Curr Derm Rep (2017) 6:29–34
DOI 10.1007/s13671-017-0167-8

PSORIASIS (J WU, SECTION EDITOR)

Update on Ustekinumab for Psoriasis

John K. Nia[1] · **Peter W. Hashim**[1] · **Grace Kimmel**[1] · **Ahmad Aleisa**[1] · **Ariana C. Farahani**[1] · **Mark G. Lebwohl**[1]

Published online: 27 January 2017

Abstract
Purpose of Review This review will highlight the latest data on ustekinumab, as well as provide anecdotal evidence and insight into unanswered questions regarding its safety and the populations' best suited for its use.
Recent Findings In numerous clinical trials, ustekinumab has been found to be safe and efficacious. Many targeted psoriasis medications affecting the same pathway have since been approved as treatments. Recent data supports the notion that ustekinumab does not increase risk of cardiovascular events, and in fact, may be protective against them.
Summary Targeted biologic medications for psoriasis have given insight into the complex interactions of the immune system. With these medications, patients suffering from psoriasis can now achieve up to 100 % skin clearance. Ustekinumab (Stelara®; Janssen Biotech, Inc.), a fully human monoclonal antibody against the p40 subunit of interleukin (IL) 12 and IL 23, was approved in 2009 for the treatment of moderate-to-severe plaque psoriasis and has become a standard against which other biologics are tested. Future studies should be directed toward exploring the long-term safety of ustekinumab, as well as efficacy of ustekinumab beyond 5 years of therapy.

Keywords Psoriasis · Ustekinumab · Biologic · Infection · Malignancy · MACE · Efficacy

This article is part of the Topical Collection on *Psoriasis*

✉ John K. Nia
John.Nia@mssm.edu

[1] Department of Dermatology, Icahn School of Medicine at Mount Sinai, 5 E. 98th Street, New York, NY 10029, USA

Introduction

The evolution of biologics for psoriasis is likely one of the greatest translational research success stories to date [1]. Biologic therapies for psoriasis have elucidated disease pathways and confirmed theories of the pathophysiology and key mediators in psoriasis and psoriatic arthritis [2]. Success in treating immune-mediated dermatologic conditions has also carried over into other fields of medicine, including rheumatology and gastroenterology. Nearly 7.5 million Americans suffer from psoriasis, and physicians are frequently opting to treat these patients with biologics as a first line treatment. [3, 4] Ustekinumab is a fully human monoclonal antibody targeting IL-12 and IL-23, inhibiting the Th1 and Th17 immune pathways. After receiving FDA approval for moderate-to-severe plaque psoriasis in 2009, ustekinumab quickly became the standard against which many promising novel biologics were compared.

High efficacy, favorable safety profile, and infrequent dosing all make ustekinumab an ideal treatment for patients who have been struggling with psoriasis. This article focuses on reviewing to date knowledge of ustekinumab, specifically its efficacy and safety.

Mechanism of Action

Ustekinumab is a human IgGκ monoclonal antibody that binds to the p40 protein subunit shared by IL-12 and IL-23 cytokines, preventing their interactions with the heterodimeric IL-12 receptor subunit. IL-12 and IL-23 are naturally occurring cytokines involved in inflammatory and immune responses. Lesional skin in psoriasis patients has demonstrated increased expression of IL-12 compared to non-lesional skin [5]. IL-12 and IL-23 are produced primarily by antigenic stimulation of dendritic cells and macrophages [6].

IL-12 is composed of a p35 and a p40 subunit, the latter being largely expressed in psoriatic lesional skin; its receptor is made up of IL-12RB1 and IL-12R2 subunits. Binding of IL-12 to its receptor causes activation of a JAK-STAT signaling pathway, causing T-cells to be assigned to the Th1 pathway and downstream secretion of its effector interferon gamma (IFN-γ) [7].

IL-23 is composed of p19 and p40 subunits (both of which are largely expressed in lesional skin). It binds to a receptor made of the IL-12RB1 and IL-23R subunits [8]. Similar to IL-12, binding of the p40 subunit with IL-12RB1 and the p19 subunit with IL-23R signals through JAK-STAT signaling, activating STAT3 causing a Th17 driven response [9].

