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HEALTH TECHNOLOGY BRIEFING SEPTEMBER 2020

Tofacitinib for Ankylosing Spondylitis

NIHRIO ID	24128	**NICE ID**	10290
Developer/Company	Pfizer Ltd	**UKPS ID**	651585

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Tofacitinib is in clinical development for the treatment of active ankylosing spondylitis (AS) in adults who have responded inadequately to conventional therapy. AS is a long-term condition in which the spine and other areas of the body become inflamed. The inflammation can lead to back pain, fatigue and in serious cases, to severe disability as the bones of the spine fuse into a fixed position or joints become progressively damaged. Some patients with AS do not respond well to current treatment options, resulting in a clear unmet medical need.

The active substance in tofacitinib works by blocking the action of enzymes (proteins) known as Janus kinases. These enzymes play an important role in the process of inflammation that occurs in rheumatoid, psoriatic arthritis and ulcerative colitis. By blocking the enzymes' action, tofacitinib helps reduce the inflammation and other symptoms of these diseases. Tofacitinib is administered orally. If licensed, tofacitinib would offer an additional treatment option for patients with active AS, who have responded inadequately to conventional therapy.

PROPOSED INDICATION

Treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.[a]

TECHNOLOGY

DESCRIPTION

Tofacitinib (Xeljanz) is a potent, selective inhibitor of the Janus kinase (JAK) family. In enzymatic assays, tofacitinib inhibits JAK1, JAK2, JAK3, and to a lesser extent tyrosine kinase 2 (TyK2). In contrast, tofacitinib has a high degree of selectivity against other kinases in the human genome. In human cells, tofacitinib preferentially inhibits signalling by heterodimeric cytokine receptors that associate with JAK3 and/or JAK1 with functional selectivity over cytokine receptors that signal via pairs of JAK2. Inhibition of JAK1 and JAK3 by tofacitinib attenuates signalling of interleukins (IL) IL-2, -4, -6, -7, -9, -15, -21 and type I and type II interferons, which will result in modulation of the immune and inflammatory response.[1]

Tofacitinib is currently in clinical development for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy. In phase III clinical trial (NCT03502616), patients received 5mg of tofacitinib administered orally twice per day.[2,3]

INNOVATION AND/OR ADVANTAGES

Until recently, the therapeutic options for patients suffering from active AS comprised non-steroidal anti-inflammatory drugs (NSAIDs) and tumour necrosis factor (TNF) inhibitor therapy. Although these are effective in a significant proportion of patients, not all patients respond and some are intolerant to these therapies.[4] Apart from biologic disease-modifying anti-rheumatic drugs (DMARDs), there are limited options available for AS patients who have an inadequate response or contraindication to NSAIDs.[5] Additionally, most biologic DMARDs are given by injection or infusion, leaving a void to be filled for a product that can be taken orally. Drug administration time and convenience are greatly saved with JAK inhibitors because of the oral administration.[6]

In a phase II clinical trial (NCT01786668), tofacitinib 5 and 10 mg twice daily demonstrated greater clinical efficacy versus placebo in reducing signs, symptoms and objective endpoints of active AS in adult patients with a similar 12-week safety profile as reported in other indications.[7]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Tofacitinib has a marketing authorisation in the EU/UK for the following:[1]

- In combination with methotrexate (MTX) for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs. Tofacitinib can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate.
- In combination with MTX for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy.

[a] Information provided by Pfizer Ltd on UK PharmaScan

- As monotherapy for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.

The most common adverse reactions (occurs in ≥1/100 to <1/10 patients) that occur as a result of tofacitinib include: pneumonia, influenza, herpes zoster, urinary tract infection, sinusitis, bronchitis, nasopharyngitis, pharyngitis, anaemia, headache, hypertension, cough, abdominal pain, vomiting, diarrhoea, nausea, gastritis, dyspepsia, rash, arthralgia, pyrexia, peripheral oedema, fatigue and blood creatine phosphokinase increase.[1]

Tofacitinib is currently in phase II and III clinical development for other indications, including Juvenile Idiopathic Arthritis.[8]

PATIENT GROUP

DISEASE BACKGROUND

Axial spondyloarthritis involves inflammation of the sacroiliac joints and spine. If inflammation is visible on x-ray (as erosions, thickening of the bone, or fusion of joints), the disease is classified as AS (also referred to as radiographic axial spondyloarthritis). If x-rays of the sacroiliac joints and spine are normal, but there are other objective signs of inflammation (elevated C-reactive protein or evidence on magnetic resonance imaging) the disease is classified as non-radiographic axial spondyloarthritis.[9,10]

AS is a rheumatological autoimmune disease that may be axial, affecting sacroiliac joints and spine, or peripheral. It not only affects joints but also soft tissues such as tendons and ligaments. There are extra-articular manifestations such as anterior uveitis, psoriasis, inflammatory bowel disease.[9] In more advanced cases, this inflammation can lead to fibrosis and calcification, resulting in the loss of flexibility and the fusion of the spine, resembling "bamboo" with an immobile position. The main clinical manifestations include chronic back pain and progressive spinal rigidity as well as inflammation of the hips, shoulders, peripheral joints and fingers/toes and fatigue.[11,12]

