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Oral Immunosuppressive Treatment of Myasthenia Gravis in Denmark: A Nationwide Drug Utilization Study, 1996-2013

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Running title: Treatment of myasthenia gravis in Denmark

Abstract: Although immunosuppressants in the treatment of myasthenia have been available for several decades, population-based studies describing drug utilization in myasthenia patients are scarce. We aimed in this study to describe the treatment of myasthenia in Denmark in more recent years with emphasis on use of oral immunosuppressant agents.

We identified a nationwide cohort of incident myasthenia patients in Denmark from 1996 to 2013 and tracked their use of drugs over the entire period using data from nationwide registers. Patients with myasthenia were classified according to utilization of specific immunosuppressants (e.g. prednisolone) as "never user" or "ever user". We used Kaplan-Meier (K-M) and Proportion of Patients Covered (PPC) curves to describe treatment onset and termination.

We identified 928 patients (52% female) with incident myasthenia in the study period. Overall, 638 (69%) were treated with prednisolone and 506 (55%) with azathioprine. Treatment with prednisolone and azathioprine within two years of myasthenia diagnosis was initiated in 462 (56%) and 366 (45%). Only one out of four myasthenia patients (n=231) did not receive oral immunosuppressive treatment at any time in the study period. Prednisolone was stopped in most patients, whereas treatment with azathioprine was often continued throughout follow-up.

In conclusion, we found that treatment of myasthenia in Denmark in recent years corresponded well to the expected clinical course of myasthenia and that most patients underwent long-term immunosuppression.

Myasthenia gravis (myasthenia) is a relatively rare autoimmune disorder characterized by focal and/or generalized fatiguable muscle weakness. In most patients with myasthenia, antibodies to components of the neuromuscular junction, usually the acetylcholine receptor (AChR), can be found [1,2].

Myasthenia patients are typically categorized according to age of onset, antibody status, thymus status and/or degree of muscle involvement (i.e., generalized myasthenia *versus* ocular myasthenia), all of which can influence treatment strategy and prognosis [1,3,4].

Pyridostigmine is the first-line treatment in myasthenia and offers relief to most patients [1,5,7]. The drug is administered almost exclusively for this indication and is initiated, with few exceptions, in all patients with myasthenia. A A large proportion of myasthenia patients also require long-term immunosuppression with glucocorticoids and/or other immunosuppressants in order to achieve sufficient symptom control [3,7]. Although immunosuppressants for the treatment of myasthenia have been available for several decades [12–15], studies describing how these drugs are used in myasthenia patients are scarce [16–19], and only two of these studies were conducted in large settings comprising multiple institutions [16,17]. To our knowledge, no previous studies have provided long-term follow-up of myasthenia patient cohorts in a nationwide setting with emphasis on immunosuppressive treatment.

Nationwide Danish registers offer unique opportunities to identify incident myasthenia patients and track their use of drugs over a significant period of time [20–23]. We used data from these population-based registers to describe the treatment of myasthenia in Denmark in more recent years with emphasis on use of oral immunosuppressant agents. Further, we compared our main findings with recommendations in published guidelines.

Materials and Methods

Using Danish nationwide registers, we identified a cohort of patients with first-ever diagnoses of myasthenia between 1996 and 2013 and tracked their use of medications for myasthenia for a median follow-up time of 6.2 years following their diagnosis.

Data Sources

We linked data from the following registries: 1) The Danish Civil Registration System [24]; 2) The Danish Patient Registry [20]; 3) The Danish Prescription Registry [21]; 4) The Danish Pathology Registry [25]; 5) The Danish Cancer Registry [26]. We also used data from an *ad hoc* registry, the Antibody Registry, created by merging test results on acetylcholine receptor antibody (AChR-ab) from two laboratories providing services for roughly half the Danish population since 1977 [22]. Our data sources have been described in more detail elsewhere [23,27].

Myasthenia guidelines

International guidelines unanimously state that pyridostigmine is the mainstay in the treatment of myasthenia [5–11]. Corticosteroids are recommended in patients where pyridostigmine provides insufficient relief, or from the outset of treatment in severe cases. According to international guidelines, corticosteroid treatment can be administered alone or in combination with another immunosuppressant, depending on efficacy and side effects of the administered corticosteroid [6,9,11].

Treatment of myasthenia in Denmark is primarily undertaken by neurologists affiliated to one of the four university hospital-based centres in the country. National guidelines on myasthenia treatment in Denmark have only been available since 2011. According to the first version of these guidelines,

steroid-sparing agents are preferable to corticosteroid treatment, due to the side-effects of the

latter [28,29]. Accordingly, physicians are encouraged to initiate treatment with non-steroidal

immunosuppressants soon after corticosteroids are initiated, and, further, to taper corticosteroids

to the lowest efficient dose [30]. Azathioprine is recommended as the first line of non-steroidal-

immunosuppressant in patients in need of long-term immunosuppression.

Identifying myasthenia patients

We identified discharges (1977-2013) and outpatient visits (1995-2013) with a diagnosis code of

myasthenia in the Patient Registry [20]. From the National Prescription Registry, we retrieved all

information on dispensed prescriptions for pyridostigmine during 1995 through 2014. In the

Antibody Registry, patients with a recorded positive AChR-ab test were identified and the first date

of a positive test was noted.

Using a validated method [22], we classified patients as suffering from myasthenia when they met

both of following criteria: (i) a primary diagnosis code of myasthenia in the Patient Registry; and (ii)

at least two pyridostigmine prescriptions in the Prescription Registry (Fig.1).

We defined myasthenia onset as the earliest date of the following events: date of diagnosis code or

the date of the first pyridostigmine prescription. Based on this date, we calculated the age at onset

of myasthenia and the duration of myasthenia. Patients were classified into early onset *versus* late

onset myasthenia (<50 *versus* ≥50 years at date of diagnosis).

We wished only to include incident cases of myasthenia in the study and therefore we excluded

patients with a myasthenia diagnosis, or a presented prescription of pyridostigmine prior to 1996.

