Title : Recommendations for the management of secondary hypogammaglobulinaemia due to B-cell targeted therapies in autoimmune rheumatic diseases

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Recommendations for the management of secondary hypogammaglobulinaemia due to B-cell targeted therapies in autoimmune rheumatic diseases

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Abstract

Objectives: The association of B-cell targeted therapies **(**BCTT) with development of hypogammaglobulinaemia and infection is increasingly recognised. Our aim was to develop consensus recommendations for immunoglobulin replacement therapy (IGRT) for management of hypogammaglobulinaemia following BCTT in autoimmune rheumatic diseases (AIRD).

Methods: A modified Delphi exercise involved a 17-member Taskforce committee, consisting of immunologists, rheumatologists, nephrologists, haematologists, gastroenterologist, immunology specialist nurse and patient representative. The first round identified the most pertinent topics to address in the recommendations. A search string was agreed to identify publications in PubMed focusing on these areas for a systematic literature review. Original data was presented from this review to the Taskforce committee. Recommendations from British Society for Rheumatology, UK Department of Health, European League Against Rheumatism, American College of Rheumatology, and American Academy of Allergy, Asthma, and Immunology were also reviewed. The evidence was discussed a face-to-face meeting to formulate recommendation statements. The level of evidence and statements were graded according to Scottisgh Intercollegiate Guidelines Network methodology.

Results: Three overarching principles, eight recommendation statements and a research agenda were formulated. The Taskforce committee voted on these statements, achieving 82-100% agreement for each recommendation. The strength of the recommendations was restricted by the low quality of the available evidence, with no RCT data. The

recommendations cover risk factors, monitoring, referral for hypogammaglobulinaemia; indications, dosage and discontinuation of IGRT.

Conclusion: These are the first recommendations specifically formulated for BCTT-related hypogammaglobulinaemia in AIRD. The recommendations are to aid healthcare professionals with clinical decision making for patients with hypogammaglobulinaemia.

Key messages

1. These are the first recommendations specifically formulated for BCTT-related hypogammaglobulinaemia in autoimmune rheumatic diseases.

2. Benefit of BCTT should be balanced against risk of inducing sustained secondary antibody deficiency.

3. Immunoglobulin replacement decisions should involve the patient, clinician supervising the autoimmune disease, and immunologist.

Introduction

B-cell targeted therapies (BCTT) are effective for the management of a large number of conditions and are widely used by a range of specialties [1]. The association of BCTT, such as rituximab, with the development of hypogammaglobulinaemia and infection is increasingly recognised [2,3,4]. The long-term effects of rituximab on humoral immunity and infection risk merit the attention of all clinicians using BCTT [1]. There is scant data available on the natural history of hypogammaglobulinaemia and the indications for immunoglobulin replacement therapy (IGRT) in BCTT-associated hypogammaglobulinaemia. Rituximab, as an anti-CD20 chimeric murine-human monoclonal antibody, was first used as therapy for non-Hodgkin's lymphoma, and the incidence of IGRT requirement has been reported variably (e.g. 6.6% in lymphoma, 14-21% in ANCA-associated vasculitis (AAV)) [5,6,7].

Secondary immunodeficiency (SID) including secondary hypogammaglobulinaemia forms an escalating part of the clinical workload in Immunology services [9]. Currently there are no

consensus guidelines for managing this clinical problem. We have developed recommendations based on a systematic literature review and a Delphi process by a multidisciplinary panel of healthcare professionals with experience of secondary hypogammaglobulinaemia and IGRT, along with input from an expert patient. The recommendations and points to consider are intended for use by health-care professionals to aid diagnostic and therapeutic clinical decision making for patients with hypogammaglobulinaemia.

Methods

The Taskforce committee consisted of four immunologists (PDB, MYK, SKA, SAM), three nephrologists (LH, DRJ, ADS), three rheumatologists (HC, CKL, CM), two haematologists (MAK, DW), one gastroenterologist/hepatologist (AA), one paediatric nephrologist (LO), one immunology clinical specialist nurse (SW), and a patient representative (FEP). SWi was appointed as the research fellow for the systematic literature review under the supervision of MYK, DRJ and CM.

