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RISANKIZUMAB IN PSORIASIS AND CROHN'S DISEASE: A COMPREHENSIVE REVIEW

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ABSTRACT

Risankizumab, a humanized monoclonal antibody that targets interleukin-23 (IL-23), has emerged as a viable treatment option for psoriasis and Crohn's disease. IL-23 plays an important role in the development of several chronic inflammatory diseases, triggering the immunological response that underpins their clinical symptoms. Risankizumab has shown great effectiveness in decreasing skin lesions in psoriasis, with long-term benefits to the severity of the disease and individual quality of life. Similarly, in Crohn's disease, research trials have demonstrated its ability to elicit and maintain remission, providing a novel therapy option for individuals with moderate to severe illness. This review explores the mechanism of action, clinical effectiveness, safety profile, and long-term results of risankizumab in the treatment of psoriasis and Crohn's disease, offering a thorough summary of its function in treatment strategies.

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INTRODUCTION

Risankizumab-RZB is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that specifically binds to the p19 component of human IL-23 and inhibits its interaction with the IL-23 receptor. The consequent drop in IL-23 activity is associated with lower inflammatory and immunological responses. Risankizumab prevents the release of proinflammatory cytokines and chemokines(1). It is accessible in several forms internationally (2). Psoriasis is a perennial immune-driven inflammatory skin disease that is associated with psoriatic arthritis, as well as psychiatric, cardiovascular, and hepatic problems. Psoriasis has a strong hereditary component, with inheritance estimated to be 60-90% (3). Psoriasis appears as well-defined erythematous plaques coated with silvery scales. Psoriasis is categorized into two categories. Type 1 psoriasis has a positive family history, begins before the age of 40, and is related with HLA-Cw6, but type 2 psoriasis does not have a family history, appears after the age of 40, and is not connected with HLA-Cw 6. Psoriasis can take various forms, including plaque, guttate, rupioid, erythrodermic, pustular, inverse, elephantine, and psoriatic arthritis. The scalp, palmoplantar area, genitals, and nails are all affected, resulting in site variation. Any skin damage, whether mechanical, chemical, or radiational, causes psoriasis lesions at the location, which is known as the Koebner phenomenon. It indicate the disease's active status (4).

It begins with an initiation phase in which an event (such as skin damage, infection, or medicines) activates the immune system, followed by a maintenance phase in which the illness progresses chronically. In psoriasis, skin cells are changed every 3-5 days instead of the typical 28-30 days. These alterations are thought to be caused by the early maturation of keratinocytes in the dermis, which is triggered by an inflammatory cascade involving dendritic cells, macrophages, and T lymphocytes. Immune cells travel from the dermis to the epidermis and release cytokines such interleukin-36γ, tumor necrosis factor-α, interleukin-1β, interleukin-6, and interleukin-22, which trigger inflammation. These released inflammatory signals are suspected to promote keratinocytes (5). Crohn's disease (CD) is an immune-mediated inflammatory gastrointestinal disorder that affects the full thickness of the gut wall. The illness may affect any region of the gastrointestinal system. Crohn's disease can also develop extraintestinal signs, which can impact the eyes, the skin, liver, and joints (6). It causes tissue inflammation as a result of an unregulated immunological response to bacterial antigens. Key immune cells, such as CD4 and CD8 T cells, penetrate the gut, and genetic variables like Muc2 and FUT2 mutations influence mucus formation and bacterial interaction. Hyperactive T cells produce inflammatory cytokines such as IL-12, TNF-α, and IL-23, leading to mucosal inflammation. Furthermore, the humoral immune response, triggered by CD4 T cells, promotes epithelial injury. The gut microbiota

modulates inflammation by interacting with host immune receptors. CD causes transmural inflammation, tissue destruction, stenosis, fistulas, and abscesses, with disease behavior frequently changing over time. This interaction of genetic, immunological, and microbial variables maintains the immune response in Crohn's disease (7).

