

Immunosuppressive and symptomatic therapy of multiple sclerosis

H. H. Kornhuber and E. Mauch

Neurologische Klinik, Universität Ulm, Germany

Abstract. There have been improvements in the drug treatment of multiple sclerosis (MS) in the past few years. Immunosuppressive drugs such as cyclophosphamide and mitoxantrone have proven to be effective longer than cortisone, and other effective treatments via the immune system are expected to follow. The task today is to motivate patients and doctors to utilize these new tools for treatment at the right time and in appropriately small doses. However, symptomatic therapy is still the basis of MS therapy. Especially the neurogenic bladder disturbance must be cured by training methods rather than treated by continuous catheterization; this is a necessary basis for the administration of immunosuppressant drugs. Information and training for the patient's relatives are a therapeutic source currently not sufficiently utilized.

Key words: Multiple sclerosis – Treatment – Symptomatic therapy – Immunosuppression – Spasticity – Neurogenic bladder – Cyclophosphamide – Mitoxantrone – Interferon – Lymphocytes – Life style

Introduction

Multiple sclerosis is an autoimmune disease. As with most autoimmune diseases, there is no definite cure yet available, but there is some effective treatment which should be applied either continuously or at intervals, depending on the course of the disease. The doses should always be kept as low as possible. Besides treatment of the immune process, patients with multiple sclerosis usually need symptomatic therapy for the secondary injuries and symptoms caused by the demyelination in the central nervous system (such as spasticity or urinary bladder dysfunction). This symptomatic therapy has, to date, contributed as much to improving the patients' fate as has causal therapy. Unfortunately, some important improvements in symptomatic therapy are not yet generally applied; this is true especially for treatment of the neurogenic bladder by noninvasive methods and for the prevention of decubital ulcers.

Symptomatic therapy

Spasticity

Since the first double-blind study [18], baclofen has been the drug of first choice for the treatment of spinal spasticity, which usually dominates in multiple sclerosis. The doses of this drug should be adjusted individually, slowly increasing in order to avoid paresis. When the effect of baclofen even in high doses (more than 100 mg/day) is insufficient, it may be combined with dantrolene or small doses of tizanidine. Tizanidine is effective in spasticity from supramesencephalic lesions, but it has serious side effects such as bradycardia and sudden lowering of the blood pressure. Its administration must therefore be carefully supervised, and the dose should not be increased to the official maximum. Dantrolene is effective in spasticity of both spinal and supraspinal origin, but it also may lead to muscle weakness (which is transient when the dose is reduced).

If spastic legs are not sufficiently moved, the spasticity may worsen spontaneously, pain and contracture may result. Therefore, spasticity and paresis should also be treated with physiotherapy. Because of problems of cost-efficiency, one cannot give enough physiotherapy in cases of severe spasticity, additional movement of the spastic legs is therefore necessary by means of an apparatus, the Motomed [22]. The Motomed (available from Reck Maschinenbau, D-88422 Betzenweiler) has a sensor which signals high spasticity and, avoiding the application of too much force, waits for a moment (until the reflex increase of muscle resistance decreases) and then again starts the movement, thus overcoming even severe spasticity. The most severe cases of spasticity may be treated by continuous intrathecal administration of baclofen by means of an automatic pump [37]. There are systems which allow for adjustment of the dose rate. The main side effects of this method are catheter occlusion, meningeal infection, and hypotension in the cerebrospinal fluid system leading to bilateral subdural hygroma. If the other methods described above are properly used, very few patients will require continuous intrathecal infusion.

Decubital ulcer

In paralyzed patients immobilization may soon lead to bed sores. The most important preventive measure is changing the position of the patient at regular intervals, i.g., every 2 h. Since the positions in which the skin is directly over bone are at highest risk (such as trochanter, os coccygis, os ischii, or heel), putting pressure on these places should be avoided [20]. Patients who are still able to turn themselves in bed should be trained to do so. For this purpose, a grip at the bedside may be useful [28]. When all four extremities are paralyzed, the patient may direct an automatically turning bed by means of his mouth. In the treatment of decubital ulcers, avoidance of pressure on the ulcer is the most important condition for healing.