Further, we also excluded patients with positive AChR-ab test results dating prior to 1996.

Assessment of use of medications and statistical analyses

We retrieved all information on prescriptions presented by the cohort of myasthenia patients during 1995 to 2014 from the Prescription Registry.

According to the number of presented prescriptions for each drug, we classified patients as "never users" (0 prescriptions) or "ever users" (>=1 prescriptions) of prednisolone, azathioprine or "other IS" (i.e., methotrexate, tacrolimus, mycophenolate mofitil, cyclosporine or cyclophosphamide). For each drug, we defined initiation of therapy as the date of the first presented prescription for the drug in question. In the analyses, we included prescriptions for oral immunosuppressants after the myasthenia onset date. Further, we also included prescriptions for these drugs presented six months prior to diagnosis date, as such use is likely to be myasthenia-related.

Immunosuppressant "ever use" and use within two years of myasthenia onset was tabulated for early- and late onset myasthenia. The 2-year period was chosen because the vast majority of myasthenia patients reach nadir (i.e., their most severe myasthenia symptoms) within two years of onset [31]. The use of immunosuppressants was also tabulated for two 8-year time periods (1996-2003 *versus* 2004-2011) to explore temporal trends in the treatment of myasthenia. In this analysis, we excluded incident myasthenia patients with onset after 2011 to insure a minimum of two years of follow-up.

We also classified myasthenia patients according to regimens of immunosuppressive treatment, i.e., (i) no immunosuppressant, (ii) ever-use of prednisolone only, (iii) ever-use of azathioprine only, (iv) ever-use of azathioprine and prednisolone, (v) ever-use of prednisolone and/or azathioprine and "other IS". All groups are mutually exclusive.

We used Kaplan-Meier curves (K-M) to visually asses the (i) time between myasthenia onset and first immunosuppressant prescription; and (ii) duration of the first episode of treatment with prednisolone or azathioprine, i.e., the time from treatment onset to termination of treatment. Date of termination of the first treatment episode was identified as (i) the date of the latest prescription (plus 240 days) for the drug in question that was not followed by prescription renewal within the 240 days; (ii) death of the patient; and (iii) end of study period (1.1.2014). We also applied the proportion of patients covered (PPC) method to illustrate the proportion of myasthenia patients treated with prednisolone and azathioprine. Use of this method allowed us to consider multiple treatment episodes, e.g., patients who stopped corticosteroids for a period and then re-started the drug for one of more times. We thus estimated the proportion of patients with myasthenia at a given time point that were treated with the drug in question. PPC is shown to be less sensitive to assumptions regarding duration of a single prescription and provides a valuable supplement to K-M [32]. For PPC, treatment was considered as stopped 240 days after the latest presented prescription in the period 2004 through 2011. The long interval of 240 days used in both K-M and PPC calculations was chosen in an effort to minimize misclassification of continued treatment as treatment termination.

Supplementary analyses

To visually inspect the effect of varying assumptions on length of prescription duration, we produced separate K-M plots and PPC graphs of treatment termination, with the length of prescription duration for prednisolone set at 60 days, 120 days and 240 days, respectively.

The study was approved by the Danish Data Protection Agency and the Danish Medicines Agency (Lægemiddelstyrelsen) in accordance with Danish law on studies based exclusively on registries. Consent from the Danish Ethics Committee is not required for register-linkage studies.

Results

We identified 928 patients with incident myasthenia during the study period (1996-2013) with a median follow-up time of 6.2 years. Overall, there was a slight female predominance (52% (95%CI 49-55) *versus* 48% (95% CI 45-51)) and 72 percent (95% CI 69-75) were classified as late-onset myasthenia (Table 1). Thymoma was diagnosed in 9% (95% CI 7-11) (n=85) of myasthenia patients (Table 1). Approximately 75% (95%CI 72-78) of patients with myasthenia had at some point after myasthenia onset been treated with an immunosuppressant. A total of 628 (69% (95%CI 66-72)) myasthenia patients were at some point treated with prednisolone and a slightly smaller proportion of patients had been prescribed azathioprine (55% (95% CI 52-58)). Only modest variations in ever use of these drugs were seen in subgroups defined by sex (men *versus* women) or age at onset (late-onset *versus* early-onset) (Table 2a). Treatment with prednisolone and azathioprine within 2 years of diagnosis was initiated in 56% (95% CI 53-60) (n=462) and 45% (95% CI 42-48) (n=366), respectively (Table 2b). Women with early-onset myasthenia were the group with the lowest proportion treated with prednisolone, compared with the other groups (44% (95% CI 37-52) *versus* 52% (95% CI 40-64)-64% (95% CI 58-70)) (Table 2b). A trend towards more frequent use of immunosuppressant treatment among early-onset patients with myasthenia was found in the later of the two time periods compared (any immunosuppressant treatment: 47% (95% CI 39-57) in 1996-2003 *versus* 58% (95% CI 49-67) in 2004-2011), (Table 3). Comparable treatment patterns were found among late-onset myasthenia in the two time periods (Table 3). Regimens of immunosuppressant treatment during follow-up are presented in Table 4. The majority of patients had received treatment with both prednisolone and azathioprine (38% (95% CI 35-41)), and a further 11% (95% CI 9-13) of patients had been treated with one or both of these drugs and a prednisolone-sparing immunosuppressant other than azathioprine. However, about 20% of patients had received therapy with only one type of immunosuppressant during follow-up, i.e., prednisolone (19% (95% CI 17-22)), or azathioprine (5% (95% CI 4-7)) (Table 4). Finally, one quarter of myasthenia patients were never treated with immunosuppressants of any type (25% (95% CI 22-28)). A K-M plot illustrating

initiation of treatment for prednisolone and azathioprine (regardless of regimen, i.e., in mono- or polytherapy) showed that treatment was initiated within two years of myasthenia onset for the vast majority of patients (Fig. 2). It was also found that fewer early-onset myasthenia patients were treated with prednisolone and that the drug was started with a greater delay than among late-onset myasthenia patients (Fig. 2). In plots illustrating persistence with prednisolone and azathioprine (K-M and PPC), we found that prednisolone was stopped in most patients, whereas treatment with azathioprine was continued throughout follow-up in the majority of patients using this drug (Fig. 3A-D). The PPC graphs indicated that terminated treatments of these drugs may be re-initiated in the long run, particularly so for azathioprine. (Fig. 3A-D).

