Natalizumab for the treatment of relapsing-remitting multiple sclerosis

Systematic review

Endbericht

Ludwig Boltzmann Institut
Health Technology Assessment

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Content

List of figures

List of tables

List of abbreviations

AE.....Adverse Event
ARR.....Annualized Relapse Rate
CG .....Control Group
CI.....Confidence Interval
CIS.....Clinically Isolated Syndrome
CNS .....Central Nervous System
EDSS.....Expanded Disability Status Score
FDA.....Food and Drug Administration
GRADE.....Grading of Recommendations, Assessment, Development and Evaluation
GWAS .....Genome Wide Association Studies
HRQoL .....Health Related Quality of Life
IG.....Intervention Group
IHE-20 .....Institute of Health Economics (Quality Appraisal Checklist)-20
IV.....Intravenous
JCV.....John Cunningham Virus
MHC .....Major Histocompatibility Complex
MRI ..... Magnetic Resonance Imaging
MS..... Multiple Sclerosis
PPMS..... Primary Progressive Multiple Sclerosis
QALY ..... Quality Adjusted Life Year
RCT ..... Randomised Controlled Trial
RoB ..... Risk of Bias
ROBINS-I.... Risk of Bias in Non-Randomized Studies of Interventions
RRMS ..... Relapsing-Remitting Multiple Sclerosis
SAE..... Serious Adverse Event
SF-36 ..... Short Form (36) Health Survey
SoF..... Summary of Findings
SPMS..... Secondary Progressive Multiple Sclerosis
VAS..... Visual Analogue Scale
VCAM ..... Vascular Cell Adhesion Molecule
VLA ..... Very Late Antigen

Zusammenfassung

Hintergrund

weltweit leiden 2,5 Millionen Menschen an Multipler Sklerose

Weltweit leben mehr als 2,5 Millionen Menschen mit Multipler Sklerose, einer progressiven, degenerativen Erkrankung des zentralen Nervensystems [1]. In Österreich waren im Jahr 2017 ca. 13.000 Menschen betroffen [2].

neurologische Erkrankung, doppelt so viele Frauen wie Männer erkranken

Multiple Sklerose ist eine der häufigsten neurologischen Erkrankungen bei jungen Erwachsenen zwischen 20 und 40 Jahren, wobei die Verteilung nach Geschlecht (mehr Frauen als Männer leiden unter der Erkrankung) und geografische Lage (eine höhere Prävalenz wird in vom Äquator entfernten Regionen beobachtet) variiert. Letzteres ist ein möglicher Hinweis darauf, dass eine reduzierte Sonneneinstrahlung in Verbindung mit niedrigen Vitamin-D-Spiegeln ein Auslöser für die Krankheit sein könnte [3]. Darüber hinaus besitzt MS eine polygene Ätiologie, wobei die stärksten Assoziationen innerhalb des Histokompatibilitätskomplexes (MHC) gefunden wurden [4].

genetische Mutationen und Umweltfaktoren

entzündliche Prozesse im ZNS zerstören neuronales Gewebe im ZNS; Symptome abhängig von Lokalisation der Läsionen

Die typischen sklerotischen Plaques (Läsionen) resultieren von multiplen Entzündungsprozessen, die letztendlich zur Zerstörung des neuronalen Gewebes führen. Abhängig vom Ort der Läsionen manifestieren sich klinische Symptome, welche motorische Defizite, sensorische Probleme, Sprech- und Sehbehinderungen sowie Fehlfunktionen des Urogenitalsystems und kognitive Beeinträchtigungen beinhalten [5, 6]. Darüber hinaus leiden viele Patienten an chronischen neurologischen Schmerzen, welche durch Fehlfunktionen des Nervensystems verursacht werden [7].

zurzeit keine Heilung möglich

Die Krankheit kann derzeit nicht endgültig geheilt werden. Verfügbare pharmakologische Therapien zielen daher darauf ab, den Krankheitsverlauf durch Suppression bzw. Modulation des Immunsystems zu verzögern.

monoklonaler Antikörper Natalizumab (Tysabri®) blockiert Migration der Immunzellen

Der monoklonale Antikörper Natalizumab (Tysabri®) wurde 2006 von der Food and Drug Administration (FDA) und der European Medicines Agency (EMA) zur Behandlung der schubförmig remittierenden Multiplen Sklerose zugelassen. Er bindet an das Integrin-Rezeptormolekül VLA-4 (very late antigen-4) und blockiert dadurch die Transmigration von Immunzellen in das ZNS. In klinischen Studien hat sich Natalizumab im Vergleich mit Plazebo als sehr wirksam erwiesen, jedoch ist die Therapie mit einem erhöhten Risiko für progressiven multifokalen Leukoenzephalopathie (PML) verbunden.

Methoden

Evaluation der langfristigen Wirksamkeit und Sicherheit von Natalizumab

Ziel dieser systematischen Übersichtsarbeit war zu untersuchen, ob Natalizumab über einen Behandlungszeitraum von mindestens 36 Monaten wirksamer und sicherer als alternative pharmakologische Therapien (oder Placebo) in Bezug auf jährliche Schubrate, Krankheitsverlauf, Lebensqualität und Anzahl der schwerwiegenden Nebenwirkungen ist.

Literatursuche in 4 Datenbanken und einem Studienregister

303 Resultate, davon 7 Studien eingeschlossen

Eine systematische Literaturrecherche wurde in vier Datenbanken durchgeführt (Medline via Ovid, Embase via Ovid, Toxline und Cochrane Central). Dabei wurden ausschließlich prospektive Studien und Publikationen, welche seit 2011 (dem Zeitpunkt der Veröffentlichung des Cochrane Reviews) in englischer Sprache publiziert wurden, eingeschossen. Darüber hinaus wurde im Studienregister ClinicalTrials.gov nach laufenden klinischen Studien und Beobachtungsstudien gesucht. Insgesamt ergab die Suche nach Deduplikation 303 Resultate, wovon 35 Studien im Volltext ausgewertet wurden. 7 Publikationen wurden als relevant erachtet und im nachfolgenden Bericht evaluiert.

Ergebnisse

Wirksamkeit: 3 kontrollierte Studien mit insg. 1.603 Patienten, davon 610 mit Natalizumab behandelt

Zur Beurteilung der klinischen Wirksamkeit erfüllten drei Studien die Einschlusskriterien. Eine randomisierte kontrollierte Studie (RCT) und zwei nicht-randomisierte kontrollierte Studien. Insgesamt wurden 1.603 Patienten eingeschlossen, wovon 610 für einen Zeitraum von 6 bis 51 Monaten mit Natalizumab behandelt wurden. Patienten der entsprechenden Kontrollgruppe erhielten entweder Fingolimod (n = 789), Placebo (n = 47) oder unterbrachen die Behandlung mit Natalizumab (n = 81). Der RCT wurde vom Hersteller Biogen Idec gesponsert.

Sicherheit: 7 Studien (3 kontrollierte Studien und 4 nicht-kontrollierte Studien)

Zur Beurteilung der Sicherheit erfüllten sieben Studien die Einschlusskriterien. Die drei o. a. kontrollierten Studien sowie vier einarmige Studien mit insgesamt 6335 Patienten. Die Studiendauer der nicht kontrollierten Studien lag zwischen 42 und 60 Monaten. Drei Studien wurden vom Hersteller Biogen Idec finanziert.

Klinische Wirksamkeit

keine Unterschiede zwischen Natalizumab und Fingolimod

Im Beobachtungszeitraum von mindestens 36 Monaten wurden keine signifikanten Unterschiede in Bezug auf die jährliche Schubrate und den Krankheitsverlauf zwischen Natalizumab und Fingolimod, einer alternativen medikamentösen Therapie, gefunden.

im Vergleich mit Plazebo: Reduktion der Schubrate, positive Beeinflussung des Krankheitsverlaufes

Im Vergleich mit Plazebo bzw. einer Gruppe von Patienten, welche die Natalizumab-Therapie zu unterschiedlichen Zeitpunkten abbrachen, zeigte Natalizumab jedoch eine 70 % Reduktion der Schubrate (Ratenverhältnis von 0,33 bzw. 0,31). Die mittels EDSS bestimmte Veränderung im Krankheitsverlauf von mit Natalizumab behandelten Patienten betrug -0,22 bis +0,05 Einheiten. In den entsprechenden Kontrollgruppen lagen die Werte zwischen +0,19 und +0,38 Einheiten.

kein signifikanter Unterschied in Lebensqualität

Eine einzelne Studie (RCT) untersuchte die Lebensqualität der Patienten, wobei jedoch kein signifikanter Unterschied zwischen der Interventions- und der Kontrollgruppe beobachtet wurde.

Sicherheit

2.4 % bis 16 % der PatientInnen leiden unter schweren Nebenwirkungen; 35 Fälle von PML; 14 Todesfälle

Vier Studien dokumentierten Nebenwirkungen der Therapie, wobei der Anteil von Patienten mit schweren Nebenwirkungen zwischen 2,4 % und 16 % lag. Die am häufigsten genannten waren dabei Infektionen und parasitäre Erkrankungen (bis zu 4 %), Neoplasmen (bis zu 2 %) sowie Überempfindlichkeitsreaktionen (0,5 % bis 2 %). Insgesamt wurden 35 Fälle von PML gemeldet. 14 Todesfälle traten auf, von denen einer eindeutig PML zugeschrieben wurde.

Diskussion und Schlussfolgerung

Wirksamkeit: Evidenz niedrig bis sehr niedrig aufgrund von RoB, geringer Stichprobengröße und kurzer Nachbeobachtungszeit

Generell wurde die Qualität der Evidenz hinsichtlich der klinischen Wirksamkeit als niedrig bis sehr niedrig eingestuft. Die Hauptgründe dafür waren ein Mangel an RCTs und ein schwerwiegendes Risiko für Bias aufgrund des Auswahlverfahrens der TeilnehmerInnen, fehlender Daten sowie Anzeichen von selektiven Ergebnisberichten. Die Qualität der kontrollierten Studien wurde wegen geringer Stichprobengröße sowie der sehr kurzen Nachbeobachtungszeit herabgestuft.

Sicherheit: Evidenz niedrig bis sehr niedrig

Bzgl. der Sicherheit wurde die Qualität der Evidenz aufgrund von Teilberichten, Unklarheiten in Bezug auf die Klassifizierung der Interventionsgruppen sowie möglichen Abweichungen von der ursprünglichen vorgesehenen Intervention auf niedrig bis sehr niedrig herabgestuft.

unvollständige Meldung von Nebenwirkungen

Nur eine Studie lieferte Daten über die Lebensqualität. Die Meldung schwerwiegender Nebenwirkungen war aufgrund unvollständiger Berichterstattung und mangelnder Klarheit in Bezug auf die Klassifizierung der Interventionsgruppen ein wesentlicher Punkt der Beanstandung.

Studien nicht generalisierbar aufgrund unterschiedlicher Ein- und Ausschlusskriterien

Die Studien wurden in Europa, Japan und den USA sowie im multinationalen Kontext durchgeführt und besitzen dadurch eine externe Gültigkeit. Gleichzeitig verhindern Unterschiede zwischen den Ein- und Ausschlusskriterien jedoch die Generalisierbarkeit. Daten wurden im Krankenhaus oder von praktizierenden Neurologen und Ärzten aufgezeichnet. Darüber hinaus wurden schwangere Frauen, Kinder sowie Patienten mit anderen MS-Formen ausgeschlossen.

Limitation im Review-Prozess

Aufgrund der spezifischen Anforderungen dieses Berichts (Konzeption als Masterthesis), wurden Literatursuche, Auswahl der Publikationen, Datenextraktion, Evaluation des Bias-Risikos sowie die Qualität der Evidenz nur von einer Wissenschaftlerin durchgeführt. Daher konnten standardisierte Qualitätssicherungsprozesse (z. B. die Auswahl von Studien durch zwei unabhängige Gutachter) nicht angewendet werden.

Fazit

Die aktuelle Evidenz deutet darauf hin, dass Natalizumab im Vergleich mit Fingolimod keine signifikanten Unterschiede in Bezug auf die jährliche Schubrate und den Krankheitsverlauf über einen Beobachtungszeitraum von mindestens 36 Monaten aufweist. Die Qualität der zugrundeliegenden Evidenz ist jedoch als niedrig bis sehr niedrig einzustufen. In Bezug auf die Sicherheit wurden keine Daten im Vergleich mit alternativen Behandlungsmethoden gefunden.

mehr direkte Vergleichsstudien notwendig

Der Fokus zukünftiger klinischer Forschung sollte daher in direkten Vergleich von Natalizumab mit anderen krankheitsmodulierenden Medikamenten (z. B. Interferon-beta, Fingolimod) liegen. Zusätzlich sollten Nebenwirkungen vollständig und umfassendener dokumentiert werden.

