# Secukinumab Immunogenicity over 52 Weeks in Patients with Psoriatic Arthritis and Ankylosing Spondylitis

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***ABSTRACT.*** ***Objective.*** Secukinumab, a fully human antiinterleukin 17A monoclonal antibody, is efficacious for the treatment of psoriatic arthritis (PsA) and ankylosing spondylitis (AS). This study examined the immunogenicity of secukinumab in patients with PsA and AS exposed to secukinumab for up to 52 weeks.

***Methods.*** Antibody bridging assays were used to assess the immunogenicity of secukinumab in patients with PsA [FUTURE 1–3 studies, and AS (MEASURE 1–4 studies)]. Evaluations were at baseline and at weeks 16 (AS only), 24, and 52. Treatment-emergent antidrug antibodies (TE-ADA) were defined as a positive ADA signal in ≥ 1 posttreatment sample in patients negative at baseline. Positive samples were analyzed for drug-neutralizing potential, and effect of TE-ADA on secukinumab pharmacokinetics, immunogenicity-related adverse events (AE), and efficacy through Week 52 were assessed.

***Results.*** Of 1414 treated PsA and 1164 treated AS patients with samples available for immunogenicity evaluation, 5 (0.35%) and 8 (0.69%), respectively, developed TE-ADA. All but 1 PsA patient were biologic-naive; two of the 5 PsA and one of the 8 AS patients received concomitant methotrexate, and two of the 8 AS patients received concomitant sulfasalazine. Associations between TE-ADA and secukinumab dose, frequency, or administration mode were not observed. Other than one PsA patient, all TE-ADA were non-neutralizing. No TE-ADA were associated with any AE. All TE-ADA were associated with normal secukinumab pharmacokinetics and none were associated with loss of secukinumab efficacy.

***Conclusion.*** Secukinumab treatment was associated with a low (< 1%) incidence of immunogenicity in patients with PsA or AS. (clinicaltrials.gov: NCT01392326; NCT01752634; NCT01989468; NCT01358175; NCT01649375; NCT02008916; NCT02159053) (First Release November 15 2019; J Rheumatol 2020;47:539–47; doi:10.3899/jrheum.190116)

*Key Indexing Terms*:

| | | |
|---|---|---|
| SECUKINUMAB | INTERLEUKIN-17A | MONOCLONAL ANTIBODY |
| IMMUNOGENICITY | PSORIATIC ARTHRITIS | ANKYLOSING SPONDYLITIS |

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*This study was funded by Novartis Pharmaceuticals Corp., USA, which manufactures secukinumab.*

*AD reports grants and personal fees from Novartis, Eli Lilly, Janssen, Pfizer, and UCB, and grants from Amgen, AbbVie, and GSK during the conduct of the study. DDG reports grants from Novartis during the conduct of the study. IBM reports grants and personal fees from Novartis during the conduct of the study. SS and GB are employees and shareholders of Novartis Institutes for Biomedical Research; RM, LP, BP, JS, and AS are employees and shareholders of Novartis Pharma AG.*

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*Accepted for publication May 27, 2019.*

Interleukin (IL)-17A has been implicated in many aspects of the pathophysiology and resulting key clinical features of spondyloarthropathies including synovial inflammation, joint erosion, enthesitis, new bone formation, and epidermal

inflammation[1,2,3,4], and represents a rational therapeutic target for active psoriatic arthritis (PsA) and ankylosing spondylitis (AS). Secukinumab, a fully human anti–IL-17A monoclonal antibody (mAb), has shown efficacy in the treatment of moderate to severe plaque psoriasis[5,6,7,8], PsA[9,10,11], and AS[12,13,14,15], demonstrating a rapid onset of action and sustained responses with a favorable safety profile.

It is known that mAb therapies may be associated with immunogenicity and the production of treatment-emergent antidrug antibodies (TE-ADA). In turn, TE-ADA can cause immunogenicity-related adverse events (AE), including acute complications such as infusion-related reactions, allergic reactions, and anaphylaxis, as well as non-acute reactions such as delayed hypersensitivity and autoimmunity[16]. Further, TE-ADA can affect drug pharmacokinetics (PK) and clinical response, potentially decreasing efficacy, as has been observed with biologic agents[16,17,18,19].

The low incidence of immunogenicity of secukinumab in patients with moderate to severe plaque psoriasis has been assessed previously in the psoriasis phase III program in which TE-ADA occurred in < 1% of patients treated for up to 52 weeks[20]. The objective of this new analysis was to examine the immunogenicity of secukinumab in patients with PsA and AS, who were treated with secukinumab for up to 52 weeks.

## MATERIALS AND METHODS

*Study design*. The immunogenicity of secukinumab, as indicated by TE-ADA, was assessed across phase III clinical trials in patients with PsA or AS[9–15] who were exposed to secukinumab for up to 52 weeks. TE-ADA were evaluated at baseline and at weeks 16 (AS only), 24, and 52.

The phase III PsA secukinumab studies included in this analysis were FUTURE 1–3 (clinicaltrials.gov: NCT01392326; NCT01752634; and NCT01989468, respectively)[9,10,11].

In FUTURE 1[10], patients were randomly assigned in a 1:1:1 ratio to one of 2 secukinumab dose groups or a placebo group. Patients in the secukinumab groups received an intravenous (IV) dose of 10 mg/kg at baseline and weeks 2 and 4, followed by subcutaneous (SC) secukinumab at a dose of either 150 mg or 75 mg every 4 weeks thereafter. Patients in the placebo group were treated according to the same IV-to-SC administration schedule.

In FUTURE 2[9], patients were randomly assigned in a 1:1:1:1 ratio to receive SC secukinumab 300 mg, 150 mg, 75 mg, or placebo once a week from baseline to Week 4 and then every 4 weeks thereafter.

In FUTURE 3[11], patients were randomized (1:1:1) to one of 2 secukinumab dose groups (secukinumab 300 mg or 150 mg) or placebo. Patients in the secukinumab groups received SC secukinumab at a dose of 300 mg (2 × 1.0 ml autoinjector) or 150 mg (1.0 ml autoinjector + 1.0 ml placebo autoinjector) at baseline, weeks 1, 2, 3, and 4, and every 4 weeks thereafter. Patients in the placebo group (2 × 1.0 ml placebo autoinjector) were treated according to the same administration schedule as the active drug. Patients were stratified at randomization based on previous anti–tumor necrosis factor (TNF) therapy use as anti–TNF-naive or as having exhibited inadequate response to anti–TNF; at least 60% of patients in each treatment arm (secukinumab 300 mg, secukinumab 150 mg, and placebo) were anti–TNF-naive.