Ustekinumab blocks IL-12 and IL-23 from binding to the IL-12Rβ1 receptor chain of IL-12 (IL-12Rβ1/β2) and IL-23 (IL-12Rβ1/23R) receptor complexes on the surface of NK and T cells. In vitro models showed ustekinumab equally disrupted the action of IL-12 and 23, blocking STAT 3, 4 phosphorylation and ultimately IFN-γ, IL 22, and IL-17 production [10]. Similar to endogenous IgG, ustekinumab has an approximate half-life of 3 weeks [10]. Peak serum concentration of ustekinumab occurred at approximately 13.5 days after a 45 mg dose and 7 days after a 90 mg dose; steady state drug concentrations were achieved by week 28 [11].

Efficacy in Psoriasis

Compared with conventional therapies, many biologics have exhibited increased efficacy, and ustekinumab is not an exception. Efficacy in psoriasis patients is often measured by investigators by improvement in psoriasis area severity index (PASI), body surface area (BSA), and physician global assessment (PGA). Patient-related outcomes are measured by the dermatology-related quality of life index (DLQI), a ten-question patient-centered questionnaire.

Ustekinumab has demonstrated short- and long-term efficacy in the treatment of moderate-to-severe psoriasis and remains among the most thoroughly evaluated biologics in the treatment of psoriasis. Two landmarks, phase III, prospective, long-term extension studies, PHOENIX 1 [12•] and PHOENIX 2 [13•], evaluated efficacy, measured by clinical response, and safety of ustekinumab in psoriasis patients for up to 5 years. These studies demonstrated high rates of PASI 75 response, which was largely maintained over several years of treatment.

PHOENIX 1 evaluated the efficacy and safety of ustekinumab 45 and 90 mg in 753 patients over the course of 5 years ending in 2013 [12•]. The study started with a 3 month placebo-controlled period, followed by a 7 month placebo crossover and active treatment period, a randomized withdrawal and retreatment period after 10 months, and an additional open-label four-year extension after the first year. After 5 years, most patients achieved and maintained clinical response over time. The proportion of patients who achieved PASI 75 at week 76 (45 mg, 61.2%; 90 mg, 72.4%) were similar to those observed at week 244 (45 mg, 63.4%; 90 mg, 72.0%). Since the inception of PHOENIX 1, PASI 75 has been replaced by PASI 90 as the gold standard for assessing psoriasis therapies. After 5 years, ustekinumab demonstrated high rates of PASI 90 (45 mg, 39.7%; 90 mg, 49.0%) and PASI 100 (45 mg, 21.6%; 90 mg, 26.4%) response. More than half of partial responders in PHOENIX 1who were adjusted to every 8 weeks dosing achieved and maintained PASI 75 (45 mg, 57.6%; 90 mg, 55.1%) and PASI 90 (45 mg, 27.2%; 90 mg, 27.5%) after 5 years.

The PHOENIX 2 study had the same study design as PHOENIX I through the first 28 weeks. However, PHOENIX 2 addressed whether dosing intensification would improve response in partial responders. Dosing adjustments from every 3 months to every 2 months were permitted beyond week 28. This adjustment was random for up to the 1 year time point, and thereafter adjusted at the investigators' discretion. In 2015, PHOENIX 2 data showed a large portion of patients achieved PASI 75 (45 mg, 76.5%; 90 mg, 78.6%) and PASI 90 (45 mg, 50.0%; 90 mg, 55.5%). Improved response was generally demonstrated following dosing adjustments [13•].

Psoriasis Longitudinal Assessment and Registry (PSOLAR) is a global, prospective, longitudinal, disease-based registry to evaluate safety and efficacy in patients with psoriasis [14•]. PSOLAR compares therapeutic responses among patients initiating infliximab, adalimumab, or etanercept versus ustekinumab. The most recent results from this study showed patients receiving tumor necrosis factor (TNF) inhibitors were significantly less likely to achieve a PGA of "clear" or "almost clear" compared to ustekinumab. This study showed the effectiveness of ustekinumab was significantly better versus all three TNF inhibitors for the majority of comparisons at 6 and 12 months. Of note, this registry is sponsored by Janssen Biotech.

