A phase IIa randomized clinical study testing GNbAC1, a humanized monoclonal antibody against the envelope protein of multiple sclerosis associated endogenous retrovirus in multiple sclerosis patients — A twelve month follow-up

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Abstract

GNbAC1 is a humanized monoclonal antibody targeting MSRV-Env, an endogenous retroviral protein, which is expressed in multiple sclerosis (MS) lesions, is pro-inflammatory and inhibits oligodendrocyte precursor cell differentiation. This paper describes the open-label extension up to 12 months of a trial testing GNbAC1 in 10 MS patients at 2 and 6 mg/kg. The primary objective was to assess GNbAC1 safety, and other objectives were pharmacokinetic and pharmacodynamic assessments. During the extended study, no safety issues occurred in the 8 remaining patients. No anti-GNbAC1 antibodies were detected. GNbAC1 appears well tolerated.

Keywords:

Multiple sclerosis; Human endogenous retrovirus; Monoclonal antibody; Clinical trial; Safety

1. Introduction

GNbAC1 is a recombinant humanized IgG4/kappa monoclonal antibody (mAb) which binds a protein called MSRV-Env expressed by genes from the human endogenous retrovirus type W family (HERV-W) also named "Multiple Sclerosis associated Retrovirus" (MSRV) (Perron et al., 1997).

Several studies have demonstrated links between the expression of MSRV-Env and multiple sclerosis (MS); in particular immunohistochemical analyses of post-mortem brain tissue from MS patients localize the MSRV-Env protein to MS plaques with a higher level of protein expression in active plaques compared to inactive plaques (Mameli et al., 2007; Perron et al., 2012).

In MS pathogenesis, dysregulation of both the innate and adaptive immune systems is considered as the main triggering and/or exacerbating factor. MSRV-Env activates Toll-like receptor 4 (TLR4) and has a pro-inflammatory effect mediated through its interaction with TLR4 in peripheral blood mononuclear cell (PBMC) cultures (Rolland et al., 2006). Another effect of MSRV-Env is the blockade of the oligodendrocyte differentiation necessary for the remyelination process, also mediated by an interaction with TLR4 on oligodendrocyte precursor cells (OPCs) (Kremer et al., 2013). Based on the ability of MSRV-Env to activate the innate immune system and given its direct toxicity on OPCs, MSRV-Env is a relevant therapeutic target for MS.

The mAb GNbAC1 was developed as a MSRV-Env antagonist. Pre-clinical studies showed that GNbAC1 neutralizes the MSRV-Env target (Rolland et al., 2006; Kremer et al., 2014). GNbAC1 had been studied first in a phase I clinical trial in 33 healthy subjects, showing a good safety as well as a linear pharmacokinetics (Curtin et al., 2012). The goals of the present placebo controlled dose escalation study with an open-label extension was to assess the safety profile, immunogenicity, pharmacokinetic parameters and pharmacodynamics of repeated administrations of GNbAC1 at doses of 2 and 6 mg/kg in MS patients (Derfuss et al., 2014). The results of the open-label extension phase up to 12 months of treatment are presented.

2. Material and methods

Briefly, in 2 dose cohorts (doses 2 mg/kg or 6 mg/kg of GNbAC1) of 5 patients each, 4 patients were randomized to receive GNbAC1 and one patient to receive placebo for the first administration in a blinded manner, then all patients of each of the two dose cohorts received 11 repeated administrations of GNbAC1 (either at 2 mg/kg or at 6 mg/kg) at 4 week intervals in an open-label setting. A sample size of 10 patients was considered sufficient for the safety objective of this study. Second-ary objectives included pharmacokinetics, pharmacodynamics, brain magnetic resonance imaging (MRI), immunogenicity and expanded dis-ability status scale (EDSS) measurements. The design of the trial is described in more details in Derfuss et al. (2014). The study protocol was approved by the local ethics committees and the Swiss Medicine Agency, Swissmedic.