At Week 16 in all 3 FUTURE studies, patients were classified as responders (≥ 20% improvement from baseline in tender and swollen joint counts) or nonresponders. In FUTURE 1, placebo-treated patients were randomly assigned again in a 1:1 ratio to receive SC secukinumab 150 mg or 75 mg every 4 weeks from Week 16 (nonresponders) or Week 24 (responders). In FUTURE 2 and FUTURE 3, placebo-treated patients were randomly assigned again in a 1:1 ratio to receive SC secukinumab 300 mg or 150 mg every 4 weeks from Week 16 (nonresponders) or Week 24 (responders).

The phase III studies in patients with AS included in this analysis were MEASURE 1–4 (clinicaltrials.gov: NCT01358175; NCT01649375; NCT02008916; and NCT02159053, respectively)[12,13,14,15].

In MEASURE 1[12], patients randomized to secukinumab received a 10 mg/kg IV infusion at baseline and weeks 2 and 4, followed by SC injections of 150 mg (secukinumab IV 150 mg) or 75 mg (IV 75 mg) every 4 weeks from Week 8; patients in the placebo group were treated using the same IV-to-SC schedule. Placebo-treated patients were randomly reassigned (1:1) to receive secukinumab 150 or 75 mg SC every 4 weeks from Week 16 (nonresponders) or Week 24 (responders), with response based on Assessment of SpondyloArthritis international Society 20 (ASAS20) response criteria.

In MEASURE 2[12], patients were randomized to receive SC secukinumab 150 mg, 75 mg, or placebo at baseline, weeks 1, 2, and 3, and every 4 weeks from Week 4. At Week 16, placebo-treated subjects were re-randomized to receive SC secukinumab 150 or 75 mg every 4 weeks, irrespective of the clinical response.

In MEASURE 3[15], patients were randomized (1:1:1) to one of 2 secukinumab dose groups (300 mg or 150 mg) or a placebo group. Patients in the secukinumab groups received an IV dose of 10 mg/kg at baseline and weeks 2 and 4, followed by SC secukinumab in the form of prefilled syringes at a dose of either 300 mg (IV 300 mg) or 150 mg (IV 150 mg) every 4 weeks starting at Week 8. Patients in the placebo group were treated according to the same IV-to-SC administration schedule. At Week 16, all patients in the placebo group were re-randomized to receive secukinumab either 300 mg or 150 mg (1:1) SC every 4 weeks.

In MEASURE 4[14], patients with AS were randomly assigned (1:1:1) to one of 3 treatment groups: SC secukinumab 150 mg with loading dose, SC secukinumab 150 mg without loading dose, or placebo. All patients received SC secukinumab 150 mg or placebo at baseline and weeks 1, 2, and 3, and every 4 weeks starting at Week 4. At Week 16, all placebo patients were switched to SC secukinumab 150 mg every 4 weeks. Thus, starting at Week 16, patients in all 3 arms received secukinumab 150 mg every 4 weeks.

All studies were double-blind and placebo-controlled, and full details of the study designs have been described previously[9–15]. All studies were approved by the institutional review board or ethics committee at each participating site and were conducted in accordance with the principles of the Declaration of Helsinki. Ethics approval numbers for the main institutions are included in Supplementary Table 1 (available with the online version of this article). All patients provided written informed consent.

*Blood sample and antidrug antibody analysis*. Blood samples were obtained pre-dose at baseline and throughout the studies. For this analysis, immunogenicity in patients with PsA and AS exposed to secukinumab was evaluated at baseline and at weeks 16 (AS only), 24, and 52.

ADA assessment followed the standard, sequential 3-tiered approach that is commonly used to assess ADA of therapeutic antibodies (screening, confirmation, and titration)[20,21]. In tier 1, patient-derived samples were analyzed for ADA in a screening assay (summarized in Figure 1A); in tier 2, positive samples were retested in a confirmatory assay in which specificity was assessed by performing the assay in the presence of excess secukinumab; in tier 3, confirmed ADA-positive samples were quasi-quantified by titration to obtain a titer value.

In the first step (the screening assay), the assay signal of patient-derived samples is evaluated against a predefined and validated assay signal cutpoint. If the signal is above this cutpoint, the sample is considered screening-positive, but not yet ADA-positive. In the second step, the screening-positive samples are then tested in the so-called confirmatory assay as it confirms specificity of the signal observed in the first assay. The confirmatory assay is based on the same analytical principle as the screening assay. However, before being analyzed in the assay, the patient-derived

