Upadacitinib

We **recommend** upadacitinib in AE patients who are candidates for systemic treatment.

upadacitinib: in licence for ≥ 12 years; 
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:
- Short term (8-16 weeks) vs placebo (NMA medications used in clinical practice or likely to be approved soon)
  - @@@@@ HIGH for mean difference/ standardized mean difference EASI, change in signs, POEM, peak pruritus NRS, itch
  - @@@@@ MODERATE - @@ LOW for undesirable effects

Upadacitinib is licensed for AE in adolescents (12 years and above) and adults.

**Mechanisms of action and efficacy**

Upadacitinib is a selective and reversible Janus Kinase (JAK) 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 30mg, 62% (6.1%) for 15mg, 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 EASI-75 at 16 weeks (P = .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 EASI-75 as early as week 2, and EASI-100 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 15mg and 30mg doses for AE, and at 15mg 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. 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. 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.

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 and TB screen, including a chest radiograph.

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.

Special considerations

AE patients with concomitant inflammatory diseases, such as rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis are likely to experience beneficial effects, as upadacitinib is already licensed for this indication.
References


