The complement story in Guillain-Barré syndrome: from pathogenesis to therapy

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Guillain-Barré syndrome (GBS) is a rapidly evolving neuropathy that often occurs after an acute infection. The majority of patients become severely disabled and unable to walk within a few days with approximately 20-30% of them require assisted ventilation. Up to 5-10% of the patients die during the course of the disease for pneumonia, cardiac or thromboembolic complications. GBS is a monophasic disorder that spontaneously stabilize within 2-3 weeks and subsequently progressively recover. Since the introduction of assisted ventilation, between 50% to 70% of the patients (depending on the need of artificial ventilation) recovered an independent ambulation within 6 months with only supportive therapy.

GBS is an auto immune disease caused by an attack of the immune system against the nerve triggered by an infective agent deemed to share a molecule with nerve. This has led to the use of immune therapies, and there is now evidence from controlled studies that plasma exchange and intravenous immunoglobulins (IVIg) improve the prognosis of GBS and patients' disability compared to standard supportive therapy. Despite this, almost 20% of the patients remain disabled after 6 month even if several patients may continue to recover, even if often incompletely, for 2-3 years. Several attempts have been made to further improve the prognosis of GBS including treatment with interferon, the association of steroids to IVIg but none of them proved to be effective in controlled studies.

In the last years, pathological and experimental studies have shown that complement may play a pivotal role in causing nerve damage in GBS especially when the disease is associated with antibodies against the ganglioside GM1. This was also evident in animal models of GBS where treatment with the monoclonal antibody eculizumab directed against the fraction C5 of complement was effective in improving the neuropathy. Given the previously reported benefit of this therapy in two complement-mediated disorders, paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome, it was postulated that early treatment with eculizumab in GBS might prevent or block the damage caused by anti-nerve antibodies and improve the outcome of the patients.
In this issue, Misawa et al report the results of a placebo-controlled study with eculizumab in 34 patients with severe GBS treated with IVIg.\(^9\) Patients were treated before or during IVIg treatment that was started within 2-12 days from disease onset. Given the unbalance between the number of treated (23 patients) and untreated patients (11 patients) the statistical analysis of response to therapy was based on an historical control group of 62 GBS patients.\(^10\) The study failed to reveal a significant effect of eculizumab on the primary outcome, i.e. the proportion of patients able to walk independently for 5 meters within 4 weeks (29 days) from disease onset. Even if there was a certain degree of improvement in the eculizumab treated patients in this and in some secondary endpoints, the main significant difference in favor of eculizumab was the proportion of patients who completely recovered or became able to run after 24 weeks.

The main limit of this study is the relatively small number of patents examined and the absence of a direct comparison with a control group, also because the historical control group had a lower degree of disability. It would be also interesting to compare the results in relation to the start of eculizumab treatment since it is possible that its efficacy may vary if given early in the disease (say within 2-4 days) when there is the initial effect of complement, or after a week when the nerve might be already damaged.

The importance of this study relies on the fact that it is based on the evidence that GBS is a complement-mediated disease induced by antibodies against nerve antigens. This has been clearly shown in patients with antibodies to gangliosides and particularly GM1 and GD1a or their complexes where they are triggered by an antecedent infection by certain strains of campylobacter jejuni bearing a cross-reactive surface antigen.\(^3\) This reactivity has been shown however to occur in no more than 30-40% of the patients. It is possible that the same mechanism may also occur in patients bearing other, so far unidentified antibodies, but this needs to elucidated.\(^7\) In any case, in this study the response to therapy was not different between patients with or without anti-ganglioside antibodies or with or without the axonal form of GBS that is often associated with this reactivity.
Even if this was mainly a negative study, some data may indicate that this therapy may lead to a more frequent complete recovery over six months. This should be confirmed in a large randomized controlled studies even if the extremely high cost of eculizumab and the not so clear results deriving from this study might require a better identification of the characteristics of the patients to be included.

References