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Research Paper

Acetylcholine Receptor Antibody Titers and Clinical Course after Influenza Vaccination in Patients with Myasthenia Gravis: A Double-Blind Randomized Controlled Trial (ProPATIent-Trial)

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ABSTRACT

Background: It is a continuous matter of discussion whether immune activation by vaccination in general and Influenza vaccination in particular increases the risk for clinical deterioration of autoimmune diseases. This prospective study investigated the serological and clinical course of autoimmune Myasthenia gravis (MG) after a seasonal influenza vaccination.

Methods: This randomized, placebo-controlled, double-blind study enrolled MG patients with antibodies against acetylcholine-receptors (AChR-ab). They were allocated to receive seasonal influenza vaccine or placebo. The primary endpoint was the relative change of AChR-ab-titer over 12 weeks. A relative increase of 20% was set as non-inferiority margin. Secondary endpoints were clinical changes in the modified Quantitative Myasthenia Gravis Score (QMG), increase of anti-influenza-ELISA-antibodies, and changes of treatment. The study is registered with Clinicaltrialsregister.eu, EudraCT number 2006-004374-27.

Findings: 62 patients were included. Mean ± standard deviation (median) in the vaccine and placebo group were AChR-ab-titer changes of −6.0% ± 23.3% (−4.0%) and −2.8% ± 22.0% (−0.5%) and QMG score changes of −0.08 ± 0.27 (0.17) and 0.11 ± 0.31 (0.00), respectively. The difference between groups (Hodges-Lehmann estimate with 95% CI) was - for the AChR-ab-titer change 4·0% [−13.3%, 4.5%] ($p = 0.28$ for testing a difference, $p < 0.0001$ for testing non-inferiority) and for the QMG change 0·00 [−0.17, 0.00] ($p = 0.79$ for testing a difference). The occurrence of 74 adverse events (AE) was comparable between groups. The most common AE was flu-like symptoms. One serious AE (hospitalisation following gastrointestinal haemorrhage) in the verum group was not related to the vaccine.

Interpretation: Influenza vaccination in MG is safe. Uprating the potential risk of a severe course of MG exacerbation during influenza infection compared to the 95% CI differences for the endpoints, vaccination is principally indicated in this patient population.

1. Introduction

Myasthenia gravis (MG) is an antibody-mediated autoimmune neuromuscular disorder. In the vast majority of cases, T-cell dependent autoantibodies against the nicotinergic acetylcholine receptor (AChR-ab) cause exaggerated fatigability of striated skeletal muscles with amelioration after periods of rest. Pathophysiologically, MG is a hterogenous disease with an ocular manifestation, an early or late generalized onset, thymoma associated, seronegative for AChR-ab or associated with other autoantibodies like anti-MuSK or anti-LRP4 (Sommer et al., 2008; Binks et al., 2016). Although incidence and prevalence are increasing, myasthenia gravis remains a rare disease, affecting about 78 per 100,000 people world-wide (range 15–179) (Carr et al., 2010). However,

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myasthenia gravis is considered as an index disease, from which general pathophysiological principles of antibody-mediated autoimmunity have been deduced. Clinical signs include exercise-induced fatigue either of the ocular muscles alone (ocular myasthenia) or striated skeletal muscle and the ocular, facial and bulbar musculature (generalized myasthenia). Changes in AChR-ab titers correlate intra-individually with the severity of symptoms (Tzartos et al., 1982). The thymus is altered in the majority of patients with early-onset or thymoma associated MG, but data from recently published clinical trials suggest, that patients with late-onset could also benefit from thymectomy(Sommer et al., 2008; Wolfe et al., 2016) In most cases anticholinesterase drugs, immunosuppressive treatment and thymectomy result in effective disease control (Wolfe et al., 2016). Omission of anticholinesterase drugs or immunosuppressants, administration of drugs interrupting neuromuscular transmission, and infections, in particular of the upper respiratory tract and pneumonias, can cause acute exacerbations (Hohlfeld et al., 1985). The consequential myasthenic crisis is characterized by life-threatening complications with severe weakness, swallowing difficulties and respiratory failure, which requires intensive care treatment (Thomas et al., 1997).

Influenza infections are common in the general population, affecting about 5% to 20% during winter months (RKI, Robert-Koch-Institut, 2012). Patients receiving immunosuppressive treatment, including those with myasthenia gravis, are at increased risk of influenza infections. In Germany, the Standing Committee on Vaccination at the Robert Koch Institute (STIKO) recommends seasonal influenza vaccination for people over age 60 and for those with chronic diseases, including neurologic disorders (RKI, Robert-Koch-Institut, 2012). Other countries recommend influenza vaccination for the general public starting 6 months after birth (Fiore et al., 2010).