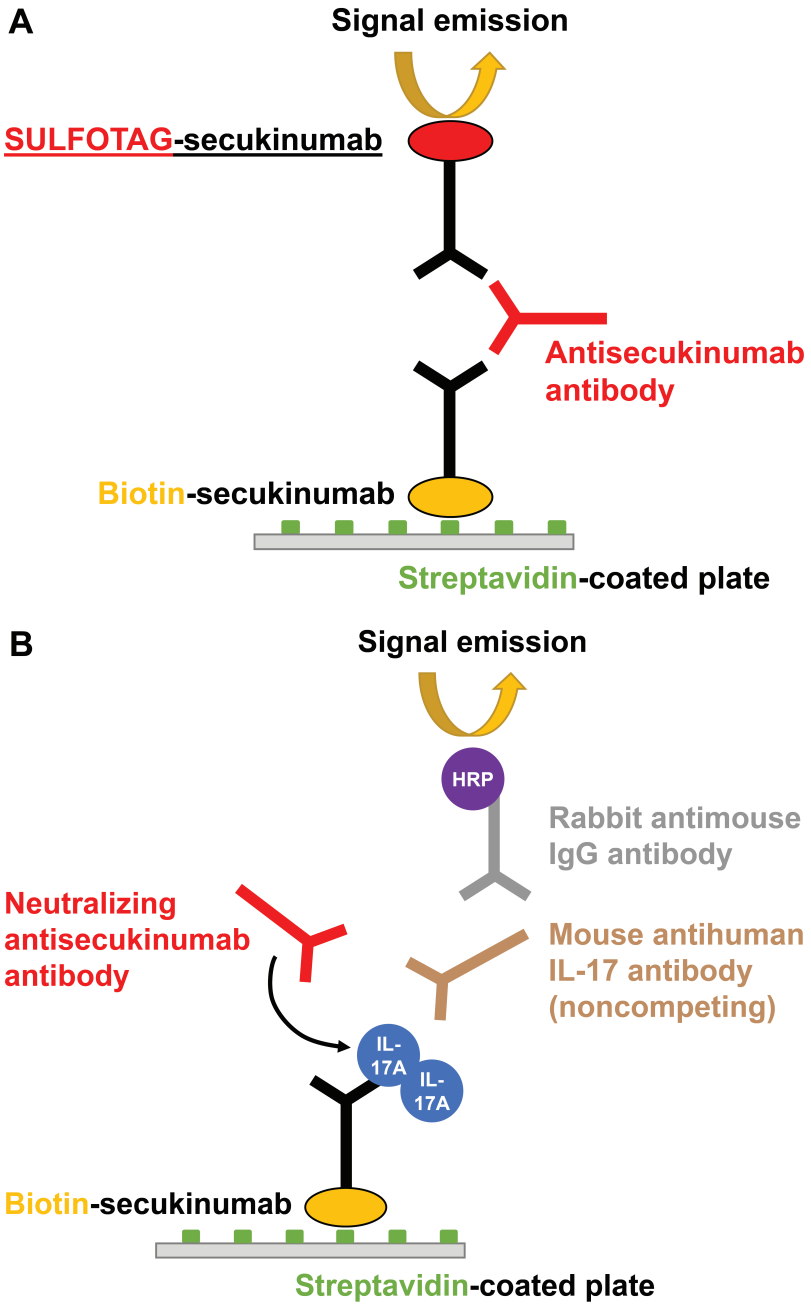


*Figure 1*. ADA and neutralizing antibody assays. A. ADA detection. Schematic diagram of the anti-secukinumab antibody assay. Biotinylated secukinumab was immobilized on a streptavidin-coated plate, and unbound biotinylated secukinumab was washed away. Free antidrug antibodies were captured by binding to immobilized secukinumab. ADA, acting as a bridge, were bound to SULFO-tagged secukinumab, added subsequently, and detected by electrochemiluminescence. B. Schematic diagram of the neutralizing antibody assay. Subject serum samples, after acid dissociation and neutralization, were applied to immobilized secukinumab, followed by addition of excess human IL-17A. In the absence of neutralizing antidrug antibodies in patient samples, IL-17A became bound to immobilized secukinumab. Excess unbound IL-17A was removed. Bound IL-17A was recognized by addition of noncompeting mouse antihuman IL-17A antibodies. The detection signal of IL-17A binding was produced by binding of horseradish peroxidase–linked rabbit anti-mouse IgG antibody to anti–IL-17A antibodies. Neutralizing ADA were detected by their ability to inhibit IL-17A binding to secukinumab competitively, thereby disrupting anti–IL-17A antibody binding. Absence of signal produced by enzyme-linked secondary antibody binding indicated the presence of neutralizing ADA. ADA: antidrug antibodies; IgG: immunoglobulin G; IL: interleukin. Figure 1A and 1B are reproduced with permission from Reich, *et al*[20]; Br J Dermatol 2017;176:752-8.

screening-positive samples are preincubated with an excess of the drug. In the case of a specific signal, the addition of drug to the sample will prevent the ADA from being detected and the assay signal will decrease. The inhibition of the assay signal is compared against a predefined and validated cutpoint. If the inhibition of the signal exceeds this confirmatory cutpoint, then the sample is considered ADA-positive. In the third step, the ADA response is semiquantified by determining a titer. The assay for titer determination is again based on the same assay principle as screening and confirmatory assay. In this assay, however, the patient-derived samples are diluted sequentially, leading to a decrease in signal with increasing dilution factor. The reported titer corresponds to the dilution at which the assay signal reaches the predefined and validated titer cutpoint of the assay.

In this study, ADA were detected according to the assay approach described above using a Meso Scale Discovery (MSD) electrochemiluminescence assay (Meso Scale Discovery), which has been previously described in detail[20]. Validation of the MSD assay determined the limits of secukinumab ADA detection in serum samples from patients before and after treatment with secukinumab and was conducted according to the US Food and Drug Administration and European Medicines Agency guidance and relevant white papers[22–29].

At baseline, before secukinumab exposure (and therefore in the absence of serum secukinumab), the MSD bridging assay was highly sensitive and able to detect 4 ng/ml of polyclonal anti-secukinumab positive control antibody. Drug tolerance (the ability of the analysis to detect ADA without interference from the drug under investigation) in the MSD assay was 53.8 $\mu$g/ml secukinumab. Therefore, after secukinumab exposure at serum secukinumab concentrations ≤ 53.8 $\mu$g/ml, the assay was sufficiently sensitive to detect concentrations down to 250 ng/ml of polyclonal anti-secukinumab positive control antibody.

TE-ADA were defined as ADA that developed following treatment with secukinumab in patients with no ADA detected before active treatment. Secukinumab immunogenicity was defined as a positive signal for TE-ADA in ≥ 1 posttreatment sample in patients who were negative at baseline. TE-ADA–positive samples were analyzed through Week 52 for the following: drug-neutralizing potential; effect of ADA on the PK of secukinumab; immunogenicity-related AE; and the effect of TE-ADA on the efficacy of secukinumab.

*Neutralizing antibody assay*. Serum samples from patients with confirmed TE-ADA were further analyzed for neutralizing ADA (antibodies that bind to secukinumab in such a way as to prevent it from binding to IL-17A, thereby neutralizing its activity). An ELISA was used to determine the neutralizing potential of the ADA, based on the presence or absence of an IL-17A binding signal (Figure 1B)[21].

*PK profiles*. Across all of the phase III studies, normal PK behavior in TE-ADA–positive patients was defined as secukinumab concentrations in individuals with TE-ADA at the various timepoints that were (1) within the observed range for all patients without ADA, and (2) showed steady-state PK behavior at weeks 24 and 52.

*Definition of loss of response*. Loss of response in patients with PsA was defined as an increase in disease activity leading to a failure to maintain > 20% reduction, compared to baseline, in both tender and swollen joint counts, on treatment after previously achieving such improvement for at least 2 consecutive visits prior to the first detection of ADA.

The definition of loss of response in patients with AS was based on the ASAS response criteria: an increase in disease activity leading to a failure to maintain ASAS20 after previously achieving such improvement for at least 2 consecutive visits prior to the first detection of ADA. ASAS20 response was defined as a relative improvement of ≥ 20% and an absolute improvement of ≥ 1 unit (on a 10-unit scale) in at least 3 of the 4 main ASAS domains (patient's global assessment of disease activity, back pain, physical function, and inflammation), with no worsening of ≥ 20% and ≥ 1 unit (on a 10-unit scale) in the remaining domain. Effect on efficacy was assessed up to Week 52.

