Upadacitinib

We **recommend** upadacitinib in AE patients who are candidates for systemic treatment.	↑↑	**100%** 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, approved from age 12. In phase 3 studies (Measure Up 1/2 and AD Up), upadacitinib with and without concomitant topical corticosteroid therapy was superior to in achieving efficacy endpoints, including the proportion achieving EASI75 response after 16 weeks of treatment in patients aged 12 years and older with moderate to severe AE.[3, 4]

In a direct head-to-head trial enrolling adult AE patients randomized to receive upadacitinib (n=342) and dupilumab (n=331) 248 patients receiving upadacitinib (72.4%) and 207 patients receiving dupilumab (62.6%) achieved EASI75 at 16 weeks (p=0.007). 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.[5]

Dosage: acute flare, short term, long term

Upadacitinib is licensed at the 15 mg and 30 mg doses for AE. Starting with the higher dose usually leads to a faster clinical response, better drug survival and adherence, and may therefore be advisable in younger adults, otherwise healthy patients. Follow up until week 52 is now available, showing long-term efficacy and safety profiles similar to the 16-week trials.[6] 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.[7] 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]

Screening and 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, the guideline group considers the same baseline screening and treatment monitoring investigations applicable to all JAK-Inhibitors. For baseline screening this is a full blood count, renal, liver and lipid profile and hepatitis B and C, HIV and TB screen.

For follow up monitoring we propose a full blood count, renal, liver and lipid profile at four weeks into treatment and then three-monthly while on therapy. The guideline group does not advocate for mandatory monitoring of creatinine phosphokinase levels in asymptomatic patients.

Combination with other treatments

We recommend combining upadacitinib, as any systemic treatment, with emollients and, whenever needed, topical anti-inflammatory treatment in AE patients. 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 approved for their treatment in some cases. 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. Upadacitinib is also approved for the treatment of giant cell arteritis.

Please refer to the special considerations in the JAK-Inhibitor introduction chapter.

References

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