Summary

Introduction

2.5 million People suffer from Multiple Sclerosis

Worldwide, more than 2.5 million people suffer from Multiple Sclerosis (MS), which is a progressive, degenerating disease of the Central nervous system (CNS) [1]. In Austria, approximately 13,000 individuals were affected in 2017, resulting in a prevalence ratio of 159 per 100,000 person-years [2].

frequent neurological disorder; more women than man affected

Multiple sclerosis is one of the most frequent neurological conditions among young adults, although younger as well as older people can be affected [4]. The distribution varies according to sex (more women than men suffer from the condition) and the geographic location. A higher prevalence is observed in regions that are situated away from the equator indicating that reduced sunlight exposure in connection with low levels of vitamin D might be a trigger for the disease [3]. Moreover, MS possesses a polygenic etiology, whereby the strongest association has been found within the major histocompatibility complex (MHC) [4].

polygenic etiology

inflammation processes within CNS lead to sclerotic plaques

The typical sclerotic plaques (lesions) within the CNS originate from multiple inflammation processes which ultimately destroy the neuronal tissue. The clinical manifestations are heterogeneous and depend on the location of the lesions. They include motor deficits, sensory problems, speech and vision impairments and malfunctions of the urogenital system and cognitive impairments [5, 6]. Furthermore, the majority of the patients suffer from chronic neuropathic pain caused by the dysfunction of the nervous system [7].

Description of the intervention

Currently, there is no definitive cure. Therefore, available pharmacological therapies aim to reduce the disease activity either by suppressing or by modulating the immune system.

monoclonal antibody natalizumab (Tysabri®) blocks migration of immune cells into CNS

The humanized monoclonal antibody natalizumab (Tysabri®) was approved for the treatment of relapsing-remitting multiple sclerosis by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2006. It binds to the integrin receptor molecule VLA-4 (very late antigen-4) and thereby efficiently blocks the transmigration of immune cells into the CNS. In placebo-controlled randomised trials, natalizumab has been shown to be highly effective [8]. However, the therapy has been associated with an increased risk of developing progressive multifocal encephalopathy (PML) which is a severe opportunistic infection of the brain. Therefore, patients receiving natalizumab therapy have to be monitored regularly.

Methods

efficacy and safety of natalizumab over longterm treatment period

The aim of the systematic review was to investigate whether natalizumab is more effective and safer than alternative pharmacological therapies or placebo over a long term treatment period (≥ 36 months) with respect to annualized relapse rate, disability progression, QoL and number of serious adverse events (SAEs).

A systematic literature search was conducted in the following four databases (Medline via Ovid, Embase via Ovid, Toxline and Cochrane Central). The search was limited to prospective studies, articles published since 2011 (the publication of the Cochrane Review analysing natalizumab treatment for relapsing remitting multiple sclerosis) and in English language. After deduplication, 303 citations were included. Furthermore, the clinical trial registry ClinicalTrials.gov was assessed for ongoing clinical trials and observational studies. In total, the search yielded 35 results, which were assessed in full-text, of which 7 were considered relevant.

literature search in 4 databases and 1 trial registry

303 hits, 35 full-text articles, inclusion of 7 studies

Results

Available evidence

For the assessment of clinical effectiveness, three studies met the inclusion criteria. One randomised controlled trial (RCT) and two non-randomised controlled studies. In total, 1,603 patients were included. Out of these, 610 were treated with natalizumab for a period between 6 and 51 months. Patients of the corresponding control group received either fingolimod (n=789), placebo (n=47) or did interrupt natalizumab treatment (n=81). The RCT was sponsored by the manufacturer Biogen Idec.

clinical effectiveness: 3 studies included (1 RCT, 2 non-randomised trials) with 1,603 patients of which 610 were treated with Natalizumab

For the assessment of safety, seven studies met the inclusion criteria. The three controlled trials above, and four single-arm studies with a total of 6,335 patients. The follow-up periods lasted between 42 to 60 months. Three studies were funded by Biogen Idec.

safety: 7 studies included (3 controlled, 4 single-arm studies)

Clinical effectiveness

No significant differences regarding the annualized relapse rate and disability progression were found, if natalizumab was compared to fingolimod therapy (rate ratio of 0.93 (95% CI. 0.74-1.17), p=0.53).

clinical effectiveness: no significant differences in comparison with fingolimod

However, compared to either a placebo control or a group of patients interrupting natalizumab therapy, natalizumab showed an approx. 70% reduction in the annualized relapse rate (rate ratio of 0.33 and 0.31, respectively). The change in EDSS scores ranged from -0.22 to +0.05 units in natalizumab treated patients compared to a difference of +0.19 to +0.38 units in the respective control groups.

significant difference in comparison with placebo

Concerning QoL, only one trial (RCT) investigated this patient-reported outcome. Yet, no significant difference was observed between the intervention and the control group.

no difference in QoL

Safety

Four studies reported adverse events. The proportion of patients suffering from SAEs ranged from 2.4% to 16%. The most frequent were infections and infestations (up to 4%), neoplasms (up to 2%) and hypersensitivity reactions (0.5% to 2%). In total, 35 cases of PML were reported. 14 deaths occurred, one of which was attributed unambiguously to PML.

4 studies reported adverse events: 2,4% to 16% of patients (35 cases of PML, 14 deaths)

Discussion and conclusion

clinical effectiveness: evidence low to very low

Concerning clinical effectiveness, the quality of evidence was low to very low. The main reasons were lack of RCTs and serious risk of bias due to selection of participants, missing data and selective outcome reporting. Studies comparing patients receiving natalizumab with either those who interrupt the treatment or with a placebo control were downgraded due to small sample size, short follow-up period and bias in the selection of the participants.

safety: evidence low to very low

Concerning safety, the quality of evidence was low to very low due to partial reporting, lack of clarity regarding the classification of the intervention groups and potential deviation from the intended interventions.

partial reporting of adverse events

In terms of outcomes, data about the quality of life was lacking in all but one study. The reporting of serious adverse events was a major point of concern due to partial reporting and lack of clarity regarding the classification of the intervention groups.

differences in in- and exclusion criteria prevent generalisation

In terms of extern validity, the data is considered generalizable to other contexts. The studies were conducted in Europe, Japan and the USA and in multinational settings. Yet, differences between inclusion and exclusion criteria prevent the generalizability. Data were recorded in hospital settings or by practising neurologists and physicians. Furthermore, pregnant women, children, or patients with other forms of MS were excluded.

limitation due to single researcher

Due to the specific requirements of this report, only one researcher performed the literature search, the selection of eligible publications and the data-extraction in addition to assessing the risk of bias and evaluating the quality of evidence for each outcome. Hence, standard quality assurance processes (e.g. selection of studies by two reviewers independently) could not be applied.

Conclusion

more head-to-head RCTs needed

The current evidence indicates that there are no significant differences between natalizumab and fingolimod in terms of ARR and disability progression over a prolonged treatment period (≥36 months). However, the quality of the body of evidence suggesting this is low to very low. In terms of safety, no evidence was found, whether natalizumab therapy is safer than any treatment alternatives.

Thus, future research should provide more head-to-head RCTs comparing natalizumab with other disease modulating drugs (e.g. interferon beta, fingolimod) along with a comprehensive documentation of adverse events.

1 Introduction

1.1 Description of the condition

Multiple Sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) which affects more than 2.5 million people worldwide [1]. In Austria, approximately 13,200 individuals were affected in 2017 with an incidence rate of 19.5 per 100,000 person-years (95% CI 14.3-24.7) and a prevalence ratio of 158.9 per 100,000 person-years (95% CI 141.2-175.9), respectively [2].

weltweit mehr als 2.5 Millionen MS Patienten

MS is commonly diagnosed between 20 and 40 years of age, although younger as well older people can be affected [4]. The distribution varies according to sex as twice as much women than men suffer from the condition and the geographic location. A higher prevalence is observed in regions that are situated away from the equator indicating that reduced sunlight exposure in connection with low levels of vitamin D might be a trigger for the disease [3]. Additionally, MS possesses a genetic component as an increased risk is observed within families or in certain ethnic communities. The strongest association has been found within the major histocompatibility complex (MHC), which is a highly variant region within the human genome. Yet, recent genome wide association studies (GWAS) identified more than 110 non-MHC risk variants, suggesting a polygenic etiology [4].

Diagnose zwischen 20 und 40 Jahren; doppelt soviele Frauen wie Männer betroffen

The pathophysiological mechanism involves autoreactive T-cells that cause the myelin sheath damage. These are supported by B-lymphocytes which produce pro-inflammatory cytokines, thereby attracting further immune cells. Ultimately, the inflammation process destroys the neuronal tissue and leads to the formation of sclerotic plaques (lesions) [1].

autoreactive T-Zellen verursachen Abbau der Myelinschicht

The diagnosis is usually based on medical history and physical examination, which are formalized as the McDonald criteria [9]. These include imaging techniques like magnetic resonance imaging (MRI) for the identification of white matter lesions as well as specific laboratory tests [10].

Diagnose der Plaques (Läsionen) mittels bildgebender Verfahren

About 85% of MS patients develop a relapsing-remitting multiple sclerosis (RRMS) in which the characteristic inflammatory events alternate with phases of partial or even full recovery [4]. This phase could last from years to even decades. Finally, however, the disease progresses into a secondary progressive form (SPMS), in which the neurological disabilities due to axonal injury and neuronal loss become irreversible [4]. Approximately 15% of the patients experience a more severe disease pattern called primary progressive multiple sclerosis (PPMS). These individuals are immediately affected by irreversible neurodegeneration events [4].

85% erkranken an schubförmig-remittierender Multiplen Sklerose (RRMS)

The clinical manifestations are heterogeneous and depend on the location of the lesions. They could comprise a variety of symptoms including motor deficits, sensory problems, speech and vision impairments and malfunctions of the urogenital system [5]. Furthermore, the majority of the patients suffer from chronic neuropathic pain that is caused by the dysfunction of the nervous system [7].

abhängig von der Lokalisation der Läsionen gibt eine Vielzahl an Symptomen

Pharmacological therapies

zurzeit keine Heilung, jedoch positive Beeinflussung (Verzögerung) des Krankheitsverlaufes möglich

Currently, there is no definitive cure. Thus, the main aim of the therapy is to reduce the disease activity and thereby delay the degenerative progression either by suppressing or by modulating the immune system [5]. Furthermore, it has been shown that any delay in treatment is associated with a greater risk of reaching score 4 (fully ambulatory, up about 12 hours a day despite relatively severe disability) on the Enhanced Disability Status Scale (EDSS) sooner. In contrast, earlier treatment results in fewer hospitalization events, a reduction of relapses and a gain of quality adjusted life years (QALYs) [5].

krankheitsmodulierende Therapien reduzieren Schubrate und Auftreten von Läsionen

During acute relapses, immunosuppressants (primarily corticosteroids) are used to alleviate of some symptoms and to reduce the duration of the relapses. In exceptional cases, a plasmapheresis is performed [8, 11]. Additionally, disease-modifying therapies have been developed, which are able to reduce the rate of relapses as well as the occurrence of MRI lesions by altering the immune system. Furthermore, they have been shown to stabilize or delay MS associated disabilities [1]. Initially, so-called first-line treatments (e.g. Interferon-beta or Glatiamer acetate) are used which exhibit a moderate efficacy together with high safety profile. Usually they induce nonspecific changes within the immune system. In case of an unsatisfactory response to first line drugs or in patients with highly active disease, second-line treatments (for instance, monoclonal antibodies like natalizumab or ocrelizumab, or the sphingosine analogue fingolimod) are available. These are more effective, but are also accompanied with increased safety issues [1, 5, 12].

trotz Therapie stetige Verschlechterung der neurologischen Funktionen

Although current treatments are able to decrease the relapse rate in RRMS, most of the patients experience a worsening of the neurological functions during the course of the disease, albeit it is slow in most patients. A large longitudinal study with 2,319 patients evaluating 22,723 patient-years, showed that the median time from disease onset to EDSS 6 (unilateral assistance necessary for ambulation) was 27.9 years [13]. The disease has a major impact on the employment status of the patients as fatigue and cognitive difficulties reduce the people's productivity. A study showed that 18% of patients with a mild disease are unemployed compared to a 92% unemployment rate of people suffering from a more severe disease [5, 14].

