Drugs in Development for Multiple Sclerosis

Stem cells, tyrosine kinase inhibitors, remyelinating agents, metabolically active molecules, and more are being tested as potential new disease-modifying treatments.

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Selection Process

ClinicalTrials.gov, the most comprehensive database of clinical trials conducted globally, lists more than 2000 clinical trials related to MS. With such a robust body of investigations it is quite a task to select the most promising therapeutic approaches that may be closer to finding their way into clinic. Therefore, the selection algorithm has to be applied (Figure). In the first phase of selection, only currently active (recruiting or not recruiting) or recently completed (within the last 3 years) phase 2 or phase 3 interventional clinical trials were selected. As a result, 107 trials currently active (non-completed, recruiting or non-recruiting subjects) and 40 completed trials were selected. In the second phase of selection, trials with fewer than 100 participants or trials testing drugs with the mechanism of action identical to currently available MS drugs were excluded. For example, clinical trials studying drugs targeting sphingosine-1-phosphate (S1P) receptors or $CD20^+$ cells, both of which are discussed in other articles in this issue, were excluded. After the second phase of selection, 34 clinical trials remained and are included in the Table and a selection of these are discussed.

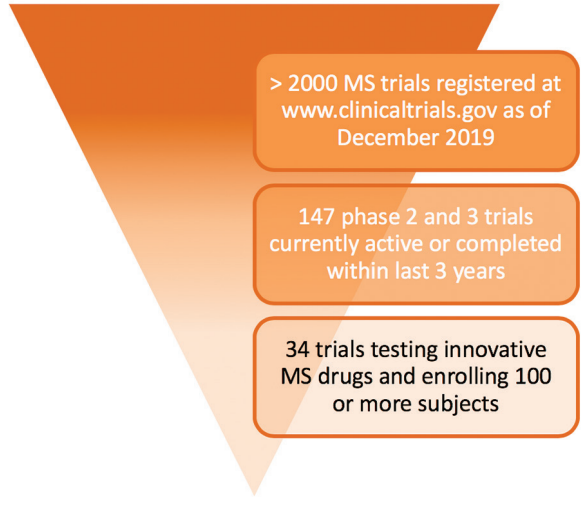

Figure. In December 2019, the US Library of Medicine database ClinicalTrials.gov had more than 2,000 clinical trials related to multiple sclerosis (MS). To select the most promising trials with reasonable probability for an innovative MS drug to be approved by the Food and Drug Administration (FDA), only currently active (recruiting or not recruiting) or recently completed (within the last 3 years) phase 2 or phase 3 interventional clinical trials were considered. Of the resulting 147 trials active (non-completed, recruiting or nonrecruiting) and completed trials, those with less than 100 participants and those testing drugs with identical mechanisms of action with already available MS drugs (eg, target S1P receptors or $CD20^+$ cells) were excluded. The remaining 34 clinical trials are included in the Table.

B-Cell Targeting Therapies Beyond Depleting Antibodies: Tyrosine Kinase Inhibitors

Selective inhibitors of tyrosine kinase (TK) or Bruton's tyrosine kinase (BTK), key components of B-cell receptor signaling that regulates B cell proliferation, survival, adhesion and migration as well as Toll-like receptor signaling[1]

