Clinical experience of natalizumab in Crohn's disease patients in a restricted distribution program

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Abstract	
	Background Natalizumab (NAT) is a humanized monoclonal antibody against α4-integrin initially approved for the treatment of multiple sclerosis, and then withdrawn from the market in 2005 due to the risk of progressive multifocal leukoencephalopathy. NAT was approved for the treatment of Crohn's disease in the United States in 2008 under a restricted distribution program. There has been limited data on NAT since then. The purpose of this study was to review the experience with NAT in Crohn's disease patients at a tertiary inflammatory bowel disease center.
	Methods A retrospective chart review was performed on all patients who received NAT for treatment of refractory Crohn's disease from January 2008 to August 2010 at Washington University Medical Center in St. Louis.
	Results A total of 20 patients were identified and included in our study. Four patients did not complete induction therapy. Seven patients had a clinical response, with 5 patients continuing treatment up to 2012. Four patients had a partial response, 3 had adverse events, and 2 experienced loss of response. Two patients were pregnant while on NAT, and neither had significant adverse pregnancy outcomes. One patient dependent on total parenteral nutrition developed recurrent line sepsis while on NAT. Of the 5 patients on long-term maintenance therapy, 4 have a positive anti-JC virus antibody. No patients developed progressive multifocal leukoencephalopathy or other neurological complications.
	Conclusion NAT remains a valuable alternative treatment option for patients with refractory Crohn's disease under a restricted distribution program.
	Keywords Crohn's disease, natalizumab, pregnancy
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Introduction

Crohn's disease (CD) is a chronic, relapsing inflammatory bowel disease characterized by transmural inflammation that can affect any part of the gastrointestinal tract. Patients are afflicted by a number of symptoms and complications, including bowel obstruction, fistulae, abscesses and extraintestinal manifestations. "Conventional" medical therapies for CD include 5-aminosalicylic acid, antibiotics, corticosteroids, and immune modulators such as methotrexate, mercaptopurine, and azathioprine. The anti-tumor necrosis factor (TNF)-α monoclonal antibodies revolutionized CD therapy. However, a number of patients are resistant or intolerant to the aforementioned agents.

Natalizumab (NAT) (Tysabri, Elan Pharmaceuticals and Biogen) is a humanized monoclonal antibody against α4-integrin that inhibits the adhesion of leukocytes to the vascular endothelium of the gut and central nervous system [1]. NAT was initially approved in the United States in 2004 for the treatment of multiple sclerosis (MS), but was withdrawn from the market in 2005 after reports of progressive multifocal leukoencephalopathy (PML) in two MS patients. Subsequently, PML was diagnosed post-mortem in a CD patient treated with NAT in a clinical trial [2]. PML is a rare

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and usually fatal demyelinating disease of the central nervous system caused by reactivation of latent JC virus infection in immunocompromised hosts. NAT was approved by the United States Food and Drug Administration (FDA) in 2008 under a restricted distribution program (Tysabri Outreach: Unified Commitment to Health, or TOUCH program). Under the TOUCH program, NAT may be used as a second line monotherapy agent for CD patients failing conventional CD therapies and anti-TNF-α biologics. NAT is given by intravenous infusion once every 4 weeks for induction and maintenance of remission.

Two randomized placebo controlled trials, Evaluation of Natalizumab as Continuous Therapy (ENACT-2) [3] and Efficacy of Natalizumab in Crohn's Disease Response and Remission (ENCORE) [4], established the efficacy of NAT in CD. Since the institution of the TOUCH program, data from clinical practice outside of clinical trials are limited to a single report [5]. This study therefore was conducted to review the clinical experience of NAT in CD in a tertiary referral center.

