MAKING THERAPEUTIC DECISIONS IN NEUROIMMUNOLOGY – ISSUES TO BE CONSIDERED

PhD Thesis

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LIST OF ABBREVIATIONS

CNS	central nervous system
MS	multiple sclerosis
RR	relapsing-remitting
SP	secondary progressive
PP	primary progressive
EDSS	Expanded Disability Status Scale
EAE	experimental autoimmune encephalomyelitis
MAG	myelin associated glycoprotein
MG	myasthenia gravis
MC	myasthenic crisis
AchR	acetylcholine-receptor
AchR Abs	acetylcholine receptor antibodies
MusK R	Muscle specific Kinase Receptor
MusK Abs	MusK Receptor antibodies
Anti-Ti Abs	titin antibodies
AZA	azathioprin
PR	methylprednisolone or prednisolone
GA	glatiramer acetate
INFB-1b	interferone beta 1-b
INFB-1a	interferone beta 1-a
LHON	Leber's hereditary optic neuropathy
Mt-DNS	mitochondrial DNA
CoQ	coenzyme Q
NADH	reduced nicotinamide adenine dinucleotide
GSH	reduced glutathione
CTLA4	cytotoxic T-lymphocyte-associated antigen-4
3'UTR	3' untranslated region
ON	optic neuritis

INTRODUCTION

Neuroimmunology covers diseases of central and peripheral nervous system with immunological involvement. Most of the neuroimmunological diseases are of autoimmune origin. Such diseases can be classified according to their pathogenesis, they can be primary diseases of the nervous system or systemic diseases with nervous system involvement. On the other hand, immune-mediated processes can affect different neurological structures: the central nervous system, the peripheral nerves or the neuromuscular junction.

The exact definition of the syndromes plays an important role in the selection of the exact therapy: since diseases with similar symptoms can be of different pathophysiological origin therefore the potentially effective treatments can be distinct.

The studies that underlie these theses were conducted in three directions: we observed and analysed the effects of well known therapies and the effects of cessation of some therapies; we studied the background factors and molecular markers which have a potential effect on the efficacy of these therapies; and we also analysed important differential diagnostic aspects.

AIMS

1. To analyze the safety and tolerability profile of the combined immunosuppressive treatment in myasthenia gravis (MG) by long-term observation of a great number of patients and with detailed evaluation of adverse events.
2. To evaluate the effect of the combined immunosuppressive treatment on the recurrence of myasthenic crisis.
3. To analyze the negative impacts of the cessation of immunomodulatory treatment on multiple sclerosis.
4. To study the epidemiology of familial MS in Hungary.
5. To examine differential diagnostic issues in MS and Leber's hereditary optic neuropathy (LHON); analysis of the coexistence of the two diseases and investigation of biochemical processes in LHON.
6. Analysis of molecular markers, their importance in diagnosis, differential diagnosis and therapy of neuroimmunological diseases: antibody spectrum in myasthenia gravis, genetic associations of autoimmune diseases; establishment of DNA- and tissue bank from Hungarian patients with MS and MG.

RESULTS

1. SAFETY OF LONG-TERM COMBINED IMMUNOSUPPRESSIVE TREATMENT IN MYASTHENIA GRAVIS.

163 patients with generalised myasthenia gravis were followed for three years in average, who were treated with combined azathioprine-methylprednisolone (PRE-AZA) medication in the Jahn Ferenc Hospital between 1996-2002. The diagnosis of MG was based on typical clinical symptoms, associated with positive EMG and with or without seropositivity of antibodies to acetylcholine receptors (AchR). 84,6% of our patients were seropositive, 15,4% were seronegative (MuSK antibodies were not examined). Immunosuppressive treatment was introduced only to patients with generalized MG, who were poor responders to the high dose cholinesterase inhibitor monotherapy or suffered previous myasthenic crisis. The patients were classified according to the Myasthenia Gravis Foundation of America (MGFA) Classification. After the observation period, we divided the patients in two groups: patients in the first group didn't experience adverse effects (AEs) in contrast to patients with AEs in the other group. The second group was further divided to "AZA AEs", "steroid AEs" and "AZA+ steroid AEs".