TABLE. SELECTED CLINICAL TRIALS FOR MULTIPLE SCLEROSIS

Drug	Type[a]	Major outcome measures (study duration)	Drug class/mechanism of action	Phase	Trial status	N	NCT number
Evobrutinib	RMS	Active lesions (12-24 wks)	Bruton TKI	2	ANR	267	NCT02975349
Evobrutinib	RMS	Annualized relapse rate (96 wks)	Bruton TKI	3	Recruiting	950	NCT04032158
SAR442168	RMS	New active lesions (12 wks)	Bruton TKI	2	Recruiting	127	NCT03889639
SAR442168	RMS	New active lesions (12 wks)	Bruton TKI	2	Recruiting	105	NCT03996291
Masitinib	PMS	Disability progression (96 wks)	TKI	3	ANR	656	NCT01433497
Imatinib	RRMS	Functional system score (28 d)	TKI	2	Recruiting	200	NCT03674099
Ibudilast	PMS	Brain atrophy and safety (96 wks)	Anti-inflammatory	2	Completed	255	NCT01982942
BIIB033	RMS	Disability and safety (72/96 wks)	antiLINGO-1 MAb	2	ANR	263	NCT03222973
Elezanumab	RMS	Disability progression (52 wks)	antiRGMa MAb	2	Recruiting	165	NCT03737851
AHSCT	RRMS	Disease activity and disability (5 yrs)	Immune reset	3	Recruiting	100	NCT03477500
AHSCT	RRMS	Disease activity and disability (5 yrs)	Immune reset	3	Recruiting	200	NCT03342638
AHSCT	MS	Disease disability change (5 yrs)	Immune reset	2	ANR	110	NCT00273364
Simvastatin	SPMS	Disability progression (3 yrs)	Statin	3	Recruiting	1180	NCT03387670
Vitamin D_3	CIS	Conversion of clinically isolated syndrome to multiple sclerosis (2 yrs)	Vitamin D_3	3	Recruiting	316	NCT01817166
Vitamin D_3	RRMS	Annualized relapse rate (2 yrs)	Vitamin D_3	3	ANR	172	NCT01490502
MD1003	PMS	Disability progression (15-27 mos)	High dose biotin	3	ANR	642	NCT02936037
Lipoic acid	PMS	Brain atrophy progression (2 yrs)	Multiple	2	Recruiting	118	NCT03161028
Nanocrystalline gold	RRMS	VEP and MS disability (48 wks)	Under investigation	2	Recruiting	150	NCT03536559
Laquinimod	PPMS	Brain volume change (24 mos)	Anti-inflammatory	2	Completed	374	NCT02284568
GNbAC1 mAb	RRMS	Active lesions (12 and 24 wks)	To target HERV	2	Completed	270	NCT02782858
IMU-838	RRMS	Number of active lesions (24 wks)	DHODH inhibitor	2	Recruiting	195	NCT03846219
Erythropoietin alfa	ON	Visual acuity and RNFLT-G (6 mos)	Neurotrophic agent	3	ANR	100	NCT01962571
Pioglitazone, montelukast, hydroxychloroquine, losartan	MS	Disability progression (1.5 yrs)	Under investigation	2	Recruiting	250	NCT03109288
Balloon venoplasty	RRMS SPMS	Clinical and safety outcomes (48 wks)	To improve CCSVI	2	Completed	104	NCT01864941
SPARC1103	MS	Muscle spasticity (24 d)	$GABA_B$ receptor agonist	2	Completed	142	NCT02027025
VSN16R	MS	Spasticity (26 days)	BKCa calcium activated K^+ channel modulator	2	Completed	160	NCT02542787
Amantadine, modafinil, methylphenidate	MS	Fatigue (5 wks)	Stimulants	3	Completed[a]	140	NCT03185065
BX-1 (dronabinol)	MS	Spasticity (16 wks)	Cannabis	3	Recruiting	384	NCT03756974
ADS-5102	MS	Walking speed (12 wks)	Amantadine ER	3	Recruiting	540	NCT03436199
ADS-5102		Walking speed (52 wks)	Amantadine ER				NCT03567057
Arbaclofen ER	RRMS SPMS	Muscle spasticity and disability (1 yr)	R enantiomer of baclofen	3	ANR	323	NCT03319732
Arbaclofen ER	MS	Muscle spasticity and global function (84 d)	R enantiomer of baclofen	3	Completed[a]	536	NCT03290131
Intranasal insulin	MS	Cognitive function (24 wks)	Insulin	2	Recruiting	105	NCT02988401
Adderall XR	MS	Cognitive function (12 wks)	Stimulant	3	Recruiting	180	NCT02676739

