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Epidemiology and current treatment of multiple sclerosis in Europe today

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Abstract—Multiple sclerosis (MS) is a chronic disease affecting the central nervous system, usually leading to early disablement in young adults. At least 350,000 persons in Europe have the disease. Wide variations exist both between and within European countries in the incidence and prevalence of the disease as well as in the general standard of care for MS patients. The needs, well-being, and social participation of people with MS are systematically influenced by their physical and cultural environment and the nature of the community services. Moreover, the rate of introduction of the new disease-modifying therapy also widely differs from country to country. This article helps clinical researchers to understand better the differences in epidemiology and in the current treatment of MS in Europe.

Key words: *incidence, multiple sclerosis in Europe, prevalence, treatment.*

EPIDEMIOLOGY OF MS IN EUROPE

During the past 50 years, more than 150 descriptive studies on multiple sclerosis (MS) in Europe have been published. Despite considerable scientific effort, much of the variations of the distribution of MS found in different European countries may reflect, at least in part, methodological differences in surveys, especially in case ascertainment and selection.

Most recent descriptive studies based on more appropriate methods contradicted the accepted belief that the distribution of MS in Europe is related to latitude (1). Until 1980, European countries from 36° to 46° north latitude were regarded as having a much lower prevalence rate of MS, about 5 to 25 cases per 100,000, compared to countries of central and northern Europe. This view was mainly based on old surveys done in Italy between 1959 and 1975. More recent studies performed in Italy and in other countries of southern Europe showed that MS prevalence is, in fact, much higher than had been previously believed (2). Therefore, the MS distribution in Europe appears to be more complex than supposed in the past, with great variations not only between areas at the same latitude but also within the countries. There are highly significant deviations from homogeneity, and the high-rate areas tend to be contiguous, forming clusters or foci. In Europe, MS is common in southern Scandinavian but not the north, in the Orkney and Shetland Islands but not the Faroes or Iceland, in Sardinia but not in Greece or Spain, and in Sicily but not in neighboring Malta.

Scandinavia

The distribution of MS in Scandinavia was studied over several years by Kurtzke (3–5). The high-frequency areas in the north appeared to describe a "Fennoscandian focus," in the southern inland lake region of Sweden. This probably is where MS originated in the early 18th century and diffused across the Baltic states, northern Europe, and other countries (4). Actually, the frequency of this disease is variable, and in some areas, incidences

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of MS have fallen; this is probably caused by a saturation effect in those places that have been subjected to intense epidemiological scrutiny.

In Denmark, an important survey of Koch Herriksen et al. between 1948 and 1986, shows incidence and prevalence rates low compared with rates of early periods (6). Incidence rates for the three decades from 1950 to 1980 were 5.1, 3.8, and 4.3, respectively. The fall incidence rate between 1950 and 1960 depended on a reduced rate in people under the age of 35. After making a correction for the impact of laboratory investigations on the timing of diagnosis, they concluded that a change in environmental factors determined the frequency of MS in the middle decade.

In western areas of Norway, the incidence for definite or probable MS seems to be unstable. It changed from 1.1 per 100,000 between 1953 and 1957 to 4.9 per 100,000 between 1978 and 1982 and to 3.4 per 100,000 between 1983 and 1987 (7–9). A recent study shows that incidence of MS in the two northernmost counties of Norway, Troms and Finnmark, has been increasing over the past 10 years, but it is still lower than on the western coast and in the eastern part of Norway (10).

Between the western and the southern parts of Finland, region variations were found in MS occurrence from 1964 to 1979 (11). A recent incidence study of definite cases from 1979 to 1993 demonstrated a persisting gradient: incidence was 5.1 per 100,000 in southern Uusimaa, 11.6 in western Seinäjoki, and 5.2 in neighboring Vaasa (12). These results suggest that the overall regional differences in Finland are because of high MS occurrence in Seinäjoki, where also an exceptionally high familial clustering of the disease had been found earlier (11). Moreover, the prevalence of MS is increasing in Seinäjoki and Uusimaa but not in Vaasa (13).

