루게릭 병ALS 의 새로운 치료를 위한 임상시도Clinical Trials

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루게릭 병ALS 진단 기준

El Escorial World Federation of Neurology Criteria
For the Diagnosis of ALS

Criteria for the diagnosis of Amyotrophic Lateral Sclerosis

The diagnoses of ALS requires the presence of

1) Signs of lower motor neuron (LMN) degeneration by clinical, electrophysiological or neuropathologic examination,
2) Signs of upper motor neuron (UMN) degeneration by clinical examination, and
3) Progressive spread of signs within a region or to other regions, together with the absence of
4) Electrophysiological evidence of other disease processes that might explain the signs of LMN and/or UMN degenerations; and
5) Neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs.

Steps in the diagnosis of Amyotrophic Lateral Sclerosis

The diagnoses of ALS is made possible by

1) History, physical and appropriate neurological examinations to ascertain clinical finding which may suggest suspected, possible, probable or definite ALS,
2) Electrophysiological examinations to ascertain findings which confirm LMN degeneration in clinically involved regions, identify LMN degeneration in clinically uninvolved regions and exclude other disorders,
3) Neuroimaging examinations to ascertain findings which may exclude other disease processes,
4) Clinical laboratory examinations, determined by clinical judgment, to ascertain possible ALS-related syndromes,
5) Neuropathologic examinations, where appropriate, to ascertain findings which may confirm or exclude sporadic ALS, coexistent sporadic ALS, ALS-related syndromes or ALS variants,
6) Repetition of clinical and electrophysiological examinations at least six months apart to ascertain evidence of progression.

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Clinical features in the diagnosis of ALS

Patients with signs of LMN degeneration (weakness, atrophy and clinical fasciculation's) and UMN degeneration (spasticity, pathologic reflexes, etc.) may be suspected as having ALS. Careful history, physical and neurological examination must search for further clinical evidence of LMN and UMN signs in four regions of the central nervous system.

Clinical features required for the diagnosis of ALS

1) Signs of LMN degeneration (weakness, wasting and fasciculation) in one or more of the four regions (bulbar, cervical, thoracic, lumbosacral). LMN findings in a region are without regard to right or left, but are indicative of the level of neuraxis involved. Therefore, spread of weakness, wasting and fasciculation's to another region is more important than spread from right to left or vice-versa.
2) Signs of UMN degeneration (increased or donic tendon reflexes, spasticity, pseudo bulbar features, Hoffmann reflex and crossover plantar response) in one or more of the four regions. These UMN signs are clinically appreciated best in the bulbar, cervical and lumbosacral regions. UMN findings in a region are also without regard to right or left. Once the physical and neurological examinations provide information on the presence or absence of LMN and UMN signs in the four regions (bulbar, cervical, thoracic, lumbosacral) they must be ordered topographically in the manner to determine the certainty of the diagnosis of ALS.
3) The topographical location of certain UMN and LMN signs in four regions of the CNS together with progression of these signs determines the certainty of the diagnoses of ALS. Progression is a cardinal feature of the clinical diagnosis of ALS. Progression of signs within a region and progression of signs to involve other regions are crucial to the diagnosis.

Clinical examinations should be repeated at least every six (6) months to assess progression.

Cases which meet the topographical criteria for probable or definite ALS but which lack progression during the twelve (12) month period diagnosis should be designated as possible ALS.

Definite ALS
is defined on clinical grounds alone by the presence of UMN as well as LMN signs in the bulbar region and at least two of the other spinal regions or the presence of UMN and LMN signs in three spinal regions. The important determinants of diagnosis of definite ALS in the absence of electrophysiological, neuroimaging and laboratory examinations are the presence of UMN and LMN signs together in multiple regions.

Probable ALS
is defined on clinical grounds alone by UMN and LMN signs in at least two regions. While the regions may be different, some UMN signs must be rostral (above) the LMN signs. Multiple different combinations of UMN and LMN signs may be present in patients with probable ALS.

Possible ALS
is defined on clinical grounds alone when the UMN and LMN signs are in only one region or UMN signs alone are present in 2 or more regions or LMN signs are rostral to UMN signs (the latter distribution of signs needs to be differentiated from multiple non-ALS processes). Monomelic ALS, progressive bulbar palsy without spinal UMN and/or LMN signs and progressive primary lateral sclerosis without spinal LMN signs and progressive primary lateral sclerosis without spinal LMN signs constitute special cases which may develop LMN or UMN signs to meet the criteria for probable ALS with time or be subsequently confirmed at autopsy by specific LMN and UMN neuropathologic findings.

Suspected ALS
will manifest only LMN signs in 2 or more regions, although UMN pathology might be demonstrated at autopsy. However, only clinical signs are considered pertinent to this classification at the time of diagnostic evaluation.

Supportive clinical features
Clinical features that support the diagnosis of ALS include one or more of the following:

6) Autonomic nervous system involvement (clinically significant abnormal cardiovascular reflexes; bowel or bladder control problems; familial or sporadic)
7) Objective sensory abnormalities (decreased vibration; sharp-dull discrimination; blunting of cold sensation; familial or sporadic)

Electrophysiological features in the diagnoses of ALS

Patients with suspected, possible, probable or definite ALS on clinical grounds should have electrophysiological studies performed to confirm LMN degeneration in clinically affected regions, find electrophysiological evidence of LMN degeneration in clinically uninvolved regions and to exclude other pathophysiological processes.

ALS may be most reliably identified when the clinical and electrophysiological findings are widespread, involving a sufficient number of regions so that other possible cause of similar EMG abnormalities are highly unlikely. The confirmation of the diagnosis of ALS depends on finding electrophysiological evidence of LMN degeneration in at least two muscles of different root or spinal nerves and different cranial or peripheral nerve innervation in two or more of the four (bulbar, cervical, thoracic, lumbosacral) regions. The features of LMN degeneration in a particular muscle are defined by electromyographic needle examination and nerve conduction studies using standard methods for each measure.

Electrophysiological features required to identify definite primary LMN degeneration include all of the following:

1) Reduced recruitment (reduced interference pattern with firing rates over 10 Hz),
2) Large motor unit action potentials (large amplitude, long duration), and
3) Fibrillation potentials.

Electrophysiological features that support the identification of possible primary LMN degeneration include one or more of the following:

1) either reduced recruitment, large motor unit potentials, fibrillation potentials or unstable motor unit potentials alone,
2) polyphasic motor unit potentials or increased single fiber density alone,
3) low amplitude compound muscle actions potentials if the disease duration is over 5 years or if there is associated atrophy,
4) low amplitude compound muscle action potentials,
5) compound muscle action potential change between proximal and distal sites of stimulation that is uniform along the length of the nerve,
6) up to 30% decrement in motor conduction velocity below established normal values if a low amplitude compound muscle action potential greater than 10 percent of normal is present,
7) up to 30% decrement in motor conduction velocity below established normal values if the compound muscle action potential is below 10% or normal,,
8) up to 20% decrement of the compound muscle action potential on 2 Hz repetitive stimulation,
9) up to 10% decrement in sensory nerve conduction velocity and action potential amplitude from established normal values,
10) complex repetitive discharges, and
11) absence of fasciculations.

Electrophysiological features compatible with UMN degeneration and not excluding ALS include one or more of the following:

1) up to 30% increment in central motor conduction velocity,
2) up to 10% decrement in somatosensory, evoked potential amplitude and up to 10% increment in somatosensory evoked potential latency,
3) mild abnormalities of autonomic function,
4) mild abnormalities of polysomnography,
5) mild abnormalities of electronystagmography.

Electrophysiological features that are inconsistent with the diagnoses of ALS or suggest the presence of additional other disease processes include one or more of the following:

1) focal reduction in compound muscle action potential or more than 10% in a 4-cm segment,
2) motor conduction velocities, F wave latencies or H wave amplitudes which are more than 30% above established normal values,
3) more than 20% decrement of repetitive stimulation at 2 Hz,
4) sensory action potential latencies more than 20% above or sensory action potential amplitudes more than 20% below established normal values,
5) unstable motor unit potentials with no other electromyographic changes,
6) more than 30% increment of central motor conduction velocity,
7) more than 10% increment in sensory evoked potential latency or more than 10% decrement in sensory evoked potential amplitude,
8) moderate or greater abnormalities in autonomic function or electronystagnography.

Employing electrophysiological evidence of LMN degeneration to confirm the diagnosis of ALS

The certainty of LMN degeneration is determined by the presence of the above finding for each muscle tested in the region.

At least two muscles of different root or spinal nerve and different cranial or peripheral nerve innneveration in each region should show electrophysiological evidence of either definite, probable or possible LMN degeneration for that region to be ranked as showing definite, probable or possible LMN degeneration.