[a] Study population as reported by study authors at clinicaltrials.gov; [b] Results not posted. Abbreviations: AHSCT, autologous hematopoietic stem cell transplantation; ANR, active nonrecruiting; CCSV, hronic cerebrospinal venous insufficiency; CIS, clinically isolated syndrome; DHODH, dihydroorotate dehydrogenase; ER, extended release; HERV, human endogenous multiple sclerosis-associated retrovirus; LINGO-1, leucine rich repeat and immunoglobin-like domain-containing protein 1; MS, multiple sclerosis, PMS, progresive MS; PPMS, primary progressive MS; ON, optic neuritis; RMS, relapsing MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS; RGMa, repulsive guidance molecule A; RNFLT-G, retinal ganglion nerve fiber layer thickness; TKI, tyrosine kinase inhibitor; VEP, visual evoked potentials.

are being studied in several clinical trials. Recently, results from a phase 2 study with evobrutinib showed that those treated with 75 mg of evobrutinib twice daily had a 75% reduction in the number of contrast-enhancing MS lesions and an 60% lower unadjusted annualized relapse rate (ARR) compared with dimethyl fumarate. In this 24-week study no significant effect of evobrutinib on disability progression was observed.[2] An upcoming phase 3 trial of evobrutinib is expected to enroll 950 participants with relapsing-remitting MS (RRMS) or active secondary progressive MS (aSPMS). The study goal is to compare the effect of evobrutinib with interferon β-1a on disease activity and disability progression. Another BTK inhibitor, SAR442168, will be studied in 2 phase 2 trials, which showed a trend towards improvement in the Multiple Sclerosis Functional Composite Scores in a small trial of 32 participants with MS.[3] The effect of masitinib, a TK inhibitor, on disability progression is being studied in a large phase 3 trial in 656 participants with primary progressive MS (PPMS) and nonrelapsing SPMS. Imatinib, also a TK inhibitor, will be compared to methylprednisolone in a short-course proof-of-concept study.

Remyelination: Where do we Stand?

Currently approved disease-modifying treatments (DMTs) for MS target immune functions and reduce central nervous system (CNS) inflammation. None of the approved DMTs was designed to improve remyelination. Remyelinating therapies, if successful in clinical trials could potentially be used in combination with an immunomodulatory DMTs. The hope for clinical benefit of a new class of remyelinating DMT is not just decreased disability progression but to lead to disability improvement. A challenge to this approach is that not only myelin loss but also axonal transection occur in both active and chronic MS lesions.[4] Therefore, promotion of oligodendrocyte function and proliferation may not lead to complete neurologic recovery."

In animal models multiple new therapeutic strategies have been reported to promote remyelination. These include recruitment and differentiation of oligodendrocyte precursors and overcoming inhibitors of remyelination. The list of agents explored in this context includes repurposed medications approved for other indications such as beztropine, quetiapine, clemastine, miconazole and clobetasol. A common feature of these agent is their capacity to cross the blood-brain barrier.[5] Clemastine is being tested in phase 2 clinical trial of 90 participants with optic neuritis. A different approach is taken with opicinumab, a monoclonal antibody targeting leucine rich repeat and Immunoglobin-like domain-containing protein 1 (LINGO-1), which is a negative regulator of myelination expressed in the CNS. A recently completed phase 2 study in 419 participants with relapsing MS patients has not resulted in significant improvement in disability scores but did show tentative efficacy signals justifying continued evaluation possible clinical benefit of opicinumab as an add on to immunomodulatory therapy.[6]

Repulsive guidance molecule A (RGMa) is implicated in decreased axonal growth and myelination, oligodendroglial regeneration, and functional recovery after trauma or inflammation. In people with MS, RGMa is upregulated thought to have effects on recovery after injury. Elezanumab, a monoclonal antibody directed against RGMa, is being studied in a phase 2 clinical trial for relapsing MS with data expected to be available in 2021.[7]

Addressing Immune Dysregulation

Immune dysregulation is thought to be an important part of the overall disease process in MS. This has led to considerable interest in treatment strategies to reset the immune system or address immunologic dysregulation. Stem cell therapies using autologous hematopoietic stem cells transplantation (AHSCT), placenta derived stem cells, and adipose tissue derived stem cells have been used in clinical trials.[8] In a recent meta-analysis of 15 studies of AHSCT in a total of 764 individuals with MS patients, the ARR was 0.037, disability progression was 17.1% at 2 years and 23.3% at 5 years, and transplantation related mortality was 2.1%.[9] Controlled AHSC trials are ongoing. In 2 studies participants will be randomly assigned to receive AHSCT vs best DMT chosen by the treating physician discretion. Another study will compare the effect of AHSCT vs AHSCT combined with intravenous immunoglobulin (IVIG). Although AHSCT significantly reduces relapses and new inflammatory activity, it generally does not lead to recovery of already lost function.

