Reumatismo, 2012; 64 (6): 350-359

Therapeutic strategies in severe neuropsychiatric systemic lupus erythematosus: experience from a tertiary referral centre

A. Bortoluzzi, M. Padovan, I. Farina, E. Galuppi, F. De Leonardis, M. Govoni

Unità Operativa Complessa e Sezione di Reumatologia, Dipartimento di Medicina Clinica e Sperimentale, Università di Ferrara e Azienda Ospedaliero-Universitaria S. Anna, Ferrara, Italy

SUMMARY

The management of neuropsychiatric systemic lupus erythematosus (NPSLE) still remains empirical and based on clinical experience due to the lack of randomized controlled trials. Objective: to report the experience accumulated in a single tertiary referral centre about treatment of severe cases of NPSLE patients and to discuss therapeutic strategies on the background of EULAR recommendations. Methods: retrospective analysis of all consecutive cases of severe NPSLE treated in our centre since 1990 to 2010, satisfying the 1999 ACR criteria. Results: among 633 SLE patients who consecutively attended our centre, 231 (36%) displayed at least one neuropsychiatric (NP) manifestation for a total of 408 events attributable to SLE. Thirty-one patients (4.8%), 27 females and 4 males, experienced 35 major NP events requiring immunosuppressive therapy (including 3 relapses and 1 new event). An aggressive immunosuppressive strategy was applied to those patients with an immune mediated inflammatory NP event and to those patients with an increased disease activity as judged by ECLAM and SLEDAI scores. Overall at the end of the therapy 74% of the patients reached clinical remission or significant improvement of their symptoms measured by mean SLEDAI (from 10.09±1.09 to 2.04±0.52, P<0.0001) and ECLAM (from 4±0.34 to 1.38±0.37, P<0.001) scores. Conclusions: the prevalence of NP involvement, described in our case series, is similar to those reported in literature as well as the treatment strategies applied. Nowadays, it is not possible to establish a standardized approach for each single NPSLE manifestation, and different therapeutic strategies must be tailored taking into account the most probable pathogenic mechanism involved, the general disease activity background, the co-morbidities, the type and the stage of the systemic involvement.

Key words: *Systemic lupus erythematosus, neuropsychiatric manifestations, treatment.*

Reumatismo, 2012; 64 (6): 350-359

INTRODUCTION

The neuropsychiatric involvement in systemic lupus erythematosus (NP-SLE) is characterized by a clinical polymorphism of neurological and psychiatric syndromes in the context of detectable disease. In 1999, on behalf of the American College of Rheumtology (ACR), a research committee published a set of case definitions for NP-SLE manifestations, including 19 clinical syndromes, 12 related to the central nervous system (CNS) and 7 to the peripheral nervous system (SNP), which were also classified in focal and diffuse in relation to the type of involvement (1). The ACR classification meticulously pointed out the definition and exclusion criteria, suggesting at the same time, the most appropriate methodology and tools for the ascertainment and investigation of each syndrome. The estimated prevalence of NP-SLE, applying the 1999 ACR nomenclature to the published cohorts of lupus patients, ranges from 12 to 91% (2-8). Such a wide variability can be explained by several factors as different study designs (prospective/retrospective), the selection criteria adopted in the inclusion of patients encompassing demographic, ethnic and clinical differences (disease duration, disease activity, duration of follow-up) as well as possible selection bias among some cohorts (2-8). A recent meta-analysis per-

Corresponding author:
Alessandra Bortoluzzi
Sezione di Reumatologia
Dipartimento di Medicina Clinica e Sperimentale
Università di Ferrara
Via Aldo Moro, 8 - 44124 Ferrara (Località CONA)
E-mail: alessandra_bortoluzzi@virgilio.it

formed on 17 selected studies took into consideration 5057 lupus patients of which 1439 with neuropsychiatric (NP) involvement for a total of 2709 events estimating a prevalence of NP-SLE of 56.3% (95%, CI 42.5-74.7%). The diffuse NP syndromes such as headache, mood disorders and cognitive deficits were the most frequently reported events, corresponding to 28.3% (18.2-44.1%); 20.7% (11.5-37.4%) and 19.7% (10.7-36%) respectively, followed by the focal ones such as seizures (9.9%; 4.8-20.5%) and cerebrovascular diseases (CVD, 8%; 4.5-14.3%) (9).

The risk factors associated with NP-SLE are represented by the high disease activity (10, 11), previous NP events (especially for seizure disorders and severe cognitive deficits) and the positivity for anti-phospholipid (aPL) antibodies especially at medium to high title (for CVD, seizure disorders, cognitive deficits and movement disorders). A recent multicenter Italian retrospective study has confirmed the presence of aPL antibodies, the high disease activity, the cumulative dose of steroids and the onset at a young age as risk factors associated with NP involvement (12). According to the type of NP event the diagnostic work-up includes serological tests, cerebrospinal fluid examination, electrophysiological studies, neuropsychological evaluation and the use of neuroimaging techniques. The study with conventional magnetic resonance imaging (cMRI) represents the reference diagnostic technique and the recommended protocol includes the acquisition of T1 and T2 sequences, FLAIR (fluid attenuated inversion recovery), DWI (diffusion weighted sequences) and T1 with contrast enhancement (gadolinium) (14, 15).

