Upadacitinib

We **recommend** upadacitinib in AE patients who are candidates for systemic treatment.	↑↑	100%  (15/15) Evidence and consensus based, see Evidence Report

upadacitinib: in licence for ≥ 12 years of age;
adults: 15 or 30 mg per day; age ≥ 65: 15 mg per day
age 12-17 (>= 30 kg bw): 15 mg per day

Certainty of evidence: Network meta-analysis from 2024[1,2]:
Short term (up to 16 weeks) vs placebo (NMA medications used in clinical practice)

15 mg
⊕⊕⊕⊕ HIGH for mean difference **EASI** -11 (-12.6, -9.4)
⊕⊕⊕◯ MODERATE for mean difference **POEM** -7 (-11.2, -2.9); **peak pruritus NRS** -2.4 (-2.8, -2)

30 mg
⊕⊕⊕⊕ HIGH for mean difference **EASI** -13.5 (-15.2, -11.9); **POEM** -10.7 (-14.8, -6.5); **peak pruritus NRS** -3.3 (-3.6, -3.1)

For upadacitinib versus other drugs, see Evidence Report

Mechanisms of action and efficacy

Upadacitinib is a relatively selective and reversible Janus Kinase (JAK) 1 inhibitor. There is one phase 2 trial including 167 adult patients that investigated three different doses of upadacitinib (30 mg/d, 15 mg/d and 7.5 mg/d) for AE compared to placebo.[3] The trial was conducted over 16 weeks. Upadacitinib was superior to placebo for all dosage groups in EASI (mean change (SE) 74% (6.1%) for 30 mg, 62% (6.1%) for 15 mg, 39% (6.2%) for 7.5 mg and 23% (6.4%) for placebo (p=0.03, <0.001, <0.001). There were also significant improvements seen with regard to the SCORAD index, NRS pruritus, and POEM scores. The trials published since have shown similar efficacy.[4-6]

In a direct head-to-head trial enrolling adult AE patients randomized to receive upadacitinib (n=348) and dupilumab (n=344) 247 patients receiving upadacitinib (71.0%) and 210 patients receiving dupilumab (61.1%) achieved EASI75 at 16 weeks (*p*=0.006). All ranked secondary end points also demonstrated the superiority of upadacitinib vs dupilumab, including improvement in Worst Pruritus NRS as early as week 1, achievement of EASI75 as early as week 2, and EASI100 at week 16. Rates of serious infection, eczema herpeticum, herpes zoster, and laboratory-related adverse events were higher for patients who received upadacitinib, whereas rates of conjunctivitis and injection-site reactions were higher for patients who received dupilumab.

Dosage: acute flare, short term, long term

Upadacitinib is licensed at the 15 mg and 30 mg doses for AE, and at 15 mg for rheumatoid arthritis, psoriatic arthritis and ankylosing spondilitis. Follow up until week 52 is now available, showing long-term efficacy and safety profiles similar to the 16 week trials.[7] There is no study that has looked at acute flare treatment, and there are currently early phase AE trials in children >6 months.

Safety

The cumulative incidence rates of adverse events were 78.6% for 30 mg, 76.2% for 15 mg, 73.8% for 7.5 mg and 62.5% for placebo in the phase 2 trial and have been similar in the studies reported since.[3] Upper respiratory tract infections and acne were the most frequently reported adverse events for upadacitinib. The cumulative incidence rates of severe adverse events were 0% for 30mg, 2.4% for 15mg, 4.8% for 7.5mg and 2.4% for placebo. Low withdrawal rates were reported in the placebo and upadacitinib groups (n<5 for each group). In a phase 3 trial, 272 Japanese patients (age 12-75 years) with moderate-to-severe AE were randomized in a 1:1:1 ratio to receive 15 mg upadacitinib, 30 mg upadacitinib or placebo (each in combination with a TCS) to evaluate the safety of upadacitinib in combination with TCS. Treatment-emergent adverse event (TEAEs) were reported for 56.0%, 63.7% and 42.2% of participants, respectively at week 24. The most frequently reported TEAEs were acne (13.2%, 19.8%, 5.6%), nasopharyngitis (13.2%, 15.4%, 15.6%), and herpes zoster infection (0%, 4.4%, 0%). No thromboembolic events, malignancies, gastrointestinal perforations or deaths occurred.[8]

Monitoring

The manufacturer advises that patients are screened for viral hepatitis B and C and TB. Lipid and liver profiles need to be measured at baseline and regularly following treatment initiation. Screening and monitoring for any haematological abnormalities is also advised, no later than 12 weeks.

