

Review article

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# **Biologic therapies in patients with neuropsychiatric Systemic Lupus Erythematosus – a review**

## **Short title: Biologic therapies in NPSLE**

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## Abstract

Neuropsychiatric (NP) involvement is a prevalent and often severe feature of Systemic Lupus Erythematosus (SLE). Diverse factors are involved in its aetiopathogenesis and treating this condition is often quite challenging. However, clinical trials of biologic therapies in patients with SLE exclude those with severe NP manifestations. The place for the use of biologic approaches is thus even more problematic than it is for other aspects of SLE. Here we review the current evidence for the use of biologic therapies in the treatment of NPSLE.

## Key words

Systemic Lupus Erythematosus, Neuropsychiatric, Biologic therapies, B-cell targeted therapy, Belimumab, Rituximab

## Introduction

The last two decades have seen a revolution in the treatment of patients with more common autoimmune rheumatic diseases notably rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis with the successful introduction of a range of biologic therapies. Targeting the molecules and cells which evidence suggests are likely to be involved in the aetiopathogenesis of these diseases has been a major advance [1]. Although these drugs are not a panacea, and infection, particularly during the first three months of treatment, remains an issue with some of the biologic drugs (notably those that block TNF-alpha) [2], the overwhelming benefit to hundreds of thousands of patients around the world is undeniable.

In contrast, the introduction of biologic therapies for the more sinister autoimmune rheumatic conditions vasculitis and, notably, systemic lupus erythematosus (SLE) has been far less compelling. Only one drug, Belimumab, which blocks a B-cell activating factor (BAFF) known as BAFF/BLyS, has been approved by the Federal Drug Administration in America and the European Medicines Association for the treatment of lupus and to date is restricted to those patients who have skin and joint involvement [3]. Many of the other drugs that have been tried, notably Rituximab [4] (which blocks the CD20 molecule on B-cells); Abatacept [5] (which blocks the interaction between antigen presenting cells and T-

cells); Tabalumab [6] (anti-BLys) and Rontalizumab [7] (anti-interferon (IFN)  $\alpha$ ) have failed to meet their primary endpoints in large-scale international trials (although Tabalumab did in fact meet its endpoint in one such clinical trial).

Post-hoc analyses have offered some encouragement in the trials of the above agents. For example, in the Rituximab trials, data have indicated that there was a serological and a limited clinical response [8]. There has also been a widespread recognition that Rituximab does help patients with lupus, but that the poor drug trial design, which, notably, allowed the use of far too high a dose of concomitant glucocorticoids and/or immunosuppressive drugs, strongly mitigated against any chance that Rituximab might have had of showing benefit. Paradoxically, although Rontalizumab did not meet its primary endpoints, Silfalimumab, with the same target, did achieve this [9].

The majority of companies, when setting up clinical trials in lupus, invariably design two sorts of clinical trials. One type focuses on renal disease which has “hard” endpoints such as a protein/creatinine ratio, serum creatinine and glomerular filtration rate, while the other type of trial focuses on non-renal lupus. Both types of trial, however, make a point of excluding patients with significant central nervous system (CNS) lupus. As a consequence, there have been no clinical trials at all of patients with this challenging aspect of the disease.

However, CNS disease may occur in up to half of lupus patients [10]. We felt it would be useful to review, critically, those publications describing the use of biologics in NPSLE.

## Neuropsychiatric SLE

Lupus is often thought of as a disease with diverse manifestations and nowhere is this truer than in the central nervous system. Virtually anything from “migraine to madness” may be a feature of central nervous system involvement in SLE. Although the American College of Rheumatology (ACR) classification criteria [11] list only seizures and psychosis as CNS lupus features, a working party set up by the ACR proposed a set of twelve CNS manifestations and seven peripheral nervous system (PNS) manifestations which they felt captured the full range of neurological possibilities [12].

In 2012, Borowoy and colleagues reported the prevalence of neuropsychiatric SLE (NPSLE) in 1253 adult patients of a multicenter Canadian cohort according to four different definitions. Using the ACR classification criteria it was 6.4%, but higher the less strict the definition (up to 38.6% when including manifestations included in ACR, SLAM, SLEDAI or SLICC indices) [13].

