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Review Article

Secukinumab - a stupendous option in psoriasis management

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ABSTRACT

Psoriasis is a chronic inflammatory skin disease with increased epidermal proliferation related to dysregulation of the immune system. In spite of several therapeutic strategies available for the treatment of this condition, the disease causes untold suffering particularly in the severe variant of the disease. Secukinumab is a human IgG1 monoclonal antibody that binds to the cytokine interleukin-17A (IL-17A) inhibiting the pro-inflammatory effects that are involved in the development of plaque psoriasis. Secukinumab 300mg is to be given via subcutaneous injection at weeks 0, 1, 2, 3 and 4 and once monthly thereafter. The efficacy of secukinumab has been evaluated in three phase 3 clinical trials. The drug showed an overwhelming improvement in the primary end points as assessed by PASI 75 and modified IGA scores. The only major concern with secukinumab is the increased risk of nasopharyngitis and mucocutaneous candidiasis due to the interference with host defence mechanisms by targeting IL-17. Secukinumab has also shown favorable response in the treatment of psoriatic arthritis, ankylosing spondylitis from clinical trials. The drug has been approved by the US FDA in January 2015 for the treatment of moderate to severe psoriasis in patients who require systemic therapy. Nevertheless long term safety data are still awaited. While the results of these trials have been extremely gratifying, it remains to be seen if the stupendous performance displayed in clinical trials could be translated in real world practice.

Keywords: Secukinumab, Psoriasis, Novel drug, Interleukin-17A, PASI 75

INTRODUCTION

Psoriasis is an auto-immune, chronic, dermatological disease associated with a significant impairment in the patient's quality of life.[1] The disease is known to affect approximately 1-3% of the population.[2] A myriad of pharmacological options are available to relieve the symptoms of the disease.

Some of the common drugs used to treat psoriasis includes topical corticosteroids, Vitamin D analogues, Anthralin, Topical retinoids, Salicylic acid, Coal tar, Calcineurin inhibitors, Photochemotherapy or psoralen plus ultraviolet A (PUVA), Goeckerman therapy, Narrow band UVB therapy, Methotrexate, Cyclosporine and novel biological agent. Inspite of the plethora of options available for the treatment of psoriasis, there are inherent limitations associated with each of these medications as listed in Table 1. Secukinumab is the most recent drug approved by the US FDA for psoriasis and we have attempted to summarize the mechanism of action, efficacy, safety and current status of this novel molecule.

MECHANISM OF ACTION

Secukinumab is a fully humanized anti interleukin (IL)-17A antibody that specifically binds to Interleukin (IL)-17A receptors. In recent years, IL-17A has been recognized to play a important role in the disease pathology.[2] The IL-17A is a pro-inflammatory cytokine that is produced by Th17 cells and has been isolated from the plaque lesion of psoriatic patients.

EFFICACY

Secukinumab was evaluated in two phase III clinical trials namely (Langley R G et al) ERASURE (Efficacy of Response and Safety of Two Fixed Secukinumab Regimens in Psoriasis) and FIXTURE (Full Year Investigative Examination of Secukinumab vs. Etanercept Using Two Dosing Regimens to Determine Efficacy in Psoriasis). The ERASURE study comprised of three groups which includes secukinumab at doses of 300mg (N=245), 150mg (N=245) or placebo (N=248) while the FIXTURE study included secukinumab at doses of 300mg (N=327), 150mg (N=327), etanercept 50mg (N= 326) or placebo (N=326).

Table 1: Limitations of current drugs used in psoriasis.