The therapeutic approach still remains one of the most critical aspects of the current knowledge on the NP-SLE. The recent EULAR recommendations suggest assessing lupus patients with NP involvement in the same way as non-lupus patients who have similar clinical manifestations and with the initial assumption to exclude secondary causes such as infections, metabolic and endocrine disorders or adverse drug reactions (16). The aim of our study was to review the experience accumulated in our reference centre by analyzing the therapeutic strategies adopted and their effectiveness in a cohort of patients with SLE complicated by severe NP involvement.

PATIENTS AND METHODS

The Section of Rheumatology of the University of Ferrara is located inside the Sant'Anna Teaching Hospital and it is a tertiary referral centre for SLE with particular interest in the field of NP complications in systemic autoimmune diseases. The health care district in which it is located has a mean population of about 346,000 individuals (2002 census estimates) almost entirely composed of white Caucasian people. It is recognized as the "hub" referral centre of the regional "hub and spoke" network for Systemic Lupus Erythematosus. The case histories of patients with SLE, diagnosed according to the 1997 revised ACR criteria (17), were retrospectively analysed. All the patients came consecutively to our observation at our clinic in a 20 years period (from 1st January 1990 till 31st December 2010). All patients were evaluated for signs or symptoms of NP involvement retrieving information from clinical and laboratory documentation (medical records of inpatient, outpatient folders). The minimum level of fullness of clinical documentation and data were defined. These included demographic, medical, laboratory and instrumental history. In all patients these following comorbidities were recorded: hypertension, diabetes, smoking, obesity, valvular heart disease. Sero-immunologic tests included antinuclear antibodies (by indirect immunofluorescence method with Hep-2 as substrate), anti-dsDNA antibodies (by indirect immunoflorescence with Crithidiae luciliae as substrate), antibodies to extractable nuclear antigen (ENA, by enzyme linked immunoassorbent assay), anticardiolipin antibodies (aCL) and β-2glicoprotein1 (anti-βGP1) antibodies (standardized elisa kit) and Lupus anticoagulant (LA, by kaolin clotting time and Russel viper venom test, according to the recommenda-

tions of the Scientific and Standardization Committee of the International Society of Thrombosis and Hemostasis (18). Titers of aCL were determined and classified in the presence of a cut-off significant for values above 40 GPL/MPL units. When appropriate, cytological and chemical examination of the cerebrospinal fluid, cMRI with and without paramagnetic contrast agent, brain SPECT, performed after iv injection of 99mTc-HMPAO and electrophysiological tests (EEG, EMG, nerve conduction and evaluation of multimodal evoked potentials), performed according to standardized methods. The data collected were stored, after informed consent, in a dedicated and computerized database (FileMakerPro 8.0). The following data set were considered: sex, age at onset of the major NP picture treated, age at the time of NP recurrence, the regimens used as induction therapy (with particular reference to the dosage and timing of therapy), the clinical course of the NP manifestations before and after induction treatment. When available, the results of neuro-imaging studies and the disease activity assessment obtained by calculating two of the most widely used available indices, ECLAM (19) and SLEDAI (20), were recorded before and after treatment. A NP event was considered as severe, according to the modified McCune's definition (21), if this included focal events such as seizures, psychosis, transverse myelitis, mood disorders or cognitive deficits occurring in the context of active disease (22). In addition to the above-mentioned events, major refractory and persistently active events, despite conventional treatments instituted, were also included (23).

Statistical analysis

Due to the small size of the sample, with data distributed in a non-Gaussian way, statistical analysis was conducted by running nonparametric tests. The comparison between quantitative variables was performed by the Mann-Whitney'test. For the comparison of qualitative variables, the Fisher's exact applied to the relevant contingency tables, was used. A value of $P \leq 0.05$ was assumed as the limit for statistical significance. Statistical calculations were performed using the software GraphPad Prism© 1.5 for Microsoft® Windows platform.

RESULTS

The analysis of a retrospective cohort of 633 lupus patients who attended our centre in a period of 20 years, from 1990 to 2010, identified 231 (36%) patients with NP-SLE diagnosed according to 1999 ACR classification criteria corresponding to a total amount of 408 events. Thirty one patients (4.8%) 27 males and 4 females, mean age at onset of clinical symptoms of 45 years (range 19-78 years), experienced a severe NP event (for a total of 31 events), three patients experienced a recurrence of the same event and one patients, after a period of observation of 16 months, had a second major event. Overall, 35 events treated with immunosuppressive therapy were considered. In 12 cases (38.7%), the NP complication was observed at disease onset. In the remaining cases the average duration of illness at the time of the first event was 59 months (SD ± 75 months). The mean follow-up available was 149 months (range 36-231).