The patients visited our out-patient department every 3 months for clinical and laboratory assessment. They filled a detailed questionnaire regarding the potential AEs of the treatment. We asked specifically for the usual AEs of both drugs and inquired the patients if they had experienced any new signs or symptoms during the treatment course. Laboratory tests (complete blood count and differential, platelet count, liver enzymes, urinalysis, serum glucose, ionogram, urea and creatin) were carried out every 2 weeks for the first 3 months of the treatment, every 4 weeks for the first year of treatment, and every second month afterwards.

Discussion:

In our prospective, open, observational long-term study of 163 patients the AE profile and safety of the combined AZA+ PRE therapy was analysed. The overall proportion of AEs in our study was high (61.4%), however most of the AEs could be attributed to steroids and were reversible following the discontinuation of the steroid treatment, which was possible in 76.7% of the patients after 12-18 months. The overall proportion of AEs due to AZA treatment was 20%. Serious AEs resulting in treatment discontinuation were observed in only 10 patients. Hematological alterations were the most frequently observed AEs of the AZÁA treatment: leukopenia, anemia, pancytopenia as well as hepatotoxicity were observed. AZA AEs were not dose-dependent, there was no significant difference in the dose of AZA between the group of patients with and without AEs. We emphasize that in contrast to previous reports, we found a substantially lower proportion of severe infections (1.8%). The latency of the AZA-related AE development was variable, but tended to be longer in patients with hematologic AEs. The frequency of malignant tumors was not higher than expected in an age-matched population. Probability of developing AEs correlated with the severity of MG at the beginning of the treatment. The proportion of patients, who began the treatment immediately after a myasthenic crisis or who were in a severe class IV, had significantly higher risk of developing AEs.

2. LONG-TERM EFFECTS OF COMBINED IMMUNOSUPPRESSIVE TREATMENT ON MYASTHENIC CRISIS

Sixty-nine patients with consecutive episodes of MC between 1990-1996 and 1997-2004 were treated and followed prospectively in our study. In the first period, between 1990-1996, patients were not regularly treated with immunosuppressants on long term in Hungary. We could identify 27 patients without immunosuppressive treatment with long-term observational data (in average 80 months) during this period. They comprise the untreated (non-IM) historical control group. From 1997 all patients, who suffered a MC were uniformly treated on long-term with PR-AZA and were prospectively followed. We had 42 such patients: they were followed for 64 months (at least 6 months) in average. Patients with shorter follow-up or patients who died during the MC were not eligible for the study.

There were no significant differences between the study groups regarding the basic demographic and clinical data. The clinical symptoms and characteristics of the baseline crisis were also similar in the two groups. Next, we analysed the effect of combined PR-AZA treatment on the recurrence of MCs. Recurrent crisis occurred in 59.3% in the non-treated and 19% in the treated group ($p<0.001$). Since a delayed effect of PR-AZA has been suggested, we also examined the number of crisis throughout the first 6 months and beyond, up to a maximum of 126 months. Indeed, a reduced frequency of recidive crises beyond half a year ($p<0.001$) explained the observed statistical difference, as the number of repeated crises within 6 months after the baseline crisis did not differ between the two groups. There were significantly fewer admissions to the ICU in the treated group during the follow-up period, compared to the untreated group, and the number of occasions of mechanical ventilation was also lower. However, we did not find any significant difference in the length of mean ICU stay and duration of mechanical ventilation per crisis between the two groups. The number of plasma exchanges during the crisis and the dose of pyridostigmine were also similar in the two groups. There was no difference in the functional outcome one month after the onset of baseline MC, either.