In a sensitivity analysis where we varied the assumptions regarding prescription duration of prednisolone, we found that the number of patients terminating their therapy was inversely related to the assigned duration of the prescription in the K-M plots. By contrast, in PPC plots, varying prescription duration assumptions resulted in minor changes in proportions of patients treated (Fig. 4).

Discussion

In this nationwide study of myasthenia patients, we found that most patients were treated with prednisolone and/or azathioprine and that this treatment was usually initiated within two years of myasthenia onset. Further, we found that treatment with azathioprine was less likely to be stopped whereas treatment with prednisolone was often discontinued in the long term. To our knowledge, this is the first study to describe the course of medical treatment of myasthenia in a nationwide setting over an extensive period of time.

Our findings are in line with recently published guidelines [5,6,9,11] where it is recommended, in mild to moderate myasthenia, to start with pyridostigmine as monotherapy using an escalation protocol, typically reaching peak dose within weeks. If the symptoms are not relieved by

pyridostigmine, treatment with corticosteroids, alone or in combination with a steroid sparing immunosuppressant, is recommended. Further, it is suggested that corticosteroids should be tapered to the lowest possible dose when treatment goals are achieved. Thus, our findings on use of prednisolone and azathioprine in a real-world setting reflect guideline recommendations.

Studies describing drug utilization in myasthenia patients are sparse. A population-based Norwegian study by Andersen *et al.* reported that 51% of myasthenia patients received immunomodulating treatment, a proportion which is considerably lower than in our study (16). The follow-up in the study from Norway was shorter and the cohort most likely consisted of both prevalent and incident myasthenia patients, which may have influenced the results, e.g., due to inclusion of patients with prevalent myasthenia that no longer were in need of immunosuppressant treatment. In a study from Israel comprising 137 patients with myasthenia followed at one centre, 72% of patients younger than 70 years and 65% of patients older than 70 years were treated with corticosteroids [18]. Again, this study may have been affected by the inclusion of prevalent cases. In another single-centre study of patients with generalized myasthenia in Hong Kong Chinese, 76% of patients were treated with prednisolone and 59% with azathioprine [19]. Comparisons across the above-mentioned studies are not straightforward due to differences in settings, type of myasthenia patients included (i.e., all types *versus* generalized only), and possibly local predilections for particular immunosuppressant drugs. In spite of these potential differences, the results of the present study seem in line with the sparse previous reports [16,18,19].

In our study, we applied K-M plots to evaluate initiation and discontinuation of therapy. We found that treatment with immunosuppressants often was initiated within two years of myasthenia onset, which is consistent with the clinical course described by Grob *et al.* [31] and in accordance with guidelines. Evaluation of drug discontinuation and possible remission of disease is, however, more difficult to assess using the K-M plot, since this method only considers the patients' first treatment

period and therefore does not take into consideration that patients may re-initiate treatment, e.g. due to worsening of symptoms. Also, the K-M plot is sensitive to assumptions regarding prescription duration and therefore more prone to misclassification. To overcome this shortcoming, we also included a more robust method, i.e., the proportion of patients covered (PPC) method [32], which includes information on all treatment episodes and provides data on how many patients are treated with a given drug at a given time point. We applied this method to prednisolone and azathioprine treatment in the present study. Our results show that use of Kaplan-Meier plots only to evaluate the proportion of patients using immunosuppressants would have led to considerable underestimation of long-term use of these drugs in myasthenia treatment. The PPC graphs, when compared to K-M plots, are compatible with the relapsing nature of myasthenia, and further indicate that immunosuppressant treatment is necessary for very long time periods in the majority of patients with myasthenia where such treatment is initiated. Finally, the high degree of continuation or re-initiation of azathioprine therapy indicates that this drug is generally well tolerated.

Our study has a number of strengths. We identified patients with myasthenia in Denmark using a simple, validated algorithm based on presented prescriptions of pyridostigmine and a register diagnosis of myasthenia [22]. Access to health services is free of charge in Denmark and expenses towards pyridostigmine are partially reimbursed. Further, all prescriptions for pyridostigmine presented at community pharmacies are recorded in the Prescription Registry [21]. The method employed to identify patients with myasthenia nationwidely reduced selection bias.

Another major strength of our study is that we utilized nationwide data gathered in registers that are continuously updated which eliminated recall bias and which may otherwise be particularly problematic in studies assessing long-term use of multiple drugs.

Our study also has a number of potential weaknesses. Firstly, we did not assess patients clinically, but based our diagnosis exclusively on register data. However, the algorithm used in the present study has been estimated to have a sensitivity of 88% and a positive predictive value of 93% [22]. Secondly, we had no information on severity and progression of the disease in the individual patient and we were therefore not able to evaluate the indication for initiating or terminating treatment. Thirdly, lack of information on type of myasthenia prevented us from assessing long-term treatment of ocular *versus* generalized myasthenia. Fourthly, we only included oral immunosuppressant treatment in our study. We had no information on rituximab which is increasingly being used to treat severe myasthenia unresponsive to other immunosuppressant treatments. However, the number of myasthenia patients on this therapy in Denmark is still limited; this is also true of use of repeated immunoglobuline infusions or plasmapheresis in patients who are not suffering from myasthenia crisis (David Gaist, personal communication). Finally, patients with thymoma may have been misclassified to some extent, due to lack of complete data on this malignant disorder prior to 1997.