Materials and methods

We performed a retrospective chart review of all adult patients who received any number of NAT doses for treatment of refractory CD at the Washington University in St. Louis Medical Center from January 2008 to August 2010. The Institutional Review Board approved the study in September 2010 (HRPO number 10-1217). Twenty patients were treated and were all included in our study. Demographic and clinical data were extracted from the institutional electronic medical records. The phenotypes of CD were assessed using the Montreal classification [6]: age of onset (A1 <16 years old, A2 17-40 years old, A3 >40 years old), location of the disease (L1 ileal, L2 colonic, L3 ileocolonic, L4 isolated upper disease), and behavior (B1 non-stricturing non-penetrating, B2 stricturing, B3 penetrating, P perianal disease modifier).

Clinical response was defined operationally per the NAT prescribing information, namely sufficient therapeutic benefit as assessed by the treating physician to warrant continuation of NAT beyond the 12 weeks of induction therapy with discontinuation of corticosteroids within six months of starting NAT. Patients were typically assessed for general well-being, abdominal pain, abdominal mass, number of liquid stool, perianal abscess or fistula, oral ulcers, arthralgia or arthritis, dermatological complications, ophthalmological complications, fever, anemia, or weight loss. Partial clinical response was defined as partial improvement of symptoms as assessed by the treating physician. Primary non-response was defined as no improvement of symptoms. Loss of response was defined as initial clinical response after induction therapy followed by recurrence of symptoms. A Kaplan-Meier curve was constructed using the SPSS statistical program (IBM, Armonk, New York).

Results

Patients' characteristics

A total of twenty patients were treated and included in our study (Fig. 1). The demographics and clinical characteristics of the 20 patients were summarized in Table 1, including
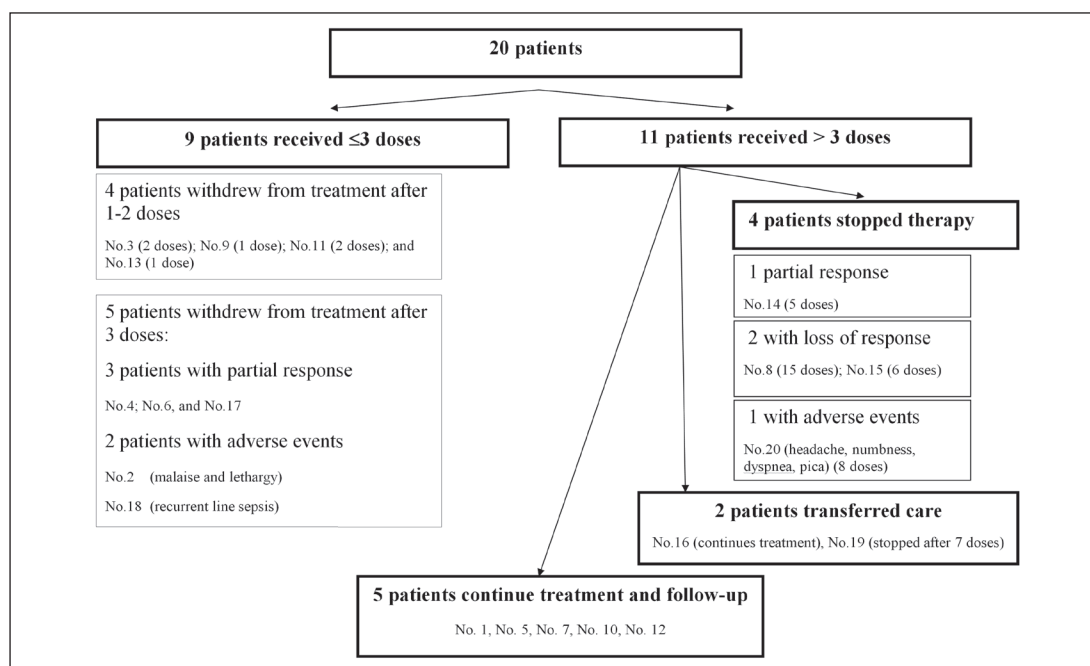

Figure 1 Patients' flow chart

the disease behavior according to Montreal classification, surgical history, smoking status, prior treatment history with immunosuppressants and anti-TNF-α agents, and concomitant therapy while receiving NAT treatment.

