Clinical evaluation of natalizumab for formulary consideration


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Importance of the field: Natalizumab is a monotherapy for relapsing forms of multiple sclerosis (MS) and maintaining remission in Crohn’s disease (CD). Evaluation of natalizumab’s clinical relevance must be performed before considering its place in treatment of these diseases.

Areas covered in this review: MEDLINE and PubMed searches were performed using the keywords multiple sclerosis, Crohn’s disease, natalizumab and clinical trials. The manufacturer’s product information was consulted to extract additional data. Pivotal clinical trials included: Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis (AFFIRM), Safety and Efficacy of Natalizumab in Combination With Interferon Beta-1a in Patients With Relapsing Remitting Multiple Sclerosis (SENTINEL), Efficacy of Natalizumab as Active Crohn’s Therapy (ENACT)-1 and 2 and Efficacy of Natalizumab in Crohn’s Disease Response and Remission (ENCORE).

What the reader will gain: AFFIRM and SENTINEL showed improvements in progression of MS. ENACT-1 failed to show a significant effect, but the follow-up trials ENACT-2 and ENCORE were able to demonstrate a response to natalizumab.

Take home message: Two trials on efficacy of Tysabri for treatment of MS demonstrated positive results. Efficacy for CD was mixed. More research demonstrating head-to-head evidence against other agents is necessary to determine if Tysabri’s benefits are significant.

Keywords: comparative effectiveness, Crohn’s disease, multiple sclerosis, Tysabri

1. Introduction

Managing chronic conditions can place a great clinical and economic burden on society. Crohn’s disease (CD) and multiple sclerosis (MS) are just two chronic autoimmune disorders. CD is a chronic
autoimmune disease of the gastrointestinal tract. It can affect any part from the mouth to the anus and is characterized by transmural inflammation [1]. The most common sites of inflammation in patients are the small bowel particularly in the colon and localization in the terminal ileum [2]. Estimated incidence rates for CD range from 3.1 to 14.6 cases per 100,000 person years, and prevalence is estimated to be 26 -- 199 cases per 100,000 person-years. In the US, it is estimated that 10,000 -- 47,000 people are diagnosed with CD yearly and as many as 630,000 people suffer with it. Risk factors for CD are Caucasian race, a positive family history especially with identical twins; mutations in the NOD 2 gene associated with early-onset disease; smoking; early age bacterial infections; and increased intestinal permeability [2,3]. Treatment for CD includes pharmacotherapy as well as surgery. Current treatment guidelines from the American College of Gastroenterology outline a ‘step-up’ approach starting with conventional agents for mild disease and more intense treatment with immunomodulators or biological agents for more severe disease; however, in practice patients may prefer a more aggressive approach, utilizing biological agents earlier on in the disease [4]. Hanauer and Hommes et al. proposed that ‘top-down’ therapy with biologics may have the potential to induce and prolong the maintenance of remission, and reduce or eliminate the concurrent use of steroids, but this theory remains to be proven [5,6].

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<th>Drug name</th>
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<td>Phase</td>
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<td>Launched indications</td>
<td>Crohn’s disease, Multiple sclerosis, relapsing-remitting</td>
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<td>Pharmacology description</td>
<td>α4β1 integrin antagonist, α4β7 integrin antagonist</td>
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<td>Route of administration</td>
<td>Parenteral, intramuscular, Parenteral, intravenous</td>
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MS is a progressive disease of the central nervous system. As many as 400,000 individuals in the US suffer from this disease. MS is more common in women than men, although men are prone to more progressive forms of the disease. The prevalence of MS is 100 -- 150 per 100,000 and is more common in Caucasians than other racial and ethnic groups [7,8].

