Tofacitinib for psoriatic arthritis – second or subsequent line

SUMMARY

NIHR HSRIC ID: 5753

Tofacitinib is intended to be used for the treatment of active psoriatic arthritis following the failure of conventional disease-modifying anti-rheumatic drugs (DMARDs) or following failure of biological DMARDs. Tofacitinib is a novel oral janus kinase (JAK) that inhibits JAK1, 2 and 3 in vitro, with functional specificity for JAK1 and 3 thus resulting in the modulation of the immune response. If licensed, tofacitinib will provide an additional oral treatment option for patients with active psoriatic arthritis.

Psoriatic arthritis is an inflammatory arthritis that is associated with psoriasis of the skin and nails and typically develops within 10 years of psoriasis being diagnosed. An estimated 5-10% of people with psoriasis and 25-40% of people with psoriatic arthritis have severe arthritis with progressive joint lesions. Approximately 2.4% of people with psoriatic arthritis are potentially eligible to receive treatment with biological DMARDs.

The clinical management of psoriatic arthritis aims to supress joint, tendon, and entheseal inflammation and reduce functional limitations and joint damage. Current guidelines recommend treatment with one or two conventional DMARDs before proceeding to TNF inhibitors. Tofacitinib is currently in two phase III clinical trials comparing its effect on clinically important changes in arthritis against placebo and adalimumab. These trials are expected to complete in 2016.
TARGET GROUP

- Psoriatic arthritis; active – second line following failure of conventional disease-modifying anti-rheumatic drugs (DMARDs); or third line following failure of biological DMARDs.

TECHNOLOGY

DESCRIPTION

Tofacitinib (Xeljanz, tasocitinib, CP-690 550, CP 690550) is a novel oral janus kinase (JAK) inhibitor that inhibits JAK1, 2 and 3 in vitro, with functional specificity for JAK1 and 3. Inhibition of JAK1 and 3 blocks signalling of several cytokines, including IL-2, 4, 7, 9, 15 and 21, which are required for lymphocyte activation, proliferation and function; it may therefore result in modulation of the immune response. Inhibition of JAK1 attenuates signalling by pro-inflammatory cytokines IL-6 and IFN-γ. Inhibition of JAK2 may attenuate erythropoietin signalling. Tofacitinib is administered orally at 5-10mg twice daily on a continuous basis.

Tofacitinib does not have Marketing Authorisation in the EU for any indication. It is currently in phase IV clinical trials for rheumatoid arthritis, and in phase III clinical trials for ulcerative colitis, Crohn’s disease and chronic plaque psoriasis. In addition, a topical formulation of tofacitinib is in phase II trials for atopic dermatitis and dry eye syndrome.

INNOVATION and/or ADVANTAGES

If licenced, tofacitinib will provide an additional oral treatment option for patients with active psoriatic arthritis.

DEVELOPER

Pfizer.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Psoriatic arthritis is an inflammatory arthritis that is associated with psoriasis of the skin and nails, it usually develops within 10 years of psoriasis being diagnosed. The pain, swelling and stiffness associated with psoriatic arthritis can affect any joint in the body, but commonly affects joints in the hands, feet, knees, neck, spine and elbows, and the severity of the condition can vary in individuals. Psoriatic arthritis can also affect larger joints such as hips, knees and spine. Psoriatic arthritis is a highly heterogeneous and complex disorder, which presents major challenges in diagnosis and treatment. Psoriatic arthritis has a chronic relapsing course, characterised by flares and remission, which may be life-long. The cause of psoriatic arthritis is not known. Genetic, immune system and environmental factors may play a role and it is likely that the skin and joint diseases have similar aetiology, although they may not occur together.
This topic is relevant to:

**CLINICAL NEED and BURDEN OF DISEASE**

The prevalence of psoriasis in the general population is estimated at 2-3% and the prevalence of inflammatory arthritis in people with psoriasis is estimated at up to 30%\(^1\). The incidence of psoriatic arthritis is 6.6 per 100,000, and in about 80% of cases the presence of psoriasis precedes the onset of psoriatic arthritis\(^7\). An estimated 5-10% of people with psoriasis and 25-40% of people with psoriatic arthritis have severe arthritis with progressive joint lesions\(^8\). Joint damage has been shown radiologically in up to 47% of people with psoriatic arthritis at a mean interval of two years\(^1\). Approximately 2.4% of people with psoriatic arthritis are potentially eligible to receive treatments with biological DMARDs\(^9\). There is a clinical need for additional effective treatments for psoriatic arthritis, and especially for oral therapies\(^a\)

Psoriatic arthritis can significantly affect the ability to work and to carry out daily tasks, and can have detrimental impact on quality of life\(^1\). People with psoriatic arthritis have a 60% higher risk of mortality\(^1\) and their life expectancy is estimated to be reduced by approximately three years\(^10\). In 2013-2014, there were 5,277 hospital admissions for psoriatic arthritis (ICD10 L40.5) in England and Wales, resulting in 3,181 bed days and 5,436 finished consultant episodes\(^11\).

