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Editorial

Multiple Sclerosis: pathogenesis and therapeutics

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Abstract: Multiple sclerosis (MS) is demyelinating disorder of the central nervous system of autoimmune aetiology. Numerous treatment options are available to patients with MS, however these need to be improved as side effects and long term effectiveness are limited. Herein, we present therapeutic approaches to disease management as well as neuropathic pain management in patients with MS. In addition, new onset of disease has been described to be attributed to certain compounds that induce blood brain barrier disruptions in addition to certain vitamin deficiencies. Since the current treatment of MS remains elusive and are limited, recent advances offer an optimistic outlook.

Keywords: multiple sclerosis, autoimmunity, immunotherapy, drugs, MS

The World Health Organization (WHO) estimated that over 2.5 million people globally suffer from multiple sclerosis (MS). With the present global population growing to an unparalleld height of 7.0 billion in 2011 and recently reaching 7.5 billion (24 April 2017), it is estimated to reach 8.5 billion by 2030, the incidence and onset of MS in young adults is expected to rise exponentially. It is estimated that over 400,000 people have MS in the United States, with 700,000 Europeans and 23,000 Australians also affected; with > 200 new cases being diagnosed each week in United States alone. There are 4 subtypes of MS, (i) (i) relapse/remitting MS (RRMS, 85 % of people with MS are initially diagnosed with RRMS), (ii) secondary progressive MS (SPMS, 40 %), (iii) primary progressive MS (PPMS, 15 %) and (iv) progressive relapsing MS (PRMS, 5 %).

MS is a chronic disabling disorder of the central nervous system (CNS) with inflammatory aetiology, although, genetic and environmental factors cannot be discounted. MS affects young adults with females being more commonly diagnosed than males by 2-3:1 ratio. T helper type 1 (Th1) cells, Th17, CD8+ T cells and macrophages play a crucial role in mediating an inflammatory mileau leading to autoimmune attack against protein constituents within the myelin sheath. As a result there is axonal damage and neurodegeneration. In fact, myelin basic protein (MBP), proteolipid protein (PLP) and myelin oligodendrocyte glycoprotein (MOG) have been proposed as candidate autoantigens involved in the pathogenesis of MS based on autoreactive T cells and autoantibodies which are present in patients with MS. MBP, MOG and PLP are also encephalitogenic in murine experimental autoimmune encephalomyelitis (EAE), an animal model for MS. Although the pathogenesis of MS is not clear, inflammation, changes in immnune cells, viral and genetic factors play a crucial role in disease initiation and progression. More recently however, much focus has been on matrix metalloproteinases (MMPs) as mediators of blood-brain barrier disruption and CNS inflammation, thus contributing to disease pathogenesis. Indeed, Boziki and Grigoriadis focus on clinical and experimental evidence of MMPs pathogenic role in MS and in EAE. In addition, the role of vitamin D in MS, its biology, actions, biochemistry and epidemiology studies are demonstrated by Simpson et al. Recent studies support a strong and consistent inverse association of vitamin D with MS risk and clinical score, and understanding the role and actions of vitamin D in MS onset and progression will aid in development of

therapeutic interventions using vitamin D as a therapy. Furthermore, demyelination apprears to have a direct association with vitamin B deficiency and is a further detriment of MS. In fact, both MS and vitamin B deficiency results in severe myelin degeneration. Nemazannikova et al., discuss the potential role of vitamin B (B1, B2, B3, B4, B5, B6, B7, B9, B12) in MS. The anti-inflammatory and re-myelinating attributes of vitamin B complex are promising, although with limited clinical studies.

The specific treatments against MS that are currently on the market include, Bayer Healthcare Betaferon/Betaseron (interferon beta-1b), Novartis' Extavia (interferon beta-1b) and Gilenya (fingolimod; a novel sphingosine-1-phosphate‐receptor modulator), Biogen's Idec Avonex (interferon beta-1a), Tysabri (natalizumab; monoclonal antibody against alpha4-integrin) and Tecfidera (dimethyl fumarate), Teva's Copaxone (glatiramer acetate), EMD Serono/Pfizer's Rebif (interferon beta-1a), Sanofi-Genzyme's Aubagio (teriflunomide)and newly approved Roche's Ocrevus (ocrelizumab, humanized anti-CD20 monoclonal antibody). The current drugs available typically focusing on speeding recovery from relapses, slowing the progression of the disease and managing MS symptoms, however, there is still need for treatment options to stop progression with a well-tolerated safety profile. As such, there is an unmet need in the MS market particularly in altering / mainly stopping disease progression, inducing and maintaining remission, improved drug delivery methods and cheaper drugs / therapeutic options.

Recent advances in MS therapeutics include, monoclonal antibodies, immunotherapy / vaccines, potassium channel blockers and protein growth factors. In this regards, Androutsou et al., describe MOG based immunotherapeutics. The genomic organization of the human MOG gene, characteristics of human MOG protein and structural features of MOG are discussed, as well as, immunotherpeutic approaches against MOG in EAE animal models and in human studies. Heliopoulos and Patousi present the latest therapeutic monoclonal antibody treatments in MS (Natalizumab, Alemtuzumab, Daclizumab, Orelizumab and Ofatumumab), their mechanisms of action, clinical studies and adverse events. Importantly, although most MS treatments are focused on improving motor impairments, little is focussed on sensory disturbances such as pain in patients with MS. It is important to understand the mechanisms of pain development which will aid in new improved treatment options. In this regard, Duffy et al., describe the mechanisms of neuropathic pain associated with MS, drugs and interventions used against MS and pharmacological interventions for the treatment of MS related neuropathic pain (such as, tricyclic antidepressants, serotonin and noradrenalin reuptake inhibitors, anticonvusives, opioid analgesics, cannabinoids). In addition using the EAE model they gather insights of mechanisms and modes of decreasing and/or measuring neuropathic pain and describe the involvement of inflammation.

Numerous drugs are available to patients with MS which prolongs disease progression, although, a cure is yet available. A large amount of studies have reported developments towards more specific monoclonal antibodies or vaccines and immunotherapeutics against MS, and such strategies have entered into human clinical trials. It is anticipated that within the next 5-10 years, new treatment options will become available to patients with MS to treat their disease. Understanding the interactions of drugs and therapeutics on pain management is also crucial for identifying the most optimal drug treatment. Finally, understanding the mechanisms by which MMPs, vitamin D deficiency and vitamin B deficiency act on initiation and progression of MS will aid in new improved therapeutic treatments for the disease.

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