Definite LMN degeneration by EMG has the same significance as clinical LMN degeneration and can upgrade the certainty of the clinical diagnoses of ALS in the same fashion as if the clinical signs of LMN degeneration were present in that region.

- Evidence of intoxication (epidemiological evidence or elevated blood, urine, tissue or cerebrospinal fluid level of lead, mercury, arsenic, cadmium, manganese, aluminum, organic pesticides, lupin seeds, etc.),
- Evidence of physical injury (epidemiological evidence of antecedent electrical or radiation injury or severe trauma),
- Evidence of vasculitis (elevated erythrocyte sedimentation rate and cerebrospinal fluid abnormalities consistent with spinal cord vasculitis, i.e., markedly elevated cerebrospinal fluid protein) or ischemic injury to spinal cord without sensory signs,
- Evidence of pre-existing mild or moderate spinal cord spondylotic compression, not amenable to surgical correction or not responding to surgical correction, which progressed with clinical signs consistent with at least probable ALS.

Clinical laboratory features inconsistent with the diagnosis of ALS:

There is no clinical laboratory finding which, if present with the proper clinical and electrophysiological signs of ALS and appropriate neuroimaging studies, rules out the diagnosis of ALS.

ALS-related syndromes which present with the ALS phenotype as defined have been described with laboratory abnormalities (acquired or genetic), time-linked exposure to chemical, physical or infectious agents and pre-existing structural abnormalities. The correction of laboratory abnormalities, removal of chemical or physical agents, treatment of the associated disease (infection, tumor, structural abnormality) may or may not result in correction or stabilization of the ALS phenotype in ALS-related syndromes.

If correction of the abnormality does not result in improvement, the patient will be considered to have an ALS related syndrome.

If correction of the abnormality does not result in improvement, then the patient will be considered to have an ALS related syndrome.

If correction of the abnormality does not result in improvement then the patient will be considered to have sporadic ALS for the purpose of clinical studies and the therapeutic trials.

Neuropathological features of the diagnosis of ALS:

The clinical diagnosis may be supported or excluded by biopsy studies in the living patient and the pathological diagnosis may be proven or excluded by autopsy examination.

Pathological studies in the living patient with sporadic ALS:

Indications of biopsies:

Biopsies of the skeletal muscle, peripheral nerve and other tissues are not required for the diagnosis of amyotrophic lateral sclerosis, unless the clinical, electrophysiological or laboratory studies have revealed changes that are atypical for ALS. In addition, the muscle biopsy may be used to demonstrate LMN involvement in a body region that had not been shown to be involved by other techniques.

Muscle biopsy:

Features required for the diagnosis:
Disseminated single angulated atrophic muscle fibers, or small or large groups of such fibers.

Features that strongly support the diagnosis:
Angulated atrophic muscle fibers that are strongly positive when stained with oxidative enzyme stains and with non specific esterase or that show immunoreactive surface staining with anti-NCAM antibodies.

Features that are compatible with, and do not exclude the diagnosis:

1) Scattered hypertrophied muscle fibers,,
2) No more than a moderate number of target or targeted fibers,,
3) Fiber type grouping of not more than mild-to-moderate extent,,
4) The presence of a small number of necrotic muscle fibers.

Features that rule out the diagnoses or suggest the presence of additional disease:

1) Significant infiltration with lymphocytes and other mononuclear inflammatory cells,
2) Significant arteritis,
3) Significant numbers of muscle fibers involved with the following structural changes: necrosis; rimmed vacuoles; nemaline bodies; central cores; accumulation of mitochondria (ragged red fibers),
4) Large fiber type grouping,
5) Giant axonal swellings from accumulation of masses of neurofilaments, but not of PAS positive bodies, in intramuscular nerves.

Pathological studies at autopsy, other than in cases surviving for prolonged periods on life support systems

Gross pathological changes

Features required for the diagnosis:
There are positive diagnostic features on gross pathological examination.

Features that support the diagnosis:
There are no positive diagnostic features on gross pathological examination.

Features that support the diagnosis:

1) selective atrophy of the motor cortex,
2) grayness and atrophy of the anterior spinal nerve roots compared with normal,
3) grayness of the lateral columns of the spinal cord,
4) atrophy of skeletal muscles.

Features that rule out the diagnosis of ALS or suggest the presence of additional disease:

1) abnormal pulmonary function test not explained by other causes,
2) abnormal speech studies not explained by other causes,
3) abnormal swallowing studies not explained by other causes,
4) abnormal larynx function studies not explained by other causes,
5) abnormal isokinetic or isometric strength test in clinically uninvoled muscles,
6) abnormal muscle biopsy with evidence of denervation.

Inconsistent clinical features
Clinical findings inconsistent with the diagnoses of ALS include one or more of the following not explained by physiological changes associated with aging or other disease processes:

1) sensory dysfunction,
2) sphincter abnormalities,
3) autonomic nervous system dysfunction,
4) anterior visual pathway abnormalities,
5) movement abnormalities associated with probable Parkinson's disease defined by DATATOP criteria,
6) cognitive abnormalities associated with clinical Alzheimer's disease as defined by NINCDS-ADRDA criteria.

If these clinical findings occur, then close attention should be paid to the possible diagnosis of other disease processes.

Lower motor neuron and upper motor neuron signs may occur together with other clinical signs in disease where the pathologic process is not primary motor neuron degeneration.

Types of ALS

The clinical signs of progressive LMN and UMN degeneration seen in ALS may
a) occur alone (sporadic ALS),
b) be present incidentally with other pre-existing disease processes that have not developed in parallel with the ALS (coexistent sporadic ALS),
c) Occur in association with laboratory-defined or epidemiologically defined abnormalities that are time-linked to the ALS (ALS-related syndromes), or
d) Occur in association with clinical, genetic or epidemiological features which develop in parallel with the ALS (ALS variants).

The physical and neurological examinations will allow for the clinical diagnosis of ALS to a particular degree of certainty as defined above; however, the history of the disease onset, toxic exposures, past medical history, injuries, family history, geographic location, etc., must be incorporated with the clinical examinations in determining whether the patient may have an ALS related syndrome or an ALS variant.

ALS-related syndromes must meet the clinical, electrophysiological and neuroimaging criteria for possible, probable or definite ALS. ALS-related syndromes have unique laboratory-defined or epidemiologically defined features which are time-linked to the development of the ALS phenotype. If correction of the associated laboratory-defined same weight as one region with definite evidence of LMN degeneration in upgrading the certainty of diagnosis of ALS.

A single region with electrophysiological evidence of probable LMN degeneration or two regions with electrophysiological evidence of possible LMN degeneration can be used to upgrade the certainty of the diagnosis of ALS from possible ALS to probable ALS but not from probable ALS to definite ALS.

Neuroimaging features in the diagnosis of ALS

Neuroimaging studies should be selected in order to exclude other conditions which may cause UMN and/or LMN signs that may stimulate sporadic ALS.

Neuroimaging features required for the diagnosis of ALS:
- There are no neuroimaging tests which confirm the diagnosis of ALS.

Neuroimaging features that support the diagnosis of ALS include one or more of the following:

1) minimal bony abnormalities on plain x-ray of skull or spinal canal,
2) Minimal abnormalities on head or spinal cord MRI scans without spinal cord and/or root compression,
3) Minimal abnormalities on spinal cord myelography with post-myelography CT tomography showing no spinal cord and/or root compression.

Neuroimaging features that are inconsistent with the diagnosis of ALS include one or more of the following:

1) significant bony abnormalities on plain x-ray of skull or spinal canal,
2) minimal abnormalities on head or spinal cord MRI scans without spinal cord and/or root compression,
3) minimal abnormalities on spinal cord myelography with post-myelography CT tomography showing no spinal cord and/or room compression.

Neuroimaging features that are inconsistent with the diagnosis of ALS include one or more of the following:

1) significant bony abnormalities on plain x-rays of skull or spinal canal that might explain clinical findings,
2) significant abnormalities of head or spinal cord MRI suggesting intraparenchymal processes, arteriovenous malformations or compression of brainstem/spinal cord and/or cranial nerve or spinal nerve roots by bony abnormalities, tumor, etc. MRI of craniocervical function if bulbar onset and/or MRI or pertinent spinal region if spinal onset,
3) significant abnormalities of spinal cord myelography with/without CT tomography or CT tomography alone suggesting lesions as noted above,
4) significant abnormalities on spinal cord angiography suggesting arteriovenous malformations.

