Multiple Sclerosis and Related Disorders 101 (2025) 106564

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Original article

Effectiveness of anti-CD20 therapies following natalizumab discontinuation: insights from a cohort study

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ARTICLE INFO

Keywords:
Multiple sclerosis
Natalizumab
Rituximab
Ocrelizumab
Ofatumumab
Anti-CD20

ABSTRACT

Background: Natalizumab (NTZ) is a highly effective multiple sclerosis (MS) treatment but carries a high risk of progressive multifocal leukoencephalopathy in JCV-positive patients. Switching to other therapies is sometimes necessary despite the risk of increasing disease activity, even with other highly effective treatments, such as anti-CD20 therapies.
Objective: To evaluate anti-CD20 therapies effectiveness after NTZ discontinuation.
Methods: A retrospective study including MS patients who switched NTZ to anti-CD20 therapies: rituximab (RTX), ocrelizumab (OCR), and ofatumumab (OFA). Demographic, clinical, and safety data were analyzed.
Results: We included 59 patients (41 female). Mean disease duration at data collection was 7,88 ± 6,62 years. The main reason for NTZ discontinuation was safety concerns related to JCV seroconversion and serum titer increase ($n = 52$). RTX patients had significantly longer and more active disease before transition. Comparing annualized relapse rate (ARR) and EDSS before and after switch, RTX significantly reduced ARR (0,65 vs 0,08; $p = 0007$) but led to a significant EDSS increase (3,65 vs 4,15; $p = 0022$). No significant changes were observed for OCR and OFA. ARR reduction was greater with RTX than OCR and OFA ($p = 0018$), though EDSS variation did not differ. Survival analysis showed no difference in time to disease activity between groups. In this cohort, 70 % of disability progression was due to progression independent of relapse activity (PIRA).
Conclusion: Anti-CD20 therapies appear to be a safe option after NTZ discontinuation, with no rebound disease and stable EDSS. PIRA was the main driver for disability progression, emphasizing the need to control smoldering disease.

1. Introduction

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system, and significant progress has been made in disease-modifying therapies (DMT) over the past few years (Amin and Hersh, 2023). The increasing range of alternatives enables patients to switch to a DMT that better suits their needs and offers greater potential benefits. Adverse effects, inefficacy, and safety concerns are the main reasons for discontinuing a DMT. An example is the risk of progressive multifocal leukoencephalopathy (PML) in patients treated with natalizumab (NTZ) who are positive for John Cunningham Virus (JCV). For these patients it may be recommended to switch to another DMT; however, initiating a moderate or low efficacy treatment carries a high risk of rebound disease activity. Switching from NTZ to a first-line therapy does not require a washout period, but when transitioning to a second-line or induction therapy a one-month washout period is recommended (Bigaut et al., 2021).

Historically, fingolimod and dimethyl fumarate have been the most common approved DMT choices following a switch from natalizumab. However, as new highly effective DMT emerged, new options have become available for switching from NTZ in highly active MS patients (Zanghì et al., 2021). Ocrelizumab (OCR) is considered an effective option and is often used as the first choice. Existing evidence of OCR's efficacy after NTZ discontinuation, demonstrating its superiority over

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https://doi.org/10.1016/j.msard.2025.106564
Received 9 February 2025; Received in revised form 2 June 2025; Accepted 3 June 2025

fingolimod, dimethyl fumarate, and cladribine, supports this decision (Zanghì et al., 2021; Zhu et al., 2023). Additionally, OCR seems to be a safer alternative than maintaining NTZ on extended interval dosing (Santiago-Setien et al., 2023). Rituximab (RTX), although used off-label, has shown superior efficacy and safety compared to fingolimod after discontinuing natalizumab (Alping et al., 2016). Evidence regarding the efficacy and safety of ofatumumab (OFA) remains limited, resulting in uncertainties when selecting a new DMT.

The objective of this study was to evaluate the effectiveness of anti-CD20 therapies following natalizumab discontinuation.

