Clinical Perspectives in IBD: A JAK Inhibitor in Crohn's Disease

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Chapter	Transcript
Chapter 1: Overview of Crohn's Disease & Importance of Adequate Disease Control	Hello, my name is Dr. Tauseef Ali. I'm a practicing gastroenterologist from SSM Health Saint Anthony Hospital, Oklahoma City. Crohn's disease is a chronic and progressive inflammatory condition that imposes substantial challenges on patients and healthcare facilities. It usually follows a relapsing and remitting course, with periods of flare-ups followed by periods of remission. However, even during periods of remission, there is still persistent subclinical inflammation. Without intervention, this may lead to bowel damage, giving rise to complications such as strictures, fistulas, and abscesses. These complications may elevate the likelihood of hospitalization or the need for surgical intervention. From my clinical experience, patients who achieve control of both symptomatic and objective outcomes early in their disease typically have better long-term outcomes.
Chapter 2: A JAK Inhibitor's Phase 3 Crohn's Disease Program Design	Upadacitinib, an oral Janus kinase inhibitor, is indicated for adults with moderately to severely active Crohn's disease who have had an inadequate response or intolerance to one or more TNF blockers. It's not recommended for use with other JAK inhibitors, biologic therapies for Crohn's disease, or potent immunosuppressants such as azathioprine and cyclosporine. The Phase III clinical trial program in Crohn's disease for upadacitinib comprised 3 studies, two induction trials, U-EXCEL and U-EXCEED, and a maintenance trial, U-ENDURE. In U-EXCEL and U-EXCEED, patients were treated with an induction dose of 45 mg of upadacitinib or placebo for 12 weeks.

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	At week 4, patients on stable dose of corticosteroids at baseline began a protocol specified taper. In fact, this is the first pivotal trial in moderate to severe Crohn's disease to mandate a steroid taper in induction. Individuals who demonstrated a clinical response while on upadacitinib became eligible for re-randomization in U-ENDURE. This was a 52-week, double-blind, placebo-controlled maintenance trial that employed a 1:1:1 randomization, assigning patients to receive either 15 mg of upadacitinib, 30 mg of upadacitinib, or placebo. Please note per the dosing recommendations in the USPI, upadacitinib 30 mg daily may be considered for patients with refractory, severe, or extensive disease. The study's co-primary endpoints were CDAI clinical remission and endoscopic response, both measured at week 12, the end of induction trials, and week 52, the end of maintenance trial. Patient demographics were generally balanced across the treatment arms. Approximately half of the population was male, and their mean age was in their late 30s.
Chapter 3: A JAK Inhibitor Achieved Greater Efficacy across Symptomatic and Objective Endpoints in Crohn's Disease Relative to Placebo	In U-EXCEL and U-EXCEED, 46% and 36% of patients, respectively, attained CDAI Clinical remission by week 12, a significantly higher percentage compared to those in placebo where 23% and 18% attained remission. Importantly, the significant difference in remission rates versus placebo persisted at week 52. Here, 42% of those administered 15 mg and 55% of those administered 30 mg of upadacitinib had attained CDAI clinical remission at week 52 versus only 14% of those on placebo.

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	Here are data from a subgroup analysis of patients with prior biologic failure. You can see that response to upadacitinib was observed as early as two weeks into the study, with a greater proportion of patients achieving clinical response at week 2 in upadacitinib treated patients compared with placebo. This is noteworthy as it enables patients to benefit from one of the short-term STRIDE-II treatment goals in a relatively brief time frame. You see a similar picture when looking at the endoscopic response, the study's co-primary endpoint. Significantly more patients achieved endoscopic response at week 12 compared with placebo, 46% versus 13% in U-EXCEL and 34% versus 3% in U-EXCEED. This was also the case at week 52, with 28% and 41% of patients receiving upadacitinib showing endoscopic response versus 7% of those receiving placebo. The data presented here demonstrate that a significantly greater proportion of patients receiving corticosteroids at baseline achieved corticosteroid-free remission during the upadacitinib induction treatment compared to those on placebo. Notably, not only did 30 to 40% of patients on upadacitinib attain corticosteroid free CDAI remission at week 12 in both U-EXCEL and U-EXCEED, but nearly half of patients receiving upadacitinib achieved remission at week 52 in U-ENDURE.
Chapter 4: The Safety Data of a JAK Inhibitor in Crohn's disease	Incidence of general categories of treatment emergent adverse events are presented here. Incidence of adverse events leading to withdrawal was around 5% in the induction studies and 7 to 12% in U-ENDURE. Upper respiratory tract infection was the most common adverse event in both stages of the study, reported at a higher rate in the upadacitinib arms than the placebo arm, affecting 13% of patients in the induction studies and 12 to 14% of patients in the maintenance study.