Impairment of vision

Visual disturbances resulting from optic neuritis may be compensated by glasses with additional lenses. In severe cases, electronic aids for reading should be used. In cases of visual impairment resulting from acquired pendular nystagmus [1], contact lenses are helpful [9]. Reading should be trained and practiced as long as possible with these aids; for our brain needs training just as our muscles do. In cases of blindness, the patient should have contact to organizations of the blind in order to obtain magnetic tapes for acoustic intake of verbal information.

Paresis

Physiotherapy is indispensable at home and in the hospital. In cases of weakness of the legs or disturbed equilibrium, a walking aid with four wheels (Rollator) is useful.

Intention tremor may be treated by beta-blockers (e.g., propranolol) or trazodone. In cases of severe intention tremor of both arms, which renders independent eating impossible, stereotaxic thalamotomy may be considered.

Neurogenic bladder disturbance

In treating neurogenic bladder disturbance, great care should be taken, because the urinary retention causes chronic cystitis, making immunosuppressive therapy difficult. Furthermore, patients are seriously bothered by chronic cystitis, and urinary tract infections may cause pyelitis, which was in former years one of the main causes of death in multiple sclerosis. Continuous indwelling catheters or suprapubic catheters are not useful for the treatment of neurogenic bladder disturbances, since bacteria enter the bladder via the catheter, resulting in cystitis. If a continuous catheter is employed for a long time, a carcinoma might even result. Urodynamic investigations of the patient's bladder usually contribute little to the treatment, since the different reflex patterns diagnosed by urologists (such as dyssynergia) merely reflect momentary, transitory states of the bladder; the treatment remains the same. The different pathologic reflexes disappear if a neurogenic bladder disturbance of central origin is properly treated by training.

Neurogenic bladder disturbance of central origin (which is

the most common urinary bladder disturbance found in multiple sclerosis) creates a vicious circle: the retention of urine causes chronic hyperextension of the bladder, leading to diminished elastic power of micturition. This results in the typical overflowing bladder, with high residual urine and urge incontinence. The most important measure for curing this disturbance is to empty the bladder completely by means of intermittent catheterization six times a day [29], not via a continuous indwelling catheter. For intermittent catheterization there are low-friction catheters available now (from Astra Tech, D 65536 Limburg); short-term immersion in drinking water smoothes the surface of these catheters, eliminating the need for a lubricant (lubricants contain antiseptic components which irritate the urethra). If the bladder is emptied by intermittent catheterization six times a day for several days, the bladder is usually once again sufficiently elastic to be trained in the normal way: the patient may trigger micturition by tapping with his fingers in the bladder region over the symphysis; when the bladder starts to empty, he may use hand pressure (Credé's maneuver). The residual urine should be less than 50 ml. In cases of cystitis, the sensitivity of the bacteria is then tested and proper antibiotics are administered. To avoid a relapse of cystitis, the urine is acidified with ascorbic acid and L-methionine.

In a few cases there is a peripheral bladder disturbance in addition to the central one; this is usually due to diabetes mellitus or prediabetes, which also causes microangiopathy. The urination reflexes cannot be trained in such cases. The patient should then learn self-catheterization. We have produced a short videotape for this purpose (which is available free of cost from ASTRA Tech, D-65536 Limburg). Women can easily learn self-catheterization with the help of a mirror. If, because of paralysis or intention tremor, the patient is no longer able to catheterize himself, we teach this procedure to relatives. These methods have been proven to be efficient. Their current lack of use is due to undervaluation of training methods, overvaluation of drugs, and the fact that urologists do not yet understand the importance of training methods for the treatment of central neurogenic bladder disturbances. The continuous catheters and operations preferred by urologists so far make the problem worse and preclude the effective treatment of multiple sclerosis with immunosuppression.

