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Ustekinumab in the treatment of psoriatic arthritis: latest findings and clinical potential

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Abstract: Ustekinumab (UST) is a fully human immunoglobulin G1κ (IgG1κ) monoclonal antibody against common sub-unit p40 of interleukin-12 (IL-12) and interleukin-23 (IL-23). IL-12 and IL-23 are essential components of the Th1 and Th17 inflammatory pathways, respectively, and are the key mediators of psoriasis. Psoriatic arthritis (PsA), an important systemic inflammatory disorder, has similar pathogenesis to psoriasis. Many of PsA patients do not respond to tumor necrosis factor (TNF) inhibitor therapy, highlighting the need for additional treatment modalities with distinct mechanisms of action. Also, many patients stop responding to these agents after a certain period of use. A significant number of patients have a recurrent course or a persistent disease process. To meet these challenges a new agent working on different inflammatory aspect of PsA is needed. UST has been demonstrated to be effective, safe on short-term use and convenient in the treatment of plaque psoriasis and PsA. Long-term safety is still a concern. Until recently, the exact role of UST in the management of PsA had not been very clear. This article reviews the mechanism of action, pharmacokinetics, efficacy, safety profile and the clinical potential of UST in patients with PsA. We also discuss the three major trials conducted to show the efficacy and safety of UST in PsA.

Keywords: Psoriatic arthritis, ustekinumab, psoriasis, PSUMMIT-I

Introduction

Ustekinumab (UST) is a fully human immunoglobulin G1κ (IgG1κ) monoclonal antibody against the common sub-unit p40 of interleukin-12 (IL-12) and interleukin-23 (IL-23) [Krueger *et al.* 2007]. In September 2009, the US Food and Drug Administration (FDA) approved its use for adult patients with moderate-to-severe plaque psoriasis. It has also been approved in Canada and Europe to treat moderate-to-severe plaque psoriasis. Like psoriasis, psoriatic arthritis (PsA) is an important systemic inflammatory disorder characterized by the association of inflammatory arthritis with skin psoriasis. Tumor necrosis factor (TNF) inhibitors have proven highly effective for PsA, with significant improvements in articular and dermatologic involvement, enhanced quality of life and functional status, and inhibition of radiographic joint damage [Antoni *et al.* 2005; Gladman, 2002; Mease *et al.* 2004, 2005]. However, not all PsA patients respond to TNF inhibitor therapy, highlighting the need for additional treatment modalities with distinct mechanisms of action. Also, many patients stop responding to these agents after a certain period of use. A significant number of patients have a recurrent course or a persistent disease process. To meet these challenges, a new agent working on different inflammatory aspect of PsA is needed. Until recently, the exact role of UST in the management of PsA had not been very clear. This article reviews the mechanism of action, pharmacokinetics, efficacy, safety profile and the clinical potential of UST in patients with PsA.

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Mechanism of action of ustekinumab in PsA

Like psoriasis, acquired immunity involving the Th17/IL-23 axis is considered to play an important role in PsA [Di Cesare *et al.* 2009; Lowes *et al.* 2008]. However, differences have been suggested between arthritis-specific pathology and cutaneous psoriatic lesions.

IL-12B, *IL-23R* genes, psoriasis and PsA

Cargill and colleagues have shown that psoriasis susceptibility is associated with single-nucleotide polymorphisms (SNPs) within the interleukin-23 receptor (*IL-23R*) and *IL-12B*, the gene that encodes for subunit of ligand of IL-23R [Cargill *et al.*, 2007]. Both contribute to susceptibility to psoriasis independently. Later in 2009, Nair and colleagues reported that the two genes contributed to psoriasis susceptibility in an additive fashion [Nair *et al.* 2008]. Given the active involvement of IL-12 and IL-23 in the pathogenesis of psoriasis and genetic susceptibility with SNPs within *IL-23R* and *IL-12B*, it will be interesting to know if similar exist for PsA. Recently, it was shown that PsA-like psoriasis is associated with variation in both of the above genes [Filer *et al.* 2008]. The effect sizes seen were smaller with PsA than psoriasis but were statistically significant [Filer *et al.* 2008]. Since, the criteria for enrolling PsA patients in this article was to get the DNA samples from the patients with psoriasis and inflammatory arthritis, concluding association of genes solely with PsA would be impossible.