A comprehensive analysis done in Gothenburg, Sweden, shows that incidence for definite and probable MS dropped progressively from a stable rate of 4.2 per 100,000 between 1950 and 1964 over successive 5-year periods between 1974 and 1988 to 2.0 per 100,000. While in the same years, the prevalence was stable (14). The most recent study in Vastebottern County, in northern Sweden, indicates an onset adjusted crude prevalence of MS of 125 per 100,000. The prevalence of MS is higher than previous reports from other major areas in Scandinavian (15).

United Kingdom

Recent epidemiological studies confirm the high overall frequency of MS in the United Kingdom (UK) and, with notable exceptions, continue to show a temporal trend of increasing prevalence in each newly surveyed district. Serial estimates of point prevalence in Wales in 1985 and 1988 were 117 per 100,000 and 120 per 100,000, respectively (16). Swingler and Compston show an increase in prevalence in Wales over 50 years, reflecting the dissemination of the disease over time in practically every region where serial studies had been performed (17). These data probably are due to a steady reduction in mortality from MS, which occurred following World War II, and to changes in definition, classification, and laboratory methods of the diagnosis. Unfortunately, comparisons of several completed surveys are very difficult because until the mid-1980s, all studies used the system of classification suggested by Allison and Millar while now the Poser et al. criteria is used (18,19). Further surveys show a national difference in MS frequency, with 137 percent more MS in Scotland than in England and Wales (20).

A recent study in the Tayside Health Board area, Scotland, shows a prevalence similar to that found in revised figures from the Grampian region in Scotland but significantly higher than recent estimates from England and Wales (21). Methodological differences may account for most of the reported differences between the north and south, although evidence still suggests that MS is more prevalent in northern Great Britain and northern Ireland than in England and Wales.

Continental Europe

Most of continental Europe appears to be a puzzle of distinct ethnic groups, mixed by centuries of population movement, with different frequency rates. This genetic heterogeneity makes interpreting the epidemiological data difficult.

In southern Lower Saxony, Germany, mean annual incidence increased from 2.6 per 100,000 to 4.6 per 100,000 and prevalence increased from 51 to 118 per 100,000, between 1969 and 1989 (22). In a recent study from southern Hesse, in Germany, the prevalence among Germans was four times of that found in other ethnic groups residing in the study area. It is likely that Germanic ancestry carries a higher risk of MS compared to other populations of continental Europe (23).

In western Poland, prevalence transiently decreased from 51 to 43 per 100,000 between 1965 and 1981 (24). Other contemporary surveys include the estimate of prevalence for native Estonians, Russians, and other nationalities of 55, 29, and 42/100,000, respectively, in southern Estonia (25).

France may emerge in time as a region that has a prevalence for MS, which is genuinely lower than would be expected from its geographical position within Europe, if sociohistorical and ethnic factors are unimportant in determining the distribution (20). The prevalence rate ranges from 38 per 100,000 to 58 per 100,000 according to the different studies (26).

A recent survey done in Valladolid, northern Spain, indicates the country as a high-risk area for MS with prevalence rates over 50 per 100,000 (27). This has been confirmed by another study performed in the Balearic Islands (Menorca), showing a prevalence rate of 68.6 per 100,000 and the incidence rate of 3.4 per 100,000 a year (28).

Occasionally, reports show the low prevalence of MS among Gypsies compared to other white population in Bulgaria, which according to the literature is a low prevalence area. These reports have found that the prevalence of MS in Gypsies is 19.1 per 100,000 in the first region and 18.4 in the second. This result suggests that MS is less common in Gypsies than in other whites living in the same areas (29).

Italy and Mediterranean Islands

In Italy, previous epidemiological studies showed a low prevalence of MS, ranging between 4 and 21 cases per 100,000, whereas more recent studies found values between 39 and 102 cases per 100,000 in different areas, supporting the consideration of an increase in prevalence of MS in past decades. These data might be due to a true change or only reflect improved case identification and ascertainment.

