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CASE SERIES

Dental Adverse Effects of Anti-CD20 Therapies

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ABSTRACT

Introduction: Over the past few years, anti-CD20 therapies like rituximab, ocrelizumab or ofatumumab have seen an increase in interest in the treatment of neurological autoimmune disorders such as multiple sclerosis (MS), neuromyelitis optica spectrum disorders (NMOSD), or resistant forms of generalized myasthenia gravis (MG). They are generally well-tolerated, but recent reports have highlighted severe dental disorders in patients undergoing anti-CD20 therapies. The aim was to describe a series of cases and to compare with the available scientific literature.

Methods: We reviewed 6 patient cases with dental disorders during anti-CD20 therapy that were reported to the pharmacovigilance center. A disproportionality analysis was also conducted on Vigibase® for each anti-CD20 and each adverse effect described in the cases.

Results: Six cases of dental and gingival conditions in relatively young patients were reported (median age: 40.5 years old [min: 34; max: 79]). Oral conditions were developed in four patients with MS treated with ocrelizumab and in two patients receiving rituximab (one patient with MG and one with NMOSD). The onset of oral conditions ranged from 10 days to 2 years after treatment initiation. Notably, all patients treated with ocrelizumab experienced gingival recession. Various dental pathologies were observed, including tooth loss, dental pain, caries, brittle teeth, dental fractures, dental abscesses, and periodontitis.Analysis of Vigibase® revealed 284 worldwide cases of dental and gingival conditions under ocrelizumab, 386 cases under rituximab, and 80 under ofatumumab. Significant associations were found between these therapies and dental pathologies, particularly tooth abscesses and infections.

Conclusion: To our knowledge, this is the first case series reporting dental conditions developed in patients long-term treated with anti-CD20 treatments. This issue, literature data, and Vigilyze® analysis might be considered a safety signal that necessitates being confirmed with more robust data, such as a retrospective study with a control group. Meanwhile, proactive measures are essential like frequent dental checkups and dental hygienic measures to prevent oral health problems associated with anti-CD20 therapies.

Hélène Bartak and Tasnim Fareh have contributed equally to this work.

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Keywords: Multiple sclerosis; Anti-CD20; Ocrelizumab; Rituximab; Immunosuppressants; Dental and gingival conditions; Dental infections; Oral dysbiosis

Key Summary Points

Why carry out this study?

Several patient cases with dental and gingival disorders during anti-CD20 therapy for multiple sclerosis, neuromyelitis optica spectrum disorders, or resistant forms of generalized myasthenia gravis were reported to the pharmacovigilance center by the Multiple Sclerosis tertiary center of the Nice University Hospital. Moreover, recent reports have highlighted severe dental disorders in patients undergoing anti-CD20 therapies. Thus, we decided to underscore these issues in this case series.

In general, few are known about dental side effects during treatments, and the information on these side effects may be beneficial to clinicians and patients.

The hypothesis was that anti-CD20 therapies may induce dental and gingival disorders whereas these side effects were unexpected (not described in the Summary of Product Characteristics of ocrelizumab, rituximab, or ofatumumab), and have not been identified in clinical trials or as a post-marketing safety signal until now.

What was learned from the study?

The case series together with the analysis of the available data and literature indicated a plausible connection between dental and gingival pathologies and the prolonged use of anti-CD20 therapies. Tooth abscesses and infections were the Preferred Terms significantly associated with the three anti-CD20 therapies. However, gingival recession seemed to be associated more explicitly with ocrelizumab.

This study prompted us to formulate the hypothesis that long-term anti-CD20 therapy, causing B-cell depletion and IgA deficiency, may induce a shift in bacterial flora (dysbiosis), potentially leading to chronic inflammation and resulting in periodontal pathologies such as gingival recession, gingivitis, periodontitis or bone loss. Additionally, infectious reactivation seemed to be possible.

Proactive measures seem to be essential to prevent oral health problems under anti-CD20 therapies, such as frequent dental checkups before the initiation of treatment, during treatment and following discontinuation, associated with dental hygienic measures.

INTRODUCTION

Over the past few years, anti-CD20 therapies have seen an increase in interest in the treatment of neurological autoimmune disorders such as multiple sclerosis (MS), neuromyelitis optica spectrum disorders (NMOSD), or resistant forms of generalized myasthenia gravis (MG).