## RESULTS

*ADA assay results*. A total of 1414 of 1417 patients randomized in the 3 PsA trials and 1164 of 1166 patients randomized in the 4 AS trials and treated with secukinumab had samples analyzed for immunogenicity evaluation. Overall, 5 (0.35%) patients with PsA and 8 (0.69%) patients with AS developed TE-ADA over 52 weeks (Figure 2).

For patients with PsA, one of 603 patients (0.17%) in FUTURE 1 and one of 397 (0.25%) patients in FUTURE 2 studies developed TE-ADA, as did 3 of 414 (0.72%) patients in FUTURE 3. Of the 5 patients with PsA who developed TE-ADA, 2 had received concomitant methotrexate (MTX) and one of these 2 patients had also received corticosteroids.

In the AS studies, these patients developed TE-ADA: 2 of 371 patients in MEASURE 1 (0.54%), 1 of 220 patients in MEASURE 2 (0.45%), 1 of 226 patients in MEASURE 3 (0.44%), and 4 of 347 patients in MEASURE 4 (1.15%; Table 1). One of the 8 patients with AS who developed TE-ADA received concomitant MTX; 2 out of these 8 patients received concomitant sulfasalazine, and 3 of these 8 patients received concomitant corticosteroids. In MEASURE 4, one patient experienced persistent immunogenicity with TE-ADA–positive signals at weeks 16 and 52. No boosted immunogenicity (i.e., increase of titer values over time) was observed. This patient had no abnormal PK, immunogenicity-related AE, or loss of efficacy response.

As shown in Table 1, the frequency of TE-ADA did not appear to vary with increasing doses of secukinumab. At the timepoints that immunogenicity was measured, 96% of patients had secukinumab serum concentrations below the drug tolerance level of 53.8 µg/ml, confirming sufficient assay sensitivity for measuring immunogenicity during treatment with secukinumab[30]. Other than one patient with PsA, all TE-ADA were non-neutralizing and none of the TE-ADA were associated with any immunogenicity-related AE (Table 1).

*Effect of TE-ADA on serum levels of secukinumab*. In all 3 PsA studies and the 4 AS studies, the TE-ADA were associated with normal secukinumab PK.

The individual trough concentrations in ADA-negative and ADA-positive patients during 52 weeks of secukinumab treatment are shown in Figure 3. They demonstrate that TE-ADA have no effect on serum levels of secukinumab. In both indications, the trough serum secukinumab concentrations of TE-ADA-positive patients show steady-state PK behavior and are within the range of the serum concentrations observed in ADA-negative patients.

*Drug tolerance and serum levels of secukinumab*. Figure 4B shows that in patients with AS, Week 16 concentrations were higher than at the later timepoints because of the loading regimens during the first month. As also shown in Figure 4 and across both indications, steady-state behavior is apparent at weeks 24 and 52 (i.e., mean concentrations remained stable at these 2 timepoints). Mean and median concentrations are