In 10 patients there was the presence of other organ involvement (3 serositis, 3 arthritis, 1 kidney, 1 skin, 1 kidney and skin, 1 arthritis and serositis). Comorbidities were documented in 14 patients (hypertension in 5, dislipidaemia in 3, one case of diabetes, the coexistence of dislipidaemia and hypertension in 2 patients, and lastly, one patient had valvular heart disease, obesity, hypertension and dyslipidemia). Nine patients (29%) were positive for anti-ENA antibodies (anti-Ro/SSA in 4 cases, anti-Sm in 1, anti-Ro/SSA and anti-Sm in 1, anti-Ro/SSA and anti -La/SSB in 2 cases, anti-Ro/SSA, anti-Sm and anti-RNP in one case). The anti-dsDNA antibodies were positive in 11 patients (35.5%). Five patients had a double positivity for aPL (including the aCL and anti-ß2GP1 antibodies) and LA, in 7 patients aPL antibodies were present and in 2 patients, only the LA. Anticoagu-

Table I - Neuropsychiatric manifestations and therapeutic strategies applied in our cohort of 31 patients with severe neuropsychiatric involvement.

Events	Number of events	Number of patientes - Treatment
Acute psychosis	8 events (1 relapse)	3 CYC 2 PULSE CSs + PULSE CYC 2 PEX + CYC 1 PULSE CSs
Peripheral neuropathy	5 events (1 relapse)	1 IVIg + PULSE CSs , then CYC 1 IVIg + PULSE CSs, then MMF 1 PEX+ PULSE CSs, then AZA 1 CSA 1 PULSE CSs
Severe cognitive deficits	3 events	2 CYC 1 MMF
Cerebro-vascular disease	3 events	1 PULSE CSs + RTX 1 PULSE CSs + CYC 1 AZA
Acute confusional state	3 events	1 PEX + PULSE CSs + PULSE CYC + IVIg 1 PEX + PULSE CSs + PULSE CYC 1 PULSE CSs
Refractory headache	3 events	2 AZA 1 IVIg + PULSE CSs + CYC
Optic neuritis	2 events	1 PEX + CYC 1 PULSE CSs
Aseptic meningitis	2 events	2 PULSE CSs
Sm-like syndrome	2 events	2 PULSE CSs
Chorea	2 events (1 relapse)	1 PULSE CSs + CYC 1 PULSE CSs
Myastenia gravis	1 events	PEX + AZA, then RTX

CYC: ciclophosphamide; CS: corticosteroid; MMF: mycophenolate mofetil; RTX: rituximab; AZA: azathioprine; CSA: cyclosporine; IVIg: high dose intravenous immunoglobulin; PEX: plasmapheresis.

lant and antiplatelet therapy was added in 19 and in 4 patients respectively, given the positivity for aPL, LA, the coexistence of anti-phospholipid syndrome and when required by the clinical picture.

The observed NP manifestations were the following: psychosis (8 cases, one recurrence), acute confusional state (3 cases), peripheral polyneuropathy (5 cases including one recurrence), optic neuritis (2 cases), aseptic meningitis (2 cases), chorea (2 cases, including a relapse), cognitive dysfunction (3 cases), demyelinating syndrome (2 cases), cerebrovascular accident (CVA) (3 cases), severe headache (3 cases), seizures (1 case) and myasthenia gravis (1 case). Five patients underwent an electroencephalogram, which resulted abnormal in one case. An examination of the cerebrospinal fluid was carried out in 3 cases yielding normal results in all patients. All patients received symptomatic treatment for the specific NP context (anti-epileptics, anti-depressants, benzodiazepines), prescribed according to what was suggested by the Neurologist and Psychiatrist consultants. The NP events and the therapeutic strategies adopted for each NP manifestation observed in our 31 patients are reported in table I.

Oral high dose steroid (1-2 mg / pro-kg / day) or pulse corticosteroid (CS) resulted the most widely used medication (20 cases, 57.1%), alone or in combination. The use as monotherapy has been reserved for the SM-like forms, aseptic meningitis or if the clinical picture or patient's comorbidities would restrict the use of immunosuppressant. Among the immunosuppressant, the CYC was the most frequently administered agent (16 events).