Currently, three anti-CD20 are used on or off-label, depending on specific diseases or national authorizations. Rituximab, an anti-CD20 chimeric monoclonal antibody, is the oldest one and has shown efficacy in many autoimmune disorders [MS [1, 2] MG [3], NMOSD [4]]. Ocrelizumab, an anti-CD20 humanized monoclonal IgG1 antibody, is indicated in active relapsing remitting MS and primary progressive MS [5], while ofatumumab, a fully human antibody that also recognizes CD20, is used in active relapsing forms of MS [6, 7]. Anti-CD20 therapies are generally well-tolerated and have similar toxicity profiles. Their main adverse effects are infectious risks arising from their B cell depletion mechanism of action [8].

Despite the common occurrence of dental conditions in the general population, recent reports have highlighted severe dental disorders in patients undergoing anti-CD20 therapies. We report six cases and review the available scientific literature.

METHODS

With the collaboration of the MS tertiary center of the Nice University Hospital, we reviewed the patient cases with dental disorders during anti-CD20 therapy that were reported to the pharmacovigilance center. On November 5th, 2023, a disproportionality analysis was conducted on Vigibase®, the World Health Organization's (WHO) pharmacovigilance database, the largest worldwide database of reported side effects. From this database, we estimated the Information Component (IC), a measure of the disproportionality between the observed and the expected reporting of an adverse effect (AE) under a particular medication. A positive IC value indicates that one specific drug-AE pair is reported more often than expected based on all the reports in the database. For each anti-CD20 (rituximab, ocrelizumab, and ofatumumab) and each adverse effect described in the cases below, the information component (IC) was estimated. Here, we reported the IC025, the lower 95% confidence interval bound for IC value. Positive IC025 is the conventional threshold for statistical significance in signal detection.

RESULTS

We report 6 cases of dental and gingival conditions impacting the quality of life in relatively young patients (median age: 40.5 years old [min: 34; max: 79]) from one week to several years after initiating anti-CD20 therapy for neuroinflammatory diseases. Oral conditions were developed in four patients with MS treated with ocrelizumab (cases 1–4) and in two patients receiving rituximab [one patient with MG (case 5) and one with NMOSD (case 6)] (Table 1).

Ocrelizumab Cases

Patients had been diagnosed with MS several years before starting ocrelizumab treatment (median: 4.5 years [3–21]), which was administered every six months according to the standard schedule. Three of the patients had risk factors for dental pathologies, such as smoking, cannabis consumption, and concomitant medication, such as psychotropics that can dry out the mouth [9, 10], antecedents of corticotherapy, and two patients had a history of caries or aphthae. None of the patients had any specific severe dental history, and they all had a consultation with a panoramic dental X-ray before starting the immunosuppressive drug. The dental conditions appeared from 10 days to 2 years after the treatment initiation. All these patients experienced a gingival recession. Two of the patients also suffered from tooth loss and dental pain as a result of the gingival recession. Other dental problems, caries, brittle teeth, dental fractures, dental abscesses, and periodontitis were also reported. The two patients who lost teeth received crowns, implants, or bridges. Antibiotics were prescribed for dental abscesses. One patient had a gel application and underwent scaling to consolidate the gum. A gum graft was proposed for two patients. Ocrelizumab continues for the four patients with close dental monitoring (biannual dental checkup) and rigorous hygienic routines. Two patients recovered with sequelae, and two patients did not recover.

Rituximab Cases

Rituximab was administered at a dose of 1000 mg once to twice a year for twelve and six years for the patients with MG and NMOSD, depending on CD19+ CD27+ lymphocyte repopulation [3, 11]. Both patients had a history of dental pathologies, one with a full dental bridge and the other with several previously treated teeth. The onset of dental conditions ranged from 6 to 12 years after treatment initiation. Both patients reported dental pain, with decayed roots due to maxillary teeth infection associated with a loose dental bridge in one case