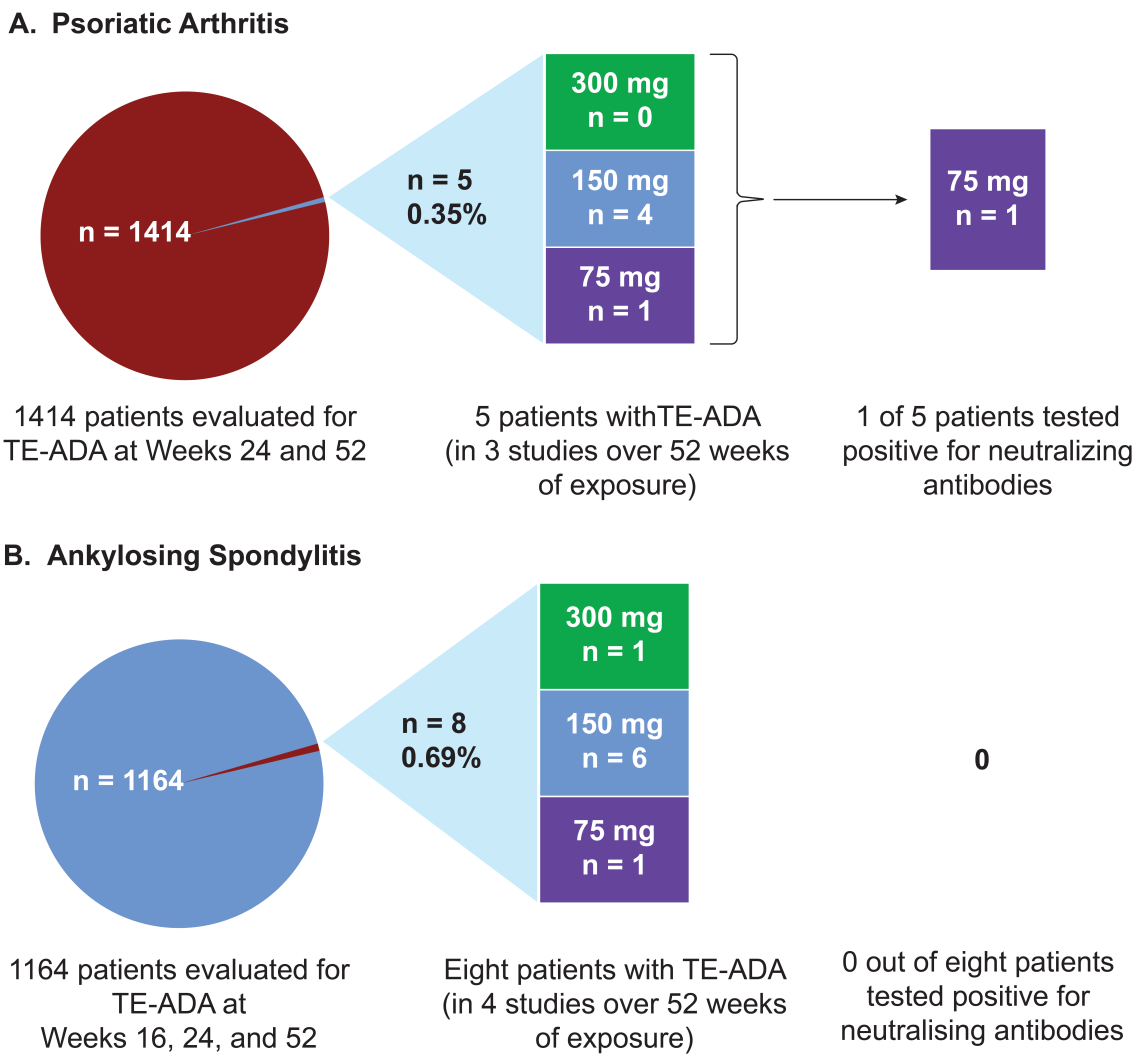


*Figure 2*. Summary of secukinumab immunogenicity across clinical studies of (A) PsA* and (B) AS#. * Immunogenicity in patients with PsA (FUTURE 1–3 studies, N = 1414). Four out of 5 patients were biologic-naive. Two out of 5 patients received concomitant methotrexate. # Immunogenicity in patients with AS (MEASURE 1–4 studies, N = 1164). One out of 8 patients received concomitant methotrexate. Two out of 8 patients received concomitant sulfasalazine. All TE-ADA were non-neutralizing. AS: ankylosing spondylitis; PsA: psoriatic arthritis; TE-ADA: treatment-emergent antidrug antibodies.

about 2-fold higher with the 300-mg than with the 150-mg dose level. Only a few patients receiving the 75-mg and 150-mg doses had serum secukinumab levels higher than the drug tolerance threshold at weeks 24 and 52, whereas this occurred more frequently at the 300-mg dose level. For individual drug concentrations higher than the drug tolerance level of the ADA assay (symbols above the dashed line), weak ADA responses may have been missed (false negatives).

*ADA effects on efficacy and safety*. As shown in Table 1, there were no observed effects of TE-ADA on the efficacy of secukinumab, and none of the TE-ADA were associated with immunogenicity-related AE.

## DISCUSSION

In this study, secukinumab treatment was associated with a low incidence of immunogenicity in PsA and AS patients, as shown by TE-ADA detection in only 0.35% of PsA patients and 0.69% of AS patients over 52 weeks in a database of more than 2500 patients from clinical studies. These results are consistent with the low incidence of immunogenicity (0.40%) seen with secukinumab through Week 52 in clinical studies of patients with moderate to severe plaque psoriasis[20].

Drug tolerance is an important aspect in immunogenicity analysis and represents the ability of the analysis to detect ADA without interference from the drug under investigation[31], in this case, secukinumab. Levels of secukinumab

*Table 1*. Overview of patients with TE-ADA[#].

| Study | Secukinumab Dose | Prior Biologics | ADA (titer)/N-Ab | AE, Possibly IG-related~ | Effect on Efficacy≠ | PK Behavior∞ |
|---|---|---|---|---|---|---|
| PsA studies | | | | | | |
| FUTURE 1, N = 603 | Placebo - 75 mg | None | Wk 24 (no titer*)/Yes | No | None | Normal |
| FUTURE 2, N = 397 | Placebo - 150 mg | None | Wk 52 (2.99)/No | No | None | Normal |
| FUTURE 3, N = 414 | 150 mg | Infliximab | Wk 52 (2.14)/No | No | None | Normal |
| | 150 mg | None | Wk 24 (1.00)/No | No | None | Normal |
| | 150 mg | None | Wk 52 (2.59)/No | No | None | Normal |
| AS studies | | | | | | |
| MEASURE 1, N = 371 | 10 mg/kg → 150 mg | None | Wk 52 (2.39)/No | No | None | Normal |
| | Placebo -150 mg | None | Wk 52 (10.61)/No | No | None | Normal |
| MEASURE 2, N = 220 | Placebo - 75 mg | None | Wk 52 (39.39)/No | No | None | Normal |
| MEASURE 3, N = 226 | Placebo - 300 mg | None | Wk 52 (1.02)/No | No | None | Normal |
| MEASURE 4, N = 347 | 10 mg/kg → 150 mg | None | Wk 16 (6.35)/No | No | None | Normal |
| | | | Wk 52 (2.96)/No | | None | |
| | 150 mg no load | None | Wk 16 (2.70)/No | No | None | Normal |
| | 150 mg | None | Wk 24 (2.80)/No | No | None | Normal |
| | Placebo - 150 mg | None | Wk 52 (2.89)/No | No | None | Normal |

[#] Only positive ADA results at the respective study week are shown. ~ IG-related AE refers to preferred terms in the SMQ hypersensitivity. ≠ PsA: failure to achieve > 20% reduction in both tender and swollen joint counts for at least 2 consecutive visits prior to the first detection of ADA; AS: failure to achieve ASAS20 while on treatment after previously achieving ASAS20 for at least 2 consecutive visits at any time prior to first detection of ADA; assessment for effect on efficacy has been done only up to Week 52. ∞ Normal PK: concentrations at various timepoints in individual ADA-positive patients that fit into the observed range for all patients without ADA. * Insufficient sample volume to determine titer. TE-ADA: treatment-emergent anti-drug antibodies; AE: adverse events; IG: immunogenicity; N-Ab: neutralizing antibodies; PK: pharmacokinetic PsA: psoriatic arthritis; AS: ankylosing spondylitis.

below the drug tolerance threshold at the time of immunogenicity measurement confirm sufficient assay sensitivity for measuring immunogenicity during treatment with secukinumab. In line with this concept, the secukinumab concentration in most (96%) of the samples was below the drug tolerance limit of the assay, a result that is similar to that observed in patients with moderate to severe plaque psoriasis treated with secukinumab[20].

The presence of ADA has been identified as an important contributor to reduced treatment efficacy and increased risk of AE in patients receiving biologic therapy[32]. Therefore, low incidence of immunogenicity could be an important clinical consideration when selecting a therapy for patients with chronic immune-mediated inflammatory diseases. Indeed, available evidence based on a systematic literature review suggests that the immunogenicity of different biologics and biosimilars used to treat PsA and AS varies widely[32]. As yet, we cannot explain the low immunogenicity levels on the basis of target biology, as has been proposed for tocilizumab on the basis of IL-6 receptor activity upon B cell activation and immunoglobulin production[33,34]; nevertheless, there is emerging literature concerning the role of IL-17A in B cell activation and regulation, and this remains a theoretical possibility requiring future studies[35].

