COVID-19 vaccine-readiness for anti-CD20-depleting therapy in autoimmune diseases

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Summary

Although most autoimmune diseases are considered to be CD4 T cell- or antibody-mediated, many respond to CD20-depleting antibodies that have limited influence on CD4 and plasma cells. This includes rituximab, ob-linutuzumab and ofatumumab that are used in cancer, rheumatoid arthritis and off-label in a large number of other autoimmunities and ocrelizumab in multiple sclerosis. Recently, the COVID-19 pandemic created concerns about immunosuppression in autoimmunity, leading to cessation or a delay in immunotherapy treatments. However, based on the known and emerging biology of autoimmunity and COVID-19, it was hypothesised that while B cell depletion should not necessarily expose people to severe SARS-CoV-2-related issues, it may inhibit protective immunity following infection and vaccination. As such, drug-induced B cell subset inhibition, that controls at least some autoimmunities, would not influence innate and CD8 T cell responses, which are central to SARS-CoV-2 elimination, nor the hyper-coagulation and innate inflammation causing severe morbidity. This is supported clinically, as the majority of SARS-CoV-2-infected, CD20-depleted people with autoimmunity have recovered. However, protective neutralizing antibody and vaccination responses are predicted to be blunted until naive B cells repopulate, based on B cell repopulation kinetics and vaccination responses, from published rituximab and unpublished ocreli-zumab (NCT00676715, NCT02545868) trial data, shown here. This suggests that it may be possible to undertake dose interruption to maintain inflam-matory disease control, while allowing effective vaccination against SARS-CoV-29, if and when an effective vaccine is available.

Keywords: autoimmunity, B cell, CD20, COVID-19, immunotherapy, multiple sclerosis, ocrelizumab, rheumatoid arthritis, rituximab

Introduction

Although many people consider CD4 T helper type 17 (Th17) cells to be central effectors in autoimmunity, response to therapy has indicated that B cell-depleting drugs exhibit high efficacy in autoimmune and neuroim-munological diseases [1–3]. As such, not only are CD20-depleting agents approved for B cell-related cancers, but they are increasingly being used on- and off-label in autoimmune diseases [1,4]. Ocrelizumab has recently been licensed for the treatment of multiple sclerosis (MS), and antibodies including ofatumumab and ublituximab are in development for MS [5–7]. In addition, rituximab, which is approved for rheumatoid arthritis (RA) and pemphigus vulgaris, is frequently used off-label in MS, neuromyelitis optica spectrum disorders (NMOSD) and a variety of other autoimmunities [1,3,5,8]. Such off-label use provides valuable insight into the biology of CD20-depleting therapy [3]. For this reason, cells within the memory B cell subsets appear to be important targets for disease control, and their depletion and slow repopulation may, in part, account for the long-term disease control seen from short-term treatment cycles with alemtuzumab, cladribine, ocrelizumab

and rituximab [2,3,9,10]. Using rituximab to deplete repopulating memory B cells when they reach predefined levels can maintain clinical remission while reducing the frequency of infusions in RA, NMO, MS and other conditions [3,11–13]. Translating this knowledge may help to improve the benefit : risk balance of ocrelizumab [9]. This is currently highly relevant, as repeated 6-monthly CD20 depletion is associated with immunoglobulin (Ig)M and then IgA and IgG hypogammaglobulinaemia in some individuals, and also a small but increased risk of severe infections [14–16].

Immunological issues of COVID-19

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) has killed hundreds of thousands of humans in a global pandemic [17]. Severe COVID-19 is often associated with lymphopenia [18], initially causing great concern over the use of immunosuppressive agents. In some cases, this led to the cessation or delay of treatment of autoimmunity [19,20]. However, it is increasingly evident that lymphopenia is a consequence rather than a cause of infection [20,21]. While the immune system eliminates SARS-CoV-2 in most individuals (Fig. 1), viral escape, immune exhaustion and elevated cytokine release can lead to hyperactivation of the innate immune response, vascular damage and hypercoagulation (Fig. 1), which can lead to significant morbidity, acute respiratory distress, multi-organ failure and, in some cases, death [17,18,22]. While immunotherapy may have some value in treating severe COVID-19 [23], the development of a SARS-CoV-2 vaccine is considered to be important for protecting the uninfected [24]. A vaccination programme should help to create herd immunity against the COVID-19 virus [25]. Therefore, not only is it relevant to determine how disease-modifying treatments (DMT) influence susceptibility to infection and length of the carrier state, it is also important to consider how DMT may influence immunity to reinfection and potential vaccine responses [20].

