THREE YEAR SAFETY AND EFFICACY DATA OF NATALIZUMAB IN CYPRIOT PATIENTS WITH RELAPSING REMITTING MULTIPLE SCLEROSIS

CPC-091

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INTRODUCTION

The purpose of our study (NAT) was to evaluate the long term safety and efficacy of Natalizumab in patients with Relapsing Remitting Multiple Sclerosis (RRMS), to assess the frequency of occurrence of anti-JC Virus (JCV) antibodies, and, finally to implement a strategy for the prevention of Progressive Multifocal Leukoencephalopathy (PML).

Natalizumab is a recombinant humanised anti-α4-integrin antibody produced in a murine cell line by recombinant DNA technology and is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following patient groups:

- Patients with high disease activity despite treatment with a beta-interferon or
- Patients with rapidly evolving severe relapsing remitting multiple sclerosis.

METHODS

Twenty-two patients were studied prospectively for 3 years.

Eligibility criteria were:

1. Patients with RRMS, with EDSS 0-5.5, who failed to respond to treatment with beta- Interferon(s) and/or glatiramer acetate. Failure is defined as >1 intravenous steroids requiring relapses in the previous year while on therapy for 18 months, at least 9 T2-hyperintensive lesions in cranial and/or spinal MRI or at least 1 Gadolinium(Gd)-enhancing lesion.
2. Patients with RRMS, with EDSS 0-5.5, with rapidly evolving disease, defined by >1 disabling relapses in one year (worsening of EDSS score by 2 points if initial EDSS<=4 and by 1 point if initial EDSS>=4) with >=1 Gd-enhancing lesions on brain MRI or a significant increase in T2 lesion load.

Twenty (90,9%) of the patients included in our study had RRMS with high disease activity despite treatment with beta-Interferons and/or Glatiramer Acetate (i.e. fulfilled criterion 1). Eleven of those (55%) had tried (and failed) treatment with one interferon, five (25%) had tried two types of immunomodulatory agents, three patients (15%) had failed treatment of one interferon and an immunosuppressive agent (Mitoxantrone) and one patient (5%) had failed treatment with two interferons and Mitoxantrone.

Two patients (9,1%) had rapidly evolving severe RRMS (i.e. fulfilled criterion 2).

The mean age of onset of the disease was 30.1 years (Range 19-46 years). The mean duration of the disease was 8.6 years (range 1-18 years), (Table 1).

TABLE 1 | Patient Characteristics

	NAT (N=22)
Characteristics	
• Mean age of onset	30,1 years (19-46)
• Mean duration of MS at start of NAT	8,6 years (1-18)
• Mean EDSS score before NAT	4,2 (2,5-6)
Gender	
• Male	36%
• Female	64%
Type of MS	
• High disease activity despite treatment	91%
• Rapidly evolving severe RRMS	9%

Overall, in the 12 months before treatment with Natalizumab, the mean annual relapse rate was 2.5 (range: 1-5) and the mean worsening of EDSS was 0.9 (range: -0,5 -3).

The mean annual relapse rate was 2.35 (range: 1-4) and the mean worsening of EDSS was 0.8 (range: -0.5 -2.5) in the high disease activity despite treatment group.

In the rapidly evolving MS group, the mean annual relapse rate was 4 (range: 3-5) and the mean worsening of EDSS was 2.3 (range: 1,5-3).

All patients had hematological, biochemical, urinal, serum immunoglobulin evaluations, CD4-CD8 ratio measurements and chest X-Rays prior to treatment initiation and hematological and biochemical evaluations every three months following NAT administration.Patients were informed of any possible side-effects and had direct access with their treating neurologists at all times.

The Expanded Disability Status Scale (EDSS) was applied before treatment and every six months after treatment with NAT.

The patients were treated with 300 mg of Natalizumab intravenously every 4 weeks. Imaging examinations were performed before and after treatment initiation. JVC antibody testing was performed two years after initiation of therapy with Natalizumab.

RESULTS

Three years after treatment with Natalizumab, the intention to treat analysis (i.e. including the patients that discontinued treatment) showed an overall mean annual relapse rate of 1.12, signifying a 55.2% reduction from baseline.

Four patients (18.2%) remained relapse-free. Four patients (18.2%) had a relapse reduction of 75%. Three patients (13.6%) had a relapse reduction of 50%. Two patients (9,1%) had a relapse reduction of less than 50%. Two patients (9,1%) did not show any change in the number of relapses and one patient (4,5%) had an increase in the annual number of relapses compared with the year before treatment with Natalizumab (Fig.1).