In conclusion, we found that treatment of myasthenia in Denmark in recent years corresponded well to the expected clinical course of the disorder and that most patients underwent long-term immunosuppression. Automated medical and administrative registers can be used to evaluate long-term myasthenia treatment. Certain limitations of these sources could be overcome by addition of minimal data sets collected in the clinics with information on, e.g., myasthenia type and severity.

Conflict of interest

The authors report no conflicts of interest in this work.

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[1]   Gilhus NE, Verschuuren JJ. Myasthenia gravis: subgroup classification and therapeutic strategies. Lancet Neurol 2015;14:1023–36. doi:10.1016/S1474-4422(15)00145-3.

[2]   Meriggioli MN, Sanders DB. Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity. Lancet Neurol 2009;8:475–90. doi:10.1016/S1474-4422(09)70063-8.

[3]   Gilhus NE, Skeie GO, Romi F, Lazaridis K, Zisimopoulou P, Tzartos S. Myasthenia gravis — autoantibody characteristics and their implications for therapy. Nat Rev Neurol 2016;12:259–68. doi:10.1038/nrneurol.2016.44.

[4]   Guptill JT, Soni M, Meriggioli MN. Current Treatment, Emerging Translational Therapies, and New Therapeutic Targets for Autoimmune Myasthenia Gravis. Neurotherapeutics 2016;13:118–31. doi:10.1007/s13311-015-0398-y.

[5]   Sanders DB, Wolfe GI, Benatar M, Evoli A, Gilhus NE, Illa I, et al. International consensus guidance for management of myasthenia gravis Executive summary. Neurology 2016;87:419–25. doi:10.1212/WNL.0000000000002790.

[6]   Melzer N, Ruck T, Fuhr P, Gold R, Hohlfeld R, Marx A, et al. Clinical features, pathogenesis, and treatment of myasthenia gravis: a supplement to the Guidelines of the German Neurological Society. J Neurol 2016;263:1473–94. doi:10.1007/s00415-016-8045-z.

[7]   Skeie GO, Apostolski S, Evoli A, Gilhus NE, Illa I, Harms L, et al. Guidelines for treatment of autoimmune neuromuscular transmission disorders. Eur J Neurol 2010;17:893–902. doi:10.1111/j.1468-1331.2010.03019.x.

[8]   Kerty E, Elsais A, Argov Z, Evoli A, Gilhus NE. EFNS/ ENS Guidelines for the treatment of ocular myasthenia. Eur J Neurol 2014;21:687–93. doi:10.1111/ene.12359.

[9]   Nicolle MW. Myasthenia Gravis and Lambert-Eaton Myasthenic Syndrome. Contin Minneap Minn 2016;22:1978–2005. doi:10.1212/CON.0000000000000415.

[10]   Gilhus NE. Myasthenia Gravis. N Engl J Med 2016;375:2570–81. doi:10.1056/NEJMra1602678.

[11]   Sussman J, Farrugia ME, Maddison P, Hill M, Leite MI, Hilton-Jones D. Myasthenia gravis: Association of British Neurologists' management guidelines. Pract Neurol 2015;15:199–206.

[12]   Schwarz H. Mestinon (Pyridostigmine Bromide) in Myasthenia Gravis. Can Med Assoc J 1956;75:98–100.

[13]   Lindberg C, Andersen O, Lefvert AK. Treatment of myasthenia gravis with methylprednisolone pulse: a double blind study. Acta Neurol Scand 1998;97:370–3. doi:10.1111/j.1600-0404.1998.tb05968.x.

[14]   Palace J, Newsom-Davis J, Lecky B. A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis. Myasthenia Gravis Study Group. Neurology 1998;50:1778–83.

[15]   Tindall RSA, Rollins JA, Phillips JT, Greenlee RG, Wells L, Belendiuk G. Preliminary Results of a Double-Blind, Randomized, Placebo-Controlled Trial of Cyclosporine in Myasthenia Gravis. N Engl J Med 1987;316:719–24. doi:10.1056/NEJM198703193161205.

[16]   Andersen JB, Owe JF, Engeland A, Gilhus NE. Total drug treatment and comorbidity in

myasthenia gravis: a population-based cohort study. Eur J Neurol 2014;21:948–55. doi:10.1111/ene.12439.

[17] Ramos-Fransi A, Rojas-García R, Segovia S, Márquez-Infante C, Pardo J, Coll-Cantí J, et al. Myasthenia gravis: descriptive analysis of life-threatening events in a recent nationwide registry. Eur J Neurol 2015;22:1056–61. doi:10.1111/ene.12703.

[18] Hellmann MA, Mosberg-Galili R, Steiner I. Myasthenia gravis in the elderly. J Neurol Sci 2013;325:1–5. doi:10.1016/j.jns.2012.10.028.

[19] Lee CY, Lam CL, Pang SYY, Lau KK, Teo KC, Chang RSK, et al. Clinical outcome of generalized myasthenia gravis in Hong Kong Chinese. J Neuroimmunol 2015;289:177–81. doi:10.1016/j.jneuroim.2015.10.018.

[20] Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol 2015;7:449–90. doi:10.2147/CLEP.S91125.

[21] Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data Resource Profile: The Danish National Prescription Registry. Int J Epidemiol 2017;46:798–798f. doi:10.1093/ije/dyw213.

[22] Pedersen EG, Hallas J, Hansen K, Jensen PEH, Gaist D. Identifying Patients with Myasthenia for Epidemiological Research by Linkage of Automated Registers. Neuroepidemiology 2011;37:120–8. doi:10.1159/000331481.

[23] Pedersen EG, Pottegård A, Hallas J, Friis S, Hansen K, Jensen PEH, et al. Use of azathioprine for non-thymoma myasthenia and risk of cancer: a nationwide case-control study in Denmark. Eur J Neurol 2013;20:942–8. doi:10.1111/ene.12108.

[24] Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol 2014;29:541–9. doi:10.1007/s10654-014-9930-3.