Response to NAT

Eleven patients continued treatment with NAT after completing the 3 induction doses (Fig. 1 and Table 2). Out of these, 7 patients achieved clinical response and stopped steroids. The response rate was 35% among the 20 patients included in the study, and 64% among the patients receiving more than 3 doses of NAT. Five of the 7 patients with clinical response also had improvement in CRP. The other 2 clinical

responders had no post-treatment data on CRP, but had other objective evidence of response- one had radiological improvement; and the single patient with active perianal disease experienced closure of a fistula. Two patients with initial clinical response were subsequently followed up at other practices. Five patients have continued NAT treatment and follow up to date. The mean age of responders was 34 years (range 24-51) (vs. 34 years for non-responders). On average, the responders had duration of CD of 14 years (range 6-23), same for the non-responders. None of the responders were active smokers, although two were former smokers. Clinical response was not associated with disease location. Four responders had a history of perianal or enterocutaneous fistula, but only one had perianal fistula when NAT was initiated.

Of the 11 patients who completed induction therapy, 4 subsequently stopped NAT. One patient stopped after 5 doses due to partial response. Two other patients stopped therapy due to loss of response after receiving 6 and 15 doses respectively. The patient who lost response after 15 doses required colectomy for refractory disease. The fourth patient had an initial response but stopped treatment after 8 doses due to the development of headache, numbness, dyspnea, and pica. His symptoms resolved after discontinuation of NAT.

Nine patients stopped NAT after 1-3 induction doses. Of these, 4 withdrew from NAT therapy after receiving only a single dose (n=3) or two doses (n=1) due to lack of clinical benefits. Five patients discontinued NAT after receiving all three induction doses, either due to partial response (3 patients) or adverse events (one patient experienced recurrent line sepsis and another patient experienced malaise and lethargy). One of the three partial responders was an active smoker and was not able to taper steroid after induction therapy. In fact, all 4 patients with concomitant steroid at the initiation of NAT eventually discontinued treatment due to inadequate clinical response to NAT.

A Kaplan-Meier curve (Fig. 2) reveals that patients dropped out of treatment program rapidly after induction therapy. The

Table 1 Patients' demographics and characteristics

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Number of patients (n)	20
Mean age (year)	34.4 (range 18-53)
Female (n)	12 (60%)
Race (n)	
Caucasian	15 (75%)
African-American	5 (25 %)
Mean age at diagnosis (year)	20
Mean duration of Crohn's disease (years)	14.4 (range 2-34)
Montreal Classifications	
L1 ileal	3 (15%)
L2 colonic	5 (25%)
L3 ileocolonic	12 (60%)
B1 non-stricturing non-penetrating	11 (55%)
B2 stricturing	9 (45%)
B3 penetrating	2 (10%)
P perianal disease	6 (15%)
History of perianal fistulae (n)	5
Patients with active fistulae (n)	1
History of surgical resection (n)	16 (80%)
Smokers (n)	3
Prior immunosuppressant (n)	19 (95%)
Azathioprine	13 (65%)
Mercaptopurine	8 (40%)
Methotrexate	11 (55%)
No. of prior anti-TNF-α agents treated (n)	
1	6 (30%)
2	10 (50%)
3	4 (20%)
Concomitant therapy with natalizumab (n)	7 (35%)
Prednisone	4 (20%)
Antibiotics	3 (15%)