2. Methods

2.1. Subjects

We conducted a retrospective study, including MS diagnosed patients according to the McDonald 2017 criteria who switched from NTZ to anti-CD20 therapies: RTX, OCR and OFA. We selected the patients through the hospital pharmacy records of patients treated with natalizumab in our center. Included patients were at least 18 years old and had periodic medical evaluations in our hospital. We excluded patients who had less than six months of treatment. Their medical files were reviewed, and demographic and clinical data collected. In our hospital the standard protocol when discontinuing NTZ is a washout period of 4 weeks.

2.2. Study endpoints

The outcomes of this study were the annualized relapse rate (ARR), Expanded Disability Status Scale (EDSS) and disability progression.

Disability progression was defined for patients with a baseline EDSS score of 0 as an increase of at least 1.5 steps, for baseline score between 1.0 and 5.5 as an increase of at least 1.0, and for baseline score greater than 5.5 as an increase of at least 0.5 steps (Sharmin et al., 2022).

Disease activity was defined by the occurrence of a relapse, progression in disability, an increase in T2 lesion load on MRI, or the appearance of new T1 gadolinium-enhancing lesions on MRI.

Progression independent of relapse activity (PIRA) was defined for patients who experienced disability progression during the follow-up period (based on initial vs. final EDSS), without any evidence of disease activity (clinical or radiological relapses).

2.3. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics software version 28. Normality was assessed using the Kolmogorov-Smirnov test. Categorical variables are represented using frequencies. Ordinal or discrete variables are reported as means as they are better perceived but were studied using median values and were compared through Mann-Whitney U and Kruskal-Wallis tests. Categorical and ordinal variables were compared using Wilcoxon and Chi-squared tests. Kaplan-Meier survival analysis was used to assess the rates of disease activity with each anti-CD20 therapy throughout the disease follow-up.

2.4. Ethics

The present research was approved by the Ethics Board of Coimbra University Hospital Centre.

3. Results

This cohort included 59 patients that were followed for an average of 28.58 ± 27.23 months since switching to the anti-CD20 therapies.

Baseline demographic characteristics and clinical data are reported in Table 1. This cohort included 59 patients, 69,5 % of whom were female, and 91,5 % had relapse-remitting MS (RRMS). At the time of clinical data collection, the mean disease duration was 7,88 ± 6,62 years. Patients were treated with NTZ for a mean time of 24,32 ± 15,96 months ($p = 0767$). In our department, the practiced washout period for transitioning NTZ to anti-CD20 therapies is 4 weeks.

Table 1
Demographic and clinical data of patients by anti-CD20 therapy.

	Total	RTX	OCR	OFA	*p-value*
Number of patients, n (%)	59 (100)	23 (39)	29 (49,2)	7 (11,9)	–
Female, n (%)	41 (69,5)	17 (73,91)	19 (65,52)	5 (71,43)	0852
Disease phenotype, n (%)					
- RRMS	54 (91,5)	20 (87,0)	27 (93,1)	7 (100)	0889
- PPMS	1 (4,3)	1 (3,4)	0		
- SPMS	2 (3,4)	2 (8,7)	1 (3,4)	0	
	3 (5,1)				
Mean age at NTZ → anti-CD20 switch, years	41,10 ± 13,21	45,96 ± 2,73	37,21 ± 2,44	41,29 ± 3,52	0071
Mean disease duration[1], years	7,88 ± 6,62	11,0 ± 1,52	5,79 ± 1,02	6,29 ± 1,95	**0009**
ARR before transition[2]	0,27	0,65	0,03	0	**0000**
EDSS before transition	2,84	3,65	2,4	2	**0025**
Reason for NTZ switch, n (%)					
- Safety	52 (88,1)	17 (73,9)	28 (96,6)	7 (100)	0079
- Inefficacy	5 (21,7)	1 (3,4)	0		
- Adverse events	6 (10,2)	1 (4,3)	0	0	
	1 (1,7)				
Mean NTZ treatment duration, months	24,32 ± 15,96	23,57 ± 13,09	24,03 ± 15,56	28,00 ± 26,15	0767
Mean anti-CD20 treatment duration, months	28,58 ± 27,23	48,57 ± 6,88	17,97 ± 2,01	6,86 ± 0,99	**0000**
Switch to other DMT, n (%)	13 (22,0)	9 (39,1)	4 (13,8)	0	**0030**
Reason for anti-CD20 switch, n (%)					
- Safety	3 (23,1)	3 (33,3)	0	0	0091
- Inefficacy	8 (61,5)	6 (66,7)	2 (50)	0	
- Adverse events	2 (15,4)	0	2 (50)	0	
Disease activity, n (%)	14 (23,7)	10 (43,5)	4 (13,8)	0	**0013**
Disability progression, n (%)	10 (16,9)	6 (26,1)	3 (10,3)	1 (14,3)	0341
	7 (70)	3 (50)	3 (100)	1 (100)	0625
• **PIRA, n (%)**					