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**

- NICE technology appraisal in development. Apremilast for treating active psoriatic arthritis in people for whom disease-modifying anti-rheumatic drugs have been inadequately effective, not tolerated or contraindicated (ID682). Expected August 2015.

\(^{a}\) Expert personal communication.
Other Guidance

- Scottish Intercollegiate Guidelines Network. Diagnosis and management of psoriasis and psoriatic arthritis in adults (121). 2010\(^5\).
- British Society of Rheumatology. Guidelines for anti-TNF-a therapy in psoriatic arthritis. 2005\(^5\).

CURRENT TREATMENT OPTIONS

The clinical management of psoriatic arthritis aims to suppress joint, tendon and enthesal inflammation, and reduce functional limitations and joint damage\(^13\). This includes a range of physical therapy and pharmacological treatments. Guidelines recommend treatment with one or two conventional DMARDs before proceeding to tumour necrosis factor-alpha (TNF-\(\alpha\)) inhibitors\(^{13,14}\).

Pharmacological treatment options include\(^{15,16}\):

Non biological therapies:
- Analgesics.
- Corticosteroids – limited role in psoriatic arthritis\(^17\).
- Non-steroidal anti-inflammatory drugs (NSAIDs).
- DMARDs, including methotrexate (MTX)\(^{18,19}\), sulfasalazine, leflunomide, gold salts (very rarely used), and anti-malarials (very rarely used). Usually administered within three months of diagnosis to stabilise joint function, either as monotherapy or in combination with biological agents\(^20\).

Biological therapies:
- TNF-\(\alpha\) inhibitors such as etanercept, infliximab, adalimumab and golimumab.

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Status</th>
<th>Source of information</th>
<th>Location</th>
<th>Design</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01882439; tofacitinib vs placebo; phase III.</td>
<td>Pfizer.</td>
<td>Ongoing.</td>
<td>Trial registry(^21).</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
<td>Randomised, placebo-controlled.</td>
<td>n=390 (planned); aged ≥18 years; active arthritis at screening/baseline as indicated by ≥ 3 tender/painful and 3 swollen joints; active plaque psoriasis at screening; inadequate efficacy or lack of tolerance to previously administered TNF inhibitor.</td>
</tr>
<tr>
<td>NCT01877668; tofacitinib vs adalimumab vs placebo; phase III.</td>
<td>Pfizer.</td>
<td>Ongoing.</td>
<td>Trial registry(^22).</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
<td>Randomised, active- and placebo-controlled.</td>
<td>n=400 (planned); aged ≥18 years; diagnosis of psoriatic arthritis of &gt; 6 months; meet the classification criteria for psoriatic arthritis (CASPAR) at screening; not adequately treated with DMARDs; concurrent treatment with methotrexate, leflunomide or sulfasalazine required; no previous treatment with TNF inhibitors; must have 3 or more swollen and tender joints; active psoriasis skin lesions.</td>
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</tbody>
</table>
## Schedule

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Randomised to tofacitinib 5mg or 10mg orally for 6 months, or placebo for 3 months and then tofacitinib 5mg or 10mg orally for 3 months.</th>
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<tbody>
<tr>
<td></td>
<td>Randomised to tofacitinib 5mg or 10mg orally, daily plus subcutaneous (SC) placebo injections every 2 weeks for 12 months; or 40mg adalimumab SC every 2 weeks plus daily placebo tablets for 12 months; or placebo tablets for 3 months followed by tofacitinib 25mg orally, daily for 9 months, both with placebo SC injections every 2 weeks for 12 months.</td>
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## Follow-up

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<thead>
<tr>
<th>Follow-up</th>
<th>Active treatment 6 months.</th>
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<td></td>
<td>Active treatment, 12 months; follow-up at 3 months intervals.</td>
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</table>

## Primary outcome/s

<table>
<thead>
<tr>
<th>Primary outcome/s</th>
<th>ACR20&lt;sup&gt;b&lt;/sup&gt;:</th>
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<tbody>
<tr>
<td></td>
<td>ACR20.</td>
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</tbody>
</table>