IL-12 and IL-23 are essential for the induction and maintenance of the Th1/Th17 immune response, respectively, which is the main cytokine profile of psoriasis [Di Cesare *et al.* 2009; Lowes *et al.* 2008]. IL-23 activates Th17, which produces interleukin-17 (IL-17), activating dendritic cells to produce IL-12, hence stimulating Th1 [Di Cesare *et al.* 2009; Lowes *et al.* 2008].

Similar involvement of IL-12 and IL-23 in the pathogenesis and similar susceptibility loci might predispose one to think that a drug affecting these should produce similar results in psoriasis and PsA. Given the frequent association of both entities, it is difficult to conclude any true relation. We discuss the clinical potential of UST in the management of PsA later in the article.

Pharmacokinetics

Zhu and colleagues analyzed the data from phase II trials of UST in patients with PsA to characterize the population pharmacokinetics of subcutaneous UST and compared them with those from patients with moderate-to-severe plaque psoriasis [Zhu *et al.* 2010]. They concluded that the pharmacokinetics of UST in patients with PsA is comparable with that of patients with moderate-to-severe plaque psoriasis in terms of population typical mean values for apparent clearance (CL/F), apparent volume of distribution (V/F) and absorption rate constant. Apart from the body weight and antibody status of patients, none of the other factors including previous treatment modalities were responsible for intersubject variability in CL/F and/or V/F. The comparable pharmacokinetics in PsA patients further strengthens the fact that UST should produce similar results in both psoriasis and PsA [Zhu *et al.* 2010]. Although, such hypothesis would need more proof and we will discuss in details below about the safety and efficacy of UST in PsA.

Efficacy

Six large clinical trials have shown UST to be an excellent drug in the management of psoriasis. Before reviewing the three large trials of UST in PsA, a brief review of UST in psoriasis will be helpful in comparing and assessing its true role in PsA.

Two small phase I studies conducted by Kauffman and colleagues (n = 18) and Gottlieb and colleagues (n = 21) showed comparable results when UST was used intravenously and subcutaneously, respectively [Gottlieb *et al.* 2007; Kauffman *et al.* 2004]. A Psoriasis Area and Severity Index score of 75 (PASI 75) was achieved in 67% of the patients between 8 and 16 weeks after study drug administration. Of the 17 subjects who received study drug, 13 (76%) achieved PASI 75, and none of the patients who received placebo achieved PASI 75. These early studies demonstrated excellent clinical improvement [Gottlieb *et al.* 2007; Kauffman *et al.* 2004].

A phase II, multicenter, randomized, double-blind, placebo-controlled trial (n = 320) was conducted in the US, Canada and Europe. At the primary endpoint of 12 weeks, PASI 75 was achieved in 52% of patients who received 45 mg, 59% of those who received 90 mg, 67% of those who received 4-weekly 45 mg doses, 81% of those who received 4-weekly 90 mg doses, and 2% of those who received placebo [Krueger *et al.* 2007].

The phase III PHOENIX 1 and PHOENIX 2 studies evaluated the longer term safety and efficacy of UST compared with placebo. At the primary endpoint of week 12, 67.1% of patients receiving 45 mg, 66.4% of patients receiving 90 mg, and 3.1% of those receiving placebo achieved PASI 75 [Leonardi *et al.* 2008; Papp *et al.* 2008]. The PHOENIX 2 trial additionally assessed whether dosing intensification would improve

clinical response rates in patients who partially responded to initial treatment [Papp *et al.* 2008]. Overall, the study provided impressive long-term efficacy rates and suggested that higher dosages given more frequently may benefit those patients who are considered partial responders [Papp *et al.* 2008].

Another phase III trial, ACCEPT (n = 903) was designed to compare UST with etanercept for the treatment of psoriasis. At the primary endpoint of 12 weeks, the percentage of patients achieving a PASI 75 response in the UST 45 mg group, UST 90 mg group and etanercept 50 mg group was 68%, 74% and 57% respectively [Griffiths *et al.* 2010].