In a comparison of one and 5-years effectiveness of adalimumab, etanercept, and ustekinumab, ustekinumab was found to have the highest efficacy when compared with etanercept. Dose escalation was more frequent with etanercept and adalimumab when compared to ustekinumab [15].

This prospective, multicenter study provides the comparative effectiveness between ADA, ETA, and USTE in real-life treatment of psoriasis patients. USTE had the highest overall effectiveness during the first 5 years of treatment compared with ETA. Dose escalation was more frequent in ETA and ADA compared with USTE. During the first year of treatment USTE and ADA had a higher chance of attaining PASI75 compared to ETA.

In our experience, patients treated with ustekinumab often see clear or almost clear skin as early as 4 months after initiating treatment. We have found that adjusting patients from dosing every 12 weeks to every 8 weeks often significantly improves patients' responses, especially in partial responders.

As seen in the PHOENIX trials, responses are relatively well maintained over long courses of treatment.

Effect of Weight on Response

The high prevalence of obesity among patients with psoriasis is well established [16]. Data pooled from PHOENIX 1 and 2 studies to assess the impact of weight on treatment efficacy showed trends toward lower efficacy and drug concentrations in patients treated with 45 mg ustekinumab. The same data set showed less of an effect of weight on efficacy in the population receiving 90 mg ustekinumab [12, 13, 17]. Data from PSOLAR reinforced the effect of weight on response to biologic therapy; patients with lower weight experienced superior results compared with heavier patients [14•].

In our experience, weight can play a significant factor in patient response to ustekinumab. Often, patients weighing just below the 100 kg necessary to receive double the dose have inferior treatment responses. To further complicate this, our heavier patients often have more severe psoriasis as well as cardiovascular and metabolic comorbidities that exacerbate this dilemma. When insurance allows, we try to increase frequency and dosage for patients. At our practice, patients receiving 90 mg of ustekinumab every 8 weeks see the best results, with no increase in adverse events. Thus far, there has not been any resistance from payers when patients increase their frequency of dosing.

Immunogenicity

Previous treatment may also impact clinical response. PHOENIX 2 investigators found partial responders were more likely to have failed treatment with at least one conventional systemic or biological agent compared to non-responders [13•]. PSOLAR demonstrated patients with prior TNF inhibitor use had less of a response compared to bionaive patients, whereas prior ustekinumab use had no effect on response [14•]. With other biologic therapies, specifically TNF inhibitors, intermittent treatment leads to an increased formation of anti-drug antibodies (ADA) [18]. PHOENIX 1 and 2 patients receiving 45 mg ustekinumab were more likely to develop ADAs compared with those on the 90-mg dose. Only 4.4% of psoriasis patients developed ADAs after ustekinumab treatment was stopped and restarted [19]. One study conducted in Taiwan found that compared with patients without anti-ustekinumab antibodies (AUA), patients positive for AUA had lower PASI improvements and drug levels [20]. In clinical practice, we have had similar experience. Patients started on TNF inhibitors who are partial responders or non-responders often see less dramatic improvements in their psoriasis when started on ustekinumab. We discourage patients from taking drug holidays when they are doing well, as we have seen loss of response when reinitiating therapy after periods of missed doses.

