# CD20-mediated B cell depletion in acetylcholine receptor autoantibody-positive myasthenia gravis

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ABSTRACT

Myasthenia gravis (MG) is an autoimmune disorder characterized by muscle weakness and fatigue, mediated in the majority of cases by IgG1 autoantibodies targeting the acetylcholine receptor (AChR). As AChR autoantibodies have been shown to be pathogenic, therapies targeting B cells have been applied in patients with AChR MG for more than a decade. Recently, a phase 2 trial of the CD20-targeting agent, rituximab, in AChR MG unfortunately failed to meet its primary endpoint. Converging data however from non-randomized clinical series, some of which with more participants than the phase 2 trial, as well as a randomized trial in new onset disease support efficacy of rituximab in AChR MG, especially early onset disease. In this opinion article, we summarize both clinical data and mechanistic principles on the use of CD20 depletion therapy in AChR MG, which we believe lend support to the argument that CD20 depletion can still be a useful therapeutic strategy for patients with AChR MG.

**Key words:** acetylcholine receptor (AChR), myasthenia gravis, autoantibody, rituximab, muscle specific kinase (MuSK).

## Introduction

Myasthenia gravis (MG) is an autoimmune disorder characterized by muscle weakness and fatigability, most commonly mediated by autoantibodies targeting extracellular components of the neuromuscular junction (NMJ), the acetylcholine receptor (AChR), muscle-specific kinase (MuSK), and low-density lipoprotein receptor–related protein 4 (LRP4) [1]. Serum AChR antibodies are found in up to 85% of MG cases and AChR MG can initiate as ocular with involvement limited to ophthalmic muscles [2,3]; early onset AChR MG is associated with thymic hyperplasia. MuSK MG is associated with bulbar symptoms (e.g. dysarthria, dysphagia), lack of thymic involvement, resistance to symptomatic treatment with pyridostigmine and an excellent response to CD20 B cell depletion, thus underlining mechanistic differences between AChR and MuSK MG [3–8]. In general, therapies of MG include symptomatic treatment with cholinesterase inhibitors in the case of AChR MG [9], and immunotherapy. In life-threatening myasthenic crises, where respiratory muscles can be affected, acute therapy includes intravenous immunoglobulin and plasma exchange [10]. Chronic immunotherapy can be divided into broadly-acting immunosuppressants such as corticosteroids [11], and non-steroid immunosuppressants (azathioprine, mycophenolate, methotrexate, cyclosporine or tacrolimus) [12–16]; and targeted immunosuppression with CD20-mediated B cell depletion, inhibition of the complement pathway, and antagonists of the neonatal Fc receptor [17,18]. Finally, thymectomy has been shown to be moderately effective in a phase 3 trial and can be considered in young patients with non-thymomatous AChR MG [19].

## Pathophysiology

MG is a prototypic antibody-mediated autoimmune disease. Different mechanisms underlie the presence of AChR and MuSK autoantibodies, and these autoantibodies do not typically co-occur [20]. The more prevalent AChR autoantibodies are predominantly of the IgG1 subclass and can: 1. block the acetylcholine binding site on the receptor, 2. cross-link the receptor leading to its internalization, and 3. activate complement-dependent cytotoxicity (CDC) as well as antibody-dependent cytotoxicity (ADCC) [21]. Activation of complement leads to formation of the membrane attack complex that both damages and reduces the surface area of the post-synaptic membrane, thereby decreasing the density of AChR molecules and voltage-gated sodium channels, and hence, the amplitude of endplate potentials and the efficiency of the neuromuscular transmission.

The majority of AChR autoantibody-seronegative MG patients produce antibodies against MuSK, which is found in the post-synaptic membrane of the NMJ, along with AChR. MuSK is part of the agrin-induced pathway leading to clustering of AChRs and associated synaptic differentiation, consequently its targeting by autoantibodies results in impaired AChR clustering and affects NMJ function causing MG symptoms [22]. MuSK autoantibodies are mainly of the IgG4 subclass. Characteristics of IgG4 antibodies include Fab-arm exchange, functional monovalency resulting in

a lack of ability to cross-link the antigen, and a limited ability to initiate complement and ADCC [23,24]. These characteristics notwithstanding, MuSK autoantibodies are pathogenic (just like AChR autoantibodies), as shown by passive transfer and active immunization studies in laboratory animals [25].