The PEARL trial was a 36-week, double-blind, placebo-controlled study in which 121 Taiwanese and Korean (moderate-to-severe psoriasis) patients were randomized to receive either UST 45 mg at week 0, 4 and 16, or placebo at weeks 0, 4 and UST 45 mg at weeks 12 and 16 [Tsai *et al.* 2011]. Efficacy (and safety) rates in these Asian patients were largely consistent with the global phase II and phase III studies involving predominantly Caucasian populations [Leonardi *et al.* 2008; Papp *et al.* 2008; Tsai *et al.* 2011].

Au and colleagues studied the role of UST in 20 subjects with moderate-to-severe psoriasis of the palms and soles [Au *et al.* 2013]. They treated patients who have previously failed topical steroids with UST at weeks 0, 4 and 16. Dose was adjusted according to weight, 45 mg UST subcutaneously for subjects weighing < 100 kg and 90 mg for subjects weighing ≥100 kg. After 16 weeks' treatment, 35% (7/20) of subjects achieved clinical clearance, 60% (12/20) improved two or more points on the Palm-Sole Physician's Global Assessment scale, and 67% (6/9) of those receiving the 90 mg UST dose achieved clinical clearance compared with 9% (1/11) receiving 45 mg (p = 0.02). At 24 weeks, mean values showed 56% improvement in Dermatology Life Quality Index, and 34% improvement in pain Visual Analogue Scale score (all $p < 0.05$). It was concluded that UST dosed at 90 mg is effective in controlling signs and symptoms of palmoplantar psoriasis [Au *et al.* 2013].

This brief review of clinical trials of UST in moderate-to-severe psoriasis supports its excellent role as a treatment modality for patients with moderate to severe psoriasis. Below we review in detail the three major trials (one phase I and two phase II) of UST in patients with PsA.

In 2009, the first phase II, double blind, randomized, placebo-controlled and crossover study of UST was published, which showed significant improvements in articular and dermatologic involvement in PsA patients [Gottlieb *et al.* 2009]. A total of 146 patients with active PsA, defined as having three or more tender joints, three or more swollen joints, and either an elevated C-reactive protein (CRP) or morning stiffness lasting 45 minutes or more were recruited from dermatological practices. Patients also needed to have active skin psoriasis with at least one plaque of 2 cm diameter or greater. All patients were randomly allocated to receive therapy with either subcutaneous UST (mostly 63 mg) at weeks 0, 1, 2 and 3, followed by placebo at weeks 12 and 16 (n = 76) or placebo at weeks 0, 1, 2 and 3, followed by UST at weeks 12 and 16 (n = 70). The primary endpoint was the percentage of patients achieving an American College of Rheumatology (ACR) 20 response at week 12. The first 12 weeks were placebo-controlled and patients were followed up to week 36. Patients who had received UST at weeks 0, 1, 2 and 3 received no further treatment till week 36. At week 12, 42.1% of the UST-dosed cohort achieved an ACR20 response compared with only 14.3% of the placebo-dosed cohort. Interestingly, at week 36, despite 33 weeks of no treatment in UST group, roughly three-quarters of patients retained their ACR20 response. The placebo-dosed cohort received UST (63 mg) at weeks 12 and 16; their ACR20 response 12 weeks later was 45%. Also, the median percentage improvement in morning stiffness at week 12 was 50% in the UST-dosed group compared with 0% in the placebo cohort. Patients with higher CRP values achieved better results.

In summary, this study showed the PsA patients responded well to UST. Two important points need to be considered here. The first was whether we could compare these results with TNF blockers, which have been shown to be effective and safe in PsA patients. The second big question is about the safety profile of this drug. Both these questions remain unanswered, as the patient population in this study was not comparable with those of the phase II and III studies of infliximab, adalimumab and etanercept in PsA. The patients in this study were recruited from dermatology practices. The baseline characteristics of the study population were different from those seen in the

trials conducted through rheumatology practices. For example, the percentage of patients using concomitant methotrexate (MTX) and non-steroidal anti-inflammatory drugs (NSAIDs) was only 20% and 50%, respectively. Most of the patients in trials of TNF blockers were on NSAIDs, MTX or oral corticosteroids. The baseline CRP values were lower in the UST study. In addition, about a quarter of patients treated in this study had previously received TNF inhibitors. Safety issues were not studied in this study.