A study on prevalence of MS in the L'Aquila district, central Italy, showed a rate of 53 per 100,000, supporting the consideration of Italy as an area in which MS has a high prevalence (30). The incidence of MS found in a recent study done in Bagheria confirms the high frequency of MS in Sicily and indicates that MS is homogeneously distributed (at least in the northwestern and central parts of Sicily) independently from the altitude and from the presence of evident features of Norman domination (31). According to these data, in an epidemiologic survey conducted in the city of Catania, the prevalence rate was found to be 58.5 per 100,000 and the mean annual 2.3 per 100,000 (32). There is no gradient between continental Italy and Sicily, with the exception of Sardinia. All descriptive studies conducted on this island during the last two decades show a twice prevalence and incidence of MS compared with continental Italy. The Sardinian study, done on a sample representing a fifth of the entire Sardinian population (33), confirmed that the MS risk is much higher than in the rest of Italy and indeed is identical to the risk actually found in most of the UK and the other parts of northern Europe. The Sardinians represent a distinct, homogeneous population from early split in the Caucasoid group, whose prehistoric area of origin is not known. The most recent survey performed in northwestern Sardinia, Sassari, indicates a prevalence of 144.4 per 100,000 population and a notable increase in MS incidence over time (34). This finding disproves the hypothesis that this disease distribution follows a latitude-related gradient, prompting the assumption that the frequency of MS in Sardinia is one of the highest in the world and prompting the hypothesis of an MS "Sardinian focus."

CURRENT TREATMENT OF MS IN EUROPE

The erratic course of MS makes evaluating treatment difficult. Since remissions and relapses occur sporadically and unpredictably, it is difficult to assess whether improvement is due to experimental therapy or to a naturally occurring remission. Aside from symptom management, MS is treated from two perspectives. The first is to treat the relapse and the second is to treat the progression of the disease.

Treatment of Acute Release

The occurrence of a relapse of the disease, especially if it has functional consequences, most commonly indicates the use for corticosteroids (CS) in MS. The standard treatment of MS relapses consists of a short course of a high dose of intravenous methylprednisolone (IVMP), 1000 mg/d for 3 to 5 days (35). A recent meta-analysis shows that a high dose of methylprednisolone administered either orally or intravenously can accelerate the recovery from MS relapses (36). The administration of pulsed high-dose methylprednisolone is a well-tolerated

procedure, and bone density is not reduced by intermittent methylprednisolone treatment (37).

Since intravenous treatment is inconvenient, almost three-quarters of neurologists in the UK recommend oral CS instead of IVMP for the treatment of some acute relapses (38). Comparison between these different routes of administration of CS is a controversial issue. A randomized, controlled trial of CS in optic neuritis shows that IVMP treatment followed by oral CS is superior to oral CS alone (39). Moreover, there is no significant difference in the effect of oral CS and placebo. A small trial comparing identical doses of intravenous and oral methylprednisolone (500 mg/d for 5 days) followed up for 4 weeks does not show any differences between the two routes of treatment (40).

A randomized placebo-controlled double-blind study, enrolling 80 MS patients with acute relapse, compared the efficacy of two commonly used steroid regimens (IVMP 1000 mg/d for 3 days versus oral methylprednisolone (OMP) 48 mg/d for 7 days, followed by 24 mg/d for 7 days and then 12 mg/d for 7 days) (41). In this study, there was no difference in the decrease of the Expanded Disability Status Scale (EDSS) score between intravenously and orally treated patients. To date, it seems premature to draw a definite conclusion based on the current literature. More studies are needed to elucidate this issue. If clinical efficacy and equivalence can be confirmed in further studies, oral CS will have a clear advantage over intravenous administration in clinical practice. In fact, an oral regiment is convenient for the patient, is easy to administer, and reduces hospital admission and treatment costs (saving £472,000 a year if all MS relapses were treated with oral prednisolone instead of methylprednisolone) (38).