Blood and urine samples were collected at baseline and at each drug administration. Adverse events (AEs) were recorded at each visit. Brain MRI was performed at screening and 28 days after the first, 6th and 12th drug administrations. EDSS was assessed at baseline and after the 6th and 12th drug administrations. Methods for GNbAC1 measurement, anti-drug antibody detection and MRI techniques are described else-where (Curtin et al., 2012; Derfuss et al., 2014). Descriptive statistics were computed for the pharmacokinetic, safety, and pharmacodynamic data using SAS® Version 9.2 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Demographic characteristics

Ten patients (7 males and 3 females; 1 relapsing remitting MS patient, 3 primary progressive MS patients, 6 secondary progressive MS patients) were randomized into the 2 cohorts. Eight patients (1 patient with relapsing remitting MS and 7 patients with a progressive form of MS) completed the extension up to 12 months, 2 were withdrawn after 6 months, and none of them for safety reasons (one patient completed the study before protocol extension approval, the other one withdrew his consent).

3.2. Drug safety

Overall, 135 AEs occurred during trial, AEs occurring in more than 10%of patients are reported in Table 1. Only one serious AE – a biliary pancreatitis in a patient known for recurrent biliary lithiases – was observed and assessed as unlikely related to the study treatment. Nine of 135 AEs were judged to be possibly related to study drug (chorea, orthostatic tremor, chest pain (2), γ-glutamyl transferase increased, electrocardiogram QT prolonged, blood urea increased, blood creatinine increased and glomerular filtration rate decreased), and all other AEs were considered as un-likely related or unrelated to study drug. During the open-label extension, the most frequent AEs were gait disturbance (9 episodes) re-ported by 2 patients in the 2 mg/kg group and 1 patient in the 6 mg/kg group, nasopharyngitis (8 episodes) reported by 3 patients in the 2 mg/kg group and 2 patients in the 6 mg/kg group, and leukocyturia (7 episodes) reported by 1 patient in the 2 mg/kg group and 2 patients in the 6 mg/kg group. During the extension to 12 months, no new safety findings were observed compared to those reported before (Derfuss et al., 2014). No infusion reactions and no hypersensitivity were observed. There were no particular safety signals and no dose-associated trend for safety risks.

3.3. Pharmacokinetics

The repeated administration pharmacokinetics of GNbAC1 was characterized by a mean elimination half-life of 37 days and 27 days for the 2 mg/kg and the 6 mg/kg doses, respectively. The pharmacokinetics of GNbAC1 was dose-linear. The steady-state was reached after the fourth or fifth administration. Accumulation ratios (ratio of concentrations at Day 113 over Day 29) were between 2.9 and 3.5 for the 2 and the 6 mg/kg doses respectively.

GNbAC1 concentration in the cerebrospinal fluid (CSF) was assessed in one subject dosed at 6 mg/kg one month after the last drug administration and the CSF/serum concentration ratio of GNbAC1 was 0.2%.There was no evidence of anti-drug antibody production against GNbAC1 during the whole study duration.

MRI and EDSS data are presented as Supplementary material.

Table 1. Treatment emergent adverse events in a single dose phase and in the 12-month open label extension, observed in more than 10% of patients, by system organ class (SOC) and preferred term (PT).

				GnbAC1		
Single dose phase[a]	**SOC**	**PT**	**Placebo (n = 2)**	**2 mg/kg (n = 4)**	**6 mg/kg (n = 4)**	**Overall (n = 10)**
			n	**n**	**n**	**n**
Adverse events (AE)			2	3	4	9
AE leading to discontinuation			0	0	0	0
SAE			0	0	0	0
	General dis. & admin. site cond.	Fatigue	0	0	2	2
	Infections and infestations	Rhinitis	0	1	1	2
	Nervous system disorders	Headache	1	1	0	2

			GNbAC1		
Repeated dose phase			2 mg/kg (n = 5)	6 mg/kg (n = 5)	Overall (n = 10)
			n	n	n
Adverse events (AE)			5	5	10
AE leading to discontinuation			0	0	0
SAE			0	1	1
	Cardiac disorders	Sinus bradycardia	1	1	2
	General dis. & admin. site cond.	Chest pain	2	0	2
		Fatigue	1	2	3
		Gait disturbance	2	1	3
	Infections and infestations	Cystitis	2	1	3
		Nasopharyngitis	3	2	5
		Rhinitis	0	2	2