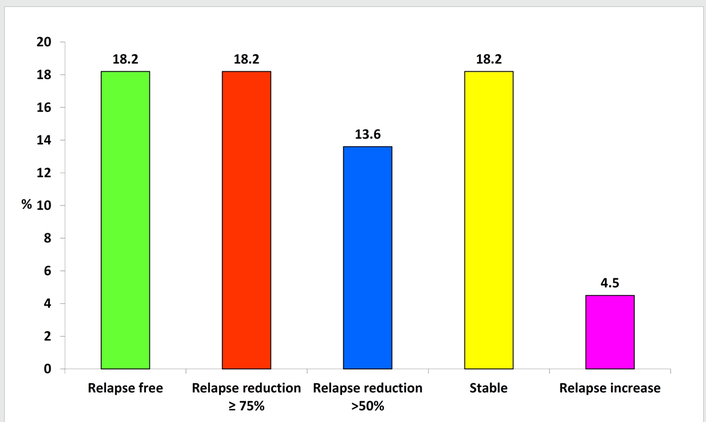

FIGURE 1 | The effect of NAT in the annual number of relapses after 3 years of treatment / completers

An improvement of 0,3 points on the mean EDSS Score was observed at three years of treatment compared to baseline (Fig. 2)

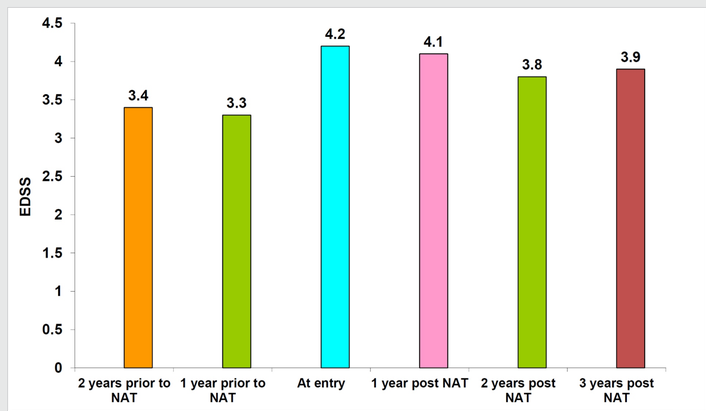

FIGURE 2 | Mean EDSS scores before and after 3 years of treatment with Natalizumab / completers

One patient (4,5%) showed improvement on the EDSS Score by 3 points. Two patients (9,1%) improved by 2 points, one patient (4,5%) by 1,5 points, one patient (4,5%) by 1 point and five patients (22,7%) by 0.5 points. One patient (4,5%) remained stable and five patients (22,7%) had an increase on their EDSS Score compared to baseline.

Sub-group analysis of the rapidly evolving severe RRMS group showed that both patients remained relapse-free and an improvement of 1.7 points on the mean EDSS was observed compared to baseline (Fig. 3,4).

In the high disease activity despite treatment group, the mean annual relapse rate was 0.9 (62.5% decrease from baseline). An improvement of 0.3 points on the mean EDSS was observed compared to baseline (Fig. 3,4).

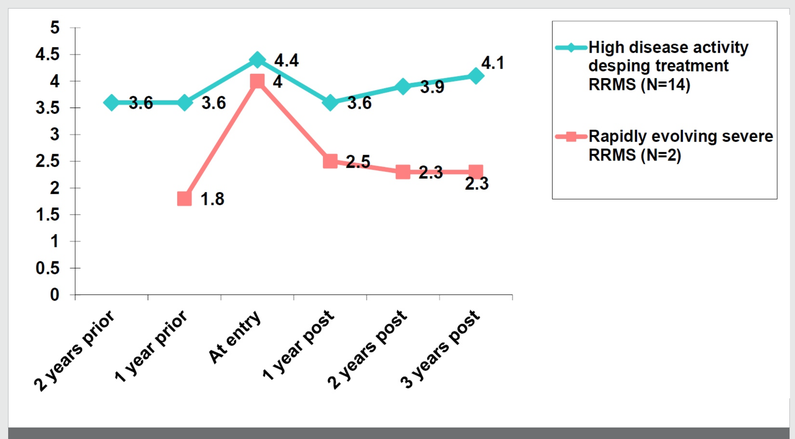

FIGURE 3 | Changes in EDSS scores before and after treatment with Natalizumab / completers

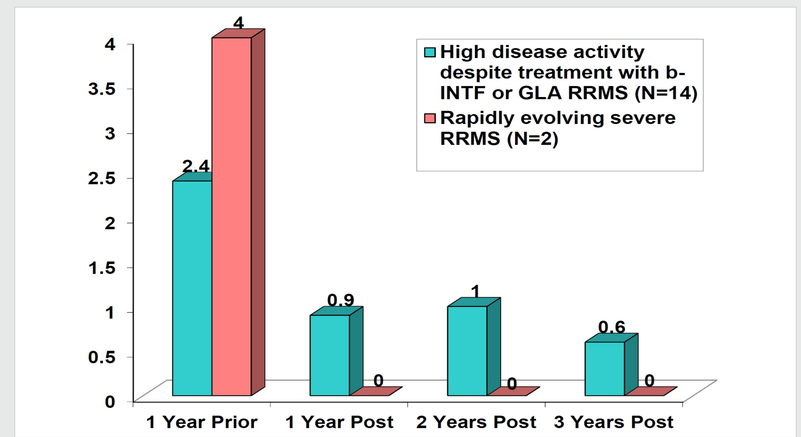

FIGURE 4 | Mean number of relapses pre and post treatment with Natalizumab / completers