[25] Bjerregaard B, Larsen OB. The Danish Pathology Register. Scand J Public Health 2011;39:72–4. doi:10.1177/1403494810393563.

[26] Gjerstorff ML. The Danish Cancer Registry. Scand J Public Health 2011;39:42–5. doi:10.1177/1403494810393562.

[27] Pedersen EG, Hallas J, Hansen K, Jensen PEH, Gaist D. Late-onset myasthenia not on the increase: a nationwide register study in Denmark, 1996-2009. Eur J Neurol 2013;20:309–14. doi:10.1111/j.1468-1331.2012.03850.x.

[28] Waljee AK, Rogers MAM, Lin P, Singal AG, Stein JD, Marks RM, et al. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. BMJ 2017;357:j1415.

[29] McDonough AK, Curtis JR, Saag KG. The epidemiology of glucocorticoid-associated adverse events. Curr Opin Rheumatol 2008;20:131–7. doi:10.1097/BOR.0b013e3282f51031.

[30] Danish Myasthenia Guidelines. Dan Soc Neurol n.d. http://neuro.dk/wordpress/kliniske-retningslinjer/danske-behandlingsvejledninger/.

[31] Grob D, Arsura EL, Brunner NG, Namba T. The Course of Myasthenia Gravis and Therapies Affecting Outcomea. Ann N Y Acad Sci 1987;505:472–99. doi:10.1111/j.1749-6632.1987.tb51317.x.

[32] Rasmussen L, Pratt N, Hansen MR, Hallas J, Pottegård A. Using the "Proportion of Patients Covered" and the Kaplan-Meier Survival Analysis to describe Treatment Persistence. (Under review) n.d.

Table 1. Characteristics of incident myasthenia patients, 1996-2013.

	Numbers (%)
Women	484 (52.2)
Men	444 (47.8)
Age at myasthenia onset, years	
<50	263 (28.3)
50-70	335 (36.1)
>70	330 (36.6)
Duration of follow-up from the time of diagnosis, years[1]	
<5	390 (42.0)
5-10	294 (31.7)
>10	244 (26.3)
Co-morbidity[2]	
Thymoma	85 (9.2)
Diabetes	158 (17.0)
Inflammatory bowel disease	14 (1.5)
Rheumatoid arthritis	13 (1.4)
Polymyalgia rheumatica	20 (2.2)

1. From onset of myasthenia to end of follow-up, i.e. death, migration or end of study (1.1.2014) whichever came first

2. Ever registration of diagnosis in the National Patient Registry

Table 2 Use of immunosuppressants in the treatment of myasthenia in Denmark, 1996-2013. (A) Ever use, (B) Use within 2 years of myasthenia diagnosis (1996-2011)[1]. Numbers (percentages) unless otherwise stated.

A. Ever use, 1996-2013

	Early-onset[2]			Late-onset[3]		
	Men	Women	Total	Men	Women	Total
	(n=82)	(n=190)	(n=272)	(n=362)	(n=294)	(n=656)
Prednisolone	57 (69.5)	118 (62.1)	175 (64.3)	252 (69.6)	211 (71.2)	463 (70.1)
Azathioprine	48 (58.5)	109 (57.4)	157 (57.7)	197 (54.4)	152 (51.7)	349 (53.2)
Other IS[4]	11 (13.4)	43 (22.6)	54 (19.9)	26 (7.2)	46 (15.6)	72 (11.0)
Any of above	64 (78.0)	135 (71.1)	195 (71.7)	272 (75.1)	226 (76.9)	464 (70.7)

B. Within 2 years of myasthenia diagnosis, 1996-2011[1]

	Early-onset[2]			Late-onset[3]		
	Men	Women	Total	Men	Women	Total
	(n=75)	(n=176)	(n=251)	(n=318)	(n=253)	(n=571)
Prednisolone	39 (52.0)	77 (43.8)	116 (46.2)	185 (58.2)	161 (63.6)	346 (60.6)
Azathioprine	33 (44.0)	71 (40.3)	104 (41.4)	144 (45.3)	118 (46.6)	262 (45.9)
Other IS[4]	< 5	< 20	20 (8.0)	10 (3.1)	22 (8.7)	32 (5.6)
Any of above	44 (58.7)	88 (50.0)	132 (52.6)	201 (63.2)	177 (70.0)	378 (66.2)

[1]Incident myasthenia patients after 2011 are excluded to insure two years of follow-up

[2]Myasthenia-onset < 50 years

[3]Myasthenia-onset ≥ 50 years

[4]Methotrexate, cyclosporine, tacrolimus, cyclophosphamide, mycophenolate mofetil.

Table 3. Trends in the treatment of myasthenia in Denmark, 1996-2013. (A) Treatment within two years of myasthenia onset of incident myasthenia patients 1996-2003, (B) Treatment within two years of myasthenia onset of incident myasthenia patients 2004-2011[1]. Numbers (percentages) unless otherwise stated.

A. 1996-2003 (n=366)

	Early-onset[2]			Late-onset[3]		
	Men	Women	Total	Men	Women	Total
	(n=40)	(n=83)	(n=123)	(n=128)	(n=115)	(n=243)
Prednisolone	17 (42.5)	31 (37.3)	48 (39.0)	74 (57.8)	74 (64.3)	148 (60.9)
Azathioprine	14 (35.0)	30 (36.1)	44 (35.8)	57 (44.5)	59 (51.3)	116 (47.7)
Other IS[4]	< 5	< 5	< 5	< 5	< 15	12 (4.9)
Any of above	20 (50.0)	38 (45.8)	58 (47.2)	80 (62.5)	82 (71.3)	162 (66.7)

B. 2004-2011 (n=456)

	Early-onset[2]			Late-onset[3]		
	Men	Women	Total	Men	Women	Total
	(n=35)	(n=93)	(n=128)	(n=190)	(n=138)	(n=328)
Prednisolone	22 (62.9)	46 (49.5)	68 (53.1)	111 (58.4)	87 (63.0)	198 (60.4)
Azathioprine	19 (54.3)	41 (44.1)	60 (46.9)	87 (45.8)	59 (42.8)	146 (44.5)
Other IS[4]	< 5	< 15	15 (11.7)	8 (4.2)	12 (8.7)	20 (6.1)
Any of above	24 (68.6)	50 (53.8)	74 (57.8)	121 (63.7)	95 (68.8)	216 (65.9)

[1] Incident myasthenia patients after 2011 are excluded to insure two years of follow-up
[2] Myasthenia-onset < 50 years
[3] Myasthenia-onset ≥ 50 years

[4] Methotrexate, ciclosporine, tacrolimus, cyclophosphamide, mycophenolate mofetil.