Kosten steigen mit Schweregrad der Erkrankung

The overall costs of the disease rise with increasing severity. The estimated average costs per year range from 22,800 euros (mild disease) to 57,500 euros (severe disease) [5]. During the early stages they are mainly caused by the pharmacological treatment. Later, however, they increase due to the limitations at work, increased hospitalization, the requirements for accessing rehabilitation centres or the needs for assistance during relapse and recovery [5].

1.2 Description of the intervention

The humanized monoclonal antibody natalizumab (Tysabri®) was approved by the Food and Drug Administration (FDA) for the treatment of relapsing-remitting multiple sclerosis after a priority review from two ongoing trials (SENTINEL and AFFIRM) in 2004. Yet, after two cases of progressive multifocal leukoencephalopathy (PML), which is an uncommon and severe opportunistic brain infection, Biogen Idec and its former associated partner Elan Pharmaceuticals suspended both, commercialisation and clinical trials in 2005. After a comprehensive investigation and submission of the 2-year results of SENTINEL and AFFIRM, the drug was reintroduced in July 2006 [8]. Natalizumab was authorized in the European Union in June 2006 and is indicated as single disease modifying therapy in adults with highly active relapsing remitting multiple sclerosis either as second-line treatment or in treatment naïve patients with rapidly evolving severe relapsing remitting multiple sclerosis [15].

monoklonaler Antikörper Natalizumab 2006 in USA und Europa zugelassen

schwere Nebenwirkung PML

How the intervention might work

Natalizumab binds to the integrin molecule VLA-4 (very late antigen-4), which is expressed on the surface of T cells, B cells, monocytes, macrophages, natural killer cells, dentritic cells, neutrophils and eosinophils. In turn, these cells are unable to attach to VCAM-1 (vascular cell adhesion molecule 1) that is located on the endothelial cells of the blood vessels. Thereby, natalizumab effectively blocks the migration of the immune cells into the CNS [12, 16, 17].

Natalizumab verhindert Migration von Immunzellen in das zentrale Nervensystem

The efficacy and safety of natalizumab was previously evaluated in a systematic review published in 2011 by Pucci and colleagues [8]. It was based on three randomised controlled trials (AFFIRM 2006, SENTINEL 2006 and GLANCE 2009). The authors found significant evidence in favour of natalizumab therapy, as patients of the intervention group exhibited a reduced the risk of experiencing at least one new exacerbation after 2 years by 30% to 50% and of experiencing progression at 2 years by 10% to 40%, if compared to either those receiving interferon-beta or a placebo control group [8]. In terms of QoL, the comparison of the mean difference in the SF-36 scale (Short form (36) health survey) between intervention and control group favoured natalizumab treated patients. Regarding safety, the analysis showed that the number of patients experiencing at least one severe AE did not differ between groups. Furthermore, the frequency of serious AE (including MS relapses) was less common in the natalizumab treated group than in the control group (18% versus 21%) [8]. In summary, natalizumab was well tolerated, although the protocol was insufficient to evaluate the risk of progressive multifocal leukoencephalopathy [18].

erster systematischer Review 2011 basierend auf drei randomisierten Kontrollstudien

Natalizumab wirksam und sicher im Vergleich mit Plazebo

The relative benefit and acceptability of current therapies for the treatment of people with RRMS was determined by two further systematic reviews using network meta-analyses to compare multiple treatments [19, 20]. Tramacere and coworkers analysed 39 studies with a median duration of two years, yet only one trial investigating natalizumab therapy (AFFIRM 2006) was included. The other review published by the group of Filippini combined the results of two natalizumab RCTs (AFFIRM 2006 and SENTINEL 2006) in a group of 44 trials that were analysed. Natalizumab was considered either as third most effective drug [19] or (along with INFß-1a) as superior to all other treatments in preventing clinical relapses in RRMS compared to the placebo group for a duration of two years [20].

2 Netzwerk-Analysen reihen Wirksamkeit von Natalizumab entweder an erster (in Kombination mit Interferon-beta) oder dritter Stelle aller getesteten Medikamente

Ziel dieser systematischen Übersichtsarbeit: Vergleich Natalizumab mit alternativen MS Medikamenten

The rationale of this review is to compare the efficacy and safety of natalizumab with alternative immunomodulating therapies or placebo. The treatment effect of natalizumab will be calculated by including randomized and non-randomized controlled trials that have been undertaken since the publication of the first systematic. Potential long-term effects will be evaluated by including observational studies.

1.3 Research objectives

Forschungsziele

1. To estimate the effect of the treatment with the monoclonal antibody natalizumab by analysing the number of relapses (Annualized Relapse Rate – ARR) and the proportion of participants who experienced disability worsening (Enhanced Disability Status Score – EDSS) over specified time periods depending on the length of the studies under investigation.
2. To investigate whether the patient-reported quality of life (QoL) outcome is related to the disability status of the participants.
3. To determine the safety of natalizumab either applied as a first line treatment or as secondary regimen by determining the number of serious adverse events.

1.4 Research question

Forschungsfrage

Is the treatment with natalizumab effective and safe for patients with relapsing-remitting multiple sclerosis in comparison to alternative therapies (or placebo)?

2 Methods

2.1 Criteria for considering studies for this review

The inclusion criteria for relevant studies are summarized in Table 2.1-1. **PICO-Fragestellung**

Table 2.1-1: Inclusion criteria

Population	Adult patients (18-65 years) with a diagnosis of Relapsing-remitting Multiple Sclerosis according to the accepted diagnostic criteria.
Intervention	Natalizumab, 300 mg, IV, every 28 days
Control	Alternative therapy or placebo
Outcomes (crucial)	*Efficacy/Effectiveness* • Number of relapses (Annualized Relapse Rate – ARR) • Disability worsening (Enhanced Disability Status Score – EDSS) • QoL *Safety* • Number of Serious adverse events (SAEs)
Study design	*Efficacy/Effectiveness* • Randomised controlled studies (RCTs) • Prospective (non-randomised) controlled trials with a minimum treatment period of 36 months *Safety* • Randomised controlled studies (RCTs) • Prospective (non-randomised) controlled trials with a minimum treatment period of 36 months • Prospective single-arm studies with a minimum treatment period of 36 months
Publication period	2011-2018
Language	English

Types of participants

For this review, adult patients (18-65 years) with a diagnosis of RRMS (according to the accepted McDonald criteria) regardless of age, sex, severity of disease or treatment duration were included. However, persons with Clinical isolated syndrome (CIS) were excluded as not all people who are diagnosed with CIS later develop MS [21].

RRMS Patienten, 18-65 Jahre

Type of intervention

The effect of standard natalizumab treatment (300mg, IV, every 28 days) was compared to other immunomodulating therapies irrespective of their dosing regimen. Alternatively, a placebo control was considered, if no other therapy was used.

Natalizumab versus immunmodulierende Therapien

Types of outcome measures

The following outcomes were considered as critical.

kritische Endpunkte
Jährliche Schubrate

1. Annualized relapse rate (ARR). A relapse is defined as new or recurrent neurological symptoms that is not associated with fever or other acute diseases and which lasts for more than 24 hours and is followed by a period of at least 30 days of stability or improvement [9].

Krankheitsverlauf mittels EDSS

2. Disability progression measured by the Expanded Disability Status Scale (EDSS). EDSS is a common measure for MS disability with a score from 0 to 10 in half point increments on an ordinal scale, where '0' represents 'normal' and '10' is death from MS. Progression is defined as the difference between the baseline EDSS score and the EDSS score measured at different time-points during follow-up. A clinically meaningful change is generally considered as a persistent worsening of at least 1.0 in EDSS that is recorded outside a relapse and confirmed by a follow-up assessment, if the baseline EDSS score ranged between 0 and 5.5 or a 0.5 point increase, if the baseline EDSS was greater than 5.5 [22].

Lebensqualität

3. Quality of Life (QoL). Any test which measures the patient-reported outcome quality of life would be accepted.

Anzahl an schweren Nebenwirkungen

4. The number of serious adverse events (SAEs). If available, data about the number of infections and neoplasms will be collected. Due to the treatment, the immune system of the patients is altered, which might favour the formation of these conditions. Additionally, the number of PML cases would be of interest as this severe opportunistic infection is a known to be associated with natalizumab treatment.

In terms of safety, the number of adverse events will be considered as further outcome. Data about hypersensitivity reactions and the proportion of participants with antibodies against JCV or natalizumab will be reported.

Types of studies

RCT und Beobachtungsstudien über 36 Monate

For evaluating effectiveness, RCTs which studied natalizumab therapy for the treatment of RRMS patients were included. Due to their high methological quality, RCTs independently of the length of their respective follow-up period were included. As comparator, any alternative therapies or – in case no other therapies were applied – a placebo control was considered. Prospective, non-randomized controlled trials with a minimum treatment period of 36 months were included in order to evaluate the effectiveness of natalizumab over this prolonged treatment period. In contrast, retrospective studies and those with a follow-up of less than 36 were excluded.

In terms of safety, prospective single-arm studies with a minimum treatment period of 36 months or more were additionally included in order to be able to assess long-term adverse events. Retrospective studies as well as case series or case reports were excluded.

2.2 Search methods for identification of studies

Literatursuche in 4 Datenbanken und einem Studienregister

seit 2011 publizierte Artikel in Englisch

The systematic literature search was conducted in the following four databases: Embase (via Ovid), Medline (via Ovid), Cochrane CENTRAL and Toxline. The search was limited to articles written in English and those published from 2011 onwards. The specific search strategy can be found in the appendix. Registered clinical trials were identified by searching the ClinicalTrials.gov registry.

2.3 Data collection and analysis

Datenextraktion

The data from the selected studies were systematically extracted into the data-extraction tables (see appendix, Table 8.1-3). From each included study, data on the study characteristics (country of origin, sponsor and duration period as well as the design, number of patients, inclusion and exclusion criteria) was recorded. The baseline patient characteristics included data on age, sex, time since MS diagnosis, prior MS therapy, number of relapses in previous year and mean number of EDSS score at baseline. Outcome data was retrieved upon the annualized relapse rate and the disability progression measured by the Expanded Disability Status Scale. In addition, data about patient-reported quality of life was collected. Furthermore, the number of serious adverse events and adverse events was extracted from the studies. Besides, information about the duration of the follow-up, the number of those lost to follow-up as well as details of the intervention itself (dose, frequency) was recorded. No further data processing was applied.

2.4 Assessment of risk of bias in included studies

Evaluierung des RoB für randomisierte Kontrollstudien mittels RoB 2.0

The risk of bias in randomized controlled trials was assessed using the revised Cochrane risk of bias tool for individually randomized trials (RoB 2.0) [23]. For every study outcome, five domains (bias arising due to the randomization process, deviations from the intended intervention, missing outcome data, measurement error or selection of the reported result) were assessed by answering provided signalling questions corresponding to each domain. To summarize the quality of evidence as 'low' risk of bias, every outcome domain has to be judged as low risk. If any domain would be assessed as either 'some concerns' or high' risk of bias, the whole study would be classified accordingly.

Evaluierung des RoB für nicht-randomisierte Kontrollstudien mittels ROBINS-I

For assessing the risk of bias in non-randomized controlled trials, the risk of bias in non-randomized studies of interventions (ROBINS-I) was applied which compares the effects of two or more interventions [24]. Basically, it covers seven domains: two of which are addressed before the start of the intervention (bias due to confounding and in the selection of participants into the study), the third classifies the intervention itself (bias in the classification

of the interventions), while the other four consider issues after the start of the intervention (bias due to deviations from intended interventions, missing data, measurement of outcomes and selection of the reported result). Again, signalling questions are used for the domain-level judgement as either 'low', 'moderate', 'serious', 'critical' risk of bias. A 'no information' option can be used in cases where the text of the publication does not provide any details for an appropriate answer. Downgrading the risk of bias in an individual domain automatically results in downgrading the overall risk of bias of the respective study.

Evaluierung des RoB für nicht kontrollierte Studien mittels IHE-20

For observational, single-arm studies, the IHE-20 Quality appraisal checklist for case series studies was applied [25]. It consists of 20 questions that address 8 topics (study objective, design, population, intervention, outcome measures, statistical analysis, results and conclusions as well as completing interests and sources of support). The questions relating to each topic can be answered with either 'yes', 'no' or 'partial'/'unclear' and serve as guidance to assess the quality of the study in general.