A modified Delphi exercise was carried out to identify topics required for the recommendations. The first round of the Delphi consisted of an open email round to the Taskforce Committee members, to each identify five areas which they felt required addressing in the recommendations. A search string was then agreed to identify publications in PubMed; "(Immunologic Deficiency Syndromes"[Mesh] NOT "HIV Infections"[Mesh]) AND (("Antibodies, Monoclonal"[Mesh] OR "Abatacept"[Mesh] OR "TACI receptor-IgG Fc fragment fusion protein"[Supplementary Concept]) OR ("Immunoglobulin G/administration and dosage"[Mesh] AND "Immunoglobulin G/therapeutic use"[Mesh])) NOT ("case reports"[pt] OR "Review"[pt])".

The results were limited by using the filters 'abstracts', 'English language' and 'published in last 10 years'. Scottish Intercollegiate Guidelines Network (SIGN) checklist screening of each article was performed prior to inclusion [10]. Relevant British Society of Rheumatology (BSR) [11], United Kingdom (UK) Department of Health (DoH) [12, 13], European League Against

Rheumatic Disease (EULAR) [14, 15, 16], American College of Rheumatology (ACR), and American Academy of Allergy Asthma and Immunology (AAAAI) guidelines [17] were reviewed for additional material, yielding a further 7 publications. The literature search revealed a predominance of retrospective cohort studies.

The evidence was discussed by the committee at a face-to-face meeting to agree on the wording of the statements, and to divide them into overarching principles, recommendations and a research agenda. The statements were graded according to SIGN methodology. The level of evidence is determined by both the study design and the methodological quality of the individual studies [18]. The grades of each recommendation are established on the strength, as well as level of supporting evidence and the considered judgment of the guideline developers [18]. The recommendations were voted for the strength of recommendation using the Survey Monkey platform (SurveyMonkey, San Mateo, USA) on a four-point Likert scale; Strongly Agree, Agree, Disagree, Strongly Disagree and No expertise. These recommendations were voted on with the aim of achieving at least 70% agreement (combined "strongly agree" and "agree") with each statement [19].

Results

The themes that emerged from the modified Delphi process are listed in Table 1. The systemic literature review provides the established evidence base for these recommendations (Wijetilleka et al, submitted for publication). The face to face meeting resulted in the development of 3 overarching principles (based on patient education, educational needs, shared decision making), and 8 recommendations.

[Insert Table 1 here]

Overarching principles (OP)

OP 1: Patients and their parents/carers should be specifically informed about the possibility and implications of developing hypogammaglobulinaemia secondary to BCTT. There should

be a locally agreed pathway for patients to report infections. (16/17 [94%] agree or strongly agree)

Due to the variation in local services, a locally agreed pathway for patients to report infections should be implemented, such as reporting the infection to their general practitioner, secondary care service or clinical immunology service. If no local policy is in place, this should be developed for patients. A method of recording infections is advised. Diaries should be distributed to patients when possible. The patient's infection history can be monitored accurately pre- and post-IGRT if the patient reporting diary has been completed by the patient or carer. A diary of the documented infection frequency can help monitor the response to IGRT.

OP 2: Healthcare professionals using BCTT should be aware of local referral pathways for hypogammaglobulinaemia and its complications. (17/17 [100%] agree or strongly agree)

Hypogammaglobulinaemia secondary to BCTT is likely to be an increasingly prevalent clinical issue because of the rise in the use of targeted anti-B-cell therapy in haematological and autoimmune conditions. The importance of education and communication between secondary/tertiary care physicians with primary care physicians is paramount for seamless and conjoined care. The specific needs of patients receiving BCTT should be clearly communicated. The areas highlighted for primary care to be aware of for patients are the increased risk of infection, to be vigilant of infection, use of prompt and prolonged courses of antibiotics, and the role of vaccination.

OP 3: The commencement of IGRT and its route of administration, should follow a shared decision-making process between the patient, the clinician supervising the care of the underlying autoimmune disease and a Clinical Immunology service. (17/17 [100%] agree or strongly agree).

The Taskforce recognised the importance of shared-decision making to provide the best care and support for patients. This includes clear communication between all teams involved, informing patients of the risks and benefits of IGRT, routes of IGRT administration and

management plans. Clinicians supervising treatment of the autoimmune disease felt the decision regarding the route of immunoglobulin administration should be decided between the patient and the Clinical Immunology service providing the treatment.

