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PSORIASIS (J WU, SECTION EDITOR)

Update on Risankizumab for Psoriasis

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Abstract

Purpose of Review This review highlights the latest data on risankizumab, including efficacy and safety data from recent clinical trials.

Recent Findings In multiple phase 3 clinical trials, risankizumab was shown to be safe and efficacious. Risankizumab demonstrated superior efficacy to leading active comparators for the induction and maintenance of clear skin and was shown to have a safety profile similar to other biologic therapies currently on the market.

Summary Targeted biologic medications for plaque psoriasis have provided insight into the complex immune pathways that are now understood to lead to the development of several autoimmune diseases including plaque psoriasis. Risankizumab, a novel, fully human monoclonal antibody against the IL-23p19 subunit, is currently under investigation for the treatment of moderate-to-severe plaque psoriasis and shows promise to provide complete and lasting skin clearance with convenient dosing for patients. Future studies are needed to explore the long-term safety and efficacy of risankizumab beyond 5 years of therapy.

Keywords Psoriasis · Risankizumab · Biologic · IL-23 · Efficacy · Safety

Introduction

Psoriasis is a chronic, immune-mediated skin disease that is estimated to affect 2.2% of the adult US population [1]. Plaque psoriasis is the most common form and accounts for approximately 85% of the disease [2]. It has been shown to adversely affect patient's quality of life and put patients at an increased risk of developing comorbidities including joint disease, cardiovascular disease, metabolic syndrome, and depression [3]. Over the past 20 years, there have been significant advances in the field of psoriasis treatment with the discovery of immune-mediated pathways that have led to the development of targeted immunotherapies [4, 5]. Currently approved biologic medications to treat moderate-to-severe plaque psoriasis include tumor necrosis factor alpha (TNF-a) inhibitors, interleukin (IL)-17 and IL-17 receptor inhibitors, IL-12/23 inhibitors, and IL-23p19 inhibitors. Despite the large number of approved biologic medications, there remains an unmet need for treatments that provide complete and lasting skin clearance with convenient dosing. Risankizumab is a selective IL-23 antibody currently being studied for moderate-to-severe plaque psoriasis and other inflammatory disease indications. Multiple phase 2 and 3 studies of risankizumab have shown impressive results thus far. This article focuses on reviewing to date information on risankizumab, specifically efficacy and safety.

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

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Mechanism of Action

Risankizumab (ABBV-006, formerly BI 655066) is a novel, fully humanized monoclonal antibody of the IgG1 subclass that selectively binds the IL-23 p19 subunit and blocks the activity of IL-23 [6]. IL-23 is a heterodimer consisting of two subunits, p19 and p40. The p19 subunit is specific to the IL-23 molecule, while the p40 subunit is shared by IL-12 and IL-23. IL-23 is a naturally occurring cytokine secreted primarily by activated dendritic cells and macrophages. It is involved in inflammatory and immune responses and has been shown to have increased expression in psoriatic lesional skin [7, 8]. Binding of IL-23 to the IL-23 receptor signals through the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway to activate STAT 1-4, but especially

STAT-3, ultimately leading to activation of the helper T (T_H17) pathway. T_H17 cells secrete IL-17A which has been shown to promote the development of psoriatic lesions [9]. Risankizumab blocks IL-23 from binding to the IL-23 receptor, thereby inhibiting downstream IL-17A activation.

Efficacy in Psoriasis

Efficacy in psoriasis is measured by improvement in multiple investigator-reported scores including the psoriasis area severity index (PASI), body surface area (BSA), and static physician global assessment (sPGA). Patient-related outcomes are measured by the dermatology-related quality of life index (DLQI), a questionnaire with scores ranging from 0 to 30, with lower scores indicating less impact on quality of life. Risankizumab has demonstrated excellent efficacy in the treatment of moderate-to-severe plaque psoriasis and has been shown to have results superior to leading active comparators in clinical trials to date.

