Therapeutic strategies in childhood multiple sclerosis

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Abstract: Multiple sclerosis (MS) in children and adolescents accounts for 3–10% of the whole MS population, and is characterized by a relapsing course in almost all cases. The frequency of relapses is higher than in adult onset MS, at least in the first years of evolution. The objective of treatment is to speed the recovery after a relapse, to prevent the occurrence of relapses, and to prevent disease progression and neurodegeneration. The use of drugs for MS in children and adolescents has not been studied in clinical trials, so their use is mainly based on results from trials in adults and from observational studies. There is a consensus to treat acute relapses with intravenous high-dose corticosteroids. The possibility of preventing relapses and disease progression is based on the use of immunomodulatory agents. Interferon-beta (IFNB) and glatiramer acetate (GA) have been demonstrated to be safe and well tolerated in pediatric MS patients, and also to reduce relapse rate and disease progression. Cyclophosphamide and natalizumab could be offered as second-line treatment in patients with a poor response to IFNB or GA. New oral and injectable drugs will be available in the near future: if safe and well tolerated in the long-term follow up of adults with MS, they could be tested in the pediatric MS population.

Keywords: adolescence, childhood, cyclophosphamide, glatiramer acetate, interferon beta, intravenous immunoglobulin, intravenous methylprednisolone, mitoxantrone, multiple sclerosis, natalizumab

Introduction

The onset of multiple sclerosis (MS) typically occurs in adults at about 30 years of age; however the onset before 18 years of age is being increasingly recognized worldwide, accounting for 3–10% of all individuals with MS [Banwell *et al.* 2007]. The clinical features of pediatric MS (Ped-MS) have been delineated in several retrospective, prospective and longitudinal studies. Overall, they are not different from those of the adult form, but some findings seem to be peculiar to Ped-MS, being more frequent in comparison with adult MS (A-MS):

- the onset with cerebellar and brainstem dysfunction [Banwell *et al.* 2007; Ghezzi *et al.* 2002];
- the polysymptomatic presentation, with fever, headache, lethargy, meningism, seizures (acute disseminated encephalomyelitis-like onset), especially in very young patients [Banwell *et al.* 2007];
- the evolution with a high number of relapses, specially in the first years of the disease, and

an annualized relapse rate of 1–1.9, which is higher than in A-MS [Gorman *et al.* 2009; Renoux *et al.* 2007; Ghezzi *et al.* 2002; Gusev *et al.* 2002];

- the evolution, with a predominance of the relapsing–remitting (RR) course, in more than 90% of cases, and the very low frequency of the primary progressive course [Banwell *et al.* 2007];
- the progression, with a longer interval but a lower age to reach mild and severe disability.

In fact, the majority of Ped-MS patients develop mild and severe disability, as well as the shift to the secondary progressive phase of MS, after a longer disease interval but at a younger age, compared with A-MS [Renoux *et al.* 2007; Boiko *et al.* 2002]. So, at a given age, patients with onset in childhood are more disabled than those with a later onset.

The frequency of relapses (or the interattack interval) in the first few years after disease onset is a negative prognostic factor as it correlates with

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an increased disease severity and with an earlier entry into the secondary progressive phase of MS [Banwell *et al.* 2007].

Recent studies have demonstrated that approximately one third of children and adolescents with MS develop cognitive dysfunction early: processing speed, attention, language and working memory are involved, with a negative impact on academic functioning and on social relationships [Amato *et al.* 2008; Banwell and Anderson, 2005; MacAllister *et al.* 2005].

The high number of relapses in the first years of the disease, and the high frequency of patients with the RR course suggest that the inflammatory process is more pronounced in children with MS compared with adults. This pattern is also suggested by the frequent pleocytosis in the cerebrospinal fluid (CSF) [Pohl *et al.* 2004], and by the aspect of magnetic resonance imaging (MRI) lesions [Waubant *et al.* 2009; Chabas *et al.* 2008]. It seems reasonable to expect that drugs targeting the inflammatory process could have a positive beneficial effect in patients with Ped-MS. As in A-MS, the objective of the treatment is to prevent the occurrence of brain damage, and to limit the damage once it has occurred. In other words:

- to speed the recovery and prevent disability after a relapse;
- to prevent the occurrence of relapses;
- to prevent disease progression, disability and cognitive impairment.

