Vaccine response in patients receiving anti-B-cell targeted therapy

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SUMMARY

Infection prevention is of major importance in patients with haematological malignancies, who are immunocompromised because of disease-related and therapy-related factors. However, in patients receiving anti-B-cell therapies, such as rituximab or ibrutinib (an irreversible BTK inhibitor), measures for infection prevention are hardly studied. In this review we considered vaccine response in patients receiving rituximab treatment and we investigated if an adequate vaccine response can be achieved in patients treated with ibrutinib. For rituximab, no protective titers are obtained in patients with haematological malignancies, but in rheumatoid arthritis 30-50% of patients achieve protective titres. Vaccine response following ibrutinib seems low but it is insufficiently studied to make evidence based recommendations.

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INTRODUCTION

Infections are a major source of morbidity and mortality in haematological malignancies, in part because of the immune deficiency inherent to the disease itself (cytopaenia in acute myeloid leukaemia, lymphoid dysfunction and hypogammaglobulinemia in lymphoid malignancy and myeloma), in part because of chemotherapy induced neutropenia and mucositis. As a consequence, infection prevention through vaccination has always been advocated in guidelines. Studies trying to document actual vaccine response have shown poor to absent response because of the concomitant immune suppression by steroids and chemotherapy.

Thanks to the development of new molecular targeted therapies, neutropenia and mucosal damage have greatly diminished during the past twenty years, improving the prospects on quality of life and survival for haematological patients. The most important progress in treatment of lymphoid malignancy has been the introduction of anti-CD20 antibodies (rituximab, ofatumumab, obinutuzumab) and more recently of Btk- and PI3K-inhibitors (ibrutinib, acalabrutinib, idelalisib, duvelisib). Patients are treated with these therapies and live for extended periods of time. Since the novel treatments are (at least theoretically) accompanied by strong B-cell suppression, we want to explore in this article what is known on acquired immunity and vaccine response in patients receiving these treatments.

ANTI-B-CELL THERAPY AND ACQUIRED IMMUNITY

ANTI-CD20 ANTIBODIES

Rituximab (MabThera®/Rituxan®) was the first monoclonal antibody used in clinical practice for the treatment of cancer. It binds specifically to the transmembrane antigen CD20, which is expressed on the cell surface of pre-B lymphocytes and mature B lymphocytes.

CD20 is thought to be involved in the regulation of intracellular calcium, cell cycle and apoptosis.

Rituximab is now a standard component of care for follicular lymphoma, diffuse large B-cell lymphoma, chronic lymphocytic leukaemia (CLL), and mantle cell lymphoma.[1-3]

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Rituximab is also used in the treatment of rheumatoid arthritis, which allows us to look outside the context of haematological malignancy in relatively less immune suppressed patients.

Treatment with rituximab results in depletion of circulating B-cells but the circulating immunoglobulin levels remain nearly unchanged. Both the PRIMA and the RESORT trial, looking at the prevalence of hypogammaglobulinemia and infections in follicular lymphoma, show no clear drop in immunoglobulins during two years of rituximab maintenance.[4,5] The overall need for immunoglobulin substitution for symptomatic disease has been reported in this setting at 6.6% by Casulo *et al*.[6]

Obinutuzumab is a glyco-engineered type 2 anti-CD20 antibody with increased ADCC (antibody dependent cellular cytotoxicity) potential, developed in DLBCL (GOYA study), FL (follicular lymphoma) (GALLIUM and GAUSS study) and B-CLL.[7-10] Although the circulating B-cell depletion is known to be more severe than following rituximab, there are no published data on the evolution of immunoglobulins following treatment with obinutuzumab.