Table 1 Patient's details

Case	1	2	3	4	5	6
Age	39	37	34	42	79	55
Sex	Female	Male	Male	Female	Female	Female
Neurological disease	MS	MS	MS	MS	MG	NMOSD
Year of first diagnosis	2014	2015	2013	1999	1998	2012
Treatment	OCR	OCR	OCR	OCR	RTX	RTX
Date of treatment onset	2018	2018	2018	2020	2006	2012
Previous oral condition	No	Sporadic caries and aphthae	No	Sporadic caries	Full dental bridge	16 teeth previously treated
Oral diseases after anti-CD20 treatment	Dental caries Gingival recession Dental pain Teeth brittle Dental fracture Dental abscesses Lost teeth	Gingival recession Dental pain Periodontitis Lost teeth	Gingival recession	Gingival recession Dental pain	Dental pain Decayed roots Maxillary teeth infection The dental bridge came loose	Dental pain Numerous apical infectious dental cysts
Time to onset	One year	Ten days after each injection	Two years	Two years	Twelve years	Six years

Table 1 continued

Case	1	2	3	4	5	6
Dental care	Crowns Implant Antibiotics Biannual dental checkup Rigorous hygienic routine Gum graft proposed	Gel Bridge Scaling Biannual dental checkup Rigorous hygienic routine	Biannual dental checkup Rigorous hygienic routine	Biannual dental checkup Rigorous hygienic routine Gum graft with orthodontic treatment planned	Maxillary teeth extraction	Maxillary teeth extraction
Evolution	Resolved with sequels	Resolved with sequels	Unresolved	Unresolved	Resolved with sequels	Resolved with sequels
Other risk factors	Venlafaxine, mirtazapine (dryness of the mouth) Tobacco Corticotherapy (methylprednisolone 1 g/day three days in 2018)	Tobacco Cannabis Several corticosteroid boluses (methylprednisolone 1 g/day three days in 2018)	Tobacco Several corticosteroid boluses (methylprednisolone 1 g/day three days in 2018)	None	None	Immunodeficiency Several corticosteroid boluses
Naranjo imputability score [12, 13]	2 (possible)	4 (possible)	2 (possible)	5 (probable)	5 (probable)	2 (possible)

MS multiple sclerosis, *MG* myasthenia gravis, *NMOSD* neuromyelitis optica spectrum disorders, *OCR* ocrelizumab, *RTX* rituximab

and numerous apical infectious dental cysts in the other case. One of the patients had a history of corticotherapy as a risk factor and hypogammaglobulinemia with grade 2 lymphopenia and no longer CD19+ lymphocytes on immunological test results despite rituximab discontinuation. The treatment for these two patients consisted of tooth extraction. Both recovered with sequelae of maxillary teeth extraction.

Disproportionality Analysis

We queried Vigibase® for worldwide cases of dental and gingival conditions similar to those described in the cases above under ocrelizumab, rituximab, and ofatumumab. We found 284 cases under ocrelizumab, 386 cases under rituximab, and 80 under ofatumumab. For ocrelizumab, most dental conditions were significant (Table 2).

The most significantly associated dental pathologies for rituximab were "tooth infection," "tooth abscess," and "tooth fracture." At least, for ofatumumab, significant IC025 was observed for "dental abscess", "tooth infection", and "toothache".

DISCUSSION

Gum recession or dental problems have not been identified in clinical trials or as a post-marketing safety signal until now. They are unexpected AE and not described in the Summary of Product Characteristics of ocrelizumab [5], rituximab [12], or ofatumumab [7].

In our case series, four patients were treated with ocrelizumab and two with rituximab. All the patients under ocrelizumab suffered from gum recession. Gingival recession is the tooth root exposure due to gum tissue loss and gingival margin retraction. It can cause tooth sensitivity, pain, and aesthetic problems. Besides, none of the patients under ocrelizumab described dental issues before the onset of the treatment. Two patients had sporadic caries or aphthae, and two others reported no history of dental conditions. Surprisingly, the onset of severe dental problems occurred 1 to 2 years after the initiation of ocrelizumab therapy, with one case showing emergent symptoms approximately ten days after each injection. The chronology of the events suggests a possible causality link with the anti-CD20 treatments. The Naranjo score, a tool to assess the probability of a causal relationship between a drug and an AE [13, 14] yielded a possible imputability for four cases (score = 2 for cases 1, 3 and 6; score = 4 for case 2) and a probable imputability for two patients (score = 5 for cases 4 and 5).

