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Prospective data collection of off-label use of rituximab in Australian public hospitals

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Key words
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Abstract

Background: Rituximab is a chimeric, anti-CD20 monoclonal antibody registered for the treatment of B-cell malignancies and refractory rheumatoid arthritis in Australia. In addition to these approved indications, there has been growing interest in the use of off-label rituximab in the management of a variety of diseases.

Aims: To determine the current usage of off-label rituximab in Australia, we collected nationwide data.

Methods: Information regarding patients receiving rituximab for off-label indications was prospectively collected for a 6-month period from Australian public hospitals. Data recorded included clinical indication, dosing schedule, previous therapy and efficacy assessment. The level of evidence for the use of rituximab was determined for each off-label indication.

Results: During the 6-month period, a total of 364 instances of off-label rituximab use was recorded in the national database. A total of 63 underlying diagnoses was identified. These were subclassified into haematological disorders (19%), autoimmune connective tissue diseases (12%), vasculitis (12%), neurological disorders (12%), transplant-related uses (12%), haematological malignancies (11%), muscle disorders (8%), renal diseases (6%), dermatological conditions (5%), other conditions (2%) and ocular diseases (1%). Forty per cent of these requests were supported only by level 4 evidence of benefit. Data highlighted the non-standardised approaches to drug approval mechanisms, dosing schedules and monitoring for efficacy.

Conclusions: Off-label rituximab is prescribed for a diverse range of clinical conditions. Determining a safe and effective means of regulating this use within an evidence-based framework remains an ongoing challenge.

Introduction

Rituximab is a chimeric, anti-CD20 monoclonal antibody first registered for clinical use by the US Food and Drug Administration (FDA) in 1997 and by the European Medicines Agency the following year. It has revolutionised the treatment of non-Hodgkin lymphoma (NHL), and a decline in the mortality rates since its introduction has been observed.[1] In Australia, the Therapeutic Goods Administration (TGA) first registered rituximab in 2002, and initial listings were for the treatment of relapsed or refractory low-grade or follicular NHL and CD20+ diffuse large B-cell NHL. Rituximab has subsequently become a major therapeutic agent in the management of several B-cell malignancies[2] and has subsequently been registered for use in refractory rheumatoid arthritis. In addition to these approved indications, there has been growing interest in the B-cell depleting properties of rituximab in the management of a heterogeneous group of autoimmune and inflammatory diseases.[3–5]

Rituximab results in the death of CD20 expressing B cells by antibody-dependent cell-mediated cytotoxicity, complement-mediated lyses or apoptosis.[6] CD20 is expressed on the surface of B cells from the pre-B-cell stage through to memory B cells but not on antibody-producing plasma cells. Thus, treatment responses to rituximab in autoimmune conditions are more complex than a reduction in autoantibody production. Depletion of B cells results in altered T-cell stimulation through a

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reduction in cytokine production and antigen presentation. Furthermore, rituximab has been shown to result in a skewing towards a Th2 response and restoration of T-regulatory cells.[4,6]

The term 'off-label' can be defined as the use of a registered medicine for an indication not included in the approved prescribing information or administered at a non-approved dose or dosing schedule.[7] Off-label prescribing is common in hospitalised patients, with estimates of up to 70% of adults receiving at least one off-label medication during an admission[8] and even higher rates recorded for paediatric inpatients.[9] The increasing use of high-cost biologics, such as rituximab, for off-label indications raises several important issues, including cost-effectiveness, funding mechanisms and long-term safety.[5] We prospectively collected nationwide data on the use of off-label rituximab within Australian public hospitals, with the view of providing essential information for national drug regulatory and funding bodies to assist in the development of governance models around off-label use of high-cost biological therapeutic agents.

Methods

Information regarding patients receiving rituximab, for non-TGA approved indications, was prospectively collected for a 6-month period from May 2012 until October 2012. Taking advantage of a communication network provided by existing state- and territory-based therapeutic advisory groups, all public hospitals within Australia were invited to contribute cases, and treating specialists, unit data managers or pharmacists were requested to complete a brief online questionnaire for these patients that could be completed in under 5 min. Information was collected on clinical indication, patient age and sex, dosing schedule, approval mechanism, funding mechanism, prior therapy, and efficacy parameters. Data were collected using a web-enabled, password-protected database. The database was screened periodically for duplicate entries, and these were deleted. For each of the clinical indications collected, a literature search was conducted to assess the available level of evidence for rituximab use. Level of evidence from 1 to 5 for treatment benefit, harm or lack of response was recorded. Grading score was based on the Oxford Centre for Evidence-Based Medicine, 2011 Levels of Evidence (Table 1).