Surprisingly, there are limited published data concerning the influence of ocrelizumab on immune subsets, vaccine responses, durability of response and the safety of extending infusion intervals. This prompted us to report data available within the public domain that addressed some of these safety concerns [9]. These data indicate that delaying ocrelizumab [9] and rituximab [10,26] re-infusion should be associated with minor risk of disease reactivation, based on B cell subset depletion and repopulation kinetics [9].

CD20-B cell-depleting agents do not markedly expose people to life-threatening COVID-19

Based on previous understanding of the immune response to SARS-CoV and SARS-CoV-2, animal studies of the elimination of coronaviruses, informative COVID-19 case reports and preliminary reports of COVID-19 pathology [20,27–29], the biology of MS, MS treatments and COVID-19 have suggested that halting treatment may cause more harm than good through ineffective disease control [20,30]. This indicates that a more pragmatic approach, supported by others in the field of MS and other conditions, may be of value [9,31,32]. It appears that the innate immune response, and perhaps later anti-viral CD8 T cell responses, could eliminate the SARS-CoV2 before significant antibody responses have developed [20,28,33] (Fig. 1), suggesting that most MS treatments that largely exhibit limited persistent effects on the innate immune and CD8 T cell responses would have limited influence on COVID-19. SARS-CoV-2 is eliminated by the majority of people with MS and other autoimmunities on immunotherapies, without significant consequences [34–56] (Table 1). Anti-viral antibodies, notably those targeting the receptor binding domain of the viral spike protein, clearly neutralize the virus [57,58] and can contribute to the elimination of the primary SARS-CoV-2 infection in humans [58,59]. However, B cells do not appear to be an absolute requirement for recovery. This is shown by the recovery of people genetically lacking B cells, such as with X-linked hypogammaglobulinaemia [60,61], and is reinforced by the finding that the vast majority of people treated with CD20 B cell-depleting agents in MS recover from COVID-19 [37–56] (Table 1). Furthermore, B cell depletion is unlikely to influence, or be significantly influenced by, the vascular pathology and hypercoagulopathy that are major pathological features in COVID-19 that contribute to the acute respiratory distress syndrome, cardiovascular, cerebrovascular and other non-pulmonary morbidities [9,20,22,62,63] (Fig. 1). Importantly, it provides another rationale as to why immunosuppressive treatments in MS and other autoimmunities [44,64,65] have not noticeably influenced COVID-19 susceptibility and prognosis. People with MS appear to respond to SARS-CoV-2 in a similar way to the general population, where severe disease is notably influenced by age and comorbidities, such as diabetes and obesity [18,43,44,66]. While this information is further consolidated by biology and the clinical evidence (Table 1), it may focus attention away from issues of being infected with SARS-CoV-2 [20] to methods of avoiding SARS-CoV-2 infection in uninfected individuals, as discussed below.