In the same study, changes in physical function with treatment with UST were also studied and reported later [Kavanaugh *et al.* 2010]. Physical function was assessed using the disability index from the Health Assessment Questionnaire-Disability Index (HAQ-DI) in all randomized patients. health-related quality of life (HRQoL) was evaluated using the Dermatology Life Quality Index (DLQI) in a subset of patients (84.9%) with at least 3% body surface area (BSA) psoriasis involvement at baseline. At baseline, overall mean HAQ-DI and DLQI scores were 0.9 and 11.5, respectively, indicating impaired physical function and moderate effect on HRQoL. At week 12, UST patients had significantly more improvement (decrease) in the mean HAQ-DI (−0.31) and DLQI (−8.6) scores *versus* placebo (−0.04 and −0.8, respectively; $p < 0.001$ for both comparisons). At week 12, 58.7% (37/63) of UST-treated patients had a DLQI score of 0 or 1 (no negative effect of disease or treatment on HRQoL) *versus* 5.5% (3/55) for placebo ($p < 0.001$). Although the short duration of the placebo-controlled period and the relatively small patient population are potential limitations of the study, the findings in terms of improvement of quality of life of PsA patients on UST are very relevant and important [Kavanaugh *et al.* 2010]. The modest efficacy shown in this multicenter phase II study in patients with PsA led to phase III trials to investigate the efficacy and safety of UST in active PsA.

Recently, results of the phase III, multicenter, double blind and placebo-controlled PSUMMIT I study (Table 1) were presented, which assessed the efficacy and safety of UST in reducing signs and symptoms of active PsA in 615 patients who were naïve to biological drugs [McInnes *et al.*, 2013]. A total of 615 adult PsA patients with active disease with ≥5 swollen joint count (SJC) and ≥5 tender joint count (TJC) (CRP ≥0.3 mg/dL) were randomized to receive UST 45 mg, 90 mg or placebo at weeks 0, 4, and 12 weeks, thereafter. Patients using disease-modifying anti-rheumatic drug (DMARD) and/or NSAID therapy were permitted in the study. Stable concomitant MTX use was also permitted but patients with past history of use of any TNF blockers were excluded. At week 16, patients with <5% improvement in TJC and SJC entered blinded early escape (placebo entered into UST 45 mg; UST 45 mg entered into UST 90 mg group). The primary endpoint was ACR20 response at week 24. Secondary endpoints at week 24 included: ACR 50/70, Disease Activity Score (DAS) 28 using CRP (DAS28-CRP) response; change from baseline (BL) in HAQ-DI; PASI 75 response (in patients with ≥3% BSA involvement); and percentage change from baseline in enthesitis and dactylitis scores (in patients affected at baseline). Adverse events (AEs) are reported through the placebo-controlled period (week 16) and through week24.

The results showed that significantly greater proportions of UST-treated *versus* placebo patients had ACR20 response at week 24. Significant improvements were also observed with UST 45 mg and 90 mg for ACR50/70 responses and DAS28-CRP responses at week 24 *versus* placebo. At week 24, 66 % and 68 % of patients receiving UST 45 mg and 90 mg, respectively, reported a European League Against Rheumatism (EULAR)/DAS28-CRP response compared with 34 % of placebo patients ($p < 0.001$). The DAS28 is a measure of disease activity in patients with arthritis calculated by assessing the number of tender and swollen joints (out of a total of 28), inflammation, and the patient's assessment of global health. The changes from baseline in HAQ-DI at week 24 were significantly greater in the UST than in the placebo group, and significantly greater proportions of UST-treated patients had a clinically meaningful change from baseline in HAQ-DI. Nearly half of the patients used concomitant MTX at baseline; this did not alter the likelihood of benefit of UST *versus* placebo. While ACR responses were greater with UST than placebo regardless of MTX use, differences were numerically larger among patients not taking MTX. Of 440 patients with ≥3% BSA involvement at baseline, significantly larger proportion of UST patients achieved PASI 75 at week 24. Among patients affected with enthesitis ($n = 425$) or dactylitis ($n = 286$) at baseline, significantly greater improvements in enthesitis and dactylitis were observed at week 24 in the UST group than placebo.