1- At time of data collection; 2- ARR in the 12 months before transition.
RTX, Rituximab; OCR, Ocrelizumab; OFA, Ofatumumab; RRMS, relapse-remitting multiple sclerosis; PPMS, primary-progressive multiple sclerosis; SPMS, secondary-progressive multiple sclerosis; NTZ, Natalizumab; ARR, annualized relapse rate; EDSS, expanded disability status scale; PIRA, progression independent of relapse activity; DMT, disease modifying therapy.

Most patients discontinued NTZ due to safety concerns ($n = 52$), but also due to inefficacy ($n = 6$) and adverse events ($n = 1$). Inefficacy was due to clinical progression, relapses, and MRI activity of the disease. The adverse event was an infusion-related vagal response with desaturation. Adherence to NTZ was not a problem in any of the patients.

During treatment with anti-CD20 therapies, our patients underwent MRI monitoring at a mean interval of 1.59 years. The duration of anti-CD20 treatment was significantly longer in RTX treated patients, with a mean of 48,57 ± 6,88 months, while OCR had a mean of 17,97 ± 2,01 months, and OFA a mean of 6,86 ± 0,99 months ($p = 0009$).

The RTX group had a baseline more active disease, with higher ARR (0,65 vs 0,03 vs 0; $p = 0000$) and EDSS (3,65 vs 2,4 vs 2; $p = 0025$).

In Figs. 1 and 2 we compare the ARR and the EDSS before and after the transition from NTZ to the anti-CD20 therapies.

In RTX patients the ARR was significantly lower after the transition (0,65 vs 0,08; $p = 0007$), but a significant increase in EDSS occurred

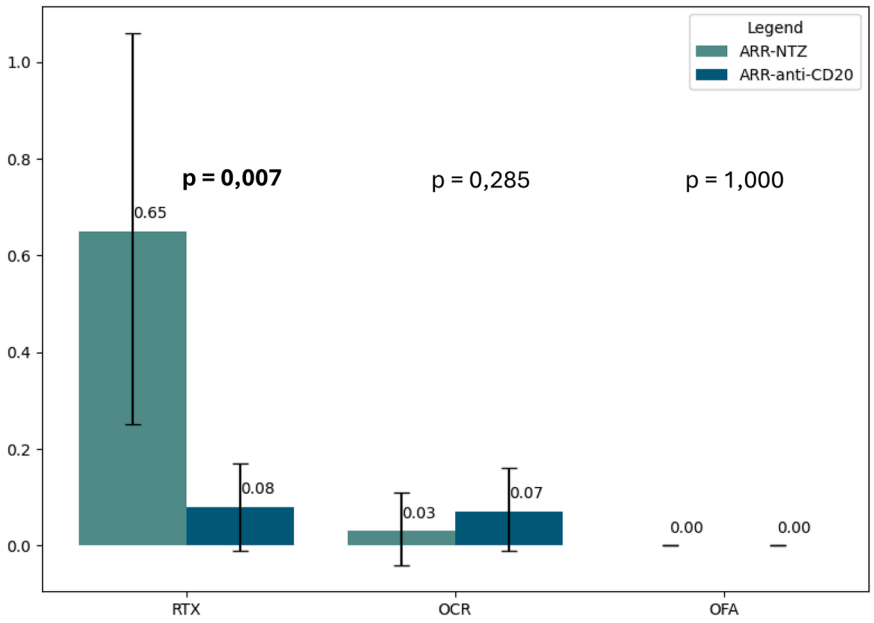

Fig. 1. ARR before and after anti-CD20 therapy
RTX, Rituximab; OCR, Ocrelizumab; OFA, Ofatumumab; ARR-NTZ, annualized relapse rate in the 12 months before transition; ARR-anti-CD20, annualized relapse rate during anti-CD20 treatment.