Ocrelizumab is the only DMT that is licenced across the spectrum of primary progressive and relapsing MS [5]. In comparison to other high-efficacy DMT used in MS it has limited monitoring requirements, fewer restrictions on usage compared to cladribine and alemtuzumab and off-label alternatives are widely used, and pharmacovigilance reports have been released [8,40,67]. Therefore,
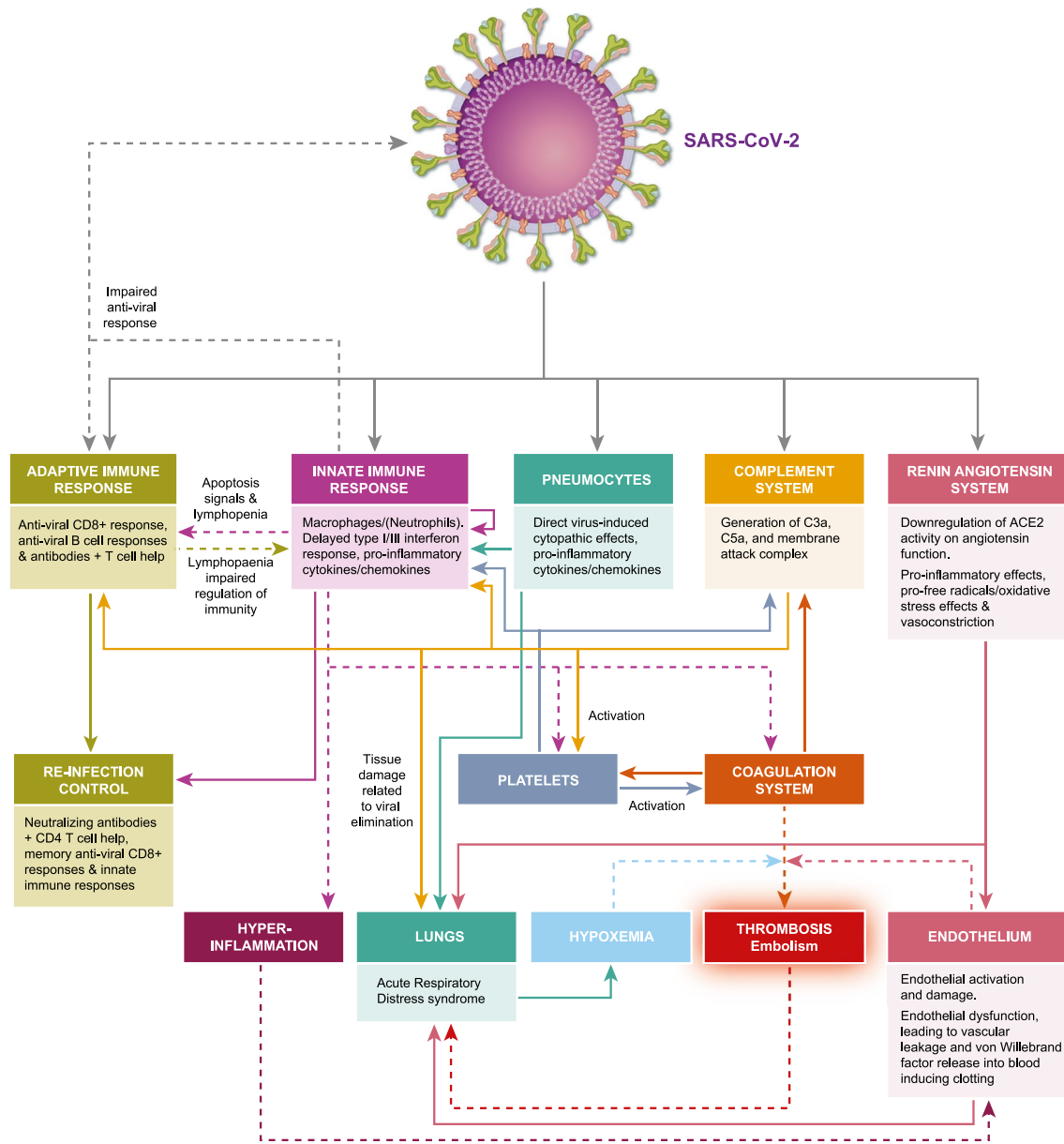
Fig. 1. Pathobiology of COVID-19. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects cells in the lung and the gut via the angiotensin-converting enzyme 2 (ACE2). This blocks ACE2-induced formation of anti-oxidant angiotensin, facilitating oxygen free-radical formation and vascular damage. The innate immune response provides the initial line of defence against the virus, while a CD8 anti-viral T cell response and neutralizing and complement-fixing antibody response serve to remove the virus in the majority of people. However, the virus triggers suppression of interferon responses and other viral escape mechanisms that in a minority of people stimulate the innate immune response leading to lymphocyte apoptosis that blocks their regulatory signals and, in some cases, releases a cytokine storm that drives hyper-innate inflammation. This, in part, causes acute respiratory distress. Importantly, this augments vascular damage that accentuates the respiratory distress and leads to von Willebrand factor release into the blood. This contributes to the formation of microthrombi, contributing to respiratory distress and vascular embolism that may be fatal. Adapted from Henry *et al.* 2020 [22].

it is perhaps not surprising that there is currently more information about the influence of CD20 depletion and COVID-19 disease outcome than for other high-efficacy DMT in MS [49,44] (Table 1). This is consistent with, albeit limited, information in people with rheumatic diseases [66,68] indicating that people generally recover, while the few reported deaths may be linked to co-morbidities [44]. The suggestion that rituximab treatment may increase risk of infection should be considered in the context of possible sampling biases, although this

Table 1. Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in people treated with CD20-depleting antibodies in multiple sclerosis

CD20 antibody	Total no. infected	No. hospitalised	No. in intensive care	No. of deaths	Reference
Ocrelizumab	1	1	0	0	[37]
Ocrelizumab	1	1	0	0	[38]
Ocrelizumab	2	0	0	0	[39]
Ocrelizumab	34	2	0	0	[40]
Ocrelizumab	100	26	5	n.r.	[41]
Ocrelizumab	1	1	0	0	[42]
Ocrelizumab	1	0	0	0	[43]
Ocrelizumab	11	5	2	n.r.	[44]
Ocrelizumab	26	n.r.	2	0	[45]
Ocrelizumab	59	n.r.	n.r.	2	[46]
Ocrelizumab	10	n.r.	n.r.	n.r.	[47]
Ocrelizumab	2	0	0	0	[48]
Ocrelizumab	38	10	3	0	[49]
Ocrelizumab	7	3	0	0	[50]
Ocrelizumab	1	1	0	0	[51]
Ocrelizumab	2	0	0	0	[52]
Ocrelizumab	1	0	0	0	[53]
Subtotal	297	50	12	2	
Rituximab	7	1	0	0	[39]
Rituximab	21	≤ 2	0	0	[40]
Rituximab	2	n.r.	1	1	[45]
Rituximab	9	n.r.	n.r.	0	[46]
Rituximab	6	n.r.	n.r.	n.r.	[47]
Rituximab	17	9	3	1	[49]
Rituximab	1	1	1	1	[54]
Rituximab	41	9	6	n.r.	[55]
Subtotal	104	22	11	3	
Anti-CD20	34	9	n.r.	2	[56]
Total	435	81	23	7	

