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Risankizumab (Skyrizi®) in Moderate to Severe Psoriasis: A Mini Review

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Abstract

Psoriasis is an autoimmune disease that affects nearly about 2%-3% of population across the globe. Role of biologics in moderate to severe psoriasis increased after observing efficacy of TNF-alpha antagonist such as etanercept, infliximab. The USFDA approved risankizumab in 2019 in the treatment of moderate to severe plaque psoriasis. This drug targets interleukin-23 (IL-23 by binding to its subcomponent, the protein p19. The results of landmark trials UltIMMa-1 and UltIMMa-2, IMMvent, IMMerge and IMMhance along with SustaIMM is a phase II/III trial shows that risankizumab effective at 150 mg every 12 weeks after initial two doses at week-0 and 4. Improvement of disease activity measured as PASI 90/ sPGA 0/1 or other outcomes favors risankizumab over placebo or adalimumab or ustekinumab at week 16 and 52. Long-term follow-up findings also consistent with its earlier outcomes. Risankizumab well tolerated and no major TRAEs observed in the short term, long term and during follow-up studies. Pharamacoeconomic analysis using ICER favors risankizumab due to its incremental gains due to improved quality of life and DALY. Risankizumab considered as enticing option for treating physician and patients incase patients with moderate to severe psoriasis.

Keywords: Psoriasis • Risankizumab • Biologics

Description

Psoriasis is an autoimmune disease that affects nearly about 2%-3% of population across the globe [1]. Psoriasis is a persistent condition characterized by a course of remission and recurrence so that majority of patients require sustainable care. Its chronicity and relapsing nature adversely compromises patient's quality of life. Biologic agents are recommended among the patients with moderate-severe psoriasis after failures of systemic therapy and phototherapy [2]. Currently available biologics in the management of psoriasis includes adalimumab, infliximab, ustekinumab, secukinumab, brodalumab, ixekizumab, guselkumab, and risankizumab [3]. High quality of evidence from the pooled data generated by Singh et al., for risankizumab showed that risankizumab significantly improves the clinical effectiveness among the patients with moderate to severe psoriasis vulgaris in comparison to placebo or active arm [4].

Risankizumab selectively inhibits the IL-23 by binding to its subunit 19 and prevents the differentiation and activity of T-helper cell 17 and 22. This mechanism controls the epidermal hyperplasia, epidermal cell proliferation and leukocyte infiltration resulting in prevention of formation of mature psoriatic plaques [5]. Risankizumab administered either intravenously or subcutaneously. It undergoes liner pharmacokinetic in the absorption and distribution followed by subcutaneous administration across the various doses in therapeutic ranges. It gets metabolized into small peptides and amino acids similar to endogenous immunoglobulins such as IgG. Because of endogenous metabolism, ethnic variation or age related variation or hepatic and renal impairment does not alter its pharmacokinetic parameters and less chances of potential drug-drug interactions [6].

Efficacy outcomes of risankizumab

The efficacy of risankizumab among the patients with moderate to severe psoriasis were conducted in multi-centric, multinational Phase III randomized, double-blind, clinical trials. These trials are UltIMMa-1 and UltIMMa-2, IMMvent, IMMerge and IMMhance [7-10]. SustaIMM is a phase II/III trial, designed to study the efficacy of risankizumab among Japanese patients [11]. The polled data analysis of these studies observed that various clinical efficacy endpoints such as Psoriasis area severity index (PASI 90), Dermatology life quality index (DLQI), and Static physician's global assessment 0 or 1 (sPGA 0/1) favors risankizumab in comparison with active control or placebo [4].