MS is a chronic inflammatory disease of the central nervous system that affects the myelin sheath of nerve fibers. MS patients often experience various symptoms, such as fatigue, spasticity, pain, and cognitive impairment. Some studies indicate that MS can cause oral disorders because of xerostomia (dry mouth) and other symptoms that affect the face, muscles, and energy levels, making it hard to take care of oral hygiene [10, 15–17]. These factors can increase the risk of dental and gingival conditions, such as caries, periodontal disease, and infections. A systematic review suggested that MS patients are more prone to periodontal disease (gum infection) than healthy people [18]. Still, a recent study did not find a clear association between MS and most oral health conditions [19]. Both studies agreed that there is a need for more high-quality research to establish the evidence in this area. Therefore, the potential implication of MS in the described adverse effects introduces a confounding factor that cannot be overlooked.

Noticeably, the patients of the above case series under anti-CD20 had neurological autoimmune disorders for many years, and dental problems developed only after anti-CD20 treatment initiation.

We can argue that the four patients under ocrelizumab presented other risk factors for oral conditions, such as tobacco, cannabis, and exposure to drug-inducing potential xerostomia as venlafaxine [9, 10]. However, these risk factors were already present long before the onset of the treatment and the described dental conditions. As for chronic inflammatory diseases, they may have contributed to the occurrence of

Table 2 Number of declared dental adverse effects and estimated IC025 from the WHO's pharmacovigilance database (Vigibase®) for each anti-CD20 therapy

Dental diseases (preferred term)		Ocrelizumab, *n* = 284	Rituximab, *n* = 386	Ofatumumab, *n* = 80
Tooth fracture	*n*	52 (18.3%)	59 (15.3%)	7 (8.7%)
	IC025	**1.7**	**0.2**	− 1.2
Tooth infection	*n*	61 (21.5%)	108 (28%)	18 (22.5%)
	IC025	**1.7**	**0.9**	**0.4**
Tooth abscess	*n*	40 (14.1%)	83 (21.5%)	17 (21.2%)
	IC025	**1.3**	**0.7**	**0.5**
Gingival recession	*n*	12 (4.2%)	6 (1.5%)	4 (5%)
	IC025	**1.2**	− 1.8	− 0.4
Loose tooth	*n*	14 (4.9%)	8 (2.1%)	1 (1.3%)
	IC025	**1.1**	− 1.7	− 4.5
Teeth brittle	*n*	7 (2.5%)	5 (1.3%)	1 (1.3%)
	IC025	**0.8**	− 1.4	− 3.5
Toothache	*n*	52 (18.3%)	52 (13.5%)	25 (31.2%)
	IC025	**0.8**	− 1.0	**0.3**
Periodontitis	*n*	13 (4.6%)	21 (5.4%)	2 (2.5%)
	IC025	**0.8**	0	− 2.6
Dental cyst	*n*	0 (0%)	2 (0.5%)	0 (0%)
	IC025	–	− 1.3	–
Tooth loss	*n*	33 (11.6%)	42 (10.9%)	5 (6.3%)
	IC025	0	− 1.4	− 2.8

n number, *IC025* Information Component (5% lower bound)
Positive IC025 is the conventional threshold for statistical significance in signal detection

oral AEs, but they are not likely to be the leading cause.

The prescription of immunomodulators or immunosuppressants, standard in treating MS, raises a potential risk of increased dental and gingival infections among patients [20, 21]. This risk is further compounded when considering a patient's history of corticosteroid administration [22, 23]. Research indicates that individuals undergoing long-term disease-modifying treatments (DMT) for MS exhibit a higher vulnerability to pathological changes in the oral cavity compared to their healthy counterparts [10, 16, 24]. Furthermore, the nature of oral pathologies varies depending on the specific DMT employed, as illustrated in Table 3, which outlines the diverse adverse effects of different MS drugs.