Discussion:

Our results suggest that combined PR-AZA treatment does not prevent the recidive crises before 6 months after the first crisis. In contrast, or data indicate a highly significant decrease in the frequency of recidive MCs beyond 6 months: the risk of a recidive crisis was much lower in the treated group. This treatment has no effect on the MC itself as it did not influence the duration of the crisis, nor the functional outcome after one month.

3. EFFECTS OF INTERRUPTED IMMUNOMODULANT THERAPY ON THE NEUROLOGICAL STATE OF MULTIPLE SCLEROSIS PATIENTS

Between 1999 and 2001, there was a special situation in Hungary. The patients who had received GA therapy from 1996, were forced to stop treatment in 1999 and were able to resume it only from 2001. During this 16-month period these patients were regularly examined and prospectively followed. In contrast, patients on INFB-1b could continue treatment without cessation. Due to this special situation we were able to analyze the effect of halting treatment on the course of the disease.

Six MS centres in Hungary including the Jahn Ferenc Hospital MS centre participated in this multicentric study. All patients had relapsing-remitting MS and the demographic data of the two study groups were homogenous. The EDSS score, which indicates the grade of disability (scores 1-10), was obtained during a

neurological examination every three months, or more often if the symptoms suggested exacerbation. In consequence of the continuous GA therapy from 1996 to 1999, the annual relapse rate decreased significantly as compared with the 2-year period prior to the immunomodulatory treatment. The annual exacerbation rates in the 2-year period prior to the beginning of the study did not differ between the patient groups treated with GA and INFB-1b. However, we found a significant increase in the annual exacerbation rate relative to the treatment period after the 16-month therapy-free period. In addition, the annual relapse rate was significantly higher in patients, who were forced to stop GA compared to patients treated continuously with INFB-1b. EDSS scores were not different.

Discussion:

Due to the interrupted therapy, negative trends in the disease course could be already seen after 16 months. The annual relapse-rate increased significantly compared to the course while on treatment and also to the continuously treated INFB-1b treated group.

4. EPIDEMIOLOGY OF FAMILIAL MULTIPLE SCLEROSIS IN HUNGARY

The prevalence of familial MS is between 5-10% in high-risk areas. By analyzing data of 1500 patients in five MS centres, familial aggregation of MS in Hungary was examined. The patients were diagnosed according to the McDonald's criteria and had relapsing-remitting (RR), secondary progressive (SP) or benign MS. We found aggregation of MS in 15 families involving 33 patients, including a monozygotic twin pair. The male/female ratio was 1:2.75 similar to sporadic MS in Hungary. One patient of the concordant monozygotic twin pair suffered of SPMS (EDSS score of 8), while the other had a benign form of the disease. We also found a dizygotic twin pair, whose father had died of MS 20 years previously. In another family, three generations were affected (mother, son and granddaughter).

Discussion:

In our cohort represening 25% of all MS patients in Hungary, we found a 2% familial rate. The significant difference in the phenotype of the monozygotic twin pair underlines the importance of environmental factors.

5. LEBER'S HEREDITARY OPTIC NEUROPATHY (LHON) AND MULTIPLE SCLEROSIS

5.1. LHON presenting as multiple sclerosis-like disease of the CNS

DNA were isolated from 72 patients with bilateral optic neuropathy and tested for the three pathogenic mtDNA LHON point mutations. Pathogenic LHON mutations were found in 12 patients. In addition, 27 maternal relatives were examined. As expected, all maternal relatives were homoplasmic for the LHON mutation found in the related patients. All 39 genetically defined carriers were examined neurologically to determine the frequency of MS-like diseases. Two LHON patients (women) presented multifocal neurological symptoms. One was homoplasmic for the G11778A and the other for the T14484C mutation.

Discussion:

We examined 39 patients with genetically defined LHON mutations, 12 patients with LHON and 27 symptom free carriers, to determine the frequency of multicentral neurologic manifestations, especially MS like symptoms. We found two

patients with MS-like diseases. In both cases, the CNS involvement was also indicated by brain MRI.