Number of people that have been infected with the COVID-19 virus that have been documented in case reports and registries from published and social media reports. It is not possible to exclude that people reported in case reports, registries and pharmacovigilance studies are repeat reporting. In addition, infection was defined by symptoms and was not always confirmed via viral nucleic acid testing or serology. n.r. = not reported.

could be supported by data reported in social media from Sweden [40,54] (Table 1). It is evident that both rituximab and ocrelizumab cause IgM hypogammaglobulinaemia in some people within a few treatment cycles, and this and IgA and IgG hypogammaglobulinaemia increases with repeated infusions, potentially contributing to infection [9,14–16]. A delayed IgM response to SARS-CoV-2, which usually appears a few days after symptom onset, may contribute to disease severity [69,70]. With time, CD20 depletion is also associated with reduced IgA responses [15], and similarly early IgA responses may also be important for efficient clearance of SARS-CoV-2 [15,71,72]. However, as yet there is no compelling evidence that CD20 depletion increases the severity of COVID-19 compared to the general population [40,41], although in people with genetically dysfunctional B cells this has been suggested [62]. In addition, hypogammaglobulinaemia may inhibit SARS-CoV-2 cross-reactive, protective antibodies generated from immunity from previous coronavirus infection, which has been shown

at the T and B cell level [73,74], and seen previously with SARS and common cold-causing coronaviruses [75]. In contrast, it has been questioned whether benefit may be imparted [37,43], as B cell depletion could lead to limited antibody-mediated enhancement of macrophage activity and complement-mediated damage and antibody levels have been associated with severe COVID-19 [71,76,77]. Although some people seroconvert and generate an anti-SARS-CoV-2 response, this is expected to be, and sometimes is, blunted or absent due to the inhibition of antibody responses by anti-CD20 B cell depletion [39,50–53]. The antibody titre required for protection against SARS-CoV-2 and the quality and the neutralizing potential of the antibody response after CD20 depletion are currently unknown [39,50–53]. However, even in non-immunosuppressed, notably asymptomatic, cases that produce low-titre antibody responses, many people do not produce a marked or long-lasting neutralizing antibody response [78–80]. Perhaps benefit may be achieved by vaccination to boost immunity.

Infection of SARS-CoV-2 infection induces immunity

Although there is much hope for the impact of vaccination on generating immunity to SARS-CoV-2, there is no guarantee of protection or prolonged protection [24,80]. Repeated infection is observed with other endemic human coronaviruses that cause common colds, suggesting that recurrent reinfections may also occur with SARS-CoV-2 [81]. This strongly supports the contribution of macrophages in viral control and the limited and transient induction of adaptive immunity [81]. Possible reinfection with SARS-Cov-2 has also been suggested by the finding of positive, polymerase chain reaction (PCR)-detected SARS-CoV-2 nucleic acid swabs after a number of negative swabs [82]. However, it is clear that this may be due to non-infective viral particles or artefacts created by sampling location and the testing systems used. PCR-positive swabs can be found in faeces long after loss of nasopharyngeal-positive PCR findings, indicating that the virus may persist for some time and that the PCR test detects fragments of the viral nucleic acid and not necessarily infective virus [83,84]. Importantly, contact tracing of hundreds of people with positive tests after previous negative tests and hospital discharge failed to detect any evidence of the production of infective virus and subsequent viral spread to contacts [84]. Importantly, animal model studies show that immunity to SARS-COV-2 develops after primary infection that can rapidly eliminate the virus on re-exposure [28,29,85]. This can be stimulated via vaccination in animals and in humans to generate neutralizing antibodies [86,87]. In most, but not all cases, neutralizing antibodies persist for a number of months [79,80], and following SARS coronavirus infection SARS-CoV-specific antibodies were detectable for a year or two before they disappeared [88], due probably to lack of antigenic stimulation following elimination of the virus. However, as new responses will be generated from CD20+ naive B cells, these responses would be anticipated to be blunted by B cell depleting agents.