A disproportionality analysis of the WHO's pharmacovigilance database (Table 2) identified tooth abscesses and infections as Preferred Terms significantly associated with the three anti-CD20 therapies. This could be attributed to a higher rate of infectious disease reporting, considering their frequency and expectation as infectious adverse effects under immunosuppressant therapies. Interestingly, gingival

Table 3 Oral adverse effects under different drugs indicated in MS with their frequency extracted from the summary of product characteristics

Drugs used in MS	Oral adverse effects	Frequency
Ofatumumab [7]	Oral herpes	≥ 1/100, < 1/10
Ocrelizumab [5]	Oral herpes	
Alemtuzumab [25]	Stomatitis	≥ 1/1000, < 1/100
	Oral herpes	≥ 1/10
	Tooth infection	≥ 1/100, < 1/10
	Oral candidiasis	
Cladribine [26]	Oral herpes	
Teriflunomide [27]	Tooth infection	
	Toothache	
Glatiramer acetate [28]	Tooth abscesses	
	Caries	
Dimethylfumarate [29]	No oral disease was reported	–
Fingolimod [30]		
Mitoxantrone [31]		
Natalizumab [32]		
Ponesimod [33]		

recession is an AE significantly more reported with ocrelizumab (IC025 = 1,2).

The literature retrieved two cases of dental and gingival conditions, including gingival recession under ocrelizumab.

In the first case [34], a 28-year-old woman with relapsing–remitting MS undergoing ocrelizumab treatment exhibited necrotizing periodontitis (a severe form of gum infection) in the months following the initiation of therapy. Notably, she experienced a recurrence of symptoms shortly after a new dose of ocrelizumab, alongside generalized recession and documented bone loss as revealed by her orthopantomogram. It is pertinent to mention that this case closely mirrors case 2 of our series regarding chronology, semiology, and evolution.

The second case [10], recently published, features a 40-year-old woman receiving 600 mg IV ocrelizumab every six months, concurrently with oral prednisolone at a dosage of 20 mg/day for MS diagnosed in 2020. Notably, she displayed signs of MS for nine years. Unfortunately, the duration of her ocrelizumab treatment and the onset of oral conditions remain unspecified. These conditions encompassed localized gingival inflammation, indications of necrotizing ulcerative gingivitis, gingival recession, halitosis, and bone loss.

Both cases involved women with MS who also had smoking habits and stress factors, and their oral conditions significantly improved after treatment with personal and professional hygiene.

We did not find similar case reports with rituximab and ofatumumab.

The overall differences in the reported dental adverse effects between the anti-CD20 therapies can stem from a range of causes. Among them,

we can mention the treated populations. In fact, anti-CD20 treatments do not all have the exact same indications, and recommendations can vary across countries [35]. Moreover, the route of administration can be another factor (intravenous injections for ocrelizumab and rituximab; subcutaneous injections for ofatumumab). Bioavailability is less important with subcutaneous administration than intravenous injection, and may limit adverse effects [36, 37]. Furthermore, studies with mice models have observed a better lymph node targeting with SC administrations of anti-CD20 therapies [38, 39]. The varying adverse effects observed can also be a consequence of the structural differences between the molecules. Ofatumumab is a fully human antibody, whereas ocrelizumab is humanized and rituximab chimeric. Ocrelizumab is expected to have higher immunogenicity than ofatumumab but lower immunogenicity than rituximab. Thus, not only do the molecules have not the same immunogenicity [40], but also each of these targets different epitopes on anti-CD20, inducing different immune responses and mechanisms of action. For instance, although the major mechanisms of B cell depletion by these antibodies occur through Complement Dependent Cytotoxicity (CDC) and Antibody-Dependent Cellular Cytotoxicity (ADCC), rituximab and ofatumumab are known to trigger greater CDC, whereas ADCC predominates over CDC activity in ocrelizumab [36]. Therefore, these different characteristics could partly explain the various dental adverse effects observed with anti-CD20 therapies.

Identifying non-infectious conditions like gingival recessions or bone loss in the reported case series and existing literature prompts an investigation into mechanisms beyond bacterial infections. Anti-CD20 therapies are recognized for inducing complete B cell depletion [41]. They bind specifically to the CD20 transmembrane antigen, a non-glycosylated phosphoprotein located on pre-B and mature B lymphocytes, causing a rapid decrease in circulating B cells and immunoglobulin levels without affecting lymphoid stem cells or plasma cells. Although some studies suggest that the reduction in B cells caused by anti-CD20 treatments can reverse dysbiosis in the microbiome of MS patients [42], it is essential to acknowledge that B cells contribute to bacterial homeostasis through the production of IgA antibodies [43, 44] Consequently, the long-term consequences of B cell depletion and IgA deficiency may lead to dysbiosis [45–48].

