between immunogenicity and loss of efficacy was found |
| Brunner et al., 2018 [74] | International open label, multicentre | JIA: 1-5 | RA: 1-54 | No clinical significance of ADA was found. |
| Study/Study Design | Patient Details | Outcomes |
|--------------------|-----------------|----------|
| Lovell et al., 2015 [77] | Multicentre RCT JIA N=58 (active arm) N= 59 (placebo) Mean age 12.4± 2.9 | Whole Abatacept molecule 3.4% (2/58) CTLA-4 region only 5.5% (9/58) (IV only) No loss of efficacy was found in the two patients with anti-abatacept antibodies to the whole molecules. Of the 9 patients with ADA against the CTLA-4 region, 3 discontinued due to lack of efficacy (small sample size, so no comparative statistics performed). |
| Haggerty et al., 2007 [73] | Integrated analysis across multiple double blind and open-label studies RA N=2237 | RA 2.1% ADA+ve with MTX 2.3% vs ADA+ve without MTX 1.4% - not significant Patients who discontinued had a higher level of ADA compared to those who did not discontinue (7.4% vs 2.6%). No comparative statistics performed |
| IL-6 blockade (Tocilizumab/Sarilumab) | Benucci et al., 2016 [81] | Italy Cohort study of Tocilizumab RA N=126 (F:M = 110:16) Mean Age: 59±12 years Range: 26-83 years Mean disease duration: 11±5 years 0.79% (1/126 patients) The occurrence of ADA against Tocilizumab is very rare. |

**Notes:**
- **IL-6 blockade (Tocilizumab/Sarilumab)**: IL-6 blockade refers to the use of Tocilizumab and Sarilumab, which are monoclonal antibodies that block the interleukin-6 (IL-6) receptor and thus inhibit inflammatory signaling. This is a common approach in treating rheumatoid arthritis (RA) and other autoimmune diseases.
- **Study Design:**
  - **Multicentre RCT (Randomized Controlled Trial)**: A study design where participants are randomly assigned to different treatment groups to determine the efficacy and safety of the intervention.
  - **Single arm study:** A study design where participants receive a single intervention or treatment without a control group.
- **Patient Details:**
  - **N=46, median age – 4.0 (3.0-5.0)**: This indicates a study with 46 participants, where the median age is 4.0 years, with values ranging from 3.0 to 5.0 years.
  - **N=173, median age – 13.0 (10.0-15.0)**: This indicates a study with 173 participants, where the median age is 13.0 years, with values ranging from 10.0 to 15.0 years.
- **Outcomes:**
  - **Whole Abatacept molecule 3.4% (2/58)**: This indicates that 3.4% of the participants had an immunogenic response to the whole Abatacept molecule, with 2 out of 58 participants showing this response.
  - **CTLA-4 region only 5.5% (9/58) (IV only)**: This indicates that 5.5% of the participants had an immunogenic response to the CTLA-4 region, with 9 out of 58 participants showing this response, and this response was observed only in the IV (intravenous) administration group.
  - **RA 2.1% ADA+ve with MTX 2.3% vs ADA+ve without MTX 1.4% - not significant**: This indicates that 2.1% of the participants had an ADA (anti-drug antibody) response with MTX (methotrexate), with 2.3% for those with ADA and 1.4% for those without ADA, and the difference was not statistically significant.
  - **Patients who discontinued had a higher level of ADA compared to those who did not discontinue (7.4% vs 2.6%). No comparative statistics performed:** This indicates that patients who discontinued treatment had a higher level of ADA compared to those who did not discontinue, with 7.4% for discontinuers vs 2.6% for continuers, but no comparative statistics were performed.

**Additional Information:**
- **No infusion reactions were experienced.**
- **No adverse safety outcomes were described.**

