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HEALTH TECHNOLOGY BRIEFING
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Anifrolumab for moderately to severly active, autoantibody-positive systemic lupus erythematosus

NIHRIO ID	7491	**NICE ID**	9782
Developer/Company	AstraZeneca UK Ltd	**UKPS ID**	654721

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Anifrolumab is currently in clinical development for the treatment of moderately to severely active, autoantibody-positive systemic lupus erythematosus (SLE). SLE is an autoimmune disease where the body's immune system attacks its own tissues and organs. Patients will often have periods where their symptoms flare-up and periods where their symptoms settle down. The exact causes of SLE are unknown but are believed to be due to a combination of genetic, environmental and hormonal factors. Recent evidence suggests that activation of the type I interferon (IFN) system which is a group of proteins involved in the regulation of the activity of the immune system may play a central role in development of SLE.

Anifrolumab is a drug designed to specifically block type I IFN signalling by binding to part of the type I IFN receptor and therefore preventing activity of all IFNs that are involved in the inflammatory pathway. If licensed, anifrolumab will offer an add-on treatment option for patients with moderately to severely active SLE.

PROPOSED INDICATION

Management of moderately to severely active, autoantibody-positive systemic lupus erythematosus (SLE) as an add-on therapy to standard of care treatment.[a,1]

TECHNOLOGY

DESCRIPTION

Anifrolumab (MEDI456) is a fully human $IgG1_K$ monoclonal antibody that binds to interferon (IFN) alpha receptors 1 (IFNAR1) and blocks type I IFN signalling.[2,3] Evidence supports activation of the type I interferon (IFN) system as a central pathogenic mediator in SLE.[4] Multiple genetic polymorphisms increase type I IFN signalling and are associated with increased susceptibility to SLE.[2] Cell signalling by all type I IFNs is mediated by the type I IFN-α/β/ω receptor (IFNAR), consequently blockade of IFNAR may reverse some of the immune dysregulation that occurs in SLE.[4] Anifrolumab was engineered with a triple mutation L234F/L235E/P331S in the heavy chain to reduce engagement with the cell surface receptor FcϒR and potential Fc-mediated effector functions, such as antibody-dependent cell-mediated effector functions and complement-dependent cytotoxicity.[2,3]

Anifrolumab is in clinical development for the treatment of adults with moderately to severely active SLE. In the phase III clinical trial (NCT02446899) participants are given 300mg of anifrolumab by intravenous (IV) infusion every 4 weeks for a total of 13 doses.[1]

INNOVATION AND/OR ADVANTAGES

Treatment of SLE is challenging because of the limited efficacy and poor tolerability of standard therapy so innovative new therapies are urgently needed.[4,5] Currently the only treatment with Marketing Authorisation in the UK for the treatment of SLE is belimumab. If licensed, anifrolumab would be the first treatment option for SLE that targets the type 1 IFN signalling system.[6]

Results from the phase III clinical trial TULIP-2 (NCT02446899) show that by targeting the type I IFN receptor, anifrolumab reduced disease activity in patients with SLE.[7]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Anifrolumab does not currently have Marketing Authorisation in the EU/UK for any indication.

Anifrolumab received a fast track designation by the US FDA for SLE in 2016.[8]

Anifrolumab is currently also in phase II development for the treatment of rheumatoid arthritis and lupus nephritis.[9]

PATIENT GROUP

DISEASE BACKGROUND

SLE is an autoimmune disease in which the immune system attacks its own tissues, causing widespread inflammation and tissue damage in the affected organs.[10] In people with SLE, cells that

[a] Information provided by AstraZeneca UK Ltd on UK PharmaScan

have undergone apoptosis are not cleared away properly. The signs and symptoms of SLE vary among affected individuals and can involve many organs and systems including the skin, joints, kidneys, lungs, central nervous system and haematopoietic system.[11] Some patients experience periods where their disease flares up (relapses) and periods where their symptoms settle down (remission) whereas some patients do not notice any difference and symptoms are constant.[12] The severity of SLE can range from mild to life-threatening.[10] Mild SLE causes joint and skin problems and tiredness. Moderate SLE causes inflammation of other parts of the skin and body, including the lungs, heart and kidneys. Severe SLE causes severe damage to the heart, lungs, brain or kidneys and can be life threatening.[12]