Figure 1 indicates the contributory factors linked to the cause of CNS lupus manifestations. In many cases no single aetiopathogenic mechanism is responsible. Rather the diversity of CNS features reflects the complex potential combination of factors indicated in the figure. This topic has been reviewed in detail recently [14].

True cerebral vasculitis has been found rarely in brain biopsies during life but was also reported in 10% of cases at post-mortem [15]. In the past twenty years it has increasingly been recognised that thrombotic change linked to the presence of antiphospholipid antibodies, including anti- $\beta_2$  Glycoprotein 1, is a major potential cause of involvement of the CNS in lupus [16]. Lupus patients may thus suffer strokes relatively early in life, occasionally being a presenting feature of the disease.

A cross-reaction between antibodies to double-stranded DNA and the N-methyl-D-aspartate (NMDA) receptor might be an important contributory factor to particular clinical features [17]. The NMDA receptors, although widely distributed throughout the brain, are localised within glutamatergic synapses in the amygdala and hippocampus. These sub-regions are linked to cognitive functions such as emotional processes and memory, respectively. An important point linked to this cross-reacting antibody (and others) is that the antibodies need to penetrate the blood/brain barrier (or to be produced intrathecally) before they can cause genuine pathology.

The role of anti-ribosomal P antibodies is controversial [18]. The frequency with which these antibodies are found is varied in lupus populations. Probably, in most of them, it is about 15-20%, perhaps higher in some ethnic groups. The initial suggestion that their presence in the serum of lupus patients was strongly associated with depression and psychosis in SLE patients [19] has not been universally accepted, although levels in the spinal fluid are likely to be more relevant to clinical manifestations than serum levels.

The capacity of cytokines and chemokines to promote intrathecal antibody production to manipulate neurotransmitter release and recruit immune cells [14] strongly implicates (at least some of) these molecules in the development of NPSLE.

The presence of IL-6 in the cerebrospinal fluid has been noted [20], although more recent studies have focused on the TNF-related weak inducer of apoptosis (TWEAK) [21].

There are some data to suggest that stress is able to induce an increase in the production of nitric oxide (NO) in the brain via the iNOS pathway [22]. It is believed that inflammatory cytokine components, immune complexes and even antiphospholipid antibodies have an effect on this pathway, which has been reported to be active in patients with NPSLE.

Various intrathecal markers of NPSLE have been identified. These include the chemokine ligand known as CXCL10, RANTES, FRACTALKINE, the plasminogen activator inhibitor 1 and matrix metalloproteinase 9 [14].

## Biologic drugs in the treatment of NPSLE

### Methods

We performed a literature search in Medline database, using combinations of the following terms: Lupus, Neuropsychiatric, Rituximab, Epratuzumab, Belimumab, Tabalumab, Atacicept, Abatacept, Sifalimumab and Rontalizumab. We were looking for publications of randomized controlled trials (RCTs), observational studies and case reports of adult patients with NPSLE treated with biologic drugs, published in English, French, German, Spanish and Portuguese. After excluding articles that were not relevant or that contained duplicated data, we identified 16 articles.

### Results and discussion

Most studies reporting the use of biologic drugs in SLE show their results using a global disease activity score and do not present the outcome in specific organ systems.



However, some studies do assess the efficacy of these therapies in NPSLE, notably 15 studies with Rituximab and one with Belimumab. We could not find any data about the use of other B-cell targeting therapies (apart from Rituximab and Belimumab) or IFN $\alpha$  targeted therapies, namely Sifalimumab and Rontalizumab, in NPSLE.

## Belimumab

Belimumab is currently the only specific targeted drug approved for the treatment of SLE, having shown efficacy in two phase III clinical trials [3, 23]. Some observational studies have subsequently been published, reporting the “real-life experience” with this drug [24-26]. However, as patients with severe neuropsychiatric manifestations were excluded from the clinical trials and the observational studies, there is currently little evidence about the use of Belimumab in NPSLE.