Safety

Few biological agents have been evaluated for their safety in psoriasis as extensively as ustekinumab. Given the mechanism of action and the patient population, questions have risen in regards to infection, major adverse cardiovascular events (MACE), and malignancy. Most of our knowledge about the long-term safety of ustekinumab is derived from PHOENIX 1, PHOENIX 2, and PSOLAR trials and is reflected in our daily practice [12, 13, 21]. With its ability to interfere with IL-12 and IL-23, ustekinumab carries a theoretical risk of predisposing patients to bacterial, viral, and fungal infection. In 2003, Fieschi et al. [22] examined 41 patients with an IL-12RB1 chain deficiency and found the only opportunistic infections were caused by weakly virulent salmonella or mycobacteria. However, ustekinumab has proven itself not to increase risk of infection. PSOLAR investigators found that exposure to the studied biologics (adalimumab, infliximab, etanercept) other than ustekinumab was significantly associated with serious infection (hazard ratio = 1.96, $P < .001$) [21••]. Dávila-Seijo et al. [23], examined data on infection from the Spanish Registry of Adverse Events for Biological Therapy in Dermatological Diseases. Interestingly, they found a significant tendency of ustekinumab toward decreasing the rate of overall infections over time [23]. Unlike TNF inhibitors, no cases of LTBI reactivation were observed in patients treated with ustekinumab receiving concomitant INH prophylaxis for LTBI [24]. Prophylaxis with isoniazid or rifampin is effective in preventing tuberculosis reactivation in patients with LTBI receiving biological therapy [25]. In patients with hepatitis B and C virus, one small study ($n = 14$) found that antiviral prophylaxis appears to minimize the risk of viral reactivation in patients with concurrent psoriasis and HBV infection [26]. Major adverse cardiovascular events (MACEs) have surfaced to be a potential concern with ustekinumab. This has been a controversial issue after a higher risk of MACEs was noted with IL-12/23 blockers in early studies. Two major meta-analyses were conducted to evaluate the risk of MACEs associated with IL-12/23 blockers and they came to conflicting conclusions [27, 28]. However, the incidence rate of MACEs in PSOLAR was found to be 0.33/100 patient years, lower than other biologics [21••]. In concordance with results from PSOLAR, Rungapiromnan et al. [29] reviewed 38 randomized controlled trials with over 18,000 patients and found no statistically significant difference in risk of MACEs associated with the ustekinumab.

More recently, Hjuler et al. [30••] examined the effects of biologic therapy on coronary artery disease progression. Patients undergoing treatment with anti-TNF agents or ustekinumab were compared to control patients with psoriasis who did not receive systemic therapy or phototherapy. Coronary artery disease progression was evaluated at baseline and 13 months using non-contrast coronary artery calcium

(CAC) CT and contrast-enhanced coronary CT angiography. Comparing the two groups, the CAC scores increased over time in controls (14 [29]; $P = 0.02$) but did not significantly worsen in the biologic group (mean [SD] yearly CAC change, −16 [56]; $P = 0.15$) (intervention vs controls; $P = 0.02$). The biologic group also demonstrated a stable severity of luminal narrowing (Wilcoxon W = 76, $n = 483$; $P = 0.39$), whereas controls showed a significant increase in this parameter (Wilcoxon W = 281, $n = 414$; $P = 0.02$).

Similarly, ustekinumab did not appear to increase the risk of malignancy. Rates of malignancy in patients receiving ustekinumab were similar to those of patients receiving placebo. Moreover, rates of malignancies other than non-melanoma skin cancer in the general population are comparable to those in patients receiving ustekinumab. Most recent analysis of safety data from PSOLAR identified no increased risk of malignancy with ustekinumab [21••].

Other Indications

Palmoplantar Psoriasis

Palmar plantar psoriasis (PPP) is associated with a higher degree of pain and an increased morbidity compared to psoriasis patients without palm and sole involvement. It is also notoriously difficult to treat using previous conventional therapies.

In an open label, a 24-week study to evaluate the safety and efficacy of ustekinumab in patients with moderate-to-severe PPP, 20 subjects received either 45 mg (patients weighing ≤100 kg), or 90 mg (patients weighing >100 kg) of ustekinumab subcutaneously at weeks 0, 4, and 16. After 16 weeks of treatment with ustekinumab, 7 of 20 subjects achieved clinical clearance, (defined as a Palm–Sole PGA of clear or almost clear). After 16 weeks of treatment, 6 out of 9 subjects who received 90 mg of ustekinumab achieved clinical clearance, compared with only 1 of 11 subjects who received 45 mg [31]. An observational study conducted in Denmark examined 11 patients with PPP receiving 45 mg ustekinumab and found complete or partial response to treatment in only 5 out of the 11 patients [32]. In our experience, PPP is exceptionally difficult to treat; ustekinumab may provide a treatment option in patients who prove to be refractory other treatments.