Employing neuroimaging evidence to confirm the diagnosis of ALS

The absence of abnormalities in appropriately performed neuroimaging studies will raise patients with clinical and/or electrophysiological evidence of probable ALS to definite ALS.

1) Plaques of multiple sclerosis.
2) A focal cause of myelopathy.

Light microscopic studies

Features required for the diagnosis:

1) Some degree of loss of both of the following neuronal systems. Large motor neurons of the anterior horns of the spinal cord and motor nuclei of the brainstem (V motor, VII motor, I and X somatic motor, and XII); and large pyramidal neurons of the motor cortex and/or large myelinated axons of the corticospinal tracts.
2) The following cellular pathological changes in the involved neuronal regions described above; neuronal atrophy with relative increase in lipofuscin and loss of Nissl substance. There should be evidence of different stages of the process of neuronal degeneration, including the presence of normal-appearing neurons, even in the same region.
3) Evidence of degeneration of the corticospinal tracts and the same level.

Features that strongly support the diagnosis:

1) Lack of pathological change in the motor neurons of cranial nerves III, IV and VI, the intermediolateral column of the spinal cord, and Onuf's nucleus.
2) The occurrence of one or more of the following cellular pathological changes in the involved neuronal systems described above:
   - Axonal spheroids with accumulation of masses of neurofilaments,
   - Bunina bodies,
   - Basophilic cytoplasmic inclusions,
   - Non-basophilic hyaline bodies ("Lewy body-like structures") seen in H&E stained sections,
   - Increased immunocytochemical staining for phosphorylated neurofilments in perikarya of the motor neurons;
   - Atrophy or loss of the arborizations of the dendrites of the motor neurons of the anterior horns of the spinal cord and brainstem motor nuclei.
   - Wallerian degeneration in the anterior roots.

Features that are compatible with, and do not exclude, the diagnoses:
Variable involvement of Clark's nucleus and the spinocerebellar tracts; posterior root ganglia, the posterior columns of the spinal cord and peripheral sensory nerves; the brainstem reticular neurons and the anterolateral columns of the spinal cord; the thalamus; subthalamic nucleus; and the substantia nigra.

Features that rule out the diagnosis or suggest the presence of additional disease:
Major pathological involvement of other parts of the nervous system, including: cerebral cortex other than the motor cortex; basal ganglia; substantia nigra; cerebellum; cranial nerves II and VIII; dorsal root ganglia.

The following cellular pathological changes in the involved neuronal systems described above:

- Extensive central chromatolysis;
- Extensive active neuronophagia;

feature does not result in correction of the ALS phenotype, then the patient with an ALS-related syndrome should be considered in the same way as a patient with sporadic ALS.

ALS-related syndromes include
1) Monoclonal gammopathy (monoclonal gammopathy of unknown significance, Waldenstroms's macroglobulinemia, osteosclerotic myeloma, etc.),
2) Dysimmune motor system degeneration (autoimmune; high-titer GM1 ganglioside antibody; etc.),
3) Nonmalignant endocrine abnormalities (hyperthyroidism, hyperparathyroidism, hypogonadism, etc.),
4) Lymphoma (Hodgkin's and non-Hodgkin's lymphoma). Cases of sporadic ALS associated with insulinoma, lung, colon or thyroid cancer are thought not to be casually related,
5) Infection (HIV-1, HTLV-I, encephalitis lethargica, varicella-zoster, brucellosis, cat-scratch disease, Creutzfeldt-Jakob disease, syphilis, delayed post-poliomyelitis, etc.),
6) Acquired enzyme defects (detoxification enzymes, etc.),
7) Exogenous toxins (lead, mercury, arsenic, thallium, cadmium, manganese, aluminum, organic pesticides, lupin seeds, etc.),
8) Physical injury (electric shock, radiation therapy, etc.),
9) Vascular (vasculitis; ischemic (Dejerine anterior bulbar artery syndrome, etc.),
10) Spondylotic myelopathy (painless myelopathy with no sensory signs, stabilization or progression post-surgery).

ALS Variants must meet the clinical, electrophysiological and neuroimaging criteria for possible, probable or definite ALS. The predominant presentation is that seen in sporadic ALS, but includes one or more features such as:

1) Familial pattern of inheritance (multiple phenol-types characterized by age of onset; site of onset; length of survival; and presumed type of inheritance.)

Familial ALS variants in genetic linkage studies should be characterized by an established genetic mode of inheritance over at least two generations and at least one clinically definite or autopsy confirmed case and compelling evidence excluding other possible causes. Affected sub pairs occurring in one generation alone may not result from a single gene effect.

Examples:
a) ALS with defined inheritance and known gene product (hexosaminidase A/B deficiency, superoxide dismutase deficiency)
b) ALS with defined inheritance and chromosome linkage but no gene product (chromosome 21 associated familial ALS or chromosome 2 associated juvenile familial ALS)
c) ALS with defined inheritance and no known linkage or gene product (most cases or familial ALS).

2) Geographic clustering (including disorders seen in the Western Pacific, Guam, Kii Peninsula, North Africa, Madras, etc.)
3) Extrapyramidal signs (bradykinesia; cogwheel rigidity; tremor; clinically significant onset of supranuclear eye signs (pursuit abnormalities); familial or sporadic)
4) Cerebellar degeneration (spinocerebellar abnormalities; familial or sporadic)
5) Dementia (progressive cognitive abnormalities; familial or sporadic)

The absence of neuroimaging abnormalities cannot raise possible ALS to probable ALS.

Clinical laboratory features in the diagnosis of ALS

The diagnostic process employed to confirm the diagnosis of sporadic ALS includes repeated clinical examinations, repeated electrophysiological examinations, neuroimaging to exclude other disorders and clinical laboratory examinations or exclude other disorders or support the diagnosis of ALS related syndromes.

Clinical laboratory features required for the diagnoses of ALS
- There are no clinical laboratory tests which confirm the diagnosis of ALS.

Clinical laboratory features that support the diagnosis of ALS include one or more of the following:

- normal complete blood count, platelet count, sedimentation rate, prothrombin time,
- normal electrolyte (Na+, K+, C1, Cl02-, Mg2+, P04) renal (BUN, creatinine) and liver function (bilirubin, SGOT, SGPT, LDH) test,
- creatine kinase (CK) elevation not more than 5 times upper limit of normal,
- normal hexosaminidase A and B activity (if possible of deficiency indicated by suggestive family history or onset under 30 years of age),
- normal cerebrospinal fluid cell count, protein (not more than 65 mg/dl), absence of intrathecal immunoglobulin synthesis, oligoclonal immunoglobulins and evidence of elevated intrathecal antibodies or infectious agents (syphilis, HIV-1, HTLV-I, etc.), if indicated,
- normal parathyroid hormone level if calcium is borderline elevated,
- normal free thyroid hormone concentrations if any thyroid function abnormalities
- (borderline elevations in T4, T3, TSH); normal glycosylated hemoglobin, if indicated,
- Normal serum protein electrophoresis and serum immunoelectrophoresis with immunofixation; normal urine immunoelectrophoresis with immunofixation, if indicated,
- Minimal abnormalities in screening test for collagen vascular diseases (anti-nuclear antibody; anti-DNA antibodies; rheumatoid factor, complement, anti-tissue specific antibodies), if indicated,
- Minimal elevation in screening test for anti-neural antigen (GM1, GM2, GD1b ganglionides, myelin-associated glycoprotein, acetylcholine esterase, etc.) or anti-neuromuscular antigen (acetylcholine receptor, striated muscle, etc.) antibodies, if indicated.

Clinical laboratory features that support the diagnosis of ALS related syndromes

- Abnormalities consistent with monoclonal gammopathy with/without significant elevation in monoclonal anti-neural antigen antibody,
- Significant elevations in polyclonal anti-neural antigen (Gm1, Gm2, GD1b gagnliosides, myelin-associated glycoprotein, acetylcholine esterase, etc.) antibody,
- Significant elevation in parathyroid hormone, thyroid hormone or other significant endocrine abnormalities,
- Abnormalities consistent with lymphoma (Hodgkins' or non-Hodgkin's lymphoma),
- Evidence of infection (HIV-1, HTLV-I, borrelia, syphilis, brucellosis, cat-scratch disease, varicella-zoster, influenza, Creutzfeldt-Jakob disease),

- Neurofibrillary tangles;
- The presence of abnormal storage material;
- The presence of significant spongiform change;
- The presence of extensive inflammatory cell infiltration.

Electron-microscopic studies

Features required for the diagnosis:
Ultrastructural studies are not required for the diagnosis of ALS

Features that strongly support the diagnosis:

1) Accumulation of interwoven bundles of 10 nm neurofilaments in axonal spheroids or motor neuron perikarya, and thicker linear structures associated with dense granules (Hirano et al. 1984 J. Neuropath. Ex. Neurol. 43:461),
2) Bunina bodies (Hart et al. 1944 Acta Neuropath. 38:225).

