Clinical adverse effects of natalizumab
Protocol for a meta-analysis of randomized double-blind placebo-controlled clinical trials

Hao Li, MDa, Fang-Hong Shib, Shi-Ying Huang, MDa, Shun-Guo Zhang, MDa, Zhi-Chun Gu, MDb, Ji-Fu Weic, PhDc,∗

Abstract

Background: Natalizumab (NAT), a humanized monoclonal antibody, which binds to α4β1 and α4β7 integrins, is approved for the treatment of multiple sclerosis (MS) and Crohn’s disease (CD). An uncommon but serious adverse event from NAT treatment is known as progressive multifocal leukoencephalopathy (PML). However, clinical comprehensive safety evidence of NAT is limited.

Methods: We will search Medline, Embase, Cochrane library, and ClinicalTrials.gov website from inception to May 9, 2018. Double-blind, randomized placebo-controlled trials reporting safety data of NAT will be eligible for inclusion. Outcome variables will include adverse events (AEs) varying degrees and AEs occurring in ≥5% patients with NAT or placebo. STATA software (version 12, Statacorp, College Station, TX) will be utilized to assess risk of bias and synthesize data. Outcomes will be reported by weight mean difference (WMD), risk ratios (RRs), and their 95% confidence intervals (95% CIs). I² statistic will be used to evaluate heterogeneity among studies.

Results: This systemic review and meta-analysis will evaluate serious AEs and AEs of NAT as compared to placebo.

Conclusion: Our study will provide a comprehensive picture of AEs of NAT.

Abbreviations: AEs = adverse events, CD = Crohn’s disease, CIs = confidence intervals, MS = multiple sclerosis, NAT = natalizumab, RRs = risk ratios, WMD = weight mean difference.

Keywords: adverse events, Crohn’s disease, meta-analysis, multiple sclerosis, natalizumab

1. Introduction

Natalizumab (NAT) is a humanized monoclonal antibody, which binds to α4β1 and α4β7 integrins, is improved for the treatment of multiple sclerosis (MS) and Crohn’s disease (CD).[1,2] The first clinical trial of NAT for treating MS was published in 1999.[3] To date with nearly 20 years of clinical use of NAT, several published randomized, double-blind, placebo-controlled clinical trials have suggested that NAT remains a very effective option for patients with MS.[4] However, a risk of an uncommon but serious adverse event, namely progressive multifocal leukoencephalopathy (PML) in MS patients receiving natalizumab, leads to NAT withdrawal from the market in 2006.[5] NAT was reintroduced to the market later in 2006 after considering its clinical benefits over risks. The most common serious adverse events (AEs) of NAT for patients with MS are relapsing MS, cholelithiasis and the need for rehabilitation therapy.[6] Although efficacy and safety of NAT have been evaluated or are being evaluated in some large-scale, long-term randomized clinical trials. Evidences of reported AEs in clinical trials of NAT are limited. A comprehensive evaluation of safety of NAT is still needed. In this study, we will present an overview of the safety data of NAT therapy in patients with MS or CD by conducting a systemic review and meta-analysis.

2. Methods

This systemic review and meta-analysis will be performed by following the principle of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and a priori established protocol (PROSPERO: CRD42018095002).[7] Ethical approval is not required because this is a literature-based systemic review and meta-analysis, which will not involve any subject directly.
2.1. Literature search strategy and study selection

We will perform a systemic literature search of relevant databases including Medline, Embase, Cochrane Library, and the ClinicalTrials.gov website from inception to May 31, 2018. The search strategy will be enacted according to the guidance offered from the Cochrane Handbook with the following Medical Subject Heading (MeSH) terms and variants: "natalizumab" or "Tysabri" or "antegren", and "multiple sclerosis" or "MS" or "Crohn's disease" or "CD" and "clinical trial" or "controlled clinical trial" or "randomized controlled trial" and "placebo" and any possible spellings of "natalizumab" and "multiple sclerosis" and "Crohn's disease". The search strategy is listed in Table 1. HL and FHS will select and confirm all the publication most relevant to our study including detailed reporting of AEs independently. Disagreements will be resolved by consensus or by consulting a third author (SYH). Literatures that are not conformed to the inclusion criteria or reported incomplete AEs results will be excluded. Details of the selection process are shown in Figure 1.