TNF, tumor necrosis factor
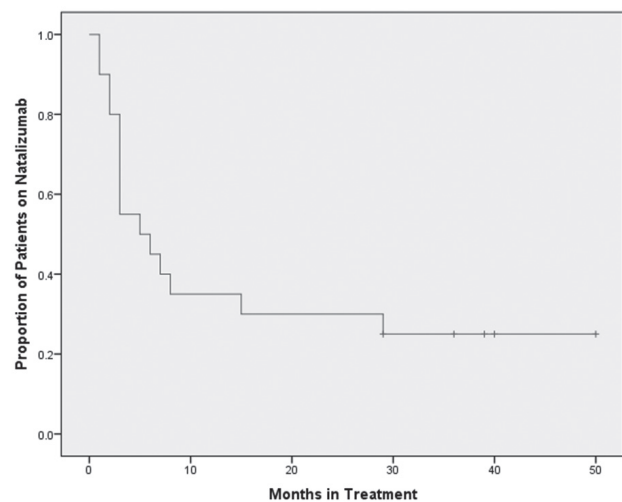
Figure 2 Retention of patients on natalizumab treatment (N=20)

Table 2 History of treatment and clinical course

Patient	Montreal Classification	Duration of disease (year)	Prior anti-TNF	Prior AZA/6MP/MTX	Response to NAT	Comments
No.1	A2L3B1P	6	IFX, CTZ	AZA	clinical response	since 07/2009; CRP 4 → 1.6; (+) JCV Ab, stopped NAT in 04/2012
No.2	A3L3B2	22	ADA	6MP, MTX	drug intolerance	stopped after 3 doses due to increased malaise and lethargy
No.3	A3L3B2P	20	IFX	6MP	incomplete Tx	stopped after 2 doses, active smoker
No.4	A2L3B1	12	IFX, ADA	6MP, MTX	partial response	concomitant steroid; stopped after 3 doses
No.5	A3L4B2	23	IFX, ADA	AZA, MTX	clinical response	since 03/2009; improvement on MRI; (+) JCV Ab and continues NAT
No.6	A2L2B1	11	IFX, ADA	6MP, MTX	partial response	stopped after 3 doses
No.7	A3L2B1P	9	IFX	AZA, 6MP, MTX	clinical response	since 05/2008; perianal fistula closed; CRP 1.8 → 0.9; (+) JCV Ab and continues NAT
No.8	A2L3B1	16	IFX, CTZ	AZA	loss of response	partial response initially, then colectomy after 15 infusions
No.9	A2L3B1P	15	IFX, ADA, CTZ	AZA	incomplete Tx	stopped after 1 dose
No.10	A2L3B2B3P	12	IFX, ADA	AZA	clinical response	since 09/2009; CRP 345 → 2.5; (-) JCV Ab
No.11	A2L2B1	5	IFX, ADA, CTZ	AZA, MTX	incomplete Tx	stopped after 2 doses, also with nausea and vomiting
No.12	A2L3B2B3	23	IFX, ADA	AZA	clinical response	since 02/2009; radiological improvement; (+) JCV Ab and continues NAT
No.13	A2L2B1	6	IFX, ADA	AZA, MTX	incomplete Tx	stopped after 1 dose complaining of increased bloody stools and abdominal pain
No.14	A2L2B1	2	IFX	AZA	partial response	concomitant steroid; stopped after 5 doses
No.15	A2L3B1	8	IFX, ADA	AZA, 6MP	loss of response	first dose when 32 week pregnant, but stopped after 6 doses; active smoker
No.16	A2L4B2	14	IFX, ADA	none	clinical response	since 03/2008; CRP 24.5 → 0.2; stopped due to pregnancy at 10 week of gestation, and resumed 4 months later; transferred care but continued NAT
No.17	A3L1B2	34	IFX, ADA	6MP, MTX	partial response	could not taper steroids after 3 doses; active smoker
No.18	A2L3B2	17	IFX, ADA	6MP, MTX	drug intolerance	recurrent line sepsis, stopped after 3 doses
No.19	A2L3B2	11	IFX, ADA, CTZ	AZA, MTX	clinical response	concomitant steroid, transferred care and stopped NAT after 7 doses; CRP 6.2 → <0.4
No.20	A3L3B1P	22	IFX, ADA	AZA, MTX	drug intolerance	Stopped after 8 doses due to headache, numbness, dyspnea, and pica