Features that are compatible with, and do not exclude the diagnosis:
The presence of intra-axonal polyglucosan bodies.

Features that rule out the diagnosis or suggest the presence of additional disease;

1) The presence of significant numbers of definite viral particles,
2) The presence of significant amounts of abnormal storage materials.
3) Extensive vacuolation of neuronal perikarya.

루게릭 병ALS 진단

다른 루게릭병 유사 질환 가능성이 완전 배제때까지 보류

임상시도 Clinical Trials

새로운 치료의 안정성과 유효성을 판단하는 최선의 방법,

안전하고 유효한 새로운 치료를 임상에 도입하는 최선의 방법

*임상시도Clinical Trials*후보 선정

*전임상연구Preclinical Research*에서새로운 치료 아이디어와

그 치료의 임상시도에 대한 자신감 확보

임상시도Clinical Trials 성격

근거중심의학*Evidence-BasedMedicine*

1. 체계적
2. 객관적
3. 합리적
4. 개방적
5. 인본적

임상시도Clinical Trials 단계

1 상 *Phase I*:20 명 이하, 새로운 치료의 안정성 검증

2 상 *Phase II*:100 명 이하, 새로운 치료의 용량, 경로, 간격 결정

3 상 *Phase III*:100 명 이상, 새로운 치료의 통계적 유효성 검증

*임상시도*Clinical Trials 이해

의학과 의료의 접점

지식과 열정의 접점

희망와 절망의 접점

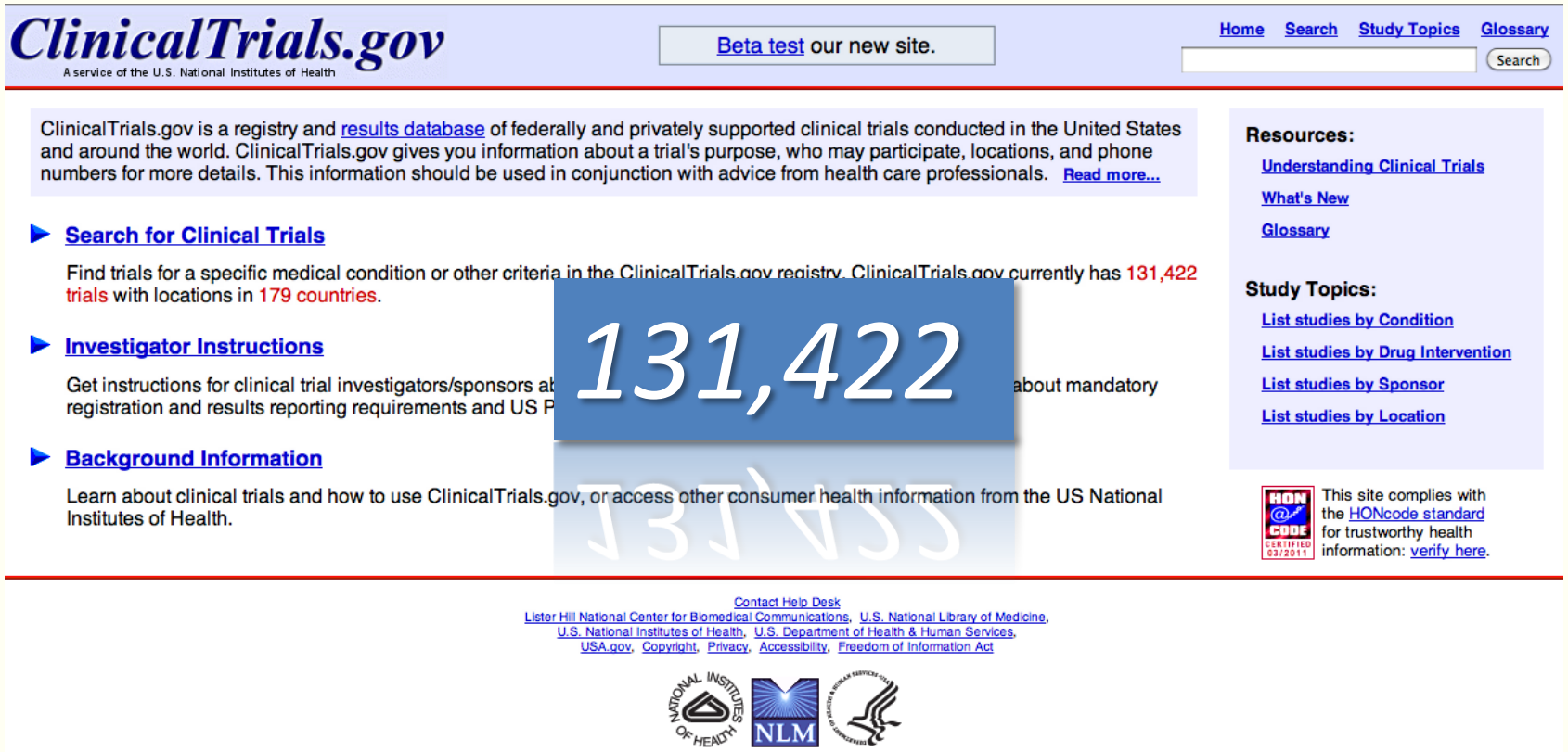
임상시도Clinical Trials 제한점

1. 시간
2.비용
3. 대상군 대조군 선정
4. 대상질환의 경중도
5. 일반화문제
6. 공공복지와 민간이권 문제

임상시도Clinical Trials 강조점

새로운 치료의 발견을 위한 연구자와 참여자의 공동 노력

임상시도*Clinical Trials* 검색



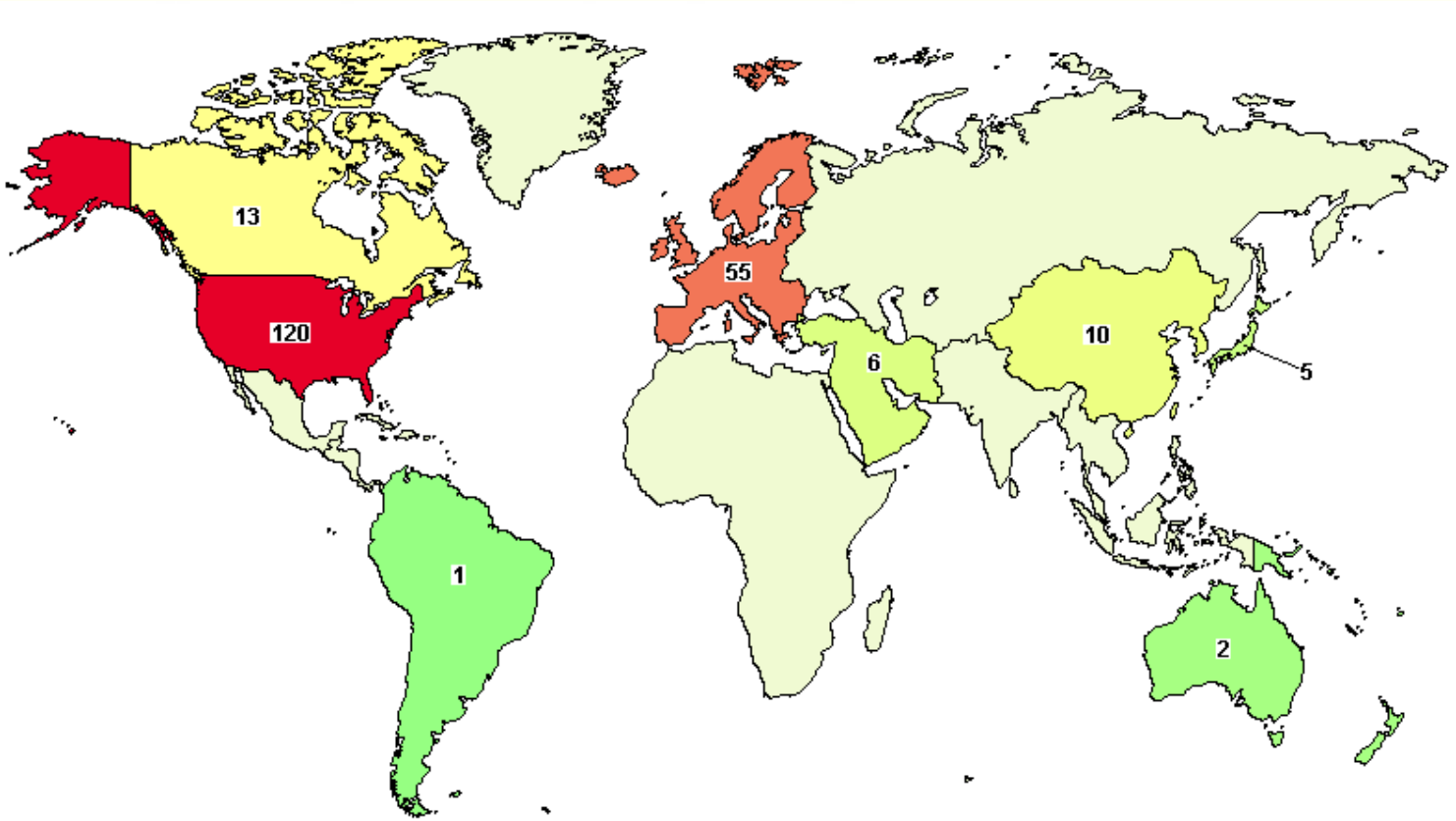
루게릭병 임상시도 *Clinical Trials*

Found 198 studies with search of: amyotrophic lateral sclerosis

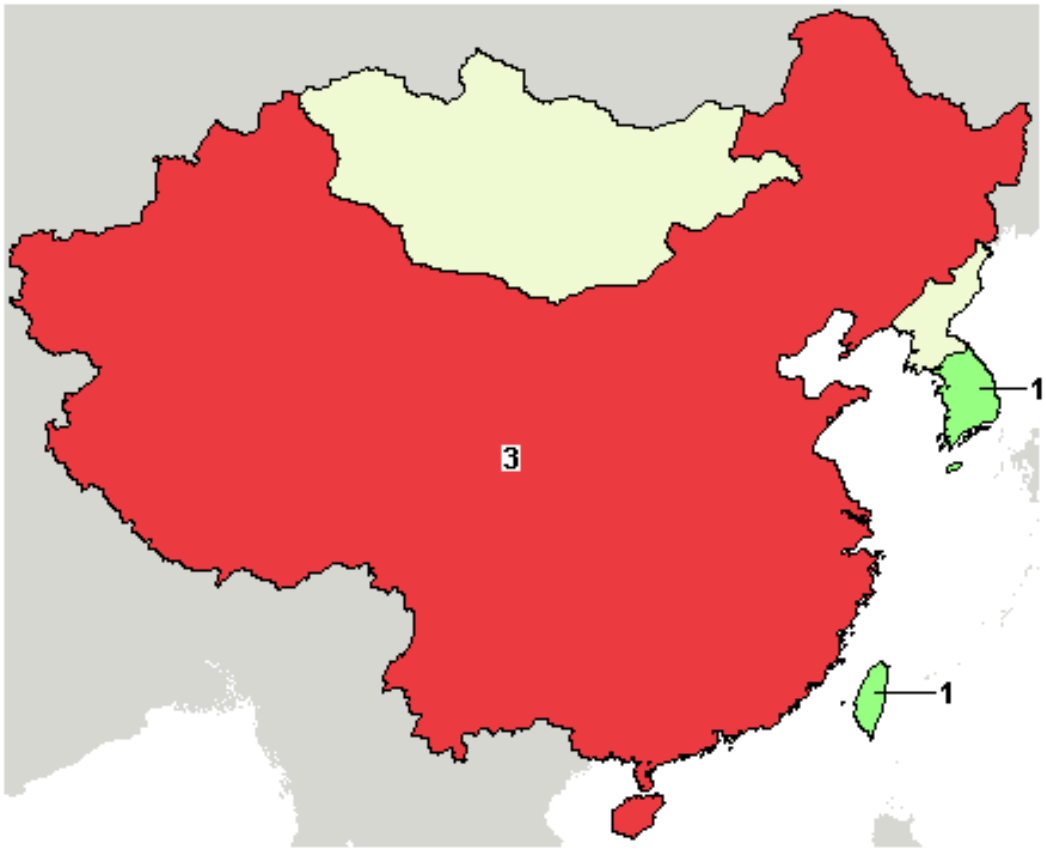
Hide studies that are not seeking new volunteers.
Hide studies with unknown recruitment status.

Rank	Status	Study
1	Terminated Has Results	Study to Investigate the Safety and Efficacy of Lithium in Volunteers With Amyotrophic Lateral Sclerosis (ALS) Condition: Amyotrophic Lateral Sclerosis Interventions: Drug: Lithium Carbonate; Drug: Riluzole; Drug: placebo
2	Recruiting	Phase II/III Randomized, Placebo-controlled Trial of Arimoclomol in SOD1 Positive Familial Amyotrophic Lateral Sclerosis Conditions: Amyotrophic Lateral Sclerosis 1; Acquired Amyotrophic Lateral Sclerosis; Amyotrophic Lateral Sclerosis Intervention: Drug: Arimoclomol
3	Unknown †	Far Infrared Irradiation for Control, Mana… …f Amyotrophic Lateral Sclerosis (ALS) Condition: Amyotrophic L… Interventions: Radiation: Far … 20µm wavelength); Radiation: Far infrared radiation
4	Recruiting	Study of Cognitive and Emotional Disord… …ral Sclerosis Condition: Amyotrophic Lateral Sclerosis Intervention: Other: MRI + 18FDG-PET + neuropsychological assessments ; 18FDG performed especially for the research
5	Recruiting	Aerobic Exercise Training in Amyotrophic Lateral Sclerosis Condition: Amyotrophic Lateral Sclerosis Interventions: Other: Aerobic exercise training; Other: Standard physical therapy (Stretching/Range-of-motion)
6	Terminated	Amyotrophic Lateral Sclerosis and Frontotemporal Dementia Conditions: Frontotemporal Dementia; Amyotrophic Lateral Sclerosis Intervention:
7	Recruiting	High Fat/High Calorie Trial in Amyotrophic Lateral Sclerosis Condition: Amyotrophic Lateral Sclerosis Interventions: Dietary Supplement: Oxepa; Dietary Supplement: Jevity 1.5; Dietary Supplement: Jevity 1.0