Risks for MS seem to be environmental and genetic [9]. There is a greater occurrence in the northern hemisphere of the world and first degree relatives of MS patients have a higher risk of developing MS. Viral and bacterial infections have been suggested as stimuli triggering the autoimmune response in susceptible individuals, but other risks that may worsen the inflammatory cascade are reactive metabolites and metabolic stress. There are four different forms of MS: primary progressive (PPMS),
secondary progressive (SPMS), secondary progressive with relapse (SPMS with relapse), and remitting-relapsing (RRMS) [10]. The majority (65%) of patients with MS have RRMS, which is characterized by episodes of disease activity separated by periods of inactivity [11,12].

The management of patients with MS involves an active plan for long-term treatment of symptoms, the underlying disease process and adverse effects of pharmacotherapy. There are a number of treatment guidelines available to clinicians to manage MS in their patients [13-17]. At the same time as this current research Boster et al. published treatment guidelines directly pertaining to the intense treatment of MS in rapidly declining patients [13]. Corticosteroids have limited use for acute relapses and immunosuppressants are recommended and approved for treatment of secondary, or chronic, progressive, progressive relapsing, or worsening relapsing MS [18].

The problem with both disease states is that current pharmacological agents are not meeting the needs of the most severe cases and often require burdensome regimens that are hard for patients to adhere to. Current therapies existing for MS are shown to prevent relapses with rates only as high as 33%. In addition, some patients develop neutralizing antibodies against IFN-b within 6 -- 8 months after beginning treatment resulting in loss of clinical efficacy and the need to change therapy in order to manage their disease progression [19]. Symptoms that arise when a patient is experiencing an episode of disease activity often require hospitalization and additional medication, which can exert an unavoidable financial burden on a managed care organization.

Natalizumab, (Tysabri, Biogen Idec and Elan Pharmaceuticals) is an FDA approved drug as monotherapy for treatment of patients with relapsing-remitting forms of MS to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations (Box 1). It is used when MS is highly active despite the use of IFN-b or if it is severe and rapidly getting worse. In 2006, the FDA and European Medicines Agency (EMEA) approved natalizumab for two specific groups of patients with relapsing-remitting MS: those with a relapse within the last 12 months despite immunomodulatory treatment with IFN-b (and glatiramer acetate (GLAT)) during the past 12 months and for treatment in naï¨ve patients with at least two severe relapses within the last 12 months [20]. It is also approved in the USA for inducing and maintaining clinical response, and remission in adult patients with moderate to severely active CD with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and TNF-a inhibitors [21-23].

Natalizumab works by binding to the a4 subunit of a4b1 and a4b7 integrins expressed on the surface of almost all leukocytes except for neutrophils. The specific mechanism by which natalizumab exerts its effects on both disease states is not fully understood. In MS, it is believed that lesions occur when activated inflammatory cells cross the blood–brain barrier (BBB). Natalizumab blocks the interaction of infiltrating leukocytes with endothelial cells in the brain; the clinical effect of natalizumab is secondary to this. In CD, the interaction between the α4β7 integrin and the endothelial receptor mucosal addressin cell adhesion molecule (MAdCAM-1) is believed to be an important contributor to the chronic inflammation, the hallmark of the disease. MAdCAM-1, mainly found on gut endothelial cells, plays a
vital part in homing T lymphocytes to gut lymph tissue found in Peyer’s patches. Expression of MAdCAM-1 is increased at active sites of inflammation in patients with CD, suggesting that it may play a role in recruiting leukocytes to the mucosa contributing to the inflammatory response found in CD. Therefore, the clinical effect of natalizumab may be secondary to blocking the interaction of α4β7 with MAdCAM-1 thereby reducing inflammation [24-33]. This unique approach to reduce inflammation in both disease states differs from TNF-α inhibition by other biologic agents such as infliximab and adalimumab.

One of the most dangerous side effects of monotherapy with natalizumab is progressive multifocal leukoencephalopathy (PML). This is an opportunistic infection caused by the JC virus. Most people have been exposed to this virus in their childhood, but immunosuppression puts individuals at an increased risk of developing PML [34]. Due to the risk of PML, in the US, natalizumab is only available through the TYSABRI Outreach: Unified Commitment to Health (TOUCH) program, regulated by the manufacturers.