As diagnosis of MS has a major impact on patients and their families, psychological and social support should be offered to reduce the emotional impact of MS, to face the physical and psychological limitations in family, school and social activities, and to strengthen the compliance with medication. In addition to pharmacological treatment, the care of children and adolescents with MS requires a multidisciplinary team, with occupational and physiotherapists, psychologists and social workers, in addition to pediatric or adult neurologists [Banwell *et al.* 2007].

The effects of drugs in Ped-MS have not been formally evaluated in clinical trials, so their use is based on results in A-MS, experts' opinion, case reports, and data from observational studies. There are no approved guidelines for the

treatment of Ped-MS, but recently a proposal has been published by a group of adult and child neurologists, with the objective of defining a shared approach for the treatment of children and adolescents with MS [Ghezzi *et al.* 2010].

In the present review, the most relevant studies related to the treatment of Ped-MS are presented, with a hint to possible future therapeutic strategies.

Management of acute MS relapses

Corticosteroids remain a mainstay of treatment for relapses in MS of adults, with class I and class II evidence of speeding functional recovery after acute attacks [Goodin *et al.* 2002]. Based on the evidence from A-MS studies, there is a general consensus to treat acute relapses of MS in children and adolescents with intravenous methylprednisolone 10–30 mg/kg for 3–5 days [Ghezzi *et al.* 2010; Banwell, 2005; Ghezzi 2005], although the effectiveness of corticosteroids has not been clearly demonstrated by specific studies. In adults with MS, oral corticosteroids [Morrow *et al.* 2004; Barnes *et al.* 1997] have a similar effectiveness and the benefit of a more practical route of administration, but this schedule of administration has not been tested in pediatric patients.

The treatment of acute relapses with corticosteroids hastens the recovery but does not modify the long-term evolution of the disease [Compston and Coles, 2002; Optic Neuritis Study Group, 1997]. Only a single class II study [Zivadinov *et al.* 2001] has shown that regular pulsed corticosteroids are useful in the long-term management: in a cohort of 88 adult MS randomly assigned to pulses of methylprednisolone (MP) (5 g over 5 consecutive days every 4 months for 3 years, subsequently every 6 months for 2 years) or MP at the same dose schedule only for relapses, the relapse rate was equivalent but disability was less in subjects treated with pulsed MP.

In patients with a severe attack and/or an incomplete recovery after high-dose corticosteroids, a second pulse of corticosteroids can be offered [Banwell, 2005]. Alternatively, intravenous immunoglobulins can be administered, usually 2 g/kg over 2–5 days. This treatment does not have proven efficacy in treating acute relapses, and only has beneficial effects in preventing some relapses in adults with RRMS,

demonstrated by studies with methodological limitations and small size [Elovaara *et al.* 2008; Banwell, 2005; Goodin *et al.* 2002].

For patients suffering from severe steroid-resistant relapses, plasma exchange can be offered as a therapeutic option, based on results of randomized studies in adults and sporadic use in single MS pediatric cases [Lehmann *et al.* 2006; Weinshenker *et al.* 1999; Takahashi *et al.* 1997].

Treatment to prevent relapses and disease progression

First-line disease-modifying treatment of Ped-MS

Three beta-interferons (Avonex® 30 µg given intramuscularly [i.m.] once a week, Rebif® 22 µg or 44 µg given subcutaneously [s.c.] three times a week, Betaferon® 250 µg given s.c. every other day) and glatiramer acetate (GA; Copaxone®, 20 mg given s.c. every day) are licensed for the treatment of RRMS, and one beta-interferon (Betaferon® 250 µg given s.c. every other day) for the treatment of secondary progressive MS.