Prevention of Relapses and Disability

The management of MS is in a major period of change. Following the 1993 publication of the landmark North American study of interferon β-1b (IFN β-1b), several major trials with disease-modifying therapy (IFN β-1b, IFN β-1a, and Copolymer 1 (Cop 1)) have shown some benefits for relapsing-remitting MS (RRMS), while only one for secondary progressive MS (SPMS) (42–47).

Long-term therapies with disease-modifying agents open fresh questions to clinicians about who should be considered for treatment, when such treatment should be initiated, and how long treatment should be continued. Most clinicians in Europe feel that reducing the relapse rate justifies treatment in all or some people with RRMS, and on average, clinicians indicate that approximately half of the people with SPMS would receive treatment (48).

An international MS consensus meeting in Paris, France, has addressed general criteria for consideration therapy (49). Patients to be considered for initiation therapy should have (1) definite MS according to the current or revised Poser et al. criteria (19,50); (2) a disease course that includes clinical attacks (which excludes for now the form of primary progressive MS (PPMS), for which no therapy has been proven effective); and (3) an ongoing active disease, as indicated by clinical history or repeated clinical or magnetic resonance imaging (MRI) examinations. “Ongoing active disease” is evidenced as acute or subacute changes in clinical (relapses or progression) or MRI (active lesions, i.e., new T2- or gadolinium-enhancing lesions) parameters. It is also acknowledged that treatment should be begun as soon as possible in all eligible patients. Therapy should be continued unless a benefit is clearly lacking, side effects are intolerable, new data reveal other reasons for cessation, or a more effective approved therapy becomes available. If no benefit exists when using the current approved disease-modifying drugs, one should consider using other immunomodulatory agents that show promise but have not yet been proved efficacious in large randomized placebo-controlled clinical trials.

All patients must agree to a regular follow-up assessment by the prescribing physician; contact and communication between the managing clinician and MS patients are essential to maintain the patient-doctor relationship. About two-thirds of patients advocate routine visits every 3 or 6 months, but in general, people with MS would prefer more frequent visits (48). Because no safety data exist on the use of disease-modifying agents in pregnancy, patients should be advised to take appropriate measures to avoid pregnancy, and treatment should not be administered to women who are pregnant or breast-feeding. Men should consider that effects of treatments on their sperm are unknown.

It is recognized that a subgroup of patients may have “benign MS,” as suggested by a long history of clinical or MRI inactivity (51). Nevertheless, given the uncertainty as to these patients’ continued stability (i.e., disease inactivity), some physicians may choose to treat such patients.

Many factors may prompt initiation of therapy in the individual patient, such as an increase in frequency of relapses, severity of relapse, MRI scan and/or number of lesions, prevention of disease progression, and market availability. Number of relapses is the main reason for initiating therapy in MS patients (52). Across Europe, the mean number of relapses that individuals suffered was about four relapses before disease-modifying therapy was initiated. The most notable difference by country is that in Mediterranean countries (Spain, Greek, Italy), physicians tend to start disease-modifying treatment after fewer relapses and in the northern European countries, when the patient begins to deteriorate. Thus, more patients with SPMS are treated in these latter countries. In the UK and the Netherlands, patient request is mentioned significantly more frequently than in the other European countries, indicating the importance of the patient in choosing treatments (48).

At present in Europe, approximately 65 percent of RRMS patients and 50 percent of SPMS patients are on disease-modifying therapy (Avonex, Betaferon, Copaxone, or Rebif). Prescription of these disease-modifying therapies for RRMS is lowest in the UK and highest in Italy, Germany, and France. Not all people with MS receive long-term treatments, largely because clinicians still have questions relating to their use. Long-term efficacy and tolerability are by far the most important questions of concern, since there are fewer clinical and MRI data on patients treated with INF β or Cop 1. The question of mechanism of action is the next highest ranked factor, but some answers to this question are now available (43,53–55). Other minor factors are short-term efficacy and frequency of administration.

Interferons

INF β (1a and 1b) is presently a first-line treatment in RRMS and there is also evidence for its use in SPMS (47). New indications include early treatment after the first attack and PPMS; the latter is currently being examined in clinical trials (56,57).