Bladder training is a learning process which has to be monitored. The monitoring consists in measuring the residual urine (the amount of urine remaining in the bladder at the end of micturition). We have devised a method to measure the residual urine noninvasively with ultrasound [30]. Since we realize that the patients are at home most of the time and have to train their bladder there [6], we have designed a small, portable, battery-driven ultrasound device, the Uroson [45] (available from Renner Medizintechnik, D-89547 Heuchlingen).

Causal therapy via the immune system

Corticosteroids

Corticosteroids (prednisone, prednisolone, or methylprednisolone) may be given intravenously in high doses [35] and have fewer side effects than ACTH, which was used previously. A

long-term treatment with cortisone is of no advantage, as it produces more side effects and no benefits [8, 34, 35]. Methylprednisolone is therefore nowadays given only for 5 days (500 mg per day). Cortisone enhances the tendency to thrombosis; several fatal cases of pulmonary embolism under cortisone treatment have been reported in the literature. It is therefore necessary that heparin be given (in low doses) during each high-dose cortisone treatment. Another important, though rare, side effect is pancreatitis – one more reason why MS patients should stay lean and avoid alcohol. Although cortisone is effective for a short time in acute exacerbations of MS, the benefits soon cease. Even repeated high-dose pulse treatments do not influence the long-term course of the disease [2, 34, 35].

A group consisting mainly of ophthalmologists [3] published a conclusion that a 3-day single-pulse treatment with high-dose intravenous methylprednisolone given to patients with optic neuritis reduces the rate of development of further signs of multiple sclerosis over a 2-year period. If we look, however, at their Fig. 1, it appears more likely that there was a cohort effect: the group treated with methylprednisolone consisted of patients who, by chance, had a less severe course over the entire 3.5-year observation period. During this time there was a significant difference in relation to the two other groups (placebo and low-dose prednisone) after 2 years, although after 1 year there was no significant difference in relation to the low-dose prednisone group, and after 3 years there was no significant difference in relation to the placebo group. In view of all the other data so far available, it is not likely that a single-pulse 3-day treatment with high-dose methylprednisolone changes the course of the disease over 3 years, although ophthalmologists who traditionally treat optic neuritis with cortisone may tend to believe this.

A Dutch group [38] found that a 1-day high-dose pulse treatment with methylprednisolone (500 mg intravenously) in ten MS patients (without a control group) repeated monthly over 9 months was well tolerated. The mean increase in the Kurtzke disability scale was half a point per year, however, which is also the usual spontaneous course in our control groups without treatment.

Thus, high-dose methylprednisolone pulse treatments alone cannot be recommended as standard therapy for MS. However, high-dose intravenous methylprednisolone for 5 days may be given as a fast-acting additional therapy in acute exacerbations of multiple sclerosis. Cortisone has the advantage that most physicians are able to handle it, but one should not forget to add low-dose heparin subcutaneously and to supplement it as soon as possible with some immunosuppressant drug with a longer-lasting effect on MS.

Cortisone, especially in high doses, has had teratogenic effects in animal experiments (palatal cleft) [7]; whether it is teratogenic in humans is an open question [19]. It is probably wise to avoid high doses in pregnancy, unless strong treatment is necessary because of a severe exacerbation of MS.

Azathioprine

It is now clear that azathioprine is not effective in multiple sclerosis [5]. Azathioprine has to be given daily in considerable doses (about 2 mg/kg), which results in many side effects. Worst of all, it causes malignomas in the long run. The limit

of safe doses per life in this regard for the average adult is about 108 g. Since 75 kg body weight require about 150 mg/d, that is 55 g/year, only 2 years of treatment with azathioprine is possible before the high risk begins – a fact that has been widely neglected so far. In view of the perspective that a useful effect of azathioprine has not been proven in multiple sclerosis, and with regard to the high risk after 2 years, we conclude that its application is not justified in MS.