The causes of SLE are unknown but are believed to be linked to environmental, genetic and hormonal factors.[10] Some of the environmental triggers linked to SLE include; stress, viruses and infections, household chemicals and toxic exposures.[13] Normal variations (polymorphisms) in many genes can affect the risk of developing SLE and in most cases multiple genetic factors are thought to be involved. In rare cases, SLE is caused by mutations in single genes. Most of the genes associated with SLE are involved in immune system function and variations in these genes likely affect proper targeting and control of the immune response. In people with SLE, cells that have undergone apoptosis are not cleared away properly. The relationship between this and the cause or features of SLE are unclear but researchers suggest that these dead cells may release substances that cause the immune system to react inappropriately and attack the body's tissues, resulting in the signs and symptoms of SLE.[11] Evidence supports activation of the type I IFN system as a central pathogenic mediator in SLE.[4] IFNs constitute a fundamental part of the defence against viral infections. During viral infections, large amounts of IFNs are produced activating the antiviral machinery in IFN-exposed cells resulting in inhibition of viral replication.[14] High levels of IFN appear to be a heritable phenotype that associates with SLE with a polygenic form of inheritance. Increased INF regulated gene expression (known as the IFN signature) in the blood and tissues correlates with the presence of auto-antibodies and with SLE disease activity.[14,15] Between 60% and 80% of adults with SLE have an increased type I IFN gene signature.[5]

SLE is a disease that can affect persons of all ages, ethnic groups and both sexes.[16] However, 90% of new patients presenting with SLE are women of childbearing age and lupus is most commonly seen in those of Afro-Caribbean, Asian and Hispanic heritage.[16,17] After the age of 50 the percentage of women with lupus falls to 75% and the percentage of men with the disease rises to 25%.[18]

CLINICAL NEED AND BURDEN OF DISEASE

In the UK, in 2012, the prevalence of SLE was 97.04 per 100,000 and there were around 4.9 new diagnoses of SLE cases per 100,000.[17,19]

In England, in 2018-2019, there 5,784 finished consultant episodes (FCE) for SLE (ICD-10 code M32) which resulted in 5,174 admissions and 6,418 FCE bed days.[20]

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PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Currently there is no cure for SLE but there are medications available that can help relieve the symptoms, making the disease easier to live with and to reduce the chances of organ damage.[21,22] The drugs used to treat lupus will depend on the severity of disease and which parts of the body are affected.[23]

Exposure to sunlight can make symptoms worse so patients with SLE should apply high SPF sunscreen and wear clothing that covers the skin. Since people get most of their vitamin D as a result of direct sunlight on the skin there is a risk of vitamin D deficiency and therefore people with SLE may need to make an extra effort to include vitamin D in their diet or to take vitamin D supplements.[21]

CURRENT TREATMENT OPTIONS

Currently the only drug with Marketing Authorisation in the UK for treatment of SLE is belimumab.[24]

Although some of the following do not have Marketing Authorisation for the treatment of SLE, they are often prescribed by physicians to ease symptoms associated with SLE:[21,25]

- Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibruprofen, naproxen and
- Hydroxychloroquine
- Corticosteroids such as prednisolone
- Rituximab
- Immunosuppressants such as azathioprine, methotrexate, mycophenolate, mofetil and cyclophosphamide

PLACE OF TECHNOLOGY

If licensed anifrolumab will offer an add-on treatment option for patients with moderately to severely active SLE.

CLINICAL TRIAL INFORMATION

Trial	**TULIP-2, NCT02446899; A Multicentre, Randomised, Double-blind, Placebo-controlled, Phase 3 Study Evaluating the Efficacy and Safety of Anifrolumab in Adult Subjects with Active Systemic Lupus Erythematosus** **Phase III - completed** **Location(s): 4 EU (not incl UK) USA, Canada and other countries**
Trial design	Randomised, parallel assignment, double-blind, placebo controlled
Population	N=373; adults aged 18 to 70 years; diagnosis of SLE according to the ACR 1982 revised criteria; currently receiving medication for SLE
Intervention(s)	300mg anifrolumab (IV) every 4 weeks for a total of 13 doses
Comparator(s)	Matched placebo
Outcome(s)	The number of participants who achieve the British Isles Lupus Assessment Group Based composite Lupus Assessment (BICLA) Response at week 52

	See trial record for full list of other outcomes.
Results (efficacy)	Anifrolumab achieved a statistically significant and clinically meaningful reduction in disease activity at week 52 with 47.8% of patients receiving anifrolumab responding compared with 31.5% of patients on placebo as measured by BICLA.[5] See trial record for full results
Results (safety)	See trial record

ESTIMATED COST

The estimated cost of anifrolumab is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Belimumab for treating active autoantibody-positive systemic lupus erythematosus (GID-TA10626). Expected publication date: March 2021.
- NICE technology appraisal guidance in development. Systemic lupus erythematosus – prasterone [ID392]. Expected publication date to be confirmed.
- NICE technology appraisal. Belimumab for treating active autoantibody-positive systemic lupus erythematosus (TA397). June 2016.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Specialised Rheumatology Services (Adult). A13/S/a.
- NHS England. 2013/14 NHS Interim Clinical Commissioning Policy Statement: Rituximab for the treatment of Systemic Lupus Erythematosus in adults. A13/PS/a.

OTHER GUIDANCE

- European League of Associations for Rheumatology (EULAR). Update of the EULAR recommendations for the management of systemic lupus erythematosus. 2019.[26]
- British Society for Rheumatology. Guideline for the management of systemic lupus erythematosus in adults. January 2018.[27]

ADDITIONAL INFORMATION

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