INF β-1b (Betaferon) is given subcutaneously (8 MIU (millioninternational unit) every other day), while INF β-1a is given intramuscularly only once a week (Avonex, 6 MIU) or subcutaneously three times a week (Rebif, 6 MIU, or 12 MIU). In Europe, where Betaferon (INF β-1b) was granted a product license in late 1995, Avonex (INF β-1a) in 1997, and Rebif (INF β-1a) in 1998, there is a tenfold variation between countries in prescribing of INF β and no correlations between sales of INF β and numbers of neurologists in the respective countries. The take-up of prescriptions has been slow. In many countries, this has resulted from delay in establishing guidelines for clinical use, which are closely linked to the decision on who will pay. For example, the UK still has plans for management entry of all forms of INF β through a trial organized by the Department of Health (35). Since few comparative studies of these compounds have been performed, it is difficult to decide which of the two molecules should be used (INF β-1a or-1b).

Differences in the reduction of the number of the relapses have been negligible. It is not yet known whether the absence of an effect on EDSS progression in SPMS patients treated with INF β-1a in comparison with the INF β-1b study reflects differences in study design or differences in efficacy (47,58). Recent studies demonstrated that the INF β-1b molecule is more immunogenic than the INF β-1a molecule, as reflected by a greater occurrence of binding and neutralizing antibodies that can prevent the biologic effect of INF β (59,60). This may be due to the nonglycosylated chemical structure of the INF β-1b, which can produce aggregates and enhance antibody production.

The optimal dosage of INF has not yet been established. A definite dose effect has been reported in the INF β-1b trial (42,44) and more recently in patients treated with INF β-1a (53,61–64). However, individual variability in response can be dramatic, and a lack of dose response might reflect a plateau of the biological effect at a higher dose.

Adverse effects are similar with two preparations, except for the high frequency of skin reactions and rare necrosis with the subcutaneous preparations. Injection site necrosis was seen in 1 to 3 percent of INF β-1b-treated patients (42).

With no convincing evidence favoring INF β-1a or INF β-1b, a subjective element remains in deciding which INF β to prescribe, depending on the patient's and physician's perceptions and the pros and cons of the various dosage regimens and routes of administration.

Glatiramer Acetate (Copolymer 1)

Glatiramer acetate (Copaxone), formerly known as copolymer 1, is the acetate salt of a mixture of synthetic polypeptides containing four amino acids. Approved by the Food and Drug Administration (FDA) in 1996, it has been recently approved in 15 European countries to

reduce relapses in patients with RRMS. Glatiramer acetate will be marketed in Europe starting in the last quarter of 2001 after the granting of national marketing authorizations. Germany will be among the first launch countries—it has the largest population of MS patients in Europe. Glatiramer acetate represents an alternative to INF β therapy and may be the most useful for patients who become resistant to INF β treatment owing to serum interferon β-neutralizing activity. It has a more favorable adverse effect profile compared to other agents available to treat MS, and it is not associated with the risks of depression, menstrual disorders, or changes in hematological and biochemical parameters. The clinical efficacy, safety, and tolerability of daily subcutaneous injections of 20-mg glatiramer acetate have been documented in several placebo-controlled trials (65,66,45). Sustained clinical benefits of glatiramer acetate also have been recently reported in RRMS patients observed for 6 years (67). Several MRI studies have shown the positive effect of glatiramer acetate on gadolinium-enhanced and T2 lesions (68,69). The most recent study (a double-blinded randomized placebo-controlled European-Canadian multicenter, lasting 9 months) has demonstrated that there is a significant reduction in the total number of enhancing lesions in treatment with glatiramer acetate compared with placebo. The changes in T2 lesion volume also provide evidence that early treatment in the disease process may prevent the accumulation of the MRI-measured burden of disease. Thus, glatiramer significantly reduced MRI-measured disease activity and burden. All effects increased over time (70).