There is a large body of evidence, based on results of randomized, double-blind, placebo-controlled trials with class I evidence, that these immunomodulatory agents (IAs):

- reduce relapse rate and, to a lesser degree, the progression of disability in adults with RRMS [PRISM Study Group, 1998; Jacobs *et al.* 1996; Johnson *et al.* 1995; The IFNB Multiple Sclerosis Study Group and the UBC MS/MRI Analysis Group, 1995; The IFNB Multiple Sclerosis Study Group, 1993];
- delay the time to a second MS attack [Comi *et al.* 2009, 2001; Kappos *et al.* 2006; Jacobs *et al.* 2000] and the risk of confirmed disability [Kappos *et al.* 2007b], if given in subjects at their first demyelinating episode;
- have a profound effect on MRI lesions and activity [Soriani *et al.* 2009]; in patients treated with interferon-beta (IFNB)-1a 22 µg weekly, this drug reduced cerebral atrophy, compared with placebo [Filippi *et al.* 2004].

The effect of IAs to reduce relapse rate and disease progression has been confirmed in post-marketing studies, with a clear demonstration that IAs are also more effective in everyday clinical practice if started earlier [Trojano *et al.* 2009, 2007].

There is also some evidence that IFNB improves cognitive functioning [Patti *et al.* 2010; Kappos *et al.* 2009; Fisher *et al.* 2000].

These positive clinical effects of IAs in adults, and their overall positive safety profile, have encouraged the use of these drugs in Ped-MS patients. At present, there have been no formal clinical trials of IAs in the Ped-MS population; the effect of these medications has been evaluated in some preliminary studies on a small number of cases [Mikaeloff *et al.* 2001; Waubant *et al.* 2001], mainly addressed to evaluate their safety, and subsequently in studies including a larger number of cases [Ghezzi *et al.* 2009a, 2005; Banwell *et al.* 2006; Tenenbaum and Segura, 2006; Pohl *et al.* 2005; Kornek *et al.* 2003], also providing data on the clinical effects.

In two studies, the data of patients treated with IAs were compared with those of an untreated group. In a study of 16 patients randomly assigned to IFNB-1a 30 µg i.m. weekly or placebo, the active treatment reduced relapse rate, disability progression and MRI measures [Pakdaman *et al.* 2006]. In a cohort of 197 Ped-MS patients, 24 patients treated with IFNB showed a significant reduction in relapse rate compared with subjects who did not receive any therapy [Mikaeloff *et al.* 2008].

The main demographic and clinical findings of the cohorts of Ped-MS patients treated with IAs are summarized in Table 1. In comparison with the pretreatment phase, a reduction of relapse rate is reported in almost all studies, as well as a stabilization of disability, assessed by means of Expanded Disability Status Scale (EDSS) score, confirming the positive effect on disease evolution observed in A-MS patients.

The frequency of adverse events reported in these studies is similar to those observed in a meta-analysis of A-MS patients [Filippini *et al.* 2003] (Table 2). The wide range of frequency of adverse events, summarized in Table 2, is likely to be due to the use of different methods of evaluation and IFNB types.

Data in children are less consistent: Tenenbaum and Segura [2006] treated eight children under 10 years of age with Rebif, and observed a statistically significant reduction of relapse rate. Ghezzi *et al.* [2009a] treated 23 patients under 12 years of age with IAs, finding a reduction of

Table 1. Main demographic and clinical data of patients treated with interferon-beta (IFNB) and glatiramer acetate, according to literature data.