In the remaining cases, cyclosporine A (CSA, 2 mg/kg/die), mycophenolate mofetil (MMF, 200 mg/day), azathioprine

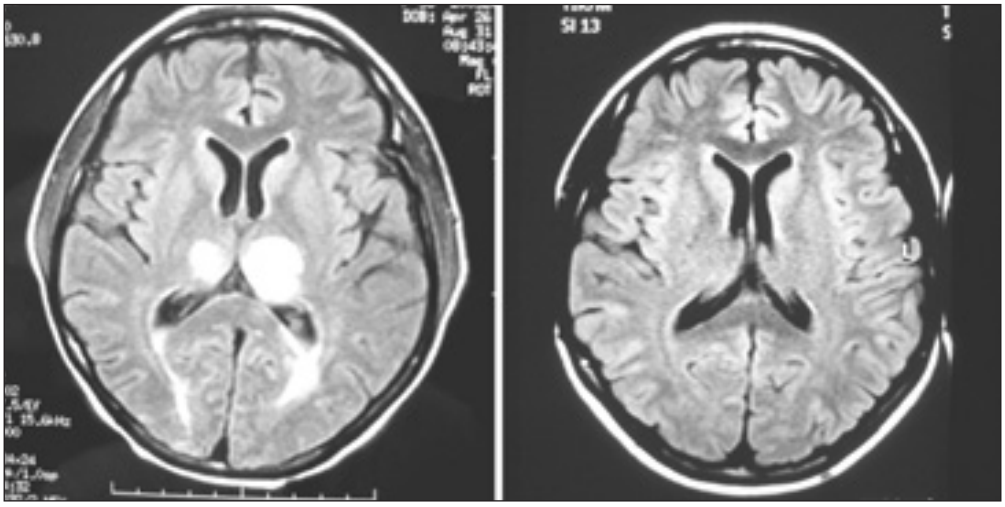

Figure 1 - Case report of a 31-year-old patient with an ongoing acute confusional state occurred after a recent HELLP syndrome. The figures show the dramatic improvement of some supratentorial large hyperintense lesions on MRI-FLAIR sequences before (left) and after (right) treatment with i.v. CYC (1000 mg), and 3 CS pulses (1 g) combined with PEX.

(AZA, 3 mg/kg/day) and rituxmab (RTX, cumulative dose: 2 g) were used. Plasmapheresis (PEX) and the infusion of high dose intravenous immunoglobulin (IVIg) (400 to 1000 mg/kg/day) were used in 7 and 4 cases, respectively, in combination with high-dose steroid and/or immune suppressants. The average number of sessions of PEX were 6 (usually three close sessions during the acute phase, followed by weekly procedures with an average exchange of two plasma litres). Overall, a significant improvement in the mean value of SLEDAI (from 10.09±01.09 to 04.02±0.52, P<0.0001) and ECLAM (from 4±0.34 to to 1.38±0.37, P<0.001) was reported. The induction therapy permitted the achievement of a stable remission or a significant improvement of the NP manifestations in 74% of cases. In figure 1 an example of an acute NP event documented by MRI findings and treated with cyclophosphamide was reported. This is a case of HELLP syndrome (hemolysis, elevated liver function tests, low platelets) a rare complication of pregnancy (24). NP picture was characterized by the sudden onset of an acute confusional state during a lupus flare. Brain conventional MRI T2 and FLAIR-sequences demonstrated large supra and infra-tentorial hyperintense lesions which promptly regressed after treatment with i.v. CYC (1000 mg), and 3 CS pulses (1 g) combined with PEX (Fig. 1).

With regards to the safety of treatments,

Table II - Adverse events recorded in our cohort of 31 patients with severe neuropsychiatric involvement.

Molecule	Adverse events
Steroid	Palpitations
	Flushing
	Photophobia
	Malaise
	Cushing's Syndrome
	Steroid myopathy
	Osteopenia (not compatible with sex and age)
PEX	Malaise
	Palpitations
IVIg	Significant worsening of a pre-existing pancytopenia
CYC	Leukopenia (2 cases, severe in one case)
	Sepsis
	Amenorrhea
CSA	Systemic hypertension
MMF	Recurrent urinary tract infections (concomitant urinary and fecal incontinence)

CYC: ciclophosphamide; MMF: mycophenolate mofetil; RTX: rituximab; CSA: cyclosporine; IVIg: high dose intravenous immunoglobulin; PEX: plasmapheresis.

we recorded a total of 16 side effects in 14 patients, both within short (<12 weeks, 11 events) and medium-long term (>12 weeks, 5 events). In 4 patients (12.9% of cases) these adverse events led to the treatment withdrawal. Adverse events recorded were stratified according to the specific treatments (Tab. II). In most cases they were mild, transient requiring symptomatic treatment only.

DISCUSSION

The therapeutic approach to the NPSLE still represents a challenge for the clinician and the almost complete absence of randomized clinical trials makes it often empirical and mainly based on individual expertise. In 2011, the publication of the EULAR recommendations for the management of NP involvement, developed from a systematic review of over a thousand publications in the literature as well as on expert opinion, pointed out some aspects in the evaluation of patients with signs and/or symptoms of NP. The preliminary approach to the patient with NP involvement should be similar to that in "non-lupus" patient and should be focused on the exclusion of secondary causes (16) and based on the correct recognition of the more relevant and the more probable pathogenic mechanism underlying each current NP event aiming, "cum bona fide", at a distinction between inflammatory or thrombotic. The patient should also be carefully monitored to assess the severity, the onset modalities (acute, subacute; focal or diffuse) the evolving pattern (rapid or slow) and the underlying disease context (active, inactive, with or without anti-phospholipid antibodies and so on), for each NP event. Furthermore, it is important to check for NP epiphenomena, which may be correlated with already stabilized organ involvement.