Early Studies

A phase 1 randomized, double-blind, placebo-controlled proof of concept study in 39 patients with moderate-to-severe plaque psoriasis showed rapid, substantial, and sustained improvement for risankizumab versus placebo at 12 and 24 weeks. At week 12, 87% of patients receiving risankizumab achieved PASI 75 (75% reduction from baseline PASI) versus 0% of the placebo group ($p < 0.001$). Clinical improvement was seen as early as 2 weeks after risankizumab administration [10•]. A subsequent head-to-head phase 2 trial comparing risankizumab to ustekinumab (Stelara®; Janssen Biotech, Inc.) showed that risankizumab induced greater skin clearance than ustekinumab. In this trial, 166 patients were randomized 1:1:1:1 to receive risankizumab 18 mg subcutaneously at week 0, risankizumab 90 mg or 180 mg subcutaneously at weeks 0, 4, and 16, or ustekinumab weight-based dosing at weeks 0, 4, and 16. The primary endpoint was a 90% or greater reduction from baseline in PASI (PASI 90) at week 12. Seventy-seven percent of the risankizumab group (pooled 90 mg and 180 mg subjects) achieved PASI 90 at week 12 compared to 40% of the ustekinumab group ($p < 0.001$). Almost half of the patients on risankizumab (45% of the pooled 90 mg and 180 mg patients) achieved complete skin clearance (PASI 100) at week 12 versus 18% in the ustekinumab group [11••].

Phase III Studies

Similar efficacy data has been reproduced by four phase 3 trials: UltIMMa-1, UltIMMa-2, IMMvent, and IMMhance. The UltIMMa-1 and UltIMMa-2 trials [12••] were replicate phase 3 randomized, double-blind studies of 500 patients each evaluating the efficacy of risankizumab compared with ustekinumab and placebo for plaque psoriasis over a period of 52 weeks. In both UltIMMa-1 and UltIMMa-2, patients with moderate-to-severe plaque psoriasis were randomized 3:1:1 to treatment with risankizumab (150 mg subcutaneously at 0, 4, and 16 weeks), ustekinumab (45 or 90 mg by weight, at weeks 0, 4, and 16), or placebo. At the end of the 16-week placebo-controlled period (Part A), those subjects initially assigned to placebo were switched to risankizumab 150 mg every 12 weeks; other patients continued their originally assigned treatment for weeks 16–52 (Part B). Co-primary endpoints were the proportion of patients achieving PASI 90 and sPGA score of 0 or 1 (clear or almost clear) at week 16. Results of these two pivotal trials were recently published by Gordon et al. in *Lancet* [12••]. Co-primary endpoints were met for both studies, and risankizumab showed superior efficacy to both placebo and ustekinumab in the treatment of moderate-to-severe plaque psoriasis. At week 16 of UltIMMa-1, PASI 90 was achieved by 75% of the risankizumab patients compared to 5% of the placebo patients and 42% of the ustekinumab patients. Similarly, at week 16 of UltIMMa-2, PASI 90 was achieved by 75% of the risankizumab patients compared to 2% of the placebo patients and 47% of the ustekinumab patients ($p < 0.0001$ vs placebo and ustekinumab for both studies). Clear or almost clear skin (sPGA of 0 or 1) was achieved by 88% of the risankizumab patients in UltIMMa-1 versus 8% of the placebo patients and 63% of the ustekinumab patients. In UltIMMa-2, 84% of patients receiving risankizumab achieved sPGA of 0 or 1 at week 16 compared with 5% of patients receiving placebo and 61% of patients receiving ustekinumab ($p < 0.0001$ vs placebo and ustekinumab for both studies). Clinical results were more rapid in those treated with risankizumab than ustekinumab as demonstrated by a greater proportion of patient achieving PASI 90 at week 8 for risankizumab than ustekinumab (44% vs 19% for UltIMMa-1 and 47% vs 26% for UltIMMa-2). These results were improved with continued treatment every 3 months and were maintained to week 52. At week 52, complete skin clearance (PASI 100 or sPGA 0) was achieved by up to 60% of patients treated with risankizumab since week 0 compared with 21–30% of those treated with ustekinumab. Just as significant, patient-reported quality of life improved in a greater number of patients on risankizumab than those on ustekinumab. At week 16, 66% of patients on risankizumab achieved DLQI of 0 or 1, indicating no impact of psoriasis on quality of life, versus 43–46% of patients on ustekinumab. Further improvements were noted in DLQI responses for patients on risankizumab at week 52, up to 75% of patients, whereas those on ustekinumab continued to achieve a DLQI of 0 or 1 at a rate of 44–47% [12••].