Patients, physicians and dispensing pharmacists have to be enrolled in this program in order for the patient to receive the medication [35]. This program allows healthcare professionals to monitor patients for any adverse effects of the medication. This presents a great opportunity for pharmacists to get involved with direct patient care and monitoring for toxicity of natalizumab. In Europe, the EMEA has released suggested good practices regarding the safe and effective use of Tysabri including use by physicians with access to MRI to regulate changes in brain structure and the release of a physician pack to guide the physicians’ use of natalizumab in patients [36].

The purpose of this paper is to evaluate the clinical relevance of natalizumab in the treatment of CD and MS by analyzing available data as well as demonstrate the utility of pharmacists in managing patients receiving this therapy. We will look at available clinical evidence, most of which compares natalizumab to placebo. Although the efficacy of natalizumab has been demonstrated for MS, long-term studies of natalizumab beyond 1 year are necessary to justify the addition to formularies and demonstrate real benefit of natalizumab over other available treatments.

2. Methods

Since one of the objectives in our research is to determine whether natalizumab demonstrates the safety and efficacy in patients with relapsing MS and CD, a literature search in MEDLINE and PUBMED was performed to identify relevant publications between 1966 and April 2009. The medical subject heading (MeSH) terms ‘Multiple sclerosis’ or ‘Crohn’s disease’, ‘Natalizumab’ and ‘Clinical trials’ were used to perform key word searches of each database. Manual searches of reference lists were also performed in order to identify potential studies that may have been missed using the computer-assisted search strategy. Abstracts of relevant publications were read to determine if the clinical trials meet the selection criteria. The manufacturer’s product information was searched to identify any studies that may not be published. Our selection criteria included only large multi-center, randomized controlled trials comparing natalizumab with a placebo or control therapy for the induction of remission in relapsing MS or CD. All data were analyzed on an intention-to-treat basis. The definitions of treatment success, remission and clinical improvement were clearly set by the investigators of each publication.
Our computer-assisted search resulted in 97 hits for multiple sclerosis (MS), and 94 hits for Crohn’s disease. Among 97 hits, we selected two trials (Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis (AFFIRM) and Safety and Efficacy of Natalizumab in Combination With Interferon Beta-1a in Patients With Relapsing Remitting Multiple Sclerosis (SENTINEL)) as our primary research sources for MS as these two trials met the criteria mentioned above. Since natalizumab was only approved by the FDA for use in CD in January 2008, there have been only a handful of studies available for the use of this drug in Crohn’s disease. Based on the criteria above, we decided to focus on three studies Efficacy of Natalizumab as Active Crohn’s Therapy (ENACT) 1 and 2 and the Efficacy of Natalizumab in Crohn’s Disease Response and Remission (ENCORE) trials. All the studies we chose for MS and CD included large populations of subjects, randomization, placebo-control and appropriate endpoints for measuring the safety and efficacy of natalizumab in MS and CD, which further increase the universality and credibility of the results [37-40].

3. Results

Natalizumab was analyzed for 116 weeks in the AFFIRM trial in patients with RRMS. When the primary endpoint at two years was assessed, natalizumab given every four weeks had a cumulative probability of progression of 17 versus 29% for placebo and a relative risk reduction of 42% for the sustained progression of disability (hazard ratio, 0.58; 95% CI, 0.43 -- 0.77; p < 0.001). For the primary endpoint at one year, natalizumab had 0.26 relapses per year compared to 0.81 relapses per year for placebo. This translated into a relative risk reduction of 68% in the annualized rate of clinical relapse (p < 0.001), and it was also maintained at two years to meet one of the secondary endpoints (p < 0.001). Natalizumab also showed statistically significant results with other secondary endpoints. Natalizumab had an 83% reduction in the mean number of new or enlarging hyperintense lesions over two years measured by T2-weighted MRI (p < 0.001) and a 92% reduction in lesions detected by gadoliniumenhanced MRI at both one and two years (p < 0.001). Overall, natalizumab was very well tolerated, with fatigue (27% versus 21%, p = 0.048) and allergic reaction (9 versus 4%, p = 0.012) being more common in the treatment group. Hypersensitivity reactions of any kind occurred in 25 patients receiving natalizumab (4%) where the reactions in 8 patients (1%) were classified as serious [37].

