

**NIHR Innovation Observatory
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Secukinumab for non-radiographic axial spondyloarthritis – second or subsequent line

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LAY SUMMARY

Spondyloarthritis (SpA) are a group of chronic inflammatory rheumatic diseases that affects the spine. Axial SpA is a subtype of the disease that primarily involves joints, tendons and bones around the pelvis. SpA is predominantly a genetically determined condition that has a strong association with a type of gene called HLA B27. The term non-radiographic axial SpA refers to a new group of diseases that can be identified before structural changes of the joints can be detected. Non-radiographic axial SpA usually starts in late adolescence or early adulthood. Onset after the age of 45 is rare. Symptoms include lower back pain with predominant night pains, morning stiffness and impaired physical function as well as chest pain, pain and swelling of peripheral joints and extra-articular tenderness.

First line treatment options for SpA normally include non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, however, these are only effective in approximately half of patients. Secukinumab (Cosentyx) is a new treatment option that acts by inhibiting the processes that leads to bone loss and inflammation, thereby reducing the symptoms of the disease. It is administered by injection under the skin (subcutaneous). If licenced, secukinumab could provide an additional treatment option for patients who are intolerant or do not respond adequately to NSAIDs.

This briefing reflects the evidence available at the time of writing. A version of the briefing was sent to the company for a factual accuracy check. The company was available to provide comment. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

Non-radiographic axial spondyloarthritis (active with objective signs of inflammation) – after inadequate response or intolerance to conventional treatment

TECHNOLOGY

DESCRIPTION

Secukinumab (Cosentyx) is a fully human IgG1/κ monoclonal antibody that selectively binds to and neutralises the proinflammatory cytokine interleukin-17A (IL-17A). Secukinumab works by targeting IL-17A and inhibiting its interaction with the IL-17 receptor, which is expressed on various cell types including keratinocytes. As a result, secukinumab inhibits the release of proinflammatory cytokines, chemokines and mediators of tissue damage and reduces IL-17A-mediated contributions to autoimmune and inflammatory diseases. Clinically relevant levels of secukinumab reach the skin and reduce local inflammatory markers. As a direct consequence treatment with secukinumab reduces erythema, induration and desquamation present in plaque psoriasis lesions. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. IL-17A plays a key role in the pathogenesis of plaque psoriasis, psoriatic arthritis and ankylosing spondylitis and is up-regulated in lesional skin in contrast to non-lesional skin of plaque psoriasis patients and in synovial tissue of psoriatic arthritis patients. The frequency of IL-17-producing cells was also significantly higher in the subchondral bone marrow of facet joints from patients with ankylosing spondylitis.^{1,2}

In a phase III trial (NCT02696031) subjects receive 150 mg secukinumab subcutaneous injection weekly for five doses and 150 mg monthly as maintenance therapy.³ Five weekly treatments are given prior to the monthly dosing, with the fifth weekly treatment being the first of the monthly doses.⁴

Secukinumab is approved by the European Medicines Agency (EMA) for the treatment of moderate to severe plaque psoriasis in patients who are candidates for systemic therapy, active psoriatic arthritis when response to previous disease-modifying anti-rheumatic drug therapy has been inadequate, and active ankylosing spondylitis when response to conventional therapy has been inadequate.⁵

The most common side effects reported with secukinumab (which affect more than 1 in 10 people) are upper respiratory tract infections. Because secukinumab may increase the risk of infection, it must not be given to patients with serious active infections such as tuberculosis.⁵

Secukinumab is in phase II development for atopic dermatitis, contact dermatitis, congenital ichthyosis and netherton syndrome; and in phase III development stage for paediatric (age 6+) psoriasis and Juvenile Psoriatic Arthritis (JPsA) and Enthesitis-related Arthritis (ERA).¹

INNOVATION and/or ADVANTAGES

Evidence from a clinical trial has indicated that secukinumab improves the clinical signs and symptoms of ankylosing spondylitis following two years of continued therapy.⁶ If licensed, secukinumab will offer an additional treatment option for patients with active non-radiographic axial spondyloarthritis who have previously been treated with non-steroidal anti-inflammatory drugs, and have been intolerant or not responded adequately.