Azathioprine

Azathioprine is a nonspecific immunosuppressant, which is still widely used in Europe for patients with RRMS who do not respond to INF β therapy or in the eastern countries where the market availability of INF β is limited.

A well-known meta-analysis of five randomized, double-blind, placebo-controlled trials supported the conclusion that oral azathioprine (2 to 3 mg/kg/d) reduces the rate of relapse in MS but has no effect on the progression of disability in patients with RRMS, PPMS, and relapsing-progressive MS (71). A case-control study demonstrated that the overall risk of cancer from azathioprine is low in MS patients, although the data suggested a dose-response relationship and possibly an increased risk after about 10 years of continuous treatment (72). A recent report showed adverse effects from azathioprine in 55 percent of patients. The drug intolerance manifested early in the course of therapy, causing drug withdrawal within 2 months of initiation (73). Although withdrawal to adverse events in clinical trials was between 9 to 12 percent above placebo, the higher level of intolerance recently reported may be because patients in the outpatient setting are less motivated and, as such, are more likely intolerant to side effects than patients within trials (71).

Mitoxantrone

Mitoxantrone is a synthetic antineoplastic agent, which inhibits both DNA (deoxyribonucleic acid) and RNA (ribonucleic acid). The first double-blind, placebo-controlled, trial was conducted by the Italian mitoxantrone study group (74). Fifty-one RRMS patients were randomized to receive mitoxantrone (8 mg/m^2, monthly for 1 year) or placebo. The mean number of relapses was statistically significantly different between the mitoxantrone and placebo group during both the first and the second year, with a reduction by approximately 70 percent in the mitoxantrone group. Moreover, there was a noticeable trend toward a reduction in the number of new lesion on T2-weighted images in the mitoxantrone group.

In a multicenter, open, randomized trial, the French and British Mitoxantrone Study Group assessed the efficacy of this therapy on the development of inflammatory lesions by monthly MRIs with gadolinium enhancement over a 6-month period (75). Patients with very active RRMS and SPMS who developed one gadolinium-enhancing MRI lesion during a 2-month baseline period were randomized to receive either 20 mg of intravenous mitoxantrone plus 1 g of intravenous or only 1 g of IVMP each month. Twice as many patients receiving mitoxantrone experienced no relapses during the 6-month trial period as patients receiving methylprednisolone alone.

The European Mitoxantrone in Multiple Sclerosis (MIMS) Group has completed a large double-blind, randomized, placebo-controlled trial in patients in an active stage of MS using a three-group parallel design of 12 mg/m^2 or 5 mg/m^2 of mitoxantrone or placebo every 3 months. In this study, mitoxantrone showed a significant benefit on both relapses and disability. More frequently adverse events were nausea, alopecia, urinary tract infections, menstrual disorders, amenorrhea, transient leucopenia, and elevation of γ-glutamynaltransferase (76). Although mitoxantrone seems a promising agent in MS treatment, further study is

needed to assess both long-term efficacy and safety before more widespread use of this drug in MS treatment can be considered.

Methotrexate

Despite being available for many years, methotrexate has only recently been evaluated in MS. Methotrexate treatment can be considered in patients with progressive (especially secondary) MS, as long as no other therapies are available for this group.

Goodkin et al. reported data from a randomized double-blind placebo-controlled study that included 60 patients with chronic progressive MS (77). Sixty patients were randomized to receive oral methotrexate in a dosage of 7.5 mg or placebo once weekly for 2 years. Significantly, less progression of impairment was observed in the methotrexate group than in the placebo group. The difference in outcome between treatment groups was evident within 6 months of initiating therapy and was sustained throughout the 2-year study period. No serious adverse effects were associated with this treatment.

Intravenous Immunoglobulin

Intravenous immunoglobulins (IVIG) have been used successfully in several immunological disorders and have become attractive as a treatment of MS because of their putative remyelination-inducing effect combined with immunomodulating action. Two earlier studies failed to show efficacy of IVIG in patients with RRMS or progressive MS (78,79).