	<i>n</i>	Age at MS onset (years)	Treatment duration (months)	Side effects	Clinical results
AVONEX Waubant <i>et al.</i> [2001]	9	11	17	<ul style="list-style-type: none"> • Flu-like symptoms (44%) • Injection site reaction (11%) 	No impact on relapse rate
Pakdaman <i>et al.</i> [2006]	16 (8 treated)		48	<ul style="list-style-type: none"> • No significant side effects • No treatment discontinuations 	In treated group: <ul style="list-style-type: none"> • significantly fewer relapses and disability progression. • fewer new MRI lesions
Ghezzi <i>et al.</i> [2009a]	77	11.4	53.6	<ul style="list-style-type: none"> • Flu-like syndrome (24.7%) • Headache (19.5%) • Myalgia (9.1%) • Fatigue (6.5%) • Skin injection reaction (6.5%) • Psychological disturbances (2.6%) • Increased liver enzymes (5.2%) • Thyroid dysfunction (10.4%) • Lymphopenia (1.3%) 	<ul style="list-style-type: none"> • Decreased relapse rate (from 2.5 to 0.4) • Final EDSS unchanged • 26% of patients lost to follow up or stopped the therapy (after 3.9 years) • 30% of patients shifted to other drugs (mean follow up duration 5.3 years)
REBIF Tenenbaum and Segura [2006]	24	9.3	44.4	<ul style="list-style-type: none"> • 2 serious adverse events (chronic arthritis 1, attempted suicide 1) • Flu-like symptoms (58%) • Myalgia/arthritis (17%) • Injection site reaction (75%) • Abnormal liver enzymes (33%) 	<ul style="list-style-type: none"> • Significant reduction of relapse rate • Decreased EDSS in subjects ≤ 10 years old
Pohl <i>et al.</i> [2005]	51	13.4	21.6	<ul style="list-style-type: none"> • Injection site reaction (71%) • Flu-like symptoms (65%) • Gastrointestinal symptoms (10%) • Abnormal liver enzymes (35%) • Abnormal blood counts (39%) • Discontinued 9/51 	<ul style="list-style-type: none"> • Decreased relapse rate (from 1.9 to 0.8) • EDSS score stable in 48/51
Ghezzi <i>et al.</i> [2009a]	39	12.6	59.9	<ul style="list-style-type: none"> • Injection skin reaction (18%) • Flu-like syndrome (7.7%) • Headache (7.7%) • Myalgia (5.1%) • Fatigue (2.8%) • Nausea (2.8%) • Lymphopenia (7.7%) 	<ul style="list-style-type: none"> • Decreased relapse rate (from 3.2 to 0.9) • Final EDSS unchanged • 64% of patients shifted to other treatments (mean follow up duration 3.6 years)
BETAFERON Banwell <i>et al.</i> [2006]	43	10.9	29.2	<ul style="list-style-type: none"> • No serious or unexpected events • Flu-like symptoms (35%) • Injection site reaction (20.9%) • Abnormal liver enzymes (21%) • Discontinued 25/43¹ 	<ul style="list-style-type: none"> • Reduction of relapse rate of 50%

(continued)

Table 1. Continued

	<i>n</i>	Age at MS onset (years)	Treatment duration (months)	Side effects	Clinical results
COPAXONE Kornek <i>et al.</i> [2003]	7	13.7	24	<ul style="list-style-type: none"> • No laboratory abnormalities • Transient systemic reaction (14%) 	<ul style="list-style-type: none"> • 28% relapse-free • No change in mean EDSS
Ghezzi <i>et al.</i> [2009a]	14	13.1	74.6	<ul style="list-style-type: none"> • Occasionally chest pain • No hematological abnormality 	<ul style="list-style-type: none"> • Decreased relapse rate (from 2.9 to 0.2) • Final EDSS slightly improved
AVONEX/REBIF/BETAFERON Mikaeloff <i>et al.</i> [2001]	13	13.1	12	<ul style="list-style-type: none"> • Flu-like symptoms (69%) • Injection site reaction (19%) • Transient abnormal liver enzymes (6%) 	<ul style="list-style-type: none"> • Treatment failure in 25% • EDSS stable at the end of follow up
Mikaeloff <i>et al.</i> [2008]	12	Mean 11.0	17.1	NA	<ul style="list-style-type: none"> • Significant delay to the subsequent attack • Less frequent (but not significant) occurrence of severe disability
EDSS, Expanded Disability Status Scale.					

relapse rate and a stabilization of EDSS at the end of follow up. IAs were well tolerated, with a frequency of adverse events similar to those observed in the whole cohort of adolescents.