Short-term efficacy outcomes

Studies designed to test the efficacy of risankizumab after 12-16 weeks were included under short term efficacy [10-12]. Efficacy parameter analyzed in this periods were PASI 90 and sPGA score of 0 or 1. Outcomes of these studies observed that risankizumab group showed significantly higher proportions than the placebo group. The sensitivity analyses of response rate of PASI 90 and sPGA score of 0 or 1 was significantly favors the risankizumab over placebo group as early as 4-weeks of treatment ($p<0.001$). A similar analysis also performed in studies where active comparator (ustekinumab and adalimumab). These study outcomes shows that there was a significant proportion of patients shows clearance of psoriatic plaque with sPGA 0 or 1 ($p<0.05$) as early as 4-weeks of treatment and significantly higher proportion of patients achieved PASI 90 at week-8 ($p<0.01$). Proportions of patients with total remission (i.e. PASI 100 and sPGA 0) in risankizumab was significantly higher than placebo, ustekinumab and adalimumab at week-16. In IMMerge trial, a non-inferiority trial between risankizumab and secukinumab. Adjusted difference in the proportion of patients achieved PASI 90 score in risankizumab and secukinumab was 8.2% (95%CI − 2.2, + 18.6), it indicates that risankizumab was non-inferior to secukinumab.

Quality of Life (QoL) outcomes

QoL of study population scored based on Health Related-QoL (HR-QoL), the Dermatology Life Quality Index (DLQI), the Psoriasis Symptom Scale (PSS) and the Work Limitations Questionnaire (WLQ). Patients in the risankizumab group score were significantly favored over placebo, placebo, ustekinumab or adalimumab. The pooled data analysis of DLQI of above study (OR 6.95 (95% CI 5.53-8.75); I2 = 95%, P-value<00001).

Long-term efficacy outcomes

To test the durable response of risankizumab, patients were analyzed using efficacy outcomes such as PASI and sPGA and QOL outcomes such as DLQI and PSS at week 52. Patients receiving risankizumab had

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shown significantly higher clearance and QOL score than the patients in ustekinumab [7]. IMMvent study, patients responding intermittently to adalimumab was re-randomized to risankizumab and adalimumab respectively. The score of PASI, sPGA, DLQI and WLQ scores at week 44 were significantly favored risankizumab than the adalimumab group [8]. IMMhance patients from risankizumab group was re-randamized to risankizumab and placebo group to test the patient's outcomes in continuous therapy over treatment withdrawal [10]. In IMMerge trial, the PASI 90 response rate at week 52 was 87% with risankizumab and 57% with secukinumab ($p<0.001$). Risankizumab was significantly ($p<0.001$) more effective than secukinumab for all ranked secondary endpoints at week 52, including PASI 75, PASI 100 and sPGA 0 or 1.

Patients showed sustained improvement at week 44 and 104 among risankizumab than its withdrawal group. The duration for relapse rate was analyzed among patients re-randomized to understand the long-term efficacy of risankizumab over treatment conceal. The median time for relapse was significantly favored over the concealed group.

Long-term open-label extension studies

UltIMMa-1, UltIMMa-2 and IMMvent studies were continued to test the durable response of risankizumab over other active control groups. Long-term treatment with risankizumab 150 mg every 12 weeks effectively maintained the PASI 90 response rate over ustekinumab (84% vs 47%, $p<0.05$). The proportion of patients achieving a DLQI scores were also favored risankizumab patients at week 72 from baseline (81% vs 50%). similarly among the patients of IMMvent study entered into LIMMitless also favored risankizumab group over adalimumab group at week 84 [9].

The phase II/III SustaIMM trial conducted among Japanese patients with moderate to severe psoriasis. The response rate of PASI 90 at week 16 was significantly higher than the placebo (72% vs 2%). Patients of placebo group were reallocated to risankizumab 75 mg and 150 mg and followed till week 52. Patients in the 150 mg group showed consistently good response with PASI 90 (93%), PASI 100 (42%) and DLQI 0 or 1 (80%).

Safety of the risankizumab

In the short term (≤16 weeks) risankizumab was well tolerated among the study participants of UltIMMa-1, UltIMMa-2, IMMvent, and IMMhance trials. Most common adverse event was upper respiratory tract infection with an incidence of 13%. Other notable adverse effect was Inject-Site Reactions (ISRs), patients receiving risankizumab experienced mild to moderate ISRs and this was consistent with other biological agents and placebo. Majority of these reactions were of mild to moderate severity. Most notable ISRs were pain, erythema, pruritus, hemorrhage, hematoma, swelling, bruising and induration. None of the study participant in risankizumab group discontinued from the study due to ISRs. (See Table 1) The longer-term tolerability profile of risankizumab: the safety data of risankizumab was remained consistent with to short term data. In the study of LIMMitless, they observed the safety profile of Risankizumab for 2.5 years. In this study there was no new safety signals observed that can impact the overall tolerability to the study participants [11]. This indicates that risankizumab well tolerated in short term, long term course. This is essential because psoriasis is a chronic relapsing and remitting disease which requires long term therapy.

