Remission Time after Rituximab Treatment for Autoimmune Bullous Disease: A Proposed Update Definition

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Key Words

Rituximab · Pemphigus · Pemphigoid · Treatment · Remission time

Abstract

A therapeutic endpoint is a very important tool to evaluate response in clinical trials. In 2005, a consensus statement identified two late endpoints of disease activity in pemphigus: complete remission off therapy and complete remission on therapy, both definitions applying to patients without lesions for at least 2 months. The same period of time was considered for partial remission off/on therapy. These definitions were later applied to bullous pemphigoid and are considered in most studies on autoimmune bullous disease. These endpoints were established for different adjuvant agents, but at that moment, rituximab was not considered. Rituximab is known for the long duration of its effect, and in most studies relapses have been reported later than 6 months after treatment. In our opinion, time to remission after rituximab treatment should be redefined.

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Rituximab is a chimeric murine/human monoclonal antibody approved for the treatment of CD20(+) B cell non-Hodgkin lymphoma in 1997. In recent years, ritux-

imab has also been indicated in the treatment of non-malignant disorders such as refractory rheumatoid arthritis and polyangiitis. After the successful treatment of CD20(+) B follicular lymphoma-associated paraneoplastic pemphigus [1, 2], multiple case reports and an increasing number of series of pemphigus and different autoimmune bullous diseases treated with rituximab have been published.

Rituximab induces a prolonged decrease in normal B lymphocyte and immunoglobulin levels. There is a clear lack of data about mechanisms involved in rituximab metabolism and elimination. The estimated median half-life of drug in autoimmune disease was 12–36 days [3]. After 3 months of treatment, rituximab median concentrations of 25 µg/ml were observed in responder patients with follicular non-Hodgkin lymphoma [4] and a median of 12.9 µg/ml in patients with severe pemphigus [5]. A single course of rituximab usually leads a depletion of B cells from peripheral blood typically lasting for 7–8 months, with levels returning to normal after 1 year; however, clinical benefit can persist for several months longer [6].

A therapeutic endpoint is a very important tool to evaluate the therapeutic response in clinical trials. In 2005, a consensus statement identified two late endpoints of disease activity in pemphigus [7]: complete remission off therapy and complete remission on therapy; both definitions apply to patients without lesions for at

least 2 months. Complete remission off therapy was defined as 'the absence or new/established lesions while the patient is off all systemic therapy for at least 2 months'. Complete remission on therapy was defined as 'the absence or new/established lesions while the patient is receiving minimal therapy'. Minimal therapy was defined as 'less than or equal to 10 mg/day of prednisone (or equivalent) and/or minimal adjuvant therapy for at least 2 months'. Minimal adjuvant therapy was defined as 'half of the dose required to be defined as treatment failure' [cyclophosphamide 2 mg/kg/day; azathioprine 2.5 mg/kg/day (if the thiopurine S-methyltransferase level is normal); methotrexate 20 mg/week, or mycophenolate mofetil 3 g/day]. A partial remission off therapy is defined as 'the presence of transient new lesions that heal within 1 week without treatment and while the patient is off all systemic therapy for at least 2 months'. A partial remission on minimal therapy is defined as 'the presence of transient new lesions that heal within 1 week while the patient is receiving minimal therapy, including topical steroids' [7]. The same definitions were later applied for

bullous pemphigoid [8]. These endpoints were established for different adjuvant agents, but at that moment rituximab was not considered.

Most studies of the efficacy of rituximab in pemphigus and autoimmune blistering diseases applied the same response criteria: complete or partial remission off or on therapy when patients were at least 2 months without or with minimal treatment. Since in different studies relapses have usually been reported after 6 months of rituximab treatment [9, 10] and rituximab effect has been proven to last longer than that of the other adjuvant drugs included in the consensus definitions, in our opinion the time for considering partial and/or complete remission on minimal therapy as well as off therapy when using rituximab should be at least 6 months.

Disclosure Statement

Pilar Iranzo has served as advisor to the Roche-Genentech Rituximab in Pemphigus Vulgaris Meeting. None of the authors has any conflict of interest to be disclosed.

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