The low incidence of immunogenicity of secukinumab observed in these clinical studies is consistent with secukinumab being a fully human mAb[36,37]. However, there are other possible mechanisms associated with immunogenicity, even with human antibodies. These include potential epitopes formed within the highly diverse amino acid composition of the complementarity-determining regions of immunoglobulin G molecules, the loss of tolerance to self-sequences, and product-specific attributes such as dosing frequency, dose amount, administration route, and formulation factors such as impurities, host cell proteins, and the tendency to aggregate[38]. The low immunogenicity incidence for secukinumab found in the PsA and AS analysis is consistent with results from 2 different *in vitro* immunogenicity assays (Major Histocompatibility Complex-associated Peptide Proteomics and T cell activation assays), in which secukinumab was consistently associated with relatively low numbers of potential T cell epitopes and low T cell response rates[38]. Additionally, it aligns well with a recent *in vitro* immunogenicity study in which low numbers of preexisting T cells were observed for secukinumab[39]. Further research is required to confirm the association between these *in vitro* findings and the incidence of clinical immunogenicity.

The results presented here add to the consistent evidence of low immunogenicity incidence with secukinumab[20,32] and therefore, provides useful information for clinicians considering therapeutic options for patients with PsA and AS.

Secukinumab treatment was associated with TE-ADA in only 0.35% of PsA patients and 0.69% of AS patients over 52 weeks in a database of more than 2500 patients from clinical studies. The formation of ADA was not linked with immunogenicity-related AE, loss of clinical response, and/or deviations in the expected PK of secukinumab. These results are consistent with the low incidence of immunogenicity

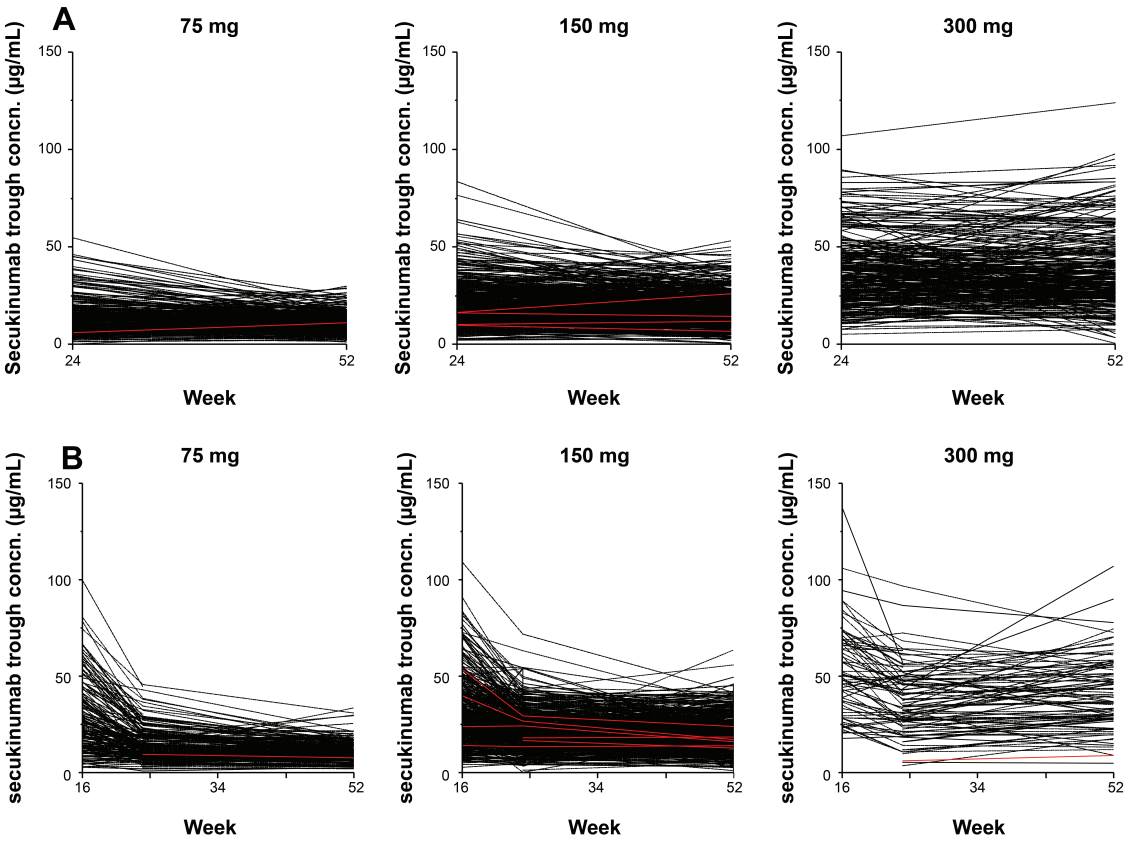


*Figure 3*. Individual trough concentrations in TE-ADA–negative and TE-ADA–positive patients with (A) PsA and (B) AS. Black solid lines: individual secukinumab serum concentrations in TE-ADA–negative patients; red solid lines: individual secukinumab serum concentrations in TE-ADA–positive patients. From left to right, at 75, 150, and 300 mg dose levels with q4w dosing intervals, trough levels at weeks 16 (AS only), 24, and 52 are shown. Pooled trough levels are from the 3 PsA clinical studies and the 4 AS clinical studies. TE-ADA: treatment-emergent antidrug antibodies; AS: ankylosing spondylitis; PsA: psoriatic arthritis; q4w: every 4 weeks.

(0.4%) seen with secukinumab over 52 weeks in clinical studies of patients with moderate to severe plaque psoriasis[20].


## ACKNOWLEDGMENT

A first draft of the manuscript was developed by the first author with editorial assistance provided by Paul Coyle, Jackie Johnson, and Aine Abautret-Daly (employees of Novartis).


## ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

## REFERENCES


1. Lubberts E. The IL-23-IL-17 axis in inflammatory arthritis. Nat Rev Rheumatol 2015;11:415-29.
2. Mitra A, Raychaudhuri SK, Raychaudhuri SP. Functional role of Il-22 in psoriatic arthritis. Arthritis Res Ther 2012;14:R65.
3. Raychaudhuri SP. Role of IL-17 in psoriasis and psoriatic arthritis. Clin Rev Allergy Immunol 2013;44:183-93.
4. Sherlock JP, Joyce-Shaikh B, Turner SP, Chao CC, Sathe M, Grein J, et al. IL-23 induces spondyloarthropathy by acting on ROR- γt+ CD3+CD4-CD8- entheseal resident T cells. Nat Med 2012; 18:1069-76.
5. Blauvelt A, Prinz JC, Gottlieb AB, Kingo K, Sofen H, Ruer-Mulard M, et al; FEATURE Study Group. Secukinumab administration by pre-filled syringe: efficacy, safety and usability results from a randomized controlled trial in psoriasis (FEATURE). Br J Rheumatol 2015;172:484-93.
6. Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CE, Papp K, et al; ERASURE Study Group; FIXTURE Study Group. Secukinumab in plaque psoriasis—results of two phase 3 trials. N Engl J Med 2014;371:326-38.
7. Mrowietz U, Leonardi CL, Girolomoni G, Toth D, Morita A, Balki SA, et al; SCULPTURE Study Group. Secukinumab retreatment-as-needed versus fixed-interval maintenance regimen for moderate to severe plaque psoriasis: a randomized, double-blind, noninferiority trial (SCULPTURE). J Am Acad Dermatol 2015;73:27-36.e1.
8. Paul C, Lacour JP, Tedremets L, Kreutzer K, Jazayeri S, Adams S, et al; JUNCTURE study group. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: A randomized, controlled trial (JUNCTURE). J Eur Acad Dermatol Venereol 2015;29:1082-90.
9. McInnes IB, Mease PJ, Kirkham B, Kavanaugh A, Ritchlin CT, Rahman P, et al; FUTURE 2 Study Group. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2015;386:1137-46.
10. Mease PJ, McInnes IB, Kirkham B, Kavanaugh A, Rahman P, van der Heijde D, et al; FUTURE 1 Study Group. Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. N Engl J Med 2015;373:1329-39.

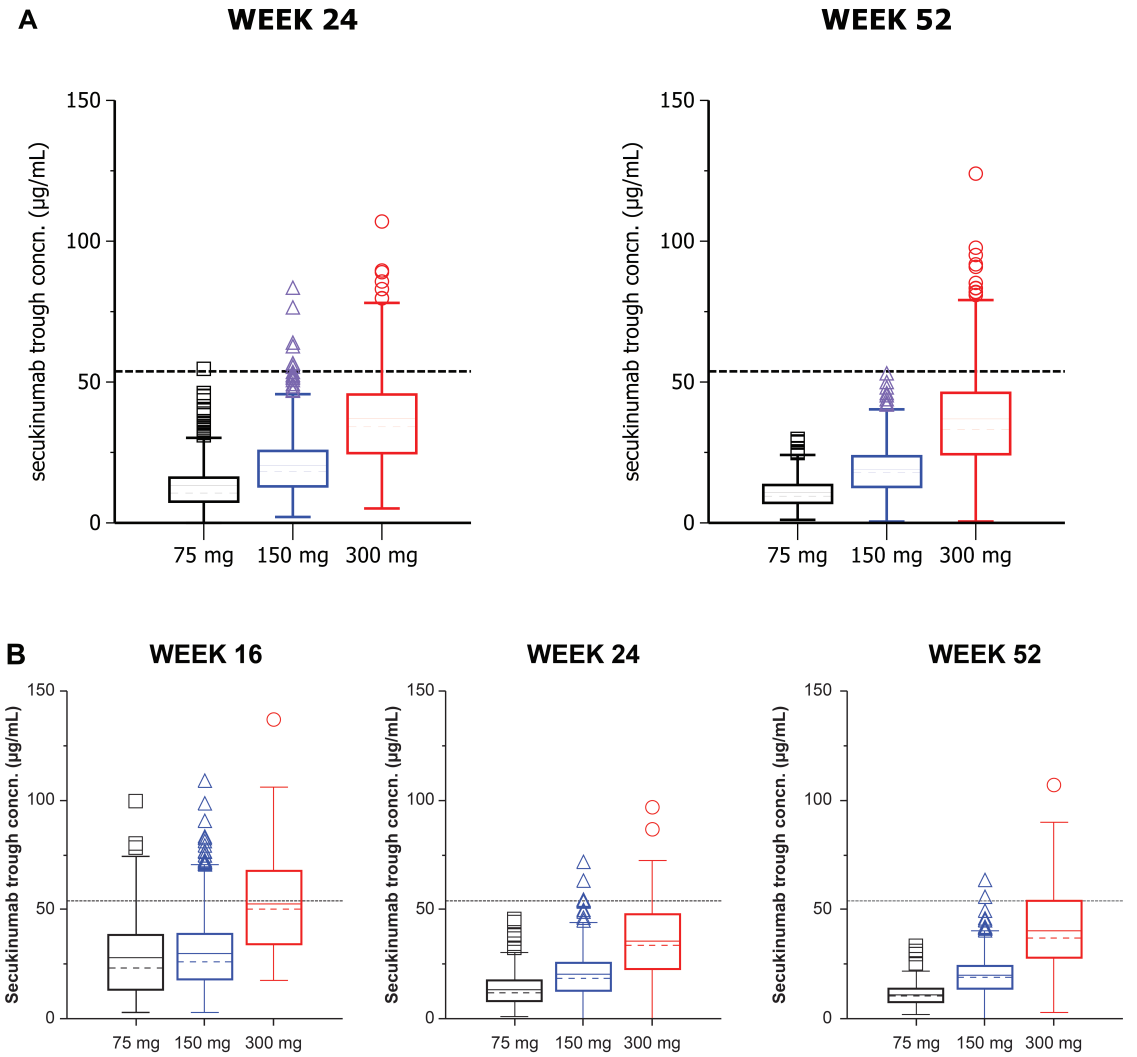


*Figure 4*. Drug tolerance and comparison of mean and median trough secukinumab serum concentrations at weeks 16 (AS only), 24, and 52 for (A) PsA (B) AS. Dashed line from Y-axis represents the drug tolerance threshold of 53.8 µg/ml. For each box-and-whisker plot, the whisker represents the range, the box represents the 25th–75th percentile, the solid and dashed lines within the box represent the mean and median trough serum concentrations, respectively. Symbols above the whisker represent outliers. AS: ankylosing spondylitis; PsA: psoriatic arthritis; concn: concentration.


