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A prospective, placebo controlled study on the humoral immune response to and safety of tetanus revaccination in myasthenia gravis

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ABSTRACT

Objective: To investigate the humoral immune response to and safety of a tetanus revaccination in patients with myasthenia gravis or Lambert-Eaton myasthenic syndrome.
Methods: A tetanus revaccination was administered to 66 patients. Before and 4 weeks after revaccination a blood sample and clinical outcome scores were obtained. Anti-tetanus IgG total, IgG1 and IgG4 titres were measured with an ELISA and disease-specific antibody titres (AChR, MuSK or VGCC) with a radio-immunoprecipitation assay. A historic healthy control group was used for comparing tetanus antibody titres with that of our patients. A placebo (saline) vaccination group was used to investigate the variability of clinical outcome scores with a 4 weeks interval.
Results: In 60 of 65 patients, a significant increase of the anti-tetanus antibody response was measured. Thymectomy did not have an impact on this responsiveness. Patients with immunosuppressive medication had a significantly lower pre and post titre compared to healthy controls, but their response was still significant. The titres of disease-specific antibodies were unchanged 4 weeks after revaccination. The clinical outcome scores showed no exacerbation of symptoms of the disease.
Conclusion: A tetanus revaccination in patients with myasthenia gravis or Lambert-Eaton myasthenic syndrome is safe and induces a significant immune response, irrespectively of their immunosuppressive medication. We observed neither immunological nor clinical relevant exacerbations associated with the tetanus revaccination.
Clinical trial registry: The tetanus trial is listed on clinicaltrialsregister.eu under 2014-004344-35. The placebo AChR MG group was part of another clinical trial, investigating influenza vaccination in myasthenic patients. This trial is listed on clinicaltrialsregister.eu under 2016-003138-26.

1. Introduction

Myasthenia gravis (MG) and the Lambert-Eaton myasthenic syndrome (LEMS) are acquired autoimmune diseases of the neuromuscular junction. The clinical hallmark of MG and LEMS is fluctuating muscle weakness, often in specific muscle groups [1]. The majority of MG patients have acetylcholine receptor (AChR) antibodies. Other antibodies, are found less frequently and are directed to muscle-specific kinase (MuSK) in MuSK MG or to voltage-gated calcium channels (VGCC) in LEMS. A large part of MG and LEMS patients need long-term immunosuppressive medication, because symptomatic treatment is insufficient. Due to the immunosuppres-

Abbreviations: AChR, acetylcholine receptor; ELISA, enzyme-linked immunosorbent assay; GMT, geomean titre; HC, healthy controls; IM, immunosuppressive medication; LEMS, Lambert-Eaton myasthenic syndrome; MG, myasthenia gravis; MG-ADL, MG specific Activities of Daily Living; MGC, MG Composite score; MGFA, Myasthenia gravis Foundation America classification; MuSK, muscle-specific kinase; NOACs, new oral anti-coagulants; QMG, Quantitative Myasthenia Gravis score; RIA, radio immunoprecipitation assay; TT, tetanus toxoid; VGCC, voltage-gated calcium channels.

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sive therapy, patients have an increased risk of infection [2], which can aggravate the symptoms, sometimes resulting in myasthenic crisis. For some of these infections vaccines are available. An example is the annual influenza vaccination which is recommended for all patients with an autoimmune disease. However, safety and efficacy of vaccination remain matter of debate [2]. Prospective studies in systemic lupus erythematosus and autoimmune vasculitis suggest that vaccination in these autoimmune diseases is effective [3,4] and safe [5]. Little is known about safety and effectiveness of vaccination in myasthenic patients. Tetanus toxoid is a frequently used vaccine with a well-known safety profile and antibody response in healthy individuals as well as in immunocompromised individuals with HIV or after stem cell transplantation [6,7]. Therefore, we choose this vaccine to prospectively investigate the clinical safety and humoral immune response in patients with MG or LEMS.

2. Materials and methods

2.1. Patients

This study contained 51 patients with AChR MG, 6 patients with MuSK MG, 9 patients with LEMS, a historical control group of 20 healthy individuals (HC group) revaccinated with tetanus toxoid and 23 AChR MG patients injected with a placebo (placebo AChR MG group).