CD20 antibodies inhibit vaccine responses

It has been shown that rituximab depletes naive B cells in the blood, lymphoid tissue and, to some extent, the bone marrow, and can also disrupt germinal centre formation in secondary lymphoid tissues [3,89,90]. Although the influence of ocrelizumab on B cell subsets and vaccine responses have not been published, trial (NCT02545868) data have been reported in meetings and adopted in the Summary of Product Characteristics produced as part of the regulatory label [67,91]. Importantly, the data have been deposited on a trial registration site (www.clinicaltrials.gov) allowing data extraction, as shown here (Fig. 2). It is evident that there is a lower frequency of seroconversion and reduced titre to 23-valent pneumococcal polysaccharide vaccine (23-PPV) (Fig. 2a,b) with or without a booster vaccine (Fig. 2c), keyhole limpet haemocyanin (KLH) neoantigen (Fig. 2d), tetanus toxoid vaccine (Fig. 2e,f) and seasonal influenza vaccines (Fig. 2g–i). The percentage of people with MS who gave a positive response (titre ≥ 0·2 IU/ml or fourfold increase in titre is baseline levels ≥ 0·1 IU) to tetanus vaccine 8 weeks after vaccination was 23·9% in the ocrelizumab group compared to 54·5% in the control group (no DMT except interferon beta). The geometric mean anti-tetanus toxoid-specific antibody titres at 8 weeks were 3·74 and 9·81 IU/ml, respectively. Although these vaccine booster responses to tetanus toxoid were clearly blunted (Fig. 2c), the titres were generally above protective levels (0·16 IU/ml) [92], even at baseline. The percentage of people with MS on ocrelizumab with seroprotective titres against five influenza strains ranged from 20·0–60·0 and 16·7–43·8% prevaccination, and at 4 weeks post-vaccination from 55·6–80·0%, in people treated with ocrelizumab and 75·0–97·0% in the control group, respectively (Fig. 2g). However, haemaggulination inhibition titres were reduced (Fig. 2h). Similarly, while there was a positive response to five or more serotypes in polyvalent pneumococcal vaccine (23-PPV) at 4 weeks after vaccination (71·6% in the ocrelizumab group and 100% in the control group), the frequency of seroconversion and antibody titres were, however, markedly reduced (Fig. 2a). Furthermore, a booster of the 13-PPV vaccine administered 4 weeks later did not markedly enhance the response to 12 serotypes, in common with 23-PPV (Fig. 2c), further indicating the blunting of the vaccine responses. This was also seen using KLH (Fig. 2d). It is likely that this would be reduced further following repeated infusion of ocrelizumab, as hypogammaglobulinaemia, notably within IgM production, develops and increases while IgG hypogammaglobulinaemia develops over a longer time-frame [9,15].

The relatively poor vaccine response in people treated with ocrelizumab was predictable, and consistent with that seen following vaccination in people treated with rituximab, suggesting that this is an issue for all classes of anti-CD20 antibodies used in the treatment of cancer and autoimmune diseases. There was a reduced titre and seroconversion rate (37·5 *versus* 75·0% healthy controls) of people with NMOSD following vaccination against influenza (H1N1) virus 3–5 weeks after treatment with rituximab [93]. Furthermore, vaccine responses to *Streptococcus pneumoniae* and influenza were still impaired in people with idiopathic thrombocytopenia and RA 6 months after treatment [94,95]. This conclusion was also supported by studies in RA following treatment with rituximab, with a more markedly blunted seroconversion and titre when vaccinated during periods of peripheral B cell depletion with influenza

