Clinical Study Report – Assessment of Safety

Study title:
Intrathecal therapy with monoclonal antibodies in progressive multiple sclerosis

EudraCT number:
2008-002626-11

Study drug:
Rituximab

Report period:
2009-07-02 – 2016-06-01

Report date:
2017-06-22

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Signature of Sponsor / Coordinating Investigator

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Summary and comments

Objectives of the study was to evaluate the feasibility and safety of intrathecally administered Mabthera in patients with progressive Multiple Sclerosis (MS) and to estimate efficacy via biochemical markers and clinical variables.

The primary endpoint of the study was to document safety parameters during the study.

Secondary endpoints of the study were:

- Clinical scoring
- Questionnaires regarding MS quality of life, symptom inventory and fatigue
- Neurofilament-Light (NFL)' levels in the CSF
- Immunological markers in blood and CSF such as absolute numbers of major lymphocyte subset as well as regulatory cell subset

1. Introduction

The study population consisted of patients with severe progressive MS. The patients were recruited at Norrland's University Hospital (NUS) in Umeå and at Akademiska University Hospital in Uppsala.

All patients received rituximab as Mabthera®.

A total of 23 patients were enrolled in the study. The study started to include patients 2009 09 16 (first subject first visit) and ended 2016 06 01 (last subject last visit).

2. Worldwide Marketing Approval Status

Not applicable in this investigator initiated clinical trial.

3. Actions Taken in the Reporting Period for Safety Reasons

Adverse Events have been followed for all patients enrolled in the study and reported in accordance with current regulations and approved protocol.

3.1 Study discontinuation

All patients completed the study.

3.2 Study drug discontinued

No patient discontinued with study medication.

4. Changes to Reference Safety Information

Not applicable when it is an investigator initiated clinical trial.

5. Inventory of Clinical Trials Ongoing and Completed during the Reporting Period

- STRIX - Switch To RItuXimab in MS
  A phase 2 open label study of Rituximab in MS patients previously treated with self-injectables using a target based therapy approach

- STRIX ext - Switch To RItuXimab in MS extension
  An extension study of STRIX-MS - a phase 2 open label study of Rituximab in MS patients previously treated with self-injectables using a target based therapy approach

- ITT-PMS ext - Intrathecal therapy with monoclonal antibodies in progressive multiple sclerosis.
  An extension trial of Intrathecal therapy with monoclonal antibodies in progressive multiple sclerosis.

6. Estimated Cumulative Exposure

6.1 Cumulative Subject Exposure in the Development Programme

Not applicable.

6.2 Patient Exposure from Marketing Experience

Not applicable.

7. Cumulative Summary Tabulations

7.1 Reference Information

Latest in Sweden approved summary of product characteristics dated 2016-05-26.

7.2 Cumulative Listings of Serious Adverse Reactions during the Reporting Period

Reporting period: 2009 09 16 – 2016 06 01.

Four Serious Adverse Events, no SUSAR, have occurred in this study during the reporting period.

	Patient number	**Study drug**	**Adverse Event** CTC AE	**SAE**	**Causality assessment**
1	0006	Rituximab	Viral infection	Yes	Possibly related
2	0009	Rituximab	Dizziness	Yes	Unlikely related
3	0010	Rituximab	Meningitis	Yes	Related
4	0011	Rituximab	Urinary tract infection	Yes	Unlikely related

1. SAE Suspected viral infection:
The patient was hospitalised with a suspected sepsis. Temperature, blood culture, urinary culture, pulmonary x-ray and screening for infections were done. At the clinic the patient didn't have fever and normal vital signs. The patient recovered without treatment. Diagnosis was assessed as possible viral infection. The last dose of study medication was five months before the event started. Causality assessment: possibly related.
2. SAE Dizziness:
The patient was hospitalised due to an episode of dizziness that appeared when she was out in the sun a warm day, possibly also double vision. A lumbar puncture was done, to rule out an infection, but no abnormalities were detected. The symptoms disappeared the following day and patient has been feeling well after that. Causality was assessed as unlikely related.
3. SAE Meningitis:
The patient came to hospital due to several weeks of headache. Lumbar puncture showed pleocytosis. Suspected low virulent bacterial infection in CNS. Cerebrospinal fluid and blood culture was negative. Rickham reservoir was removed. The stitches were removed nine days later and patient was treated with antibiotic intravenously, a combination of Meronem and Vancomycin, for ten days. The headache improved and the patient was completely recovered at the day of discharge. The causality was assessed as related to the study procedure, not to study drug.
4. SAE Urinary tract infection:
The patient was hospitalised overnight and due to urinary tract infection. The patient was treated with two doses of antibiotics intravenously and thereafter oral antibiotics and recovered completely. Causality was assessed as unlikely related to the study medication.