8	Recruiting	Clinical Trial on The Use of Autologous Bone Marrow Stem Cells in Amyotrophic Lateral Sclerosis (Extension CMN/ELA) Condition: Amyotrophic Lateral Sclerosis

198


13
120
55
10
6
5
1
2
Colors indicate number of studies with locations in that region
Least
Most
Labels give exact study count

우리나라 루게릭병 임상시도Clinical Trials"단하나"



Interventions: Drug: Dexpramipexole; Drug: Placebo

47 **Completed** [Amyotrophic Lateral Sclerosis Web Based Patient Care Database: ALSConnection.Org]
Condition: Amyotrophic Lateral Sclerosis
Intervention: Behavioral: ALS Registry

48 **Recruiting** [Olanzapine for the Treatment of Appetite Loss in Amyotrophic Lateral Sclerosis (ALS)]
Condition: Amyotrophic Lateral Sclerosis (ALS)
Intervention: Drug: Olanzapine

49 **Unknown †** [Non-Invasive Ventilation in Amyotrophic Lateral Sclerosis]
Conditions: Amyotrophic Lateral Sclerosis; Chronic Respiratory Failure
Interventions: Device: Non invasive ventilation delivered with one of the ventilator specifically designed for NIV and given to the
Device: Non invasive ventilation

50 **Unknown †** [Effect of Lithium Carbonate in Patients With Amyotro
Condition: Amyotrophic Lateral Scleros
Intervention: Drug: lithium

51 **Completed** [Growth Hormone in Amyotrophic Lateral Sclerosis]
Condition: Amyotrophic Lateral Scleros

한양대학교병원
신경과 + 코어스템

52 **Recruiting** [Safety and Efficacy Study of Autologous Bone Marrow Derived Stem Cell Treatment in Amyotrophic Lateral Sclerosis]
Conditions: Amyotrophic Lateral Sclerosis; ALS
Interventions: Biological: HYNR-CS inj; Biological: Control group

[redacted]
Condition: Amyotrophic Lateral Sclerosis
Interventions: Drug: pioglitazone; Drug: placebo

54 **Completed** [Efficacy of Noninvasive Ventilation in Amyotrophic Lateral Sclerosis (ALS)]
Conditions: Amyotrophic Lateral Sclerosis; Motor Neuron Disease
Intervention:

55 **Completed** [Amyotrophic Lateral Sclerosis (ALS) Gulf War Study]
Condition: Amyotrophic Lateral Sclerosis
Intervention:

56 **Completed** [Hyperlipidemia and Statin Therapy in Amyotrophic Lateral Sclerosis]
Condition: Amyotrophic Lateral Sclerosis
Intervention:

57 **Not yet recruiting** [Early Stage Amyotrophic Lateral Sclerosis Phrenic Stimulation]
Conditions: Amyotrophic Lateral Sclerosis; Respiratory Insufficiency
Interventions: Device: phenique nerve stimulation NeurX™ (Synapse Biomedical); Device: sham phrenic nerve stimulation

루게릭병 치료 임상시도Clinical Trials 분류

1. 줄기세포 치료
2. 약물 치료
3. 임플란트 치료
4. 단일항체*Monoclonal Antibody*치료
5. 리보핵산 억제재*RNAi*치료
6. 보톡스 치료
7. 두뇌접속 *Brain Interface*

루게릭병 치료 임상시도Clinical Trials 분류

1. 줄기세포 치료
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6. 보톡스 치료
7. 두뇌접속 Brain Interface

줄기세포 치료 *임상시도* *Clinical Trials*

루게릭병 줄기세포 치료 효과 나타나

(텔아비브 로이터=연합뉴스) 운동신경세포가 서서히 죽어가는 치명적인 질환인 루게릭병(근위축성측삭경화증) 줄기세포치료법이 초기 임상시험에서 안전하고 효과가 있는 것으로 밝혀졌다.

