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Upadacitinib: A New Weapon in the Arsenal Against DMARD-Resistant Rheumatoid Arthritis

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ABSTRACT

Upadacitinib is an inhibitor of JAK-1 (Janus associated kinase 1) used to treat mild to severe rheumatoid arthritis (RA). On the basis of successful outcomes from a phase III clinical trial program, upadacitinib got its first-ever approval in United States on August 16, 2019, for treating patients with mild to serious RA, who were unresponsive to methotrexate. Upadacitinib, was created for its great specificity for janus kinase 1 (JAK-1). Upadacitinib is currently being marketed in form of 15 mg extended-release tablets, with a daily dose of 15 mg delivered orally. It can be used alone or in addition with methotrexate or other available DMARDs.

Abbreviations: ACPA: Antibodies Against Citrullinated Proteins; ALC: Absolute Lymphocyte Count; ATP: Adenosine Triphosphate; CKs: Cytokine Receptors; CYP3A4: Cytochrome P450 3A4; DMARDs: Disease-Modifying Antirheumatic Drugs; EMA: European Medicines Agency; EPO: Erythropoietin; Fc RS: Fc Receptors; FDA: Food and Drug Administration; FLS: Fibroblast-Like Synoviocytes; HDL-C: High Density Lipoprotein Cholesterol; IFN: Interferon; Ig E: Immunoglobulin E; IL: Interleukin; JAK: Janus Associated Kinase; LCL-C: Low Density Lipoprotein Cholesterol; MAPK: Mitogen- Activated Protein Kinase; MTX: Methotrexate; NF-B: Nuclear Factor B;OD: Once Daily; PI3K: Phosphoinositide 3-Kinase; RA: Rheumatoid Arthritis; STATs: Signal Transducers and Activators of Transcription; SYK: Spleen Tyrosine Kinase;TREM1: Triggering Receptor Expressed on Myeloid Cells 1;TYK: Tyrosine Kinases

Pathophysiology

RA is a developmental autoimmune condition evidenced by extra-articular involvement and inflammatory arthritis. It's a chronic inflammatory condition with no known cause that mostly affects synovial joints [1]. The inflammatory stage of RA begins in peripheral lymphoid organs where autoreactive T cells are initially exposed to self-antigens by dendritic cells [2]. These autoreactive T cells then use cytokines and co-stimulatory molecules to activate autoreactive B cells [3]. As a result, immunological complexes are deposited in the synovium and autoantibodies, such as antibodies against citrullinated proteins (ACPA), are secreted. Immune complexes attach to the Fc receptors (FcRs) on mast cells, neutrophils, and macrophages and release cytokines that trigger an inflammatory cascade [4]. Activated endothelial cells allow innate and adaptive immune cells to progressively invade synovial fluid. By stimulating other synovial cells, further generation of cytokines with paracrine and autocrine characteristics contributes to persistent chronic inflammation [5]. As a consequence, chondrocytes and activated FLS create a disintegrin and metalloproteinases and thrombospondin domain (ADAMTS), which damages cartilage tissue and causes the development of

synovial pannus. Different intracellular transduction processes that are induced by pro-inflammatory cytokines ultimately control the production of a variety of cytokines. Nuclear Factor B (NF-B), Mitogen-Activated Protein Kinase (MAPK), Spleen Tyrosine Kinase (SYK), Phosphoinositide 3-Kinase (PI3K), IL-17, and JAK-STAT are only a few of the pathogenic signaling pathways that have been linked to RA [6,7]. The Jakinibs are now the most effective medications, despite the fact that multiple signaling pathways have been addressed in RA [8].

Janus Kinase (JAK)

JAK kinases are tyrosine kinases that catalyze the passage of phosphate from adenosine triphosphate (ATP) to a variety of substrates, including CKs (cytokine receptors). JAK inhibitors operate as competitive ATP inhibitors, preventing ATP from attaching to JAKs' tyrosine kinase region. Founded on compositional differences in the ATP binding pocket of JAK1 and JAK2, upadacitinib was developed to selectively constrain ATP binding to JAK1 [9]. JAK1, JAK2, JAK3, and tyrosine kinase 2 are members of the JAK (Janus kinase) family of cytoplasmic protein tyrosine kinases (TYK2). JAKs bind to type I and type II cytokine receptors, transmitting extracellular cytokine signals to signal transducers and activators of transcription (STATs), which translocate to the nucleus and control effector gene transcription [10]. Small compounds that block JAKs, specifically targeting cytokine signaling pathways important in RA development, have made recent improvements in the management of RA [11].

Pharmacodynamics

Other JAK inhibitors include Tofacitinib and Baricitinib, which are approved by FDA for treating mild to serious RA and are currently under clinical development. Baricitinib serve as selective inhibitor of JAK1 & JAK2 and as moderate inhibitor of TYK2, whereas tofacetinib act as potent inhibitor of JAK1 & JAK3, and moderate inhibitor of JAK2 & TYK2. In biochemical and cellular studies, upadacitinib exhibits a higher specificity for JAK1 than for JAK2, JAK3, or TYK2. As a result, upadacitinib has the great promise to preferentially constrain cytokine signaling linked with JAK1-dependent inflammatory pathways, while having minimal influence on cytokine signaling for body systems incorporating JAK2 (EPO receptor signaling) and JAK3 [such as, IL-15 signaling]. In a study, upadacitinib effectively reduced the JAK1-reliant cytokines IL-6, oncostatin M, IL-2, and IFNγ (as determined by STAT phosphorylation inhibition) and these properties of upadacitinib were sixty time more potent than its effect on EPO signaling [12]. LDL-C (Low density lipoprotein cholesterol) and HDL-C (High density lipoprotein cholesterol) levels and C-reactive protein contents were found to be inversely correlated in rheumatoid arthritis patients participating in upadacitinib clinical trials, with the correspondence being highest in those who experienced a prolonged exposure to the therapy [13].