In the meantime, it is mandatory to establish if there is need for any symptomatic and supportive therapy (as in the case of acute psychosis, seizures or severe depressive pictures). Depending on the outcome of these assessments, it is intuitive that the therapeutic approach should be diversified, being more or less aggressive, conservative, or only symptomatic focusing, from time to time, either on immunosuppressive/anti-inflammatory therapy or anti-aggregating/anti-coagulant treatment. In this regard, the recommendations emphasize the importance of antiplatelet/anticoagulant treatment in the presence of events correlated with positive aPL antibodies especially in the context of CVD (25-27). If there is clinical suspicion that NP complication arises from an inflammatory/neurotoxic process, especially in the presence of an underlying active disease, treatment should be based on the use of high dose steroid, alone or in combination with other immunosuppressants (28, 29).

The aim of our study was to review the therapeutic approach we adopted when facing some severe NP events that occurred in patients attending our institution in a period of 20 years. In our experience, the high-dose corticosteroids (CSs) were the drugs most frequently used, alone or in combination with immunosuppressive agents (mainly CYC), preferring intravenous boluses. Our data, in line with those reported in the literature, confirm the usefulness of steroids for some pictures as acute confusional state, aseptic meningitis, MS-like syndrome and some particularly severe psychotic pictures. Treatment regimens, which have been proposed, include the use of high dose prednisolone (PDN) (1-2 mg/kg/day) orally or pulse of methylprednisolone (MP, 500-1000 mg per day for 3 consecutive days). CSs are useful to treat aseptic meningitis and psychosis unresponsive to conventional anti-psychotics. In this regard, it is important to remember the ability of steroid to induce psychosis both in the course of disease (especially for high doses or long duration of treatment), and in healthy control populations (30, 31). The early use of high-dose steroid therapy is recommended for the transverse myelitis. Harisdangkul *et al*. have shown that pulse steroid therapy administered within the first week after onset of symptoms resulted to be significantly better than in the cases where diagnosis and treatment

were delayed over 7 days (32). The use of steroids is also contemplated for cognitive deficits. A placebo-controlled study demonstrated an improvement of cognitive performance in 50% of subjects (in total 10 patients) with cognitive impairment treated with PDN 0.5 mg/kg/day (33).

Currently, CYC is the drug recommended for the treatment of acute NP pictures associated to an immune-mediated, non thrombotic pathogenesis (34), in those events refractory to the administration of steroids or when a steroid-sparing effect is advised (19, 35). In our series, the CYC was the immunosuppressant agent most frequently used, mainly as intravenous bolus. Among all the proposed regimens, the most effective is that proposed by the National Institutes of Health, which includes the monthly intravenously administration of CYC (0.75-1 g/m^2 of body surface) for at least 2 months (36). The scheme adopted at the St. Thomas' Hospital in London, provides the administration with low doses of CYC (500 mg bolus) every 2 weeks for the first 3 times, then monthly thereafter for the remaining 6 months. This scheme proved to be effective and safer than the one proposed by the NIH group, with a significantly lower incidence of side effects (especially Herpes Zoster and ovarian failure) (37, 38). This regimen was the most frequently used in our series. A Cochrane review comparing MP and CYC for the treatment of NPSLE (39) is available but only a single randomized controlled clinical trial was selected including 32 patients (26). This study demonstrated the superiority of CYC versus MP at 24 months with a detectable response to the treatment in 94.7% (18/19) of patients treated with CYC compared to 46.2% (6/13) observed in the MP group (RR 2.05, 95% CI 1.13, 3.73). However the authors stressed that it is not possible to draw conclusive suggestions about it due to the small sample size and the heterogeneous NP manifestations included in the group.

The effectiveness of PEX for the treatment of NPSLE is anecdotal and there are no controlled studies. A regimen of combination with PEX and subsequent pulse CYC has been proposed by some authors for the treatment of severe SLE or not responsive to steroids and/or CYC (40, 41). Remission "free treatment" average of almost 6 years was observed in 12/14 patients treated with this regimen. From our experience, it emerged that PEX can be considered as an adjuvant treatment when combined with immunosuppressive therapy (CYC, alone or associated with high dose steroids), resulting effective and well tolerated used to induce a more rapid and intensive therapeutic effect. In 6 of 7 cases, PEX was done 24 hours before the administration of the immunosuppressant according to the "synchronization protocol" suggested by the Lupus Plasmapheresis Study Group (42).