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	Adverse events of special interest in this trial program are shown in this table for both induction and maintenance. Data from U-ENDURE show that the incidence of serious infections, herpes zoster, lab abnormalities, hepatic disorder, and malignancies excluding non-melanoma skin cancer was higher among patients who received 30 mg of upadacitinib versus those who received 15 mg. In clinical practice, the incidence of herpes zoster infections could be mitigated, for example, by vaccinating appropriate patients for herpes zoster. Across all arms of the studies, there was no incidence of non-melanoma skin cancer, major adverse cardiac events, or adjudicated venous thromboembolism. Overall, the safety profile observed in patients with Crohn's disease treated with the upadacitinib was consistent with the known safety profile for upadacitinib in other indications, which are presented here. To conclude, in U-EXCEL, U-EXCEED, and U-ENDURE, upadacitinib demonstrated that it can achieve clinical remission and endoscopic response among individuals with moderate to severe Crohn's disease, with efficacy outweighing risks in appropriately selected patients. **IMPORTANT SAFETY CONSIDERATIONS AND BOXED WARNING** It is important to note that upadacitinib has a boxed warning for serious infections, mortality, malignancies, major adverse cardiovascular events and thrombosis. Patients treated with upadacitinib are at an increased risk for developing serious infections that may lead to hospitalization or death. Malignancies have been observed in upadacitinib treated patients. In RA patients treated with another JAK inhibitor, a higher rate of lymphomas and lung cancers was observed when compared with TNF blockers. Additionally, a higher rate of all-cause mortality, including sudden cardiovascular death as well as major adverse cardiovascular events,

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	pulmonary embolism and venous and arterial thrombosis were observed with another JAK inhibitor compared with TNF blockers in RA patients 50 years of age and older with at least one cardiovascular risk factor. Thrombosis has also been observed in upadacitinib treated patients. Avoid upadacitinib in patients at risk of thrombosis. Consider the individual patient's risks and benefits prior to initiating or continuing therapy. Please also read the information on screen about hypersensitivity reactions, other serious adverse reactions, avoiding live vaccines and the importance of immunizations, medication residue in stool, and the most common adverse reactions. Review upadacitinib full Prescribing Information for additional information at www.rxabbvie.com/pdf/rinvoq_pi.pdf.
Upadacitinib Indications, Important Safety Considerations, and Boxed Warning	**INDICATIONS** **Upadacitinib is a Janus kinase (JAK) inhibitor indicated for the treatment of:** **Adults with moderately to severely active rheumatoid arthritis (RA)** who have had an inadequate response or intolerance to one or more tumor necrosis factor (TNF) blockers. **Adults and pediatric patients 2 years of age and older with active psoriatic arthritis (PsA)** who have had an inadequate response or intolerance to one or more TNF blockers. **Adults with active ankylosing spondylitis (AS)** who have had an inadequate response or intolerance to one or more TNF blockers. **Adults with active non-radiographic axial spondyloarthritis (nr-axSpA)** with objective signs of inflammation who have had an inadequate response or intolerance to TNF blocker therapy. **Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis (pJIA)** who have had an inadequate response or intolerance to one or more TNF blockers.

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	Limitations of Use for RA, PsA, AS, nr-axSpA, and pJIA: Upadacitinib is not recommended for use in combination with other JAK inhibitors, biologic disease-modifying antirheumatic drugs (bDMARDs), or with potent immunosuppressants such as azathioprine and cyclosporine. **Adults and pediatric patients 12 years of age and older with refractory moderate to severe atopic dermatitis (AD)** whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies are inadvisable. **Limitations of Use for AD:** Upadacitinib is not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, or with other immunosuppressants. **Adults with moderately to severely active ulcerative colitis (UC)** who have had an inadequate response or intolerance to one or more TNF blockers. **Adults with moderately to severely active Crohn's disease (CD)** who have had an inadequate response or intolerance to one or more TNF blockers. **Limitations of Use for UC and CD:** Upadacitinib is not recommended for use in combination with other JAK inhibitors, biological therapies for UC or CD, respectively, or with potent immunosuppressants such as azathioprine and cyclosporine. **IMPORTANT SAFETY CONSIDERATIONS AND BOXED WARNING** **Serious Infections: Patients treated with upadacitinib are at increased risk for developing serious infections that may lead to hospitalization or death. These infections include tuberculosis (TB), invasive fungal, bacterial, viral, and other infections due to opportunistic pathogens. Most patients who developed these infections were taking concomitant immunosuppressants, such as methotrexate or corticosteroids**. **Test for latent TB before and during therapy; treat latent TB prior to use. Consider the risks and benefits prior to initiating therapy in patients with chronic or recurrent**