5.2. Investigation of the biochemical background of LHON

The primary atiological event in LHON is a mutation in the mtDNA affecting in most cases mtDNA-encoded subunits of the respiratory chain. Complex I is embedded in the mitochondrial inner membrane mediating electron transport and oxidative phosphorylation. It catalyzes electron transport from NADH to coenzyme Q. All three pathogenic LHON mutations involve complex I subunits, therefore it is assumed that they affect some functional properties of this enzyme complex. However, the relation between complex I dysfunction and disease pathogenesis is unclear. The various mtDNA mutants are associated with up to 60% reductions in the catalytic activity of complex I in different tissues in patients with LHON. The impaired complex I activity leads to a decline in mitochondrial energy production, enhances the generation of free radicals and initiates lipid peroxidation. The cells have their endogenous defence systems to neutralise reactive oxygen species or the damage elicited by these toxic species. The main hydrophilic scavenger found in cytosolic, mitochondrial, and nuclear compartments is reduced glutathione (GSH), whereas its hydrophobic equivalent localised in membranes is α-tocopherol. Both GSH and α-tocopherol are potent inhibitors of lipid peroxidation; GSH prevents the initiation of radical formation, α-tocopherol inhibits the propagation of the chain reaction. Due to these theoretical considerations, we wanted to determine whether patients with LHON, and carriers, display any alterations in these main antioxidant systems pointing to enhanced free radical reactions. The concentration of GSH, α-tocopherol, and some other antioxidants were determined in the blood samples from nine patients, seven carrier maternal relatives and 15 control subjects All of the patients with LHON and the carriers had the homoplasmic 11778 point mutation in the mtDNA. The α-tocopherol/lipid ratio was significantly reduced ($p<0.05$) in patients with LHON and carriers compared with control subjects.

Discussion:

The marked reduction in the plasma α-tocopherol/lipid ratio most probably reflects the high consumption of the scavenger molecule by affected tissues. Our data suggest that the primary antioxidant against free radicals elicited by complex I impairment is α-tocopherol.

6. MOLECULAR MARKERS IN MYASTHENIA GRAVIS AND MULTIPLE SCLEROSIS

6.1. Multiple sclerosis and myasthenia gravis tissue- and gene bank

With collaboration of Department of Neurology of University of Pécs and Department of Neurology of the Jahn Ferenc Hospital we established a multiple sclerosis tissue bank. This bank includes clinical data, genomic DNA and CSF samples. Data and samples from 282 patients have been collected so far.

The HLA-DRB1*1501 genotype was examined altogether in 244 patients. Fourty percentage (96 patients) of the Hungarian MS population carries this single consistent susceptibility allele of the Caucasian MS.

The myasthenia gravis databank comprises clinical data, DNA and serum samples of 186 myasthenic patients.

6.2. Serological subgroups in the Hungarian myasthenia gravis patient population

In collaboration with foreign institutes we examined the distribution of anti-AchR-, anti-Titin- and anti-MuSK antibodies in 100 patients with myasthenia gravis.

Summary of results and Discussion:

We detected AchR Abs in 72 patients i.e. 72% of our patients were "seropositive". Sixteen patients had Abs against the muscle Titin protein. It is established that MuSK Abs are present only in seronegative myasthenic patients. Therefore we tested the MuSK Abs only in AchR Ab negative and in patients with unknown AchR Ab status. We had 40 such patients. Twenty-nine of them turned out to be AchR Ab negative, and 4 of them were anti-MuSK positive.

We examined the combination of various antibodies. We checked weather the AchR Ab positive patients have Abs against Titin and MuSK. In 20%, of patients with AchR Abs in the sera, Abs against the muscle Titin protein were also present but anti-MuSK Abs were not found. When analysing the AchR Ab negative patients, only one out of the 29 anti-Titin Ab-positive belonged to this group, but 4 of them were anti-MuSK positive. We concluded that Titin Abs are present mostly in patients who are AchR Ab positive while MuSK Abs are present exclusively in AchR Ab negative patients. We also examined the frequency of AchR Abs in anti-Titin positive and anti-MuSK positive patients. Sera of 15 out of the 16 anti-Titin positive patients also contained anti-AchR Abs, but none of them had MuSK Abs. MuSK Abs were not associated with other antibodies.