2.2. Outcome measures

Our systemic review and meta-analysis will assess the safety of NAT compared with placebo. For the topic of AEs, we plan to evaluate dosage effect of NAT, AEs varying degrees and AEs occurring in ≥ 5% patients. Another subgroup analysis of AEs will be performed according to disease type (MS and CD), durations of follow up and different dosages of NAT.

2.3. Data extraction

The substantial contents of each selected literature will be extracted by HL and FHS. Information should be included these items: first author’s name, NCT number, publication time, randomization and control therapies, study duration, study population characteristics (age, sex, duration of disease, renal function, liver function, number of patients), and other details such as different dosages, duration of follow-up, all reported AEs data. Any disagreements will be resolved by consensus or by consulting a third author (SYH).

2.4. Quality assessment

Bias risks of studies will be assessed by using the Cochrane tool (Statacorp, College Station, TX). Seven items are related with bias risk, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias, will be assessed by HL and FHS. Low risk, high risk, or unclear risk of bias will be judged and listed. Disagreement of bias risk will be settled by further discussion or consult to the third author (ZCG).

2.5. Data synthesis

STATA 12.0 software (version 12, Statacorp, College Station, TX) will be utilized to deal with data extracted from selected articles. Weight mean difference (WMD) and 95% confidence intervals (CI) will be presented in continuous variable and risk ratio (RRs) for dichotomous variable. I² statistic and χ² test will be used to evaluate heterogeneity across the studies. The corresponding value lower than 50% will be considered as low heterogeneity, value between 50% and 70% will be considered as moderate heterogeneity, while value above 70% will be considered as high heterogeneity. When I² is > 50%, a random effects model will be utilized to calculate the effect estimates. While if I² is < 50%, a fixed effects model will be used. In addition, if quantitative...
synthesis is no appropriate, qualitative description will be adopted to evaluate the data.

2.6. Subgroup analysis
Subgroup analysis based on different dosages of NAT, different type of diseases, durations of treatment, and placebo controls will be conducted.

2.7. Sensitivity analysis
Sensitivity analysis will be performed to identify the robustness of the results by omitting each of the study or excluding low-quality studies.

2.8. Reporting biases
Funnel test plots will be used to evaluate potential reporting biases. Begg test and Egger test will be performed if funnel plots are asymmetry by visual inspection. P > .05 in Begg test and Egger test will be considered as no significant publication bias.

2.9. Ethics and dissemination
The aims of incoming systemic review and meta-analysis are evaluating current evidence connected with the safety data of NAT for the treatment of MS or CD. No direct subjects will be included and evaluated in this study. Therefore, it does not require ethical assessment in this literature based systemic review and meta-analysis. Results of this incoming study will be disseminated as a literature systemic review and meta-analysis in a peer-reviewed related journal.

3. Discussion
MS is a chronic inflammatory disease of the central nervous system, affecting more than 2 million people worldwide with a prevalence of 5 to 30 per million people. The relative lack of data from large population countries such as China and India leads to an underestimate of MS. Genetic, environmental, and epigenetic factors drive the condition of MS. Fifteen medications for disease-modifying treatments have been approved by the Food and Drug Administration in the end of 2017. Among these medications, 4 monoclonal antibodies have been approved for MS, which are NAT, alemtuzumab, daclizumab, and ocrelizumab. NAT is the first monoclonal antibody for the treatment of relapsing remitting MS (RRMS). NAT is a nonselective anti-α4 integrin monoclonal antibody, binding in both α4β1 and α4β7 integrins, could also be utilized in the treatment of CD. CD is a relapsing inflammatory disease, which is a main component of inflammatory bowel disease, affecting the gastrointestinal tract. NAT, opposing the α4 chain of α4β7 integrin and inhibiting the interaction of α4β7 integrins with endothelial MAdCAM-1 (mucosal addressin cell adhesion molecule-1), leads to a interfere with the homing of lymphocytes to gastrointestinal lymphoid tissue.