DEVELOPER

Novartis Pharmaceuticals UK Ltd

PATIENT GROUP

BACKGROUND

Spondyloarthritis (SpA) is a group of chronic inflammatory diseases that are autoimmune in nature and includes ankylosing spondylitis (AS), non-radiographic axial SpA, certain forms of psoriatic arthritis, reactive arthritis with axial involvement, and arthritis associated with inflammatory bowel disease. Axial SpA (axSpA) is characterized by predominant involvement of the spine and/or sacroiliac joints. Non-radiographic axial SpA (NrAxSpA) and AS are considered as two stages of one disease (axSpA), however, there are patients with an abortive course of the disease who remain at the non-radiographic stage without progression to established AS (10-15%).⁷ The term nrAxSpA was coined for patients who have a clinical picture of AS but do not exhibit radiographic sacroiliitis.⁸

Earlier diagnosis has been possible since the term nrAxSpA was introduced to identify patients before structural changes in the sacroiliac joints have been detected. Data from clinical trials suggest that the development of radiographic sacroiliitis is time dependent. Studies also address the question of how progression from nrAxSpA to radiographic axial SpA occurs over time.⁹ Due to an average delay of 11 years in diagnosing AS, in 2009, the ASAS (Assessment in SpondyloArthritis International Society) proposed criteria defining the entity of axSpA which includes a broader set of patients than the 1984 modified New York (mNY) criteria for AS. The broader population of patients that are captured under the term nrAxSpA can be identified by the presence of clinical features of axSpA combined with either imaging evidence or human leucocyte antigen (HLA) B27 positivity.¹⁰

Patients with SpA may present with characteristic clinical features such as inflammatory back pain, with peripheral symptoms such as enthesitis or arthritis, and with extra-articular manifestations such as anterior uveitis, psoriasis and chronic inflammatory bowel disease. The majority of patients diagnosed with axSpA also show objective signs of inflammation on imaging such as sacroiliitis and spondylitis or on laboratory examinations such as C reactive protein (CRP) or erythrocyte sedimentation rate. Furthermore, many patients, especially those who are positive for HLA B27, have a positive family history of SpA or related diseases.¹¹

Clinical manifestations of axSpA usually begin in late adolescence or early adulthood with a mean age of onset of 26 years. Onset after the age of 45 is rare. Symptoms include lower back pain with predominant nocturnal pain, morning stiffness and impaired physical function as well as chest pain, pain and swelling of peripheral joints and extra-articular tenderness. Functional limitations relate to inflammation in the early phases of disease but also increase with duration of disease due to new bone formation. Although most patients are able to maintain functional capacity, there are some patients with progressing disease who rapidly develop ankylosis at a young age.¹⁰

CLINICAL NEED and BURDEN OF DISEASE

Accurate prevalence data for axSpA does not yet exist. A study in the UK suggests the prevalence of axSpA in a primary care population to be 1.2% using the European Spondyloarthropathy Study Group

criteria, 0.3% using the ASAS criteria, and 0.15% using the mNY criteria.¹² The EMA estimates the prevalence to be between 0.3 and 0.8% of the European population.

While AS is more common in males, women are slightly more often affected compared to men in the nrAxSpA stage. Axial SpA tends to be more severe in men, in whom the spine is more frequently involved.¹⁰ SpA is more common in Europe than rheumatoid arthritis (RA).¹³

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Axial spondyloarthritis (non-radiographic) – golimumab (ID903). Expected January 2018.
- NICE technology appraisal. TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis (TA383). February 2016.
- NICE guideline. Spondyloarthritis in over 16s: diagnosis and management (NG65). February 2017.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for specialised rheumatology services (Adult). A13/S/a

OTHER GUIDANCE

Van der Heijde D, Ramiro S, Landewe R et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Annals of the Rheumatic Diseases* (2017)

Hamilton L, Barkham N, Bhalla A et al. BSR and BHPR guideline for the treatment of axial spondyloarthritis (including ankylosing spondylitis) with biologics. *Rheumatology* (2016)

CURRENT TREATMENT OPTIONS

According to clinical guidelines, physical therapy and non-steroidal anti-inflammatory drugs (NSAIDs) comprise the first line treatment in axSpA. Non-steroidal anti-inflammatory drugs (NSAIDs) (ibuprofen, naproxen, diclofenac, celecoxib, mefenamic acid, etoricoxib, indomethacin, and high-dose aspirin) are used to control pain and show effect in up to 50-70% of patients. They are usually maintained as background therapy in patients with insufficient response. Intra-articular corticosteroids may be used for sacroiliac or peripheral joint inflammation whereas systemic corticosteroids in general are of little benefit.

Traditional non-biological disease modifying antirheumatic drugs (DMARDs) are of limited value with the exception of sulfasalazine, which is used in spondyloarthritis as off label and has shown some effect on peripheral disease and extra-articular manifestations. However, no evidence of effect in severe disease or patients with substantial spinal involvement has been seen. The treatment with biological medicinal products such as anti-tumour necrosis factor (TNF) – such as adalimumab, etanercept, golimumab, infliximab - and anti-IL 17- is recommended for patients with persistent high disease activity despite conventional treatment with NSAIDs and physiotherapy.^{10,14}

Local steroids are also recommended mainly for treatment of peripheral manifestations such as arthritis, enthesitis, dactylitis, but can also be effective in the treatment of active sacroiliitis in pure axial disease. Systemic steroids are generally not recommended in axSpA, but short-term treatment might be beneficial if rapid reduction of disease activity is required.⁷