Pediatric Psoriasis

Ustekinumab has been shown to be safe and effective in the treatment of pediatric psoriasis. The CADMUS trial [33] was the first phase 3, randomized controlled study of 110 male and female patients aged 12 to17 years old. Patients were randomly assigned to receive a standard dose adjusted by weight (0.75 mg/kg [<60 kg], 45 mg [60–100 kg], 90 mg [>100 kg]), a half-standard dose (0.375 mg/kg [<60 kg], 22.5 mg [60–100 kg], 45 mg [<100 kg]) at weeks 0, 4, followed by every 12 weeks, or placebo at week 0 and 4 with cross over to standard or half-standard dosing at week 12.

By week 4, approximately one-third of patients in each ustekinumab group were clear or almost clear. At week 12, 67.6% of patients receiving the half-standard dose and 69.4% of patients receiving the standard dose achieved a PGA of 0 or 1, and 54.1% of patients receiving the half-standard dose and 61.1% of those receiving the full dose achieved PASI 90. In time points beyond week 12, clinical response was more favorable in the standard dose compared to the half-standard dose. The most common adverse events in this study were nasopharyngitis and upper respiratory infections.

Psoriatic Arthritis

Two landmark studies in psoriatic arthritis, PSUMMIT 1 [34] and PSUMMIT 2 [35], assessed efficacy and safety of ustekinumab in patients with psoriatic arthritis. PSUMMIT 1 examined 615 biologic naive patients that were randomized to receive ustekinumab 45 mg, 90 mg, or placebo in a 1:1:1 ratio; 50% patients receiving ustekinumab also received methotrexate. 42.4% of patients receiving 45 mg ustekinumab and 49.5% of patients receiving 90 mg ustekinumab achieved a 20% improvement in their psoriatic arthritis from baseline (ACR20). In contrast, 22.8% of patients on placebo achieved ACR20 at week 24. Patients also saw improvements in skin disease, dactylitis, enthesitis, and disease activity as measured by C-reactive peptide (CRP).

PSUMMIT-2 assessed patients previously treated with TNF inhibitors. Investigators reinforced that ustekinumab was effective in treating psoriatic arthritis in patients already exposed to a TNF inhibitor, although not as effective as those who were bionaive. These two studies continued for 2 years and showed clinical and radiographical evidence that ustekinumab is safe and effective in psoriatic arthritis. Patient-reported outcomes focusing on pain, disease activity, and the impact of disease on productivity also showed strong improvement [36]. In our clinical experience, patients tend to have better improvement in their psoriatic arthritis symptoms when on TNF inhibitors compared to ustekinumab. Interestingly, when patients in our clinic whose psoriasis is not well controlled on a TNF inhibitor are switched to ustekinumab, their psoriasis improves, however their psoriatic arthritis tends to worsen.

Monitoring

Based on AAD guidelines [37], a detailed medical history and thorough physical examination are required before initiating biologics. Dermatologists must use their discretion when monitoring patients on biologic therapy and pay special attention to chronic/recurrent infections, malignancy, and neurologic and cardiac history. Baseline PPD, CBC, and LFTs are recommended

by the AAD. In our practice, we also screen patients for hepatitis B and hepatitis C before initiating ustekinumab. After biologics are initiated, AAD recommends yearly PPD and periodic LFTs, CBC, history, and physical examinations.

Vaccinations

Patients should receive all immunizations appropriate for age as recommended by current immunization guidelines. The ustekinumab package insert specifies that patients should not receive any live vaccines; if a live vaccine is required, therapy should be stopped for 6 months before and 2 weeks after vaccination. Ustekinumab has been linked with increased severity and duration of herpes zoster outbreaks; at our practice, we insist patients receive zoster vaccination prior to initiating therapy. While inactivated vaccines are safe, their efficacy is uncertain while patients' immune systems are partially blocked on ustekinumab. The pneumococcal and annual inactivated influenza vaccines are recommended and may be taken during therapy [11].