[96], hepatitis B vaccines [97], PPV-23, KLH [94] and a greater, but still blunted, vaccine response 6–10 months after infusion [96]. However, despite a relative lack of memory B cells, CD19-repopulated individuals could mount a robust recall response, as shown in people with pemphigus vulgaris [98]. This suggests that it is possible to create a time-window to vaccinate an individual due to the differential kinetics of repopulation with pathogenic memory B cells and naive B cells that will allow immunity to new infections [3,99,100]. In addition, ocrelizumab does
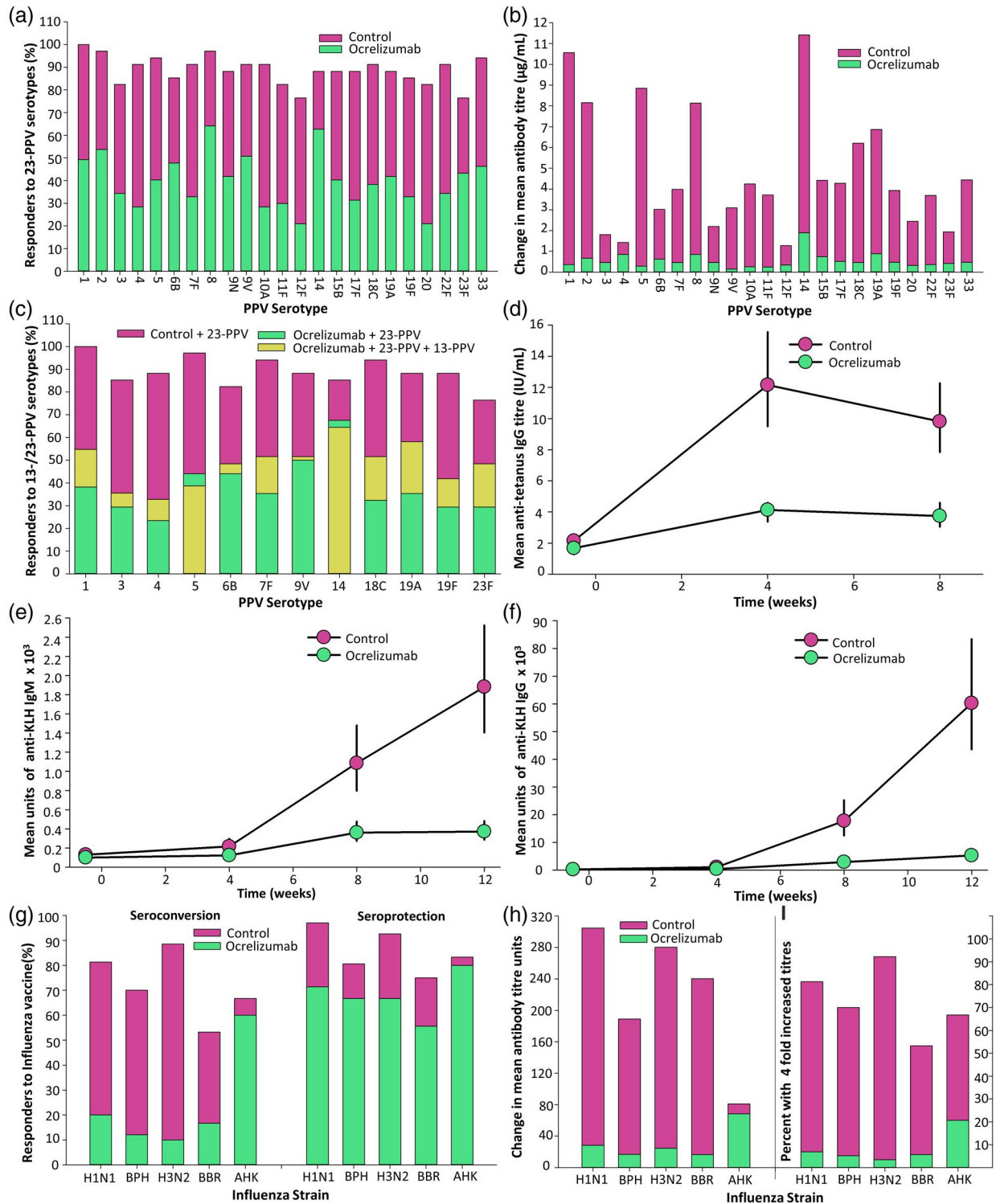
Fig. 2. Ocrelizumab inhibits vaccination responses. People with multiple sclerosis who did not receive ocrelizumab (control) or were infused with 300 mg ocrelizumab on days 0 and 15 and were vaccinated from weeks 12–24 after ocrelizumab. The experimental details and results were from www.clinicaltrials.gov NCT02545868 [91]. The results show: (a) The frequency of seroconversion in people treated with ocrelizumab following injection pneumococcal 23-polyvalent pneumococcal vaccine (PPV) vaccine, 4 weeks after vaccination ($n = 66–68$). A 23-PPV vaccine response against a serotype was defined by a twofold increase in anti-pneumococcal antibody or > 1 µg/ml compared with prevaccination levels, following Food and Drug Administration guidance. (b) The titre of response to the initial challenge with 23-PPV 4 weeks after vaccination. (c) The frequency of seroconversion in people treated with ocrelizumab following injection of a booster pneumococcal 13-PPV vaccine 4 weeks after 23-PPV ($n = 33–34$). The frequency of responders is shown 8 weeks after 23-PPV vaccination. (d) The geometric mean and 95% confidence interval (CI) anti-tetanus toxoid antibody levels measured by enzyme-linked immunosorbent assay (ELISA) before and following vaccination ($n = 34–68$). (e,f) The geometric mean and 95% confidence interval titre of (e) immunoglobulin (Ig)M or (f) IgG keyhole limpet haemocyanin (KLH)-specific antibody after vaccination with keyhole limpet haemocyanin at baseline, weeks 4 and 8 started 12 weeks after ocrelizumab infusion ($n = 34–68$). (g–i) The response to: A/California/7/2009 (H1N1, $n = 33–35$); B/Phuket/3073/2013 (BPH, $n = 31–33$), A/Switzerland/9715293/2013 (H3N2, $n = 27–30$), B/Brisbane/60/2008 (BBR, $n = 16–18$), A/Hong Kong/4801/2014 (AHK, $n = 5–6$) influenza strain vaccination 12 weeks after ocrelizumab infusion was assessed. The results represent (g) the percentage of people with seroconversion, defined either a prevaccination haemagglutination inhibition (HI) titre < 10 and ≥ 40 at 4 weeks or a prevaccination ≥ 10 and at least a fourfold increase in HI titre, and seroprotection defined by titres > 40 at 4 weeks after vaccination. (h) The change in the geometric mean HI titres before and after vaccination (I) The percentage of people with a fourfold increase in strain-specific > 40) at 4 weeks after vaccination.