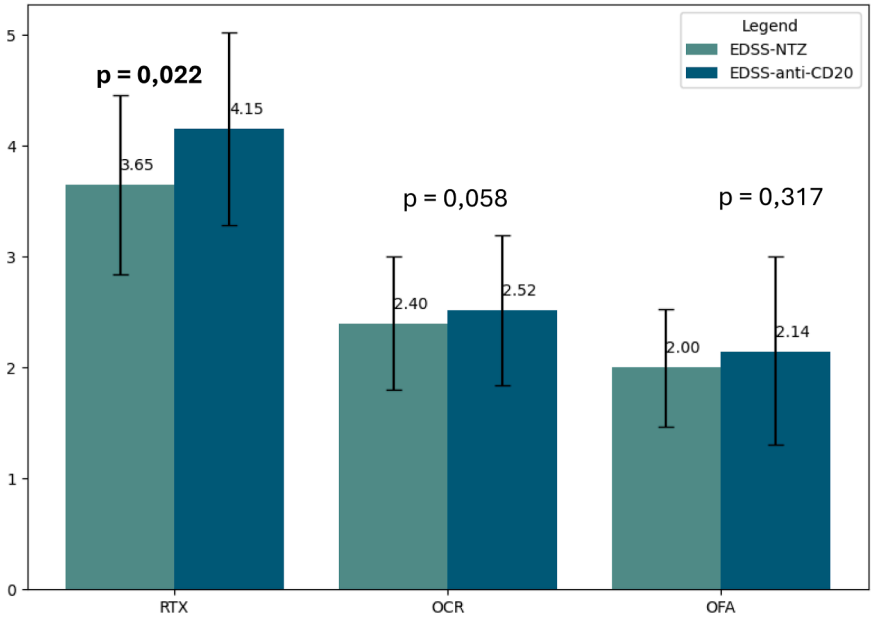

Fig. 2. EDSS before and after anti-CD20 therapy
RTX, Rituximab; OCR, Ocrelizumab; OFA, Ofatumumab; EDSS-NTZ, Expanded Disability Status Scale before transition; EDSS-anti-CD20, Expanded Disability Status Scale at last evaluation with anti-CD20 therapy.

(3,65 vs 4,15; $p = 0022$). Whereas for OCR and OFA no difference in ARR (OCR – 0,03 vs 0,07, $p = 0285$; OFA – 0 vs 0, $p = 1$) and EDSS (OCR – 2,40 vs 2,52, $p = 0058$; OFA – 2,00 vs 2,14, $p = 0317$) appeared.

The variation in ARR before and after transition (Fig. 3) was different between the 3 groups ($p = 0018$), being higher in the RTX patients. However, there were no differences in ARR between anti-CD20 therapies ($p = 0058$).

No difference showed when comparing the EDSS variation between these 3 groups, and EDSS scores remained significantly higher in rituximab-treated patients compared to those on OCR ($p = 0011$), but no different than OFA ($p = 0160$).

In this cohort, 70 % of the disability progression was due to PIRA, having no statistically significant difference between the 3 groups ($p = 0625$).

A survival analysis assessing the time to disease activity (Fig. 4) proved no difference between RTX, OCR and OFA ($p = 0170$).

Of the 59 patients, 13 had to switch from the anti-CD20 therapy to another DMT, 9 from the RTX and 4 from the OCR. Inefficacy was the reason for the switch in 8 patients, safety in 3 patients, and adverse events in 2 patients. Inefficacy was due to relapses in 4 patients (all from RTX), MRI activity in 3 patients (2 from RTX and 1 from OCR), and clinical progression in 4 patients (3 from RTX and 1 from OCR). Safety