Mechanism of action: Risankizumab is a high-affinity neutralizing antibody that binds to the p19 component of IL-23, but not to IL-12, which shares a p40 subunit with IL-23. Risankizumab is a human IgG1 kappa antibody with two mutations in the Fc region (Leu234Ala and Leu235Ala) that impair Fc gamma receptor binding. Risankizumab binds to the p19 component of IL-23, inhibiting its interaction with the IL-23 receptor and signaling, which contributes to numerous inflammatory pathways. Figure 1 shows a thorough picture showing the impact of IL-23 inhibition, including cell types and downstream cytokines, for the three authorized purposes (2).

Dosage and administration: PsO, PsA, GPP, EP, and PPP: 150 mg subcutaneous (s.c.) at weeks 0, 4, and every 12 weeks (q12w) thereafter; CD: 600 mg intravenous (i.v.) at weeks 0, 4, and 8 followed by 360 or 180 mg s.c. q8w starting from week 12 (note: the 180 mg s.c. maintenance dose is only approved in some jurisdictions, such as the United States and Puerto Rico) (8) (9).

CD: risankizumab IV 600 mg every 4 weeks over 12–24 weeks of induction therapy (10).

Drug regulatory approval: Risankizumab, marketed as SKYRIZI, was licensed in the United States in 2019 for moderate to severe Plaque Psoriasis (PsO) and moderately to severely active CD in persons 18 and older. It is authorized in 80 nations for PsO, 44 for CD. In Japan, it is authorized for PsO-related indications such as generalized pustular psoriasis (GPP), erythrodermic psoriasis (EP), and palmoplantar pustulosis (PPP). The recommended dose regimens are 150mg subcutaneous at weeks 0, 4, and every 12 weeks, and 600mg intravenous at weeks 0, 4, and 8, followed by 360 or 180mg sc q8w (every 8 weeks0) beginning with week 12. Risankizumab is now being reviewed for its commercial utility to treat adult patients having moderately to severely active UC. (2)

Clinical Trials

Risankizumab in Crohn's Disease

- Conducted two trials: ADVANCE and MOTIVATE.
- Both were phase 3 induction trials enrolling patients aged 16 to 80 with moderate to severe active Crohn's disease.
- Patients were randomly assigned to a single dose of risankizumab or placebo at weeks 0, 4, and 8.
- Interacting response technology used for random assignment, stratifying by previous failed biological agents, corticosteroid use at baseline, and SES-CD.
- Coprimary outcomes were clinical remission and endoscopic response at week 12.
- ADVANCE study included individuals unable to tolerate conventional treatments or biologics.
- MOTIVATE experiment included patients who had previously experienced biological failure.
- Both studies had an average illness duration of little over 8 years.
- Discontinuation rates were higher in the placebo arm than in the intervention arms (11).

Risankizumab was both efficacious and well tolerated as an induction treatment for individuals with moderately to highly active Crohn's disease.

Assessment of Risankizumab for Moderate-to-Severe Psoriasis

- Data from 17 clinical studies of risankizumab for moderate-to-severe psoriasis (3072 patients, 7927 Patient year (PY) exposure, treatment duration up to 5·9 years) were evaluated.
- The frequencies of adverse events (AEs) as well as safety-interest events were consistent with the established safety profile of risankizumab.
- The exposure-adjusted event rates (EAER) for severe infections was 1-2 occurrences per 100 PY, which is consistent with the PSOLAR study's findings.
- Candida infections had an EAER of 0.6 occurrences per 100 person-years, with no instances of deep or systemic candidiasis.
- The rates of herpes zoster and TB were satisfactory.
- Individuals with psoriasis may have a greater risk of cancer than the overall population, regardless of therapy.
- EAERs for NMSC and non-NMSC malignant tumors were 0.7 occurrences per 100 (12).

Safety and Efficacy

In Psoriasis: Risankizumab's phase 3 study indicated improved effectiveness in people with moderate to severe plaque psoriasis when compared to placebo or therapy cessation. The effectiveness rates were considerably greater in risankizumab-treated patients commencing at week 4 compared to placebo, and in part B, those rerandomized to continuous risankizumab versus those rerandomized to treatment withdrawal starting at week 40 or the equivalent of a single missed dose at week 28. Most patients retreated with risankizumab for 16 weeks and restored clinical response after relapsed after therapy withdrawal. Treatment-emergent adverse events were comparable to those seen with risankizumab and placebo, and no new safety issues were observed in patients for two years. The effectiveness and safety outcomes in this trial were similar with those reported in three previous phase 3 studies, validating risankizumab's benefit-risk profile. The median durations to loss of response and relapse were 30 and 42 weeks, respectively, indicating that risankizumab response lasted significantly after discontinuation (13).