In a different 116-week multiple sclerosis study known as the SENTINEL trial, it was shown that natalizumab when given in combination with IFN-β1-a administered intramuscularly versus subcutaneously every four weeks had a 24% relative risk reduction in the primary endpoint of sustained disability progression at two years when compared with a combination of placebo and interferon-β1-a (hazard ratio, 0.76; 95% CI, 0.61 -- 0.96; p = 0.02). The estimated cumulative probability of progression at two years was 23% with combination therapy and 29% with IFN- b-1a alone. Combination therapy showed a 54% reduction in the other primary endpoint, the annualized rate of clinical relapse at one year, as evidenced by a value of 0.82 with only IFN-b-1a and 0.38 when both drugs were given together (p < 0.001). This statistical difference was also maintained at two years where combination therapy had a 55% reduction based on a value of 0.75 for IFN-beta-1a and 0.34 for combination therapy (p < 0.001). Other secondary endpoints included an 83% reduction in the mean number of new or enlarging hyperintense lesions over two years measured by T2-weighted MRI (p < 0.001) and an 89% reduction in lesions detected by gadoliniumenhanced MRI at two years (p < 0.001). Anxiety, pharyngitis, sinus...
congestion and peripheral edema were reported more often in the combination treatment group. However, perhaps the most important finding in this study was two confirmed cases of progressive multifocal leukoencephalopathy (PML), one of which was fatal, in the group receiving combination therapy [37,38].

The ENACT study was two separate analyses that evaluated the use of natalizumab for induction and maintenance treatment of Crohn’s disease when given every four weeks. The 12-week induction phase of the study was called ENACT-1, and the 48-week maintenance phase was called ENACT-2. The induction therapy primary endpoint was a response, defined by a decrease in the Crohn’s Disease Activity Index (CDAI) score of at least 70 points, after ten weeks of treatment and a secondary endpoint of disease remission, defined by a CDAI score of less than 150 by the end of the study. Neither endpoint in ENACT-1 achieved statistically significant results compared with placebo. All patients who participated in ENACT-1 and had a 70 point CDAI reduction were invited to participate in ENACT-2. The patients were followed for 60 weeks, with a primary endpoint of a sustained clinical response through 36 weeks. The secondary endpoint was disease remission using the same criteria as that in ENACT-1. However, unlike in ENACT-1, there was a significant response in ENACT-2, with 61% of natalizumab-treated patients maintaining response through 36 weeks versus 28% with placebo (p < 0.001). In terms of disease remission, 44% of natalizumab-treated patients had a CDAI score below 150 versus 26% with placebo (p = 0.003). Overall, serious adverse events were similarly reported in both treatment arms of both trials, though acute infusion reactions, hypersensitivity-like reactions and infections were more common with natalizumab therapy. There were no confirmed cases of PML in ENACT, but there was one death due to PML in a separate open-label study assessing natalizumab treatment in Crohn’s disease [39].

The 12-week ENCORE study was essentially designed to test a hypothesis derived from the ENACT trials. Specifically, it was of interest to determine if elevated C-reactive protein (CRP) levels (> 2.87 mg/l) were indicative of a favorable response with natalizumab therapy in Crohn’s disease patients. The results were statistically significant for the treatment arm for the primary endpoint, induction of response (defined by a decrease in the CDAI score of at least 70 points) after eight weeks and maintained through the end of the study, and the secondary endpoint, the proportion of patients with sustained remission (defined by a CDAI score of less than 150). The primary endpoint was achieved in 48% of natalizumab-treated patients and 32% of patients receiving placebo (p < 0.001), and the secondary endpoint was achieved in 26% of natalizumab-treated patients and 16% of patients receiving placebo (p = 0.002). Reported adverse event types and frequencies were similar between the two treatment groups [40].