In summary, the anti-Titin Abs are usually present together with anti-AchR antibodies while anti-MuSK Abs are present alone. Anti-AchR Abs are associated with anti-Titin ABs in one third of the patients. AchR Abs and MuSK Abs do not appear together.

6.3. Multiple sclerosis and the *CTLA4* autoimmunity polymorphism CT60 in German, Hungarian, and Polish patients

One possible candidate for shared autoimmunity genes is the *CTLA4* gene, the gene of one of the most important T-cell costimulatory factor, the cytoxic T-lymphocyte-associated antigen-4 (CTLA-4). The CT60 polymorphism in the 3'UTR region is associated with several autoimmune diseases. Data about association with MS are conflicting. Therefore, we decided to examine the potential association of CT60 and one other *CTLA4* polymorphysm (+49A/G) in a great number of German, Polish and Hungarian MS patients. The three populations were of similar genotypes and allele frequencies. The meta-analysis showed no association of MS with CT60 or +49A/G allele frequencies. The CT60*G/G genotype was overrepresented among MS patients in all three populations, however this finding did not reach statistical significance.

Discussion:

We could not demonstrate association with MS susceptibility, with age of onset, progression and disease course in these patients. The CT60*G/G genotype was slightly overrepresented in all three populations. The frequency of +49A/G*g-CT60*G haplotype was also slightly higher in German, but not Hungarian or Polish MS patients. No difference reached statistical significance, and these polymorphism does not cause functional changes in CTLA-4 and ICOS expression. In summary, it was not possible to demonstrate an association of this common autoimmune polymorphism with multiple sclerosis in these large cohort of MS.

6.4. 3'UTR C2370A allele of the IL-23 receptor gene is associated with relapsing-remitting multiple sclerosis

Cytokines play an important role in the development of autoimmune diseases. IL-23 and IL-17 have recently been suggested to play an important role in the pathogenesis of autoimmune diseases such as MS. One of the Th17 differentiation pathways is IL-23-dependent and IL-23 is necessary for the survival and expansion of IL-17 producing autoimmune Th17 cells.

Several polymorphisms recently identified in the *IL23R* gene are associated with inflammatory bowel disease (IBD). The C2370A allele in the 3'UTR showed one of the most significant associations with IBD. Here, we examined the association of this SNP with MS. Patients with RRMS (n=223) were involved in the study, 45 patients have progressed into a secondary progressive phase following a relapsing-remitting course. The control population consisted of 200 clinically healthy subjects.

The AA genotype was significantly over-represented in the 223 MS patients compared to 200 healthy controls (10.8% vs 5.5%, $p<0.05$). The AA genotype was also significantly over-represented among patients exhibiting OCB in the CSF. Multiple regression analysis revealed that presence of the AA genotype provides a two-fold risk for the development of MS and for the presence of oligoclonal bands in the CSF. No such differences were observed when HLA-DR15-positive (n=84) or negative (n=132) subgroups were separated and compared to healthy subjects. Nor did we find any significant differences when female patients were separately analyzed, and no association was found with secondary progressive disease course.

Discussion:

Our data indicate that a genetic association exists between relapsing-remitting MS and the C2370A polymorphism of the *IL23R* gene. The AA genotype provides a two-fold risk for developing MS and oligoclonal bands in the CSF. The susceptibility was independent from HLA-DR15 status. Since association of the A2370A genotype with other autoimmune diseases was also described, our data also suggest that the *IL23R* may represent a novel common autoimmunity gene.