In a post-hoc analysis of the BLISS-52 and BLISS-76 trials, which included 1684 patients with moderately to severely active (SELENA-SLEDAI $\geq$ 6) seropositive SLE, Manzi and collaborators have looked for changes in BILAG and SELENA-SLEDAI organ domain scores at week 52 of follow up [27]. They found 45 patients with CNS involvement at baseline. The most common manifestation was headache (present in 24 patients) which

showed a very good response to Belimumab. The improvement rates reported were 20.0%, 100% and 69.2% with placebo and Belimumab 1 and 10 mg/kg, respectively.

In addition, 21 patients had neuropsychiatric involvement with a BILAG score A or B at baseline. Among those, improvement rates (improvement being defined as a step down from an A or B score to a B, C or D score) were, paradoxically, 83.3%, 75.0% and 42.9% for placebo (total n=6), Belimumab 1 mg/Kg (total n=8) and 10 mg/Kg (total n=7), respectively. These results are somewhat surprising, given the apparent efficacy of the placebo in treating patients with NPSLE scoring A or B in BILAG. Caution is needed, however, in the interpretation of this results, as the sample size was very small. Information about the specific NPSLE features treated was not provided.

The authors also calculated the worsening rates for BILAG organ domains (worsening was defined as a step up from an E, D, C or B score to a B or A score) and for SELENA-SLEDAI organ domains (worsening was defined as a positive score shift). In the CNS, the rates of worsening s assessed by BILAG, for patients without any A score at baseline, were 0.7% (4/562) for placebo, 0.5% (3/556) for Belimumab 1 mg/Kg, and 1.1% (6/562) for Belimumab 10 mg/Kg. Considering SELENA-SLEDAI, for patients with no involvement at baseline, the rates of worsening were 0.4% (2/551) for placebo, 0.6% (3/544) for Belimumab 1 mg/Kg, and 0.4% (2/544) for Belimumab 10 mg/Kg.

This study has, however, some limitations, as these trials were not designed or powered to demonstrate the efficacy of Belimumab in individual organ domains.

Wallace and colleagues pooled data from the phase II and phase III trials of Belimumab, focusing on its safety profile [28]. Psychiatric adverse events were reported more frequently with Belimumab treatment than with placebo (12.4% of patients receiving placebo and 16.0%, 22.5% and 15.9% of patients receiving Belimumab 1, 4 and 10 mg, respectively). The most frequent were depression, insomnia and anxiety. Furthermore, there was an approximate two-fold greater risk of developing a psychiatric disorder during the study if the patient had a medical history of psychiatric condition, depression, anxiety, or insomnia. This was not the case verified with other central nervous system medical history. The safety concerns may, therefore, restrict the use of Belimumab in patients with psychiatric SLE.

## Rituximab

Rituximab is a chimeric anti-CD20 antibody that directly targets B cells. It eliminates B cells through a variety of mechanisms, notably antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity and apoptosis [29].

This monoclonal antibody has been widely used in the treatment of SLE. Most publications have described open studies and many successes have been claimed [30, 31]. Unfortunately, in the two major clinical trials of Rituximab, one in renal lupus (LUNAR) [8] and one in non-renal lupus (EXPLORER) [32], the primary endpoints were not met, as discussed previously.

In respect of NPSLE, we found eight retrospective observational studies, two open clinical trials, four small case series and case reports and one systematic review of case reports and case series assessing the efficacy of Rituximab (Table 1). Most studies report the use of this B-cell depleting drug in refractory cases of NPSLE; the only exception is the open trial published by Ye and colleagues [33], conducted in patients with recent onset myelopathy, using Rituximab as the first line therapy. The study reported by Abud-Mendoza and collaborators [34] described six patients treated with Rituximab, however, two of them were less than 18 years old and in another patient the CNS manifestation reported was an haemorrhagic stroke, so these three patients were excluded from our analysis.

In Table 2 we have combined data from the 15 studies and show the efficacy of Rituximab for each NPSLE manifestation. Overall, these results are very encouraging,

showing high response rates. The worst results are seen in patients with demyelinating syndrome (most cases reported neuromyelitis optica) and in patients with mood disorder, although in this case it is difficult to be sure that the mood disorder (often depression) is a true NPSLE feature and not a comorbidity.