이스라엘의 생명공학기업 브레인스톰 세포치료(BrainStorm Cell Therapeutcis)사가 개발한 자가골수줄기세포 치료법(NurOwn)이 루게릭병 환자 12명을 대상으로 실시된 1-2상 임상시험에서 증세의 안정 내지는 증세개선 효과가 나타나고 있다고 임상시험을 기획한 생의학연구디자인(Biomedical Research Design)의 모세 노이만 박사가 중간결과를 발표했다.

일부 환자는 증상이 더 이상 진행되지 않고 안정이 유지되는 징후를 보였으며 환자에 따라 호흡, 근력, 언어기능이 개선되기도 했다.

골수줄기세포가 다른 환자에 비해 많이 주입된 한 환자는 양쪽에서 부축해 주지 않으면 걸을 수 없었으나 지팡이 없이도 걸을 수 있게 되었다.

환자자신의 골수에서 채취한 중간엽줄기세포를 브레인스톰 사가 개발한 방식으로 처리해 환자에게 주입하는 이 줄기세포 치료법은 임상시험 중간평가에서 내약성이 양호하고 안전한 것으로 나타나고 있다.

예루살렘의 하다사 메디컬센터에서 9개월 예정으로 진행되고 있는 이 임상시험의 최종결과는 금년말쯤 나올 것으로 예상된다. 이 임상시험은 안전성과 예비효과를 평가하기 위한 것이다.

브레인스톰 사는 미국 매사추세츠 대학 의과대학과 매사추세츠 종합병원에서 임상시험을 진행할 수 있도록 허가해 줄 것을 미국식품의약국(FDA)에 신청해 놓고 결과를 기다리고 있다.

skhan@yna.co.kr

2012-7-24

Autologous Cultured Mesenchymal Bone Marrow Stromal Cells Secreting Neurotrophic Factors (MSC-NTF), in ALS Patients.

This study is ongoing, but not recruiting participants.

First Received on January 17, 2010. Last Updated on August 5, 2012 History of Changes

Sponsor:	Hadassah Medical Organization
Collaborator:	Brainstorm Cell Therapeutics Ltd.
Information provided by (Responsible Party):	Hadassah Medical Organization
ClinicalTrials.gov Identifier:	NCT01051882

Rank	Status	Study
1	Recruiting	Clinical Trial on The Use of Autologous Bone Marrow Stem Cells in Amyotrophic Lateral Sclerosis (Extension CMN/ELA) Condition: Amyotrophic Lateral Sclerosis Interventions: Procedure: Laminectomy and bone marrow stem cells transplantation; Procedure: Intrathecal infusion of autologous bone marr of placebo (saline solution).
2	Enrolling by invitation	The Clinical Trial on the Use of Umbilical Cord Mesenchymal Stem Cells in Amyotrophic Lateral Sclerosis Condition: Amyotrophic Lateral Sclerosis Intervention: Procedure: stem cell transplantation
3	Recruiting	Human Neural Stem Cell Transplantation in Amyotrophic Lateral Sclerosis (ALS) Condition: Amyotrophic Lateral Sclerosis Intervention: Biological: Human Neural Stem Cells
4	Recruiting	A Dose-escalation Safety Trial for Intrathecal Autologous Mesenchymal Stem Cell Therapy in Amyotrophic Lateral Sclerosis Condition: Amyotrophic Lateral Sclerosis Intervention: Biological: autologous mesenchymal stem cells
5	Completed	Clinical Trial on the Use of Autologous Bone Marrow Stem Cells in Amyotrophic Lateral Sclerosis Condition: Amyotrophic Lateral Sclerosis Interventions: Procedure: Laminectomy and bone marrow stem cells transplantation; Procedure: Autologous bone marrow cells collection
6	Completed	Mesenchymal Stem Cells for Treatment of Amyotrophic Lateral Sclerosis (ALS) Condition: Amyotrophic Lateral Sclerosis Intervention: Biological: autologous mesenchymal stem cells
7	Active, not recruiting	Human Spinal Cord Derived Neural Stem Cell Transplantation for the Treatment of Amyotrophic Lateral Sclerosis Condition: Amyotrophic Lateral Sclerosis Intervention: Device: surgical implantation
8	Active, not recruiting	Safety/Efficacy Study for the Treatment of Amyotrophic Lateral Sclerosis Condition: Amyotrophic Lateral Sclerosis Intervention: Biological: autologous bone marrow-derived stem cells
9	Recruiting	Safety and Efficacy Study of Autologous Bone Marrow Derived Stem Cell Treatment in Amyotrophic Lateral Sclerosis Conditions: Amyotrophic Lateral Sclerosis; ALS Interventions: Biological: HYNR-CS inj; Biological: Control group
10	Active, not recruiting	Derivation of Induced Pluripotent Stem Cells From an Existing Collection of Human Somatic Cells Condition: Amyotrophic Lateral Sclerosis Intervention:
11	Active, not recruiting	Autologous Cultured Mesenchymal Bone Marrow Stromal Cells Secreting Neurotrophic Factors (MSC-NTF), in ALS Patients. Condition: Amyotrophic Lateral Sclerosis Interventions: Biological: MSC-NTF cells transplantation (i.m.); Biological: MSC-NTF cells transplantation (i.t.)
12	Active, not recruiting	Development of iPS From Donated Somatic Cells of Patients With Neurological Diseases Condition: Neurodegenerative Disorders

Dose-escalation Safety Trial for Intrathecal Autologous Mesenchymal Stem Cell Therapy in Amyotrophic Lateral Sclerosis

This study is currently recruiting participants.
Verified May 2012 by Mayo Clinic

First Received on May 18, 2012. Last Updated on May 29, 2012 History of Changes

Sponsor:	Mayo Clinic
Information provided by (Responsible Party):	Anthony J. Windebank, Mayo Clinic
ClinicalTrials.gov Identifier:	NCT01609283

Human Spinal Cord Derived Neural Stem Cell Transplantation for the Treatment of Amyotrophic Lateral Sclerosis (ALS)

This study is ongoing, but not recruiting participants.

First Received on April 28, 2011. Last Updated on June 14, 2012 History of Changes

Sponsor:	Neuralstem Inc.
Information provided by (Responsible Party):	Neuralstem Inc.
ClinicalTrials.gov Identifier:	NCT01348451

Safety/Efficacy Study for the Treatment of Amyotrophic Lateral Sclerosis (ALS)

This study is ongoing, but not recruiting participants.

First Received on March 1, 2010. Last Updated on April 27, 2011 History of Changes

Sponsor:	TCA Cellular Therapy
Information provided by:	TCA Cellular Therapy
ClinicalTrials.gov Identifier:	NCT01082653

Clinical Trial on The Use of Autologous Bone Marrow Stem Cells in Amyotrophic Lateral Sclerosis (Extension CMN/ELA)

This study is currently recruiting participants.
Verified December 2010 by Fundacion para la Formacion e Investigacion Sanitarias de la Region de Murcia

First Received on December 3, 2010. Last Updated on December 7, 2010 History of Changes

Sponsor:	Fundacion para la Formacion e Investigacion Sanitarias de la Region de Murcia
Collaborators:	Instituto de Salud Carlos III Hospital Universitario Virgen de la Arrixaca Hospital General Universitario Morales Meseguer Fundación Diógenes
Information provided by:	Fundacion para la Formacion e Investigacion Sanitarias de la Region de Murcia
ClinicalTrials.gov Identifier:	NCT01254539

The Clinical Trial on the Use of Umbilical Cord Mesenchymal Stem Cells in Amyotrophic Lateral Sclerosis

This study is enrolling participants by invitation only.