The available literature on the treatment with Copaxone is limited to a small case series [Ghezzi *et al.* 2009a; Kornek *et al.* 2003]. A reduction of relapses has been shown, together with a stabilization of disability. No major clinical adverse events and laboratory abnormalities were reported during the treatment with GA. Dyspnea, chest pain, transient systemic reaction (flushing, dizziness) and fatigue have been observed in 7–14% of pediatric patients treated with GA. Hematological and hepatic abnormalities are not reported in patients treated with GA.

The overall positive results of IFNB and GA in Ped-MS has led the European Regulatory Agency to modify the label of drugs including the following statement: “*limited published data suggest that safety profile in adolescents from 12 to 16 years of age receiving IFNB or GA is similar to that seen in adults (...)*”, whereas there is not enough information on the use of IFNB or GA in children below 12 years of age.

Clinical results have also been confirmed after a long-term follow up of more than 4 years (Table 3) [Ghezzi *et al.* 2009a].

Based on the evidence that:

- IAs are safe and well tolerated in children and adolescents with MS;
- IAs have confirmed an effect in reducing relapse rate and disease progression in this population;
- IAs are more advantageous in A-MS if administered in early phases of the disease;

a panel of experts [Ghezzi *et al.* 2010] has recommended to start early the therapy with IAs in children and adolescents with relapsing MS, to prevent the occurrence of relapses, to prevent the accumulation of disability and to reduce brain damage. Subjects at the first demyelinating episode must be monitored clinically and with MRI study; a second MRI is strongly recommended 3–6 months later. Treatment should be offered if a new clinical episode occurs or a second MRI shows disease activity (new T2 or gadolinium-enhanced [Gd+] lesions). There is no agreement on the use of IAs in Ped-MS

Table 2. Frequency of adverse events in pediatric multiple sclerosis (Ped-MS) patients treated with interferon beta, according to the studies reported in Table 1, compared to the frequency observed in adults [Filippini *et al.* 2003].

Adverse events	Frequency in Ped-MS (range)	Mean frequency in adult MS [Filippini <i>et al.</i> 2003]
Flu-like symptoms	8–71%	47%
Injection skin reaction	7–75%	61%
Headache	8–28%	50%
Myalgia	5–17%	25%
Fatigue	3–6%	18%
Nausea	3–10%	32%
Increased liver enzyme	6–33%	—
Thyroid dysfunction	8%	—

Table 3. Clinical data of a cohort of pediatric multiple sclerosis (MS) patients treated with immunomodulatory agents, after a long-term follow up [Ghezzi *et al.* 2009a].

	Avonex <i>n</i> = 77	Rebif/Betaferon <i>n</i> = 39	Copaxone <i>n</i> = 14
Mean age of MS onset	11.4 ± 3.1	12.6 ± 2.6	13.1 ± 1.5
Treatment duration	53. ± 27.0	59.9 ± 39.5	74.6 ± 35.5
Annualized pretreatment relapse rate	2.5 ± 1.9	3.2 ± 2.5	2.9 ± 1.8
Relapse rate during the treatment	0.4 ± 0.6	0.9 ± 1.1	0.2 ± 0.3
EDSS pretreatment	1.3 ± 1.0	1.7 ± 0.8	1.1 ± 0.4
Final EDSS	1.5 ± 1.2	2.0 ± 1.4	1.0 ± 0.9
EDSS, Expanded Disability Status Scale.			

patients after the first demyelinating episode, but it could be considered in some selected cases with an aggressive onset (many/large MRI lesions, Gd+ lesions).