## Secondary outcome/s

<table>
<thead>
<tr>
<th>Secondary outcome/s</th>
<th>ACR50; ACR70; Health Assessment Questionnaire (HAQ-DI); patients achieving Psoriatic Arthritis Pain Response Criteria (PsARC); Physician Global Assessment (PGA) of psoriasis score; Psoriasis Area and Severity Index (PASI); dactylitis severity score; enthesis score based upon SPARCC (Spondylarthritis Research Consortium of Canada) and Leeds indices; EuroQol EQ-5D quality of life instrument; Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F); Bath Ankylosing Spondylitis Disease Activity Index (BASDAI); Short Form 36 Health Survey (SF36) patient-reported measure of health status.</th>
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<td></td>
<td>Modified Total Sharp Score (mTSS)&lt;sup&gt;c&lt;/sup&gt;; ACR50; ACR70; HAQ-DI; PsARC; PGA score; PASI; dactylitis severity score; enthesis score based upon SPARCC and Leeds indices; EQ-5D; FACIT-F; BASDAI; SF36.</td>
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## Expected reporting date

<table>
<thead>
<tr>
<th>Expected reporting date</th>
<th>Expected completion date reported as January 2016.</th>
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## Trial

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01976364; tofacitinib; phase III.</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Pfizer.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry&lt;sup&gt;23&lt;/sup&gt;.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
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<tr>
<td>Design</td>
<td>Non-randomised.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=650 (planned); aged ≥ 18years; previous participation in qualifying psoriatic arthritis study involving tofacitinib.</td>
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<tr>
<td>Schedule</td>
<td>Tofacitinib 5mg or 10mg orally twice daily for 36 months.</td>
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<tr>
<td>Follow-up</td>
<td>Active treatment 36 months; follow-up at 3 month intervals.</td>
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<sup>b</sup>ACR: the American College of Rheumatology criteria are a core set of six outcome variables for the assessment of clinically important improvement: physical global assessment of disease activity; patient global assessment of overall well-being; functional ability; number of joints with active arthritis; number of joints with limited range of motion; and ESR. ACR20, ACR50 and ACR70 represent a 20%, 50% and 70% improvement respectively in at least three response criteria (with no more than one response variable worse by greater than 30%).

<sup>c</sup>mTSS = sum of erosion and Joint Space Narrowing (JSN) scores for 44 joints (16 per hand and 6 per foot). mTSS scores range from 0 (normal) to 448 (worst possible total score). An increase in mTSS from baseline represents disease progression and/or joint worsening, no change represents halting of disease progression, and a decrease represents improvement.
Primary outcome/s
AEs and serious AEs; laboratory test values of potential clinical importance.

Secondary outcome/s
ACR20; ACR50; ACR70; HAQ-DI; PsARC; PGA score; PASI; dactylitis severity score; enthesis score based upon SPARCC and Leeds indices; EQ-5D; FACIT-F; BASDAI.

Expected reporting date
Expected completion date reported as January 2019.

ESTIMATED COST and IMPACT

COST
The cost of tofacitinib is not yet known. The cost of selected biological treatments for psoriatic arthritis are summarised below\(^d\).\(^{24}\).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Annual cost</th>
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<tbody>
<tr>
<td>Adalimumab</td>
<td>40mg SC every 2 weeks</td>
<td>£9,155</td>
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<tr>
<td>Etanercept</td>
<td>25mg SC twice weekly, or 50mg once weekly</td>
<td>£9,295</td>
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<tr>
<td>Infliximab</td>
<td>5mg/kg IV at weeks 0, 2 and 6 and then every 8 weeks</td>
<td>£15,106</td>
</tr>
<tr>
<td>Golimumab</td>
<td>50mg SC once a month</td>
<td>£9,155</td>
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</tbody>
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IMPACT - SPECULATIVE

Impact on Patients and Carers
- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- Other: oral therapy that will avoid the need for frequent painful subcutaneous injections or infusions
- No impact identified

Impact on Health and Social Care Services
- Increased use of existing services
- Decreased use of existing services
- Re-organisation of existing services
- Need for new services
- Other:
- None identified

Impact on Costs and Other Resource Use
- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs:
- Other reduction in costs: avoiding parenteral administration could reduce staff costs and hospitalisations associated with infusions
- Other:
- None identified

\(^d\) Based on an average adult weight of 77.9kg. Assumes wastage.
Clinical uncertainty or other research question identified: expert opinion suggests that depending on the cost of tofacitinib, it should be considered for patients that are unable to tolerate or have inadequate responses to methotrexate and other DMARDs as either monotherapy or combination therapy.

REFERENCES

18. NIHR Horizon Scanning Centre. Ustekinumab (Stelara) for psoriatic arthritis with structural joint damage. University of Birmingham; September 2012. www.hsc.nihr.ac.uk

® Expert personal communication.
19 NIHR Horizon Scanning Centre. Secukinumab for active and progressive psoriatic arthritis. University of Birmingham; November 2012. www.hsc.nihr.ac.uk
20 NIHR Horizon Scanning Centre. Inflectra (infliximab biosimilar) for psoriatic arthritis. University of Birmingham; May 2013. www.hsc.nihr.ac.uk