More than 10 years have passed since the first reports of PML in a patient with MS who were treated with NAT. As of December 2017, more than 750 PML cases have been confirmed among patients treated with NAT. There is a fatality rate higher than 20% among PML patients and a substantial morbidity in survivors. Other AEs associated with NAT ranging from serious ones such as hepatic injury, meningitis, and minor ones like headache, hypersensitivity, and so on. The risk of developing opportunistic infections such as meningitis, encephalitis and herpes increases due to an immunomodulation of NAT. Up to now, there is no relevant systematic review and meta-analysis of clinical AEs of NAT.

The purpose of this systematic review and meta-analysis is to assess the safety of NAT in MS or CD patients. We will identify the influence of safety in different dosages of NAT, different diseases, and different follow up durations. Overall, we will give a comprehensive picture of AEs in patients treated with NAT. Different authors will screen articles at least 3 times independently to ensure the accuracy and reliability of the results. Herein, this systematic review and meta-analysis will be the first to evaluate the AEs of NAT in patients treated with NAT, which may offer a comprehensive understanding of NAT.

Author contributions
HL submitted the registration on PROSPERO. ZCG and JFW are the guarantors for the publication. ZCG take the responsibility for this article. All authors participated in reading and approved the final article.

Article revision: Shi-Ying Huang, Shun-Guo Zhang, Zhi-Chun Gu.
Conceptualization: Hao Li, Fang-Hong Shi, Shi-Ying Huang, Shun-Guo Zhang, Zhi-Chun Gu, Ji-Fu Wei.
Conceptualization: Hao Li, Fang-Hong Shi, Zhi-Chun Gu, Ji-Fu Wei.
Data analysis: Hao Li, Fang-Hong Shi.
Data curation: Hao Li, Shi-Ying Huang.
Study design: Fang-Hong Shi.
Study protocol: Hao Li, Fang-Hong Shi.

References
[1] Sandborn WJ, Colombel JF, Enns R, et al. Natalizumab induction and maintenance therapy for Crohn’s disease. N Engl J Med 2003;353:1912–25.
[2] Major EO, Youssy TA, Clifford DB. Pathogenesis of progressive multifocal leukoencephalopathy and risks associated with treatments for multiple sclerosis: a decade of lessons learned. Lancet Neurol 2018;17:467–80.
[3] Sheremata WA, Vollmer TL, Stone LA, et al. A safety and pharmacokineti c study of intravenous natalizumab in patients with MS. Neurology 1999;52:1072–4.
[4] Singer BA. The role of natalizumab in the treatment of multiple sclerosis: benefits and risks. Ther Adv Neurol Disord 2017;10:327–36.
[5] Ho PK, Koendgen H, Campbell N, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: a retrospective analysis of data from four clinical studies. Lancet Neurol 2017;16:923–33.
[6] Polman CH, O’Connor PW, Haverdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006;354:899–910.
[7] Shamsaei L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;350:g6747.
[8] Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
[9] Reich DE, Lucchinetti CF, Calabresi PA. Multiple sclerosis. N Engl J Med 2018;378:169–80.
[10] Thompson AJ, Baranzini SE, Geurts J, et al. Multiple sclerosis. Lancet 2018;391:1622–36.
[11] Li H, Shi PH, Huang SY, et al. A review on clinical pharmacokinetics, pharmacodynamics, and pharmacogenomics of natalizumab: a humanized anti-alpha 4 integrin monoclonal antibody. Curr Drug Metab 2018; [Epub ahead of print].
[12] Baumgart DC, Sandborn WJ. Crohn’s disease. Lancet 2012;380:1590–605.
[13] Kleinschmidt-DeMasters BK, Tyler KL. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis. N Engl J Med 2005;353:369–74.

[14] Langer-Gould A, Atlas SW, Green AJ, et al. Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. N Engl J Med 2005;353:375–81.

[15] Van Assche G, Van Ranst M, Sciot R, et al. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn’s disease. N Engl J Med 2005;353:362–8.

[16] Gandhi S, Jakimovski D, Ahmed R, et al. Use of natalizumab in multiple sclerosis: current perspectives. Expert Opin Biol Ther 2016;16:1151–62.