In almost all patients, full doses of IAs are administered. Most authors suggest initiation of IFNB at one quarter to one half of the recommended adult dose, reaching the full dose within 1–3 months if it is well tolerated. Hematological tests (blood cell count, liver enzymes, bilirubin, thyroid function) should be performed at months 0, 1, 3, and every 3 months in the first year, and then successively every 3–6 months [Ghezzi *et al.* 2010]. In a cohort of patients treated before 12 years of age, 16 of them were treated with Avonex, 5 with Rebif, 2 with GA, with the same dose used in adolescents and adults. Adverse events and tolerability were similar to those observed in the whole cohort of pediatric patients [Ghezzi *et al.* 2009a].

Failure of first-line treatment

Relapses and disease progression can occur in spite of treatment with IAs. As no medication prevents the risk of a new attack by 100%, in clinical

practice it is not simple to decide whether to continue the treatment with the same drug in a patient who continues to have relapses. Clinical findings (number of relapses, frequency of relapses during the treatment compared to the pretreatment phase, increase of EDSS score), and MRI data (new T2 lesions, Gd+ lesions) have been included as criteria to define treatment failure, but at present no consensus has been reached on the use of clinical or MRI markers [Portaccio *et al.* 2006; Rio *et al.* 2006; Freedman *et al.* 2004].

A panel of experts [Ghezzi *et al.* 2010] has suggested that patients may be deemed as failing to show an adequate response to a given medication if they meet one or more of the following criteria:

- relapse frequency, evaluated for 12 months of sustained, compliant therapy, is maintained at, or exceeds, the pretreatment relapse rate (assuming an annualized relapse rate of >1);
- severity of relapses on treatment is such that rescue therapy (intravenous immunoglobulins, plasma exchange) is consistently required for the management of acute relapses;

- physical disability accrual exceeds at least 2 points on the EDSS, sustained for more than 3 months.

The presence of two or more new T2 lesions or one Gd+ lesion on MRI scans obtained at least 1 year after sustained therapy with IFNB is indicative of a likelihood of further relapses in A-MS [Rio *et al.* 2009, 2008; Tomassini *et al.* 2006; Rudick *et al.* 2004], but this finding was not included as proof of treatment failure in Ped-MS as data are not available regarding the natural history of lesion accrual in treated and untreated patients.

For patients treated with IFNB, there is evidence that the presence and persistence of neutralizing antibodies (NABs) to IFNB is related to a lack of biological activity of IFNB [Farrell *et al.* 2008; Malucchi *et al.* 2008; Sørensen *et al.* 2006, 2005]. Patients failing IFNB or demonstrating IFNB NABs can be offered therapy with GA [Capobianco *et al.* 2008]; an increase of IFNB dosage can also be considered for patients without NABs. Patients failing GA therapy can be considered for treatment with IFNB.

In a study of 130 Ped-MS patients, approximately 30% of cases altered treatment between IFNB and GA: the change of treatment regimen appeared to be advantageous, as the relapse rate continued to be lower with respect to the pre-treatment value [Ghezzi *et al.* 2009a].

For patients with a very active form of MS, treatment with second-line drugs should be considered.

Second-line treatments in Ped-MS

Natalizumab (NA), mitoxantrone and cyclophosphamide (Cy) can be offered as options for adults with very active/rapidly progressing RRMS and poor response despite treatment with IFNB or GA.

NA has shown a strong effect on disease activity in a double-blind, placebo-controlled trial [Polman *et al.* 2006] reducing the relapse rate by 68% and slowing disease progression by 54% after 2 years of treatment. In a *post-hoc* study, disease activity was suppressed completely in 29.5% of cases and they remained free of clinical and radiological activity (defined by the criteria of new/enlarged lesions, or Gd+ lesions) after 2 years of treatment [Havrdova *et al.* 2009].

NA is administered i.v. every 28 days and is well tolerated; however, the occurrence of JC-virus-mediated progressive multifocal leukoencephalopathy (PML), with a risk of about 1:1000, the possible increased risk of melanoma, the potential hepatotoxicity must be taken into account [Kappos *et al.* 2007a; Yousry *et al.* 2006]. Many postmarketing studies are ongoing in adults to establish these risks in clinical practice.