Table 4. Regimens of immunosuppressive treatment of myasthenia in Denmark, 1996-2013.

Numbers (percentages) unless otherwise stated.

	Early-onset[1]		Late-onset[2]		Total
Use of immunosuppressive drugs	Men	Women	Men	Women	
	(n=82)	(n=190)	(n=362)	(n=294)	(n=928[5])
Never use (pyridostigmine only)	18 (22.0)	55 (28.9)	90 (24.9)	68 (23.1)	231 (24.9)
Ever use					
Prednisolone, only[3]	15 (18.3)	21 (11.1)	73 (20.2)	64 (21.8)	173 (18.6)
Azathioprine, only[3]	6 (7.3)	12 (6.3)	18 (5.0)	10 (3.4)	46 (5.0)
Prednisolone and azathioprine	32 (39.0)	59 (31.1)	155 (42.8)	106 (36.1)	352 (37.9)
Prednisolone/azathioprine & Other IS[4]	10 (12.2)	35 (18.4)	23 (6.4)	34 (11.6)	102 (11.0)

[1]Myasthenia-onset < 50 years

[2]Myasthenia-onset ≥ 50 years

[3]In combination with pyridostigmine

[4]Methotrexate, ciclosporine, tacrolimus, cyclophosphamide, mycophenolate mofetil.

[5]The group "Other IS, only" is not included in the table hence the total number dos not in the "Total column" add up to 928.

Fig. 1 Identification of potential incident cases of myasthenia gravis in nationwide Danish registers.
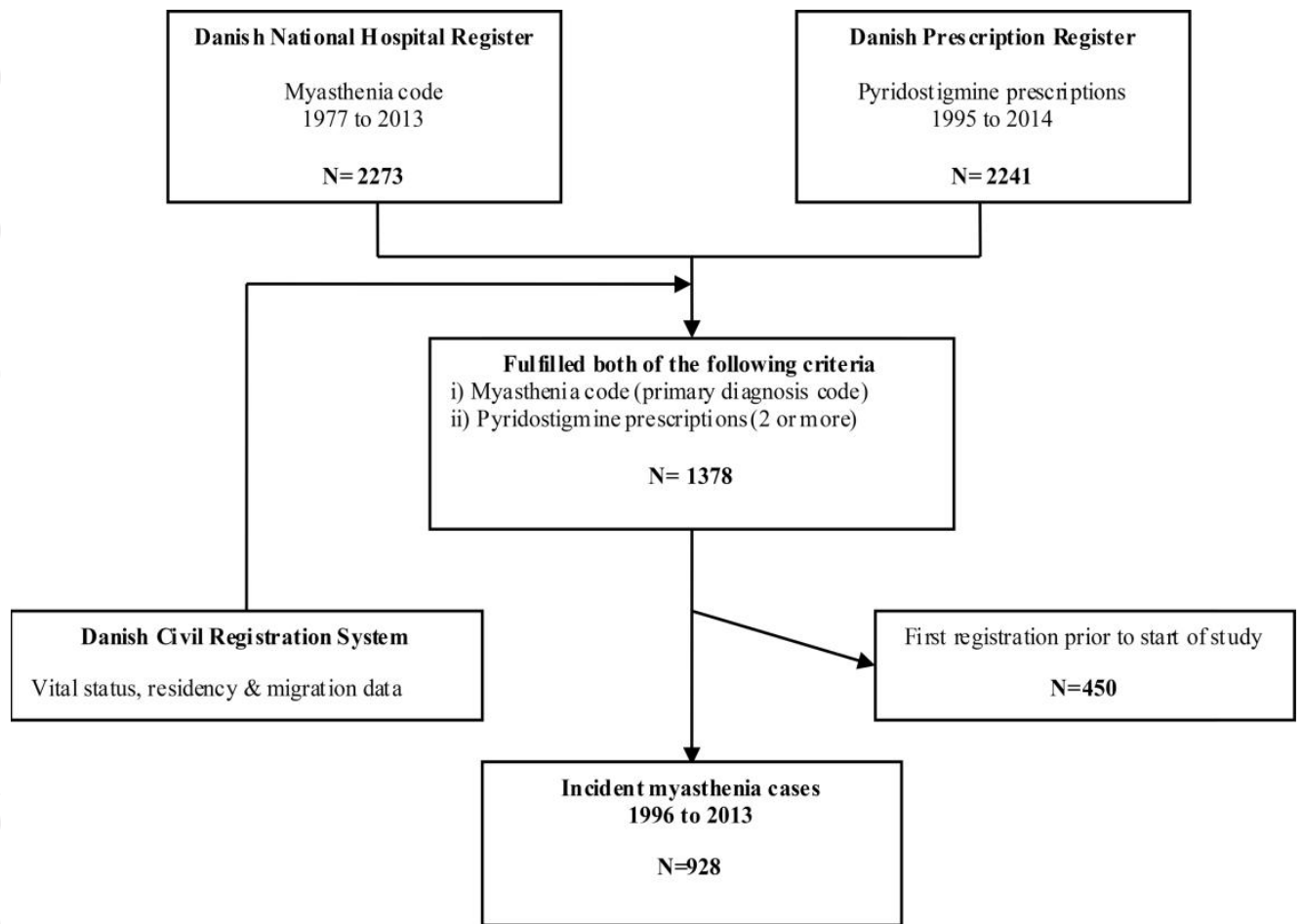
Fig.2 Initiation of therapy in early- and late-onset myasthenia in Denmark, 1996-2013. Kaplan-Meier

plots A-B. (A) prednisolone, (B) azathioprine.

