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Review

Efficacy of vaccination against influenza in patients with multiple sclerosis: The role of concomitant therapies

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ABSTRACT

Multiple sclerosis is a chronic progressive demyelinating disease affecting over 2.1 million patients worldwide. Patients affected by MS are exposed to an increased risk of infection from communicable diseases, which may lead to severe disease relapses.

Studies have analysed the issue of vaccination of MS-affected patients. These studies, however, deal mostly with safety-related issues documenting that most vaccines have been proven to be safe in MS patients and that vaccination is not associated with an increased risk of relapses. By contrast, evidence on the efficacy is comparatively scant and not yet systematised in a comprehensive picture. This aspect is however important, as both MS and its treatment alter the immune responses, a situation that may be associated with a reduced vaccine efficacy.

We have now reviewed the literature and assessed the effects of the therapy for MS on vaccine efficacy; we focused on the vaccine against influenza as for the other vaccines the information is still too scant. The majority of drugs appear not associated with a reduced response to vaccination against influenza, with the notable exception of mitoxantrone and glatiramer acetate. For a few drugs, among which natalizumab, information is not sufficiently clear and additional studies are needed to draw a definite conclusion.

These results highlight the importance to evaluate the efficacy of vaccination in patients treated with immunosuppressant drugs.

1. Introduction

Multiple sclerosis (MS) is a chronic progressive demyelinating disease of the central nervous system characterised by a complex array of symptoms that vary both over time and among individuals [1]. It affects over 2.1 million patients worldwide, has a heterogeneous course and is the second cause of disability among adults aged between 20 and 40 years [2].

In about 80–85% of the patients, MS initiates with a relapsing–remitting form(RRMS), characterised by a sequence of discrete exacerbations (relapse) and followed by partial or complete recoveries [3,4]. Other clinical manifestations such as the progressive relapsing and the primary progressive MS may also occur with lower frequency and a higher disease severity.

The introduction of a series of novel drugs has ameliorated impressively the therapy of multiple sclerosis over the last 20 years [5]. The first of these drugs has been beta-interferon (beta-IFN) 1b approved in the United States (1993) and in Europe (1995) for relapsing–remitting MS (RRMS). Subsequently, nine other disease-modifying treatments (DMTs) have been approved in the USA including beta-IFN 1a (two formulations), glatiramer acetate (GA), mitoxantrone, natalizumab, fingolimod, teriflunomide and dimethyl fumarate (Table 1). As a side effect, however, these drugs may increase the susceptibility to infections of MS patients, because of their immune-suppressive/modulating mechanism of action [6]. In addition, infections increase the risk of relapses and these, at variance with the ones occurring in non infected patients, are more easily associated with neurological

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Table 1
Currently approved and under review multiple sclerosis disease-modifying therapeutics.

Disease-modifying therapeutics	Year of approval	Available study of vaccine efficacy	Possible mechanism of interaction with vaccines
Interferon beta-1b	1993	Olberg 2014, Mehling 2013 and Schwid 2005	Various including: Decreased INF-gamma production, inhibition of antigen presentation
Interferon beta-1a (Avonex®)	1996	Olberg 2014, Mehling 2013 and Schwid 2005	–
Glatiramer acetate	1996	Olberg 2014	Shift from Th1 towards Th2 cytokines
Mitoxantrone	2000	Olberg 2014	Reduced proliferation of B- and T-lymphocytes
Interferon beta-1a (Rebif®)	2002	Olberg 2014, Mehling 2013 and Schwid 2005	–
Natalizumab	2006	Olberg 2014	Blockade of the alpha-4 subunit of the VLA-4 receptor
Fingolimod	2010	Mehling 2011	Binding to S-1-P preventing lymphocytes to exit lymph nodes
Teriflunomide	2012	Bar-Or 2013	Interference with lymphocytes proliferation
Dimethyl fumarate	2013	None	Enhancement of endogenous mechanism(s) to counteract oxidative stress
Alemtuzumab	Phase III	McCarthy 2013	CD-52 antibody-dependent cellular cytolysis
Laquinimod	Phase III	None	Inhibition of antigen presentation to T cells
Daclizumab	Phase III	Extrapolated by other pathologies	Increases in CD-56 bright NK cells
Ocrelizumab	Phase III	Extrapolated by other pathologies	CD-20 antibody-dependent B cell cytolysis

sequelae [7,8]. Vaccination represents therefore a mainstay in the prevention of communicable infectious diseases among patients with MS [6]. Vaccination, however, in MS as in many other diseases, raises concerns of safety and efficacy [9–13].