2.5 Data synthesis

Datensynthese auf Outcome-level mittels GRADE

Based on the evidence and the risk of bias tables, data on each selected outcome category was assessed across studies and evaluated using the GRADE approach (Grading of Recommendations, Assessment, Development and Evaluation) [26]. Additionally, the main results were presented in a Summary of findings (SoF) table (Table 4-1). Finally, the research question was answered in plain text format with reference to the GRADE evidence table (Table 4-1).

3 Results

Results of the search (Flow chart)

After removing duplicates, 303 records were retrieved by the systematic search strategy. 35 articles were considered as potentially eligible after screening the titles and abstracts of the publications. The evaluation of the corresponding full-text resulted in the inclusion of 7 studies for the qualitative synthesis.

Literaturauswahl
303 Hits, davon
7 Studien inkludiert

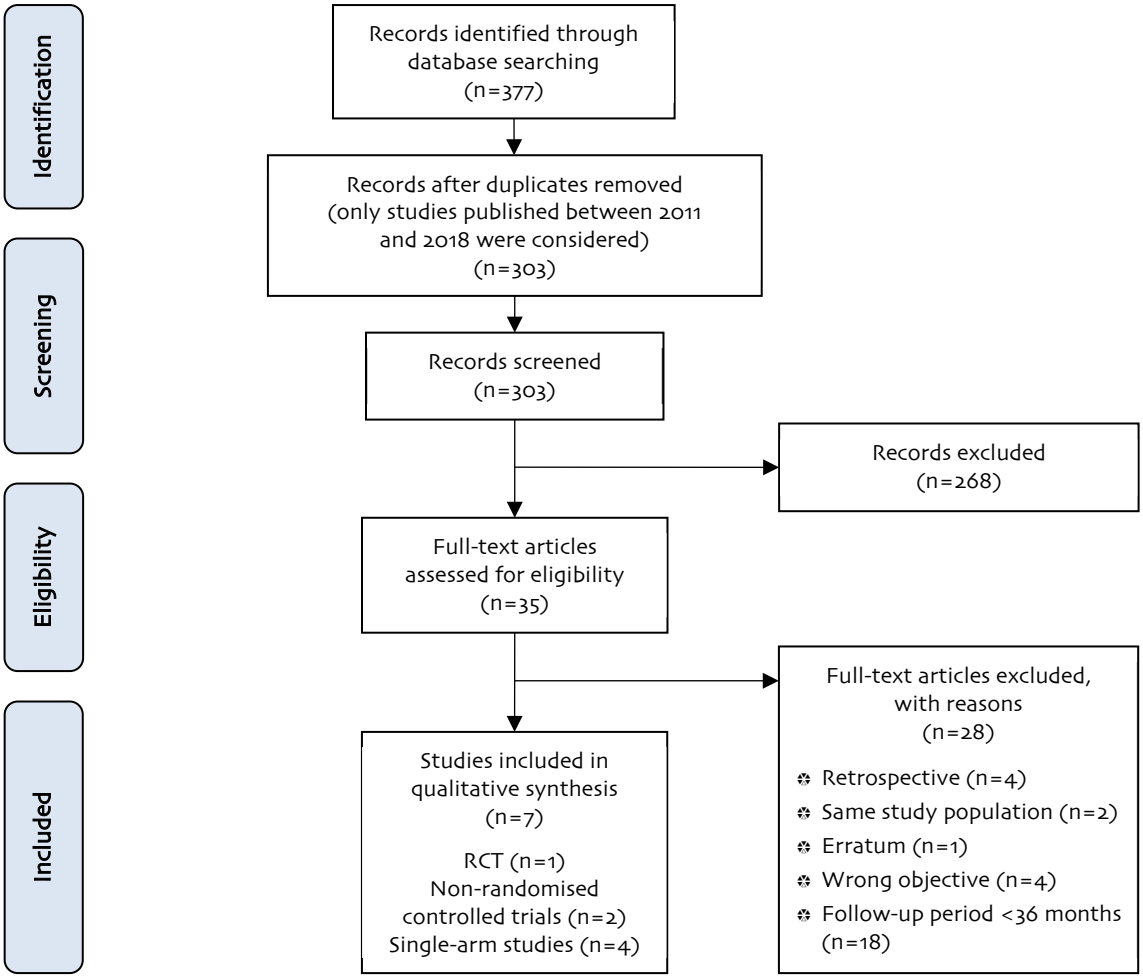

Figure 3-1: Flow chart of the study selection.

3.1 Efficacy/Effectiveness

Included studies

1 RCT und 2 nicht randomisiert Kontrollstudien

For investigating the efficacy and effectiveness, respectively, three studies met the inclusion criteria: one randomised controlled study [27] and two non-randomised controlled trials [28, 29].

Vergleich mit entweder Fingolimod, Plazebo oder Therapieabbrecher

The studies were performed in Japan [27], Italy [28] and Denmark [29] and included 1,603 patients with a mean age of 35.1 to 39.5 years. Approximately 70% of the participants were female with a mean number of relapses between 1.05 and 2.29 in the year prior to study enrolment. Out of these patient group, 610 received natalizumab treatment for a follow-up period between 6 months to 51 months. Patients of the corresponding control groups received either fingolimod (n=789) [29], placebo (n=47) [27] or did interrupt natalizumab treatment followed by one of three options ((1) switching to another disease-modifying therapy, (2) discontinuing all treatment or (3) beginning intravenous mitoxantrone hydrochloride) (n=81) [28]. The randomised controlled trial was sponsored by the manufacturer Biogen Idec. Table 3.1-1 summarizes the main characteristics of the studies.

Table 3.1-1: Overview of the main study characteristics

Study	Saida et al.[27]	Clerico et al.[28]	Koch-Henriksen et al.[29]
Design	RCT	Non-randomised controlled trial	Non-randomised controlled trial
No of patients	94	130	1379
Lenght of follow-up (months)	6	12	51
Conflict of interest	sponsored by Biogen	none	none

RCT: Japan, Sponsor: Biogen, 94 PatientInnen (davon Natalizumab: 47), Studiendauer 6 Monate

The RCT included 94 patients, of which 47 were in the intervention group (IG) and 47 in the control group (CG) [27]. Patients were excluded if they had received prior treatment with natalizumab, immunosuppressants or a positive test result for Aquaporin4 antibodies. During the 6 months study period, 5 patients (5.3%) were lost to follow-up.

nicht randomisierte Studien insg. 1.509 PatientInnen (130 und 1.379), Studiendauer 12-51 Monate

The non-randomized studies included in total 1,509 patients. Clerico et al. [28] included 130 patients, of which 6 patients (4.6%) were lost to follow-up. Of the remaining 124 patients 43 patients received natalizumab therapy for a further period of 12 months, while 81 patients were included in the control group. In the non-randomised trial performed by Koch-Henriksen et al. [29], the outcomes of natalizumab treatment were compared with fingolimod therapy. Of 1,379 participants, 70 patients (5.1%) were lost during follow-up. After propensity score matching, the data of 928 individuals were used for the analysis (IG n=464).

In terms of differences between inclusion and exclusion criteria between the two non-randomised trial, Clerico et al. [28] included patients which under natalizumab therapy had a clinical and MRI imaging MS stability as defined by the absence of documented relapses and the absence of EDSS progression during the preceding 6 months. Further exclusion criteria were pregnancy, severe depression, known alcohol and drug addiction and any clinical condition in addition to MS. In contrast, Koch-Henriksen et al. [29] included RRMS patients which under first-line treatment with interferon-beta or glatiramer acetate experienced at least one significant relapse in the year prior to enrolment. Furthermore, treatment-naïve patients were included, if they suffered within a year from two serious relapses with residual symptoms and an active magnetic resonance imaging scan with gadolinium positive lesion(s) or a significant increase in T2 lesions compared to earlier MRI scans. The exclusion criteria were not further specified.

Unterschiede: stabile PatientInnen (unter Natalizumab-Therapie) versus MS-PatientInnen, bei denen die vorherige Therapie keine Wirkung zeigte versus unbehandelte PatientInnen mit schweren Verlaufsformen

Effect of the intervention

Annual relapse rate

The annual relapse rate was investigated in three studies [27-29]. In the study which directly compared natalizumab with fingolimod, the crude ARRs after treatment were 0.30 (95% CI 0.26-0.34) and 0.31 (95% CI 0.27-0.35), respectively. The corresponding adjusted rate ratio was 0.93 (95% CI: 0.74-1.17) with a p-value of 0.53, indicating no difference between the two therapies [29].

kein Unterschied in der jährlichen Schubrate zwischen Natalizumab und Fingolimod behandelten PatientInnen

In the two further studies, the ARRs of natalizumab treated patients were 0.24 (SD0.48) [28] and 0.53 (95% CI: 0.29-0.99) [27], respectively. The corresponding values of the comparator groups ranged from 0.73 (SD 0.85) to 1.73 (95% CI: 1.22-2.45). Thus, a significant difference was observed, if patients of the intervention group were compared to either a group of natalizumab interrupters [28] or a placebo control [27].

Wirksamkeit gegenüber Plazebo oder Therapieabbrechern

Disability progression

Data about the disability progression were available from all included studies [27-29]. Yet, only the RCT [27] and one non-randomised controlled study [28] indicated absolute differences.

No significant difference (p-value 0.86) was observed between natalizumab and fingolimod treated patients [29]. In the intervention group 40.1% improved, 31.0% remained unchanged and 28.9% worsened, when comparing the EDSS score at the end of the follow-up to the baseline score. Similarly, 39.9% of the fingolimod-treated patient improved, 32.5% remained unchanged and 27.6% worsened [29].

kein Unterschied im Krankheitsverlauf zwischen Natalizumab und Fingolimod behandelten PatientInnen

Data from the other two studies showed that the disability of natalizumab treated patients either improved (the mean EDSS score differed by -0.22 arbitrary units (from baseline 2.5 to 2.3, [27]) or remained constant (absolute change in EDSS score of 0.05 arbitrary units (from baseline 3.31 to 3.36) [28]). In both control groups, however, the disability progressed either by +0.19 arbitrary units (from baseline 2.1 to 2.3) [27] or by +0.38 arbitrary units (from baseline 3.42 to 3.80) [28].

Verbesserungen im Krankheitsverlauf von Natalizumab behandelten PatientInnen im Vergleich zu Kontrollgruppen

QoL

RCT: Kein signifikanter Unterschied in der Lebensqualität

The patient-reported outcome QoL was investigated only in the RCT using a visual analogue scale (VAS) ranging from 0 to 100, where 0 was considered "poor" and 100 "excellent". The calculated mean change over time was a -4.8 point reduction in the natalizumab group versus a -2.9 point reduction in the control group with a corresponding p-value of 0.942, indicating no significant difference between the two groups [27].

3.2 Safety

Included studies

7 eingeschlossene Studien mit 12.270 PatientInnen, davon erhielten 7.168 Natalizumab

In terms of safety, seven studies met the inclusion criteria. Besides the studies described in the section of clinical efficacy and effectiveness, further four observational, single-arm studies were included which will be described below. In total, the data of 12,270 patients were analysed (1603 in the controlled, 6335 in the single-arm studies), of which 7,168 received natalizumab therapy.

4 nicht kontrollierte Studien, ~70% Frauen, FU 42-60 Monate, 3 Studien finanziert von Biogen

The interim analyses from two multinational studies, the Tysabri observational program (TOP) study [30] and the Safety of Tysabri re-dosing and treatment (STRATA) study [31], were included. In addition, one study from Italy [32] and one from the USA [33] met the inclusion criteria. The single-arm studies included patients from 35.8 to 41.3 years of age, with a female percentage between 69.1% and 74.4%. The follow-up periods lasted between 42 months [32] to 60 months [30, 31, 33]. Three studies were funded by Biogen Idec [30, 31, 33]; no sponsor related information was available from the fourth study.

unterschiedliche Einschlusskriterien

PatientInnen zweier Studien waren bereits TeilnehmerInnen von klinischen Studien

Differences in between studies were found regarding the inclusion criteria. In two studies patients were recruited, if they had already been part of another trial investigating natalizumab therapy. Zivadinov and colleagues evaluated participants from the voxel-wise magnetization transfer ratio (VWMTR) [34] study five years later in order to investigate potential long-term effects of natalizumab therapy. In contrast to other studies, RRMS as well as secondary progressive MS patients were included [33]. Participants of the STRATA study initially received natalizumab therapy in a randomised controlled feeder-study. Yet, due to the withdrawal of the drug due to cases of PML in 2005, the participants experienced a treatment gap. To investigate the effect of this treatment interruption, eligible and willing patients were enrolled in the STRATA study [31].