Cost

Cost is a critical factor patients consider when starting a biologic. As of 2014, ustekinumab cost $53,909 for the first year of treatment (including induction dose at week 0 and 4) [38]. Wu et al. [39] compared health care costs, resource utilization, and dose escalation in patients receiving ustekinumab and adalimumab. Patients on ustekinumab had significantly more days with medical services, higher average total costs (more than $14,000/year), and were more likely to have a dose escalation. However, after a review of cost-effectiveness for biologics, Rouse et al. [40] found that ustekinumab is, in fact, a cost-effective treatment for moderate-to-severe psoriasis when less frequent dosing, higher adherence, sparse side effects, and lower direct and indirect costs are taken into account.

Conclusion

Ustekinumab has proven to be an effective treatment for patients with moderate to severe psoriasis. By inhibiting IL-12 and IL-23, ustekinumab has higher target specificity than earlier biologic therapies and causes less suppression of the immune system. This has been demonstrated in clinical studies and in practice, where ustekinumab use has not been associated with increases in the risk of infection or signs of immunosuppression.

Patient adherence to ustekinumab is very high, aided by dosing intervals that are less frequent than all currently available injected or oral psoriasis therapies. [41] Efficacy, tolerability, and ease of use also contribute to patient satisfaction. Overall, ustekinumab should be considered as a first-line agent in treating moderate-to-severe psoriasis and psoriatic arthritis.

Compliance with Ethics Standards

Conflict of Interest John Nia, Peter W. Hashim, Grace Kimmel, Ahmad Aleisa and Ariana Farahani declare that they have no conflict of interest.

Mark G. Lebwohl reports is an employee of the Mount Sinai Medical Center which receives research funds from Janssen Research and Development, other from Abbvie, other from Amgen, other from Anacor, other from Boehringer Ingleheim, other from Celgene, other from Eli Lilly, other from LLC, other from Kadmon, other from Medimmune/AstraZeneca, other from Novartis, other from Pfizer, other from ViDac, outside the submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Lebwohl M. Biologics for psoriasis: a translational research success story. J Invest Dermatol. 2015;135(5):1205–7.
2. Bartlett BL, Tyring SK. Ustekinumab for chronic plaque psoriasis. Lancet. 2008;371(9625):1639–40.
3. Au SC, Madani A, Alhaddad M, Alkofide M, Gottlieb AB. Comparison of the efficacy of biologics versus conventional systemic therapies in the treatment of psoriasis at a comprehensive psoriasis care center. J Drugs Dermatol. 2013;12(8):861–6.
4. Abuabara K, Wan J, Troxel AB, Shin DB, Van Voorhees AS, Bebo Jr BF, et al. Variation in dermatologist beliefs about the safety and effectiveness of treatments for moderate to severe psoriasis. J Am Acad Dermatol. 2013;68(2):262–9.
5. Famenini S, Wu JJ. The efficacy of ustekinumab in psoriasis. J Drugs Dermatol. 2013;12(3):317–20.
6. Benson JM, Peritt D, Scallon BJ, Heavner GA, Shealy DJ, Giles-Komar JM, et al. Discovery and mechanism of ustekinumab: a human monoclonal antibody targeting interleukin-12 and interleukin-23 for treatment of immune-mediated disorders. MAbs. 2011;3(6):535–45.
7. Harden JL, Krueger JG, Bowcock AM. The immunogenetics of psoriasis: a comprehensive review. J Autoimmun. 2015;64:66–73.
8. Oppmann B, Lesley R, Blom B, Timans JC, Xu Y, Hunte B, et al. Novel p19 protein engages IL-12p40 to form a cytokine, IL-23, with biological activities similar as well as distinct from IL-12. Immunity. 2000;13(5):715–25.
9. Kagami S, Rizzo HL, Lee JJ, Koguchi Y, Blauvelt A. Circulating Th17, Th22, and Th1 cells are increased in psoriasis. J Invest Dermatol. 2010;130(5):1373–83.
10. Benson JM, Sachs CW, Treacy G, Zhou H, Pendley CE, Brodmerkel CM, et al. Therapeutic targeting of the IL-12/23 pathways: generation and characterization of ustekinumab. Nat Biotechnol. 2011;29(7):615–24.
11. Stelara [package insert]. Horsham, PA: Janssen Biotech, Inc; 2014.
12. • Kimball AB, Papp KA, Wasfi Y, Chan D, Bissonnette R, Sofen H, et al. Long-term efficacy of ustekinumab in patients with moderate-

to-severe psoriasis treated for up to 5 years in the PHOENIX 1 study. J Eur Acad Dermatol. 2013;27(12):1535–45. **This study demonstrated the stable clinical response for patients receiving ustekinumab through 5 years**