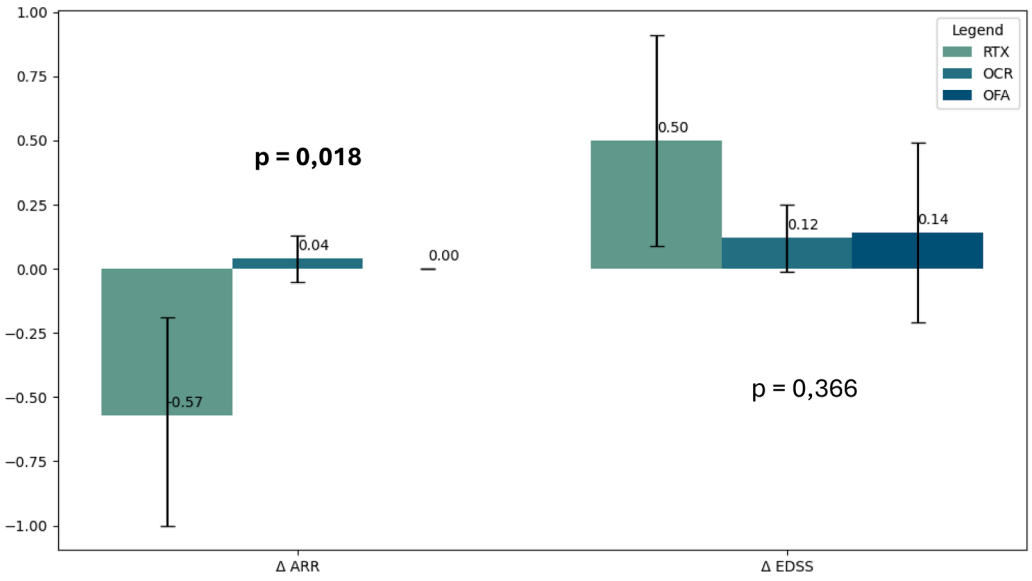

Fig. 3. ARR and EDSS variation before and after anti-CD20 therapy
RTX, Rituximab; OCR, Ocrelizumab; OFA, Ofatumumab; Δ ARR, variation in the annualized relapse rate before and after natalizumab to anti-CD20 transition; Δ EDSS, variation in the Expanded Disability Status Scale before and after natalizumab to anti-CD20 transition.

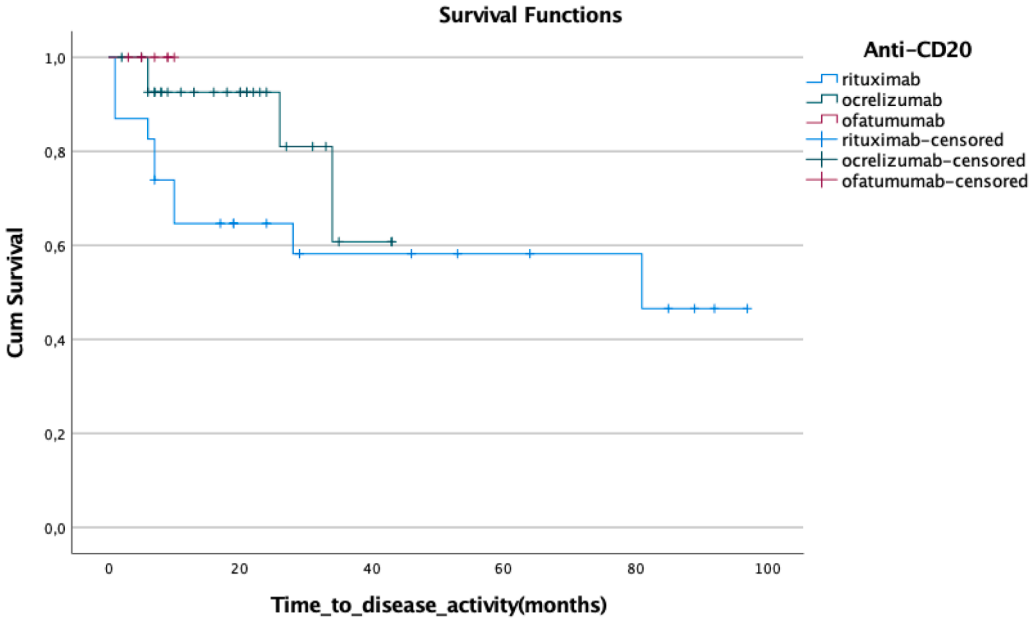

Fig. 4. Kaplan-Meier curves of time to disease activity according to each anti-CD20 therapy.

problems happened with RTX patients, and were related to recurrent urinary infections, thyroid neoplasia, and hypogammaglobulinemia, on three different patients. The adverse events registered for RTX were 2 patients with urinary infections, 1 patient with zoster infection and flu syndrome, and 1 patient with hypogammaglobulinemia. For OCR we registered 1 patient with gingivitis and 1 patient with urinary infection and spondylodiscitis. No adverse events or safety problems were registered for OFA.