In summary, anti-CD20 antibodies have an impact on circulating B-cells and although there are no clear data confirming a major decrease in Ig levels, reactivation of hepatitis and need of IVIG in some publications suggest that humoral immunity is affected. The relatively stable Ig levels can be explained by the fact that plasma cells are long-lived and do not express CD20. Nevertheless, in patients with previous hepatitis B infection who have been treated with rituximab, hepatitis B reactivation with fulminant hepatitis, hepatic failure, and death have been described, and antiviral prophylaxis is mandatory.[11]

IBRUTINIB

Ibrutinib is a covalent inhibitor of Bruton's tyrosine kinase, a critical enzyme in the B-cell receptor signalling pathway which is necessary for B-cell development, maturation, survival and proliferation. Ibrutinib leads to a decreased B-cell activity and the induction of B-cell apoptosis. It is shown to have a profound anti-tumour activity in haematological malignancies such as chronic lymphocytic leukaemia, mantle cell lymphoma and Waldenström's Macroglobulinemia.[12-14]

Ibrutinib is well tolerated. In patients with chronic lymphocytic leukaemia and del 17p, the current practice guidelines recommend ibrutinib as an upfront treatment option.[15]

Ibrutinib has been associated with the development of pneumonia in 4-18% of patients.[16,17]

Sun *et al*. studied the impact of ibrutinib on reconstitution of normal B cells and immunoglobulins in the early studies in B-CLL and found IgG levels to remain initially stable and decrease after six months, IgA and normal B cells to slowly increase. The incidence of infections decreased with time.[18] There are no long term data on the immunoglobulin levels in patients on extended treatment in the big registration trials (RESONATE 2 and 3).[19, 20]

As with rituximab, hepatitis B reactivation has been described following treatment with ibrutinib, but there are no clear guidelines for prophylaxis as yet.[21, 22]

VACCINE RESPONSE

LOSS OF ADAPTIVE IMMUNITY

It is known that patients with haematological malignancies have a decreased vaccine response (30-40% vs. 85% in general population), but with an appropriate vaccination scheme we may still manage to achieve an adequate response.[23] Based on recent literature we will try to answer the question if immunisation of patients receiving anti-B-cell therapy is possible, and if patients respond differently to a vaccine with neo-antigens versus a vaccine with recall antigens and if the immuno-biological type of the vaccine, polysaccharide (T-cell independent) or protein (T-cell dependent), plays a role herein.

VACCINE RESPONSE AFTER RITUXIMAB

A number of publications in the past fifteen years have shown that the humoral immune response after vaccination in rheumatoid arthritis patients under rituximab treatment is significantly reduced.[24-30] Rehnberg *et al*. showed that cellular and humoral vaccine responses were decreased in RA patients receiving rituximab. They observed a total absence of influenza-specific IgG production in 55% of patients after rituximab treatment.[29] Van Assen *et al*. found that 26,1% of rituximab-treated patients achieved seroprotective titres after influenza vaccination in RA patients. Previous influenza vaccination increased pre- and post-vaccination titres.[27] Bingham *et al*. found that recall responses to the T cell-dependent protein antigen tetanus toxoid and responses to DTH (delayed-type hypersensivity) were preserved in rituximab-treated RA patients. Nevertheless only 57% of patients showed an adequate response to T cell-independent pneumococcal vaccine PPSV23 and only 47% to neo-antigen KLH vaccine.

In patients treated with rituximab for haematological malignancies vaccine responses to influenza vaccine, pneumococcal vaccine (PPSV23) and other common vaccines are reported to be impaired or absent and therefore vaccinations are not recommended in cancer patients with rituximab-containing treatment within six months after administration.[31-34]

These findings suggest that polysaccharide and primary immunizations should be given prior to or six months after rituximab treatment, whenever possible.

KEY MESSAGES FOR CLINICAL PRACTICE

1. **Treatment with anti-CD20 antibodies is not necessarily associated with depletion of circulating antibody levels, but this does not mean they leave protective immunity unchallenged, as can be seen with reactivation of hepatitis B.**
2. **Vaccination of patients with lymphoid malignancy is known to be defective because of the disease related immune deficiency.**
3. **Vaccine response to pneumococcal antigen and to influenza is decreased by anti-CD20 antibodies both in rheumatoid and haematological disease. Patients should be vaccinated before treatment when possible.**
4. **Vaccine response following ibrutinib is insufficiently studied to make evidence based recommendations.**

VACCINE RESPONSE AFTER IBRUTINIB

Recently three clinical trials have been published investigating whether patients receiving ibrutinib for chronic lymphocytic leukaemia show adequate humoral immune responses after vaccination. Two studies investigated the response after influenza vaccination and one study after pneumococcal vaccination, both vaccines should evoke T-cell dependent antibody responses.

