EXPERT OPINION

Obinutuzumab (GA101) – a different anti-CD20 antibody with great expectations

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The anti-CD20 monoclonal antibody (mAb) rituximab has revolutionised treatment approaches and improved outcome for patients in a wide range of B-cell malignancies [1-3]. Furthermore, this change in clinical practice using combining rituximab with chemotherapy (immuno-chemotherapy) has substantially changed the mindset of the clinical community about the ability of mAb to be effective anticancer therapies. However, despite the unprecedented success of rituximab, a proportion of patients with $CD20^+$ malignancies respond poorly to, or relapse shortly after receiving rituximab-containing immuno-chemotherapy and increasing numbers are becoming 'rituximab-refractory' as more patients receive this mAb. The current challenge lies in providing new anti-CD20 antibodies that will provide increased efficacy over that achieved with rituximab and clinical benefit in those patients who have developed resistance to rituximab. The clinical and financial success of rituximab has prompted intense interest and activity in the pharmaceutical industry to develop the next generation of successful anti-CD20 mAbs. This activity has led to the preclinical development and subsequent clinical testing of many novel anti-CD20 mAbs, each of them designed with minor or more significant modifications in mAb structure aimed at further improving efficacy over rituximab. One of the most promising new anti-CD20s to emerge is obinutuzumab and the initial preclinical data generated using this mAb have led to great expectations and investment in clinical trials that it might prove to be superior to rituximab and improve outcome for patients further.

Obinutuzumab is a humanised type II anti-CD20 mAb with a glycoengineered Fc portion and a modified elbow hinge designed to increase direct cell death, but at the expense of reduced CDC activity [4]. By contrast, the other mAb currently in clinical testing are type I anti-CD20 mAb or 'rituximab-like' mAb. These type I mAbs redistribute CD20 into membrane lipid rafts and potently activate complement-dependent cytotoxicity (CDC) [5,6]. Both subtypes of anti-CD20 show equal ability in activating Fcγ receptor (FcγR)-bearing immune effector cells [5,6]. The glycoengineered Fc portion of obinutuzumab has been reported to result in 50- to 100-fold greater binding to the FcγRIII and to lead to substantially increased antibody-dependent cellular cytotoxicity (ADCC). In keeping with these enhanced and novel mechanisms of action, preclinical studies have shown impressive and superior efficacy both *in vitro* studies and in xenograft *in vivo* models over rituximab [4,7,8]. Recent work using primary CLL samples has identified lysosomes and reactive oxygen species (ROS) as important mediators of obinutuzumab-induced non-apoptotic programmed cell death (PCD) *in vitro* [9]. In the setting of immune effector cell function failure, this PCD mechanism of tumour cell kill, which is Fc independent may be important when Fc-FcγR-dependent mechanisms are impaired. Failure of Fc-dependent mechanisms and ADCC may occur, for example, in patients with low-affinity FcγRIIIa, or patients with immune effector cell failure most commonly secondary to chronic depletion by

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chemotherapy regimens. Whether this mechanism of direct mAb-induced PCD is important clinically is yet to be determined. The preclinical data simply provide compelling evidence for a substantially different mechanism of action of obinutuzumab over rituximab and other type I anti-CD20 mAb, which requires further investigation. Encouragingly, GA101 has demonstrated superior tumour growth inhibition compared with rituximab in subcutaneous lymphoma xenograft models as monotherapy [4], or in combination with cyclophosphamide in a FL xenograft model, and greater B-cell depletion than rituximab in non-human primates [4] and hCD20 transgenic mice [8].

When considering other anti-CD20 mAb effector mechanisms of tumour clearance, the relative importance of one mechanism over another remains uncertain. However, it appears that anti-CD20 mAbs eliminate their targets by engaging in a range of effector pathways, including mAb Fc-FcγR interactions including ADCC and phagocytosis, CDC as well as the direct induction of PCD alluded to above. More recently, evidence has emerged to suggest another mechanism with a potential role for passive antibody-induced immunisation (anti-CD20 mechanisms of action reviewed in ref [10] and references therein).

Intriguing emerging clinical evidence supports the contribution of CD20 loss to rituximab resistance, with antigen loss observed in a proportion of patients who have relapsed after rituximab [11].

This data challenges the view that CD20 is a stable target which does not shed/internalise on mAb ligation. More recently, 'shaving' of rituximab/CD20 complexes by phagocytic cells on saturation of immune effector mechanisms due to high burden of circulating mAb targets has been described as well [12]. Rituximab-induced CD20 loss occurred through internalisation of CD20 and its trafficking to lysosomes in normal B-cells and a large panel of primary B-cell malignancies, albeit with marked heterogeneity between individual samples [13]. Studies are ongoing to determine whether the degree of internalisation correlates with clinical resistance to rituximab. This recently characterised internalisation, unlike shaving, does not require phagocytes. Importantly, the type II anti-CD20 mAb tositumomab induced significantly less antigenic internalisation contributing to its enhanced ability to deplete B-cells in hCD20 mice [13]. However, the mechanisms of resistance in $CD20^+$ tumours are yet to be determined, and may lie in the failure of immune effector cell recruitment and/or function. This hypothesis requires further clinical investigation.