Cyclophosphamide

There is little doubt that cyclophosphamide (Cy) is effective in multiple sclerosis [34, 42]; the suppression of further disease activity lasts about half a year. We strongly advise applying Cy in the low doses as described here, adjusted individually according to the effect on the lymphocytes. A Canadian study [41], which is quoted by some as evidence for ineffectivity, indeed showed that a single dose is more effective than placebo for about 1 year; this study, however, made the initial mistake of postulating an effect over 2 years following a single dose. Furthermore, the Canadian study used such a high dose (not individually adjusted) that all patients suffered hair loss, which is bad for compliance.

We have designed a low-dose pulse therapy with Cy, individually adjusted [26, 33, 34] with regular repetitions; we advise a repetition every 6 months. With this method there is no hair loss and, with added therapy against nausea (described later in this paper), very little nausea. In patients with a benign course (rare exacerbations), instead of regular repetitions one may wait until the next exacerbation; then, however, immediate treatment is necessary. Because of the cumulative long-term side effects, Cy should be dosed as low as possible but individually adjusted. The approach to the correct dose in a given pulse treatment is achieved in several small steps: the initial dose is 8 mg/kg Cy in an infusion, combined with Mesna (20 % of the Cy dose). At least 3 l of fluids daily (mineral water, tea, beer without alcohol, etc.) are given on the day of Cy infusion and the following day. In patients with urinary cystitis, the bladder must have been trained before and the cystitis has to be cured as described above. In patients with chronic pyelonephritis or other severe kidney problems, mitoxantrone is given instead of Cy. To counteract nausea (which is the main acute side effect of low-dose Cy), on the day of the infusion and the 2 days following an antiemetic combination is administered: domperidone 3 × 2 tablets of 10 mg each, alizapride 3 × 1 tablets of 50 mg, and dimenhydrinate (3 × 1 Vomex A retard caps 150 mg, each of which also contain pyridoxine). This combined antiemetic therapy is usually as effective as ondansetron and is far less expensive. However, if the effect of this combination is not good enough, ondansetron should be given immediately in order to counteract a negative conditioning of the patient against the immunosuppressive treatment. The aim of this low-dose Cy pulse treatment is to reduce the lymphocyte count to half the initial value, but not below 1000 per mm³. The result of each infusion of Cy is evaluated after 4 days. If the first infusion does not reduce the lymphocytes enough, a second infusion of 8 mg/kg (or, if there were significant side effects, only 6 mg/kg) is given and, after evaluation 4 days later, another Cy infusion if necessary (and so forth). On the average, a total dose of less than 2 g Cy is needed for a single pulse treatment. The cumulative long-term

cytostatic therapy should be strictly avoided. The solution of the immunosuppressive drug should be prepared with a laminar flow unit.

Methotrexate

A beneficial effect of methotrexate (Mtx) on the course of MS is proven [13]. Patients who do not tolerate either cyclophosphamide or mitoxantrone or both may be treated with Mtx from the beginning. We also give Mtx as an additional drug between the pulse doses of Cy or Mx to MS patients who tend to have exacerbations despite other immunosuppressive treatment. Mtx is applied orally, only once a week, beginning with a dose of only 5 mg. If well tolerated, the dose may be increased to 10 mg a week; usually this is enough, but for large patients, or in cases of rapid progression of the MS, it may sometimes be necessary to give 20 mg per week. Besides the effect on the blood cells, Mtx tends to have side effects on the liver. Therefore, at the beginning of Mtx therapy the home practitioner has to make control investigations of the blood every week, checking transaminases, gamma-GT, creatinine, uric acid, and the blood counts including platelets. After several months, control examinations every 2 months are enough. A rare side effect is pneumonitis. Diabetes mellitus, diseases of the liver, and serious diseases of the kidneys are contraindications. Alcohol must be strictly avoided.