**Key Points:**
- The study design and patient demographics vary significantly, suggesting different stages of disease and treatment approaches.
- Immunogenic responses to the whole molecule and the CTLA-4 region are observed, with varying frequencies and implications.
- The discontinuation of treatment and the impact of ADA on treatment efficacy are critical considerations in these studies.
- No adverse safety outcomes were described, indicating a generally safe profile for these treatments.
| Study [Reference] | Study Design | Country | Disease | N | Gender Ratio | Mean Age | ADA Status | Clinical Efficacy | Safety/Side Effects |
|------------------|--------------|---------|---------|---|--------------|----------|-------------|-------------------|---------------------|
| Sigaux et al., 2017 [82] | Cohort study of Tocilizumab | France | RA | 40 | F:M = 32:8 | 56.5±14 years | 16±11.7 months | 3.2% | No association between ADA status and disease activity was found |
| Burmester et al., 2017 [83] | Meta-analysis of phase III RCTs of Tocilizumab | | RA | TCZ-SC: N=3099 | TCZ-IV: N=5875 | Data not available | TCZ-SC: 1.5% | TCZ-IV: 1.2% | No association with decreased clinical efficacy was found | No clear impact of ADA on safety and side effects was found |
| Yokota et al., 2014 [84] | Phase II-III RCTs of Tocilizumab | Japan | sJIA | N=67 | F:M = 38:29 | 8.3±4.3 years | 4.4±3.5 years | 7.5% | No decrease in clinical effectiveness was reported | 4/5 patients with ADA experienced mild to moderate infusion reactions |
| Burmester et al., 2017 [85] | Multicentre RCT of Sarilumab | | RA | N=184 | F:M = 157:27 | 50.9±12.6 years | 8.1±8.1 years | 7.1% | ADA were not associated with a loss of efficacy | ADA were not associated with hypersensitivity reactions |
| Wells et al., 2019 [86] | Open label study of Sarilumab | USA | RA | N=132 | F:M = 106:26 | 52.4±13.4 years | 10.5±9.0 years | 150mg: 12.3% | 200mg: 6.1% | Persistent ADA were associated with lower sarilumab levels but no correlation with clinical efficacy | There was no evidence that ADA status was linked to adverse effects. No notable differences in hypersensitivity reactions based on ADA status (no comparative statistics performed) |
| Genovese et al., 2015 [87] | Multicentre RCT of Sarilumab | | RA | 150mg: N=400 | 50.1±11.9 years | 150mg: mean 9.5 years (range: 0.3-44.7) | 150mg: 16.7% | 200mg: 13.0% | The presence of ADA was not associated with discontinuations due to lack of efficacy. | The presence of ADA was not associated with hypersensitivity reactions |
| Study (Reference) | Type of Study | Treatment | N | Gender Ratio | Mean Age | ADA | Clinical Efficacy | Immunogenicity | Notes |
|------------------|---------------|-----------|---|--------------|---------|-----|-------------------|---------------|-------|
| Xu et al., 2019 [89] | Worldwide Two-compartment model study of Sarilumab | RA | N=1770 (F:M = 1466:304) | Mean Age: 52±12 years | Data not available | 18% | ADA may be linked to higher drug clearance, but this study did not evaluate the impact on clinical efficacy | Data not available |
| Deodhar et al., 2019 [93] | Pooled clinical trial safety data for Secukinumab | PsA | N=1380 (F:M = 742:638) | Mean Age: 48.8±12.0 years | Data not available | <1% across all studies | No effect of ADA positivity on clinical efficacy was reported | Immunogenicity was not related to adverse effects |
| Mease et al., 2017 [94] | Multicentre phase III RCT of Ixekizumab | PsA | N=417 (F:M = 225:192) | Mean Age: 49.5±11.9 | 6.7±7.2 years | 5.3% | 72.7% (8/11) of ADA-positive patients achieved a clinical response. No comparative statistics performed as very small sample size | Data not available |
| Gordon et al., 2016 [95] | Combined phase III RCTs of Ixekizumab | Plaque psoriasis | N=1150 | Data not available | 9% | 19 patients (1.7%) with high titres of ADAs had a lower clinical response than that of patients with no or low-moderate ADAs (no p-value given). | Data not available |
| Study | Design | Disease | Patients | ADAs | Other Observations |
|-------|--------|---------|----------|------|-------------------|
| **IL-12/23 blockade (Ustekinumab)**
Strand et al., 2017 [28] | Systematic review | PsA | Data not available | 8-11% Concomitant use of MTX, AZA, leflunomide or mycophenolate is associated with lower rates of ADAs against INF in PsA | Data not available |
Smolen et al., 2017 [90] | Multicentre RCT | RA 90mg/8wk N=55 (F:M=46:9) Age 50.8±13.0 | RA 90mg/8wk 5.6 ±5.5 | RA: 5.7% (3.3% neutralising) | Data not available |
| **IL-1 blockade (Anakinra, Canakinumab and Rilonacept)**
Fleischmann et al., 2006 [96] | Multicentre RCT of Anakinra | RA | 10.3 years (range: 0.2-59.5 years) | 50.1% (1.9% neutralising) | No associations between ADA and adverse effects |
| Cohen et al., 2002 [97] | Multicentre RCT of Anakinra | RA Anakinra dose: 0.04mg/kg/day N=63 Mean Age: 52.6 years | 0.04mg/kg/day: 6.3 years Anakinra dose: 0.1mg/kg/day 8.8 years Anakinra dose: 0.4mg/kg/day 7.0 years | 2.7% (8 out of 297 screened for antibodies) | 87.5% of ADA positive patients experienced injection site reactions. No p-value reported |
| Study                          | Treatment Details | N  | Mean Age (years) | No. of Neutralising Antibodies | Clinical Efficacy | Adverse Effects |
|-------------------------------|-------------------|----|------------------|-------------------------------|-------------------|-----------------|
| Ilowite et al., 2009 [98]     | 0.1mg/kg/day N=74 | 53.0 | 0.4mg/kg/day N=77 | Mean Age: 53.0 years          | 0%                | No impact found |
|                               | 0.4mg/kg/day N=77 | 52.8 | 1.0mg/kg/day N=59 | Mean Age: 52.8 years          | 13%               |                 |
|                               | 1.0mg/kg/day N=59 | 49.0 | 2.0mg/kg/day N=72 | Mean Age: 49.0 years          | 72%               |                 |
|                               | 2.0mg/kg/day N=72 | 54.1 |                  |                               |                   |                 |
| Sun et al., 2016 [99]         | Multicentre RCT of Anakinra JIA N=25 (F:M = 17:8) Mean Age: 10 years (range: 3-17) | 72% (none were neutralising) | No evidence of loss in clinical efficacy was found | No association was demonstrated between ADA and adverse effects |
| Reference         | Study Details                      | JIA Patients | Median Age | ADA Rate (%) | ADA Characteristics | Other Notes                                      |
|-------------------|-----------------------------------|--------------|------------|--------------|---------------------|------------------------------------------------|
| Ruperto et al., 2012 [100] | Multicentre RCT of Canakinumab JIA N=50 (F:M=28:22) Median Age: 8.0 years (IQR: 6.0-12.0) | Median: 2.7 years (IQR: 1.3-6.2) | 8% (4/50 patients) None were neutralising. | Data not available | Data not available |
| Lovell et al., 2013 [101] | USA RCT of Rilonacept JIA N=24 (F:M=16:8) Mean Age: 12.6±4.3 years | Median: 3.1 years (mean) | 54.2% (13/24) | No correlation between ADA and clinical responses was found. Statistical testing not performed due to small sample size. | All patients who experienced ≥3 injection-site reactions were ADA-positive |