Immunogenicity

Risankizumab is a monoclonal IgG antibody. Like all therapeutic proteins, risankizumab has the potential for immunogenicity. Its therapeutic proteins have potential to cause autoimmunity [12]. Anti-drug antibodies and neutralizing antibodies among the patients treated with risankizumab were detected in 263 (24%) and 150 (14%) respectively. High titres of antibody observed in ≈ 1% of risankizumab-group. This indicates that majority of patients with auto antibody or neutralizing antibodies does not alter the therapeutic potential.

Dosage and administration of risankizumab

Currently this drug was approved in USA, EU and Japan for the treatment of moderate to severe psoriasis in adults. Two doses of 75 mg each injection (total of 150 mg) administered subcutaneously at start of therapy followed by week 4 then every 12 weeks. Instead other biologics has to be administered once every 2 weeks in case of brodalumab, once in every 4 weeks secukinumab and ixekizumab, once every 8 weeks for guselkumab. This implies that risankizumab will have better compliance and acceptable over other biologics mentioned above [13].

Place of Risankizumab in the Management of Moderate to Severe Plaque Psoriasis: Landmark clinical trials to test the efficacy and safety of risankizumab with placebo or active comparator were UltIMMa-1, UltIMMa-2, IMMvent, IMMhance and IMMerge. In these trials, efficacy outcomes such as PASI 90 and sPGA 0 or 1 observed at week-16. Results of these studies favor risankizumab over placebo, ustekinumab and adalimumab along non-inferiority with secukinumab (Sect. 1.1). Lon-term efficacy outcomes (PASI 90 and sPGA 0 or 1) measured at week-54 favors risankizumab over placebo, ustekinumab, adalimumab, and secukinumab (Sect. 1.3.). QoL outcomes also favor the risankizumab over its comparator (sect. 1.2). Extension of above studies results shows that durable efficacy outiomces (sect.1.4).

Pharamacoeconomic of Risankizumab: compared the total cost of risankizumab therapy among moderate to severe psoriasis patients with other biologics (i.e. ustekinumab, adalimumab, secukinumab, infliximab, ixekizumab, brodalumab, and guselkumab). This study observed that the overall Incremental Cost Effectiveness Ratio (ICER) of risankizumab was lower than the other biologic therapy. Similarly in public health care providers of Poland suggested that the risankizumab therapy for severe psoriasis is more cost-effective than ustekinumab. The private health care system of Brazil also observed that effectiveness of risankizumab (based on PASI 75, 90 and 100) makes economically cheaper than the other biological therapy (i.e. adalimumab, etanercept, guselkumab, infliximab, ixekizumab, secukinumab and ustekinumab). Overall, with the Incremental Cost Effectiveness Ratio (ICER) suggest that risankizumab is a cost-effective strategy for achieving higher levels of skin clearance within the biologic-eligible target population [14].

Table 1. Comparison of Treatment-Emergent Adverse Events (TEAEs) and serious TEAEs at week 16.

Proportion of study participants	Risankizumab	Ustekinumab,	Adalimumab	Placebo
TEAE	49%	52%	57%	48%
Serious TEAE	2%	5%	3%	4%
TEAEs leading to discontinuation	0.7%	1.3%	2.0%	3.0%
Serious infections	0.4%	1.7%	0.3%	0.3%
Injection-Site Reactions (ISRs)	2%	4%	6%	1%

Conclusion

Risankizumab targeted therapy for psoriasis is an effective and relatively safer treatment for the management of moderate to severe plaque psoriasis. Even though, the cost of risankizumab therapy higher than the other biological agents for the treatment of patients with moderate to severe psoriasis, the incremental gain due to improved QOL and Quality Adjusted Life Years (QALY) makes preferred choice for the treatment of moderate to severe psoriasis.

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