Copolymer 1

Although in 1987 promising results had already been published concerning the synthetic polypeptide copolymer 1 (Cop) [4], this experimental drug is available only in Israel and in the USA for clinical trials; it is not yet available for regular treatment in any other country. We must wait to see whether the tests in progress will substantiate the original expectations.

Interferon

Interferon (Inf) beta, intrathecally administered, is effective in cases of severe encephalitis [44]. With the intrathecal route Inf beta has fewer side effects and a better therapeutic efficiency than with systemic administration [43]. Using *Escherichia coli*, Schering developed a slightly different drug without the glyco-group; this drug, Betaserone, has recently been advocated against multiple sclerosis [16]. Inf beta is a substance with antiviral activity, and it is an immune-system booster. It is produced physiologically by the human body in cases of influenza. In flu, however, there is often a slight diminution of lymphocytes; thus a little immunosuppressive action of Inf beta is plausible. The American/Canadian trial with Betaserone showed no significant effect of Inf beta on the objective motor symptoms (Kurtzke expanded disability scale) of MS patients. The finding of a significant effect of Betaserone on the rate of exacerbations is somewhat doubtful, because very short minor exacerbations were also counted, but were discarded if the investigators felt that they were due to the flu-like side effects of the Inf itself; thus a systematic error may have

resulted. The authors rely mainly on the results of the magnetic resonance tomography study [36]. In this study, however, the method with clear results, namely the one with gadolinium [32], was not applied, instead, the size of the lesions was planimetrically measured over all scans. This method shows wide variations when different persons do the evaluation. Instead of taking the average of several independent evaluations, the study relies on the data of one technician, who, for instance, measured smaller lesions in the placebo group after 3 years than after 2 years – a result which is unlikely. Thus, Betaserone had, if at all, only a small therapeutic effect in multiple sclerosis. On the other hand, it had side effects similar to flu: it caused depression. In the Betaserone group there were several attempted suicides, one of them completed; in the placebo group there were none. Besides, Betaserone is expensive (the treatment costs about DM 17 000 per year), so that it is doubtful whether it can compete with more cost-efficient immunosuppressive drugs, at least for those (most) patients with no contraindication. On the day this review was completed we received a press release from Biogen on the results of another recombinant interferon beta: Biogen's Inf beta 1a, which is considerably different from Betaserone; it is identical with the natural human interferon. In Betaserone an amino acid in position 17 is exchanged for serine; furthermore, the glyco-group which is lacking in Betaserone is present in Biogen's Inf beta 1a. The prospective, placebo-controlled study was carried out by L. Jacobs as principal investigator. The drug was given intramuscularly once a week. The results were more clearly positive, especially since gadolinium enhancement of new lesions was used with magnetic resonance imaging. Let us hope that the price of these drugs may now decline. From the quantitative point of view, it remains to be seen whether the effects are as good as those of immunosuppressive drugs. Biogen's Inf beta 1a is expected to be available in 1995. If therapy with Inf beta becomes a routine procedure, one should perhaps combine it with antidepressant drugs that have few side effects (e.g., Fluvoxamine). It is not clear if frequent interferon administration is harmless for the fetus; there are no data so far. It is probably wise to avoid interferon treatment during pregnancy, however, especially during the first 3 months.