First Received on December 7, 2011. Last Updated on June 18, 2012 History of Changes

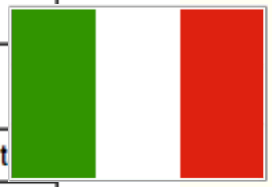
Sponsor:	General Hospital of Chinese Armed Police Forces
Information provided by (Responsible Party):	General Hospital of Chinese Armed Police Forces
ClinicalTrials.gov Identifier:	NCT01494480

Human Neural Stem Cell Transplantation in Amyotrophic Lateral Sclerosis (ALS) (hNSCALS)

This study is currently recruiting participants.
Verified July 2012 by Azienda Ospedaliera Santa Maria, Terni, Italy

First Received on July 9, 2012. Last Updated on July 11, 2012 History of Changes

Sponsor:	Azienda Ospedaliera Santa Maria, Terni, Italy
Collaborators:	Azienda Ospedaliero Universitaria Maggiore della Carita Università di Padova Italy
Information provided by (Responsible Party):	Angelo Luigi Vescovi, Azienda Ospedaliera Santa Maria, Terni, It



줄기세포 치료 *임상시도*Clinical Trials 요약

1.6개국,9연구팀(대한민국, 미국, 스페인, 이태리, 중국,이스라엘)

2.주요 시술 방법

-환자 골수 채취 중배엽성 간질 세포 *MSC (MesencymalStromal Cells)*
-수막강내주사 *IT (intrathecal injection)*

3. 마무리 단계

줄기세포 치료 기전에 대한 일반적 오해

줄기세포가 퇴행된 신경세포를 대체하지 않는다.

즉, 줄기세포치료는 퇴행되어가는 신경세포의 치환요법이 아니다.

*루게릭병 치료 임상시도*Clinical Trials 분류

1. 줄기세포 치료
2. 약물 치료:dexpramipexole and ceftriaxone
3. 임플란트 치료
4. 단일항체*Monoclonal Antibody*치료
5. 리보핵산 억제재*RNAi*치료
6. 보톡스 치료
7. 두뇌접속 *Brain Interface*

약물 치료 임상시도 *Clinical Trials*

Phase 3 Study of Dexpramipexole in ALS (EMPOWER)

This study is ongoing, but not recruiting participants.

First Received on January 20, 2011. Last Updated on July 12, 2012 History of Changes

Sponsor:	Biogen Idec
Information provided by:	Biogen Idec
ClinicalTrials.gov Identifier:	NCT01281189

Clinical Trial Ceftriaxone in Subjects With ALS

This study is ongoing, but not recruiting participants.

First Received on July 5, 2006. Last Updated on December 13, 2011 History of Changes

Sponsor:	Massachusetts General Hospital
Collaborator:	National Institute of Neurological Disorders and Stroke (NINDS)
Information provided by (Responsible Party):	Merit E. Cudkowicz, MD, Massachusetts General Hospital
ClinicalTrials.gov Identifier:	NCT00349622

Ceftriaxone임상시도 조기종료됨.
최종분석과 결과발표가 곧 있을 예정.

Statement on the Clinical Trial of Ceftriaxone

August 10, 2012

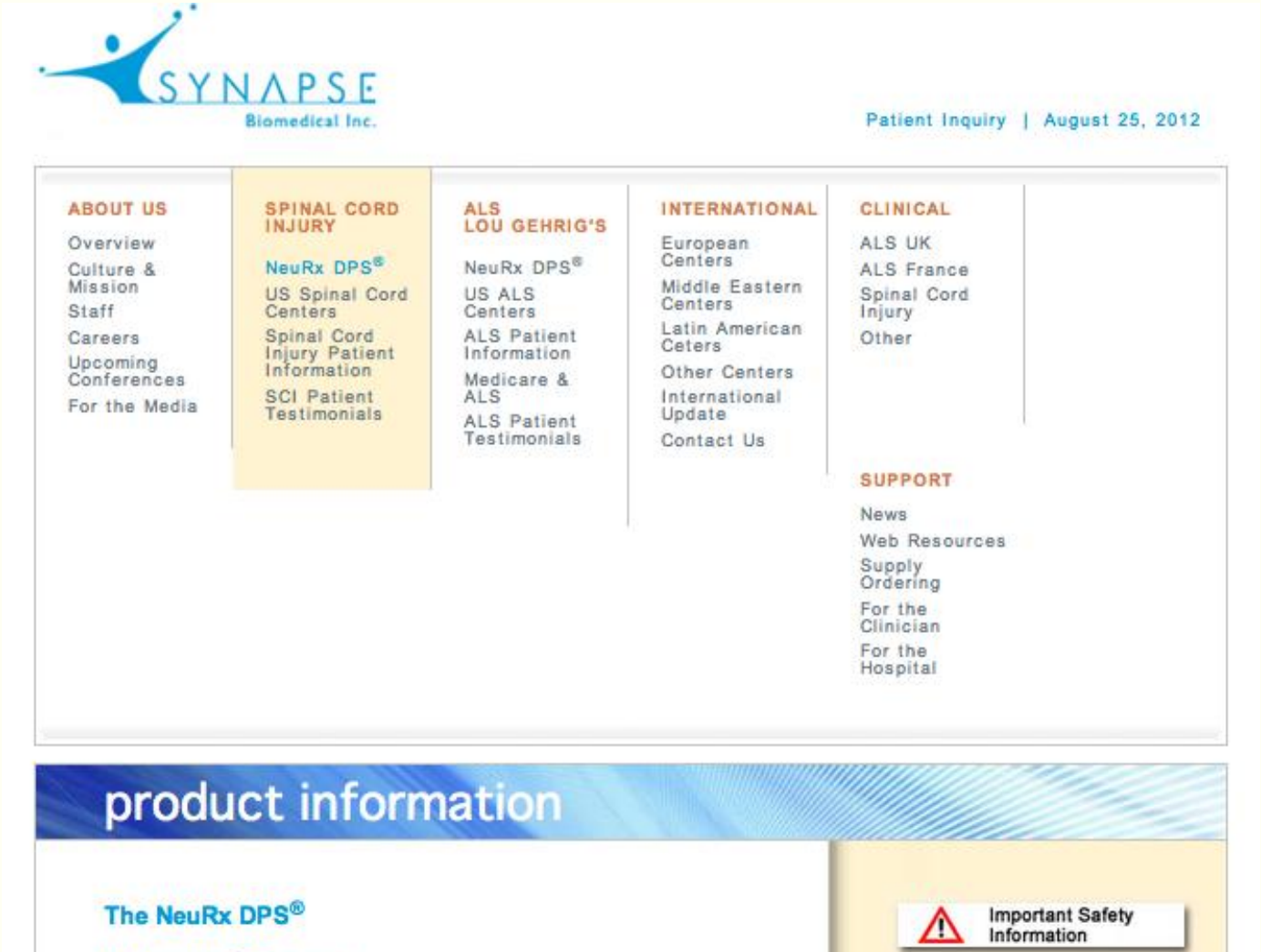
In July 2012, the DSMB for the clinical trial of ceftriaxone in ALS recommended that based on existing data the trial be stopped because the study was unlikely to reach the pre-determined efficacy criteria. Pre-clinical research identified ceftriaxone as a promising treatment for ALS, therefore it was important for people with ALS to find out if the drug could be beneficial in ameliorating the disease. The study used a novel seamless adaptive design. Final analysis and presentation of the results will occur after completion of site monitoring and database lock. The important contributions of patients, their families and the hard work of the investigators and their teams made it possible to implement the trial. While all had hoped for a more positive result, the trial has moved ALS research forward.