Recommendations

Recommmendation 1: The decision to start IGRT should be informed by the degree of hypogammaglobulinaemia, SPUR (serious, persistent, unusual or recurrent) infections, demonstration of impaired antibody responses to polysaccharide antigens and poor response to antibiotic prophylaxis. (Grade of evidence 2+; strength of recommendation D; 17/17 [100%] agree or strongly agree)

There is no absolute level of IgG where IGRT should be commenced. Hypogammaglobulinaemia is most often asymptomatic and may be transient in this group of patients [1, 2, 20]. The SPUR infection history should be taken into account in the decision to commence IGRT, as asymptomatic hypogammaglobulinaemia is not usually an indication for IGRT. The decision to commence IGRT should also consider individual co-morbidities (e.g. bronchiectasis, neutropenia, co-prescription of immunomodulatory drugs - particularly corticosteroids). A patient may demonstrate failure of antibody response to polysaccharide antigens such as pneumococcus (as the unconjugated polysaccharide vaccine rather than the conjugate vaccine), though in some cases it may not be practical to test vaccinate. The specific antibody results and criteria of failure to respond to vaccination could be discussed with the local Immunology service. The lack of standardisation of response criteria for specific antibodies will make this interpretation difficult [21]. BCTT is recognised to blunt specific antibody response after vaccination [22, 23, 24].

The ultimate aim of antibiotic prophylaxis is for a patient to have no bacterial infections. However, this may not always be achievable, for example in patients with established bronchiectasis. While there are no current standards for defining a poor response to antibiotic

prophylaxis – this state could be said to exist if there were continued or severe infections in spite of on-going relevant antibiotic prophylaxis.

Complete IgA deficiency is a common finding, most often asymptomatic and found incidentally in healthy individuals (1 in 500 to 800). It is not a contra-indication to IGRT, as reactions to very low levels of IgA in immunoglobulin products are rare and precautions can be undertaken.

Recommendation 2: The pre-disposing factors for the development of clinically significant hypogammaglobulinaemia during or after BCTT include a pre-existing low IgG level and previous and/or concomitant immunosuppressive therapies. (Grade of evidence 2- to 2+; strength of recommendation D; 17/17 [100%] agree or strongly agree)

Several studies reported baseline IgG prior to rituximab treatment to be the most important predictor of hypogammaglobulinaemia [2, 4, 25, 26]. The risk of hypogammaglobulinaemia seems to be influenced by the underlying autoimmune disease, for example an increased risk is seen in AAV compared with RA [27]. This is based on limited observations and the reasons for this variable risk are not well established [2,24]. There is conflicting evidence regarding whether cyclophosphamide increases the risk of hypogammaglobulinaemia in BCTT patients [2, 26]. Other immunosuppressive medications may also be contributory, particularly corticosteroids [4].

Recommendation 3: Patients with AIRD who have hypogammaglobulinaemia and SPUR infections should be referred to a Clinical Immunology service for assessment. (Grade of evidence 4; strength of recommendation D; 14/17 [82%] agree or strongly agree)

In addition to symptomatic patients, a referral to Clinical Immunology services should be made in asymptomatic patients with hypogammaglobulinaemia with an IgG level of 3g/L or lower. We acknowledge the absence of specific evidence base for selection of this particular IgG level in AIRD patients, but feel as a group that an absolute level may be helpful for decision-making. Boughton et al reported in chronic lymphocytic leukaemia patients, the majority of infections occurred when IgG < 3g/L [28]. Referral could also be considered for

AIRD patients with SPUR infections but without hypogammaglobulinaemia to assess other risk factors [29]. It was considered that the monitoring and management of IGRT should be supervised in conjunction with a Clinical Immunology service.

Recommendation 4: Immunoglobulin levels should be measured prior to commencement of BCTT and repeated every 6 to 12 months for the duration of BCTT and a minimum of one year after stopping treatment. In selected patients it may be appropriate to monitor for longer. (Grade of evidence 2+; strength of recommendation D; 17/17 [100%] agree or strongly agree).