Table 1. PSUMMIT I efficacy results at week 24.*

	Placebo (n = 206)	UST 45 mg (n = 205)	UST 90 mg (n = 204)
ACR 20 (%)	22.8	42.4	49.5
ACR 50 (%)	8.7	24.9	27.9
ACR 70 (%)	2.4	12.2	14.2
DAS28-CRP response (%)	34.5	65.9	67.6
Median HAQ-DI change from baseline	0	−0.3	−0.3
Median % change in enthesitis score	0	−42.9	−50
Median % change in dactylitis score$	0	−75	−70.8

*Table is developed from the results shown in PSUMMIT study published and presented at 2012 EULAR Annual Congress.
$Among patients affected at baseline; $p < 0.001$ for all parameters *versus* placebo.
ACR 20, American College of Rheumatology 20 response; ACR 50, American College of Rheumatology 50 response; ACR 70, American College of Rheumatology 70 response; DAS28-CRP, Disease Activity Score in 28 joints using the C-reactive protein level; EULAR, European League Against Rheumatism; HAQ-DI, Health Assessment Questionnaire-Disability Index; UST, ustekinumab.

Interestingly, the improvements in enthesitis scores (−83.3, −74.2 and −87.5) and dactylitis scores (−100 in all patients) in the UST 45 mg, 90 mg and crossover groups, respectively, continued through week 52.

The significant results shown by PSUMMIT I led later to the PSUMMIT II trial (Table 2), which was another phase III, multicenter, randomized, double blind, placebo-controlled study including 312 adults with PsA designed to evaluate the efficacy and safety of UST in adults with PsA [Ritchlin *et al.* 2012]. PSUMMIT I studied the PsA patient naïve to TNFα agents and, practically, many PsA patients are treated with these agents. It was essential to study the role of UST in patients who have been treated with anti-TNF treatment previously, to know the real clinical potential of UST. This trial included patients diagnosed with active PsA who had at least five tender and five swollen joints and CRP levels of at least 0.3 mg/dL despite treatment with DMARDs and/or NSAIDs and/or prior exposure to anti-TNF treatment, including 8–14 weeks of exposure to currently available anti-TNFα treatments and/or documented evidence of anti-TNFα intolerance/toxicity with 8–14 weeks' exposure. Concurrent MTX use was also permitted. Within the trial, 180 patients had prior exposure to anti-TNFα treatments and 132 patients were anti-TNFα naïve.

Patients were randomized to three groups: UST 45 mg or UST 90 mg at weeks 0, 4 and then every 12 weeks or placebo. At week 16, patients with <5% improvement in TJC and SJC were entered into blinded early escape as in PSUMMIT I. The primary endpoint was ACR 20 response at week 24. Secondary endpoints at week 24 included ACR 50 and ACR 70 response, DAS28-CRP response, PASI 75 in patients with at least 3% BSA involvement at baseline, improvements in enthesitis and dactylitis scores, and improvements in HAQ-DI scores.

ACR 70 responses for both UST groups were greater, though not significantly, than for the placebo group at week 24. Significant improvements from baseline to week 24 were also observed in physical function, as measured by the HAQ-DI, in the UST 45 mg and 90 mg treatment groups compared with placebo-treated patients [Ritchlin *et al.* 2012].

Safety profile

UST is generally supported as being well tolerated throughout the clinical trials involved in establishing its role in the world of psoriasis and PsA [Gottlieb *et al.* 2007; Griffiths *et al.* 2010; Kauffman *et al.* 2004; Krueger *et al.* 2007; Leonardi *et al.* 2008; Papp *et al.* 2008].

The phase I trials studying the role of UST in psoriasis were able to assess its short-term safety. No serious related AEs were reported and the majority of AEs were mild in intensity [Gottlieb *et al.* 2007; Kauffman *et al.* 2004]. Gottlieb and colleagues reported the most commonly seen AEs were upper respiratory infections, creatine phosphokinase (CPK) elevations, and lymphopenia [Gottlieb *et al.* 2007]. Kauffman and colleagues reported headache and common cold symptoms to be the most common AEs after single injection [Kauffman *et al.* 2004].

Table 2. PSUMMIT II efficacy results at week 24.