The study was conducted under the sponsorship of the Council of Australian Therapeutic Advisory Groups, and ethics approval from the Western Sydney Local Health District Human Research Ethics Committee was obtained. The study was classified as being of low or negligible risk and conducted as a clinical audit, not requiring patient consent so long as the contributed information was de-identified. Accordingly, patient-related information was fully de-identified as were contributing hospitals, with only the size of the hospital and location by state or territory being recorded. Data for the Australian Capital Territory was pooled with New South Wales, while no cases were obtained from the Northern Territory.

Table 1 Levels of evidence

Level	Evidence
Level 1†	Systematic review of randomised trials
Level 2†	Randomised trial or observational study with dramatic effect
Level 3†	Non-randomised controlled cohort/follow-up study
Level 4†	Case-series or case-control studies or historically controlled studies
Level 5†	Mechanism-based reasoning

†Level may be downgraded due to study quality, inconsistencies between studies or if the effect is very small. Level may be upgraded if there is a large effect. Modified from OCEBM Levels of Evidence Working Group. 'The Oxford 2011 Levels of Evidence'. Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653.

Results

During the 6-month study period, a total of 364 approvals for off-label rituximab was recorded. Subject and hospital characteristics are summarised in Table 2. The age range of patients treated varied widely: range 1–89 years of age, with a median of 46 years. Figure 1 demonstrates the age spectrum within the cohort, with peak prescribing in the 41- to 50-year age band. There were five requests recorded in the 81- to 90-year-old age group. There was a slight female preponderance (58% female), likely reflective of the higher incidence of autoimmune diseases in women. Over a third (36%) of

Table 2 Subject and hospital demographics

Characteristics	Approvals (n = 364)
Age range	1–89 years
Median age	46 years
Sex	Female: 211 (58%)
	Male: 153 (42%)
Previous rituximab	Yes: 131 (36%)
	No: 218 (60%)
	Not recorded: 15 (4%)
Previous disease targeting therapy	No: 45 (12%)
	Yes: 279 (77%)
	Unknown: 40 (11%)
Hospital size	>500 beds: 227 (62%)
	250–500 beds: 135 (37%)
	<250 beds: 2 (1%)

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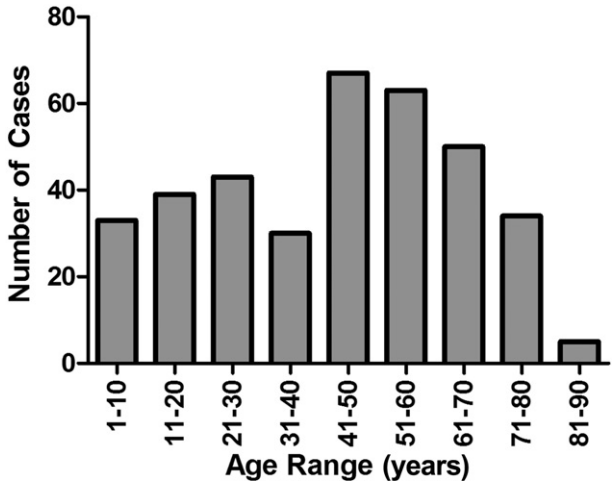

Figure 1 Age distribution of patients receiving off-label rituximab.

the subjects had received rituximab previously. The majority of approvals was generated from large hospitals, defined by having greater than 500 inpatient beds (62%).

To investigate the completeness of data, we used compulsorily collected high-cost, off-label, drug utilisation information provided by the South Australian Department of Health. Over the study period, there were 35 total episodes of off-label rituximab prescribing in South Australian public hospitals, of which our voluntary data collection captured 26, meaning we captured 74% of episodes for this state. The actual rate of rituximab use in South Australia was 4.24 treatment episodes per 100 000 population, which compared favourably with the rates per state from the prospective voluntary nationwide data collection (range 1.64–5.86, median 3.47 cases per 100 000 population).

Interestingly, the approval process for use of off-label rituximab was not uniform across Australian public hospitals. The majority of requests was approved by a local drug and therapeutics committee (78%); however, various other approval mechanisms were operational, including clinical department heads or local health administrators.