These recommendations are based on the licensed therapies and the agreed national dosage recommendations. Certain centres use lower dose BCTT regimens (e.g. in rituximab dosing). The exact monitoring of hypogammaglobulinaemia will therefore vary in these centres, as it is dependent on the dosing regimen for the BCTT agent [11].

Long term monitoring should consider the patients' SPUR infection history, comorbidities such as bronchiectasis and use of other immunosuppressive treatments like corticosteroids and azathioprine. It is sensible to consider longer term monitoring of immunoglobulins following BCTT, which may be needed in a selection of cases. Marco *et al.* reported a median of 18 months for development of hypogammaglobulinaemia, and a median time of 35 months (1 – 70 months) to the most severe hypogammaglobulinaemia [1].

Recommendation 5: In hypogammaglobulinaemia related to BCTT, initial dosing of IGRT should be 0.4g/kg/month. The route of administration should take into account patient preference, comorbidities and local availability. (Grade of evidence 4; strength of recommendation D; 17/17 [100%] agree or strongly agree).

IGRT practice in the UK follows the DoH guidelines, which state initiation at 0.4/kg/month[12]. The dose of IGRT should be adjusted in accordance to the clinical response, IgG trough levels, infection frequency and individual patient factors [30].

The options for route of administration of IGRT include subcutaneous and intravenous infusions at home or electively in hospital [31]. The subcutaneous administration can also be performed as a rapid push[1], however this is dependent on the type of IGRT and manufacturer. No data is available on rapid push for hypogammaglobulinaemia in AIRD patients.

Important parameters were highlighted for the decision of which route of administration to choose. These included the frequency and severity of infections, comorbidities individualised to the patient, venous access and the availability of support at home such as an infusion partner. There is broad experience in the Immunology Nursing community in the management of these key issues. The effect on quality of life,the patient's tolerance of treatment and side-effects of treatment should be considered. There is evidence available from studies in primary immunodeficiency (PID), both for subcutaneous and intravenous routes [32, 33]. Health-related quality of life (assessed via the 36-item Short Form Health Survey version 2) improved in adult PID patients 12-months post commencement of IgG-treatment compared to pre-treatment [34].

Recommendation 6: Low IgG level is not an absolute contra-indication to commencing or continuing BCTT. The decision should be based on an individualised benefit-risk analysis. (Grade of evidence 2+; strength of recommendation D; 17/17 [100%] agree or strongly agree).

Hypogammaglobulinaemia is not an absolute contraindication to continuing BCTT. The majority of patients who develop hypogammaglobulinaemia do not develop complications of recurrent/severe infection. Hypogammaglobulinaemia may be transient. Roberts et al noted the nadir IgG was non-sustained in 50% of cases with moderate/severe hypogammaglobulinaemia [2]. The decision to stop BCTT or other immunosuppressive drugs should be balanced against ongoing AIRD activity, the benefit derived from BCTT and the availability of alternative therapeutic options. There is no clear evidence in support of one class of agent over another in this setting. Formal assessment of bone marrow status was not felt to be indicated and need not be taken into account when deciding on IGRT.

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[1]Rapid push refers to subcutaneous push using a manual syringe and butterfly needle, without using an infusion pump.

Recommendation 7: The decision to continue IGRT should be reviewed annually and based upon clinical and laboratory parameters. (Grade of evidence 4; strength of recommendation D; 16/17 [94%] agree or strongly agree).

Patients should be reviewed after an adequate trial of IGRT. The failure of IGRT to effectively prevent infections was discussed, though felt not to be common. In the decision to stop IGRT, individual considerations would include the efficacy, tolerability and adverse effects of IGRT. The potential risks of IGRT including thromboembolism and haemolysis were noted. In the UK, the National Health Service (NHS) has developed the Immunoglobulin Quality Dashboard, which requires that patients receiving IGRT undergo an annual review with documentation sent to the general practitioner [35].

Physicians should also be aware that recovery of endogenous immunoglobulin production may occur over time and may be suggested by persistently raised trough IgG levels. Other laboratory parameters (e.g. IgA level, IgM level and B-cell number), may also provide clues to recovery. If a trial off IGRT is considered appropriate, ideally this should be commenced during the spring or summer season, when the risk of infection (especially respiratory) is less.