IMMvent (ClinicalTrials.gov Identifier: NCT02694523) was a phase 3 randomized, active-comparator study designed

to evaluate the safety and efficacy of risankizumab compared to adalimumab (Humira®; Abbvie, Inc.) in adult patients with moderate-to-severe chronic plaque psoriasis. In Part A of this study, 600 patients were randomized 1:1 to 16 weeks of treatment with risankizumab (150 mg subcutaneously at 0, 4, and every 12 weeks thereafter) or adalimumab (80 mg at week 0, 40 mg at week 1, followed by 40 mg every other week). Co-primary endpoints for Part A were the proportion of patients achieving PASI 90 at week 16 and sPGA score of 0 or 1 at week 16. In Part B of the study, patients originally randomized to risankizumab continued to receive risankizumab through week 52. Patients originally randomized to adalimumab followed a treatment course based on PASI response at week 16: those with less than PASI 50 at week 16 switched to risankizumab, those with PASI 90 or greater continued adalimumab, and those with PASI 50 but less than PASI 90 were re-randomized to receive adalimumab or risankizumab. The primary endpoint for Part B was proportion of patients achieving PASI 90 at week 44. A recent press release of unpublished data by Abbvie in October 2017 announced that all primary and ranked secondary endpoints achieved statistical significance with $p < 0.001$ [13]. In Part A of IMMvent, 72% of patients in the risankizumab group achieved PASI 90 at week 16 compared with 47% of patients treated with adalimumab, while 84% of patients in the risankizumab group were clear or almost clear at week 16 compared with 60% of patients in the adalimumab group. In addition, 40% of patients in the risankizumab group achieved PASI 100 at week 16 compared to 23% of patients treated with adalimumab. In Part B of IMMvent, 66% of the patients initially on adalimumab who were re-randomized to receive risankizumab achieved PASI 90 at week 44 compared to 21% of patients who continued on adalimumab. Additionally, 40% of patients who switched to risankizumab achieved PASI 100 at week 44 compared to 7% of patients who remained on adalimumab [13].

IMMhance (NCT02672852) is a 104-week phase 3, randomized, double-blind, placebo-controlled study of 500 patients to evaluate the efficacy and safety of risankizumab, the duration of response following randomly withdrawing treatment from risankizumab, and the response to re-treatment for patients who relapse. In Part A of this study, patients were randomized 4:1 to receive risankizumab (150 mg subcutaneously at weeks 0, 4, and 16) or placebo. A recent press release of unpublished data by Abbvie in December 2017 announced that both co-primary endpoints (PASI 90 and sPGA of 0 or 1 at week 16) for Part A had been met [14]. Seventy-three percent of patients treated with risankizumab achieved PASI 90 at week 16 compared with 2% of patient treated with placebo. Eighty-four percent of patients in the risankizumab group achieved clear or almost clear skin at week 16 compared with 7% of the placebo group. Complete skin clearance (PASI 100) was achieved by 47% of those treated with risankizumab at week 16. In Part B of this study, patients who had originally received risankizumab and achieved sPGA of 0 or 1 at week 28 were re-randomized to risankizumab or placebo. Beginning at week 32, patients who relapsed (defined as sPGA 3 to 4) were retreated with risankizumab immediately, 4 weeks later, and every 12 weeks thereafter. The primary endpoint of Part B was sPGA of 0 or 1 (clear or almost clear skin) at week 52. Among those patients who achieved sPGA of 0/1 at week 28, 87% of those randomized to continue risankizumab maintained clear or almost clear skin at week 52 compared to 61% of patients who were withdrawn from risankizumab [14].