The Tysbari Global Observational Program in Safety for Rest of World (TYGRIS -- ROW) safety study recruited all patients who had participated in earlier natalizumab trials to evaluate the risk this medication may pose for the development of PML. Of the participating 3,116 patients, 44 were referred to the Industry Advisory Council (IAC) to be closely examined for PML. Only one patient from these 44 could not be excluded from a diagnosis of PML. However, this patient who had MS and progressive neurologic disease could not be confirmed as having PML either because data on cerebrospinal fluid testing and followup MRI were not available. At the time of this study, only three definite cases of PML have been linked to treatment with natalizumab. Two of these cases occurred in a MS study and one
case occurred in a CD study. The estimated incidence of PML is 1 per 1,000 patients considering average treatment duration of 17.9 months [41,42].

4. Discussion

The AFFIRM trial was a very pivotal study for the use of natalizumab in multiple sclerosis. The primary and secondary endpoints were all met, with the exception of adverse events. For a healthcare professional, this means the drug is efficacious. The chance of the disease progression is decreased and therefore the risk of progression decreased. The occurrence and growth of hyperintense lesions is decreased with natalizumab. The adverse events profile was not statistically significant versus placebo, but adverse events occurred during use of natalizumab. For patients, this means the drug will work. They will stay healthier longer and have a better quality of life. There is a risk of side effects, but the benefits of the drug clearly outweigh the risk.

The SENTINEL trial was conducted to see if natalizumab is still effective when used in combination with IFN-β1-a compared to IFN-b1-a alone. Currently, natalizumab is only FDA indicated as monotherapy, however this study could be used to compare natalizumab with other established treatments for MS and for future use in combination therapy. The results showed that the combination is more efficacious than IFN-b1-a alone. This is due to the fact that favorable results were also observed in the AFFIRM trial, making it difficult to draw conclusions about the suggested efficacy of combination therapy. In addition, the lack of a natalizumab-only arm in the SENTINEL study further adds to the uncertainty of the results because it is not clear what effect glatiramer acetate had on efficacy.

There have been several trials studying the use of combination therapy to treat MS [43]. SENTINEL and a smaller scale combination trial Glatiramer Acetate and Natalizumab Combination Evaluation (GLANCE) were just two trials involving natalizumab combinations. Results have been mixed, but the use of combination therapy is a standard for treating other diseases such as rheumatoid arthritis, diabetes, cancer and hypertension. Based on recent data, it is postulated that there are multiple pathological pathways contributing to the clinical consequences of MS. Due to this complexity and the fact that patients respond differently to different available treatments, it would make sense to approach treatment using multiple therapies.

GLANCE, a small (110 participants) double-blind, placebo-controlled trial demonstrated no statistical significance in the combination group that received subcutaneous glatiramer acetate and monthly intravenous natalizumab and the control group that received glatiramer acetate and a placebo [44]. As stated earlier, it is not clear whether or not it was natalizumab or glatiramer that was having a greater effect due to the lack of a natalizumab treatment arm. In the future, trials that consider natalizumab alone versus in combination with another agent could provide better information regarding the combination of natalizumab with other treatments.

Unfortunately two cases of PML, the most severe adverse effect of natalizumab, were reported. These cases of PML developed while the patients were receiving both natalizumab and IFN-b1a concurrently [38,40-42]. Two years later, one of the patients died from PML. This study supports the necessity of the TOUCH prescribing program so that healthcare professionals and patients can recognize and treat PML
before it’s too late. It also led to the previously mentioned changes in the FDA and EMEA indications for Tysabri in treating MS and CD.

Since the approval of natalizumab in the US and in Europe, there have been 31 cases of PML, of which 8 have been fatal [45-54]. MS patients are at an increased risk of developing PML, but it is estimated that the risk of developing this viral infection are still 1 in 1,000 in natalizumab treated MS patients within the first 24 months of therapy and increases beyond 24 months [55-59]. This may be attributed to changes in the viral load of the JC virus, the causative agent of PML, or susceptibility from previous cytotoxic agent exposure, such as other monoclonal antibodies [60-62]. Because of the increasing number of cases of PML, both the FDA and the EMEA plan to analyze the safety of natalizumab farther [63-70]. Since the approval of natalizumab, the EMEA and FDA have issued numerous updates on natalizumab regarding its safety.