not appear to impair pre-existing humoral immunity [101], suggesting that people with MS who receive the SARS-CoV-2 vaccine if and when it becomes available will be able to start treatment with ocrelizumab without risking vaccine-acquired immunity. However, the effect of ocrelizumab-induced hypogammaglobulinaemia on the levels of protection from prior immunizations is unknown, and warrants further investigation.

Repopulation kinetics of ocrelizumab

If COVID-19-related vaccine responses become a key concern among people with MS or other autoimmune diseases choosing treatment options, the selection of B cell-depleting agents that allow quick repopulation of B cells may be relevant for optimum vaccine readiness. Continuous B cell depletion with ocrelizumab and rituximab will clearly limit naive B cell repopulation; however, memory B cell depletion persists for a significant time after depletion with rituximab and alemtuzumab, consistent with the slow repopulation of this subset [99,100,102,103]. This suggests a possibility for extended interval dosing or dosing interruption to allow immature B cells to recover to facilitate vaccination, while maintaining low levels of pathogenic memory B cells. Data suggest that this is feasible, at least with rituximab [98]. The timing required for this to occur for ocrelizumab is likely to be substantially longer. Repletion with rituximab occurs within approximately 6 months of treatment, and is completed within 12 months due to repopulation of the immature/mature (naive) B cell pool [26,98]. Monthly subcutaneous treatment with ofatumumab takes a median of 49 weeks (range = 14–102 weeks) for CD19 B cell repletion after six 60-mg cycles of treatment, and immature (CD19+, CD38+, CD10+) cells repopulate quickly [104]. This may have some merits for ofatumumab if the rapid repopulation of B cells can be confirmed with more prolonged