	Placebo	UST 45 mg	UST 90 mg
ACR 20 (%)	20.2	43.7 ($p < 0.001$)	43.8 ($p < 0.001$)
ACR 20 in patients previously treated with TNFα agents (%)	14.5	36.7 ($p = 0.006$)	34.5 ($p = 0.011$)
ACR 50 (%)	6.7	17.5 ($p = 0.018$)	22.9 ($p = 0.001$)
PASI 75 (%)	5	51.3 ($p < 0.001$)	55.6 ($p < 0.001$)

ACR 20, American College of Rheumatology 20 response; ACR 50, American College of Rheumatology 50 response; PASI 75, Psoriasis Area and Severity Index score of 75; TNFα, tumour necrosis factor α; UST, ustekinumab.

Following the reporting of the phase II results reported by Krueger and colleagues, serious AEs following administration of UST began to appear in the literature. Serious AEs included a single case each of coronary artery disorder, urinary tract infection, congestive heart failure, cellulitis, viral syndrome, and elevated liver-enzyme levels [Krueger *et al.* 2007].

The PHOENIX trials were the first large-scale studies conducted to assess the safety profile of UST treatment in patients with moderate-to-severe psoriasis The most common serious AEs in UST-treated patients included infections in nine (0.7%) patients and cardiac disorders in nine (0.7%) patients [Leonardi *et al.* 2008; Papp *et al.* 2008].

The PEARL trial also showed similar results in terms of safety of UST. No serious AEs, malignancy or cardiovascular (CV) events were reported at week 12 [Tsai *et al.* 2011]. Serious AEs reported between weeks 12 and 36 weeks included two patients in the UST 45 mg group (i.e. one with a facial bone fracture and one with Henoch– Schonlein purpura) and five patients in the placebo group who had crossed over to UST 45 mg, (i.e. two patients with uncomplicated appendicitis and one each with reactivated pulmonary tuberculosis (TB), muscle injury, and benign parathyroid tumor [Tsai *et al.* 2011].

The ACCEPT trial continued to show similar results in terms of safety of UST. The 12-week data from this trial revealed that three patients were newly diagnosed with nonmelanoma skin cancer (NMSC) in the UST arms; however, given the short trial duration, the clinical relevance is to be studied further [Griffiths *et al.* 2010].

In 2011, Igarashi and colleagues reported that the most common AE in the treated patients was nasopharyngitis (45 mg, 10/64, 15.6%; 90 mg, 10/62, 16.1%). Increased triglycerides and CPK, and seasonal allergies, including allergic rhinitis, were amongst other more common reported side effects [Igarashi *et al.* 2012].

In 2012, a 4-year safety analysis reported by Reich and colleagues of 3117 patients who received at least one dose of UST during the Phase II study, the PHOENIX I or II studies, or the ACCEPT study, demonstrated consistent safety up to 4 years [Igarashi *et al.* 2012]. Interestingly, there was no indication of an increasing trend in the incidence of serious infections, NMSC, malignancies other than NMSC, and major adverse cardiovascular events (MACEs) compared with the expected levels based on population-matched rates. They specifically studied the CV events in placebo-controlled groups and concluded that there was no increased risk of myocardial infarction (MI) or stroke in UST-treated patients compared with the general population as well as non-UST-treated psoriasis patients. Another important conclusion reported was that the MACE rates were notably stable during both placebo-controlled and uncontrolled trials [Reich *et al.* 2011].

The safety profile of UST has been well examined in the trials studying its role in moderate-to-severe psoriasis. The review reported by Reich and colleagues further supports UST as being well tolerated [Reich *et al.* 2011]. Below we review the safety evaluation reported in two major phase III trials studying its role in PsA.

Both phase III trials studied the AEs in both UST and placebo groups [Kavanaugh *et al.* 2010; McInnes *et al.* 2013]. During PSUMMIT I, AEs are reported through the placebo-controlled period (week 16). Through week 16, the proportion of patients with at least one AE was similar between patients receiving UST (41.8%) and placebo (42.0%), with infections being the most common AE; 1.7% (UST) and 2.0% (placebo) had at least one serious AE.