The clinical indications for rituximab were recorded for 353 of the 364 cases, and a total of 63 different conditions made up these approvals (Table 3). These were subclassified into haematological disorders $n = 67$ (19%), autoimmune connective tissue diseases $n = 44$ (12%), vasculitis $n = 42$ (12%), neurological disorders $n = 42$ ($n = 12\%$) transplant-related uses $n = 41$ ($n = 12\%$), haematological malignancies $n = 38$ (11%), muscle disorders $n = 29$ (8%), renal diseases $n = 22$ (6%), dermatological conditions $n = 16$ (5%), other conditions $n = 8$ (2%) and ocular diseases $n = 4$ (1%). Level 4 evidence of benefit existed for 40% of these conditions ($n = 23$). Good-quality or level 1 evidence existed for only two of the indications (<1%): granulomatosis with polyangiitis and rheumatoid arthritis. Although rheumatoid arthritis is a registered indication in Australia, many patients may not meet the strict approval criteria for funding of therapy through the Pharmaceutical Benefits Scheme operated by the Federal Government, and thus are included in the off-label group. For systemic lupus erythematosus (SLE), level 1 evidence is available, demonstrating a lack of benefit over placebo for rituximab on patients receiving background immunosuppression.[10,11] This conflicts with initial case series and reports demonstrating a positive impact of rituximab therapy in this condition.[10–13] Conflicting efficacy data were found for a total of nine conditions (13%), with some studies demonstrating a benefit from rituximab while others reporting adverse outcomes or no response. Conditions with conflicting data included mixed connective tissue disease[14] and ulcerative colitis.[15,16]

Analysis excluding haematological malignancies demonstrated that other immunomodifiers had been trialled in the majority of cases (76%) compared with no prior treatment in less than 1% of cases. The prior treatment was unknown or not recorded in the remainder (23%). In those cases, where prior treatment had been administered, often multiple agents had been utilised: one agent (18%), two agents (28%), three agents (31%) and four or more (23%). In some cases, up to nine previous therapies had been trialled. Commonly administered drugs or therapeutic procedures included corticosteroids, mycophenolate mofetil or mycophenolic acid, cyclophosphamide, intravenous immunoglobulin, and plasma exchange.

Table 4 details the dosing regimens implemented. The most frequently used method consisted of two fixed doses given fortnightly, likely adopted from the dosing schedule used most commonly in clinical trials of rituximab-treated rheumatoid arthritis. The second most widely used schedule is based on the NHL treatment protocol, using a body surface area calculated dose administered weekly for 4 weeks. However, a surprisingly wide variety of other dosing methods and schedules were recorded, for which there is little or no evidence base. Some approvals to use this agent allowed for clinicians to dose as they saw fit.

Prospectively set parameters for assessing the efficacy of rituximab were defined by the approval process used in 117 (48%) of cases. The most common methods to assess for response included laboratory measures (32%), clinical response (17%) or a combination of the two (15%). Other means of monitoring included radiographic imaging, weaning of other immunosuppression, B-cell

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Table 3 Spectrum of clinical conditions instigating off-label rituximab prescribing and level of evidence for use