Butzkueven and colleagues included RRMS patients who met the criteria for natalizumab prescription in their respective countries and had three or fewer natalizumab infusions before enrolment. Female participants were supposed to be postmenopausal, surgically sterile, or willing to practice effective contraception [30]. Totaro and co-authors included patients who were on immunomodulatory treatment for at least 12 months and who had experienced either two relapses in the last year or a single relapse with incomplete recovery and residual disability. In addition, patients with severe and fast evolving MS (defined as 2 or more relapses with increased disability during the previous year) were recruited, even if they have not previously been treated with immunomodulatory treatments [32].

Serious adverse events

Four studies reported serious adverse events [27, 28, 30, 31]. The proportion of of natalizumab treated patients suffering from SAEs ranged from 2.4% [28] to 16% [31]. The most common ones were infections and infestations (up to 4%), neoplasms (up to 2%) and hypersensitivity reactions (0.5% to 2%). Only two studies documented SAEs in the respective control groups: either 1.2% (1/81) [28] or 23% (11/47) [27] of the patients suffered from serious adverse events. In total, 35 cases of PML were reported [28, 30, 31, 33] and 14 deaths occurred [30, 31, 33], one of which was attributed to PML [33].

4 Studien dokumentierten schwere Nebenwirkungen

2.4%-16% der PatientInnen (insg. 35 Fälle von PML und 14 Todesfälle)

Adverse events

The number of adverse events was documented in three studies [27, 30, 32]. Overall, 2.2% [30] to 72% [27] of patients treated with natalizumab reported AEs, among which headaches and infections were reported most frequently.

3 Studien dokumentieren Nebenwirkungen

Hypersensitivity reactions were reported in 3.5% [32] to 5.0% [31] of the participants, while 0.9% [30] to 2.1% [27] of the patients developed antibodies against natalizumab. 43% [33] to 67% [31] of the patients were tested seropositive for JCV.

2.2%-72% der PatientInnen

4 Grading of evidence

Risk of bias in included studies

RCT: niedriges RoB, nicht randomisierte Kontrollstudien: hohes RoB

The individual studies were assessed with the revised Cochrane risk of bias tool for individually randomized trials (RoB 2.0) [23], the risk of bias in non-randomized studies of interventions (ROBINS-I) [24] and the Institute of Health Economics (IHE)-20 checklist for single-arm studies [25]. The assessments are presented in the Table 8.2-1–Table 8.2-3 in the Appendix.

The randomized controlled trial (REF) was considered as having a low risk of bias (RoB) in all domains analysed. However, a conflict of interest was present as the study was funded by the manufacturer. Both non-randomised controlled studies were considered as having a serious RoB. The study by Clerico [28] was downgraded due to high RoB in the selection of the participants and the classification of the intervention groups as well as due to the possibility of deviating from the intended interventions. The reasons for downgrading the study performed by Koch-Henriksen [29] were bias due to missing data and possible selection of the reported results.

nicht kontrollierte Studien: mittleres bis hohes RoB

The overall risk of bias in the single-arm studies varied from moderate [30, 31, 33] to high [32]. The major factors contributing to a risk of bias were non-consecutive selection of patients, partial description of the eligibility criteria, lack of blinding, lack of documentation of potential losses to follow-up and lack of clarity concerning the reporting of co-interventions. A conflict of interest was present in three of four studies as they were funded by the manufacturer.

GRADE

Bewertung der Stärke der Evidenz mittels GRADE

The strength of evidence was rated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) schema [26] for each endpoint individually. Basically, Grade uses four categories to rank the strength of evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effective
- **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
- **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effective
- **Very low** = Evidence either is unavailable or does not permit a conclusions

The ranking according to the GRADE scheme for the research question can be found in Table 4-1.

Stärke der Evidenz niedrig bis sehr niedrig

Overall, the strength of evidence for the efficacy of natalizumab in comparison to an alternative therapy with fingolimod is very low in the outcomes of ARR and disability progression. Regarding QoL and number of serious adverse events, no evidence was found.

However, natalizumab therapy seems to be effective and safe in terms of ARR, disability progression and number of serious adverse events, if compared to a placebo control. No significant difference was found regarding QoL. Yet, the strength of evidence supporting the data is low.

Table 4-1: Summary of findings table

Outcomes	Absolute effects	Relative effects	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Annualized relapse rate (ARR)	Natalizumab: 0.30 vs Fingolimod: 0.31 (p=0.53)	Rate ratio[a]: 0.93 (95%CI: 0.74-1.17)	1,058 (2 observational trials)	⨁◯◯◯ VERY LOW[c]	-
	Natalizumab: 0.24 vs control group[b]: 0.73 (p=0.004)	Odds ratio: 0.33 (95% CI: 0.15-0.70)	94 (1 RCT)	⨁⨁◯◯ LOW[d,e]	
	Natalizumab: 0.53 vs placebo: 1.73 (p=0.001)	-			
Disability progression (assessed with EDSS[f])	-	Natalizumab (40.1% improved, 31.0% unchanged, 28.9% worsened) vs Fingolimod (39.9% improved, 32.5% unchanged, 27.6% worsened) (p=0.53)	1,058 (2 observational trials)	⨁◯◯◯ VERY LOW[c]	-
	Natalizumab: +0.05 vs control group[b]: +0.38 (p=0.004)	-			
	Natalizumab: -0.22 vs placebo: 0.19 (p=0.019)	-	94 (1 RCT)	⨁⨁◯◯ LOW[d,e]	Analysis not prespecified
Quality of life (assessed with VAS[g])	Natalizumab: -4.8 points vs placebo: -2.9 points (p=0.942)	-	94 (1 RCT)	⨁⨁◯◯ LOW[d,e]	-
Number of serious adverse events	Natalizumab: 7/47 (15%) vs placebo: 11/47 (23%)	-	94 (1 RCT)	⨁⨁◯◯ LOW[d,e]	Including MS relapses
	Natalizumab: 2 (4.6%) vs. control group[b]: 1 (1.2%)	-	124 (1 observational trial)	⨁◯◯◯ VERY LOW[c]	
	Natalizumab: 636/5915 (10.75%)	-	5,915 (2 observational trials)	⨁⨁◯◯ LOW	

Abbreviations: *RCT = Randomised controlled trial, EDSS= Expanded disability status score, VAS = Visual Analogue Scale*

Explanations: *a) adjusted for all covariates b) Natalizumab interrupters c) serious risk of bias due to selection of the participants and selective outcome reporting d) small sample size e) short follow-up period f) EDSS scale ranges 0 (normal) to 10 (death) in 0.5 point increments g) VAS ranging from 0 (poor) to 100 (excellent)*

5 Discussion

This report evaluated the efficacy and safety of natalizumab therapy in RRMS patients seven years after the publication of the first systematic review. In the investigated publication period between 2011 and 2018, three studies were identified which compared natalizumab with alternative therapies or placebo.

klinische Wirksamkeit: 1 RCT, 2 nicht-randomisierte kontrollierte Studien

Concerning clinical effectiveness, evidence was available from three studies [27-29]. One RCT with 94 patients (IG=47) and two non-randomised controlled trials with 130 (IG=43) and 1,379 patients (IG=520), respectively, were included. A single study provided a direct comparison of natalizumab with an alternative therapy suggesting that natalizumab is equally effective as the treatment with fingolimod in regard of the annualized relapse rate (REF). Both drugs were able to reduce the ARR to 0.30 (95% CI 0.26-0.34) and 0.31 (95% CI 0.27-0.34), respectively. Similarly, no significant differences in terms of disease progression between the two treatments were reported. A similar percentage of each group improved (IG: 40.1% vs. CG: 39.9%) remained unchanged (IG: 31.0% vs. CG: 32.5%) or worsened (IG: 28.9% vs. CG: 27.6%).

In contrast, the comparison of natalizumab-treated patients with either those interrupting natalizumab treatment [28] or a group receiving a placebo control [27], suggested a benefit of the intervention in both studies (estimated RR=0.33 and RR=0.31, respectively). Regarding disability progression, significant changes in the EDSS scores between intervention and control groups were observed in both trials. However, neither of the variations represented a clinically meaningful change, which is considered as a difference between 1.0 or more if the EDSS at baseline was 0 to 5.5, or 0.5 or more for higher baseline EDSS scores [22].

1 Studie dokumentierte QoL: kein signifikanter Unterschied im Vergleich mit Plazebo (niedrige Stärke der Evidenz)

In terms of patient-reported quality of life, no evidence was available on whether natalizumab is superior to other treatment alternatives. QoL data form the RCT comparing natalizumab with a placebo control [27] revealed no significant difference between intervention and control groups (p=0.942), which could be explained by the small sample size and the short duration of the follow-up period. In contrast, data from the AFFIRM and SENTINEL trials showed an improved QoL of natalizumab treated patients compared to those receiving either placebo or interferon-beta, respectively, after 24 months of therapy [35].

Sicherheit: keine verfügbare Evidenz im Vergleich mit alternativen Therapien;

jedoch Daten von nicht-kontrollierten Studien vorhanden

Concerning safety, three controlled and additional four prospective single-arm studies with in total 6,872 patients on natalizumab therapy were analysed. No evidence was found whether natalizumab therapy is safer than the alternative treatment with fingolimod. Yet, if compared to placebo, a reduction in the amount of serious adverse events was observed in the intervention group (15% versus 23%). However, if MS relapses were excluded from the analysis, the proportion of patients suffering from SAEs was higher in the natalizumab-treated group than in the placebo control group (6% versus 2%) [27]. In the single-arm studies, the percentage of serious adverse events in patients who received natalizmab ranged from 2.3% to 16%.

unvollständige Dokumentation von Nebenwirkungen

The reporting of AEs was generally incomplete. Only three studies reported the number of adverse events, which ranged from 2.2% [30] to 72% [27] in natalizumab treated patients.

Overall completeness and applicability of evidence

Gründe für die Abwertung: fehlen von RCTs, hohes RoB, kleine Stichprobe, kurzer Beobachtungszeitraum

Concerning the effectiveness of natalizumab in comparison to alternative therapies, the quality of evidence was low to very low. The main reasons were a lack of RCTs and a serious risk of bias due to selection of participants, missing data and indication of selective outcome reporting.

In particular, only one trial comparing natalizumab with an alternative disease modifying therapy met the inclusion criteria. In contrast to the conclusion of the study that both treatments are equally effective, other publications observed a difference between the two treatments in favour of natalizumab [19, 36]. Similarly, a recent network meta-analysis comparing the effectiveness of available MS drugs ranked natalizumab (RR 0.56; 95% CI 0.47 to 0.66) as third and fingolimod (RR 0.72; 95% CI 0.64 to 0.81) as fourth most effective drugs in preventing the recurrence of relapses in RRMS patients after 24 months of treatment [19]. Furthermore, data from a retrospective non-randomized controlled trial revealed a higher percentage of relapse-free patients (80% vs 66%, $p=0.015$) as well as a higher percentage of disability-improved patients (15% vs 6%, $p=0.033$) in the natalizumab treated group than in the fingolimod treated group. Additionally, natalizumab therapy was associated with a reduction in MRI-activity (14% vs 38%, $p=0.001$) and a higher percentage of patients with no evidence of disease activity (70% vs 44%, $p<0.001$), suggesting that natalizumab is superior to fingolimod in patients non-responding to first-line agents [37]. In addition, the analysis from the Austrian MS Treatment Registry showed a statistically significant difference in the mean annualized relapse rates during a 24 months observation period, revealing a greater reduction in the natalizumab treated group (ARR 0.12 vs. 0.19, $p=0.005$). Yet, no significant differences were observed between the two groups regarding the probability of experiencing a relapse, EDSS progression or EDSS regression [36].

Two studies were investigating the efficacy of natalizumab compared with either those who interrupt the treatment or with a placebo control. The evidence from the RCT comparing patients receiving natalizumab therapy with a placebo control group was considered as being low due to the small sample size and the short follow-up time. The non-randomized trial was attributed with a very low level of evidence due to its high RoB. Both studies showed a benefit of natalizumab therapy in line with the literature [8].