NA was demonstrated to be effective in two single cases with very active MS and failure to first line treatments [Appleton and Boggild, 2009; Boriell *et al.* 2009], and in three MS patients with many relapses and MRI activity who were treated with NA 3-5 mg/kg every 28 days, obtaining a suppression of disease activity [Huppke *et al.* 2008]. NA was safe and well tolerated in a cohort of 38 subjects with juvenile Crohn's disease, treated with this drug [Hyams *et al.* 2007].

Preliminary data of a cohort of 17 cases with active MS (3.1 relapses in the previous year) and MRI activity (2.3 Gd+ lesions at baseline), a mean age of 14.2 years, and a mean of 10 NA infusions have been presented recently [Ghezzi *et al.* 2009b]. Following NA treatment, the relapse rate decreased from 3.1 to 0.1, EDSS from 2.7 to 2 at the last observation, and no subject developed Gd+ lesions during the treatment. NA was well tolerated and the dose was the same as used in adults.

Data are not available on long-term follow up of NA, and further studies are necessary to better define the role of NA as a second-line treatment of Ped-MS, although these preliminary data show that NA is very effective and well tolerated in Ped-MS.

Mitoxantrone is approved for the treatment of active MS in adults, and it could also be offered as a second-line therapy in selected Ped-MS patients with active MS, but the increased risk of severe adverse events such as leukemia, cardiomyopathy, infections and infertility, in addition to side effects such as nausea, vomiting and hair loss, strongly limit the use of this drug. In particular, some recent studies have shown a high risk of leukemia, 1:333 in a study including 5472 cases [Ellis and Boggild, 2009] and 1:140 in an Italian multicenter survey of 2854 cases [Martinelli *et al.* 2009]. There are no data on the use of mitoxantrone in Ped-MS.

Cy is not licensed for MS treatment, but it has a powerful effect of reducing disease activity in A-MS. In a recent paper Cy has been used in a group of 17 Ped-MS patients with a mean age of 15 years and evidence of disease activity, as they received a mean of 2.5 steroid courses in the previous year, in spite of other first- (14 cases) and second-line (9 cases) treatments [Makhani *et al.* 2009]. Three different treatment regimens were used: induction therapy alone, induction therapy with pulse maintenance therapy, and pulse maintenance therapy alone. The dose ranged from 500 to 1000 mg/m². EDSS score was reduced in most cases after 1 year. Three children remained relapse free, 12 reduced their annualized relapse rate from 3.8 to 1.6. Adverse events were frequent (nausea and vomiting in 15 patients, lymphopenia in 16, anemia in 10, alopecia in 10, menstrual disorders in 5 out of 10 girls; in rare cases thrombocytopenia, hematuria, infections, fatigue, urticaria, myalgias); they were severe in a few patients (amenorrhea in 3, sterility in 1, osteoporosis in 2, bladder cancer in 1). For these reasons the authors concluded that Cy should be considered a second-line treatment for carefully selected and monitored children with aggressive MS refractory to first-line therapies.

To conclude, limited published data seem to suggest that NA and Cy are effective in Ped-MS with active course. Further studies are necessary to define the dose, the treatment duration, and the occurrence of short- and long-term adverse effects.

New treatments

Many new oral drugs are under evaluation in phase II or phase III trials [Gasperini and Ruggieri, 2009]:

- Cladribine is a new oral immunosuppressant with a strong effect in reducing clinical relapses, disease progression, and MRI activity. A phase III trial has randomized 1326 patients to receive two different cumulative doses of cladribine or placebo in a 1:1:1 ratio [Giovannoni *et al.* 2010]; the active treatment significantly reduced the annualized relapse rate (0.14 and 0.15, respectively, versus 0.33), the risk of disease progression, and brain lesion count on MRI. A phase III trial evaluating the effect of cladribine to delay the conversion to MS after a first demyelinating episode is ongoing.
- Fingolimod is another powerful oral immunomodulating agent; in a phase III trial including