Condition	*n* = 353 (%)	Level of evidence		
		Benefit	No benefit	Harm
Haematological disorders	67 (19)			
ITP	23 (7)	3	–	–
Autoimmune haemolytic anaemia	11 (3)	4	–	–
Acquired haemophilia	10 (3)	4	–	–
TTP	9 (3)	3	–	–
Autoimmune cytopenia	7 (2)	4	–	–
Aplastic anaemia	4 (1)	4	–	–
Hereditary haemophilia	2 (1)	No evidence	–	–
Cold agglutinin disease	1 (<1)	3	–	–
AI connective tissue diseases	44 (12)			
SLE	27 (8)	4	1	
Rheumatoid arthritis	6 (2)	1	–	–
Mixed connective tissue disease	1 (<1)	4	–	4
Scleroderma	3 (1)	4	3	–
Sjögren syndrome	1 (<1)	2	–	–
Antiphospholipid syndrome	6 (2)	4	–	–
Vasculitides	42 (12)			
Granulomatosis with polyangiitis	22 (6)	1	–	–
ANCA vasculitis	7 (2)	1, 4	–	–
Cryoglobulinaemic vasculitis	6 (2)	2	–	–
Other vasculitis	3 (1)	†	–	–
Buerger-like vasculitis	1 (<1)	No evidence	–	–
Panarteritis nodosa	1 (<1)	4	–	–
Small intestinal vasculitis	1 (<1)	†	–	–
Eosinophilic polyangiitis	1 (<1)	4	–	–
Neurological disorders	42 (12)			
Neuromyelitis optica	15 (4)	4	–	–
Paraneoplastic and AI encephalitis	9 (3)	4	–	–
Opsoclonus myoclonus ataxia	5 (1)	4	–	–
CIDP	5 (1)	4	–	–
Neuropathy unspecified	3 (1)	†	–	–
Autoimmune neuroretinitis	1 (<1)	†	–	–
Multiple sclerosis	1 (<1)	–	2	–
Stiff person syndrome	1 (<1)	4	4	–
Rasmussen syndrome	1 (<1)	5	–	–
AIDP	1 (<1)	4	5	–
Transplant	41 (12)			
Antibody-mediated rejection transplant (lung, cardiac, renal)	18 (5)	3	–	–
PTLD liver, renal or cardiac	10 (3)	3	–	–
Recurrence of FGS	3 (1)	4	4	–
Prophylaxis of transplant rejection	3 (1)	4	–	–
GVDH post-BMT	3 (1)	4	–	–
Post-BMT EBV	3 (1)	3	–	–
HBV liver failure for transplant	1 (<1)	–	–	5
Haematological malignancy	38 (11)			
Lymphoma unspecified	25 (7)	†	–	–
Mantle cell lymphoma	7 (2)	3	–	–
Acute lymphoblastic leukaemia	2 (1)	3	–	–
Chronic lymphocytic leukaemia	1 (<1)	2	–	–
Castleman disease	1 (<1)	4	–	–
MALT lymphoma	1 (<1)	3	–	–
Waldenstrom macroglobulinaemia	1 (<1)	2	–	–
Neuromuscular disorders	29 (8)			
Polymyositis/dermatomyositis/myositis	14 (4)	4	–	–
Myaesthenia gravis	11 (3)	4	–	–

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Table 3 Continued

Condition	*n* = 353 (%)	Level of evidence		
		Benefit	No benefit	Harm
Lambert–Eaton syndrome	2 (1)	4	–	–
MUSK myaesthenia gravis	2 (1)	4	–	–
Dermatological conditions	16 (5)			
Pemphigus	6 (2)	3	–	–
Cicatricial pemphigoid	5 (1)	3	–	–
Mucocutaneous lichen planus	2 (1)	4	–	–
Chronic idiopathic urticaria	2 (1)	4	–	–
Eczema	1 (<1)	4	–	–
Renal disease	22 (6)			
GN/Nephrotic syndrome	12 (3)	†	–	–
Membranous GN	7 (2)	3	–	–
Minimal change nephrotic syndrome	2 (1)	2	2	–
Goodpasture disease	1 (<1)	4	–	–
Other	8 (2)			
Interstitial lung disease	3 (1)	†	–	–
Diabetes (anti-insulin antibodies)	1 (<1)	2	–	–
Post-EBV encephalopathy	1(<1)	No evidence	–	–
Chronic fatigue syndrome	1 (<1)	4	–	–
Ulcerative colitis	1 (<1)	2	–	4
IgG4-related sclerosing disease	1 (<1)	4	–	–
Ocular disorder	4 (1)			
Graves' ophthalmopathy	2 (1)	3	–	–
Inflammatory orbitopathy	1 (<1)	5	–	–
Behcet scleritis	1 (<1)	3	–	–

†Diagnosis encompassing a spectrum of clinical conditions: literature review for level of evidence not possible. AI, autoimmune; AIDP, acute inflammatory demyelinating polyneuropathy; ANCA, antineutrophil cytoplasmic antibody; BMT, bone marrow transplant; CIDP, chronic inflammatory demyelinating polyneuropathy; EBV, Epstein–Barr virus; FGS, focal glomerular sclerosis; GN, glomerulonephritis; GVHD, graft versus host disease; HBV, hepatitis B virus; ITP, idiopathic thrombocytopenic purpura; MALT, mucosa-associated lymphoid tissue; MUSK, muscle specific kinase; PTLD, post-transplant lymphoproliferative disease; SLE, systemic lupus erythematosus; TTP, thrombotic thrombocytopenic purpura.

counts or a combination of these methods. In many instances, the defined measures were not explicit, for example a non-specific 'clinical response'. However, in other cases, well-defined criteria were outlined, including use of recognised clinical grading scores, such as the Birmingham vasculitis score, inflammatory markers and quantitative testing of auto-antibodies.