The Austrian Immunoglobulin in MS (AIMS) trial randomized 150 patients with RRMS to receive either IVIG at a low dosage of 0.15 to 0.2 g/kg body weight or physiological saline every month over a 2-year period. The EDSS score had an improvement of one point or more in 31 percent of the IVIG-treated patients, compared with 14 percent of the placebo group. IVIG treatment was associated with a 59 percent reduction in the annual relapse rate compared to placebo, and this drop in relapse rate following IVIG was noticeable within the first 6 months of treatment. Side effects were rarely observed (80). A study by Achiron et al. reported a significant reduction in relapse rates in patients with RRMS receiving bimonthly IVIG 0.4 g/kg infusion after a loading dose of 0.4 g/kg/d for 5 days compared with the placebo group (81). There was a trend toward reduced neurological disability in the IVIG group, whereas a minor increase occurred in the placebo groups. Distribution of the change in disability over time was significantly in favor of the IVIG treatment.

Sorensen et al. examined the effect of IVIG on disease activity using frequent gadolinium-enhanced MRI scans in a crossover study of 26 patients with RRMS or SPMS (82). IVIG treatment consisted of infusion of 1 g/kg body weight per day for 2 consecutive days at monthly intervals. The results showed that IVIG treatment significantly reduced the mean number of new and total gadolinium-enhancing lesions by approximately 60 percent compared with placebo. There was no significant reduction of relapse frequency between the two groups. An unexpectedly high number of acute and chronic adverse events occurred in this study. More than 50 percent of patients experienced one or more adverse events from IVIG treatment.

A final recommendation concerning IVIG in MS cannot be given at present. General use of IVIG in MS should await the result of further placebo-controlled, double-bind trials, and currently, the optimal dosage regimen and the mode of action of IVIG remain unclear.

Combination Therapy

On data, with the limited number of treatments available, potential combination therapies are few. Combinations ideally target different aspects of the disease pathology, have discrete and preferably exclusive side-effect profiles, and are synergistic rather than simply additive. These treatment regimes often cannot be tested in animal models, so circumstantial clinical experiences in patients should be gathered systematically. Combination therapies, however, offer particular challenges that will need to be overcome, including the ethical position concerning placebo-controlled trials and the size of the trail necessary to show improved benefit of the combination over monotherapy. Furthermore, one must borne in mind that treatment combinations might produce unpredictable effects that may even worsen the disease course in individual patients.

In Europe, many trials on combination therapy are planned or underway. A 2-year study evaluating the clinical efficacy of IFN β-1a versus IFN β-1a plus azathioprine is undergoing in France (83).

A multicenter French-Italian study is comparing the effect of monthly mitoxantrone plus methylprednisolone, followed by IFN β-1b verses methylprednisolone alone and followed by IFN β-1b over a 3-year period (83). In a recent published Italian study, 161 patients with RRMS

were randomized in two treatment arms: 8 MIU of INF β-1b subcutaneously injected every other day either alone or combined with 1,000 mg of monthly IVMP (84). The primary aim of the study was to investigate whether the combination of monthly IVMP and INF β therapy over a 12 month treatment period can reduce the frequency of neutralizing antibodies against INF β in RRMS patients. Moreover, the study provided data on safety and tolerability of the combination therapy used. The results showed a lower probability to develop neutralizing antibodies during the first year in patients treated with the combination therapy than in those treated with INF β alone.

Complementary Therapy

Complementary therapies are unavoidable aspects of MS management, and at least some of these are potentially beneficial to people with the disease. The most common treatments used in Europe are nutrition supplements, vitamins and minerals, yoga and meditation, and calcium aminoethylphospate. Alternative treatments that have received increasing attention are cannabis and their active components (cannabinoids); studies in several European countries (trials on marijuana in Amsterdam) aim to address the question of whether cannabinoids can alleviate symptoms such as postoperative pain and muscle pain in people with MS.

These therapies are attractive to people with MS because they are perceived as the natural option and as a means by which they may gain some personal control over the disease. However, there is no evidence to support any effect of these interventions or of other complementary therapies on the course of MS.

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