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Rituximab hypersensitivity reactions and tolerance of ofatumumab therapy

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ABSTRACT

B-cell depleting agents play a key role in a variety of disease entities. Rituximab, a murine-human chimeric anti-CD20 monoclonal antibody, as one of these major agents, has been associated with hypersensitivity reactions, which not only include the classic hypersensitivity ranging from immediate (type 1) to delayed (type IV), but also infusion-related reactions (IRRs). Whilst these typical hypersensitivity reactions occur in the setting of prior exposure, IRRs may occur in first exposure. Factors to consider include chimeric composition of agent, for example, rituximab with murine component, which may be responsible for such hypersensitivity reactions. In these individuals, alternate anti-CD20, such as oftatumumab, a fully human monoclonal antibody may be used. We report three cases of rituximab hypersensitivity in patients with auto-immune disease, and in whom ofatumumab therapy was given and subsequently tolerated.

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The clinical applications of anti-CD20 monoclonal antibody therapies (mAbs) continue to expand. Initially used for B-cell lymphoproliferative disorders, their indications have widened to include conditions which involve autoantibody producing or T cell-activating B cells (1) and is now used to treat refractory rheumatoid arthritis, as well as relapsing remitting multiple sclerosis.

While rituximab, a murine-human chimeric anti-CD20 mAb, was the first agent to have gained widespread use, alternative agents have been introduced in recent times These include humanised agents, such as ocrelizumab, veltuzumab and obinutuzumab, as well as the fully human agent, ofatumumab (1). Though having the same target, *i.e.* CD20, these next generation mAbs are not only suggested to have better binding affinity to B cells and increased complement dependent cytotoxicity (2), but in some cases also to potentially have less immunogenic adverse reactions (3).

While infusion-related reactions (IRRs) remain the most common adverse reaction in rituximab treatment, significant reactions have also been documented (4, 5). These include type I and type III hypersensitivity reactions (6). Human anti-chimeric antibodies (HACA) to rituximab have been implicated in a few of these immunogenic reactions and in some cases, have become contraindications for future rituximab use (5). The newer monoclonal antibodies are humanised or fully human and hence will not react with HACA antibodies resulting in a better safety profile with similar efficacy.

We present three cases initiated on ofatumumab therapy with a history of type one or three hypersensitivity reactions to rituximab therapy.

Case 1

A 74-year-old female with chronic severe myasthenia gravis resulting in multiple hospital admissions, was treated with rituximab due to refractory disease despite mycophenolate, cyclosporine and intravenous immunoglobulin. She had a remarkable response and was asymptomatic for 9 months when she relapsed.

On day five of first rituximab infusion on second cycle, she developed generalised urticaria. Subsequent infusion was postponed for a few days and treated with prednisolone and antihistamines. After the second dose, she developed urticaria again immediately post–infusion, managed with a short course of prednisolone as well as ongoing cetirizine. She then received a third infusion and within minutes she developed generalised erythema, flushing, itchiness and irritation in throat. She was treated with adrenaline and event tryptase was elevated at 24μg/L (reference range <11.9μg/L). Subsequent HACA titres to rituximab were strongly positive and skin prick test (SPT) was not pursued. Baseline tryptase was 9.5μg, consistent with IgE mediated hypersensitivity.

Over the next 8 years, her symptoms remained relatively controlled with prednisolone, methotrexate and hydroxychloroquine; however, in 2017, she experienced a progressive decline in function due to her disease. In view of excellent response to previous B cell deple-

Table I. Clinical summaries of patients transitioned to ofatumumab therapy with prior rituximab and relevant histories of reactions.

Case	Clinical summary	Rituximab adverse reaction	Rituximab infusion number	Ofatumumab adverse reaction	Ofatumumab infusion number	Progress
1	Myaesthenia gravis	Type 1 Hypersensitivity	2	Infusion related reaction but subsequently tolerated	1	Clinical improvement
2	Systemic lupus erythematosus	Type 1 Hypersensitivity	3	Infusion related reaction but subsequently tolerated	1	Clinical improvement
3	Overlap mixed connective tissue disease	Type 3 Immune complex	6	Nil	Nil	Clinical improvement

tion therapy, ofatumumab was initiated as per neurologist preference. Midway through her first infusion she developed an erythematous maculopapular rash on her abdomen and back. There were no other systemic symptoms. The infusion was stopped immediately and cetirizine 20mg given. The rash subsided after an hour and the infusion was restarted at half the original rate. There was no event tryptase taken. She was able to complete the infusion without further incident and subsequently demonstrated clinical improvement.

Case 2

A 44-year-old female with severe systemic lupus erythematosus (SLE) characterised by polyarthritis, pancytopenia and rash responded to rituximab and corticosteroids after failing hydroxychloroquine, leflunomide and methotrexate therapies. She relapsed after 7 years and was re-treated with rituximab resulting in sudden onset chest pain, tachycardia and vomiting during second cycle of rituximab in 2013. Subsequent cardiology work-up was negative. Her event tryptase at 14 μg/L was markedly elevated from her baseline (1μg/L). Given the history of type one hypersensitivity rituximab desensitisation was undertaken. However, she continued to experience chest tightness and nausea during the desensitisation program, and as such this was ceased. In-*vivo* testing protocol as previously demonstrated by Wong and Long (2017) was undertaken (4). Both SPT (10mg/mL) and intradermal test (IDT) (0.1mg/mL, 1mg/mL and 3mg/mL) were negative.