Discussion

This represents the largest Australian national audit of off-label rituximab use, and highlights the extensive and heterogeneous nature of medical conditions where this monoclonal antibody is now considered a therapeutic option. The spectrum of clinical conditions involves multiple medical disciplines. Our data indicate that rituximab is used in refractory cases where multiple other therapies have been trialled and presumably failed or led to unacceptable side-effects. Level 1 evidence of efficacy existed only for rheumatoid arthritis and granulomatosis with polyangiitis. Although rheumatoid arthritis is an approved indication, many patients may not meet the criteria for government funding support, and thus are included in the off-label group. Interestingly, rituximab

Table 4 Dosing schedules for the 364 off-label rituximab requests

Dose calculation	Single dose	Fortnightly (2 doses)	Weekly (4 doses)	Other dosing interval
Weight-based/BSA (*n* = 156)	19	21	78	38
Fixed dose (*n* = 175)	15	94	38	28
Other method (*n* = 18)	2	6	4	6

BSA, body surface area.

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has recently gained US FDA approval for the treatment of granulomatosis with polyangiitis. Only level 4 evidence is available to support the use of rituximab for 40% of the indications due to lack of sufficiently powered clinical trials or the rarity of the conditions. Indeed, many of the listed conditions are extremely rare, and a high level of evidence leading to a registered indication is unlikely to arise. This is in keeping with a previously published report on off-label rituximab use, which found that there was 'inadequate evidence base' for the use of rituximab in 47.1% of patients.[17]

In 2006, a working party established consensus recommendations for evaluating the appropriateness of off-label medicine use in Australia.[7] Three categories for appropriate off-label prescribing were identified, including (i) off-label use justified by high-quality evidence, (ii) use within a formal research proposal and (iii) exceptional use. In our study, high-quality evidence existed for only 8% of approvals. We cannot be certain from the data collected if any of the approvals fell into a formal research study, but presumably the majority of the approvals recorded would be classified as 'exceptional use'. The consensus recommendations provided an additional six criteria to be met for this category: (i) a serious underling disease, (ii) some evidence to support benefit, (iii) potential benefits outweigh risks, (iv) standard therapy has been trialled, (v) approved by a drug committee and (vi) written informed consent obtained. Again, from our own experience and the underlying diagnoses collected as part of the survey, the majority of cases would fulfil the first five of these additional criteria. We have no data concerning the use of written informed consent.

In this study, SLE was the condition with the highest number of individual requests for the off-label use of rituximab. Unfortunately, two randomised clinical trials (EXPLORER[10,12] and LUNAR[11]) assessing rituximab treatment for SLE have failed to demonstrate efficacy. These studies are in stark contrast to earlier uncontrolled studies demonstrating a response to rituximab for a variety of SLE manifestations, including overall activity,[13,18] lupus nephritis[19,20] and central nervous system disease.[21,22] Given this body of evidence, there has been much discussion about why the randomised trials failed to validate efficacy outcome measures. Reasons proposed for these discrepancies include the cohort of patients enrolled, continuation of background therapy and clinical scoring systems used to assess response. Thus, even when funding and recruitment are possible for large randomised trials, it may be difficult to determine efficacy for rituximab in complex disease states.

One of the other concerns with off-label prescribing is determining an effective and safe dose for a particular condition. This study highlights the wide array of dosing schedules presently being utilised. Many patients were prescribed the 375 mg/m^2 weekly dose for 4 weeks, which has been adopted from clinical trials for the treatment of NHL. The lymphocyte burden is likely to differ substantially in autoimmune conditions compared with lymphoproliferative diseases. Recent work has demonstrated that low doses of rituximab are efficacious for a variety of conditions, for example, a 100 mg fixed dose administered weekly for 4 weeks in autoimmune haemolytic anaemia.[23] In addition, two fixed 500 mg doses given 2 weeks apart have shown efficacy in pemphigus[24] and myaesthenia gravis.[25] Good pharmacokinetic data also exist for appropriateness of a single dose in the treatment of transplant rejection.[26] A study in rheumatoid arthritis patients receiving two fixed doses of either 500 mg or 1000 mg 2 weeks apart demonstrated that response rates correlated better with B-cell depletion rather than with the dose administered.[27] This suggests that tailoring doses based on B-cell analysis may be a more appropriate way of prescribing in some settings. Determining the lowest effective dose for various conditions has the potential to reduce adverse events, improve long-term safety and substantially reduce the economic burden imposed by this high-cost drug.