QoL: Messinstrument nicht weiter spezifiziert

A single study measured the patient-reported outcome quality of life. However, the intervention group was compared to a placebo control. Hence, no evidence/information about differences in QoL of natalizumab treated patients compared to patients receiving alternative therapies could be found. Moreover, the measurement tool (visual analogue scale) was not further specified in terms of validity or clinical relevant differences. Therefore, the results could not be related to other general HRQoL instruments or any of the MS-specific HRQoL questionnaires [38].

unvollständige Dokumentation von (schweren) Nebenwirkungen

Generally, the reporting of SAEs and AEs was a point of major concern as partial reporting was assumed in several trials. Furthermore, lack of clarity regarding the classification of the intervention groups and potential deviation from the intended interventions prevented a comprehensive analysis. More accurate information will be available after the publication of the systematic review of Tramacere and colleagues comparing the adverse effects of immunotherapies for people with MS or CIS [39] and the final analyses of two ongoing observational studies [30, 31].

In the present analysis, 35 cases of PML cases occurred among 6,872 natalizumab treated patients, which gives an estimated incidence risk of 0.5 cases per 1,000 patients. Until 2018, more than 700 cases have been reported globally among natalizumab treated patients [17, 40]. Based on the ongoing reporting and research in that area, the manufacturing company has provide risk tables for PML that are based on three major known risk factors: more than 2 years of natalizumab treatment, JCV seropositivity and prior use of immunosuppressants. If all criteria are satisfied in one patient, the risk of PML is 11.1 per 1,000 compared to a risk of 0.09 cases per 1,000 in JCV negative patients [41].

35 Fälle von PML in 6.872 Natalizumab behandelten PatientInnen (Inzidenzrate von 0.5 per 1.000)

In general, challenges with interpreting the data arise due to differences in outcome reporting and the heterogeneity of the study populations. Furthermore, imprecision due to small sample sizes prevented a quantitative analysis of the data.

Heterogenität der Studienpopulationen verhindert Meta-analyse

Overall, the data is considered generalizable to other contexts. The studies were conducted in Italy, Denmark, Japan, USA and in multinational settings. At the same time, however, differences between inclusion and exclusion criteria prevent the generalizability. For instance, the data were recorded in hospital setting (clinical trials) or by practising neurologists and physicians. In general, the disease status is different between patients enrolled in clinical trials compared to patients treated in clinical practice, which in general have a more severe disease [42]. Furthermore, pregnant women, children, or patients with other forms of MS were excluded.

Upcoming evidence

Currently, there are several ongoing randomised controlled trials and observational studies listed in Clinicaltrials.gov. Among these, there are three head-to-head trials: BEST-MS is comparing the efficacy of natalizumab versus fingolimod in 600 patients with a primary completion date of October 2017 (NCT01981161), COMBAT-MS is comparing rituximab versus all other frequently used immunomodulating drugs including natalizumab in 3,700 patients with a primary completion date of June 2021 (NCT03193866) and TREAT-MS, which compares traditional versus early aggressive therapy in 900 patients with a primary completion date of October 2022 (NCT03500328). Moreover, data from the ongoing Tysabri observational program (TOP), which aims to include 6000 patients with a primary completion date of December 2028 (NCT00493298), and ongoing national registries with an estimated total of 34,000 patients and an estimated primary completion date of December 2023 will provide extensive material regarding the safety of natalizumab therapy in a clinical practice setting.

3 laufende direkte Vergleichsstudien, multinationale Beobachtungsstudien sowie nationale Register

Limitations

The present work was implemented as a systematic review of the literature which had been published from 2011 (the publication of the Cochrane Review, ref) onwards. It was not intended to provide an update of the previous work of Pucci and colleagues [8], which was simply not possible due to restrictions in time, length and resources. Yet, at the same time, this focus represents a major limitation of this review.

Limitationen: Verfassung durch einzelne Autorin;

36 Monate Beobachtungszeitraum für nicht randomisierte Studien

Further constraints were applied to eligible studies depending on the respective trial design. Although the length of the follow-up period of RCTs was not restricted, a minimum treatment period of 36 months was applied to methodologically lower quality studies (like non-randomised controlled studies and single-arm studies) in order to be able to detect possible long-term as well as rare events of natalizumab therapy. Thus, numerous publications analysing shorter treatment periods had to be omited from the analysis. Additionally, drug trials with shorter follow-up periods or retrospective designs were excluded. Finally, only published studies were included. No data from posters or abstracts or any other forms of grey literature were used.

Due to the specific requirements of this report (which was planned and conducted as a Master thesis), only one researcher performed the literature search, the selection of eligible publications and the data-extraction in addition to assessing the risk of bias and evaluating the quality of evidence for each outcome. Hence, standard quality assurance processes (e.g. selection of studies by two reviewers independently) could not be applied. Additionally, the short time period did not allow further requests of clarification from the authors of the included publications.

6 Conclusion

Considering publications from 2011 onwards, this review aimed to evaluate whether natalizumab is superior to alternative therapies in the treatment of patients with RRMS over a prolonged treatment period. In case of absence of an alternative treatment, a placebo control was considered. Overall, the quality of evidence was low to very low. No significant differences were observed in the single non-randomized controlled study that compared natalizumab with the alternative therapy fingolimod in terms of ARR and disability progression. In terms of safety, no evidence was available whether natalizumab was safer than the investigated treatment alternative.

keine signifikanten Unterschiede zwischen Natalizumab und Fingolimod in der jährlichen Schubrate und der Krankheitsprogression

Thus, future research should aim to provide more accurate data on (serious) adverse events. Furthermore, a prolonged observation period for investigating the efficacy and safety of treatments for patients with chronic diseases should be considered. In addition, future studies should aim to apply MRI criteria for monitoring disease activity and the success of the therapy and to assess health-related quality-of-life using MS-specific questionnaires. Finally, more head-to-head RCTs are required to directly compare the impact of treatment alternatives in terms of superiority.

mehr RCTs, welche alternative Therapien direkt vergleichen, sowie umfassendere Dokumentation von Nebenwirkungen nötig

7 References

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8 Appendices

8.1 Evidence tables of individual studies included for clinical effectiveness and safety

Table 8.1-1: Evidence table – RCT

	Saida et al. (2017)[27]
Country	Japan
Sponsor	Biogen
Study design	multi-center, double-blind, placebo-controlled, randomized trial
Conducted in	April 2010 – August 2012
Indication	Japanese patients with RRMS
Intervention (I)	natalizumab, 300mg, IV, every 4 weeks
Comparator C)	placebo
Number of patients	47 vs. 47
Inclusion criteria	patients aged 18-65 years, diagnosed with RRMS (revised McDonald criteria), at least one clinical MS exacerbation within previous year and a EDSS score of 0.0-5.5
Exclusion criteria	all other neurological diagnoses (primary or secondary progressive MS, neuromyelitis optica (NMSO), and NMO spectrum disorder or patients with a history of a long spinal cord lesion extending over three or more vertebral bodies or a positive test for AQP4 antibodies or prior treatment with natalizumab or immunosuppressants or treatment with immunomodulatory drugs within 2 weeks of enrolment or during study; corticosteroids were not permitted within 30 days of enrolment or except for short courses for treatment of relapses during study
Primary outcome measure	rate of development of new active lesions over 24 weeks
Secondary outcomes measure	clinical relapses, EDSS scores, assessment of well-being (VAS) and safety
Baseline patient characteristics (I vs. C)	
Mean age, years (SD)	37.7 (8.6) vs. 35.1 (8.2)
Female, n (%)	34 (72) vs. 32 (68)
Mean time since MS diagnosis, years (SD)	5.9 (5.0) vs. 5.1 (4.9)
Prior MS therapy, n (%)	43 (91) vs. 40 (85)
Mean number of relapses in previous year (SD)	2.0 (1.2) vs. 1.9 (1.0)
Mean number of EDSS score (SD)	2.5 (1.6) vs. 2.1 (1.5)
Follow-up time, months	6
Loss to follow-up, n (%)	5 (5.3)
Efficacy	
Annualized relapse rate, ARR (Difference between I and C)	0.53 vs. 1.73 with p=0.001
Disability progression (Difference between I and C)	- 0.22 (0.7) vs. 0.19 (0.9) with p=0.019
QoL (VAS)	- 4.8 points vs. '- 2.9 points with p=0.942

	Saida et al. (2017)[27]
Safety	
number of serious adverse events[a] (%)	7 (15) vs. 11 (23)
infections and infestations	0 vs. 1 (2)
neoplasms	1 (2) vs. 0
PML	0 vs. 0
number of adverse events[b] (%)	34 (72) vs. 41 (87)
hypersensitivity reaction	0 vs. 0
anti-JCV antibodies	65 (63) of 103 patients[c]
anti-natalizumab antibodies	1 (2) vs. 0

Explanations: *a) including MS relapses, b) at least one adverse event (including MS relapses), c) participants from the extension study which included patients from the RCT plus patients from the pharmacokinetic study*

Table 8.1-2: Evidence table – non-randomised controlled trials

	Clerico et al. (2014)[28]	Koch-Hensiksen et al. (2016)[29]
Country	Italy	Denmark
Sponsor	NA	NA
Study design	non-randomized, prospective, controlled multicenter study	non-randomized, prospective, controlled multicenter study
Conducted in	October 2010 – October 2013	July 2011 – October 2015
Indication	evaluating MS clinical activity in patients with RRMS after 24 doses of natalizumab	to compare the clinical efficacy of natalizumab and fingolimod
Intervention (I)	natalizumab, 300mg, IV, every 4 weeks	natalizumab
Comparator C)	no treatment or DMT (interferon beta, glatiramer acetate, fingolimod) or mitoxantrone hydrochrloride	fingolimod
Number of patients	130	1379
Inclusion criteria	18 years or older with clinically definite RRMS who received 24 doses of Natalizumab, with clinical and MR imaging MS stability, and which had at least 1 MR image within 10 days after 24 doses of natalizumab	All patients, who started treatment with natalizumab or fingolimod from 1 July 2011 up to 31 March 2015. RRMS patients should under first-line treatment with interferon-beta or glatiramer acetate have had at least one significant relapse within one year. Hitherto treatment-naive patients could start second-line treatment directly if they within a year have had two serious relapses with residual symptoms and an active magnetic resonance imaging (MRI) scan with gadolinium positive lesion(s) or a significant increase in T2 lesions compared with earlier MRI scans.
Exclusion criteria	pregnancy, severe depression, alcohol or drug addition, any clinical condition in addition to MS	NA
Primary outcome measure	mean ARR	annualized relapse rate (ARR)
Secondary outcomes measure	MR imaging MS activity and mean EDSS	rates of steroid-treated relapse, proportion of patients remaining free of relapse, time to first relapse, proportion of patients in whom EDSS improved or worsened during treatment
Baseline patient characteristics (I vs. C)		
Mean age, years (SD)	37.4 (9.5) vs. 39.5 (9.8)	38.7 (10.1) vs. 39.3 (10.1)
Female, n (%)	32 (74.4) vs. 56 (69.1)	(70.5) vs. (70.5)
Mean time since MS diagnosis, years (SD)	9.96 (5.85) vs. 12.19 (7.32)	7.78 (6.2) vs. 7.69 (6.3)
Prior MS therapy, n (%)	35 (81.4) vs. 73 (90.1)	437 (94.2) vs. 437 (94.2)
Mean number of relapses in previous year (SD)	2.29 (1.53) vs. 1.84 (1.17)	1.06 (0.95) vs. 1.05 (1.1)
Mean EDSS score (SD)	3.31 (1.65) vs. 3.42 (1.73)	3.15 (1.6) vs. 3.08 (1.5)
Follow-up time, months	12	51
Loss to follow-up, n (%)	6 (4.6)	70 (5.1)

	Clerico et al. (2014)[28]	Koch-Hensiksen et al. (2016)[29]
Effectiveness		
Annualized relapse rate, ARR (Difference between I and C)	0.24 (0.48) Nat. continuers vs. 0.73 (0.85) Nat. interrupters with p=0.004	0.296 (95%CI: 0.26-0.34) vs. 0.307 (95%CI: 0.27-0.35); rate ratio of 0.93 (95%CI: 0.74-1.17) with p=0.53
Disability progression (Difference between I and C)	3.36 (1.69) vs. 3.80 (1.83) with p=0.23	186 (40.1%) improved, 144 (31.0% remained unchanged and 134 (28.9%) worsened vs. 185 (39.9%) improved, 152 (32.5%) remained unchanged, 128 (27.6%) worsened (p=0.86)
QoL	NA	NA
Safety		
number of serious adverse events (%)	3 (2.3)	NA
infections and infestations	1 (0.8)	NA
neoplasms	NA	NA
PML	1 (0.8)	NA
number of adverse events (%)	NA	NA
hypersensitivity reaction	NA	NA
anti-JCV antibodies	NA	NA
anti-natalizumab antibodies	NA	NA

