Differences in the development of adverse infusion reactions to Rituximab in patients with systemic lupus erythematosus, rheumatoid arthritis and non-Hodgkin's lymphoma – enigma variations

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Introduction:

The introduction of B-cell depletion using rituximab for the treatment of non-Hodgkin's lymphoma (1) in the late-1990s was extended within five years, to the treatment of both rheumatoid arthritis [RA] (2) and systemic lupus erythematosus [SLE] (3). While this approach remains very useful, in both of these autoimmune rheumatic diseases, it has become clear that the rates of infusion reactions vary in patients with different diseases.

How common are infusion reactions and their severity in different disorders?

Although rituximab is usually well-tolerated, its use has been linked to hypersensitivity reactions which have been classified as infusion-related, cytokine release, type I [IgE/non-IgE], mixed, type III and type IV reactions. Immediate infusion-related rituximab reactions are relatively common and seem to decrease in frequency with later infusions. There has been much interest in the role of circulating pre-existing or newly-synthesised human anti-chimeric antibodies [HACA] to rituximab. It has been noted (4, 5) that in vitro rituximab -specific IgE and Th2 cells have been identified in a patient with rheumatoid arthritis who had suffered an allergic rituximab reaction. However, HACAs do not need to be of the IgE class in order to simulate a clinical hypersensitivity reaction. Thus, some cases have been reported with IgG immunoglobulins as the culprit (6).

Non-HACA related infusion reactions can be caused by a cytokine release syndrome [CRS]. This may be difficult to distinguish from true hypersensitivity, but is associated with the acute release of

particular cytokines e.g. tumour necrosis factor, interferon-gamma, interleukin-6 and interleukin-2 (7).

Adverse infusion reactions to Rituximab in non-Hodgkin lymphoma:

A retrospective, observational, multicenter study of pharmacovigilance studied the safety of rituximab in the treatment of patients with B-cell lymphoproliferative disorders and autoimmune diseases. 374 patients received the treatment (2864 infusions); these reactions were observed more frequently in patients with hematologic malignancies (25% in indolent non-Hodgkin lymphoma, 35.9% in chronic lymphocytic leukaemia and 28.3% in high-grade non-Hodgkin lymphoma) than in patients with autoimmune disorders (9.4%). Most of the patients with an autoimmune disorder were treated with steroids and, in some cases, with immunosuppressants, and this could explain the lower incidence of these adverse reactions in this group (8).

In a Korean study, undertaken to verify the clinical features and risk factors for infusion related reactions of rituximab, corticosteroid containing prophylaxis was significantly associated with a decrease in the frequency of these events, from a 42% (among patients not given that “protection”(to a 8% (in those who were) (9).

Adverse infusion reactions to Rituximab in rheumatoid arthritis:

In 1998, Edwards and Cambridge attempted to verify, in an open-label trial, the hypothesis that B lymphocytes may be essential to disease perpetuation in patients with RA; they suggested that B-lymphocyte depletion may be a safe and effective therapy (2). A subsequent major double-blind trial confirmed the efficacy of rituximab in RA (10).

In general, adverse events during infusions occur more frequently in patients with B-cell malignancies (74% in B-NHL) than in those with autoimmune disorders (34% in RA) (11).

First infusion reactions occurred in approximately 25% of patients with RA (10). The majority of reactions were mild to moderate with symptoms like headache, flushing, rash, hypertension and pyrexia; however, severe infusion reactions that resulted in drug withdrawal are uncommon (<1%) (12).

In 2010, an analysis of safety data (including adverse events and infections) from patients treated with rituximab in combination with methotrexate in a global clinical trial program was performed. The rates of infusion reaction in the second, third, fourth, and fifth course of rituximab were 13%, 9%, 9%, and 3%, respectively. Thus, they concluded rituximab remained well tolerated over multiple courses. Serious adverse events (SAE) and infections remained stable over time and by treatment course (13).

Adverse infusion reactions to Rituximab in lupus:

A detailed description of adverse infusion reactions in 136 SLE patients noted a rate of 17.6% [totalling 5.8% of all infusions to this group] (14). The rate in this retrospective analysis was remarkably similar to that recorded [16.4%] in a randomised, double-blind placebo-controlled phase III trial in patients with lupus nephritis treated concomitantly with mycophenolate mofetil and glucosteroids (14). In this latter study, most infusion-related events occurred following the first infusion, becoming less frequent

subsequently. However only one serious infusion-related event was noted in the rituximab-treated arm due to a HACA positive patient [grade III].

Consequences and causes of variations in the numbers of patients recording adverse reactions to Rituximab in different diseases:

Interestingly, it has been suggested that a relatively higher proportion of males develop these reactions both in SLE (6) and in patients with both haematological and cancer diagnoses (15, 16). As indicated above, it may be that the development of HACAs is critical in determining the likelihood of developing infusion reactions to rituximab. In a study of 57 SLE patients from the group originally reported by Hennessy et al (13), the presence of HACAs was strongly associated with the development of infusion reactions to this B-cell depleting agent (17).

Conclusion

Rituximab and its biosimilars are widely used in the treament of B cell malignancies and the major autoimmune rheumatic diseases RA and SLE. It is evident that the risk of adverse events is higher in those patients with B cell malignancies. Patients with RA/SLE may be “protected” by the more frequent use of concomitant corticosteroids and immunosuppressive therapies.

Reassuringly, it is a safe drug in clinical practice since the adverse events it produces are usually mild to moderate and the discontinuation of the drug is infrequent.

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