Future plans for immunosuppression should be taken into account when deciding on (dis)continuation of IGRT and be considered as a clinical parameter.

Recommendation 8: There is no available evidence comparing the use of antibiotic prophylaxis with IGRT in symptomatic hypogammaglobulinaemia caused by BCTT, however an initial trial of antibiotic prophylaxis may be appropriate. (Grade of evidence 4; strength of recommendation D; 16/17 [94%] agree or strongly agree).

There is limited data regarding antibiotic prophylaxis from other immunodeficiency settings. The role of antibiotic stewardship and decisions should be made in conjunction with local Microbiology services. As to whether patients with asymptomatic hypogammaglobulinaemia

should receive prophylactic antibiotics, the committee felt that the decision should consider the IgG level and antibiotic stewardship.

There is no randomised trial comparing antibiotic prophylaxis to IGRT in any cause of secondary hypogammaglobulinaemia. There is data available for co-trimoxazole prophylaxis in patients with myeloma [36], but not in relation to hypogammaglobulinaemia or in comparison to IGRT. The DoH recommend a 3-month trial of antibiotic prophylaxis prior to making a decision regarding IGRT [12]. Antibiotic prophylaxis is often discontinued once IGRT has been established (not at commencement), dependent on patient progress.

Vaccination is important as it may improve protective immunity in patients with AIRD, and should consider the latest BSR, DoH, or EULAR recommendations for patients receiving disease-modifying anti-rheumatic drugs (DMARDs) [11, 13, 14]. Vaccination may sometimes be part of the diagnostic process ("test vaccination") in hypogammaglobulinaemia, though it is well recognised that vaccine responses may be blunted in the context of BCTT [13, 14, 23, 24].

[Insert Table 2 here]

Discussion:

These recommendations for the role and management of IGRT after treatment of AIRD with BCTT comprise 3 overarching principles and 8 recommendations (Table 2). The overarching principles provide a patient focus and promote shared decision-making.

The recommendations can provide a framework of practice for the care of patients at risk of or who develop iatrogenic hypogammaglobulinaemia due to BCTT. They would be useful both for clinicians treating patients with AIRD, haematological disorders and for Clinical Immunology professionals. These recommendations apply to currently used BCTT. However, biosimilars have already started to be introduced, and newer BCTT agents and regimes will come into practice. In addition, longer-term follow-up data will be likely to emerge on AIRD

patients treated with BCTT. Hence there will be a need for these recommendations to be updated, and we would suggest a 3-year timeframe would be appropriate.

Several clinical questions around BCTT-associated hypogammaglobulinaemia are unresolved, and we have proposed a research agenda (Table 3). We recognise the current limitations of these recommendations, particularly due to the paucity of data available on the use of IGRT for rituximab-associated hypogammaglobulinaemia. In particular, there is no data available from randomised controlled studies. Long-term outcome data from this group of patients is also not available. Under these circumstances, we have drawn from a broad church of relevant specialties using BCTT including expertise of education, handling and administration of BCTT and normal immunoglobulin. The recommendations are strengthened by the involvement of an a patient who has an AIRD and has first-hand experience of BCTT and IGRT. Where available and appropriate, discussion considered whether conclusions could be extrapolated from studies in PID, and SID due to other causes, especially haematological.

Failure to prevent potentially avoidable infections in this group of patients may require hospital admission with major clinical and financial implications. In a study of patients with a diagnosis of GPA admitted to hospital from 1993-2011, infection was the most common main discharge diagnosis, including among those who died during admission [37]. There is very limited relevant health economic data on IGRT in SID related to haematological malignancy, and no reported data in AIRD. Likewise, there is no data available on quality of life measures in BCTT-related hypogammaglobulinaemia in this group of patients. Nursing expertise has developed tremendously in IGRT for PID, with options for intravenous and subcutaneous routes (routine, rapid push, facilitated). These various treatment options should also be made available for this group of patients.

These issues are primarily important for the clinical care of AIRD patients, but there is no doubt with the financial pressures in the NHS and other healthcare systems, that the cost-effectiveness of IGRT in this setting will need to be considered. On a practical basis in the UK, these recommendations will need to be considered together with the latest iteration of the DoH clinical guidelines for immunoglobulin use (currently in the process of revision).

[Insert Table 3 here]

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