Table 8.1-3: Evidence table – single-arm studies

	Butzkueven et al. (2014)[30]	O'Connor et al. (2014)[31]	Totaro et al. (2014)[32]	Zivadinov et al. (2016)[33]
Country	multinational	multinational	Italy	USA
Sponsor	Biogen	Biogen (editorial support)	NA	Biogen
Study design	prospective, observational study, single-arm (Tysabri Observational Program-TOP)	prospective, observational, single-arm study (Safety of Tysabri re-dosing and treatment (STRATA)	prospective, observational, single-arm study	prospective, observational, single-arm study
Conducted in	July 2007 – December 2012[a]	– February 2012[i]	April 2007 – November 2010	NA
Indication	evaluate long-term safety of natalizumab monotherapy	evaluate safety of natalizumab monotherapy	evaluate efficacy and tolerability of natalizumab in a cohort of RRMS patients	re-evaluation of natalizumab-treated relapsing MS patients
Intervention (I)	natalizumab, 300mg, IV, every 4 weeks	natalizumab, 300mg, IV, every 4 weeks	natalizumab	natalizumab, 300mg, IV, every 4 weeks
Comparator (C)	NONE	NONE	NONE	NONE
Number of patients	4821	1094	343	77
Inclusion criteria	Patients with RRMS who met criteria for natalizumab prescription in their respective countries and had three or fewer natalizumab infusions before enrolment. Female participants were postmeno-pausal, surgically sterile, or willing to practice effective contraception.	patients with RRMS previously participating in a natalizumab "feeder" study (AFFIRM, SENTINEL, GLANCE, STARS)	RRMS according to the McDonald criteria; criterion A, patients on previous immunomodulation treatment for at least 12 months who had experienced either two relapses in the last year or a single relapse with incomplete recovery and residual disability, with at least 9 T2 lesions, or an increased lesion burden or at least 1 gadolinium-enhanced lesion; criterion B, patients with severe MS with a fast evolution, even if not previously treated with immuno-modulation treatments, with 2 or more relapses with increased disability during the previous year, and with new T2- or gadolinium-enhanced lesions on MRI, compared with an MRI examination performed during the previous 12 months.	participation in the natalizumab VWMTR study, age 18-65; diagnosis of MS according to the McDonald 2005 criteria of either RR or relapsing secondary-progressive disease type, EDSS score ≤ 6.5; disease duration < 30 years, received > 1 cycle of natalizumab and fulfilled the TOUCH enrolment requirements

	Butzkueven et al. (2014)[30]	O'Connor et al. (2014)[31]	Totaro et al. (2014)[32]	Zivadinov et al. (2016)[33]
Exclusion criteria	NA	concomitant immunosuppressive or immunomodulatory treatment; persistently positive anti-natalizumab antibodies, compromised immune system; prior natalizumab discontinuation because of related allergic reaction or serious adverse event; malignancy history, or any major disease precluding recombinant humanized immunomodulatory antibody use.	NA	presence of relapse and steroid treatment in the 30 days preceding the 5-year MRI scan, pre-existing medical conditions known to be associated with brain pathology (cerebrovascular disease, positive history of alcohol abuse) and pregnancy.
Primary outcome measure	long-term safety (incidence and type of serious adverse events)	safety after re-exposure to natalizumab	proportion of patients who were free from relapses/EDSS progression/ combined clinical activity/MRI activity/any disease activity	determine the association between the number of natalizumab cycles and brain volume loss, lesion burden, disability progression and relapse rate
Secondary outcomes measure	occurrence of clinical relapses, change in EDSS score	frequency of relapses, change in EDSS score	annualized clinical relapse rate	determine MRI and clinical changes between those patients who received natalizumab for 5 years and those patients who received natalizumab treatment with some periods of honeymoon and those who discontinued treatment
Baseline patient characteristics				
Mean age, years (SD)	37.2 (9.69)	41.1 (8.1)	35.8 (9.1)	41.3 (10)[b (n=60)]
Female, n (%)	3466 (72)	(69)	247 (72)	42 (70)[b (n=60)]
Mean time since MS diagnosis, years (SD)	7.3 (0-43.9)[b (n=4799)]	8 (4-34)[b (n=1088)]	10.7 (6.8)	12.7 (8.0)[b (n=60)]
Prior MS therapy, n (%)	4384 (90.9)	(94.8)	330 (96.2)	77 (100)
Mean number of relapses in previous year (SD)	1.99 (1.03)	1 (0-8)[b]	at least one relapse in 341 patients	NA
Mean EDSS score (SD)	3.5 (1.62)[(n=4728)]	2.5 (0-8)[b]	2.8 (1.5)	3.0 (0-7)[b (n=60)]
Follow-up time, months	60[c]	60	42	60
Loss to follow-up, n (%)	121 (2.5)[d]	462[j]	57 (16.6)[n]	17 (22)

	Butzkueven et al. (2014)[30]	O'Connor et al. (2014)[31]	Totaro et al. (2014)[32]	Zivadinov et al. (2016)[33]
Effectiveness				
Annualized relapse rate, ARR	12 months: 0.30 (n=4821); 24 months: 0.24 (n=3433); 36 months: 0.24 (n=2224); 48 months: 0.21 (n=1000); 60 months: 0.24 (n=355)	12 months: 0.21 (n=632); 24 months: 0.14 (n=6323); 36 months: 0.15 (n=632); 48 months: 0.10 (n=632); 60 months: 0.11 (n=632)	12 months: 0.19 (0.5) (n=203); 24 months: 0.11 (0.5) (n=102); 36 months: 0.13 (0.4) (n=30)	1.5 (1.9)[b]
Disability progression	12 months: 3.3 (1.76) (n=2064); 24 months: 3.34 (1.84)(n=1304); 36 months: 3.3 (1.84) (n=744); 48 months: 3.3 (1.92) (n=325)	12 months: 2.72 (n=616); 24 months: 2.75 (n=594); 36 months: 2.87 (n=588); 48 months: 2.91 (n=571); 60 months: 2.91 (n=561)	12 months: 3.1 (1.5)(n=218); 24 months: 3.0 (1.5) (n=112); 36 months: 2.9 (1.4) (n=36)	3.0 (0-7)[b]
QoL	NA	NA	NA	NA
Safety				
number of serious adverse events (%)	465[e] or 388 (8.0)[f,g]	171 (16)[k]	NA	NA
infections and infestations	97 or 93 (1.9)	44 (4)	NA	NA
neoplasms	24 or 24 (0.5)	25 (2)	NA	NA
PML	18 or 18 (0.4)	14[l]	0	2 (2.5)
number of adverse events (%)	107 (2.2)	NA	116 (33.8)	NA
hypersensitivity reaction	NA	55 (5)[b,m]	NA	NA
anti-JCV antibodies (%)	277 (5.7)	(67)	NA	NA
anti-natalizumab antibodies	44 (0.9)[h]	NA	NA	NA

Explanations: *a) scheduled follow-up period: 120 months; b) Median; c) Median follow-up of 26 months; d) loss-to follow-up was considered as one reason given by patients who withdrew from TOP (n=740 (15.3%)); e) all SAEs occurred during natalizumab therapy or within 6 months after natalizumab discontinuation; f) for incidence calculation, a patient is counted once per lower-level term (LTT); g) including 9 deaths; h) not routinely collected; i) variable starting point of the feeder-studies; j) 217 completed initial STRATA period, but did not enter extension study; 245 discontinued study; k) patients with at least one serious adverse event; l) until August 23, 2013; m) during first 48 weeks; n) treatment was stopped*

8.2 Risk of bias tables

Table 8.2-1: Risk of bias table – RCT

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall bias
Saida et al. (2017)[27]	Low	Low	Low	Low	Low	Low

Table 8.2-2: Risk of bias table – non-randomised controlled trials

Study	Clerico et al. (2014)[28]	Koch-Henriksen et al. (2016)[29]
Domain 1: Confounding	Moderate	Moderate
Domain 2: Selection	Serious	Moderate
Domain 3: Classification of intervention	Serious	Low
Domain 4: deviation from intervention	Moderate/Serious	Moderate
Domain5: missing data	Low	Serious
Domain 6: measurement of outcomes	Low	no information
Domain 7: selection of reported result	Moderate	Serious
Overall risk of Bias	Serious	Serious

Table 8.2-3: Risk of bias – single-arm studies

Study reference/ID	Butzkueven et al. (2014)[30]	O'Connor et al. (2014)[31]	Totaro et al. (2014)[32]	Zivadinov et al. (2016)[33]
Study objective				
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes	Yes	Yes
Study design				
2. Was the study conducted prospectively?	Yes	Yes	Unclear	Yes
3. Were the cases collected in more than one centre?	Yes	Yes	Yes	No[f]
4. Were patients recruited consecutively?	Unclear[b]	Unclear[b]	Yes	Unclear
Study population				
5. Were the characteristics of the participants included in the study described?	Yes	Yes	Yes	Yes
6. Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Partial	Yes	Partial	Yes
7. Did participants enter the study at similar point in the disease?	Yes	Unclear	Unclear	No[g]
Intervention and co-intervention				
8. Was the intervention clearly described?	Yes	Yes[c]	No	Yes
9. Were additional interventions (co-interventions) clearly described?	No	Yes[d]	No	Partial
Outcome measure				
10. Were relevant outcome measures established a priori?	Yes	Yes	Yes	Yes
11. Were outcome assessors blinded to the intervention that patients received?	Unclear	Unclear	Unclear	Unclear
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes	Yes	Yes	Yes
13. Were the relevant outcomes measured before and after interventions?	Yes	Yes	Yes	Yes
Statistical Analysis				
14. Were the statistical tests used to assess the relevant outcome appropriate?	Yes	Unclear	Yes	Yes
Results and conclusions				
15. Was follow-up long enough for important events and outcomes to occur?	Yes	Yes	Yes	Yes
16. Was the loss to follow-up reported?	Yes	Yes	No	Yes
17. Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Yes	Partial[e]	Yes	Yes
18. Were adverse events reported?	Yes	Yes	Partial	Partial
19. Were the conclusions of the study supported by the results?	Yes	Yes	Yes	Yes
Competing interests and source of support				
20. Were both competing interest and source of support for the study reported?	Yes	Yes	Partial	Yes
Overall Risk of Bias	**Moderate**	**Moderate**	**High**	**Moderate**

Explanations: *a) uncontrolled longitudinal study/case series according to the Cochrane Handbook Box 13.1a; b) multinational study;*
c) in the abstract; d) Patients were required to discontinue concomitant immunosuppressive or immunomodulatory treatment for the study's duration;
e) Estimates of random variability were only reported once; f) information provided in VWMTR study abstract; g) EDSS range (0-7)

8.3 GRADE Evidence profile tables

Table 8.3-1: Grade evidence table

Certainty assessment							Impact	Certainty	Importance
№ of studies (participants)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Annualized relapse rate									
1 (94)	RCT	not serious	not serious	not serious	very serious[a,b] (-2)	none	Natalizumab: 0.53 vs placebo: 1.73 (p=0.001)	⊕⊕◯◯ LOW	CRITICAL
2 (1058)	observational trials	serious[c] (-1)	not serious	not serious	not serious	none	Natalizumab: 0.30 vs fingolimod: 0.31 (p=0.53) Natalizumab: 0.24 vs control group[d]: 0.73 (p=0.004)	⊕◯◯◯ VERY LOW	
Disability progression (assessed with: EDSS)									
1 (94)	RCT	not serious	not serious	not serious	very serious[a,b] (-2)	none	Natalizumab: -0.22 vs placebo: 0.19 (p=0.019)	⊕⊕◯◯ LOW	CRITICAL
2 (1058)	observational trials	serious[c] (-1)	not serious	not serious	not serious	none	Natalizumab: +0.05 vs control group[d]: -0.38 (p=0.004) Natalizumab (40.1% improved, 31.0% unchanged, 28.9% worsened) vs Fingolimod (39.9% improved, 32.5% unchanged, 27.6% worsened) (p=0.53)	⊕◯◯◯ VERY LOW	
Quality of Life (assessed with: VAS)									
1 (94)	RCT	not serious	not serious	serious[e] (-1)	serious[a] (-1)	none	Natalizumab: -4.8 points vs placebo: -2.9 points (p=0.942)	⊕⊕◯◯ LOW	IMPORTANT
Number of Serious adverse events									
1 (94)	RCT	not serious	not serious	not serious	very serious[a,b]	none	Natalizumad: 7/47 (15%)[f] vs placebo: 11/47 (23%)[f]	⊕⊕◯◯ LOW	CRITICAL
1 (130)	observational trials	serious[g] (-1)	not serious	not serious	not serious	none	Natalizumab: 2/43 (4.7%) vs. control[d]: 1/81 (1.2%)	⊕◯◯◯ VERY LOW	
2 (5915)	observational (single arm) trials	not serious	not serious	not serious	not serious	none	Natalizumab: 636/5915 (10.75%)	⊕⊕◯◯ LOW	