Administration of high dose IVIg is also reported in the course of NPSLE. Some uncontrolled studies have demonstrated the usefulness for current acute severe neuropsychiatric manifestations (43), including psychosis (44). The use of IVIg should be considered in all patients with acute diffuse NP events in the case of failure to respond to conventional treatments, in the case of pregnant women, in the case of toxicity occurring in the course of other immunosuppressive therapies. In our experience, the administration of IVIg, was used in 4 cases, yielding good results especially on peripheral neuropathy.

Azathioprine (AZA) is used for the treatment of a wide spectrum of NPSLE manifestations and its role as "steroid-sparing" is widely accepted. Therapeutic successes in the course of severe NPSLE have been anecdotally reported by some authors (45, 46). In our experience AZA was used in 5 events: 2 cases of headache, 1 CVD, 1 myasthenia gravis and 1 peripheral neuropathy, in this last case as maintenance therapy. The rationale for this treatment option was mainly influenced by the pattern of the NP presentation or by the associated underlying systemic manifestations (mainly skin and/or kidney). Even the mycophenolate mofetil (MMF) were reported for the treatment of NPSLE. Grisanti and colleagues published their preliminary experience in 10 patients: an improvement

of symptoms and patterns of cerebral hypoperfusion on SPECT were reported in more than two-thirds of patients after one year of treatment at a dose of 1 g/day (47). In the only case treated by us, the MMF, at a dose of 2 g/day was fairly effective but poorly tolerated. However, it must be specified that the patient presented a subacute evolving and polymorphic NP picture (cognitive disorder, major depression, partial seizures, cognitive impairment of vascular brain) with mixed pathogenesis (immune-mediated damage, aPL syndrome, vascular disease, reactive depression) and high scores of disease activity persistently expressed. In this case the MMF showed a good steroid-sparing action.

Rituximab (RTX), a chimeric monoclonal anti-CD20 antibody was successfully used in some cases of severe NP-SLE refractory to standard treatments (48). Weide et al. have recently reported an excellent response of 2 patients with severe NP involvement after administration of RTX (375 mg/m^2, 4 times at weekly intervals, followed by maintenance therapy with infusions quarterly) and in one patient previously treated unsuccessfully with steroids, AZA, CYC and MMF (49). Another open-label trial demonstrated the efficacy of RTX in 10 cases refractory to conventional induction therapy (50). We treated two patients with RTX (using the same schedule protocol) and both had a significant improvement in their symptoms and NP picture.

Currently available literature data, coming only from anecdotal case reports and uncontrolled trials, support the potential role of RTX in second-line treatment of refractory NP-SLE. However long-term data are lacking, especially about safety. This option requires Therefore careful monitoring, especially about infections, and should be reserved for refractory cases (20, 51).

CONCLUSIONS

Overall the reported experience is consistent with the available literature, with regard to the prevalence of severe NP manifestations observed and to the proposed treatment. In agreement with the recent EULAR recommendations for the management of SLE patients with NP involvement an aggressive immunosuppressive therapeutic approach has been reserved for NP events probably caused by an inflammatory immune-mediated mechanism and/or driven by a concomitant high disease activity, as judged by SLEDAI and ECLAM scores. To the best of our knowledge, small case series are currently available in the literature and the choice of the therapeutic strategy still lies substantially on empirical and clinical evaluation taking into account the type of NP event, its severity, the most likely underlying pathogenic mechanism (inflammatory or thrombotic) and the clinical background. All these aspects must be contextualized in each patient and do not allow to standardize a therapeutic approach, confirming once again, the need for further prospective randomized studies on large series of patients, through multicentre collaboration faced with more homogenous pictures of NP events.

REFERENCES

1. ACR ad hoc Committee on Neuropsychiatric Lupus Nomenclature. The American College of Rheumatology Nomenclature and case definition for neuropsychiatric lupus syndromes. Arthritis Rheum 1999; 42: 599-608.
2. Hanly JG, McCurdy G, Fougere L, et al. Neuropsychiatric events in systemic lupus erythematosus: attribution and clinical significance. J Rheumatol 2004; 31: 2156-62.
3. Sanna G, Bertolaccini ML, Cuadrado MJ, et al. Neuropsychiatric manifestations in systemic lupus erythematosus: prevalence and association with antiphospholipid antibodies. J Rheumatol 2003; 30: 985-92.
4. Mok CC, To CH, Mak A. Neuropsychiatric damage in Southern Chinese patients with systemic lupus erythematosus. Medicine (Baltimore) 2006; 85: 221-8.
5. Mok CC, Lau CS, Wong RW. Neuropsychiatric manifestations and their clinical associations in southern Chinese patients with systemic lupus erythematosus. J Rheumatol 2001; 28: 766-71.
6. Robert M, Sunitha R, Thulaseedharan NK. Neuropsychiatric manifestations systemic lupus erythematosus: a study from South India. Neurol India 2006; 54: 75-7.