In practice, we recommend the same baseline screening and treatment monitoring investigations for all JAK inhibitors. For baseline screening this is a full blood count, renal, liver and lipid profile as well as creatinine phosphokinase levels and hepatitis, HIV and TB screen.

For monitoring purposes, we recommend a full blood count, renal, liver and lipid profile as well as creatinine phosphokinase level at four weeks into treatment and then three-monthly while on therapy.

Combination with other treatments

No studies assessing the use of upadacitinib with other systemic therapies in AE patients have been published to date, but the combination therapy with MTX is an established combination regimen in the management of rheumatoid arthritis, albeit only with the 15mg once a day dose.[9]

Special considerations

JAK inhibitors are also effective for certain other inflammatory diseases and are partially approved for their treatment. Therefore, patients with AE and with concomitant inflammatory diseases, such as AA, rheumatoid and juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis and inflammatory bowel diseases are likely to experience additional beneficial effects for these concomitant diseases. Upadacitinib is already licensed for most of these indications.

Please refer to the special considerations in the JAK inhibitor introduction chapter.

References

1. Drucker AM, Lam M, Prieto-Merino D, et al. Systemic Immunomodulatory Treatments for Atopic Dermatitis: Living Systematic Review and Network Meta-Analysis Update. *JAMA Dermatol*. Jul 17 2024;doi:10.1001/jamadermatol.2024.2192
2. Drucker AM, Flohr C, Ellis AG, et al. Systemic immunomodulatory treatments for atopic dermatitis: a living systematic review and network meta-analysis. 18.07.2024, https://eczematherapies.com/research/
3. Guttman-Yassky E, Thaci D, Pangan AL, et al. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial. *J Allergy Clin Immunol*. Mar 2020;145(3):877-884. doi:10.1016/j.jaci.2019.11.025
4. Simpson EL, Sinclair R, Forman S, et al. Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet*. Jul 25 2020;396(10246):255-266. doi:10.1016/s0140-6736(20)30732-7
5. Guttman-Yassky E, Teixeira HD, Simpson EL, et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. *Lancet*. Jun 5 2021;397(10290):2151-2168. doi:10.1016/s0140-6736(21)00588-2
6. Reich K, Teixeira HD, de Bruin-Weller M, et al. Safety and efficacy of upadacitinib in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis (AD Up): results from a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. Jun 5 2021;397(10290):2169-2181. doi:10.1016/s0140-6736(21)00589-4
7. Silverberg JI, de Bruin-Weller M, Bieber T, et al. Upadacitinib plus topical corticosteroids in atopic dermatitis: Week 52 AD Up study results. *J Allergy Clin Immunol*. Aug 14 2021;doi:10.1016/j.jaci.2021.07.036
8. Katoh N, Ohya Y, Murota H, et al. A phase 3 randomized, multicenter, double-blind study to evaluate the safety of upadacitinib in combination with topical corticosteroids in adolescent and adult patients with moderate-to-severe atopic dermatitis in Japan (Rising Up): An interim 24-week analysis. *JAAD Int*. Mar 2022;6:27-36. doi:10.1016/j.jdin.2021.11.001
9. Fleischmann RM, Genovese MC, Enejosa JV, et al. Safety and effectiveness of upadacitinib or adalimumab plus methotrexate in patients with rheumatoid arthritis over 48 weeks with switch to alternate therapy in patients with insufficient response. *Ann Rheum Dis*. Nov 2019;78(11):1454-1462. doi:10.1136/annrheumdis-2019-215764