## Conclusion

With such a diversity of factors contributing to the aetiopathogenesis of NPSLE manifestations, it may seem overly optimistic to find a single effective targeted therapy. However, the encouraging results reported with the use of Rituximab may prove otherwise. A large RCT of Rituximab in NPSLE patients would be important to demonstrate compelling evidence of its efficacy.

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## Conflicts of interest

The authors declare that there is no conflict of interest.

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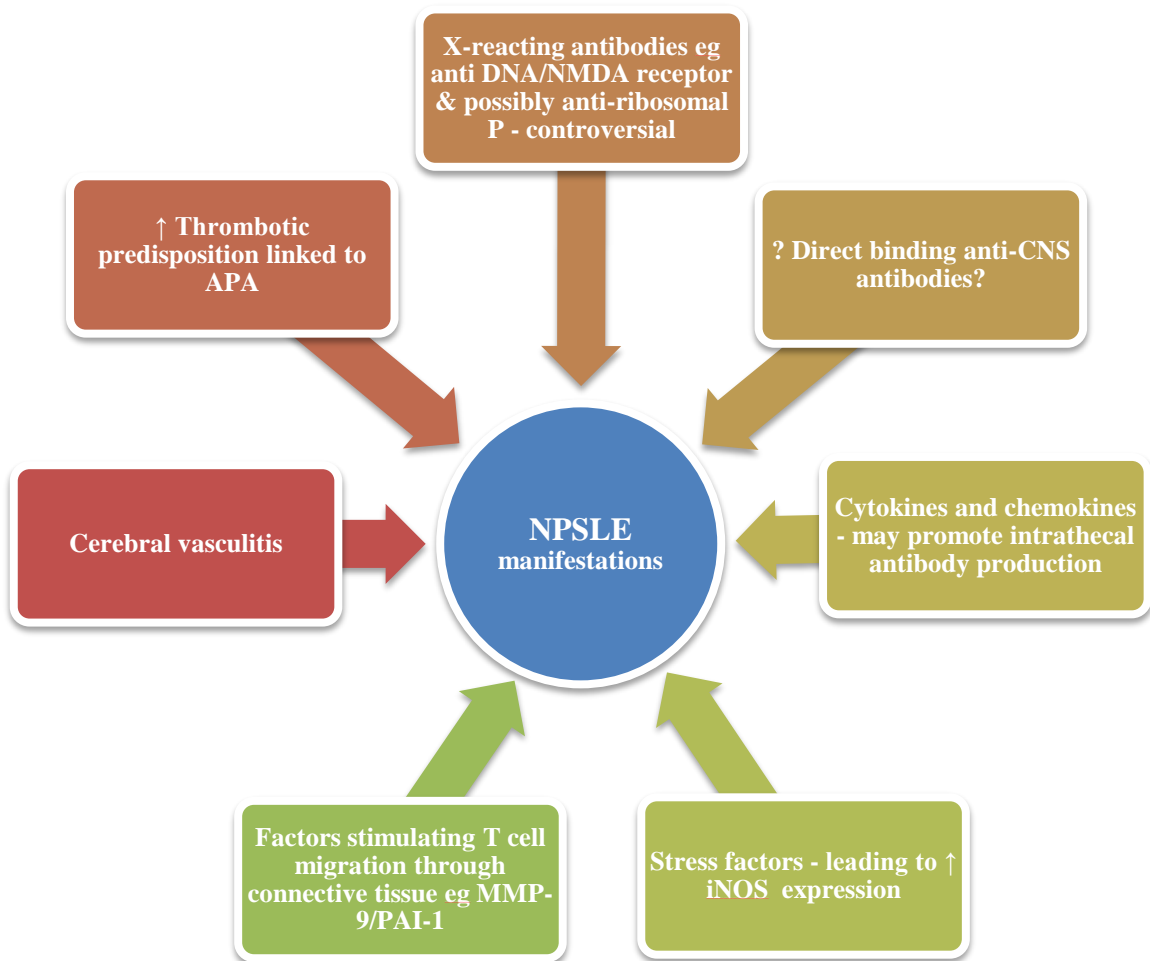
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**Figure 1: Contributing factors to NPSLE manifestations.**