In patients who do not respond to first line therapy, a TNF alpha blocker might be used. Blockade of IL-23 represents another target in axSpA. Together with transforming growth factor (TGF) beta and IL-6 it stimulates naïve precursor cells to differentiate into Th17 T cells. There are also suggestions that apremilast, an oral phosphodiesterase-4-inhibitor, might be effective in treating the disease.⁷

EFFICACY and SAFETY

Trial	NCT02696031 , EudraCT-2015-001106-33; secukinumab vs placebo, phase III
Sponsor	Novartis Pharmaceuticals UK Ltd
Status	Ongoing, recruiting
Source of Information	Trial Registry ³ , Global Data ¹
Location	14 EU countries (incl.UK), USA, Australia and others
Design	Randomised, placebo-controlled
Participants	N=555 (planned); > 18 years old; diagnosis of axial spondyloarthritis according to Ankylosing SpondyloArthritis International Society (ASAS) axial spondyloarthritis criteria; objective signs of inflammation (magnetic resonance imaging (MRI) or abnormal C-reactive protein); active axial spondyloarthritis as assessed by total Bath Ankylosing Spondylitis Disease Activity Index ≥ 4 cm; Spinal pain as measured by Bath Ankylosing Spondylitis Disease Activity Index question #2 ≥ 4 cm (0-10 cm) at baseline; Total back pain as measured by Visual Analogue scale ≥ 40 mm (0-100 mm) at baseline; Patients should have been on at least 2 different non-steroidal anti-inflammatory drugs with an inadequate response; Patients who have been on a TNF α inhibitor (not more than one) must have experienced an inadequate response
Schedule	Induction: 4x 150 mg Secukinumab subcutaneous weekly, Maintenance: 150 mg Secukinumab subcutaneous monthly
Follow-up	Up to 104 weeks
Primary Outcomes	The proportion of TNF naive participants who achieved an ASAS 40 response (Assessment of SpondyloArthritis International Society criteria) [Time Frame: Week 16]
Secondary Outcomes	The proportion of participants who achieved an ASAS 5/6 [Time Frame: Week 16] Change in BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) over time [Time Frame: Week 16] Change in SF-36 (Short Form-36 Physical Component Summary) physical Component Summary over time [Time Frame: Week 16] The proportion of patients to achieve a BASDAI 50 response [Time Frame: Week 16 and 52] Change in Sacroiliac Joint Oedema [Time Frame: Week 16 and 52] Change in high sensitivity C-reactive protein over time [Time Frame: Week 16] The proportion of participants who achieved an ASAS 20 response [Time Frame: Week 16 and 52]

	<p>Change in BASFI (Bath Ankylosing Spondylitis Functional Index) over time [Time Frame: Week 16]</p> <p>The proportion of patients who achieved an ASAS partial remission [Time Frame: Week 16]</p> <p>The proportion of participants who achieved an ASAS 20 response [Time Frame: Week 16]</p> <p>Change in ASQoL (Ankylosing Spondylitis Quality of Life scores) over time [Time Frame: Week 16 and 52]</p> <p>The proportion of patients who achieved an Ankylosing Spondylitis Disease Activity Score (ASDAS)-C-Reactive Protein (CRP) inactive disease [Time Frame: Week 52]</p>
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date April 2019. Estimated study completion date June 2020.

ESTIMATED COST and IMPACT

COST

Secukinumab is already marketed in the UK for plaque psoriasis, psoriatic arthritis and ankylosing spondylitis. Two pre-filled disposable injections (POM) with 150 mg secukinumab per 1 ml is listed as costing £1218.78.¹⁵

Secukinumab is listed under the patient access scheme for moderate to severe plaque psoriasis, active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors and active psoriatic arthritis after inadequate response to DMARDs.¹⁶

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

- | | |
|---|--|
| <input type="checkbox"/> Reduced mortality/increased length of survival | <input checked="" type="checkbox"/> Reduced symptoms or disability |
| <input type="checkbox"/> Other | <input type="checkbox"/> No impact identified |

IMPACT ON HEALTH and SOCIAL CARE SERVICES

- | | |
|---|---|
| <input type="checkbox"/> Increased use of existing services | <input type="checkbox"/> Decreased use of existing services |
| <input type="checkbox"/> Re-organisation of existing services | <input type="checkbox"/> 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

Other

None identified

OTHER ISSUES

Clinical uncertainty or other research question identified

None identified

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¹⁰ European Medicines Agency. *Guideline on the Clinical Investigation of Medicinal Products for the Treatment of Axial Spondyloarthritis*. Available from http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/10/WC500237893.pdf [Accessed 06 Dec 2017]

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