Abbreviations: *RCT = Randomised controlled trial, EDSS = Expanded disability status score, VAS = Visual Analogue Scale*

Explanations: *a) small sample size; b) short follow-up period; c) selection of the participants; d) natalizumab interrupters; e) appled test not validated; f) including MS relapses; g) missing data*

GRADE Working Group grades of evidence

High certainty: *We are very confident that the true effect lies close to that of the estimate of the effect;*

Moderate certainty: *We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;*

Low certainty: *Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect;*

Very low certainty: *We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect*

8.4 Applicability table

Table 8.4-1: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The population enrolled in the studies is similar to the target population of the intervention. The patients were of similar age and the proportion of women was similar. The patients suffered from 1 to 2 relapsles prior to natalizumab treatment and their EDSS score was comparable. However, there were also a number of differences between the inclusion and exclusion criteria. The most important one was that some studies included treatment-naïve patients while others included patients which had already received the intervention for a certain amount of time.
Intervention	The intervention under assessment is natalizumab. Its product name is Tysabri®.
Comparators	The comparators were either fingolimod (alternative treatment option), placebo or a group of natalizumab treatment interruptors.
Outcomes	The crucial outcomes considered are annualized relapse rate (ARR), disability progression measured by EDSS, quality of life (QoL) and number of serious adverse events (SAEs). Further outcomes considered are the number of adverse events.
Setting	All of the studies included were either single-centre or multi-centre studies, with clinical centres based in Europe (Italy and Denmark), USA and Japan. These contexts are considered similar to the Austrian one.

8.5 List of ongoing randomised controlled trials and observational studies

Table 8.5-1: List of ongoing randomised controlled trials and observational studies

Identifier/Trial name	Patient population	Estimated enrolment	Intervention	Comparison	Primary Outcomes	Primary completion date	Sponsor
NCT01981161/Difference in efficacy of natalizumab versus fingolimod for the treatment of multiple sclerosis BEST-MS	RRMS	600	Natalizumab	Fingolimod	disease free patients	October 2017	University Hospital, Toulouse
NCT02588053/Does long-term natalizumab therapy normalize brain atrophy rates and quality of life (QoL) in relapsing remitting multiple sclerosis (RRMS)?	RRMS	146	Natalizumab	-	change in brain atrophy rate	August 2018	US NIH Grant
NCT03516526/Towards personalized dosing of natalizumab in multiple sclerosis (PDNMS)	RRMS	60	Natalizumab	-	gadolinium enhancing T1 lesions on brain MRI	June 2019	VU University Medical Center

Identifier/Trial name	Patient population	Estimated enrolment	Intervention	Comparison	Primary Outcomes	Primary completion date	Sponsor
NCT01485003/Observational study of tysabri in early relapsing-remitting multiple sclerosis in anti-JC virus antibody negative patients (STRIVE)	RRMS	231	Natalizumab	-	Proportion of participants who are overall disease activity-free at months 12 and 24; proportion of participants who are clinical disease activity-free at months 36 and 48	October 2018	Biogen
NCT01065727/Impact study of 2 therapeutic strategies for aggressive remitting multiple sclerosis (IQUALYSEP)	RRMS	250	mitoxantrone followed by immunomodulator	Natalizumab	cost effectiveness	February 2016	Rennes University Hospital
NCT00493298/Tysabri observational program (TOP)	RRMS	6000	Natalizumab	-	Number of participants with serious adverse events	December 2028	Biogen
NCT03399981/Tysabri observational cohort study – multiple sclerosis (MS) registries	MS	34600	Natalizumab	-	prospective and retrospective analyses: number of participants with confirmed PML; number of participants with serious adverse events of other serious opportunistic infections	December 2023	Biogen
NCT03193866/Comparison between all immunotherapies for multiple sclerosis (COMBAT-MS)	CIS or RRMS	3700	Rituximab	all other frequently used immunomodulating drugs (natalizumab, fingolimod, alemtuzumab, interferon-beta, glatiramer acetate, dimethyl fumarate	confirmed disease progression in patients with EDSS $\leq$ 2.5 at baseline; confirmed disease progression in patietns with EDSS $\geq$ 2.5 at baseline; Disease-related impact on daily life	June 20121	Karolinska Institutet
NCT03500328 /Traditional versus early aggressive therapy for multiple sclerosis trial (TREAT-MS)	RRMS	900	Early aggressive Therapy: Natalizumab, Alemtuzumab, Ocrelizumab, Rituximab	traditional therapy: Glatiramer acetate, intramuscular interferon, subcutaneous interferon, pegylated interferon, teriflunomide, dimethyl fumarate, fingolimod	time to sustained disability progression	October 2022	Johns Hopkins University

8.6 List of excluded studies

Table 8.6-1: Table of excluded studies

Author	Title	Reason for exclusion
Barbin et al. (2016) [43]	Comparative efficacy of fingolimod vs natalizumab: A French multicentre observational study	Follow-up ≤ 24 months/retrospective
Baroncini et al. (2016) [37]	Natalizumab versus fingolimod in patients with relapsing-remitting multiple sclerosis non-responding to first-line injectable therapies	Follow-up ≤ 24 months
Berkovich et al. (2015) [44]	CD4 cell response to interval therapy with natalizumab	Wrong objective
Disanto et al. (2016) [45]	The Swiss Multiple Sclerosis Cohort-Study (SMSC): A prospective Swiss wide investigation of key phases in disease evolution and new treatment options	Follow-up ≤ 24 months
Fernandez et al. (2012) [46]	Natalizumab treatment of multiple sclerosis in Spain: results of an extensive observational study	Follow-up ≤ 24 months/retrospective
Fox et al. (2014) [47]	MS disease activity in RESTORE: a randomized 24-week natalizumab treatment interruption study	Follow-up ≤ 24 months
Giacoppo et al. (2017) [48]	The Italian pharmacovigilance program: an observational study of adverse effects of Natalizumab in multiple sclerosis therapy	Retrospective
Guger et al. (2018) [36]	Real-life clinical use of natalizumab and fingolimod in Austria	Follow-up ≤ 24 months
Holmen et al. (2011) [49]	A Swedish national post-marketing surveillance study of natalizumab treatment in multiple sclerosis	Follow-up ≤ 24 months
Jokubaitis et al. (2016) [50]	Predictors of long-term disability accrual in relapse-onset multiple sclerosis	Erratum
Jokubaitis et al. (2013) [51]	The Australian Multiple Sclerosis (MS) immunotherapy study: a prospective, multicentre study of drug utilisation using the MSBase platform	Wrong objective/retrospective
Kalincik et al. (2015) [52]	Switch to natalizumab versus fingolimod in active relapsing-remitting multiple sclerosis	Follow-up ≤ 24 months
Kallweit et al. (2012) [53]	Sustained efficacy of natalizumab in the treatment of relapsing-remitting multiple sclerosis independent of disease activity and disability at baseline: real-life data from a Swiss cohort	Retrospective
Kaufman et al. (2015) [54]	Radiologic MS disease activity during natalizumab treatment interruption: findings from RESTORE	Retrospective
Mancardi et al. (2011) [55]	Three years of experience: the Italian registry and safety data update	Follow-up ≤ 24 months
Marrosu et al. (2011) [56]	The cohort of the multiple sclerosis center of Cagliari	Follow-up ≤ 24 months
Melin et al. (2012) [57]	Effect of natalizumab on clinical and radiological disease activity in a French cohort of patients with relapsing-remitting multiple sclerosis	Follow-up ≤ 24 months
Outteryck et al. (2014) [58]	A prospective observational post-marketing study of natalizumab-treated multiple sclerosis patients: clinical, radiological and biological features and adverse events. The BIONAT cohort.	Follow-up ≤ 24 months
Piehl et al. (2011) [59]	Swedish natalizumab (Tysabri) multiple sclerosis surveillance study	Same study population as Holmen [49]
Planche et al. (2017) [60]	Improvement of quality of life and its relationship with neuropsychiatric outcomes in patients with multiple sclerosis starting treatment with natalizumab: A 3-year follow-up multicentric study	Wrong objective (outcomes)

Author	Title	Reason for exclusion
Prosperini et al. (2011) [61]	Natalizumab treatment in multiple sclerosis: the experience of S.Andrea MS Centre in Rome	Follow-up ≤ 24 months
Prosperini et al. (2017) [62]	Real-world effectiveness of natalizumab and fingolimod compared with self-injectable drugs in non-responders and in treatment-naïve patients with multiple sclerosis	Follow-up ≤ 24 months, retrospective
Puz, Lasek-Bal (2016) [63]	Safety and Efficacy of fingolimod and natalizumab in multiple sclerosis after the failure of first-line therapy: single center experience based on the treatment of fourty-four patients	Follow-up ≤ 24 months
Raffel et al. (2017) [64]	Inflammatory activity on natalizumab predicts short-term but not long-term disability in mulitple sclerosis	Retrospective
Rinaldi et al. (2012) [65]	Natalizumab strongly suppresses cortical pathology in relapsing-remitting multiple sclerosis	Wrong objective (outcomes)
Sangalli et al. (2011) [66]	Efficacy and tolerability of natalizumab in relapsing-remitting multiple sclerosis patients: a post-marketing observational study	Follow-up ≤ 24 months
Van Pesch et al. (2014) [67]	Safety and efficacy of natalizumab in Belgian multiple sclerosis patients: subgroup analysis of the natalizumab observational program	Follow-up ≤ 24 months
Wiendl et al. (2016) [68]	EPOCH analysis of on-treatment disability progression events over time in the Tysabri Observational Program (TOP)	Same study population as Butzkeuven [30]

8.7 Literature search strategies

Search strategy for Toxline

Search date: 16.08.2018	
1#	natalizumab relapsing remitting multiple sclerosis
	singular and plural forms were searched
	records with: all of the words
	search restricted to documents published between 2011-2018.
	languages: English
Total: 110 hits	

Search strategy for Clinicaltrials.gov

Search date: 16.08.2018	
1#	Relapsing-Remitting Multiple Sclerosis
	other terms: natalizumab
	eligibility criteria: adult (18-64)
	phase 3 and 4, with results
Total: 8 hits	

Search strategy for Cochrane Central

Search date: 16.08.2018	
1#	MeSH [Multiple Sclerosis, Relapsing-Remitting] explode all trees (707)
2#	2 MeSH [Natalizumab] explode all trees (78)
3#	#1 and #2
4#	with publication year from 2011 to 2018; in Trials.
Total: 21 hits	

Search strategy for Medline

Search date: 15.08.2018	
1#	exp Multiple Sclerosis
2#	Multiple Sclerosis.mp
3#	1 or 2
4#	exp natalizumab
5#	natalizumab.mp
6#	4 or 5
7#	3 and 6
8#	limit 7 to (human and English language and embase and (clinical trial or randomized controlled trial or controlled trial or multicenter study or phase 3 clinical trial or phase 4 clinical trial) and yr="2011-Current" and adult <18 to 64 years>)
Total: 139 hits	

Search strategy for Embase

Search date: 15.08.2018	
1#	exp Multiple sclerosis/
2#	Multiple Sclerosis.mp
3#	1 and 2
4#	exp Natalizumab/
5#	Natalizumab.mp
6#	4 or 5
7#	3 and 6
8#	limit 7 to (English language and humans and yr="2011-Current"and "all adult (19 plus years)"and (clinical study or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled trial or multicenter study or randomized controlled trial or observational study) and medline)
Total: 99 hits	

Ludwig Boltzmann Institut
Health Technology Assessment