In crohn's disease: Long-term risankizumab therapy maintained the percentage of patients in clinical and endoscopic remission throughout the trial. All endoscopic effectiveness ratings were based on central reviewer scoring. Clinical remission was attained in over 71% of patients in the observed analysis and over 64% of patients in the NRI analysis at any given visit during Week 112 of OLE medication [Figure 3A]. At any given visit through Week 104, over 42% of patients in the observed analysis and more than 41% of patients in the NRI analysis had achieved endoscopic remission (14). The FORTIFY 'Real-Life Handling' SS4 study evaluated the safety and efficacy of self-administering risankizumab via an on-body injector (OBI) for patients with CD. All patients successfully self-administered risankizumab, even with dosage failures. The study found no unexpected clinical problems or damage, and the rate of CD Activity Index (CDAI) clinical remission remained consistent throughout 16 weeks. Despite limitations, risankizumab trough serum concentrations remained stable at Week 16. (15)

Adverse events

In PsO: The research found 37 severe infections as well as 25 malignant tumors, while the frequency of malignancies remaining constant as RZB treatment duration increased. Breast and colorectal cancer were the most often reported malignancies, without any haematological malignancies. The proportion of squamous cell carcinoma to basal cell carcinoma was 1:2. There were no reports of systemic Candida infection, inflammatory bowel disease, or active TB. However, 20 instances of Candida infection were documented, including oral, vaginal, oesophageal, intestinal, and cutaneous candidiasis. There were no new safety concerns found (17).

In CD: The research included 65 individuals who had risankizumab medication for a total of 167.0 months. The treatment period lasted from 114 to 1317 days, with a median of 1014 days. Risankizumab was administered to 60 patients for more than 924 days, and all those who required IV reinduction got it in full. 48 individuals had infections, the most prevalent of which were nasopharyngitis, lower respiratory tract infection, dental herpes, and infections of the urinary

tract. Six individuals developed serious infections, although none required therapy cessation. Three individuals had opportunistic infections, whereas seven had fungal infections. Hypersensitivity responses were seen in 16 individuals, with rash and eczema being the most often reported. Six individuals had hepatic problems, totaling 15 occurrences (14).

Pharmacokinetics and Impact on Patient-Specific Covariates

- The pharmacokinetics of risankizumab are described using a two-compartment model with first-order absorption and elimination.
- Risankizumab clearance levels, steady-state volume of distribution, and terminal-phase elimination half-life were calculated for various disease populations.
- The absolute subcutaneous bioavailability, absorption rate constant were 72% and 0.18 day-1, respectively.
- Covariates such as age, body weight, sex, different laboratory values, risankizumab immunogenicity, and disease populations were assessed for their impact on risankizumab disposition.
- Body weight as well as baseline albumin levels linked with risankizumab pharmacokinetic characteristics, explaining minor discrepancies between patient groups.
- Risankizumab CL had an inverse relationship with baseline blood albumin levels, with no significant impact on exposures in participants with low and high levels. (10)

Comparison of risankizumab with other treatment options

Risankizumab to Fumaric Acid Esters: The trial compared risankizumab to fumaric acid esters (FAEs) in individuals with moderate-to-severe psoriasis. The main outcome was obtaining a Psoriasis Area and Severity Index (PASI) of 90 after 24 weeks of therapy, with risankizumab showing substantial improvements. The findings suggest risankizumab's better ability to provide clinically significant improvement in the extent and severity of psoriasis over time. The treatment populations resembled individuals with moderate-to-severe psoriasis from earlier phase III studies. The disease improvement rates were comparable to those observed in previous phase III trials after 52 weeks of therapy. Risankizumab therapy produced a faster response than FAE treatment. The safety profiles of both therapy groups were comparable with their known safety profiles, with minimal major adverse events. Risankizumab consistently outperformed FAEs in all reported endpoints, including skin, scalp, nail, and FAE.(17)