13.•• Langley RG, Lebwohl M, Krueger GG, Szapary PO, Wasfi Y, Chan D, et al. Long-term efficacy and safety of ustekinumab, with and without dosing adjustment, in patients with moderate-to-severe psoriasis: results from the PHOENIX 2 study through 5 years of follow-up. Brit J Dermatol. 2015;172(5):1371–83. **This study showed that treatment with ustekinumab was safe and effective, it went further to show that more frequent dosing improved response and was well tolerated**

14.• Strober BE, Bissonnette R, Fiorentino D, Kimball AB, Naldi L, Shear NH, et al. Comparative effectiveness of biologic agents for the treatment of psoriasis in a real-world setting: results from a large, prospective, observational study (Psoriasis Longitudinal Assessment and Registry [PSOLAR]). J Am Acad Dermatol. 2016;74(5):851–861.e4.**This is another study examining the efficacy of ustekinumab, this time comparing it to commonly used TNF inhibitors. It should be noted, however, that this study was sponsored by Janssen Research and Development.**

15. Zweegers J, Groenewoud JM, van den Reek JM, Otero ME, van de Kerkhof PC, Driessen RJ, et al. Comparison of the one and 5-years effectiveness of adalimumab, etanercept and ustekinumab in psoriasis patients in daily clinical practice: Results from the prospective BioCAPTURE registry. Br J Dermatol. 2016.

16. Debbaneh M, Millsop JW, Bhatia BK, Koo J, Liao W. Diet and psoriasis, part I: Impact of weight loss interventions. J Am Acad Dermatol. 2014;71(1):133–40.

17. Lebwohl M, Yeilding N, Szapary P, Wang Y, Li S, Zhu Y, et al. Impact of weight on the efficacy and safety of ustekinumab in patients with moderate to severe psoriasis: rationale for dosing recommendations. J Am Acad Dermatol. 2010;63(4):571–9.

18. Jullien D. Anti-drug antibodies, auto-antibodies and biotherapy in psoriasis. Ann Dermatol Venereol. 2012;139(Suppl 2):S58–67.

19. Jullien D, Prinz JC, Nestle FO. Immunogenicity of biotherapy used in psoriasis: the science behind the scenes. J Investig Dermatol. 2015;135(1):31–8.

20. Chiu H-Y, Chu TW, Cheng Y-P, Tsai T-F. The association between clinical response to ustekinumab and immunogenicity to ustekinumab and prior adalimumab. PLoS One. 2015;10(11):e0142930.

21.•• Papp K, Gottlieb AB, Naldi L, Pariser D, Ho V, Goyal K, et al. Safety surveillance for ustekinumab and other psoriasis treatments from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). J Drugs Dermatol. 2015;14(7):706–14. **This pharmaceutical sponsored registry found no increase in malignancy, MACE, serious infection, or mortality with ustekinumab**

22. Fieschi C, Dupuis S, Catherinot E, Feinberg J, Bustamante J, Breiman A, et al. Low penetrance, broad resistance, and favorable outcome of interleukin 12 receptor β1 deficiency: medical and immunological implications. J Exp Med. 2003;197(4):527–35.

23. Dávila-Seijo P, Dauden E, Descalzo MA, Carretero G, Carrascosa J-M, Vanaclocha F, et al. Infections in moderate-to-severe psoriasis patients treated with biological drugs compared to classic systemic drugs: Findings from the BIOBADADERM registry. Journal of Investigative Dermatology.