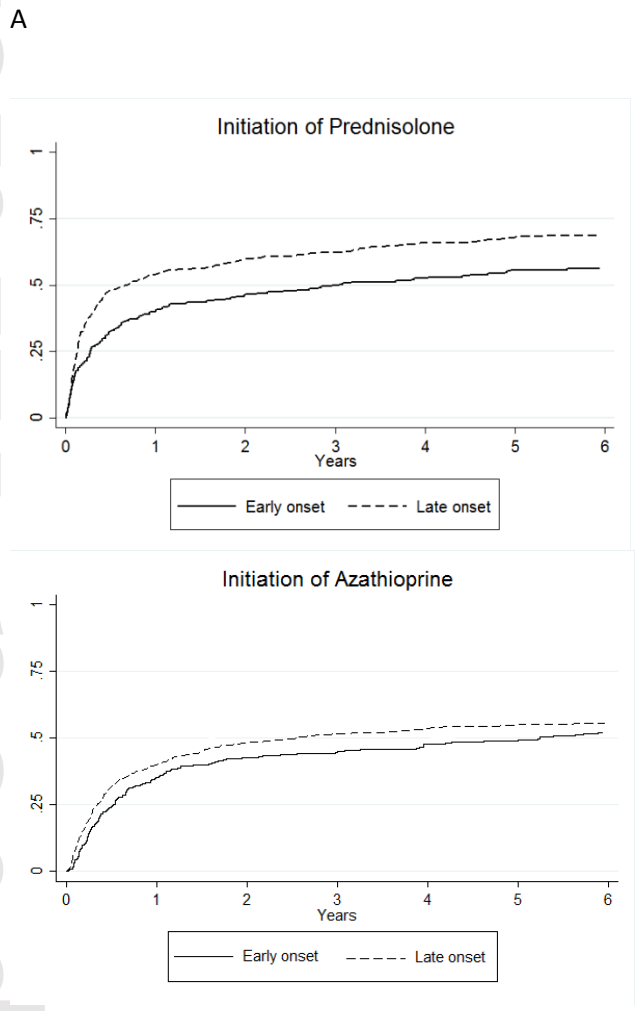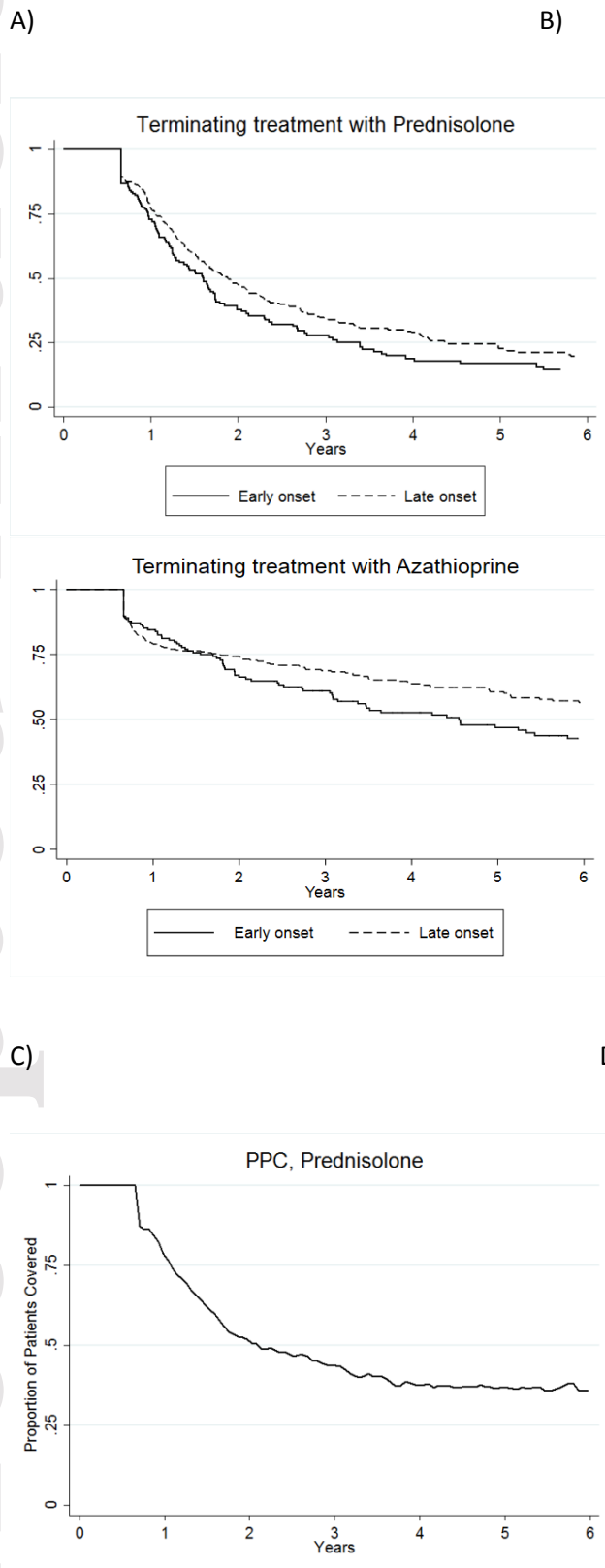A   B