Over the succeeding years, further complications arose from chronic corticosteroid use. As her SLE remained active, she was granted ofatumumab use on compassionate grounds. However, midway through her initial infusion, she experienced significant vertiginous symptoms. The infusion was held, and she was given an antihistamine. Her symptoms subsided and the ofatumumab was restarted at half the original rate. She completed treatment and has since been able to reduce her corticosteroid dose while her SLE has remained stable.

Case 3

A 64-year-old woman with severe overlap mixed connective tissue disease with primary Sjogren's Syndrome, polymyositis and peripheral demyelinating neuropathy developed worsening bulbar, proximal upper and lower limb weakness. Pulse methylprednisolone and intravenous immunoglobulin (IVIG) resulted in clinical improvement but she developed tachyphylaxis. Subsequently, she did not tolerate mycophenolate and methotrexate and had no clinical response to cyclosporine. Hydroxychloroquine was started thereafter. Five years later, disease was complicated by diagnosis of interstitial lung disease and she had a relapse with severe demyelinating neuropathy and debility. Rituximab therapy was given with disease stabilisation

One year later, she had disease progression and further rituximab was given. On the second infusion, she developed acute tongue angioedema. There were no other systemic symptoms. Blood tests showed hypo-complementaemia (C3: 0.66g/L and C4: <0.02g/L) with a normal event tryptase at 9.9μg/L. She was treated with corticosteroids and IVIG was given. HACA titres performed subsequently were borderline positive.

Due to ongoing symptoms, ofatumumab was given uneventfully on compassionate grounds. Overall, she had improvement in both subjective and objective weakness over the next three months.

Discussion

We present three cases of rituximab intolerance who subsequently tolerated another B cell depleting agent, ofatumumab. There were minor IRR to ofatumumab in two of these patients which were easily managed by reducing the infusion rate.

In 2006, Pichler had proposed categories to classify adverse reactions to biologic agents, which included reactions due to overstimulation (cytokine release syndromes) as well as hypersensitivity reactions, which includes IRRs and IgE mediated reactions (7). In a large proportion (77%) of IRRs with symptoms, such as fever, chills, nausea, dyspnea or headache are reported to occur within the first dose (8). Although the mechanism of such reactions is not entirely cleared, possibilities include activation of cells or complement (7), or a cytokine release syndrome (4). In these cases, the IRRs decrease when the rate is slowed down and symptoms are treated, with subsequent infusions more likely to be tolerated (9).

Like IRRs, IgE mediated reactions to rituximab can also occur and reported in 5–10% of infusions with distinct symptoms such as pruritus, urticaria, flushing, chest tightness, wheezing and dizziness (10, 11). In cases where an IgE mediated reaction is suspected and further treatment is necessary, then desensitisation may be an effective option (4, 11). Whilst IgE is one

of the mechanisms, both type III and type IV hypersensitivity reactions have been described. In a recent systematic analysis, serum sickness (type III) was reported in 33 patients, all with underlying rheumatic diseases, as well as type IV hypersensitivity, ranging from maculopapular exanthems, to severe cutaneous adverse reactions (12, 13). The latter are rarer, with reported five cases to date with either Stevens-Johnson syndrome and or toxic epidermal necrolysis (14).

While case reports have shown that subjects who have had hypersensitivity reactions to rituximab will usually tolerate ofatumumab (15), the outcomes are not always straightforward as exemplified by a recent report of ofatumumab anaphylaxis after rituximab hypersensitivity (16). In our experience, the use of mast cell tryptase levels, in conjunction with their respective presenting symptoms, helped identify the nature of the reactions to both rituximab and ofatumumab. Additionally, while a raised HACA to rituximab was found in case 1, this refers to the total immunoglobulin level and therefore may be raised due to an elevated specific IgE to rituximab. In retrospect, this subject could still have been considered for desensitisation in this regard. More importantly, while both case one and two demonstrated evidence of an IgE mediated reaction to rituximab neither had convincing signs or symptoms of IgE mediated allergy in their reactions to ofatumumab, which was thought to be due to IRRs. This was further confirmed when subsequent infusions were tolerated on rate reduction.

In case three, while there were some features suggestive of acute type three hypersensitivity such as low complements and normal event tryptase, serum sickness was thought not to be the cause as fever or new arthralgias were not present. Serum sickness to rituximab, albeit rare, has been reported. A systematic review of thirty-three cases revealed an average of seven days post rituximab infusion occurring in the first two doses (15).

Ofatumumab proved to be an effective treatment for our cases. It has also been a viable and effective alternative in other rituximab intolerant cases (15). As can be seen in our experience, care must be taken in defining the reactions to biological agents so that necessary treatments are not unduly avoided.

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