Currently, the relevance of these mechanisms and the striking improved efficacy seen with obinutuzumab in preclinical models remains unproven in the clinic. The initial Phase I/II studies have confirmed the safety and show promising efficacy of obinutuzumab (GA101) and are well reviewed in this edition (REVIEW), but do not as yet provide a clear signal that this mAb will provide a 'step change' in clinical efficacy. A recent randomised Phase II trial comparing rituximab with GA101 in patients with relapsed follicular lymphoma demonstrated modest increases in response rate of GA101 over rituximab, yet this failed to translate into improvements in progression-free survival [14]. Only well-designed large randomised studies will provide the evidence required to fully answer the question of enhanced clinical efficacy over rituximab. These studies are underway in a range of common B-cell malignancies and it is possible that the results may differ across different diseases and across patient groups. We still have much to learn about optimal mAb dosing and the development of dosing schedules for rituximab was at best pragmatic, albeit the early pioneers knew little of the insights we now have and delivered practice changing protocols. The current large randomised studies have elected to use higher doses of obinutuzumab, which provided a signal in the Phase II studies of improved pharmacokinetics and enhanced clinical efficacy. The B020999 Phase II study in CLL patients included 20 patients with relapsed/refractory CLL who received obinutuzumab at 1000 mg on day 1, 8, 15, 22 and then every 3 weeks for a total of 10 infusions. The 1000 mg dose was selected based on the higher efficacy of the high-dose compared with the low-dose regimen and based on pharmacokinetic data and modelling and simulation [15]. The doses of obinutuzumab (1000 mg) used in the Phase III studies are substantially higher than the 'standard of care' 375 mg/m^2 so commonly used in rituximab chemotherapy treatments. Therefore, if improvements are seen with obinutuzumab over rituximab these may simply be secondary to large doses of administered mAb or due to the other distinct mechanisms such as improved PCD, enhanced FcγR-expressing immune effector cell recruitment or reduced tendency to evoke antigenic modulation. Any improvements in clinical outcome are likely to be embraced with enthusiasm but we will have to await the results of these Phase III studies and longer follow-up to properly evaluate efficacy and toxicity. We still have much to learn and some distance to travel before we can draw any conclusions about the efficacy of obinutuzumab.

Expert opinion

The last decade has heralded a new era of immunochemotherapy with the addition of rituximab leading to improved outcome for all of the common B-cell malignancies. The success has catalysed the development of the next generation of anti-CD20 mAbs and the desire to improve clinical outcomes further. The majority of these new reagents are type I anti-CD20 mAbs, designed to have enhanced CDC or improved Fc-dependent function and FcγR binding ADCC. None of the type I mAbs have as yet proven to be superior to rituximab, although direct clinical comparisons are lacking. By contrast, obinutuzumab (GA101) is a type II anti-CD20 mAb, which behaves markedly different in preclinical investigations, with increased antibody-induced PCD and markedly enhanced ADCC. This mAb-induced PCD appears to be a non-apoptotic cell death that involves lysosomes and ROS. Recent data have also provided new insights into the

loss of CD20 antigen by 'shaving' involving phagocytosis and modulation on the tumour surface. This mechanistic data may prove to be important in enhancing anti-CD20 efficacy further as we learn more about the determinants of clinical efficacy that has largely remained so elusive. Currently, the relevance of these mechanisms and the striking improved efficacy seen with obinutuzumab in preclinical models is unproven in the clinic. The initial Phase I/II studies have confirmed the safety and show promising efficacy of obinutuzumab (GA101), without providing as yet a clear signal that this mAb will provide a 'step change' in clinical efficacy. Only well-designed large randomised studies will provide the evidence required to fully answer the question of clinical efficacy. These studies are underway in a range of the common B-cell malignancies and it is possible that the results may differ across different diseases and patient groups. We still have much to learn about optimal mAb dosing and these current studies have elected to use higher doses of obinutuzumab than those established as routine standard of care in rituximab chemotherapy treatments. Therefore, if any improvements were to be seen with obinutuzumab over rituximab in these studies, it could be argued that they may simply be secondary to large doses of administered mAb rather than the other distinct mechanisms defined in the laboratory. While this mechanistic data would be informative, clinical pragmatism will always prevail and if any improvements in clinical outcome are seen with obinutuzumab, they are likely to be embraced with enthusiasm. The results achieved with rituximab will prove difficult to better and none have surpassed these results so far. Obinutuzumab is currently the leading candidate to make an attempt for the throne in B-cell malignancies and we await the results of ongoing trials with great interest.

Declaration of interest

TM Illidge has received consultancy fees from Roche Pharmaceuticals, Bayer Schering, Seattle Genetics, Millennium and Takeda.

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