NEW PRODUCT

Upadacitinib for the treatment of rheumatoid arthritis

STEVE CHAPLIN

Upadacitinib (Rinvoq) is a new janus kinase inhibitor licensed for the treatment of rheumatoid arthritis in adults. This article discusses its indications, clinical trial efficacy and adverse effects.

THE 2018 NICE guideline on the management of rheumatoid arthritis (RA) in adults states that the aim of treatment is to achieve remission (Disease Activity Score [DAS28] <2.6) or, if that is not possible, low disease activity (DAS28 ≤3.2). It recommends early treatment with a conventional disease-modifying antirheumatic drug (cDMARD; methotrexate, leflunomide, sulfasalazine, hydroxychloroquine) and — because their onset of action may be slow — to consider bridging treatment with a systemic corticosteroid.1 Combination cDMARD therapy should be offered if monotherapy does not reach the treatment target. If this still does not achieve remission or low disease activity, a biological DMARD (bDMARD) is the next option for individuals with severe RA (DAS28 >5.1), usually combined with methotrexate (unless it is not tolerated or contraindicated).2 bDMARDs include monoclonal antibodies targeted against TNF (etanercept) or T lymphocytes (abatacept).

The oral small-molecule janus kinase (JAK) inhibitors baricitinib and tofacitinib are recommended as options for severe RA in adults whose disease has responded inadequately to a combination of cDMARDs, or those who have responded inadequately to or cannot take other DMARDs including at least one bDMARD and cannot take rituximab. They are recommended in combination with methotrexate, or as monotherapy for those in whom methotrexate is not tolerated or contraindicated.2,3

Upadacitinib (Rinvoq) is the third small-molecule JAK inhibitor to be introduced for the treatment of rheumatoid arthritis. It works by preferentially inhibiting JAK1 signalling and inhibiting IL-6 and interferon (IFN)-gamma mediated inflammatory responses.

Indications and dosage

Upadacitinib is licensed for the treatment of moderate to severe active RA in adult patients who have responded inadequately to, or who are intolerant to, one

KEY POINTS

- Upadacitinib is the third janus kinase (JAK) inhibitor to be introduced for the treatment of rheumatoid arthritis
- It is licensed to treat moderate to severe active disease in adults who have responded inadequately to, or are intolerant to, one or more DMARDs, either as monotherapy or combined with methotrexate
- The recommended dosage is 15mg orally once daily
- In clinical trials, upadacitinib achieved low disease activity in 43–48% of patients as monotherapy or combined with a conventional DMARD
- It was superior to adalimumab in achieving remission when combined with methotrexate
- Adverse effects are similar to other JAK inhibitors and did not greatly increase treatment discontinuation in clinical trials compared with placebo
- A year’s treatment with upadacitinib costs £10,508
or more DMARDs. It can be used either as monotherapy or in combination with methotrexate.

A NICE technology appraisal is currently in development for upadacitinib for the treatment of RA (ID1400), but no date yet has been set for publication of the final guidance.

The recommended dosage of upadacitinib is 15mg once daily, given orally as a prolonged-release tablet. Treatment should not start if the patient’s absolute lymphocyte count is <500 cells/mm³, the absolute neutrophil count is <1000 cells/mm³ or haemoglobin is <8g/dL. Treatment should be interrupted if levels fall below these thresholds, if the patient develops a serious infection or if liver injury is suspected.

No dose adjustment is recommended for older people (though data are limited in patients aged ≥75 years), or in individuals with mild or moderate hepatic or renal impairment. It should be used with caution in patients with severe renal impairment and is contraindicated in those with severe hepatic impairment. Treatment may be associated with an increased risk of serious infection such as tuberculosis and upadacitinib should not be initiated in patients with active tuberculosis or active serious infection. It is also contraindicated in pregnancy.

Efficacy
Upadacitinib has been evaluated in five pivotal phase 3 trials. It was compared with methotrexate as monotherapy in patients with moderate to severe active RA not previously treated with methotrexate (and mostly no other cDMARDs either) (SELECT-EARLY, n=631) or when methotrexate achieved an inadequate response (SELECT-MONOTHERAPY, n=433). It was compared with placebo as add-on therapy after a cDMARD was unsatisfactory (SELECT-NEXT, n=442); compared with adalimumab in combination with methotrexate (SELECT-COMPARE, n=1629); and with placebo in combination with a cDMARD after failure of a bDMARD (SELECT-BEYOND, n=333). These figures exclude patients randomised to treatment with a 30mg dose of upadacitinib (which offered only marginally greater efficacy and was not subsequently licensed).