The ENACT trial tested natalizumab in patients with moderate--severe Crohn’s disease versus placebo. The primary endpoint of reducing the CDAI score by 70 points was not reached by the end of ENACT-1 (12 weeks). Also, the secondary endpoint of disease remission (CDAI < 150) was not reached. The patients that did reach the primary endpoint were continued on therapy for an additional 48 weeks (ENACT-2). The endpoints were reached as patients did sustain reduced Crohn’s disease activity and many reached disease remission. This study falsely shows that natalizumab is not efficacious within the first 12 weeks of treatment, but is efficacious beyond that point in patients who did respond in the first 12 weeks. Because placebo response and remission rates were close to that in the natalizumab treatment arm, another variable has to be considered, which was addressed in the later ENCORE trial. ENACT-1 and 2 essentially demonstrated that natalizumab takes a considerable amount of time to reach a clinical effect and that it is more appropriate for maintaining remission than for inducing remission. It would be appropriate for concomitant treatment with a corticosteroid during the induction period. The ENCORE trial was conducted in an identical manner to the ENACT trials, however these patients also had elevated CRP levels (> 2.87 mg/ml). Elevated CRP levels were a requirement for entrance in the trial to further determine significance between placebo and active treatment. This requirement was necessary because the placebo response and remission rates indicated that not all CD patients were presenting with clinically active disease. Researchers found that patients who did not have clinically active CD nor active inflammation were likely to have a similar response with placebo and natalizumab.

Comparatively, in the A Crohn’s disease Clinical trial Evaluating infliximab in a New long term Treatment regimen (ACCENT) I trial, response to infliximab (Remicade) was measured at 2 weeks (57% with active treatment at 5 mg/kg) indicating this therapy has earlier onset of response. One of the primary results of this trial was remission in this trial was measured until week 30; the number of patients in remission at week 30 was 39% [71]. This is 3% lower than the number of patients maintaining remission in the NACT-2 trial even with the high placebo remission rate, indicating that natalizumab elicited slightly better remission, but this may not be clinically significant.

With regards to adalimumab (Humira), another tumor necrosis factor inhibitor, researchers found in the Crohn’s trial of the fully Human antibody Adalimumab for Remission Maintenance (CHARM) trial that a 40 mg every other week and 40 mg weekly dose produced 40 and 47% remission respectively at 26
weeks [72]. Again this is similar to the results of the natalizumab CD trials indicating that at best, each treatment produces similar remission rates.

Natalizumab is currently only FDA approved as a monotherapy when other treatments have failed. In 2008, the makers of Tysabri received FDA approval for an update for indication and dosing and administration for Tysabri for CD. It is now indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active CD with evidence of inflammation that have not had an adequate response to, or are unable to tolerate, conventional CD therapies and TNF-a inhibitors. With respect to dosing and administration, the manufacturer has now added that if a patient does not experience a response in 12 weeks that they should then be discontinued on the medication [73]. This dosing recommendation corresponds with the results from the ENACT-1 trial which would suggest that if a patient does not achieve clinical benefit of reduced CDAI score within 12 weeks, then they will not achieve clinical benefits thereafter.

Finally, the TYGRIS -- ROW safety study analyzed the adverse event profiles for patients participating in a natalizumab trial, even if they received a placebo. The blind was never broken, so there was no bias in this study. It showed that there is a risk of PML, as 44 cases were brought to the IAC. However, 43 of the cases were not PML and one was inconclusive. This shows that the risk is being recognized, and fortunately PML does not occur often. From the data, the incidence of PML was able to be calculated. This will prove very useful to healthcare professionals when considering natalizumab for therapy.