Fig.3 Termination of therapy in early- and late-onset myasthenia in Denmark, 1996-2013. Kaplan-Meier plots A+B, Proportion of Patients Covered C+D.
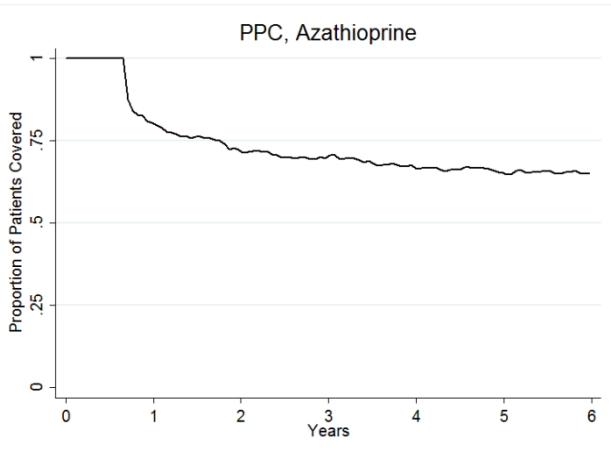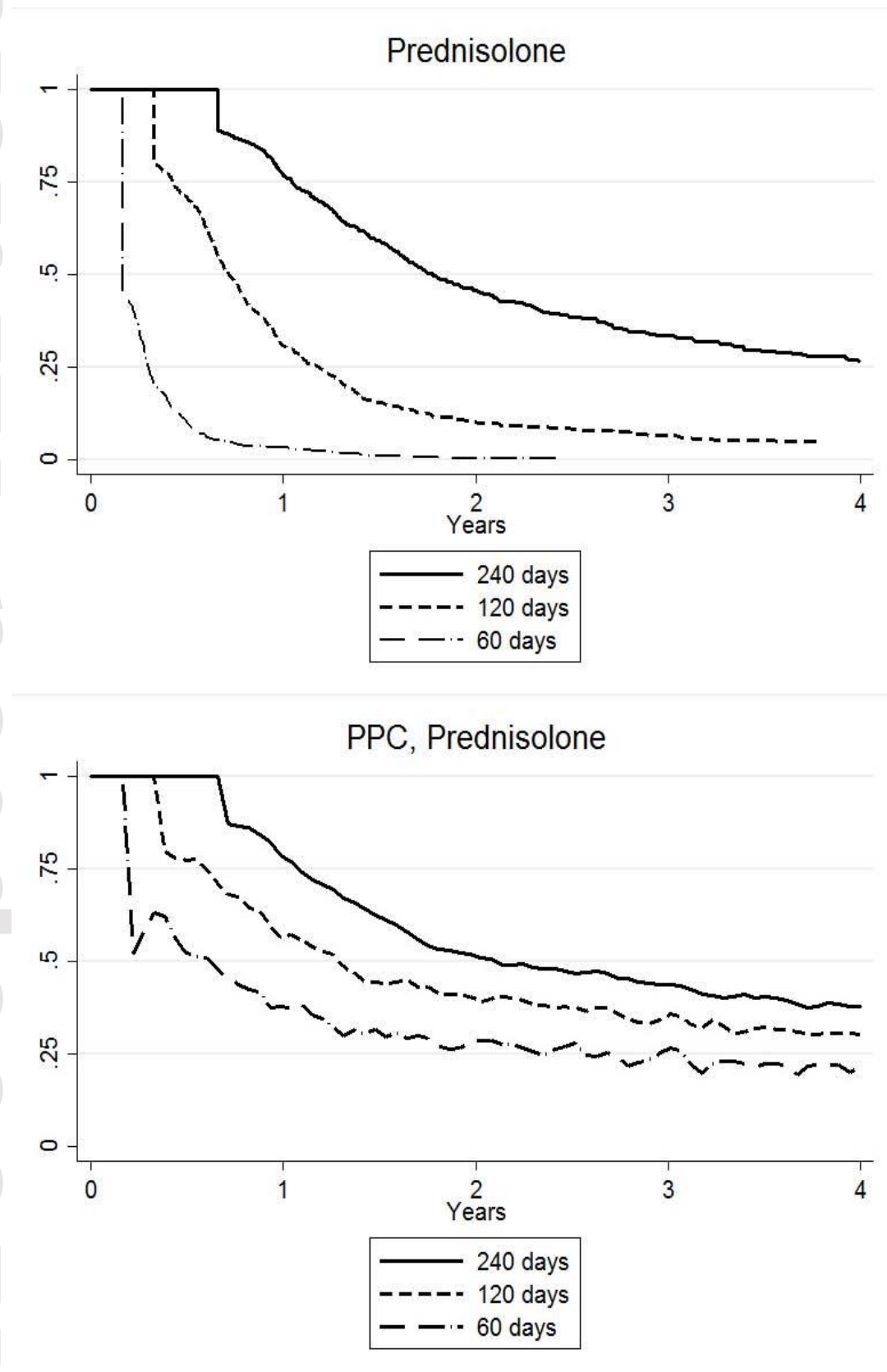
A)

B)

C)

D)

PPC, Azathioprine

Fig. 4 K-M plot and PPC plot of termination of prednisolone in myasthenia patients by assigned duration (days) of presented prescriptions.

Appendix

List of codes used in the analysis

Hospital discharges codes

Myasthenia

ICD-8: 73309

ICD-10 DG700

Diabetes

ICD-8: 249.00, 249.09, 250.00, 250.09

ICD-10: E10-E14

Rheamatoid arthritis

ICD-8: 71219, 71239

ICD-10: M050, M051, M060

Inflammatory bowel disease

ICD-8: 56301, 56319, 56904,

ICD-10: K50, K510, K511, K512, K513

Thymoma

ICD-8: 226.19, 194.29

ICD-10: DD38.4, DC37.9

Anatomical Therapeutic Classification Codes (ATC)

Pyridostigmine

N07AA02

Anti-diabetics

A10

Azathioprine

L04AX01

Other immuosuppressants

L04AX03 (methotrexate), L04AD01 (cyclosporine), L04AD02

(tacrolimus), L01AA01 (cyclophosphamide), L04AA06 (mycophenolate

mofetil)

Pathology Registry codes (SNOMED)

Thymoma

M85800, M85801, M85803, M85804, M85806, M85807,

M85811, M85821, M85831, M85841, M85851