One particular feature of the immunopathology of autoantibody-mediated disorders (including MG) is varying longevity of the cells producing the pathogenic autoantibodies [26,27]. In AChR MG, cultured bone marrow cells produced higher concentrations of AChR autoantibodies compared to lymphocytes in the peripheral blood, thymus, and lymph node, thus providing direct evidence for long-lived plasma cell (LLPC) involvement in autoantibody production, as these typically reside in the bone marrow. Moreover, the presence of germinal centers in the thymus of early onset AChR MG patients underscores their ability to produce AChR-specific LLPCs, as these are commonly the products of germinal center reactions. In MuSK MG however, autoantibody-secreting B cells appear to be much shorter-lived: depletion of their immediate progenitors, CD20+ memory cells, is succeeded by a rapid decline of mostly CD20- short-lived autoantibody-producing cells (termed plasmablasts) and, consequently, a rapid decline in MuSK autoantibody titers, as observed in MuSK-MG patients treated with rituximab [28–31].

## CD20-specific monoclonal antibodies as a therapeutic strategy in MG

Given the central role of B cells in the pathophysiology of the disease, depleting B cells or suppressing B cell function can target immunopathology and result in clinical improvement. CD20 is a 33-37 kDa transmembrane protein that regulates calcium influx and thereby signaling pathways involved in B cell differentiation into antibody-secreting cells [32]. It is expressed during several stages of B-cell maturation (**Figure 1**), i.e. in pre-B cells and mature B cells, not including stem cells and plasma cells, and is therefore an attractive target for monoclonal antibody-based therapy [33]. B cells targeted by CD20-specific monoclonal antibodies are eliminated via three main mechanisms: programmed cell death/apoptosis, complement-dependent cytotoxicity (CDC), or antibody-dependent cellular cytotoxicity (ADCC) [34]. Rituximab is a 1st generation chimeric monoclonal antibody (IgG1κ), engineered by fusing a murine Fab with a human Fc domain [35]. Its elimination half-time is estimated to be 20 days, which may vary according to sex, body weight and renal function.

## CD20-mediated B cell depletion in AChR MG

Several early, uncontrolled mostly retrospective studies support the safety and efficacy of rituximab in AChR autoantibody-seropositive MG [36–41,28,42–60] (**Table 1**). Patients were typically followed for 6, 12 or even 24 months, and were evaluated both clinically, with the use of scales such as the Myasthenia Gravis Foundation of America–post-intervention status (MGFA-PIS), the quantitative MG (QMG) score, the manual muscle testing (MMT) score, as well as serologically. These collective studies demonstrated clinical improvement and either stability or mild decline in AChR autoantibody titers, and all studies confirmed that rituximab is a safe and well-tolerated therapeutic strategy. Several of these uncontrolled studies included more than 15 patients without producing different results than the smaller studies [43,44,49,53,55,56].