4. Discussion

This study aimed to assess whether the anti-CD20 therapies were an effective and safe option for patients requiring discontinuation of NTZ. Firstly, we confirmed that safety concerns were the primary reason for this discontinuation, and inefficacy was only the main reason in a small portion of patients. However, we observed a higher ARR in the group that transitioned to RTX. We believe this is due to the limited availability of high-efficacy treatment options at that time, which led to fewer treatment changes in response to inefficacy. Overall, all the anti-CD20 therapies seem to be an effective choice, with a very low ARR in all subgroups. The ARR of RTX (0.08) and OCR (0.06) was similar to the previously reported in the literature (0.02(6), 0.07(4), respectively). There were no differences in ARR between anti-CD20 therapies.

Despite a low ARR and the significant decrease in the ARR compared to the baseline in the RTX group, these patients experienced significant EDSS progression, likely attributable to the baseline disease profile of these patients, longer disease and treatment duration. In fact, RTX was often used as off-label for patients with more advanced disease and limited effective treatment options—a patient profile that differs significantly from the ones treated in the OCR and OFA era. Indeed, from

the 6 patients that discontinued NTZ due to inefficacy, 5 transitioned to RTX.

Despite that, no significant difference emerged between the three subgroups in the survival analysis concerning time to disease activity. Previous studies show that disease activity after NTZ discontinuation depends not only on the new treatment, but also on the washout period before starting the new drug (Sorensen et al., 2014).

Interestingly, we found that the primary driver of disability progression was PIRA, underscoring the limited impact these therapies have on the chronic pathobiological processes beyond acute focal inflammation, as previously noted with OCR (Ingwersen et al., 2023).

Emerging evidence indicates that inflammation and neurodegeneration are present from the onset of MS, driving disease progression from the early stages through smoldering disease (Filippi et al., 2025).

Our findings align with previous studies demonstrating the efficacy of RTX and OCR following NTZ discontinuation compared to first- and second-line therapies (Zanghì et al., 2021; Zhu et al., 2023; Alping et al., 2016; Lo Re et al., 2015). However, this study offers valuable new evidence on OFA, which has been lacking until now.

We acknowledge some limitations in our study, the sample size as the leading one. Also, the great variability between subgroups, having too different number of patients and disease duration. The OFA subgroup is very small and has a short period of follow-up, limiting the ability to draw definitive conclusions.

5. Conclusion

The anti-CD20 therapies (RTX, OCR, and OFA) appeared to be a safe choice for patients that needed to discontinue NTZ, since patients did not have rebound disease activity and the majority had no disease progression.

In patients experiencing disease progression, PIRA was the primary contributor, emphasizing the critical need for strategies to address smoldering disease in MS management.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Carolina Cunha: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Sara Matos:** Data curation. **Catarina Bernardes:** Formal analysis. **Inês Carvalho:** Data curation. **João Cardoso:** Resources. **Isabel Campelo:** Resources. **Carla Nunes:** Writing – review & editing, Resources. **Carmo Macário:** Writing – review & editing, Resources. **Lívia Sousa:** Writing – review & editing, Resources. **Sónia Batista:** Writing – review & editing, Resources. **Inês Correia:** Writing – review & editing, Methodology, Formal analysis.

Declaration of competing interest

Carolina Cunha, Sara Matos, Catarina Bernardes, Inês Carvalho, João Cardoso and Isabel Campelo have no conflicts of interest to declare. Sónia Batista, Carla Nunes, Carmo Macário, and Inês Correia have received consulting fees from Biogen, Merck Serono, Novartis, Sanofi Genzyme, Bristol Myers Squibb, Roche, and Janssen. Lívia Sousa has received consulting fees from Biogen, Merck Serono, Novartis, Sanofi Genzyme, Janssen and Roche.

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