usage, once ofatumumab is licenced to treat MS. Repopulation of B cell subsets following ocrelizumab has not been reported previously, but we report here the influence of ocrelizumab on B cell subsets from the Phase II open-label extension study (Fig. 3a,b) [105]. It was found that CD4 and CD8 T cell numbers were relatively unaffected (Fig. 3a,b), even during active treatment (Fig. 3b). CD19 B cell subsets, including memory (CD19+, CD27+, CD38low) B cells, are completely depleted during active treatment (Fig. 3b). Even following cessation of treatment, CD19+ B cells remain low for 6–12 months after the last infusion (Fig. 3a). It is evident, however, that the memory B cell pool remained depleted for much longer, at least 18 months (Fig. 3a,b), and probably even longer in many individuals [105]. This is consistent with the durability of relapse inhibition and adds further support to the view that cells within this subset are important in MS disease pathogenesis [2,9]. However, there appeared to be some recovery of the naive (CD19+, CD21, IgD+, IgM+) B cell pool during this time (Fig. 3a), suggesting the potential to generate new antibody responses which may be crucial to mount an immune response during infections and vaccinations. As found with rituximab, naive/mature B cell repopulation will coincide with CD19 repopulation [26,97] and would take a median 62–72 weeks after three [95% confidence interval (CI) = 59·7–73·0 weeks, $n = 51$] or four cycles (95% CI = 59·1–85·4, range = 27–175 weeks, $n = 51$), respectively [105]. Such levels would require monitoring, as there is marked variability in repopulation kinetics between individuals and is, in part, a product of the ocrelizumab fixed-dosing schedule, as it is clear that the intensity of B cell depletion and repopulation speed relates to the body mass index of the individual [106,107]. This suggests that dose-adjustment for weight may have some benefit, as currently used in the treatment of people with MS with oral cladribine [107]. Cladribine can be
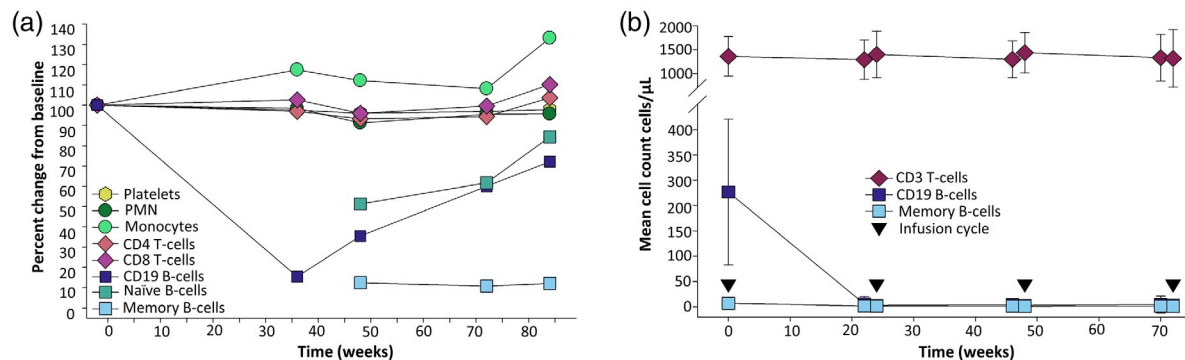
Fig. 3. Long-term depletion of memory B cells induced by ocrelizumab. These data were extracted from the ocrelizumab Phase II clinical study report [105], supplied by the trial sponsor via the www.clinicaltrialdatarequest.com portal. (a) The data represents the mean percentage change from baseline, defined as the last observation up to the first day of ocrelizumab treatment. The subjects received placebo and three cycles of 600 mg ocrelizumab every 24 weeks. This was followed by a treatment-free period to monitor B cell repletion in the Phase II extension study. The time represents the period from the last ocrelizumab infusion ($n = 22$–43). Naive [$CD19^+$, $CD21^+$, immunoglobulin $(IgD)^+$, IgM^+] and memory B cells ($CD19^+$, $CD27^+$, $CD38^{low}$) and other immune subsets were assessed ($n = 22$–43/group). (b) Depletion of memory B cells was maintained during treatment. These data were obtained from people ($n = 88$) entering the open-label extension (OLE) study after the treatment-free period that had received three or four 6-monthly cycles of at least 600 mg ocrelizumab to week 72, followed by a treatment-free period to week 144, before entering the OLE phase where 600-mg cycles of ocrelizumab were maintained at 24-week intervals. The results represent the mean ± standard deviation of cells/µl ($n = 22$–69/group weeks 22–72). Although CD19 B cell numbers were consistent with the original levels, the baseline memory B cell levels failed to return to original levels at the start of the OLE. PMN = polymorphonuclear neutrophil.

considered to be a chemical CD19-depleting agent that markedly depletes memory B cells while generally maintaining T cells within the lower limit of normal. The compound is rapidly eliminated, allowing CD19 naive B cells to recover within a median of 30 weeks after treatment [108–110]. Alemtuzumab is administered at a low dose (36–60 mg) per cycle compared to ocrelizumab (600 mg) and rituximab (500–1000 mg), and has a relatively short half-life compared to ocrelizumab [111]. Alemtuzumab markedly depletes T cells and memory B cells, but naive B cells rapidly repopulate [100,103], and vaccine-related antibody responses can be induced within 6 months of infusion [112]. This further supports the concept of a 'window for vaccination' for CD20-depleting antibodies.

However, while B cell responses to a variety of different vaccines are clearly inhibited by CD20 depletion despite some inhibition of CD20 T cells [99,113], inactivated herpes zoster vaccine can at least induce T cell responses [114]. This may be relevant if the CD8 T cell response is a vital part of the coronavirus specific immunity, as reported for SARS-CoV [27,115–118]. This feature may reduce concern about the limited antibody responses that may be generated following infection or after administration of a SARS-CoV-2 vaccine, as such asymptomatic people who have cleared SARS-CoV-2 and have a detectable anti-viral T cell response, but may not generate an antibody response [115–118]. Although adenoviral vaccines have shown some value in generating neutralizing antibodies and cytopathic T cells in early human studies [85],

live and attenuated viruses are contraindicated in immunosuppressed people [67]. It remains to be seen if SARS-CoV-2 DNA-RNA vaccines [24], will be useful in people taking immunosuppressive agents. However, it is important that people with autoimmunity continue to be offered the benefit that high-efficacy immunotherapy can provide. With time, further knowledge will emerge that may help guide treatment selection within the COVID-19 and post-COVID-19 era.

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