The effectiveness of vaccinations can be impaired by several factors, such as age, comorbid conditions, and concomitant medication. Conflicting results in terms of effectiveness were found in a meta-analysis of studies examining immunological response to influenza vaccination in patients who are at particular high risk for serious post-influenza complications and for whom immunization against this virus is strongly recommended. However, there was consensus that influenza vaccines were well tolerated in high risk patients, and all adverse reactions were generally mild and similar to those observed in healthy people (Brydak and Machala, 2000). The analysis included patients with pulmonary diseases, renal diseases, diabetes mellitus, cancer and haemophilia, and HIV infection. Controlled studies in patients with autoimmune disorders, however, are sparse and none have been performed in patients with myasthenia gravis. Although patients with autoimmune disorders are at increased risk of influenza infections due to immunosuppressive treatment, there is concern that vaccinations may trigger the immune system and lead to exacerbation of the underlying disease. So far, the issue of clinical or paraclinical deterioration following vaccination remains unclear and has not been systematically investigated in the setting of autoimmune disorders. Myasthenia gravis is well suited for this investigation because the AChR-ab causing the exercise-induced muscle weakness can be precisely determined. In consequence, myasthenia gravis is characterized as an index disease for all T-cell-dependent antibody-mediated autoimmune diseases. The present randomized controlled trial was the first to be conducted in order to investigate the effect of seasonal influenza vaccinations on AChR-ab-titers in patients with myasthenia gravis. Due to the index nature of MG, the results obtained in this setting may then stimulate further clinical research in other antibody-mediated autoimmune disorders.

2. Methods

2.1. Study Design

This phase IIIb prospective, double-blind, randomized, placebo-controlled study was conducted in a single centre in Germany during a period of three consecutive winter seasons. The study was done in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, the approval of all relevant institutional review boards and ethics committees, and local regulatory requirements. Ethics approval was obtained from the IRB of the Faculty of Human Medicine at the University of Marburg (Eudra-CT-Number: 2006–004374-27). Fig. 1 gives an overview of the study recruitment. The study protocol is available at https://www.clinicaltrialsregister.eu/2006-004374-27/DE.

2.2. Participants

The main eligibility criteria for the inclusion of patients were age 18–80 years, diagnosis of generalized myasthenia gravis (ICD10GM2006: G70.0), positive acetylcholine receptor antibodies, stable clinical course for at least 4 months before inclusion in the study (i. e. no impact on 'activities of daily living' with or without immunosuppressive and/or symptomatic treatment), and written informed consent. The main exclusion criteria were any vaccination in the last 9 months prior to study entry, history of serious or acute heart disease, severe cardiac dysrhythmias during the ECG at the screening visit, history of cancer, current infection or current pyrexia, known allergy to chicken proteins, severe adverse event in earlier vaccination, any contraindication for Mutagrip® according to the summary of product characteristics (SmPC), and current participation in another clinical trial. Participants were recruited from the patient pool of the neuro-immunological outpatient department at the university hospital Marburg, Germany. All patients signed written informed consent before entry into the study. Table 1 shows the demographic, clinical and therapeutic baseline characteristics of both groups.

2.3. Randomization and Masking

Patients were randomly allocated in a ratio of 1:1 to receive intramuscular injection of non-adjuvanted seasonal influenza vaccination (Mutagrip®) or placebo (0·9% NaCl solution). Absence or presence of immunosuppressive treatment was considered by stratified randomization. The Coordinating Centre for Clinical Trials at the Philipps-University in Marburg, Germany, did a centralised, concealed randomization to either DP or IP (1:1) by fax at visit 1, after the patients were enrolled into the study. The randomization sequence was computer generated. The randomization procedure was a covariate-adaptive procedure according to Rosenberger and Lachin.

In order to maintain masking of all investigators, a study nurse was employed for documentation, preparation and administration of injections. The randomization result was exclusively known by the nurse. In order to maintain masking of patients, patients were equipped with sleep masks during the injection procedure. The vaccine was provided from the hospital pharmacy in commercial pre-filled glass syringes. Since no pre-filled syringes identical in appearance were available, the placebo was provided in polycarbonate/polypropylene syringes.

2.4. Procedures

Commercially available influenza vaccine was used (Mutagrip®, Sanofi Pasteur MSD GmbH). In concurrence with the annual recommendations provided by the World Health Organization (WHO), different combinations were used for each season. The pre-filled syringes contained 0.5 mL vaccine. 0.9% NaCl solution was used as placebo. Patients received injections into the deltoid muscle. The follow-up period was 12 weeks per patient and included four visits. Patients had to return to the centre 3 (visit 3) and 12 weeks (visit 5) after the baseline visit (visit 1, screening and vaccination), respectively. Visits 2 and 4 were conducted via phone call 1 and 8 weeks after visit 1, respectively. Each patient underwent a 3-year post-study follow-up observational period by phone-call whereby participants were asked whether they had experienced influenza infections since the end of the study.

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