Current Medication details	Indications	Disadvantages
Topical corticosteroids	Mild psoriasis	Local side effects includes skin atrophy, telangiectasiae, purpura and striae .
Vitamin D analogues	Mild to moderate psoriasis	Local reactions such as burning and pruritus skin irritation, dryness, peeling, erythema, and edema.
Anthralin	Mild to moderate psoriasis	Irritation and staining at sites of application.
Topical retinoids	Pustular psoriasis, erythrodermic psoriasis and chronic plaque psoriasis	Major adverse effects include xerosis, pruritus, cheilitis, alopecia, dry mouth, hypertriglyceridaemia, liver toxicity and teratogenicity.
Coal tar	Scalp psoriasis, palmo plantar psoriasis and localized chronic plaque psoriasis	Can cause odour and staining of clothes.
Dithranol	Chronic stable plaque psoriasis	Skin irritation and staining
Photochemotherapy or psoralen plus ultraviolet A (PUVA)	Moderate and severe psoriasis	Psoralen tablets can cause nausea or vomitus. Long term PUVA increased risk of skin cancer. Low quality of life. PUVA requires skin and eye protection against sunlight.
Goeckerman therapy	Moderate and severe psoriasis	Less quality of life.
Narrow band UVB therapy	Used in children and pregnant women	Less side effects. Expensive. Need for frequent hospital visit. Poor quality of life.
Methotrexate	Moderate and severe psoriasis	Liver toxicity. Bone marrow toxicity
Cyclosporine	Moderate and severe psoriasis	Long term therapy can causes hypertension and nephrotoxicity
TNF alpha inhibitors	Moderate to severe psoriasis	Side-effects include infections, reactivation of tuberculosis and hepatitis B and drug-induced Lupus.

The ERASURE study revealed a substantial difference between secukinumab and placebo in the proportion of patients achieving PASI 75 score and IGA (P<0.001 for all comparisons). Secukinumab also showed improvements in the secondary end points such as maintenance of PASI 75, maintenance of 0 or 1 response on modified (IGA) scores, PASI 90, PASI 100 and Dermatology Life Quality Index (DLQI) score of 0 or 1 from week 12 to week 52 (P<0.001 for all comparisons).[1]

The FIXTURE Study showed that at week 12, both the doses of Secukinumab were superior to etanercept and placebo with respect to the key co-primary end points such as PASI 75 and IGA scores. Secukinumab had better responses than etanercept and placebo even with respect to secondary end points such as PASI 90, PASI 100, maintenance of PASI 75, maintenance of (IGA) scores and DLQI score.[1]

Secukinumab has also been compared with ustekinumab in a randomized control clinical trial among patients with moderate to severe plaque psoriasis. The drug was found to be superior to ustekinumab as assessed by PASI 90 response following 16 weeks of therapy. There was also greater improvement in patient reported symptoms and DLQI when compared with ustekinumab.

Considering the facts that ustekinumab has greater efficacy than most other biological agents, including etanercept, the superiority of secukinumab over ustekinumab is definitely remarkable. Nevertheless, the trial was funded by the makers of secukinumab and this fact should be taken in to consideration when interpreting the results of the study (Table 2).[4]

Efficacy of secukinumab in arthropathy

Secukinumab was evaluated in a randomized control clinical trial among patients with psoriatic arthritis. Patients were randomized into four groups namely secukinumab 300 mg (n=100), 150 mg (n=100), 75 mg (n=99), or placebo (n=98). Secukinumab was found to have greater improvement in an ACR20 scores than the placebo.

There was also improvement with respect to other end points such as PASI 75, PASI 90 scores, mean changes from baseline in DAS28-CRP and SF36-PCS, HAQ-DI and ACR50 and ACR 70 score compared to placebo.[7]

Secukinumab also showed gratifying results in ankylosing spondylitis where patients were given intravenous secukinumab in the initial period and maintenance therapy with the subcutaneous injection. At the end of six weeks, there was a significant improvement in assessment of Spondylo Arthritis international Society criteria for improvement (ASAS20) response.[8]

Table 2: Summary of psoriasis clinical trial studies of secukinumab.