Safety

In both UltIMMa-1 and UltIMMAa-2, safety profiles were similar across risankizumab, ustekinumab, and placebo groups. Infections were more commonly reported in patients on risankizumab and ustekinumab compared to placebo. The rates of treatment-emergent adverse events were similar for patients on risankizumab as those on ustekinumab and placebo for the duration of both studies [12••]. The most frequently reported adverse events were viral upper respiratory tract infection, upper respiratory tract infection, urinary tract infection, influenza, and headache. Two major adverse cardiovascular events were reported in the risankizumab group during UltIMMa-2, including one sudden cardiac death. Both patients had significant cardiovascular risk factors and neither event was considered to be related to the study drug by the investigator. One patient in the risankizumab group in UltIMMa-1 died of an unknown cause 161 days after the last dose of risankizumab, outside of the treatment-emergent window. Through week 52 in both UltIMMa-1 and UltIMMa-2, the rates of malignancy were similar across all treatment groups. In the pooled risankizumab groups, four patients reported non-melanoma skin cancers and one patient was diagnosed with breast cancer. One episode of non-melanoma skin cancer was reported in the placebo group; one patient treated with ustekinumab was diagnosed with prostate cancer. Two cases of latent tuberculosis were reported through week 52 in the risankizumab group. Both patients had a negative quantiferon gold at baseline. There were no episodes of serious hypersensitivity reaction reported in either study through week 52 [12••]. No new or unexpected safety signals were detected in the IMMvent or IMMhance studies [13, 14].

Going Forward

Risankizumab is currently undergoing a phase 3, single-arm, multicenter open-label extension of 2200 patients to determine long-term safety and efficacy of 150 mg risankizumab

every 12 weeks up to 3 years (LIMMITLESS, NCT03047395). It is also undergoing a 52-week head-to-head comparator study against secukinumab (Cosentyx®, Novartis, Inc.) which began in May 2018 (NCT03478787). These studies will be a key in evaluating the long-term safety and efficacy of risankizumab as well as providing head-to-head data for comparing the efficacy of risankizumab versus an IL-17 inhibitor. Abbvie announced in an April 2018 press release that a Biologics License Application had been submitted to the United States Food and Drug Administration for risankizumab for the treatment of moderate-to-severe plaque psoriasis [15].

Other Indications

Erythrodermic/Pustular Psoriasis

There is one ongoing phase 3, randomized, open-label study to assess the efficacy and safety of two different dosing regimens of risankizumab in 17 Japanese patients with erythrodermic psoriasis (EP) or generalized pustular psoriasis (GPP). Co-primary outcomes for the study are subjects achieving clinical response in GPP or EP scores at week 16. The study began in January 2017 and is scheduled to be completed in 2021 (NCT03022045).

Psoriatic Arthritis

A phase 2, randomized, double-blind, placebo-controlled, proof-of-concept, dose-ranging study in 185 patients with active psoriatic arthritis was completed in early 2018 (NCT02719171). No data from this trial has been published to date. Two phase 3, randomized, double-blind, placebo-controlled trials are planned to evaluate the safety and efficacy of risankizumab in patients with psoriatic arthritis who have a history of inadequate response or intolerance to disease-modifying anti-rheumatic drugs (NCT03675308) or biologic therapy (NCT03671148).