11. Nash P, Mease PJ, McInnes IB, Rahman P, Ritchlin CT, Blanco R, et al; FUTURE 3 study group. Efficacy and safety of secukinumab administration by autoinjector in patients with psoriatic arthritis: Results from a randomized, placebo-controlled trial (FUTURE 3). Arthritis Res Ther 2018;20:47.
12. Baeten D, Sieper J, Braun J, Baraliakos X, Dougados M, Emery P, et al; MEASURE 1 Study Group; MEASURE 2 Study Group. Secukinumab, an interleukin-17A inhibitor, in ankylosing spondylitis. N Engl J Med 2015;373:2534-48.
13. Deodhar AA, Dougados M, Baeten DL, Cheng-Chung Wei J, Geusens P, Readie A, et al. Effect of secukinumab on patient-reported outcomes in patients with active ankylosing spondylitis: a phase III randomized trial (MEASURE 1). Arthritis Rheumatol 2016;68:2901-10.
14. Kivitz AJ, Wagner U, Dokoupilova E, Supronik J, Martin R, Talloczy Z, et al. Efficacy and safety of secukinumab 150 mg with and without loading regimen in ankylosing spondylitis: 104-week results from MEASURE 4 study. Rheumatol Ther 2018;5:447-62.
15. Pavelka K, Kivitz A, Dokoupilova E, Blanco R, Maradiaga M, Tahir H, et al. Efficacy, safety, and tolerability of secukinumab in patients with active ankylosing spondylitis: A randomized, double-blind phase 3 study, MEASURE 3. Arthritis Res Ther 2017;19:285.
16. Jahn EM, Schneider CK. How to systematically evaluate immunogenicity of therapeutic proteins - regulatory considerations. N Biotechnol 2009;25:280-6.
17. Baert F, Noman M, Vermeire S, Van Assche G, D' Haens G, Carbonez A, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. N Engl J Med 2003;348:601-8.
18. Bartelds GM, Krieckaert CL, Nurmohamed MT, van Schouwenburg PA, Lems WF, Twisk JW, et al. Development of antidrug antibodies against adalimumab and association with disease activity and

treatment failure during long-term follow-up. JAMA 2011;305:1460-8.
19. Garces S, Demengeot J, Benito-Garcia E. The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: a systematic review of the literature with a meta-analysis. Ann Rheum Dis 2013;72:1947-55.
20. Reich K, Blauvelt A, Armstrong A, Langley RG, Fox T, Huang J, et al. Secukinumab, a fully human anti-interleukin-17A monoclonal antibody, exhibits minimal immunogenicity in patients with moderate-to-severe plaque psoriasis. Br J Rheumatol 2017; 176:752-8.
21. Klein U, Liang E, Vogel B, Kolbinger F, Bruin G, Lloyd P. Immunogenicity of the anti-IL-17A antibody secukinumab in healthy subjects and patients. J Invest Dermatol 2013;133 Suppl 1:S172.
22. U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for Industry Assay Development for Immunogenicity Testing of Therapeutic Proteins; Guidance. [Internet. Accessed September 16, 2019.] Available from: www.regulations.gov/document?D=FDA-2009-D-0539-0002
23. European Medicines Agency. Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins. [Internet. Accessed September 16, 2019.] Available from: www.ema.europa.eu/documents/scientific-guideline/draft-guideline-immunogenicity-assessment-biotechnology-derived-therapeutic-proteins-revision-1_en.pdf
24. European Medicines Agency. Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use. [Internet. Accessed September 16, 2019.] Available from: www.ema.europa.eu/documents/scientific-guideline/guideline-immunogenicity-assessment-monoclonal-antibodies-intended-vivo-clinical-use_en.pdf
25. Koren E, Smith HW, Shores E, Shankar G, Finco-Kent D, Rup B, et al. Recommendations on risk-based strategies for detection and characterization of antibodies against biotechnology products. J Immunol Methods 2008;333:1-9.
26. Mire-Sluis AR, Barrett YC, Devanarayan V, Koren E, Liu H, Maia M, et al. Recommendations for the design and optimization of immunoassays used in the detection of host antibodies against biotechnology products. J Immunol Methods 2004;289:1-16.
27. Ponce R, Abad L, Amaravadi L, Gelzleichter T, Gore E, Green J, et al. Immunogenicity of biologically-derived therapeutics: assessment and interpretation of nonclinical safety studies. Regul Toxicol Pharmacol 2009;54:164-82.
28. Shankar G, Devanarayan V, Amaravadi L, Barrett YC, Bowsher R, Finco-Kent D, et al. Recommendations for the validation of immunoassays used for detection of host antibodies against biotechnology products. J Pharm Biomed Anal 2008;48:1267-81.
29. Swanson SJ, Ferbas J, Mayeux P, Casadevall N. Evaluation of methods to detect and characterize antibodies against recombinant human erythropoietin. Nephron Clin Pract 2004;96:c88-95.
30. US Food and Drug Administration. Assay development and validation for immunogenicity testing of therapeutic protein products. [Internet. Accessed September 16, 2019.] Available from: www.fda.gov/downloads/drugs/guidances/UCM192750.pdf
31. Collet-Brose J, Couble PJ, Deehan MR, Nelson RJ, Ferlin WG, Lory S. Evaluation of multiple immunoassay technology platforms to select the anti-drug antibody assay exhibiting the most appropriate drug and target tolerance. J Immunol Res 2016;2016:5069678.
32. Strand V, Balsa A, Al-Saleh J, Barile-Fabris L, Horiuchi T, Takeuchi T, et al. Immunogenicity of biologics in chronic inflammatory diseases: a systematic review. BioDrugs 2017;31:299-316.
33. Snir A, Kessel A, Haj T, Rosner I, Slobodin G, Toubi E. Anti-IL-6 receptor antibody (tocilizumab): a B cell targeting therapy. Clin Exp Rheumatol 2011;29:697-700.
34. Mihara M, Ohsugi Y, Kishimoto T. Tocilizumab, a humanized anti-interleukin-6 receptor antibody, for treatment of rheumatoid arthritis. Open Access Rheumatol 2011;3:19-29.
35. Mitsdoerffer M, Lee Y, Jäger A, Kim HJ, Korn T, Kolls JK, et al. Proinflammatory T helper type 17 cells are effective B-cell helpers. Proc Natl Acad Sci U S A 2010;107:14292-7.
36. Descotes J. Immunotoxicity of monoclonal antibodies. MAbs 2009;1:104-11.
37. Harding FA, Stickler MM, Razo J, DuBridge RB. The immunogenicity of humanized and fully human antibodies: residual immunogenicity resides in the CDR regions. MAbs 2010;2:256-65.
38. Karle A, Spindeldreher S, Kolbinger F. Secukinumab, a novel anti-IL-17A antibody, shows low immunogenicity potential in human in vitro assays comparable to other marketed biotherapeutics with low clinical immunogenicity. MAbs 2016;8:536-50.
39. Spindeldreher S, Maillere B, Correia E, Tenon M, Karle A, Jarvis P, et al. Secukinumab demonstrates significantly lower immunogenicity potential compared to ixekizumab. Dermatol Ther 2018;8:57-68.