Five patients (22,7%) belonging in the high disease activity despite treatment group discontinued the study: Reasons for discontinuation were: Allergic reaction (9%), generalized atonia, fatigue and weakness (4,5%), recurring herpes infection (4,5%) and family planning (4,5%).

JC virus antibody testing was performed two years after initiation of therapy with Natalizumab to the patients that remained on the drug. Of the seventeen patients, ten (58,8%) tested positive. Three of those (30%) discontinued Natalizumab due to previous therapy with IV Mitoxantrone. Remaining patients continued therapy under close supervision by the attending neurologist.

No progressive Multifocal Leukoencephalopathy cases were reported.

Most frequently reported side-effects were: Cardiovascular side effects (41%), general side effects (41%), laboratory abnormalities (41%), gastrointestinal side effects (23%), neurological side effects (18%), allergic reactions (18%) and depression (14%).

Five patients (22,7%) required slower infusion rate due to pulse drop during their treatment. One patient (4,5%) required intravenous hydrocortisone before each treatment to prevent rigors and flashing.

The majority of our patients completing the study (87,5%) had a repeat MRI scan within the second or third year of treatment with Natalizumab. Of those, 85,7% did not present new or Gadolinium enhancing lesions.

CONCLUSIONS

- Our results show that treatment with Natalizumab is beneficial in reducing the number of relapses and slowing disease progression in both patients with MS in which prior therapeutic approaches have failed and in patients suffering from rapidly evolving Multiple Sclerosis.
- Overall, 3 years after treatment with Natalizumab, the mean annual relapse rate of the patients completing the study was 1.12, a 55,2% reduction from baseline.
- 18,2% of our patients remained relapse- free 3 years after introduction of Natalizumab.
- Interestingly, a trend of increase on the EDSS Score after the 2nd year of treatment with Natalizumab was observed in the group of patients with high disease activity despite previous treatment with INTF-β or GLA (Fig.3), even though these patients presented with sustained significant annual relapse rate reduction throughout the 3 years of NAT treatment (Fig.4). Further evaluation is therefore recommended.
- Natalizumab proved to be mostly safe and well tolerated, with 22,7% of patients discontinuing the study due to adverse drug reactions. 58,8% of patients remaining on Natalizumab for more than two years tested positive to JC virus antibodies. Of those, patients with previous immunosuppressive therapy were discontinued from Natalizumab, whereas strict follow-up criteria were implemented for the patients remaining on the drug (Fig.5).
- These results confirm those of previous studies demonstrating the long term efficacy, tolerability and safety of Natalizumab in Relapsing-Remitting Multiple Sclerosis.

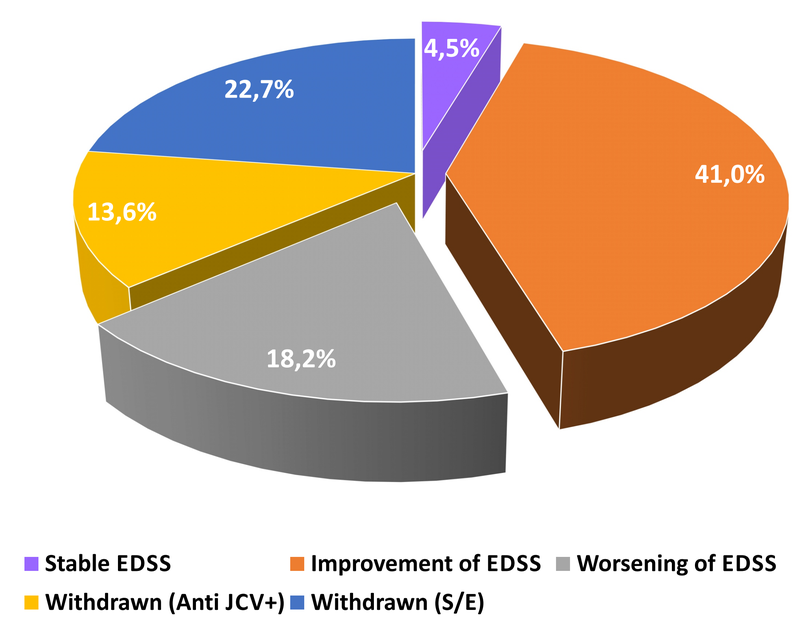

FIGURE 5 | Patient response in the treatment with Natalizumab