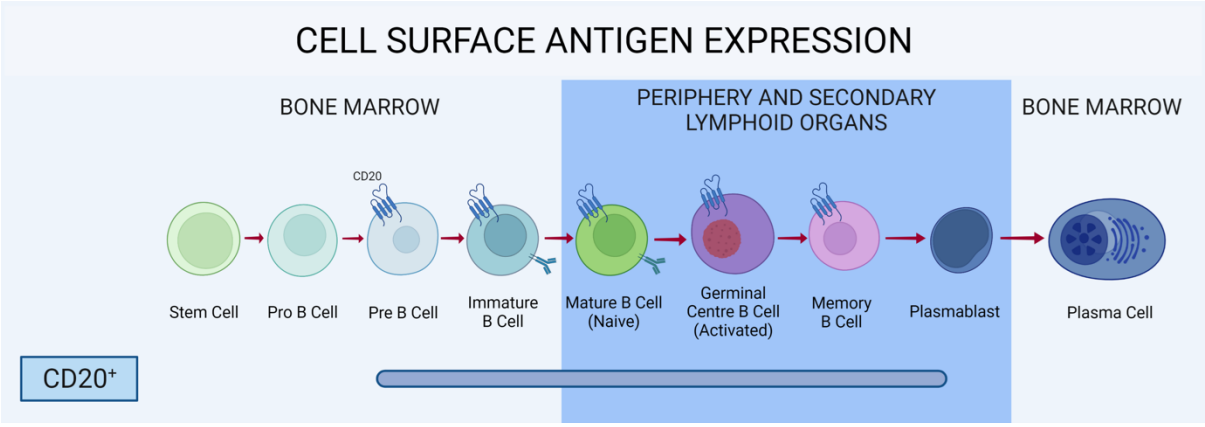


**Figure 1.** Expression of cell surface antigens through B cell maturation. CD20 is not present on plasma cells, pro B-cells and stem cells (plasmablasts being CD20+/-). Figure created with Biorender.com.

**Table 1.** Studies of CD20-mediated B cell depletion in AChR MG.

| AUTHOR | YEAR | N | TYPE OF STUDY | MAIN OUTCOMES |
|---|---|---|---|---|
| Piehl et al. [65] | 2022 | 45 | RCT (vs. placebo), double-blind, phase 2 | QMG score <4 in 71% of treated patients (p=0.007) |
| Heckmann [60] | 2022 | 10 | Retrospective, uncontrolled | 70% of patients reduced prednisone |
| Castiglione et al. [59] | 2022 | 8 | Retrospective, uncontrolled | No relapses during at least 24 months of follow-up |
| Nelke et al. [62] | 2022 | 57 | Retrospective controlled (vs. eculizumab) | Unchanged QMG in patients receiving RTX at 24 months.<br>Both treatments reduced daily prednisone similarly after 24 months (P=0.89) |
| Du et al. [58] | 2022 | 13 | Retrospective, uncontrolled | All patients achieved a MGFA-PIS of minimal manifestations |
| Ramdas et al. [57] | 2022 | 8 | Retrospective, uncontrolled | 60% of patients achieved stable remission. |
| Nowak et al. [66] | 2021 | 52 | RCT (vs. placebo), double-blind, phase 2 | 60% of patients on RTX achieved a steroid-sparing effect, as compared to 56% in the placebo arm (p=ns) |
| Doughty et al. [56] | 2021 | 28 | Retrospective, uncontrolled | 68% of patients (that were all >65) achieved a MGFA-PIS of minimal manifestations |
| Brauner et al. [61] | 2020 | 60 | Retrospective, controlled (several subgroups, early vs. late RTX) | 76% of patients receiving RTX achieved a QMG score of 2 or lower. Shorter time to remission for RTX in early onset vs. refractory MG (p=0.009). |
| Dos Santos et al. [55] | 2020 | 20 | Prospective, uncontrolled | 90% of patients achieved a MGFA PIS of I or better. |
| Sahai et al. [54] | 2020 | 7 | Retrospective, uncontrolled | All 7 late-onset MG patients significantly reduced or discontinued maintenance medications. |
| Litchman et al. [53] | 2020 | 17 | Retrospective, uncontrolled | 70.6% of patients achieved clinical remission- |
| Lu et al. [52] | 2020 | 12 | Prospective, uncontrolled | Median decrease in QMG score from 18.3 (baseline) to 8.4 (P <0.001) |
| Roda et al. [51] | 2019 | 10 | Retrospective, uncontrolled | 80% of refractory patients reduced their steroid dosage by 9.6mg on average |
| Choi et al. [50] | 2019 | 9 | Retrospective, uncontrolled | 65% of patients achieved a MGFA-PIS of minimal manifestations or better |
| Topakian et al. [49] | 2019 | 39 | Retrospective, uncontrolled | 35.9% of patients achieved clinical remission |
| Jing et al. [48] | 2019 | 14 | Retrospective, uncontrolled | Mean decrease in QMG score by 6.6 |
| Singh et al. [47] | 2019 | 6 | Retrospective, uncontrolled | All patients achieved a MGFA-PIS of at least minimal manifestations-2. |
| Beecher et al. [46] | 2018 | 10 | Prospective, uncontrolled | Mean MMT score reduction from 10.3 to 5.5 (P = 0.018) |
| Landon-Cardinal et al. [45] | 2018 | 12 | Retrospective, uncontrolled | 2 patients presented an improvement of >18 points on MMS at 12-months.<br>55% of patients improved their MGFA-PIS |
| Robeson et al. [44] | 2017 | 16 | Retrospective, uncontrolled | 63% of patients achieved complete stable remission |
| Afanasiev et al. [43] | 2017 | 21 | Retrospective, uncontrolled | Mean improvement of MMS by 74.5 (p <0.001) vs. baseline |
| Peres et al. [42] | 2017 | 4 | Retrospective, uncontrolled | Mean decrease in MGCS by 53% (p<0.05) vs. baseline |
| Diaz-Manera et al. [28] | 2012 | 11 | Retrospective, uncontrolled | 91% of patients achieved an improved MGFA-PIS.<br>Decrease in the average dose of prednisone by 13.3 mg/day |
| Collongues et al. [41] | 2012 | 8 | Retrospective, uncontrolled | Decrease of annualized relapse rate from 2.1 to 0.3 (P < 0.001) vs. baseline. |
| Nowak et al. [40] | 2011 | 6 | Retrospective, uncontrolled | Reduction of mean daily prednisone by 65.1%, 85.7%, and 93.8% after cycle 1, 2, and 3, respectively and of PLEX sessions (all p values<0.05) |
| Blum et al. [39] | 2011 | 11 | Retrospective, uncontrolled | 79% of patients achieved an improved MGFA-PIS |
| Maddison et al. [38] | 2011 | 7 | Retrospective, uncontrolled | 42.9% of patients achieved an improved MGFA-PIS |
| Lindberg et al. [37] | 2010 | 5 | Retrospective, uncontrolled | Median decrease of 13 in QMG score |
| Illa et al. [36] | 2008 | 3 | Retrospective, uncontrolled | All patients achieved an improved MGFA-PIS |