Crohn's Disease

Risankizumab has been shown to be more effective than placebo for the induction of clinical remission at week 12 in patients with active Crohn's disease. Thirty-one percent of patients achieved clinical remission in the pooled risankizumab group versus 15% for placebo, ($p = 0.0489$) in a randomized, double-blind, placebo-controlled phase 2 study of 121 patients [16]. There is an ongoing open label, single group, long-term safety extension of that phase 2 study underway (NCT02513459). Three phase 3 studies to further evaluate the efficacy and safety of risankizumab for the treatment of Crohn's disease are actively recruiting at the time of writing.

Ulcerative Colitis

There is currently a phase 2/3 randomized, double-blind, placebo-controlled study of 720 patients to evaluate the efficacy and safety of risankizumab for induction of clinical remission in patients with moderately to severely active ulcerative colitis who have failed prior biologic therapy (NCT03398148). This study is ongoing and no data has been published to date.

Asthma

A 24-week phase 2, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of risankizumab as add-on therapy to standard-of-care treatment in 214 adults over the age of 17 with severe persistent asthma was scheduled to be completed in February 2018 (NCT02443298). The primary endpoint of this study is time to first asthma worsening during the planned 24-week period. No data has been published from this trial at the time of this writing.

Ankylosing Spondylitis

Ankylosing spondylitis (AS) is a chronic, non-rheumatic inflammatory disease predominantly affecting the axial skeleton. It has typically been treated with non-steroidal anti-inflammatory drugs and tumor necrosis factor inhibitors. Secukinumab (Cosentyx®, Novartis, Inc.) was approved in 2016 for the treatment of AS, indicating that the pathogenesis of AS could be through the IL-23/IL-17 pathway. A phase 2, randomized, placebo-controlled, proof of concept, dose-finding study in 159 patients randomized 1:1:1:1 to receive risankizumab 18 mg, 90 mg, 180 mg, or placebo did not meet the primary outcome at week 12 (40% improvement in disease severity score). Longer treatment up to 40 weeks with patients receiving escape treatment of 180 mg risankizumab did not improve efficacy results. Lack of efficacy was confirmed by most secondary endpoints. Risankizumab was well tolerated during this study and no new or unexpected safety signals were identified [17].

Conclusions

Many factors must be considered in the selection of therapies for patients with psoriasis [18, 19]. Risankizumab is novel IL-23p19 subunit inhibitor currently being studied for the treatment of multiple autoimmune diseases, including plaque psoriasis. The results of phase 2 and 3 clinical trials show that risankizumab has excellent efficacy in the treatment of moderate-to-severe plaque psoriasis. Selective blockade of IL-23 with risankizumab was superior to dual IL-12/23

blockade by ustekinumab, reinforcing the current paradigm of IL-23 more than IL-12 playing a central role in the pathogenesis of psoriasis. Clinical response was more rapid in patients treated with risankizumab than with ustekinumab, and responses continued to improve with maintenance dosing every 12 weeks. The safety profile of risankizumab is similar to that of other biologic medications currently on the market, with non-serious infections being the most commonly reported side effect. While further studies are needed to evaluate long-term safety and efficacy, risankizumab shows great promise to be a leading biologic medication used in the treatment of moderate-to-severe plaque psoriasis to achieve rapid, complete, and lasting skin clearance.

Compliance with Ethical Standards

Conflict of Interest Mark Lebwohl is an employee of Mount Sinai and receives research funds from: Abbvie, Amgen, Arcutis, Bausch Health (Valeant), Boehringer Ingelheim, Celgene, Eli Lilly, Incyte, Johnson & Johnson (Centocor, Janssen), Leo Pharmaceutucals, Medimmune/Astra Zeneca, Novartis, Pfizer (Anacor), Regeneron, Sciderm, UCB, Inc., and ViDac. Dr. Lebwohl is also a consultant for Allergan, Aqua, Arcutis, Inc., Boehringer-Ingelheim, Bristol-Myers Squibb, LEO Pharma, Menlo, Mitsubishi, Neuroderm, Promius/Dr. Reddy's Laboratories, Theravance, and Verrica.

Dr. Bares has nothing to disclose.

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.

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