IFX, infliximab; ADA, adalimumab; CTZ, certolizumab; AZA, azathioprine; 6MP, mercaptopurine; MTX, methotrexate; NAT, natalizumab; TNF, tumor necrosis factor; Ab, antibody; CRP, C-reactive protein.

percentages of patients who remained on NAT treatment at 6 months, 12 months, and 24 months were 45%, 35%, and 30% respectively.

Safety

One patient with short gut syndrome on chronic total parenteral nutrition experienced recurrent line infection and sepsis during the induction therapy, and therefore NAT was discontinued after 3 doses. The organisms found associated with the infection include *Stenotrophomonas*, *Alcaligenes xylosoxidans,* and *Staphylococcus*. One patient could not tolerate NAT due to malaise and lethargy and discontinued treatment after 3 doses. One patient developed headache, numbness, dyspnea and pica after receiving 8 doses of NAT, and discontinued treatment with resolution of all her symptoms before neurological evaluation. One patient who received NAT for 8 months with good clinical response discontinued the treatment after finding out she was 10-weeks pregnant. To prevent CD flares during pregnancy, she restarted NAT 4 months later after discussing with her

obstetrician and continued treatment until she was induced at 37 weeks of pregnancy due to preeclampsia. She had a normal vaginal delivery. Her infant had pneumonia, anemia, thrombocytopenia, a small intracranial bleed and seizures after birth. A follow-up EEG showed no seizure activity. The infant required 4 units of blood transfusion. However, all issues resolved within a month, and the infant develops normally afterwards. Another patient started NAT when she was 32 weeks pregnant because of severe abdominal pain, vomiting, and inability to eat, and because she had exhausted all other options. She continued treatment with NAT until she delivered uneventfully a male infant weighing 3365 g at 40 weeks of gestation.

Since the Stratify anti-JC virus antibody ELISA test was cleared by FDA in January 2012, all 5 patients on continuous NAT treatment with follow up were tested for their JC virus status. Four patients were positive and 1 was negative. One of the 4 patients with positive anti-JC virus antibody decided to discontinue treatment while the remaining 4 patients have continued treatment. All 5 patients were previously treated with immunosuppressants and none developed neurological symptoms or complications during follow up.

Discussion

We presented our real-life experience with NAT in CD patients. NAT appears to be a safe and effective therapeutic option for refractory CD in a restricted distribution program. No PML was found during follow-up in our patients. One patient developed recurrent sepsis associated with NAT treatment.

Four patients stopped treatment before completing 3 doses of NAT for induction therapy. It may be assumed that safety concerns, especially PML, contributed to the early cessation of therapy, before any therapeutic benefit might have become apparent. When we started treating patients with NAT in 2008, little data was available to address the risk of PML with patients. A recent study found that the major risk factors for NAT-associated PML are the presence of anti-JCV antibodies, treatment with an immunosuppressant before the initiation of NAT, and longer duration of NAT treatment (>24 months) [7]. The risk of PML in a patient with a positive anti-JC virus antibody who has been on NAT for more than 2 years and was previously on immunosuppressant therapy is estimated at 11.1 per 1,000 [7]. On the other hand, no case of PML has been reported in patients with negative anti-JC virus antibody. Therefore, a positive anti-JC virus antibody identifies patients at risk for PML, whereas a negative result connotes zero risk. The Stratify JCV Antibody ELISA test was cleared by the FDA on January 20, 2012. This stratification tool, with periodic testing, should alleviate some concerns of patient regarding NAT therapy.