Single case reports or small case series raised safety concerns on the risk of MS relapses or early disease onset following vaccination [1,6,7]. Further analyses, however, did not confirm such a relationship [14–16], indicating an overall safety of most of vaccinations in MS patients [6].

Little information instead exists on the effects of drugs in MS patients, on the vaccination efficacy, *i.e.* the prevention of illness among vaccinated persons enrolled in controlled clinical trials, and effectiveness, *i.e.* the prevention of illness in the "real world" vaccinated population. This aspect is of relevance because several of the newly appeared drugs may interfere with the efficacy of vaccination, thus enhancing the risk of incurrence of vaccine preventable infections. In the large majority of the studies dealing with this topic, efficacy is measured by serologic conversion/response, which is thought to correlate well with immunity at the population level.

In this analysis we have reviewed the available literature and provide an updated analysis of the studies addressing the efficacy of vaccination in patients affected by MS and in therapy with the existing immune-modulating/suppressive drugs. This review is focused on the vaccination against influenza asfor the other types of vaccinations information is too scant.

2. Methods

We searched on PUBMED up to 2013 using the terms: "Vaccine" and "Multiple sclerosis". We refined the research further including beta-interferon, glatiramer acetate, mitoxantrone, natalizumab, fingolimod, teriflunomide and dimethyl fumarate as search terms alongside "Vaccine" and "Influenza Vaccine". In this analysis we considered only the trivalent inactive influenza vaccine as live-virus vaccines are not recommended for people with MS.

We carried out an initial screening by reading each abstract to identify the articles meeting these inclusion criteria, which were conclusively assessed after a thorough analysis of their content. The retrieved studies were then read in their entirety to assess appropriateness. The citations from each included articles were also examined, in order to identify any other published study potentially meeting inclusion criteria. We limited the research to the article written in English.

As many of the drugs do not share a common mechanism of action, we explored the efficacy of vaccination in each of them separately. We do not report data on corticosteroids, although immune suppressant is widely used in MS [17], due to lack of information on vaccine response in MS patients and the fact that in other settings they do not have an impact on vaccination [6,18].

Efficacy responses to vaccines may be measured with several tests; we choose in the majority of the cases the ones suggested by the EMA guidelines. We specify in the text when alternative correlates of immune protection were considered.

3. Influenza disease in MS patients

Influenza is a disease of particular concern for patients affected by MS. Influenza epidemics cause illness in about 5–20% of the United States population every year with a yearly toll of approximately 300,000 hospitalisations and 36,000 deaths [19]. Patients affected by MS appear at higher risk of influenza-related hospitalisations, with an increased relative risk of 3.57 (CI 95% 3.06–4.15), as estimated by Montgomery et al. in a Swedish cohort of more than 20,000 patients and 200,000 controls [20]. The risk of infection-associated mortality in the same cohorts was estimated to be 5.19 (CI 95% 4.90–5.50). In Fig. 1, we report the analysis we carried out on the monthly mortality for MS in the United States compared with the number of MS patients who died for pneumonia or influenza. These data arise from the centres for disease control and prevention and highlight the burden of influenza among MS patients [21]. In RRMS patients influenza infection increases not only mortality and hospitalisation, but also the risk of relapse episodes [22]. This observation arises from a study of De Keyser et al. who evaluated the effects of influenza infection in patients with RRMS and found that 33% of 36 infected patients developed an acute relapse [22].

3.1. Vaccination and untreated patients

The efficacy in untreated MS patients was evaluated in three studies [23–25]. Miller et al. carried out a placebo-controlled trial in the autumn of 1993 [24], enrolling 104 patients who received the influenza vaccine or the placebo. Patients were followed for 6 months and neurological status and occurrence of influenza assessed. Forty-nine patients received influenza vaccine and 54 received placebo but no significant difference was observed between the two groups in terms of number of patients experiencing an influenza-like illness [24]. Several reasons, such as the occurrence of pathologies caused by other pathogens, or vaccine attenuated influenza disease, may explain the absence of reduction of influenza-like illness observed among vaccinated patients. The presence of these biases in effectiveness indicates the necessity of assessing serologic and cellular responses to vaccine which are the most reliable markers of protection to natural influenza infection [25]. Indeed, in a subsequent study, based on the humoural