2.2. Prospective tetanus vaccination study protocol

This single-centre, prospective, placebo-controlled study was performed at the Leiden University Medical Centre. A group of 66 patients, of whom 51 with AChR MG, 6 with MuSK MG, and 9 with LEMS were revaccinated with tetanus toxoid and 23 AChR MG patients received a placebo, *i.e.,* saline. At day 1 serum was obtained and clinical tests were performed before revaccination. Four weeks thereafter a second serum sample was obtained and the clinical tests were repeated.

Inclusion criteria were a confirmed diagnosis of MG or LEMS, age between 18 and 65 years and stable disease during the past 3 months. Diagnosis of MG or LEMS was based on clinical signs or symptoms suggestive of MG or LEMS and a positive serological test for AChR, MuSK or VGCC antibodies. Patients continued their medication during the study. A maximum daily dose of 30 mg of prednisolone (±5 mg) was allowed as well as the use of other immunosuppressive medication (see Table 1). Time from last pyridostigmine dose to clinical testing was kept constant in one and the same patient on the two test days, but was allowed to vary between patients. Dosage of the immunosuppressive medication had to be stable in the 3 months before revaccination till at least 4 weeks after tetanus revaccination.

The exclusion criteria were: instable disease based on medication use or a Myasthenia gravis Foundation America classification (MGFA) classification of 4 or 5, presence of a thymoma, use of vitamin K antagonist or new oral anti-coagulants (NOACs), other relevant immunosuppressive/secondary immunodeficiency conditions (not applicable on screened patients), pregnancy, no previous tetanus vaccination or tetanus revaccination in the past year.

2.3. Placebo AChR MG group

Twenty-three AChR MG patients were intramuscularly injected with a placebo (saline). These patients fulfilled the same in- and exclusion criteria and completed the same clinical outcome scores (Quantitative Myasthenia Gravis (QMG) score, MG composite (MGC) score and the MG specific activities of daily living (MG-ADL)) at the same time points, before and 4 weeks after receiving placebo.

2.4. Sampling protocol and clinical scoring

The QMG, MGC and the MG-ADL are the clinical outcome measures that were used. The QMG is a 13-item scale that measures muscle strength and endurance. The MGC is a composite scale selected from existing MG-specific scales (MG-ADL, QMG and Manual Muscle Test). The MG-ADL is a scale to assess MG symptoms that patients experience in their daily activities. For all three outcome measures, higher scores indicate more severe clinical MG [8–12]. These three clinical outcome scores were performed before and 4 weeks after tetanus revaccination. The MG-ADL was repeated by the physician by telephone at 12 weeks after revaccination.

2.5. Tetanus vaccine

A commercially available tetanus vaccine was used, manufactured by Bilthoven Biologicals (tetanus vaccine, RVG 17639) [13].

Table 1
Baseline characteristics.

	AChR MG	MuSK MG	LEMS	Total	(%)
Number of patients	50	6	9	65	
Gender, female (%)	37	3	6	46	(70.7)
Age, median years (range)	56	44.5	49.3	55	(21–65)
Duration of disease, mean years (SD)	14.6	5.5	9.7	13.1	(11.9)
MGFA classification*					
0 (%)	4	3	2	9	(13,8)
1 (%)	4	1	0	5	(7,7)
2 (%)	40	2	5	47	(72,3)
3 (%)	2	0	2	4	(6,2)
Use of immunosuppressive medication, %	46	83.3	44.4	49.2	
Prednisolone, %	14	16.7	33.3	16.9	
Mean daily dose, mg (range)	10.3	7.5	7.5		(0–15)
Azathioprine, %	30	33.3	22.2	29.2	
Mean daily dose, mg (range)	108	75	125		(25–200)
Mycophenolic acid, %	4	33.3	11.1	7.7	
Mean daily dose, mg (range)	1250	750	1500		(500–2000)
Cyclosporine, %	6	0	0	4.6	
Mean daily dose, mg (range)	140	0	0		(75–200)
Combination of immunosuppressive medication, %	18	16.7	33.3	20	
Thymectomy in the past (>1 year ago, N) (%)	29	0	0	29	(44.6)
Last tetanus vaccination, years ago (SD)	26.4	13.5	24.1	24.9	(19.5)

* MGFA classification: Myasthenia gravis foundation America classification.