In addition, therapy with upadacitinib OD was linked with substantial, concentration-dependent decreases in epidermal hyperplasia and the number of dendritic and CD3+ T cells in skin contrasted to placebo in a 16-week phase IIb research in subjects having atopic dermatitis. Clinical improvement assessments and these improvements were associated. Upadacitinib once daily significantly decreased absolute eosinophil levels by week 16 (and substantial disparities from placebo was observed from second week of therapy forward), which was connected with clinical improvement [14]. Whole blood phosphorylation of STAT3 and STAT5 (caused by IL-6 and IL-7, respectively) was inhibited by the immediate-release (IR) formulation in healthy volunteers in a dose-dependent manner; the maximum inhibition occurred 1 hour after treatment and had nearly returned to baseline by the end of the procedure period [15]. Whereas treatment with upadacitinib ER 15 or 30 mg once daily in a 16-week phase IIb study of subjects with atopic dermatitis was linked to substantial, concentration-dependent decreases in epidermal hyperplasia, as well as dendritic (CD11c+, FcR1+) and CD3+ T cells in skin contrasted to placebo. Clinical improvement assessments and these improvements were associated. Upadacitinib 30 mg once day substantially decreased absolute eosinophil counts by week 16 (big variation from placebo was detected from week 2 of therapy forward) and was associated with clinical amelioration. In comparison to placebo, upadacitinib did not substantially alter antigen specific IgE levels [16].

Upadacitinib treatment for regional ileitis patients who saw a substantial endoscopic recovery revealed indication of increased (nominal p value 0.05) gene regulation in the large intestine and ileum. Notably down-regulated pathways included those involved in cell adhesion and migration, TREM1 signaling, IFN signaling, IL-17 response, cytokine communication in immune cells, pattern recognition receptor response, and fibrosis. The expression of several genes associated to epithelia too was noticeably upregulated [17]. In clinical studies with RA subjects, upadacitinib therapy was related with a modest, temporary rise in mean absolute lymphocyte count (ALC) from beginning to 36th week; this rapidly decreased with continuing therapy to values that were very similar to baseline. In healthy participants, up to 6 times the mean maximum exposure attained with the recommended daily dosage of 15 mg, upadacitinib showed no clinically significant impact on the QTc interval [18].

Pharmacokinetics

For the extended-release preparation, the oral upadacitinib pharmacokinetic profile is dose proportionate throughout a dosage range of 7.5 to 30 mg [19]. The median time to peak plasma concentrations after repeat upadacitinib treatment in RA

sufferers was 2-4 hours with the extended-release preparation [20]. The plasma protein binding of upadacitinib is modest (52%), and its distribution across blood and plasma cellular components is comparable (blood: plasma ratio of 1.0). It can be taken with or without food, and there was no clinically significant difference in upadacitinib exposure when given with a high-fat/high-calorie meal. Following recurrent once-daily dosing, steady state plasma levels of upadacitinib are attained in four days, and aggregation after recurrent once-daily dosing is modest [20,21]. Further pharmacokinetic studies showed that upadacitinib's parent moiety, which accounts for 79 percent of the drug's total plasma radioactivity, is responsible for its pharmacological activity. Upadacitinib is primarily excreted in the urine (24 percent) and faeces (38 percent) as the unchanged drug, with approximately 34 percent being excreted as metabolites. Upadacitinib had an average terminal elimination half-life of 8 to 14 hours. Upadacitinib exposure was unaffected by body weight, sex, race, age, renal defect, or gentle to medium liver impairment. When powerful CYP3A4 inhibitors like ketoconazole are also administered, upadacitinib plasma exposure is raised; yet, when strong CYP3A4 inducers are also administered, it is lowered (e.g., rifampin). In individuals who are taking long-term therapy with potent CYP3A4 inhibitors, upadacitinib should be taken with care [21,22].

Future Directions

By and large, upadacitinib showed an ideal advantage to-take a chance with profile. Additionally, upadacitinib has demonstrated promising outcomes whether used as alone or in conjunction with csDMARDs, as well as when compared to present benchmarks like adalimumab and methotrexate. The effectiveness of upadacitinib at dosages of 15 mg and 30 mg was typically equal [23,24]. Upadacitinib's safety profile was consistent with those of other JAK inhibitors and immunosuppressants. The FDA and EMA authorised the 15 mg once daily dosage of upadacitinib for treating patients with mild-to-serious RA and an insufficient response to MTX/other cs DMARDs based on the findings of the SELECT phase III trial. For individuals who have not responded well to conventional or biologic therapy, upadacitinib is a good therapeutic choice. Progressing preliminaries will decide if upadacitinib can be utilized in inflammatory ilnesses later on [15,25].

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Conflict of Interest

The authors declare that there is no conflict of interest.

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