NMDA: N-methyl-D-aspartate; APA: anti-phospholipid antibody; MMP: Matrix Metalloproteinase 1; PAI: plasminogen activator inhibitor

**Table 1: Studies assessing the efficacy of Rituximab in adult patients with NPSLE**

Reference	Type of study	N	NPSLE features, n	Feature response (CR) %	Global response (CR) %
Narváez et al, 2011 [35]	Systematic review of case reports and case series	35	Seizures, 6	100 (100)	85 (50)
			Psychosis, 5	100 (60)	
			Myelopathy, 5	100 (40)	
			Acute confusional state, 6	60 (0)*	
			Mood disorder, 3	33 (0)	
			Demyelinating syndrome, 3	67 (33)	
			CNS vasculitis, 2	100 (100)	
			Headache, 2	100 (50)	
			Not specified, 3	100 (67)	
Vital et al, 2011 [36]	Retrospective observational study	13	Not specified	92	
Pinto et al, 2011 [37]	Retrospective observational study	12	Myelopathy, 4	100	75
			Polineuropathy, 4	100	
			Seizures, 1	100	
			Demyelinating syndrome, 1	0	
			Not specified, 2	0	
Fernandez-	Retrospective	11	Not specified	73	



Nebro et al, 2012 [38]	Retrospective observational study				
					100 (50)
			CNS vasculitis, 4		100
			Seizures, 2		(100)
Iaccarino et al, 2015 [39]	Retrospective observational study	9	Psychosis, 1		100 (0) 89 (56)
			Headache, 1		0
			Cognitive dysfunction, 1		100 (100)
Ye et al, 2011 [33]	Open clinical trial	6	Myelopathy, 6		83 (67)
Ramos-Casals et al, 2010 [40]	Retrospective observational study	6	Not specified		80
Abud-Mendoza et al, 2009 [34]	Open clinical trial	3	Myelopathy, 2 Movement disorder, 1		100
Hickman et al, 2015 [41]	Retrospective observational study	4	Not specified		100 (25)
Reynolds et al, 2009 [42]	Retrospective observational	4	Myelopathy, 1 Seizures, 1		100

	study		Psychosis, 1 Polineuropathy, 1	
Chehab et al, 2007 [43]	Case series	3	Myelopathy, 2 CNS vasculitis, 1	100
Braun-Moscovici et al, 2013 [44]	Case report	1	Demyelinating polyradiculoneuropathy	CR
Sanz et al, 2012 [45]	Case report	1	Demyelinating polyradiculoneuropathy	PR
Lateef et al, 2010 [46]	Retrospective observational study	1	Not specified	CR
Mok et al, 2008 [47]	Case report	1	Demyelinating syndrome	NR

\*One patient lost to follow up was excluded from the analysis

N: number of patients; CR: complete response; PR: partial response; NR: non-responder

**Table 2: Efficacy of Rituximab for each NPSLE manifestation**

<b>NPSLE Feature</b>	<b>N</b>	<b>Response (%)</b>
Myelopathy	20	19/20 (95)
Seizures	10	10/10 (100)
Psychosis	7	7/7 (100)
CNS vasculitis	7	7/7 (100)
Acute confusional state	6	3/5* (60)
<b>CNS</b> Demyelinating syndrome	5	2/5 (40)
Mood disorder	3	1/3 (33)
Headache	3	2/3 (67)
Cognitive dysfunction	1	1/1 (100)
Movement disorder	1	1/1 (100)
Total	63	53/62 (85)
Polyneuropathy	5	5/5 (100)
<b>PNS</b> Demyelinating polyradiculoneuropathy	2	2/2 (100)
Total	7	7/7 (100)
<b>Not specified</b>	40	33/40 (83)
<b>Total</b>	<b>110</b>	<b>93/109 (85)</b>

\*One patient lost to follow up was excluded from the analysis