2012-8-10

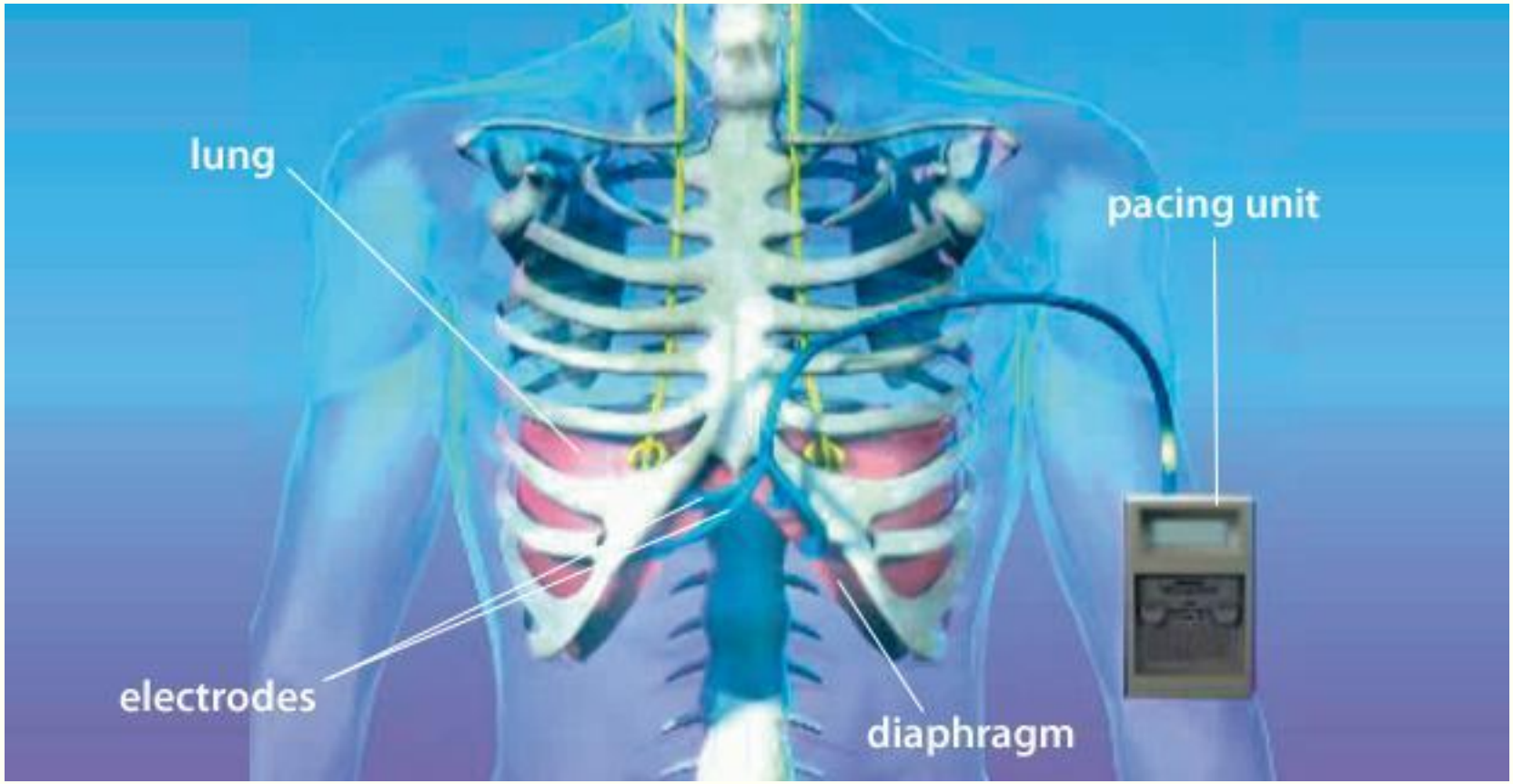
*루게릭병 치료 임상시도*Clinical Trials 분류

1. 줄기세포 치료
2. 약물 치료
3. 임플란트 치료:”NeuRx” 횡격막 박동 장치 *DPS(Diaphragm Pacing System)*
4. 단일항체*Monoclonal Antibody*치료
5. 리보핵산 억제재*RNAi*치료
6. 보톡스 치료
7. 두뇌접속 *Brain Interface*

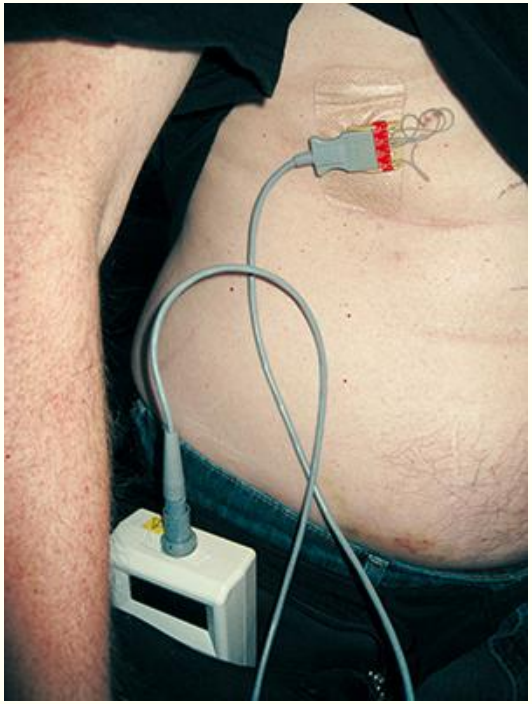
미국 시냅스사의 ”NeuRx” 횡격막 박동 장치 *DPS(Diaphragm Pacing System)*



”NeuRx” 횡격막 박동 장치 *DPS(Diaphragm Pacing System)*



최초 사용자 증례



It may be hard to jump through all the hoops," says Dwyer, "but for us, the pacer was worth it."

작년,2011-9-29, 미국 FDA 승인 받음.

FDA Approves NeuRx Diaphragm Pacing System (DPS)®

September 29, 2011

Synapse Biomedical, Inc. announces that the U.S. Food and Drug Administration (FDA) has approved its NeuRx Diaphragm Pacing System (DPS)® for treating amyotrophic lateral sclerosis (ALS) patients who have stimulatable diaphragms and are experiencing chronic hypoventilation.

The FDA Humanitarian Device Exemption (HDE) marketing approval is based on demonstration that NeuRx DPS® could help ALS patients live longer and sleep better than the current standard of care, alone. These findings are the result of a multi-center clinical trial that enrolled 106 patients and treated 86 for chronic hypoventilation.

"We are very pleased the FDA approved this next indication for use of the NeuRx DPS® to treat respiratory problems in ALS. In granting approval, it allows us to now offer individuals living with ALS more time to be able to breathe with their own muscles," said Anthony R. Ignagni, Synapse Biomedical Inc., President and Chief Executive Officer.

As the phrenic nerve to the diaphragm muscles fails, patients lose the ability to breathe without ventilator support. Approximately 30,000 people in the United States live with ALS, with an estimated subset of 3,300 with both respiratory problems and intact phrenic nerves that could benefit from the NeuRx DPS® treatment. In ALS, NeuRx DPS® is implanted through minimally invasive laparoscopic surgery and provides electrical stimulation to the diaphragm muscles. Repeated use of NeuRx DPS® conditions the diaphragm muscles, delaying respiratory failure and the need for tracheostomy and mechanical ventilation.

"We plan to work closely with the Medical Directors at the ALS Association Certified CentersSM (www.alsa.org)

유효성 평가 임상시도 진행 예정

nption (HDE) Post-Approval Study (PAS) of NeuRx Diaphragm Pacing System (DPS) for Amyotrophic L

This study is not yet open for participant recruitment.
Verified May 2012 by Synapse Biomedical

First Received on May 22, 2012. Last Updated on May 23, 2012 History of Changes

Sponsor:	Synapse Biomedical
Information provided by (Responsible Party):	Synapse Biomedical
ClinicalTrials.gov Identifier:	NCT01605006

개발자: 레이먼드 온더스 박사

Fifteen years ago, Dr. Raymond Onders, co-founder of Synapse Biomedical, began clinical research at University Hospitals Case Medical Center to help spinal cord injured patients breathe, including the late actor Christopher Reeve. In 2004, this research expanded to include patients with ALS. Presently, Dr. Onders holds the Margaret and Walter Remen Chair in Surgical Innovation and is a professor of Surgery at Case Western Reserve University School of Medicine. ALS has affected Dr. Onders and his family personally. "I lost my sister to this devastating disease this past year.I have also seen the significant benefit diaphragm pacing can provide to patients. Diaphragm pacing has improved the breathing and longevity of many of the

”NeuRx” 횡격막 박동 장치 *DPS(Diaphragm Pacing System)* 요약

간단한 시술

안정성 검증: 부작용 없음.

유효성“보류”:현재 임상시도 진행중

루게릭병 치료 임상시도Clinical Trials 분류

1. 줄기세포 치료
2. 약물 치료
3. 임플란트 치료
4. 단일항체 *Monoclonal Antibody* 치료:GSK NoGoA antibody
5. 리보핵산 억제재*RNAi*치료
6. 보톡스 치료
7. 두뇌접속 *Brain Interface*

GSK NoGoA antibody

국내 임상시도 예정.

임상시도Clinical Trials 강조점

새로운 치료의 발견을 위한 연구자와 참여자의 공동 노력

감사합니다.