7.3 Cumulative AE (non-serious) with causality related

Non-serious AE evaluated to be related to study drug were primarily vertigo and nausea in direct relation to the administration of the study medication. These events were typically short-lasting (less than a minute – 20 minutes) and only in one occasion accompanied by vomiting. Another side effect in direct connection with the study drug administration was paresthesias in the extremities. Also this was short-lasting and of mild intensity.
See appendix I.

7.4 Cumulative AE (non-serious) with causality not related

Non-serious AE evaluated not to be related to study drug appeared to conform well to the general patient population.
See appendix II.

7.5 Cumulative AE Number Observed and Rate with patient identifications

Nervous system disorders constituted the largest number of AE (i.e. vertigo and nystagmus) followed by infections and infestations (i.e. urinary tract infection and upper respiratory infection). Since the route of administration has not been used before in multiple sclerosis the immediate reactions to the study drug was not known

to us prior to the study. Infections as a side-effect from rituximab treatment is well known.

See appendix III.

8. Significant Findings from Clinical Trials during the Reporting Period

8.1 Completed Clinical Trials

- **STRIX** - Switch To RItuXimab in MS
  A phase 2 open label study of Rituximab in MS patients previously treated with self-injectables using a target based therapy approach. This trial enrolled 75 RRMS patients that were clinically stable on first-line injection formulations. The study evaluated possible changes in inflammatory disease activity measured by MRI and CSF levels of Neurofilament Light (NFL). Both these parameters were significantly reduced after therapy switch. In another part of the trial, the patient treatment satisfaction was measured before and after change of therapy from injectables to rituximab. There was a pronounced improvement in treatment satisfaction while on rituximab as compared with injectable treatments.
  Altogether, this trial demonstrated that rituximab improved the control of inflammation at the same time as the patients felt considerably more satisfied with their treatment.

  Publications from this trial:
  1. de Flon P, Laurell K, Söderström L, Gunnarsson M, Svenningson A. Improved treatment satisfaction after therapy switch to rituximab in relapsing-remitting MS. Mult Scler. 2016:DOI 10.1177/1352458516676643.
  2. de Flon P, Gunnarsson M, Laurell K, Soderstrom L, Birgander R, Lindqvist T, et al. Reduced inflammation in relapsing-remitting multiple sclerosis after therapy switch to rituximab. Neurology. 2016;87(2):141-7.

8.2 Ongoing Clinical Trials

- **STRIX ext** - Switch To RItuXimab in MS extension
  An extension study of STRIX-MS - a phase 2 open label study of Rituximab in MS patients previously treated with self-injectables using a target based therapy approach
- **ITT-PMS ext** - Intrathecal therapy with monoclonal antibodies in progressive multiple sclerosis. An extension trial of Intrathecal therapy with monoclonal antibodies in progressive multiple sclerosis. This trial is a two-year extension trial for patients that completed the ITT-PMS trial in this report. The completion date for the extension trial will be June 2018

8.3 Long-term Follow-up

A subset of patients were offered continued treatment after the extension trial with 25 mg rituximab IT every 6 months. This voluntary extension is now terminated because of the evaluation of risk-benefit not being determined favorable for long-term use. Patients that has participated in the ITT-PMS and ITT-PMSext are followed prospectively as part of their clinical care. Possible side-effects that could be related to the IT rituximab medication will be reported to competent authorities according to recommended practice.

8.4 Other Therapeutic Use of Investigational Drug

Not applicable.

8.5 New Safety Data Related to Combination Therapies

Not applicable.

9. Safety Findings from Non-interventional Studies

Not applicable.

10. Other Clinical Trial/Study Safety Information

In the STRIX trial, the intravenous administration of 2 x 1000 mg rituximab 14 days apart was tolerated well and did not contain any serious infusion reactions. Among the 75 patients that were followed for two years, six severe adverse events occurred, among which three were considered possible related (two cases of pyelonephritis and one case of influenza). No unexpected serious adverse reaction (SUSAR) was reported. For details see publication indicated above.

11. Safety Findings from Marketing Experience

Not applicable.

12. Non-clinical Data

Not applicable.

13. Literature

Not applicable.

14. Lack of Efficacy

Not applicable.

15. Region-Specific Information

Not applicable.

16. Late-Breaking Information

Not applicable.

18. Overall Safety Assessment

Intrathecal treatment with rituximab via an intraventricular catheter in doses of 25 mg appears generally safe, but involves a risk for introduction of an infection during the injection procedure. Meticulous disinfection of the skin over the reservoir is

necessary to minimize this risk. Transient injection-related symptoms of vertigo and/or paresthesia were common but generally short-lasting and mild to moderate.