Safety through week 52 was consistent with that observed during the placebo-controlled period between UST 45 mg and 90 mg groups in the incidence of AEs (66.8% and 64.7%, respectively) and serious AEs (5.9% and 3.4%, respectively). No malignancies, cases of TB, opportunistic infections or deaths occurred through week 52. Three MACEs were reported in UST-treated patients in patients with multiple pre-existing CV risk factors.

During PSUMMIT II, similar proportions of patients experienced at least one AE through week 16, the placebo-controlled period, among those receiving UST 45 mg (63.1%), UST 90 mg (60.6%) and placebo (54.8 %) with infections being the most common AE [Ritchlin *et al.* 2012]. Serious AEs reported among the groups were UST 45 mg (0%), UST 90 mg (1.0%) and placebo (4.8%). No cases of TB, opportunistic infections, MACEs or deaths occurred. Through week 24, one serious infection due to complications of pre-existing interstitial lung disease was reported in the placebo group and one skin malignancy (squamous cell carcinoma *in situ*) occurred in the UST 90 mg group.

Latent TB infection (LTBI) and ustekinumab

Activation of latent TB is of concern while using any biological therapy. Tsai and colleagues reported in their meta-analysis of all five phase III trials involving UST administration that 101⁄2898 non-Asian and 66⁄279 Asian patients were newly identified with LTBI at their baseline visits. They reported that the rates of AE representative of isoniazid (INH) toxicity (e.g. markedly abnormal alanine transaminase values) were generally comparable between control and UST-treated patients, as well as in both the dose groups [Tsai *et al.* 2012]. Igarashi and colleagues also reported that out of 158 patients 13.3% (21) were diagnosed as having latent TB at screening [Igarashi *et al.* 2012]. As activation of latent TB is one of the major concerns, after screening, INH treatment is necessary if found to be positive.

NMSC and ustekinumab

Large trials failed to confirm any clear association between the anti-TNFα agents and cutaneous malignancies. Young and Czarnecki reported cases of two patients who developed eruptive cutaneous squamous cell carcinoma soon after commencement of UST for treatment of psoriasis [Young and Czarnecki, 2012]. It is noteworthy that both these patients had independent risk factors for developing NMSCs. Both these patients carried significant risk factors for cutaneous malignancy. Both of them had history of extended periods of therapy with psoralen plus ultraviolet A (PUVA) [Young and Czarnecki, 2012]. Although larger trials have shown comparable incidence of NMSC amongst placebo and different dose groups, reports of these types definitely stress on the importance of continued postmarket data analysis.

Ustekinumab and reversible posterior leukoencephalopathy syndrome (RPLS). RPLS is a neurological disorder of unknown etiology which may present with headache, seizures, confusion and visual disturbances. One case of RPLS has been reported. The patient received 12 doses of UST over approximately 2 years and presented with headache, seizures and confusion. No additional injections were administered and the subject fully recovered [Gratton *et al.* 2011].

Immunogenicity

Immunogenicity of biological agents is always a concern while treating the patients with these agents. As per the information sheet provided by the drug manufacturers, two studies ($n = 746$) ($n = 1202$), conducted for 3 and 4 years, respectively, both showed the presence of antibodies in 5% of the patients; results were inconclusive in 78% of patients in study 1 and 82% of the patients in study 2. The presence of UST in the serum, timing of sample collection, handling, concomitant medications, and the underlying disease and health of the patient influence the results of the tests to detect antibodies. The clinical relevance of presence of anti-UST antibodies is yet to be studied.

Postmarketing data

Immune system disorders including angioedema and hypersensitivity reactions have been reported during postapproval use of UST. It is difficult to establish a causal relationship to UST exposure because these events are reported voluntarily from a population base of an uncertain size.

Use in patients with existing or recent past history of malignancy

The use of UST in patients with an existing and past history of malignancy has not been studied primarily because all the studies conducted exclude

patients with history of malignancy. It is recommended that, if considering the use of UST in a patient with a history of malignancy, the patient should be thoroughly evaluated prior to starting the treatment and should be on active surveillance for any changes.

Conclusion

In conclusion, UST has shown good results in terms of safety and efficacy in PsA patients. Especially in patients, where TNF- inhibitors fails primarily or secondarily, UST should be considered. Long-term safety is yet to be studied in details. Following proper guidelines for choosing patients and screening them, is essential for a good outcome, while considering this therapy.

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