In contrast to AHSCT, the mesenchymal cell therapy does not include depletion of the existing immunocompetent cells and, therefore, treated individuals are expected to have a better survival rate. Trials to date have included a limited number of participants and preliminary results presented at an international MS meeting in September 2019 suggested promising results after intrathecal application of autologous mesenchymal cells.

Ibudilast is an anti-inflammatory drug that is administrated orally and inhibits cyclic nucleotide phosphodiesterases, macrophage migration inhibitory factor, and toll-like receptor 4.[10] In an initial trial, ibudilast did not decrease the number of active lesions or relapses but did significantly reduce progression of brain atrophy.[11] In a randomized placebo-controlled phase 2 study, participants treated with ibudilast also had reduced brain atrophy compared with placebo but again there was no difference with respect to disability progression.[11]

Vitamins and Other Metabolic Agents

Simvastatin inhibits 3-hydroxy-3-methylglutaryl (HMG) coenzyme A reductase, the enzyme that promotes endogenous production of cholesterol. Initial clinical trials in RRMS showed no significant positive benefits of statins.[12] However, simvastatin treatment decreased the annualized whole brain atrophy rate by 43% compared with placebo in SPMS.[13] A 3-year long phase 3 clinical trial is enrolling 1,180 people with SPMS and will test whether simvastatin (80 mg daily) reduces neurologic disability progression.

There is increasing evidence that lower levels of 1,25-dihydroxy vitamin D, are associated with increased risk of MS and with greater clinical and brain MRI disease activity in established MS. The effect of vitamin D supplementation on MS activity remains inadequately investigated.[14] A recently published prospective placebo-controlled clinical trial involving 181 people with RRMS who were treated with a high oral dose of vitamin D_3, a precursor of 1,25-dihydroxyvitamin D, (100,000 IU every other week) did not demonstrate any decrease in ARR during the 96-week-long study, however.[15] There are 2 additional phase 3 clinical trials testing vitamin D_3 in participants with clinically isolated syndrome (CIS) and RRMS. These studies will address whether oral supplementation with vitamin D_3 may inhibit conversion of CIS to MS or reduce MS disease activity and disability progression.

Biotin is another supplement being studied in a high dose formulation. A high dose biotin, MD1003, was shown to increase the proportion (12.6%) of individuals with Expanded Disability Status Scale (EDSS) score improvement in a 12-month trial in participants with progressive forms of MS. No participant treated with placebo in this trial had EDSS improvement.[16] A second larger phase 3 clinical trial is currently underway to test the effect of MD1003 on disability outcomes. Initial results of the study are expected in 2020.

Lipoic acid is an endogenously produced antioxidant with multiple biologic functions including free-radical scavenging, metallic ion chelation, regeneration of intracellular glutathione, and oxidative damage repair of macromolecules. In animal models of MS, lipoic acid reduced disability and inflammation. A phase 2 placebo-controlled 2-year clinical trial, with 51 individuals with SPMS enrolled, showed that lipoic acid significantly reduced brain volume atrophy.[17] A new phase 2, placebo-controlled, randomized clinical trial will analyze the effect of lipoic acid on brain atrophy in 118 participants with SPMS.

Summary

The introduction of the first DMT for MS, interferon β, more than 20 years ago marked a new era for treatment of relapsing MS. Since then, more effective treatment options have been developed to control neuroinflammation and MS disease activity. There is a growing interest towards neuroprotective and remyelinating strategies in MS. Additionally, stem cell-based approaches may hold promise for people with more active disease. Each of the new interventions add to our understanding of the disease process of MS and may help guide us to the actual cause or causes of this disease. ■

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Disclosure
KB has disclosures at www.practicalneurology.com