18.1 Evaluation of the Risks

The risk for serious side-effects is low but not negligible. It needs to be taken into account in the final evaluation of the benefit-risk relation of the treatment.

18.2 Benefit-risk Consideration

The evaluation of the clinical and biochemical data will be crucial in order to see if there are any clear signs of beneficial effects that outweigh the risks. The extension trial will also be of great importance for this evaluation.

19. Summary of Important Risks

The most important risk with intrathecal injections is the introduction of bacteria residing in the injection canal, such as bacteria in sebaceous glands. Such bacteria are typically of low virulence and thus highly treatable, but involves the removal of the injection reservoir.

20. Conclusions

It is too early to make a valid evaluation of the benefit-risk ratio of intrathecal treatment with rituximab in progressive MS. Preliminary analysis of treatment effects indicate no major beneficial effect from the treatment, putting this treatment principle into question. The treatment schedule was highly feasible and could be handled conveniently on an outpatient basis. The results of the trial therefore forms an important basis for experience regarding this treatment modality.

18 out of 23 participants reported at least one adverse event. One severe adverse event, meningitis, occurred in connection to drug administration and was treated effectively. No deaths occurred and no participants had to discontinue due to adverse events.

Appendix I

Cumulative AE (non serious) with causality related

Adverse event CTC AE	Patientnumber	Study drug	SAE	Causality assessment
Chills	0016	Rituximab	No	Related
Nervous system disorders - Other, Vertigo	0001	Rituximab	No	Related
Nervous system disorders - Other, Vertigo	0003	Rituximab	No	Related
Nervous system disorders - Other, Vertigo	0006	Rituximab	No	Related
Nervous system disorders - Other, Vertigo	0007	Rituximab	No	Related
Nervous system disorders - Other, Vertigo	0008	Rituximab	No	Related
Vertigo	0008	Rituximab	No	Related
Nervous system disorders - Other, Vertigo	0010	Rituximab	No	Related
Nervous system disorders - Other, Vertigo	0010	Rituximab	No	Related
Nervous system disorders - Other, Vertigo	0010	Rituximab	No	Related
Nervous system disorders - Other, Vertigo	0012	Rituximab	No	Related
Nervous system disorders - Other, Vertigo	0013	Rituximab	No	Related
Nervous system disorders - Other, Vertigo	0018	Rituximab	No	Related
Nervous system disorders - Other, Vertigo	UP01	Rituximab	No	Yes
Nervous system disorders - Other, Vertigo	UP01	Rituximab	No	Yes
Nervous system disorders - Other, Vertigo	UP01	Rituximab	No	Yes
Dry eye	0013	Rituximab	No	Related
Eye disorder - Other, Double vision	0011	Rituximab	No	Related
Eye disorder - Other, Double vision	0011	Rituximab	No	Related
Eye disorder - Other, Double vision	0011	Rituximab	No	Related
Eye disorder - Other, Impaired vision	0007	Rituximab	No	Possible
Fatigue	0014	Rituximab	No	Related
Fatigue	UP01	Rituximab	No	Probable
Fever	0014	Rituximab	No	Related
Fever	0018	Rituximab	No	Related
Flu like symptoms	UP01	Rituximab	No	Yes
Headache	0001	Rituximab	No	Possible
Lip infection, labial herpes simplex	UP01	Rituximab	No	Probable
Paresthesia	0013	Rituximab	No	Related
Paresthesia	0013	Rituximab	No	Related
Paresthesia	0013	Rituximab	No	Related
Paresthesia	0008	Rituximab	No	Related
Paresthesia	0008	Rituximab	No	Related
Nausea	0003	Rituximab	No	Related
Nausea	0007	Rituximab	No	Possible
Nausea	0012	Rituximab	No	Related
Nystagmus	0003	Rituximab	No	Related
Nystagmus	0007	Rituximab	No	Related
Nystagmus	0018	Rituximab	No	Related
Nystagmus	UP01	Rituximab	No	Yes
Nystagmus	UP01	Rituximab	No	Yes
Rash	UP01	Rituximab	No	Probable
Skin and subcutaneous tissue disorders - Other, Eczema in the scalp	UP01	Rituximab	No	Probable
Upper respiratory infection	0017	Rituximab	No	Possible
Urinary tract infection	0018	Rituximab	No	Possible
Vaginal infection, fungal	UP01	Rituximab	No	Probable
Vomiting	0007	Rituximab	No	Possible
Vomiting	0015	Rituximab	No	Related
Vomiting	0016	Rituximab	No	Related