The primary endpoints were low disease activity at week 12, 14, or remission at week 12 or 24 (see Table 1). In patients who had no previous treatment with methotrexate, upadacitinib monotherapy achieved remission after six months in almost half of patients, compared with almost one-fifth treated with methotrexate. A similar difference in response rates for low disease activity after 14 weeks was evident in patients switched to upadacitinib compared with continuing methotrexate, and at 12 weeks when combined with a cDMARD and compared with placebo. In patients for whom methotrexate alone was inadequate, adding upadacitinib, adalimumab or placebo achieved remission in 29%, 18% and 6% respectively after 12 weeks. Over 48 weeks of treatment, upadacitinib was associated with superior clinical responses, including low disease activity and remission, compared with adalimumab (see Figure 1).

These differences were associated with consistent improvements in secondary endpoints (including American College of Rheumatology [ACR] 20, 50 and 70 responses and Clinical Disease Activity Index). Both upadacitinib and adalimumab significantly reduced the proportion of patients with radiographic disease progression after 48 weeks compared with placebo (86%, 88% and 74% of patients respectively). In SELECT-BEYOND (after failure of a bDMARD and in combination with a cDMARD), upadacitinib significantly improved patient-reported outcomes compared with placebo, including pain, stiffness and health-related quality of life; numbers need to treat compared with placebo across most quality of life domains were about 5–7 (except mental health, for which the difference was not statistically significant).

Adverse effects
The adverse events reported most often in clinical trials were upper respiratory tract infection (13.5%), nausea (3.5%), increased blood creatine phosphokinase (2.5%) and cough (2.2%). Neutropenia and hypercholesterolaemia (mean 1.3% increase in total cholesterol and LDL-C, and 10% increase in triglycerides) were common. The frequency of serious infections was 3.6 events per 100 patient-years, similar to that associated with other JAK inhibitors. The frequency of any opportunistic infection associated with upadacitinib was 0.6 events per 100 patient years. The mean rate of discontinuation due to adverse effects was 2.8% with upadacitinib and 2.0% with placebo.

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**Table 1.** Primary endpoints in phase 3 trials of upadacitinib 15mg daily

<table>
<thead>
<tr>
<th>SELECT Trial</th>
<th>Endpoint</th>
<th>Background treatment</th>
<th>Comparators</th>
<th>% Patients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EARLY&lt;sup&gt;4&lt;/sup&gt;</td>
<td>REM week 24</td>
<td>None</td>
<td>Upadacitinib Methotrexate</td>
<td>48%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MONOTHERAPY&lt;sup&gt;5&lt;/sup&gt;</td>
<td>LDA week 14</td>
<td>None</td>
<td>Upadacitinib Methotrexate</td>
<td>45%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NEXT&lt;sup&gt;6&lt;/sup&gt;</td>
<td>LDA week 12</td>
<td>cDMARD</td>
<td>Upadacitinib Placebo</td>
<td>48%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>COMPARE&lt;sup&gt;7&lt;/sup&gt;</td>
<td>REM week 12</td>
<td>Methotrexate</td>
<td>Upadacitinib Adalimumab Placebo</td>
<td>29%</td>
<td>≤0.001 vs placebo</td>
</tr>
<tr>
<td>BEYOND&lt;sup&gt;8&lt;/sup&gt;</td>
<td>LDA week 12</td>
<td>cDMARD</td>
<td>Upadacitinib Placebo</td>
<td>43%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

LDA = low disease activity (DAS28[CRP] ≤3.2); REM = remission (DAS28[CRP] <2.6)
**References**


10. Fleischmann RM, 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* 2019;78:1454–62. This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license. See: [http://creativecommons.org/licenses/by-nc/4.0/](http://creativecommons.org/licenses/by-nc/4.0/).


**Declaration of interests**

None to declare.

Steve Chaplin is a freelance medical writer specialising in therapeutics