Two patients discontinued treatment due to loss of response after receiving 15 and 6 doses of NAT respectively. The first patient eventually had colectomy due to severe Crohn's colitis, and the second patient is an active smoker. Refractory disease

and cigarette smoking likely contribute to the loss of response in these 2 patients. While NAT is a humanized monoclonal antibody, an antibody-mediated loss of response as seen in infliximab remains possible and further study is needed to see if anti-NAT antibody is involved in its loss of effectiveness.

Three patients (15%) in our study stopped further treatment due to adverse events, including one with malaise and lethargy, one with headache, numbness, and pica, and one with recurrent line sepsis. Headache is the most common adverse events observed in the previous clinical trials [3], although only one of our patients reported this symptom. Infection is another common and serious adverse events associated with NAT, occurring in more than 30% of patients in various studies [3,5]. In our study, we had one patient with recurrent TPN line infections. It should be noted that this patient had experienced recurrent line infections even before NAT therapy. In our small cohort, there were no other patients with infections.

In this report, we described a patient who received NAT in the first 10 weeks of pregnancy and again in the third trimester. The patient had preeclampsia and needed to be induced at 37 weeks of pregnancy. The infant had perinatal complications of anemia, thrombocytopenia, intracranial hemorrhage, and pneumonia, but those complications resolved in a month and the infant has normal development afterwards. It is not clear whether the perinatal complications were due to preeclampsia or NAT. Given that the pathophysiology of preeclampsia involves hemodynamic and inflammatory changes of placenta [8] and given that NAT affects adhesion of leukocytes to endothelium, the association of preeclampsia with NAT is plausible but so far has not been reported. Another patient who received NAT after 32 weeks of pregnancy had an uneventful delivery. There are no prior reports on the effects of NAT on pregnancy in CD patients. Although a case series of 35 MS patients receiving NAT during pregnancy did not find any adverse events that were attributable to NAT exposure, all stopped NAT once pregnancy was found [9]. In addition, newborns of mothers who received NAT during pregnancy had birth weight within normal limits and not statistically different from those not exposed to NAT, which is also consistent with our observation. These 2 patients in our series thus provide an unusual experience in NAT exposure after the third trimester. As teratogenic effects of NAT were observed in animal studies [10], and as we await larger human studies on the safety of NAT during pregnancy, patients should be advised to use effective contraception while on NAT.

All the patients in our study had failed at least one anti-TNF-α agent. In this population with moderate to severe CD, 5 of the 11 patients who completed induction therapy with NAT continued long-term treatment with good clinical response. Our results suggest that NAT should be considered as an alternative therapeutic option for those who are refractory to anti-TNF-α agents. A major caveat regarding the use of NAT in routine practice is that prior NAT therapy is commonly an exclusion criterion in many trials. Patients and physicians should be aware of this issue before committing to NAT therapy.

Summary Box

What is already known:

- Natalizumab (NAT) has been approved for Crohn's disease (CD) refractory to anti-tumor necrosis factor (TNF)-α agents
- NAT can only be prescribed in a restricted distribution program
- Limited data exists regarding the experience of NAT outside of clinical trials
- There is no prior report of NAT exposure during pregnancy in CD patients

What the new findings are:

- Our real-world experience suggests that NAT remains a viable option for CD patients refractory to anti-TNF-α

Our study is limited in that it was a retrospective study lacking a quantitative measure of response, such as the Crohn's Disease Activity Index or the Harvey Bradshaw index. However, all patients who were determined to have achieved a clinical response by the treating physician had objective evidence supportive of improvement, including a decrease of C-reactive protein, improvement on radiological imaging, or closure of a perianal fistula. In addition, they all continued on NAT for more than 30 months and remain in clinical remission up to this point.

In summary, we presented our real-world experience of NAT in treating CD patients at a tertiary referral center.

Our study showed that NAT is a viable option for treating patients with CD refractory to anti-TNF-α agents. Two patients who received NAT during pregnancy did not have adverse outcome of pregnancy despite that one patient developed preeclampsia.

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