Authors	Phase III	Sample size	Condition	Groups	Results of primary end points	Results of secondary end points
Langley R. G. et al[1]	Phase III	738	Plaque Psoriasis	• Two secukinumab SC doses at 300 or 150 mg (Once weekly for 5 wks, then every 4 wks) • Placebo	• 81% of the secukinumab 300mg group, 71% of the 150mg group and 4% of the placebo achieved PASI 75 at week 12. • 65% of the secukinumab 300mg group, 51% of the 150mg group and 2% of the placebo achieved response of 0 or 1 on modified (IGA) at week 12.	• 59% of the secukinumab 300mg group, 39% of the 150mg group and 1% of the placebo group achieved PASI 90 at week 12. • Achieved maintenance of PASI 75 and Maintenance of 0 or 1 response on modified IGA from wk 12 to wk 52. • 28% of the secukinumab 300mg group, 12% of the secukinuma 150mg and 0.8% placebo group achieved PASI 100 at week 12. • Achieved DLQI at week 12.
Langley R. G. et al[1]	Phase III	1306	Plaque Psoriasis	• Two secukinumab SC doses at 300 or 150 mg (Once weekly for 5 wks, then every 4 wks), • SC etanercept 50mg dose twice weekly for 12 weeks, then once weekly • Placebo	• 77% of the secukinumab 300mg group, 67% of the 150mg group, 44% of the etanercept group and 4% of the placebo achieved PASI 75 at week 12. • 62% of the secukinumab 300mg group, 51% of the 150mg group, 27% of the etancercept group and 2% of the placebo achieved response of 0 or 1 on modified (IGA) at week 12.	• 54% of the secukinumab 300mg group, 41% of the 150mg group, 20% of etanercept and 1% of the placebo group achieved PASI 90 at week 12. • Both the secukinumab doses groups versus etanercept group was achieved maintenance of PASI 75 and Maintenance of 0 or 1 response on modified IGA from wk 12 to wk 52. • 24% of the secukinumab 300mg group, 14% of the secukinumab 150mg, 4% of the etanercept group and 0% of the placebo achieved PASI 100 at week 12.
Thaci D MD., et al[5]	Phase III	676	Plaque psoriasis	• Secukinumab 300mg • Ustekinumab 45mg or 90mg (According to body weight at baseline)	• 79 % of secukinumab group and 57% of ustekinumab groups achieved PASI 90 at week 12. (P<.0001) . • 43% of the secukinumab group (P<.0001) and 28% of the ustekinumab group achieved PASI 100 at week 16.	• 50% of the secukinumab group and 20% of the ustekinumab group achieved PASI 75 at week 4 (P<.0001). • At week 4, achieved PASI 90, PASI 100 and IGA mod 2011 0/1 with secukinumab versus placebo groups. • Achieved DLQI score of 0/1(no impairment of HRQol) was significantly higher with secukinumab versus placebo at week 16.
Blauvelt A., et al[6]	Phase III	177	Psoriasis	• Secukinumab 300 mg • Secukinumab 150 mg • Placebo (Self-administration by pre-filled syringe (PFS) once weekly to week 4, and again at week 8)	• 75% of the secukinumab 300mg group, 69% of the secukinumab 150mg group and 0% of the placebo achieved PASI 75 at week 12 (P<.0001). • 69% of the secukinumab 300mg group, 52% of the secukinumab 150mg group and 0% of the placebo achieved IGA mod 2011 0/1 (P<.0001).	• At week 1, achieved PFS self-administered treatment and (SIAQ)

Psoriasis area-and-severity index score (PASI 75); Investigator's global assessment (IGA) mod 2011 (2011 modified Investigator's Global Assessment); 0/1 (defined as IGA score of 0 [clear] or 1 [almost clear]; Self-Injection Assessment Questionnaire (SIAQ); Dermatology Life Quality Index (DLQI).

SAFETY

Patients receiving secukinumab have a greater proclivity to develop infections such as nasopharyngitis and mucocutaneous infections with candidiasis.[1,9,10] The drug can also exacerbate inflammatory bowel disease and new onset inflammatory bowel disease can also develop in these patients.[4] Urticaria and anaphylaxis are not uncommon with secukinumab. The risk of hypersensitivity is greater among latex sensitivity individuals.