1292 patients, oral fingolimod at a dose of either 1.25 or 0.5 mg significantly reduced annualized relapse rate compared with IFNB-1a 30 µg weekly (0.20 and 0.16, respectively, versus 0.33) [Cohen *et al.* 2010]. In another study [Kappos *et al.* 2010] the same doses of fingolimod were compared with placebo after 24 months of treatment. Both doses of fingolimod reduced relapse rate (0.16 and 0.18, respectively, versus 0.40), the probability of disease progression (16.6% and 17.7%, respectively, versus 24.1%), and MRI measures.

- Teriflunomide has been demonstrated to reduce MRI activity in a phase II study, together with some positive clinical outcome measures [O'Connor *et al.* 2006]; a phase III trial is ongoing.
- Fumarate reduced several measures of MRI activity and reduced relapse rate by 32% in a phase II study [Kappos *et al.* 2008]; a phase III study is ongoing.
- Laquinimod has shown an effect on MRI and clinical measures given at the dose of 0.6 mg in a phase II study enrolling 306 patients [Comi *et al.* 2008]; a phase III trial is ongoing.

Monoclonal antibodies targeting cells involved in the immunopathological process of MS (CD20+ B cells, Rituximab; CD25+ B cells, Daclizumab; CD52 on lymphocytes and monocytes, Alentuzumab) are promising drugs for the treatment of MS. Rituximab was effective in a phase I study including RRMS [Bar-Or *et al.* 2008], and partially effective in primary progressive MS patients with evidence of MRI activity [Hawker *et al.* 2009]. It was effective in an adolescent with a severe evolution of MS [Karenfort *et al.* 2009]. Daclizumab reduced disease activity in RRMS patients who experienced persistent MS disease activity with IFNB therapy in a phase II study [Bielekova *et al.* 2009].

Alentuzumab strongly reduced the rate of sustained accumulation of disability and the annualized relapse rate in comparison with Rebif in a phase II trial [The CAMMS223 Trial Investigators, 2008]. A phase III trial is ongoing. The major risk of monoclonal antibodies is related to the development of PML [Carson *et al.* 2009].

Conclusions

At present, no formal clinical trials of IAs have been performed in Ped-MS patients, and the use of medications is mainly based on results on clinical trials in adults. IAs such as IFNB and GA

appear to be safe and well tolerated in children and adolescents with MS.

According to the suggestions of a panel of experts, IAs should be given to children and adolescents with active RRMS to reduce the risk of relapses and the risk of disease progression. A careful clinical follow up of patients must be planned to prevent and minimize adverse effects, and to adapt the treatment according to the clinical evolution of MS.

In cases that have a poor response to a drug, clinicians can consider the option to increase the dose (if possible) or to switch subjects to other first-line or second-line treatments. Cy and NA can be offered to patients with an active evolution and a poor response to first-line treatments. Further studies are needed to better evaluate their safety.

In the future many oral or injectable agents will become available for the treatment of adults with MS. Most of them seem to have a stronger clinical effect compared with currently available drugs, others will probably have an equal clinical effect but with the advantage of an oral administration. The extension of a new drug to Ped-MS needs careful demonstration of its safety in adults and careful evaluation of potentially negative effects in children given its mechanism of action. In particular, the risk of infections should be carefully considered, owing to the greater exposure to infections in young subjects, of cancer, and the potential effects on reproductive function and physical development, with careful surveillance of short- and long-term safety and tolerability. Further studies will define their possible use in Ped-MS. It will become possible to select the most useful and best-tolerated drug for each patient.

Conflict of interest statement

Dr. Angelo Ghezzi received honoraria for speaking from Bayer Schering, Biogen-Dompé, Merck-Serono, and Novartis, for consultancy from Actelion, Merck-Serono, and Novartis, received support for participation to National and International Congresses from Bayer Schering, Biogen-Dompé, Merck-Serono, Novartis, Sanofi-Aventis.

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