AChR, acetylcholine receptor; MG, myasthenia gravis; MGFA-PIS, Myasthenia Gravis Foundation of America – post-intervention status; MM, minimal manifestation; QMG, quantitative MG; MMT, manual muscle testing; MMS, myasthenic muscle score; MGCS, Myasthenia Gravis Composite Score; MG-ADL, Myasthenia Gravis Activity of Daily Life; MG-QoL, Myasthenia Gravis Quality of Life; RTX, rituximab; ns, non-significant.

Uncontrolled studies were followed by two nonrandomized retrospective controlled ones. Of those, the first examined timing of rituximab therapy MG (early administration i.e. within one year of disease onset versus later administration). Several subgroups were examined (early administration, late administration in immunotherapy naïve patients, late administration in refractory patients, and conventional immunotherapy). Differences were more pronounced when comparing early administration of rituximab with later administration in patients that were refractory to conventional immunosuppression. In this setting, median time to remission was significantly shorter when rituximab was applied early (7 versus 16 months). Apart from that however, when rituximab-treated patients were examined as one group, they fared better than patients not treated with rituximab [61]. The second retrospective controlled study compared rituximab with eculizumab, the complement C5 inhibitor approved for the treatment of AChR MG [62–64]. Although eculizumab was more effective in improving the clinical status (achieving, in contrast to rituximab, a reduction in QMG after 24 months; and a greater proportion of patients with minimal manifestations-36.9% versus 12.7% with rituximab), both groups were able to reduce thee mean prednisone daily dosage similarly. Of interest, both drugs were safe and well-tolerated with equal risk of severe infections [62].

As far as rituximab dosing is concerned, the more common induction protocols that have been used include the lymphoma induction protocol (a dose of 375 mg/m$^2$ repeated four times at weekly intervals, considered as one cycle of treatment) [72] and the rheumatoid arthritis induction protocol (two infusions of 1000 mg each, 15 days apart) [73], however different centers have applied slightly different versions ranging from more intense regimens (e.g. two cycles of 4 x 375/m$^2$ 6 months apart) to lower dosing and frequency regimens (e.g. 600 mg at months 0, 6, 12) [74]. Interestingly, a meta-analysis found lower intensity regimens to be equally effective coupled with less side effects, however formal side-to-side control of high versus low rituximab dosages in a prospective randomized study is missing [74]. After the initial induction that can span 6 to 12 months, rituximab therapy in MG can be repeated if clinically necessary or at regular intervals (6 months or yearly). Of note, in multiple sclerosis and aquaporin 4 autoantibody-positive neuromyelitis optica spectrum disorders, CD20 depletion therapy is usually administered every six months and a prolonged CD20 B cell depletion status is maintained indefinitely, often at the cost of late hypogammaglobulinemia and infection [75]. In MG, rituximab side effects were reported in less than 20% of the patients and mainly concerned infusion-related reactions and treatable infections, such as pneumonia and herpes reactivation, while hematological reactions such as cytopenia were rare [67,69,70]. Progressive multifocal leukoencephalopathy was reported in only one patient [43].