AS is around twice as common in men as women. It most often begins between 20 and 30 years of age.[9] While the cause of AS remains unclear, it is thought to be an interplay of genetic and environmental factors. The prevalence of AS has a clear correlation with the human leukocyte antigen (HLA)-B27 positive rate in specific populations. Studies have revealed that in HLAB27-positive populations, the prevalence rate of AS is ~5%–6%. Microbial infection can act as a triggering factor of the host innate immune system and AS development.[11] Some people with non-radiographic axial spondyloarthritis will develop AS (about 10% of people over 2 years, and 50% over 10 years).[10]

CLINICAL NEED AND BURDEN OF DISEASE

The prevalence of AS in the UK is believed to be 0.05%-0.23%.[9] Applying these figures to population estimates in 2020, it can be estimated there are between 33,398 and 153,632 adults with AS in the UK.[13]

Hospital Episode Statistics show that in 2018-19 there were 3,688 Finished Consultant Episodes (FCE), 3,578 admissions and 1,693 FCE bed days with the primary diagnosis AS (ICD10 code M45) in England.[14] In 2019, there were 13 deaths with AS as the underlying cause of death (ICD10 code M45) in England and Wales.[15]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

There is no cure for AS, but treatment is available to help relieve the symptoms.[16] Conventional therapy for AS and non-radiographic axial spondyloarthritis includes NSAIDs and physiotherapy.[17] NSAIDs are first line treatment but different painkillers such as paracetamol or codeine may be recommended if NSAIDs are not suitable.[16] Biological DMARDs, which includes TNF-alpha inhibitors, are typically used when the disease has not responded adequately to conventional therapy.[17] Corticosteroids have a powerful anti-inflammatory effect and can be taken as tablets or injections by people with AS. Joint replacement surgery may be recommended to improve pain and movement in the affected joint if the joint has become severely damaged. Regular follow up is recommend as symptoms tend to come and go.[16]

CURRENT TREATMENT OPTIONS

Biological disease-modifying antirheumatic drugs are recommended for the treatment of severe ankylosing spondylitis in adults whose disease has responded inadequately to, or who cannot tolerate NSAIDs include:[18]

- Adalimumab
- Certolizumab pegol
- Etanercept
- Golimumab
- Infliximab

Secukinumab is recommended as an option for treating active ankylosing spondylitis in adults whose disease has responded inadequately to conventional therapy (NSAIDs or TNF-alpha inhibitors).[18]

PLACE OF TECHNOLOGY

If licensed, tofacitinib would offer an additional treatment option of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.[b]

CLINICAL TRIAL INFORMATION

Trial	NCT03502616; EudraCT 2018-000226-58; **A3921120;** A phase 3, randomised, double-blind, placebo-controlled, study of the efficacy and safety of tofactinib in subjects with active ankylosing spondylitis (AS) **Phase III –** Active, not recruiting **Location(s):** EU (not incl UK), USA, Canada and other countries **Primary completion date:** Dec 2019
Trial design	Randomised, parallel assignment, quadruple-blind
Population	N=270; patients with active ankylosing spondylitis (AS); adults aged 18 years and older
Intervention(s)	5 mg of tofacitinib administered orally twice per day
Comparator(s)	Matched placebo

[b] Information provided by Pfizer Ltd on UK PharmaScan

Outcome(s)	Primary outcome: Assessment in Ankylosing Spondylitis (ASAS) 20 response [Time frame: week 16] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Tofacitinib is already marketed in the UK. The NHS indicative price is:[19]

- a pack of 56 x 5 mg costs £690.03
- a pack of 56 x 10 mg tablets costs £1380.06

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Ixekizumab for treating axial spondyloarthritis after NSAIDs (GID-TA10458). Expected date of issue to be confirmed.
- NICE technology appraisal. Secukinumab for active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors (TA407). September 2016.
- NICE technology appraisal. TNF-alpha inhibitors for ankylosing spondylitis and nonradiographic axial spondyloarthritis (TA383). February 2016.
- NICE guideline. Spondyloarthritis in over 16s: diagnosis and management (NG65). February 2017. Last updated June 2017.
- NICE quality standard. Spondyloarthritis (QS170). June 2018.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Specialised Rheumatology Services (Adult). A13/S/a.

OTHER GUIDANCE

- American College of Rheumatology, the Spondylitis Association of America, and the Spondyloarthritis Research and Treatment Network (ACR/SAA/SPARTAN). Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. 2019.[20]
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- British Society of Rheumatology and British Health Professionals in Rheumatology. Guideline for the treatment of axial spondyloarthritis (including ankylosing spondylitis) with biologics. 2017.[22]

ADDITIONAL INFORMATION

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