Table 3: Annual cost of different drugs used in psoriasis.[19]

Drug[19]	Annual Cost ($)
Standard of Care (SoC)	11,339
Etanercept (ETN)	52,036
Adalimumab (ADA),	64,369
Ustekinumab 45mg (UST45),	50,775
Secukinumab 150mg (SEC150),	66,666
Ustekinumab 90mg (UST90),	67,834
Secukinumab 300 mg (SEC300),	70,313
Infliximab (INF).	105,771

PHARMACOKINETICS

Secukinumab is available in two doses of 150mg and 300mg as prefilled syringes and prefilled pen or lyophilized powder for self-administered injection. The drug doses of 300mg are given at weeks 0, 1, 2, 3 and 4 and once monthly thereafter. The drug has a bioavailability ranging from 55% to 77%.

As the drug has a larger molecular size, only limited quantity of the drug is excreted in the urine. Hence, the drug is relatively safe among patients with impaired renal function. The half-life of the drug is between 22 to 31 days. The effect of liver disease on secukinumab is yet to be investigated. The main route of elimination is through intracellular catabolism. The drug does not have any interaction with cytochrome P450 enzyme inhibitors and inducers.[11]

PRECAUTIONS

Prior to initiating secukinumab a complete evaluation to rule out latent active tuberculosis (TB) needs to be carried out. The drug is to be avoided In patient with active TB infections. Live vaccines are to be avoided in secukinumab users.

CURRENT STATUS OF THE SECUKINUMAB

In lieu of the robust results across phase II / III trials with secukinumab, the drug has been approved by U. S. FDA and EMA on January 21, 2015 for the treatment of moderate to severe plaque psoriasis which needs systemic or phototherapy, psoriatic arthritits (PsA) and active ankylosing spondylitis (AS).[12] The drug is intended for those who require systemic therapy or phototherapy. Secukinumab is also being tested in other disease such as rheumatoid arthritis, dry eye, allergic contact dermatitis, atopic dermatitis, alopecia areata, pyoderma gangrenosum. Besides secukinumab there are anti - interleukin-17A (IL-17) monoclonal antibodies such as ixekizumab and brodalumab.[13,14] While ixekizumab has received marketing approval by U. S FDA, brodalumab is currently being reviewed by U. S. FDA review panel.

The annual cost of secukinumab is expected to be around 65,000 US dollars. A pharmacoeconomic study was performed using the Canadian database in which various biologic agents[(Etanercept (ETN), Ustekinumab, Adalimumab (ADA)] were compared with standard of care (SoC) therapy such as methotrexate, cyclosporine, topical corticosteroids, phototherapy.[15] Patients on Infliximab (INF) therapy had the maximum quantity adjusted life years during a 10 year period which was followed by secukinumab 300mg. Thus secukinumab 300mg appears to be cost effective than several other biologics mentioned above. It is not known if similar results would be seen in other regions of the World due to price differences across regions. Nevertheless the cost effectiveness of secukinumab requires further exploration.

Some of the challenges associated with use of secukinumab include parenteral injection and lack of information regarding the long term safety of this molecule. There is limited information regarding secukinumab use during pregnancy. Adequate pharmacovigilance is the need of the hour to study its safety in pregnancy and post marketing studies would be able to address this issue.[11,16]

CONCLUSION

Secukinumab is a novel anti - Interleukin (IL)-17A monoclonal antibody that has shown great promise in the treatment of psoriasis, psoriatic arthritis and ankylosing spondylitis. The drug has a reasonable safety profile with adverse effects that are usually expected with monoclonal antibodies. While there has been extensive clinical trials experience with secukinumab it remains to be seen, if the phenomenal results that were seen in the trials could be translated in clinical practice.

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