7. Brey RL, Holliday SL, Saklad AR, et al. Neuropsychiatric syndromes in lupus: prevalence using standardized definitions. Neurology 2002; 58: 1214-20.
8. Ainiala H, Loukkola J, Peltola J, et al. The prevalence of neuropsychiatric syndromes in systemic lupus erythematosus. Neurology 2001; 57: 496-500.
9. Unterman A, Nolte JES, Boaz M, et al. Neuropsychiatric syndromes in systemic lupus erythematosus: a meta-analysis. Sem Arthr Rheum 2011; 41: 1-11.
10. Andrade RM, Alarçon GS, Gonzalez LA, et al. Seizures in patients with systemic lupus erythematosus: data from LUMINA , a multiethnic cohort (LUMINA LIV). Ann Rheum Dis 2008; 67: 829-34.
11. Tomietto P, Annese V, D'Agostini S, et al. General and specific factors associated with severity of cognitive impairment in systemic lupus erythematosus. Arthr Rheum 2007; 57: 1461-72.
12. Govoni M, Bombardieri S, Bortoluzzi A, et al. Factors and comorbidities associated with first central nervous system neuropsychiatric event in systemic lupus erythematosus: does a risk profile exist? A large multicenter retrospective cross sectional study on 959 italian patients. Rheumatology 2012; 51: 157-68.
13. Bertias GK, Boumpas DT. Pathogenesis, diagnosis and management of neuropsychiatric SLE manifestations. Nat Rev Rheumatol 2010; 6: 358-67.
14. Kozora E, West SG, Kotzin BL, et al. Magnetic resonance imaging abnormalities and cognitive deficits in systemic lupus erythematosus patients without overt central nervous system disease. Arthritis Rheum 1998; 41: 41-7.
15. Sibbitt WL Jr, Sibbitt RR, Griffey RH, et al. Magnetic resonance and computed tomographic imaging in the evaluation of acute neuropsychiatric disease in systemic lupus erythematosus. Ann Rheum Dis 1989; 48: 1014-22.
16. Bertsias GK, Ioannidis JP, Aringer M, et al. EULAR recommendation for the management of systemic lupus erythematosus. Report of a task force of the EULAR Standing Committee for International Clinical Studies including therapeutics. Ann Rheum Dis 2008; 67: 195-205.
17. Hochberg MC. Updating the American College of Rheumatology recise criteria for the classification of sistemic lupus erythematosus. Arthritis Rheum 1997; 40: 1725.
18. Horbach DA, Oort E, Donders RC, et al. Lupus anticoagulanti s the strogest risk factor for both venous and arterial thrombosis in patients with systemic lupus erythematosus (comparison between different assys for the detection of antiphospholipid antibodies). Thromb Haemost 1996; 76: 916-24.
19. Vitali C, Bencivelli W, Isenberg DA, et al. Disease activity in sistemic lupus erythematosus: Report of the Consensus Study Group of the European Workshop for Rheumatology Research. I. A descriptive analysis of 704 European lupus patients. Clin Exp Rheumatol 1992; 10: 527-39.
20. Bombardier C, Gladman DD, Urowitz MB, et al. Derivation of the SLEDAI. A disease activity index for lupus patients. Arthritis Rheum 1992; 6: 630-40.
21. McCune WJ, Golbus J, Zeldes W, et al. Clinical and immunologic effects of monthly administration of intravenous cyclophosphamide in severe systemic lupus erythematosus. N Eng J Med 1988; 318: 1423-31.
22. Neuwelt M, Lacks S, Kaye BR, et al. Role of intravenous cyclophosphamide in the treatment of severe neuropsychiatric systemic lupus erythematosus. Am J Med 1995; 98: 32-41.
23. Narvaez J, Rios-Rodriguez V, De La Fuente D, et al. Rituximab therapy in refractory neurospychiatric lupus: current clinical evidence. Semin Arthritis Rheum 2011; 41; 364-72.
24. Appenzeller S, Souza FH, Wagner Silva de Souza A, et al. HELLP syndrome and its relationship with antiphospholipid syndrome and antiphospholipid antibodies. Semin Arthritis Rheum 2011; 41: 517-23.
25. Khamashta MA, Cuadrado MJ, Mujic F, et al. The management of thrombosis in the antiphospholipid-antibody syndrome. N Engl J Med 1995; 332: 993-7.
26. Muñoz-Rodriguez FJ, Font J, Cervera R, et al. Clinical study and follow-up of 100 patients with the antiphospholipid syndrome. Semin Arthr Rheum 1999; 29: 182-90.
27. Ruiz-Irastorza G, Hunt BJ, Khamashta MA. A systematic review of secondary thromboprophylaxis in patients with antiphospholipid antibodies. Arthritis Rheum 2007; 57: 1487-95.
28. Stojanovich L, Stojanovich R, Kostich V, Dzjolich E. Neuuropsychiatric lupus favourable response to low dose i.v. cyclophosphamide and prednisolone (pilot study). Lupus 2003; 12: 3-7.
29. Barile-Fabris L, Ariza-Andraca R, Olguín-Ortega L, et al. Controlled clinical trial of IV cyclophosphamide versus IV methylprednisolone in severe neurological manifestations in systemic lupus erythematosus. Ann Rheum Dis 2005; 64: 620-5.
30. Baca V, Lavalle C, García R, et al. Favorable response to intravenous methylprednisolone and cyclophosphamide in children with severe neuropsychiatric lupus. J Rheumatol 1999; 26: 432-9.
31. Chatham WW, Kimberly RP. Treatment of lupus with corticosteroids. Lupus 2001; 10: 140-7.
32. Harisdangkul V, Doorenbos D, Subramony