5. Conclusion

The purpose of this review was to determine the clinical relevance of natalizumab (Tysabri) in the treatment of CD and MS. In breakthrough clinical trials, those that focused on the treatment of relapsing-remitting MS produced more favorable data than those that focused on inducing and maintaining remission in CD due to the placebo response/ remission rate in both ENACT-1 and 2. Because of increased risk of PML with increased duration of therapy as well as the failure of ENACT-1 to demonstrate a significant clinical response, we recommend natalizumab to be included in formularies, but with prior authorization with clinical evidence of active inflammation or active chronic disease. With regards to MS, natalizumab seems to be a very viable treatment option. However, natalizumab should only be considered for 12 -- 24 months of therapy. Beyond this point, the risk of PML increases and masks the positive clinical results of the actual treatment.

What can solidify natalizumab as a more robust treatment option for CD is a two-year study or another study demonstrating other variables that would be likely to improve treatment with natalizumab versus placebo. With rising healthcare costs, it is not enough anymore to be just as good as existing treatment options; new medications on the market need to be better than existent treatment options. Clinical pharmacists as a part of their health organizations’ pharmaceutics and therapeutics committee are perfectly capable of evaluating current literature and data to decide whether or not natalizumab or any other newly approved therapies should be placed on formulary as well as working with doctors to monitor treatment efficacy and toxicity.

6. Expert opinion
The ultimate goal of the four pivotal trials centering on natalizumab was to establish it as a viable treatment option for CD and MS to help patients reach and maintain remission. It has proven to be an effective treatment for RRMS as demonstrated in both the AFFIRM and SENTINEL trials. On the other hand, the ENACT-1 trial did not demonstrate clinical significance versus in the number of CD patients who were able to reach remission. The follow up trial ENACT-2 as well as ENCORE were able to demonstrate that patients receiving natalizumab who did attain remission were able to maintain remission.

This research has shown that biological agents as with any other chemical entity are hit and miss. Natalizumab is indicated to treat both MS and CD, but the data for CD is not as robust as with MS. This is because the placebo response and remission rates were lower, but similar to those in the active treatment arm of the ENACT trials. ENCORE was able to tease out a reason why this happened in the previous trials. Future research should be geared towards finding other characteristics in patients with CD who are found to be responsive to CD to further pinpoint the most favorable conditions in which to administer this medication. So far researchers have only uncovered chronic inflammation as a positive prognostic factor with regards to more favorable results, but other factors could be involved.

These limitations do not stifle the potential that this research has. Natalizumab will still be considered first line in treating the two groups of RRMS patients identified by the EMEA as benefiting the most from this treatment. PML is still considered rare with a risk potential of 1 in 1,000. With over 60,000 patients currently receiving natalizumab infusions, the number of PML cases can expected to rise to at least 60, but there is more research focused on detecting, preventing and treating PML in this population. Furthermore, the TOUCH program in the USA and the guidance provided by the EMEA allow for close monitoring of natalizumab-treated patients. This is an opportunity for pharmacists to be a part of the healthcare team managing this group of patients to monitor for toxicities and collaborate and communicate with physicians regarding treatment.

With regards to combination therapy with natalizumab, this does not prove to be viable now. Once we know how to better manage PML in patients taking natalizumab, then research can be done to show whether the benefit of combination therapy with natalizumab is greater than the risk. Fears of increased risk of PML if natalizumab is given in combination with other agents are preventing further research in this direction. However, the multitude of trials focused around combination therapy to treat RRMS is showing that this field is growing. Because many pathological pathways are believed to concomitantly contribute to the CNS inflammatory processes, combination therapy among available agents as well as the potential of combination with novel agents may prove viable in the future.

Research in biological therapy has affected MS already by yielding seven agents for first line treatment of RRMS. In the future, it will continue to provide agents that target different aspects of pathological processes involved in MS. As more research and understanding is available on the many processes that are thought to occur simultaneously in MS, more new agents will be developed to target these pathways.

**Declaration of interest**
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