Risankizumab and ustekinumab: Risankizumab and ustekinumab, IL-23 and IL-12 receptor antagonists, have been proven in studies to enhance the well-being of psoriasis patients, with primary outcomes including PASI and the Dermatology Life Quality Index (DLQI). A phase-III clinical research including 322 Chinese volunteers discovered that risankizumab was more successful than ustekinumab in treating psoriasis.Two studies were included in the analysis, each with three high-quality non-randomized, double-blind, multicenter trials.However, there are several limitations: few trials with small sample sizes, short follow-up durations, and a safety review that only included findings from 16 weeks. More positive-controlled trials are required to fully assess the efficacy and safety of risankizumab and ustekinumab medications.In conclusion, risankizumab was more successful than ustekinumab in treating psoriasis, with comparable adverse responses and tolerability. Risankizumab may be a new choice for their therapy, taking into account patient compliance, tolerance, and safety (18).

Risankizumab and other biological agents: Therapeutic options for patients with moderate-to-severe CD are complicated, with a focus on therapy effectiveness and safety. A systematic review and network meta-analysis conducted by Siddharth Singh et al ; emphasizes the importance of infliximab and adalimumab (either in combination with azathioprine or as monotherapy) as first-line agents for inducing and maintaining clinical remission, and identifies IL23 blockade with ustekinumab or risankizumab as a potentially more effective strategy in patients with prior TNF antagonist exposure. This network meta-analysis can serve to enrich discussions on the risk-benefit profile of various drugs, as well as augment physician expertise, cost/resource constraints, and patient values and preferences when making treatment decisions.(19)

Contraindications, Warnings, Precautions: Risankizumab-rzaa is a monoclonal IgG antibody with no known contraindication. However, hypersensitivity to the medication or its inactive constituents may be considered a contraindication. In clinical studies, risankizumab-rzaa treatment was found to increase the risk of infection. Patients with known chronic or acute infections should not participate in risankizumab-rzaa clinical studies. Treatment should not begin in individuals with any clinically significant current infection until the infection has resolved or has been appropriately treated. Before starting risankizumab-rzaa, consider antituberculosis medication first. All age-appropriate vaccines should be performed before beginning risankizumab treatment. Antibody development can occur with any of the IL-23 antagonists, and individuals with larger antibody titers may experience lower plasma concentrations and a slower therapeutic response. The data on the use of risankizumab in pregnant women is insufficient to assess the drug's risk of serious birth abnormalities, miscarriage, or unfavorable maternal or fetal outcomes. The FDA requires a prospective, registry-based exposure cohort research that compares the maternal, fetal, and infant outcomes of women exposed to risankizumab-rzaa during pregnancy to an unexposed control group. There is no information on the presence of risankizumab in human milk, its effects on nursing babies, or milk production. The safety and effectiveness of risankizumab in pediatric patients have not been proven. (1)

CONCLUSION

Risankizumab marks a huge step forward in the treatment of psoriasis and Crohn's disease, with clinical trials revealing strong effectiveness and an acceptable safety profile. Its method of action, which targets the IL-23 pathway, enables precise control of the immune response, resulting in major improvements in the health of patients. The medicine has acquired regulatory clearance, indicating that it has excellent clinical data and addresses an unmet need in certain situations.While risankizumab has shown promise, particularly in attaining long-term remission, there are still difficulties, including expensive prices that may limit access for some patients. Furthermore, while the safety profile is typically acceptable, possible side effects and contraindications needs to be carefully examined in clinical practice.In comparison to other biological agents, risankizumab is comparable in terms of effectiveness and convenience, while pricing differences and the lack of biosimilars may represent barriers to wider usage. Looking ahead, further research and real-world studies will be critical in determining the long-term advantages and cost-effectiveness of risankizumab, eventually guiding its appropriate use in varied patient groups. As the landscape of biologic medicines evolves, risankizumab is positioned to play a crucial role in the therapy of psoriasis and Crohn's disease, emphasizing the importance of sustained investments in access to patients and education to optimize therapeutic potential.

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