Appendix II
Cumulative AE (non serious) with causality not related

Adverse Event CTC AE	Patient number	Study drug	SAE	Causality assessment
Urinary tract infection	0001	Rituximab	No	Unlikely
Hypertension	0004	Rituximab	No	Not related
Injury, poisoning and procedural complications - Other, Trauma to chest due to fall	0008	Rituximab	No	Not related
Urinary tract infection	0009	Rituximab	No	Not related
Injury, poisoning and procedural complications - Other, Tendon injury due to fall	0013	Rituximab	No	Not related
Upper respiratory infection	0013	Rituximab	No	Not related
Urinary tract infection	0015	Rituximab	No	Not related
Upper respiratory infection	0017	Rituximab	No	Not related
Urinary tract infection	0019	Rituximab	No	Unlikely
Upper respiratory infection	0019	Rituximab	No	Not related

Appendix III

Cumulative AE Number Observed and Rate with patient identifications

SOC	CTC AE	Related**	Not related***
Eye disorders	Dry eye	0013	
	Eye disorder - Other, Double vision	0011	
	Eye disorder - Other, Double vision	0011	
	Eye disorder - Other, Double vision	0011	
	Eye disorder - Other, Impaired vision	0007	
	Antal	**5**	**0**
	Procent	**7,94%**	**0,00%**
Gastrointestinal disorders	Nausea	0003	
	Nausea	0007	
	Nausea	0012	
	Vomiting	0007	
	Vomiting	0015	
	Vomiting	0016	
	Antal	**6**	**0**
	Procent	**9,52%**	**0,00%**
General disorders and administration site	Chills	0016	
	Fatigue	0014	
	Fatigue	01	
	Fever	0014	
	Fever	0018	
	Flu like symptoms	01	
	Antal	**6**	**0**
	Procent	**9,52%**	**0,00%**
Infections and infestations	Lip infection, labial herpes simplex	01	
	Meningitis	0010	
	Upper respiratory infection		0013
	Upper respiratory infection		0017
	Upper respiratory infection	0017	
	Upper respiratory infection		0019
	Urinary tract infection		0011
	Urinary tract infection	0018	
	Urinary tract infection		0001
	Urinary tract infection		0009
	Urinary tract infection		0015
	Urinary tract infection		0019
	Vaginal infection, fungal	01	
	Viral infection	0006	
	Antal	**6**	**8**
	Procent	**9,52%**	**12,70%**

* Patient identification number
** Causal relationship to study medication Related = Assessment is Yes, Related or Possible
*** Causal relationship to study medication Not related = Assessment is No, Not related, Unlikely or Unrelated.

Appendix III cont.

Cumulative AE Number Observed and Rate with patient identifications

SOC	CTC AE	Related**	Not related***	
Injury, poisoning and procedural complications	Injury, poisoning and procedural complications - Other, specify: tendon injury due to fall		0013	
	Injury, poisoning and procedural complications - Other, specify: trauma to chest due to fall		0008	
	Antal	**0**	**2**	
	Procent	**0,00%**	**3,17%**	
Nervous system disorders	Dizziness		0009	
	Paresthesia	0013		
	Paresthesia	0013		
	Paresthesia	0013		
	Paresthesia	0008		
	Paresthesia	0008		
	Vertigo	0001		
	Vertigo	0003		
	Vertigo	0006		
	Vertigo	0007		
	Vertigo	0008		
	Vertigo	0008		
	Vertigo	0010		
	Vertigo	0010		
	Vertigo	0010		
	Vertigo	0012		
	Vertigo	0013		
	Vertigo	0018		
	Vertigo	01		
	Vertigo	01		
	Vertigo	01		
	Headache	0001		
	Nystagmus	0003		
	Nystagmus	0007		
	Nystagmus	0018		
	Nystagmus	01		
	Nystagmus	01		
	Antal	**26**	**1**	
	Procent	**41,27%**	**1,59%**	
Skin and subcutaneous tissue disorders	Rash	01		
	Skin and subcutaneous tissue disorders - Other, Eczema in the scalp	01		
	Antal	**2**	**0**	
	Procent	**3,17%**	**0,00%**	
Vascular disorders	Hypertension		0004	
	Antal	**0**	**1**	
	Procent	**0,00%**	**1,59%**	
	Antal samtliga AE (Related och Not related)	**51**	**12**	
	Procent samtliga AE (Related och Not related)	**80,95%**	**19,05%**	
	Totalt antal samtliga AE (Related och Not related)			**63**

* Patient identification number
** Causal relationship to study medication Related = Assessment is Yes, Related or Possible
*** Causal relationship to study medication Not related = Assessment is No, Not related, Unlikely or Unrelated.