Furthermore, emerging evidence proposes that dysbiosis can trigger chronic inflammation, contributing to periodontal pathologies such as gingivitis, periodontitis, gingival recession, and bone loss [49–53]. In the case report [34], the patient exhibited elevated bacterial counts associated with necrotizing periodontitis.

Therefore, we can formulate the hypothesis that long-term anti-CD20 therapy may induce a shift in bacterial flora, potentially leading to chronic inflammation and resulting in gum recession or even bone loss, as evidenced in the aforementioned cases and literature. Additionally, the possibility of infectious reactivation cannot be discounted, especially in patients with multiple periodontitis or abscesses, a phenomenon potentially exacerbated by B lymphocyte depletion induced by anti-CD20 biotherapies [8].

If oral infectious diseases, such as dental abscesses, emerge as potential adverse effects of anti-CD20 therapies, the gingival recession appears to be associated more explicitly with ocrelizumab. While these oral disorders undoubtedly impact the patient's quality of life, they do not meet the criteria of severe events (i.e., fatal, life-threatening, persisting, and significantly disabling). This distinction may contribute to a potential underreporting of these adverse events.

Ultimately, oral conditions achieved stabilization in 4 out of our 6 cases, and in the two instances documented in the literature, this positive outcome was associated with patients adhering to regular dental checkups and care while concurrently receiving ocrelizumab or rituximab treatment. These cases underscore the significance of incorporating dental checkups before initiating treatment and as a consistent part of ongoing care for patients undergoing anti-CD20 therapies. This proactive dental monitoring is crucial for averting

potential dental complications in individuals receiving these therapies.

The compilation of cases we have presented, along with literature analysis and signal evaluation, strongly indicates a plausible connection between dental and gingival pathologies and the prolonged use of anti-CD20 therapies, such as ocrelizumab or rituximab. The depletion of B cells induced by these immunosuppressive treatments and IgA deficiency may lead to infectious diseases and disturbances in bacterial flora, culminating in chronic inflammation and dental disorders. However, while providing valuable insights, our case series has limitations that warrant considerations in interpreting the findings. The spontaneous notification case design poses challenges, such as introducing recall bias and limiting data accuracy and heterogeneity among patients' demographic data. The relatively small number of cases reported diminishes the statistical power and generalizability, necessitating caution in drawing broad conclusions.

There is also the possibility of underreporting dental adverse events, as not all patients may have sought or received dental care during the study period. This could result in a skewed representation of the prevalence and severity of observed conditions.

To establish a robust understanding of this potential link, further high-quality studies must be conducted, considering potential confounding factors. Confirmation of this safety signal would warrant the inclusion of relevant information in the precautions and warnings section of the product characteristics summary, alongside efforts to raise awareness among both prescribers and patients.

CONCLUSION

To our knowledge, this is the first case series reporting dental conditions developed in patients long-term treated with anti-CD20 treatments. This issue, literature data, and Vigilyze® analysis might be considered as a safety signal that necessitates being empowered and confirmed with more robust data, such as a retrospective study with a control group.

Meanwhile, proactive measures are essential. Patients should undergo thorough dental checkups before anti-CD20 therapy initiation, during treatment, and following discontinuation to prevent or promptly address any emerging dental disorders. Additionally, the systematic implementation of complementary dental hygiene measures, including regular brushing, interdental cleaning, and annual scaling, is remarkably advised within this patient population. Collectively, these precautions contribute to the proactive management of potential oral health challenges associated with anti-CD20 therapies.

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Declarations

Conflict of Interest. The authors declare that they have no conflict of interest but Christine Lebrun-Frenay is an Editorial Board member of Neurology and Therapy. Christine Lebrun-Frenay was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

Ethical Approval. No personal information or identifiable patient details are included in the manuscript. Therefore, there is no need for patient consent as the content does not disclose any confidential or sensitive information. Additionally, we would like to confirm that our case series did not involve any human subjects directly. Consequently, Institutional Review Board (IRB) approval was not sought for this particular study.

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