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	infection. If a serious infection develops, interrupt upadacitinib until the infection is controlled. **Mortality: In a postmarketing safety study in RA patients ≥ 50 years of age with at least one cardiovascular (CV) risk factor comparing another JAK inhibitor to TNF blockers, a higher rate of all-cause mortality, including sudden CV death, was observed with the JAK inhibitor.** **Malignancies: Malignancies have been observed in upadacitinib treated patients. In RA patients treated with another JAK inhibitor, a higher rate of lymphomas and lung cancers was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with upadacitinib, particularly in patients with a known malignancy (other than a successfully treated non-melanoma skin cancer [NMSC]), patients who develop a malignancy when on treatment, and patients who are current or past smokers.** NMSCs have been reported in patients treated with upadacitinib. Periodic skin examination is recommended for patients who are at increased risk for skin cancer. Advise patients to limit sunlight exposure by wearing protective clothing and using sunscreen. **Major Adverse Cardiovascular Events (MACE): In RA patients who were ≥ 50 years of age with at least one CV risk factor treated with another JAK inhibitor, a higher rate of MACE (CV death, myocardial infarction, and stroke) was observed compared with TNF blockers. Patients who are current or past smokers are at additional increased risk.** Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with upadacitinib. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur. **Discontinue upadacitinib in patients that have experienced a myocardial infarction or stroke.** **Thrombosis: Thrombosis, including deep vein thrombosis, pulmonary embolism, and arterial thrombosis, have occurred in patients treated with JAK inhibitors, including upadacitinib. Many of these adverse events were serious and some resulted in death. In RA patients who were ≥ 50 years of age with at least one CV risk factor treated with another JAK inhibitor, a higher rate of thrombosis was observed**

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	when compared with TNF blockers. Avoid upadacitinib in patients at risk. Patients with symptoms of thrombosis should discontinue upadacitinib and be promptly evaluated. **Hypersensitivity Reactions:** Upadacitinib is contraindicated in patients with known hypersensitivity to upadacitinib or any of its excipients. Serious hypersensitivity reactions such as anaphylaxis and angioedema were reported in patients receiving upadacitinib in clinical trials. If a clinically significant hypersensitivity reaction occurs, discontinue upadacitinib and institute appropriate therapy. **Other Serious Adverse Reactions:** Patients treated with upadacitinib also may be at risk for other serious adverse reactions, including gastrointestinal perforations, neutropenia, lymphopenia, anemia, lipid elevations, liver enzyme elevations, and embryo-fetal toxicity. If upadacitinib exposure occurs during pregnancy, please report the pregnancy to the surveillance program by calling 1-800-633-9110. **Vaccinations:** Avoid use of live vaccines during, or immediately prior to, upadacitinib therapy. Prior to initiating upadacitinib, it is recommended that patients be brought up to date with all immunizations, including prophylactic varicella zoster or herpes zoster vaccinations, in agreement with current immunization guidelines. **Medication Residue in Stool:** Reports of medication residue in stool or ostomy output have occurred in patients taking upadacitinib extended-release tablet. Most reports described patients with shortened gastrointestinal transit times. Instruct patients to contact their healthcare provider if medication residue is observed repeatedly. **Common Adverse Reactions in RA, PsA, AS and nr-axSpA:** The most common adverse reactions (≥1%) were upper respiratory tract infections, herpes zoster, herpes simplex, bronchitis, nausea, cough, pyrexia, acne, and headache. **Common Adverse Reactions in AD:** The most common adverse reactions (≥1%) are upper respiratory tract infections, acne, herpes simplex, headache, increased blood creatine phosphokinase, cough, hypersensitivity, folliculitis, nausea, abdominal pain, pyrexia, increased weight, herpes zoster, influenza, fatigue, neutropenia, myalgia, and influenza like illness.

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	Common Adverse Reactions in UC: The most common adverse reactions (≥5%) reported are upper respiratory tract infections, increased blood creatine phosphokinase, acne, neutropenia, elevated liver enzymes, and rash. **Common Adverse Reactions in CD:** The most common adverse reactions (≥5%) reported are upper respiratory tract infections, anemia, pyrexia, acne, herpes zoster, and headache. **Review accompanying upadacitinib full Prescribing Information for additional information, visit www.rxabbvie.com or contact AbbVie Medical Information at 1-800-633-9110.**

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