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Multiple sclerosis at the crossroads of scientific evidence and clinical translation

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Few neurological conditions have witnessed such a magnitude of clinical and therapeutic advances over recent years as multiple sclerosis (MS). In addition, there is now a greater understanding of the underlying genetic and environmental factors involved in the condition's pathogenesis. Indeed, the causality of Epstein–Barr virus infection and the development of MS has been corroborated only recently. Moreover, the relevance of comorbidities for the disease course and individual quality of life is now acknowledged. Currently, there are efforts to translate the improved understanding of MS-related comorbidities into clinical practice.

This special issue on MS comprises eight articles dealing with emerging developments in MS by experts from Austria, Germany, and Switzerland. The narrative review by *Elisabeth Olbert* and *Walter Struhal* (Tulln, Austria) deals with the emerging value of optical coherence tomography (OCT) in MS, not only for monitoring the consequences of optic neuritis [1]: their article also highlights the relevance of OCT parameters for predicting clinical outcomes, including disability, cognitive function, and brain atrophy. The current gold standard to detect intrathecal inflammation is determining cerebrospinal fluid (CSF)-restricted oligoclonal bands (OCB). However, kappa-free light chains (κ-FLC) in the CSF have methodological advantages. The review article by *Harald Hegen* and coworkers (Innsbruck, Austria) provides solid scientific evidence that intrathecal κ-FLC synthesis reaches similar diagnostic accuracy compared to the well-established CSF-restricted OCB to iden-

tify patients with MS [3]. Moreover, they summarize recent studies that even disclosed the value of intrathecal κ-FLC synthesis to predict early MS disease activity. Biomarkers may assist in diagnosing and treating MS, a condition with a highly variable and unpredictable disease course. The systematic review on experimental biomarkers in MS by *Borros Arneth* and *Jörg Kraus* (Giessen, Germany and Zell am See, Austria, respectively) covered the period 2011–2021 [4]. They summarize i) explorative and ii) clinically relevant biomarkers, and conclude that the next challenge will be validating and implementing biomarkers for different aspects of the disease in clinical practice. Three articles dealt with the real-world evidence of emerging immunotherapies for MS and their safety aspects in times of COVID-19. The narrative review by *Arkady Ovchinnikow* and *Oliver Findling* (Aarau, Switzerland) starts with an overview of the pivotal trials of the three CD20-depleting monoclonal antibodies rituximab, ocrelizumab, and ofatumumab, and the ongoing clinical trial for the third-generation CD20-depleting antibody ublituximab [7]. Moreover, they cover safety issues of CD20 depletion in times of COVID-19, as this treatment is associated with a higher chance of a blunted humoral immune response after vaccination against SARS-CoV-2 and a severe course of COVID-19. Notably, they discuss the prophylactic treatment with SARS-CoV-2-neutralizing antibodies for this subgroup of patients at risk for a detrimental COVID-19 outcome. Cladribine is a purine nucleoside analog approved in tablet form to treat highly active MS. *Tobias Moser, Tjalf Ziemssen*, and *Johann Sellner* (Salzburg and Mistelbach, Austria; Dresden, Germany) summarize the available evidence for CLAD tablets from post-marketing trials, including two observational, four long-term extension, and two comparative studies [8]. They also report that CLAD tablets appear safe regarding COVID-19 con-

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cerns, and patients mount a robust humoral immune response to SARS-CoV-2 vaccination. Natalizumab is an approved treatment for relapsing-remitting MS, for which safety during pregnancy has not been formally proven. *Klaus Berek* and coworkers' case report and review of the literature (Innsbruck, Austria) addresses the evidence for prenatal risks in the natalizumab-exposed offspring vs. the maternal risks due to rebound activity after natalizumab cessation [2]. The second case report concerns the rare but relevant differential diagnoses of atypical, inflammatory CNS lesions and the clinical utility of MR spectroscopy. In this regard, *Constanze Trostel* and coworkers (Tübingen, Germany) report the diagnostic considerations of cognitive impairment related to a tumefactive brain lesion in a woman with familial Mediterranean fever [6]. The proliferation of scientific advances and translation to clinical practice requires state-of-the-art education and hands-on training. *Isabel Voigt* and coworkers (Dresden, Germany) step in with an update on the successfully launched "Multiple Sclerosis Management" diploma course at Dresden International University [5]. This study program to acquire a Master of Science degree has gained considerable interest not only among physicians treating MS patients, and is endorsed by the German MS Society.

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