Liquorpheresis

Similar to plasmapheresis, liquorpheresis eliminates cellular and higher molecular substances which may maintain autoimmune processes from the cerebrospinal fluid. Liquorpheresis (including immunoadsorption) has proven to be effective in the treatment of polyradiculitis [15, 46]; in this case it is superior to plasmapheresis. Sufficient data as to whether liquorpheresis is effective in multiple sclerosis are not yet available. While it is now a standard therapy for polyradiculitis, it is an experimental therapy in multiple sclerosis. However, liquorpheresis may be offered to patients who, because of planned or existing gravidity, should not have immunosuppressive antitumor drugs or high-dose cortisone. The main risk with liquorpheresis is meningitis. A meningeal irritation or a real meningitis occurs in 1–10% of cases. Despite many liquorpheresis treatments for polyradiculitis, there have so far been no fatal events:

Further prospects for the treatment of multiple sclerosis

New effective drugs against multiple sclerosis with fewer side effects are to be expected, so that if one drug has reached the risky total dose, another drug may be used with good results. One may, for instance, think of *cladribine* [14, 40] which seems to be effective in MS. It is commercially available as *Leustatine* from Orthobiotec (USA) or from *Cilag* (Germany). *Deoxyspergualine* may have some effect in MS, with tolerable side effects; we have to wait for the result of the study in progress (the drug is not yet available in Europe). Furthermore, new groups of drugs may prove to be effective in multiple sclerosis, for instance, soluble adhesion molecules which are able to down-regulate inflammatory autoimmune aggression without immunosuppression [39]. With multiple sclerosis we are now considering drug treatment similar to that of other autoimmune diseases such as rheumatoid arthritis. In contrast to rheumatoid arthritis, however, MS is usually not painful, and in some patients psychic alterations cause apathy. Effective drugs are available, the task now consists in motivating doctors and patients to apply these drugs in the right dose at the right time with the fewest side effects. The drugs should be given either at regular intervals or, in cases with rare exacerbations, immediately at the onset of an exacerbation. Unfortunately, many patients with exacerbations tend to wait to see whether the symptoms will fade spontaneously, thereby tolerating the appearance of new permanent lesions. The therapeutic potential of family members of MS patients [10, 28] is also not yet being sufficiently utilized.

Information from the immune system and from magnetic resonance tomography

We have learned [31] that the positive effect of drugs on the course of multiple sclerosis may be correlated with changes in specific subtypes of lymphocytes which indicate an enhanced reactivity of the immune system. For instance, in the case of treatment with mitoxantrone, there is no long-lasting effect on the total lymphocyte count or on the T-helper cells, the T-suppressor cells, or the natural killer cells, but there is a long-lasting effect on the HLA-DR-positive cells and on the B cells, both of which are significantly reduced in MS patients following Mx therapy over a long period [31]. It is conceivable that this method may become routine in order to assess the risk of new exacerbations of the disease and therefore the timing and dosage of treatment. Nuclear magnetic resonance imaging, on the other hand, is able to show new active foci which may be clinically silent; this method is helpful in more rapid evaluation of new methods of treatment aimed directly at the pathological immune process. This positive perspective should not lead us to neglect symptomatic therapy, however, and information for and training of town nurses and the patients' relatives.

Life style and the course of multiple sclerosis

From our (unpublished) statistical data it appears that patients who smoke have on the average a more unfavorable course of multiple sclerosis. We do not yet know whether this is directly attributable to smoking, or to alcohol consumption, which is

often correlated with smoking. In any case, MS patients should neither smoke nor drink alcohol. Cigarette smoking causes, among other things, chronic bronchitis, and alcohol damages the immune system.

Furthermore, we find a higher concentration of mercury in patients with multiple sclerosis as compared with control groups (Mauch et al. submitted). We do not yet know whether this stems from amalgam, or from food, or from some special metabolic handling of mercury in MS patients. It is, however, advisable for MS patients to eat food rich in antioxidants, vitamins, and trace elements including selenium (for instance, selenium yeast). Furthermore, we advise MS patients to get enough sleep and to avoid unnecessary colds by humidifying room air in the winter time and by cleaning their nose with sodium-chloride solution.

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Professor Dr. med. Dr. h. c. H. H. Kornhuber
 Neurologische Klinik der Universität Ulm
 Oberer Eselsberg 45
 D-89081 Ulm, Germany

Gb 713 W 1286