24. Tsai TF, Ho V, Song M, Szapary P, Kato T, Wasfi Y, et al. The safety of ustekinumab treatment in patients with moderate-to-severe psoriasis and latent tuberculosis infection. Brit J Dermatol. 2012;167(5):1145–52.

25. Gisondi P, Pezzolo E, Lo Cascio G, Girolomoni G. Latent tuberculosis infection in patients with chronic plaque psoriasis who are candidates for biological therapy. Brit J Dermatol. 2014;171(4):884–90.

26. Chiu HY, Chen CH, Wu MS, Cheng YP, Tsai TF. The safety profile of ustekinumab in the treatment of patients with psoriasis and concurrent hepatitis B or C. Brit J Dermatol. 2013;169(6):1295–303.

27. Tzellos T, Kyrgidis A, Trigoni A, Zouboulis CC. Association of anti-IL-12/23 biologic agents ustekinumab and briakinumab with major adverse cardiovascular events. J Eur Acad Dermatol Venereol. 2013;27(12):1586–7.

28. Bigby M. The use of anti-interleukin-12/23 agents and major adverse cardiovascular events. Arch Dermatol. 2012;148(6):753–4.

29. Rungapiromnan W, Yiu ZZN, Warren RB, Griffiths CEM, Ashcroft DM. Impact of biologic therapies on risk of major adverse cardiovascular events in patients with psoriasis: systematic review and meta-analysis of randomised controlled trials. Brit J Dermatol. 2016:n/a-n/a.

30.•• Hjuler K, Bøttcher M, Vestergaard C, Bøtker H, Iversen L, Kragballe K. Association between changes in coronary artery disease progression and treatment with biologic agents for severe psoriasis. JAMA Dermatology. 2016;152(10):1114–21. **This study examined the effect of biologics on development of coronary artery disease. Investigators found treatment with biologic agents was associated with reduced coronary artery disease progression in patients with severe psoriasis**

31. Au SC, Goldminz AM, Kim N, Dumont N, Michelon M, Volf E, et al. Investigator-initiated, open-label trial of ustekinumab for the treatment of moderate-to-severe palmoplantar psoriasis. J Dermatolog Treat. 2013;24(3):179–87.

32. Bertelsen T, Kragballe K, Johansen C, Iversen L. Efficacy of ustekinumab in palmoplantar pustulosis and palmoplantar pustular psoriasis. Int J Dermatol. 2014;53(10):e464–e6.

33. Landells I, Marano C, Hsu MC, Li S, Zhu Y, Eichenfield LF, et al. Ustekinumab in adolescent patients age 12 to 17 years with moderate-to-severe plaque psoriasis: results of the randomized phase 3 CADMUS study. J Am Acad Dermatol. 2015;73(4):594–603.

34. McInnes IB, Kavanaugh A, Gottlieb AB, Puig L, Rahman P, Ritchlin C, et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet. 2013;382(9894):780–9.

35. Ritchlin C, Rahman P, Kavanaugh A, McInnes IB, Puig L, Li S, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. Ann Rheum Dis. 2014;73(6):990–9.

36. Rahman P, Puig L, Gottlieb AB, Kavanaugh A, McInnes IB, Ritchlin C, et al. Ustekinumab treatment and improvement of physical function and health-related quality of life in patients with psoriatic arthritis. Arthritis Care Res (Hoboken). 2016.

37. Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol. 2008;58(5):826–50.

38. Cheng J, Feldman SR. The cost of biologics for psoriasis is increasing. Drugs in context. 2014;3:212266.

39. Wu JJ, Guerin A, Gauthier G, Sundaram M. Healthcare resource utilization, healthcare costs, and dose escalation in psoriasis patients initiated on ustekinumab versus adalimumab: a retrospective claim study. J Dermatolog Treat. 2016:1–23.

40. Rouse NC, Farhangian ME, Wehausen B, Feldman SR. The cost-effectiveness of ustekinumab for moderate-to-severe psoriasis. Expert Rev Pharmacoecon Outcomes Res. 2015;15(6):877–84.

41. Hsu DY, Gniadecki R. Patient adherence to biologic agents in psoriasis. Dermatology. 2016;232(3):326–33.