				GnbAC1	
Single dose phase[a]	**SOC**	**PT**	**Placebo (n = 2)**	**2 mg/kg (n = 4)**	**6 mg/kg (n = 4)**	**Overall (n = 10)**
			n	**n**	**n**	**n**
	Investigations	ECG QT prolonged		1	1	2
		gGT increased		2	1	3
	Metabolism & nutrition disorders	Hyperglycemia		0	2	2
	Nervous system disorders	Headache		0	2	2
		Muscle spasticity		1	1	2
	Renal and urinary disorders	Leukocyturia		1	2	3
		Proteinuria		1	2	3

[a] Single dose phase data were already presented in Derfuss et al. (2014).

4. Discussion

GNbAC1 is a monoclonal antibody targeting MSRV-Env, a protein which may play a critical role in MS by its inflammatory and myelinotoxic properties. After repeated administrations over one year, GNbAC1 appears to be safe, with adverse events mainly related to medical conditions of the patients. In particular, extending treatment over one year did not suggest additional safety risks compared to the initial exposure (Curtin et al., 2012; Derfuss et al., 2014) without evidence of hypersensitivity or infusion reaction, and no induction of immunogenicity was observed.

The repeated administration pharmacokinetic profile of GNbAC1 is in line with the first pharmacokinetic observations (Curtin et al., 2012; Derfuss et al., 2014) and considering its long half-life, GNbAC1 can be administered with a four week schedule. Interestingly, the CSF-blood ratio of GNbAC1 in one observation was 0.2% indicating blood–brain-barrier penetration of the mAb; this value is in line with other published values of CSF–blood ratio observed with mAbs administered to MS patients such as those of the anti-LINGO mAb BIIB033 (Tran et al., 2014) or rituximab (Petereit and Rubbert-Roth, 2009).

No inadvertent increase in disease activity was observed in the study, which may be a concern with a new pharmaceutical mode of action as it was observed recently in a trial with atacicept, a recombinant fusion protein that suppresses B-cell function (Kappos et al., 2014). Moreover the mechanism of action of GNbAC1 appears to be devoid of immunosuppressive action, notably as no impact on lymphocyte or monocyte reaction to antigens was observed in the presence of GNbAC1 (Zimmermann et al., personal communication), which may be an effective treatment of MS.

5. Conclusion

In conclusion, repeated doses of GNbAC1 at doses 2 and 6 mg/kg were well tolerated over 12 consecutive administrations. Pharmacokinetic and pharmacodynamic observations made at 6 months are supported by the 12-month findings. These encouraging results pave the way for a proof of concept study of GNbAC1 in MS patients.

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Supplementary material: Individual EDSS scores and MRI data at baseline, 6 months and 12 months.

GNbAC1	Patient	Sex	Age (yr)	MS Form	Baseline	6 months		12 months	
					EDSS	EDSS	MRI change from baseline	EDSS	MRI change from baseline
2 mg/kg	1	male	46	SPMS	4	3.5	stable	n.a.[+]	n.a.[+]
	2	male	52	SPMS	4.5	5	new lesion*	n.a.[+]	n.a.[+]
	3	male	49	SPMS	6	6	stable	6	stable
	4	male	57	SPMS	6	6	stable	6	stable
	5	female	59	PPMS	6	6.5	stable	6.5	stable
6 mg/kg	6	female	57	RRMS	2.5	2.5	stable	2	stable
	7	male	62	SPMS	3.5	3	stable	3	stable
	8	male	51	PPMS	3	3	stable	3	stable
	9	female	47	SPMS	6.5	7	stable	6.5	stable
	10	male	65	PPMS	6	6.5	stable	6.5	stable

*New T2 hyper-intense lesion in the cerebellum

[+]non available data, patient dropped out after 6 months