6.5 Aberrant transcriptional regulatory network in T cells of multiple sclerosis

Concordance rate in MS for monozygotic (MZ) twins is 25-30%, while it is 2-5% for dizygotic (DZ) twins suggesting the possible involvement of not a single but multiple susceptibility genes in development of MS. Regulation of multiple susceptibility genes is controlled through the combinatorial action of multiple signalling and multiple transcription factors that form molecular network of genes. We performed microarray analysis of peripheral blood T cells isolated from the genetically homogeneous population of Hungarian monozygotic concordant and discordant MS twins. Molecular network of the differentially expressed genes was than analyzed by a comprehensive information platform.

In 3 of the 4 monozygotic twin-pairs both siblings were ill (concordant twins), in one case we had discordant twins with one MS patient and one healthy subject. All subjects were females, 33±5 years old and the mean disease duration of 6±5 years. All patients exhibited a typical RR disease course, except for one patient who had CIS. The patients showed a relatively mild EDSS score of 1.3±0.8. By microarray analysis, we identified 50-100 differentially expressed genes (DEG) in T cells between each MS twin pair. Then, we compared the genes of the discordant and concordant twins, and selected a panel of 34 genes that were listed in 50 differentially expressed genes of the discordant twin (MR/healthy subject) but were not included in 100 DEG of the concordant (MS/MS) twin pairs. In that way we

investigated in the genetically homogeneous population the gene expression typical for MS. We further extracted a set of 20 DEG by a cut-off point greater or equal to two-fold difference between the discordant pair. Further 43 genes were identified, that are directly linked to 20 DEG, with the computer-analysis. The search of 43 genes illustrated a complex molecular network composed of 39 nodes. By statistical analysis, the generated network showed the most significant relationship with gene regulation by the Ets transcription factor family, the gene regulation by the nuclear factor NF-κB, the Myc/Mad family, the IFN-regulatory factor (IRF), and the estrogen receptor (ER) family.

Discussion:

Our data propose the logical hypothesis that aberrant regulation of the complex transcriptional regulatory network might contribute to development of pathogenic T cells in MS. The Ets family transcription factor controls the expression of a wide range of target genes essential for cell proliferation, differentiation, transformation, and apoptosis. The NF-κB family acts as a central regulator of innate and adaptive immune responses, cell proliferation and apoptosis. It has more than 150 target genes, and is overexpressed in macrophages and oligodendrocytes of MS plaques. The IRF (interferone regulatory factors) together with NF-κB is part of the IFN-B gene enhancome, an important regulatory factor of the immune response, cell growth and apoptosis.

CONCLUSIONS

1. The long-term combined (PRE-AZA) therapy in moderately severe and severe generalized myasthenia gravis (MGFA Class III-V) is well tolerated, safe and effective treatment. The long-term treatment with AZA has a steroid sparing effect: steroid treatment could be discontinued in the majority of our cases. The adverse effects were due to steroid treatment in most of the patients.
2. We examined and proved for the first time that the number of recidive crises decreases in patients treated with PRE-AZA on long-term. This observation supports the necessity of long-term immunosuppressive treatment (PRE-AZA) after a myasthenic crisis.
3. LHON can be differential-diagnostic issue in MS, and can occur with MS or MS-like syndromes.
4. The decrease in disease activity and halt of progression in MS can be achieved only with long-term, continuous disease modifying treatment. We proved that after the discontinuation of treatment results in an increase of relapses.
5. Our study is the first epidemiological study of Hungarian familial MS cases. According to our data the prevalence of familial MS is about 2%.
6. The twin and association studies are of great importance in the genetic research of autoimmune neuroimmunological diseases. To address this issue we established DNA and tissue banks in MS and MG.
7. We studied for first time the frequency of the HLA-DRB1*1501 genotype in the Hungarian MS population.
8. We showed that the *CTLA4* CT60 SNP is not associated with MS, while the 3'UTR C2370A allele of the IL-23 receptor gene doubles the risk of RRMS and of OGP in the CSF.
9. We identified aberrant transcriptional regulatory networks in CD3+ T cells of MS twins.

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Full length articles

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