The positive effect described in the many case series and prospective open-label studies was challenged by the result of a recent phase 2 randomized controlled trial (BeatMG – NCT02110706) that consisted of 52 mild to moderately symptomatic AChR MG patients. The patients were on prednisone with or without additional immunosuppressants prior to study entry and received two cycles of rituximab (lymphoma protocol), six months apart. The study failed to meet its primary endpoints (at the end of the one-year follow up), which were a significant reduction in daily prednisone dose as well as clinical stabilization or improvement of the neurological status as assessed by the standardized scale MG composite [66]. It is however noteworthy that a post-hoc analysis showed that the patients in the rituximab arm suffered fewer relapses than patients in the placebo arm.

A thorough examination of BeatMG trial data may shed light on the factors that contributed to the negative primary outcome [76,77]: First, recruited patients had relatively mild disease, which may have precluded significant rituximab treatment-related therapeutic effects. Second, recruited patients were possibly overtreated, as prednisone had to be titrated to a stable dose prior to study initiation. The large placebo effect that was seen, i.e. improvement in patients not treated with rituximab, supports this hypothesis. Moreover, steroids lower lymphocyte count, including B cells, and may mask rituximab-associated therapeutic effect. Third, the study may have been too short (one year) to observe measurable differences [78,79]. Fourth, the primary study endpoint may have not captured the rituximab effect well (compared e.g. to a minimal manifestations post-intervention status).

In contrast to BeatMG, RINOMAX, another phase 2, randomized controlled trial (NCT02950155) that tested the efficacy of a single 500 mg rituximab infusion as an add-on induction treatment to the standard of care in 25 adult patients with early onset AChR MG (verssus 22 patients receiving placebo), succeeded in achieving a significant difference in its primary endpoint, minimal disease manifestations at week 16, as defined by QMG of <4 with daily prednisone of 10mg or less [65]. Indeed, 17 of 24 rituximab-treated patients achieved a QMG score of 4 with no need of rescue treatment, as compared to 6 of 21 in the placebo arm (p=0.007) [65]. Finally and in addition to all of the above described trials and case series, the beneficial effect of rituximab in AChR MG has been confirmed by several systematic reviews and meta-analyses of these studies, with the magnitude of the response rate however ranging widely from 30% to 80% (**Table 2**) [67–71].

**Table 2.** Systematic reviews and meta-analyses of CD20-mediated B cell depletion in AChR MG.

| AUTHOR | YEAR | STUDIES | PATIENTS | RESPONSE RATE |
|---|---|---|---|---|
| Zhao et al. [67] | 2021 | 45 | 91 | 64% |
| Bastakoti et al. [68] | 2021 | 29 | N/A | N/D |
| Di Stefano et al. [69] | 2020 | 13 | 165 | 68% |
| Tandan et al. [70] | 2017 | 47 | 99 | 30% |
| Iorio et al. [71] | 2015 | 24 | 91 | 80.4% |

N/A, not applicable; N/D, not done.