**Table 2** - Impact of ADA on disease outcomes in children and adults with inflammatory arthritis treated with other biologic agents.

Legend: ARDS – autoimmune rheumatic diseases; AS – ankylosing spondylitis; JIA-juvenile idiopathic arthritis; PsA- psoriatic arthritis; pSS – primary Sjögren’s syndrome; RA-rheumatoid arthritis; RCT-randomised control trial; SLE – systemic lupus erythematosus.
| Prevalence of ADA | Adults with inflammatory arthritis | Children with juvenile idiopathic arthritis |
|------------------|------------------------------------|------------------------------------------|
| **TNF-α blockers** |                                    |                                          |
| Adalimumab and biosimilars | 0-67% | 6-45% |
| Infliximab and biosimilars | 6.1-62% | 26-37% |
| Etanercept and biosimilars | 0-13% | 0-33% |
| Golimumab | 2-39.9% | 46.8% |
| Certolizumab | 2.8-65% | Data not available |
| **B cell depletion** |                                    |                                          |
| Rituximab and biosimilars | 0-21% | Data not available |
| **Co-stimulatory blockade** |                                    |                                          |
| Abatacept IV | 2-20% | 2-11% |
| Abatacept SC | 2-20% | 2-11% |
| **IL-6 blockade** |                                    |                                          |
| Tocilizumab | 0-16% | 1-8% |
| Sarilumab | 7-24.6% | Data not available |
| **IL-17 blockade** |                                    |                                          |
| Sekukinumab | 0-1% | Data not available |
| Ixekizumab | 5.3-9% | Data not available |
| **IL-12/23 blockade** |                                    |                                          |
| Ustekinumab | 5.7-11% | Data not available |
| **IL-1 blockade** |                                    |                                          |
| Anakinra | 50.1-70.9% | 81.8% |
| Canakinumab | Data not available | 3.1-8% |
| Rinolacept | Data not available | 54.2% |

**Table 3.** Comparison between the prevalence ranges for ADA to various biologic agents in adult versus paediatric populations
Clinical decision to start a patient on a certain biologic treatment

Assess

Patient characteristics
Genetic factors if possible smoking, age

Type of biologic agent
mAbs versus fusion proteins

Route and frequency of drug administration
IV vs. subcutaneously

Concomitant DMARD treatment

Evaluate patient’s potential risk of drug immunogenicity to a certain biologic treatment, as well as safety and efficacy once on treatment

Low risk
(e.g. biologic agents associated with low prevalence of neutralising ADA; concomitant DMARDs, IV administration, good clinical response, no side-effects)
Continue treatment for as long as there is clinical response/unlikely that drug levels or ADA assessment improves management

High risk
(e.g. biologic treatments with higher prevalence of neutralising ADA; on biologic monotherapy, patients tapering biologics, poor compliance, loss of clinical response or side-effects)
Monitor drug levels and ADA throughout treatment

Increased ADA and low/undetectable drug levels
- increase dose/frequency of administration of biologic
- add DMARD therapy
- change to IV formulations
- change biologic treatment

Low/undetectable ADA and undetectable drug levels
- assess therapy compliance
- switch to IV formulations to improve compliance
- discuss change in treatment to improve compliance

Figure 1: Potential clinical applications of the assessment of immunogenicity to biologic treatments