In untreated CLL the rate of seroconversion after influenza vaccination is 10-50% and it is shown that the response rate increases with time after the last chemotherapy.[35] Pasiarski *et al*. found in their study in 2014 that the rate of pneumococcal vaccine response in untreated CLL patients is around 60%.[36]

The results of Andrick *et al*. suggested that there is no adequate response after a single dose PCV13 pneumococcal vaccine in CLL patients under ibrutinib. Andrick's report consisted of only four CLL patients taking ibrutinib and four control CLL patients. Responses were measured 30 days after a single dose PCV13. In the control arm all four patients responded adequately to at least three serotypes, in the ibrutinib arm none of the four patients showed an adequate response. Their results suggest that pneumococcal vaccination might be more useful when given prior to ibrutinib initiation.[37]

Douglas *et al*. included thirteen CLL patients and one Waldenström macroglobulinemia patient treated with ibrutinib. All patients and 50 community-living, healthy controls of the same age received a single intramuscular dose of influenza trivalent vaccination (Fluvax® or Fluarix®). At day 30 after vaccination serum hemagglutination inhibition (HI) titres against the vaccine were measured. None of the CLL patients showed a sufficient response, but the WM patient (who had not had previous lines of therapy and had a low baseline IgG) responded adequately. Their conclusion was that there are no serological responses after influenza vaccination in ibrutinib-treated patients.[38]

Sun *et al*. vaccinated nineteen patients with one dose of an inactivated trivalent influenza vaccine. Patients of 65 years or older received a Fluzone high-dose vaccine, amongst the patients younger than 65 some received a Fluzone high-dose vaccine and some a standard-dose Afluria vaccine. They measured hemagglutinin inhibition antibody titres before and three months after vaccination. Seroconversion for at least one strain was observed in 26% (five patients) and 74% of patients achieved seroprotective titres against common influenza viruses after vaccination. Therefore, they state that routine immunization against influenza in these immune-compromised patients should be considered.[35]

Results of Douglas *et al*. and Sun *et al*. may seem contradictory. The difference in outcome between the two studies could be attributed to several factors. First of all we know that the vaccine response can emerge slower in haematological malignancies, thus the absence of response in the study of Douglas *et al*. might be due to the fact that the titres were measured too early (at four weeks after vaccination).[39] In the study of Sun *et al*. in contrast, measurements only took place after twelve weeks, which perhaps allowed documenting the slower seroconversion.

A second possible explanation for the difference in humoral immune responses could be the extent of prior treatment. As we mentioned before, seroconversion rates correlate with prior therapy.[35] Patients in the study of Douglas *et al*. had received a median of two lines of prior therapy, whereas prior treatment histories were not reported in the study by Sun *et al*.[38]

Finally, an undisclosed proportion of patients in the study by Sun *et al.* received the high-dose influenza vaccine Fluzone, the high-dose vaccination may have contributed to higher seroconversion rates.[38]

CONCLUSION

Neither anti-CD20 antibodies nor BTK inhibitors lead to severe depletion of acquired immunoglobulin levels, probably because the plasma cells are unaffected by these treatments. It is surprising that infections known to reactivate under these therapies, such as herpes or hepatitis reactivation are essentially T-cell response dependent, unless the continued balance between viral load and new antibody production remains necessary for protection.

Vaccine response to neo-antigens (influenza, pneumococcal Ag) has been studied in detail in patients with rheumatoid arthritis under rituximab treatment, but less in patients with haematological malignancy. This is even more so for ibrutinib treatment, and in both cases an expected reduction in antibody titre response is observed. Generally, no protective titres are obtained in patients receiving rituximab for haematological malignancies, but in rheumatoid arthritis 30-50% of patients achieve protective titres. Further research on this topic is required to answer the question whether it is worthwhile to vaccinate patients under ibrutinib treatment, and if so, when and how they should be vaccinated.

Moreover, closer investigation is needed to show which vaccines are of benefit and in which dose and vaccination schedule they would be needed particularly in ibrutinib-treated patients who will be treated for extended periods of time. This would allow us in the future to develop evidence-based guidelines for infection prevention under rituximab and ibrutinib treatment for haematological malignancies.

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