Mechanistically, rituximab does not directly target the long-lived plasma cells (LLPC) that contribute to production of AChR autoantibodies, but it can kill memory B cells and may therefore prevent the formation of new AChR-specific plasma cells that arise from continued autoantigenic stimulation and ongoing germinal center reactions [26,80,81]. Therefore, it is possible that two rituximab treatment cycles in established disease are insufficient (as in the BeatMG study), and follow-up period of one year does not capture the clinical benefits of the therapy [82]. Possibly in the same context, the recent retrospective controlled study that compared early and late administration of rituximab demonstrated that clinical improvement manifested faster with early administration, perhaps because less LLPCs have formed in early disease [61]. The positive RINOMAX trial results, where recent onset patients were randomized to one-off rituximab add-on administration, also support this conclusion of less LLPC presence in early disease. In refractory MG with long disease duration, it might be the case that more rituximab cycles are required over a longer period of time due to the presence of more LLPCs in the bone marrow. If this is true one would have to preserve a CD20-depleted state and prevent generation of new autoantibody-producing cells while waiting for the persistent clones to be eliminated. Accordingly, this result might be achieved faster with CD19 depletion, found to be effective in the immunologically similar neuromyelitis optica spectrum disorders [83], however its long-term safety is yet untested. CD19-mediated B cell depletion therapy (with CD19-specific monoclonal antibodies and CD19-specific chimeric antigen receptor T cells) could both target a larger fraction of antibody-secreting cells (compared to CD20), and additionally target pathogenic CD20-negative memory B cells resistant to CD20-mediated depletion [81]. Another explanation however for the diminished effect of rituximab in MG with long disease duration could be a degree of irreversible deficit of the NMJ in long-duration or refractory MG.

Although there is no definite rule as to which patients and under which conditions will benefit from CD20 depletion with rituximab or other agents, several lines of evidence support its early application in AChR MG. This however should not be interpreted as complete lack of efficacy in late, refractory MG. With specific regard to age, a systematic review showed that younger age (<45 years) was a prognostic factor for better response to CD20 B cell depletion [70], and several further studies have confirmed its efficiency in young [84] and pediatric patients [57,85,86]. On the other hand, two studies have specifically examined the use of rituximab in elderly patients and have shown significant efficacy in this population, thus underscoring that rituximab should not be excluded as an option due to advanced age [54,56]. Dosing of rituximab is also not subject to specific rules, however a reasonable approach could be to use smaller doses when administrating the treatment early in the disease course (based on the RINOMAX trial and the preceding data from Brauner *et al*) [61], and larger and repeated doses in established disease with persistent autoantibody titers, while taking at the same time caution to not depress total IgG levels and therefore increasing susceptibility to infection (based on data on autoantibody titers decreasing more after each cycle of rituximab as shown by Nowak *et al* [40]).

### Rituximab in MuSK MG and seronegative MG

Contrary to AChR MG, there is little controversy in regard to application of rituximab in patients with MuSK MG, as they respond impressively to induction therapy, with dramatic improvement, a shorter time to improvement or complete remission, and a long-lasting treatment effect without the need for repetitive dosing [87]. A multicenter, blinded, prospective review, comparing anti-MuSK-positive patients with MG treated with rituximab to those not treated with rituximab showed significantly favorable results in the rituximab arm, hence providing class IV evidence in favor of rituximab use in MuSK MG patients [88]. The clinical difference between MuSK and AChR MG response to B cell depletion is further reflected in autoantibody titers post-rituximab. In contrast to AChR MG titers, almost all patients with MuSK MG receiving rituximab show a rapid (within weeks) and marked decline in MuSK autoantibody titer. Interestingly, the intensity of rituximab induction seems to

be proportionate to the durability of the response of MuSK MG patients [89], however historic clones (not efficiently depleted by CD20-mediated therapy) can reemerge in many cases, even with intense induction, and cause relapse [31,90]. Finally, in seronegative MG, successful application of rituximab in selected cases points to B cell involvement in pathogenesis and to the fact that seronegative MG may be 'false seronegative' due to the sensitivity threshold of autoantibody detection assays [91,92].

## Conclusion

Although the response of MuSK MG patients to rituximab is impressive, the treatment should not be dismissed in AChR MG based on the randomized controlled BeatMG trial (NCT02110706) [66]. The combination of trial limitations and abundance of data from uncontrolled case series and retrospective controlled studies including patients with AChR MG successfully treated with rituximab (some of those studies with more patients than the BeatMG trial), and most importantly the recent positive RINOMAX study of early rituximab administration all lend support to the continuation of CD20 depletion application in AChR MG [65]. It seems clear that rituximab can still offer significant help to AChR MG patients given its efficacy, reasonable safety profile, targeted immunosuppression that is relevant to disease mechanisms, and reasonable pricing compared to the newer agents eculizumab and efgartigimod. However, in the aftermath of COVID-19 and given that CD20-mediated B cell depletion increases the risk for severe SARS-CoV-2 infection, caution needs to be applied and vaccination prior to application with all available vaccines is imperative [93].

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## Disclosures and competing interests

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