SH. Lupus transverse myelopathy: better outcome with early recognition and aggressive high-dose intravenous corticosteroid pulse treatment. J Neurol 1995; 242: 326-31.
33. Denburg SD, Carbotte RM, Denburg JA. Corticosteroids and neuropsychological functioning in patients with systemic lupus erythematosus. Arthritis Rheum 1994; 37: 1311-20.
34. Sanna G, Khamashta MA. Low-dose pulse cyclophosphamide in the treatment of neuropsychiatric lupus. Lupus 2003; 12: 1-2.
35. Sanna G, Bertolaccini ML, Khamashta MA. Neuropsychiatric involvement in systemic lupus erythematosus: current therapeutic approach. Curr Pharm Des 2008; 14: 1261-9.
36. Boumpas DT, Yamada H, Patronas NJ, et al. Pulse cyclophosphamide for severe neuropsychiatric lupus. Q J Med 1991; 81: 975-84.
37. Ramos PC, Mendez MJ, Ames PR, et al. Pulse cyclophosphamide in the treatment of neuropsychiatric systemic lupus erythematosus. Clin Exp Rheumatol 1996; 14: 295-9.
38. Martin-Suarez I, D'Cruz D, Mansoor M, et al. Immunosuppressive treatment in severe connective tissue diseases: effects of low dose intravenous cyclophosphamide. Ann Rheum Dis 1997; 56: 481-7.
39. Trevisani VF, Castro AA, Neto JFN, Atallah AN. Cyclophosphamide versus methylprednisolone for the treatment of neuropsychiatric involvement in systemic lupus erythematosus. Cochrane Database Syst Rev 2006; CD002265.
40. Schroeder JO, Euler HH. Treatment combining plasmapheresis and pulse cyclophosphamide in severe systemic lupus erythematosus. Adv Exp Med Biol 1989; 260: 203-13.
41. Gokhale YA, Bhide S, Rajadhyaksha S, et al. Plasmapheresis: an adjunct therapy in severe progressive neuropsychiatric lupus. J Assoc Physicians India 2001; 49: 986-9.
42. Euler HH, Schroeder JO, Harten P, et al. Treatment-free remission in severe systemic lupus erythematosus following synchronization of plasmapheresis with subsequent pulse cyclophosphamide. Arthritis Rheum 1994; 37: 1784-94.
43. Sherer Y, Levy Y, Langevitz P, et al. Successful treatment of systemic lupus erythematosus cerebritis with intravenous immunoglobulin. Clin Rheumatol 1999; 18: 170-3.
44. Tomer Y, Shoenfeld Y. Successful treatment of psychosis secondary to SLE with high dose intravenous immunoglobulin. Clin Exp Rheumatol 1992; 10: 391-3.
45. Hay EM. Psychiatric disorder and cognitive impairment in SLE. Lupus 1994; 3: 145-8.
46. Schantz V, Oestergaard LL, Junker P. Shrinking spinal cord following transverse myelopathy in a patient with systemic lupus erythematosus and the phospholipid antibody syndrome. J Rheumatol 1998; 25: 1425-8.
47. Grisanti M, Nader A, Cacciuttolo R. CNS involvement due to SLE/aPL syndrome: successful treatment with MFM. Lupus 2001; 10: S31.
48. Saito K, Nawata M, Nakayamada S, et al. Successful treatment with anti-CD20 monoclonal antibody (rituximab) of life-threatening refractory systemic lupus erythematosus with renal and central nervous system involvement. Lupus 2003; 12: 798-800.
49. Weide R, Heymanns J, Pandorf A, Köppler H. Successful long-term treatment of systemic lupus erythematosus with rituximab maintenance therapy. Lupus 2003; 12: 779-82.
50. Tokunaga M, Saito K, Kawabata D, et al. Efficacy of rituximab (anti-CD20) for refractory systemic lupus erythematosus involving the central nervous system. Ann Rheum Dis 2007; 66: 470-5.
51. Terrier B, Amoura Z, Ravaud P, et al. Safety and efficacy of rituximab in systemic lupus erythematosus. Result from 136 patients from the french autoimmunity and rituximab registry. Arthritis Rheum 2010; 62: 2458-66.