One potential limitation of this study is that we relied on voluntary notification of off-label prescribing of rituximab within Australian public hospitals. Fortunately, the true rate of off-label rituximab use was available from one jurisdiction, South Australia. The study captured 74% of these treatment episodes, and the median rate of off-label rituximab use across all state jurisdictions was only slightly lower than the actual rate for South Australia, suggesting that the study successfully captured the majority of treatment episodes nationally.

A Spanish national registry, BIOGEAS (Spanish Study Group of Biological Agents in Autoimmune Diseases), has estimated that at least 11% of all biological use is off-label.[28] A large North American study found that 25.3% of rituximab use was for off-label indications.[17] Also, we did not record adverse events or have the ability to collect data on long-term safety. Safety data for off-label medications are often extrapolated from studies on approved indications, and this approach is fraught with problems. The two patient populations differ substantially due to disease states and background immunosuppression. Furthermore, the level of acceptable risk will vary, for example, the management of haematological malignancy compared with a condition such as eczema. Important data on safety and infection risk for rituximab have been generated from national databases, such as BIOGEAS.[28] One of the particular post-marketing concerns with rituximab has been the risk of progressive multifocal leukoencephalopathy (PML). In 2006 and

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2007, the FDA, the European Medicines Agency, the World Health Organization and the manufacturer all issued safety warnings describing two subjects with SLE who developed PML after receiving rituximab in conjunction with other immunosuppressants.[29–32] PML has subsequently been reported after rituximab use for a variety of conditions, including idiopathic thrombocytopenia, rheumatoid arthritis and autoimmune haemolytic anaemia.[33] Although PML remains a very rare complication, the disease is often fatal and awareness is essential in the setting of off-label prescribing.

Conclusion

The issue of off-label prescribing of biologics for autoimmune and inflammatory conditions is likely to become increasingly complex as we see the armamentarium of such therapies expand. There is an emerging collection of medicines, not just for B-cell depletion, but also for targeting cytokines and co-stimulatory molecules. The challenge for the future remains: how do we best ensure access to these novel, potentially lifesaving therapies, for the appropriate patients while still providing appropriately regulated, safe and economically viable healthcare? Development of a national database of off-label high-cost drug use that records information such as that collected in this study, as well as clinical outcomes and adverse drug reactions, may well serve as the cornerstone to providing answers to this complex question.

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References

1 Molina A. A decade of rituximab: improving survival outcomes in non-Hodgkin's lymphoma. *Annu Rev Med* 2008; **59**: 237–50.
2 Winter MC, Hancock BW. Ten years of rituximab in NHL. *Expert Opin Drug Saf* 2009; **8**: 223–35.
3 McDonald V, Leandro M. Rituximab in non-haematological disorders of adults and its mode of action. *Br J Haematol* 2009; **146**: 233–46.
4 Dierickx D, Delannoy A, Saja K, Verhoef G, Provan D. Anti-CD20 monoclonal antibodies and their use in adult autoimmune hematological disorders. *Am J Hematol* 2011; **86**: 278–91.
5 Sharma R, Koller L, Barclay P, Liddle C. Evaluation of the off-label usage of rituximab in a large teaching hospital in New South Wales. *Intern Med J* 2007; **37**: 569–71.
6 Cooper N, Arnold DM. The effect of rituximab on humoral and cell mediated immunity and infection in the treatment of autoimmune diseases. *Br J Haematol* 2010; **149**: 3–13.
7 Gazarian M, Kelly M, McPhee JR, Graudins LV, Ward RL, Campbell TJ. Off-label use of medicines: consensus recommendations for evaluating appropriateness. *Med J Aust* 2006; **185**: 544–8.
8 Cras A, Conscience MA, Rajzbaum G, Lillo-Le Louet A, Lopez N, Tersen I *et al*. Off-label prescribing in a French hospital. *Pharm World Sci* 2007; **29**: 97–100.
9 Cuzzolin L, Zaccaron A, Fanos V. Unlicensed and off-label uses of drugs in paediatrics: a review of the literature. *Fundam Clin Pharmacol* 2003; **17**: 125–31.
10 Merrill JT, Neuwelt CM, Wallace DJ, Shanahan JC, Latinis KM, Oates JC *et al*. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. *Arthritis Rheum* 2010; **62**: 222–33.
11 Rovin BH, Furie R, Latinis K, Looney RJ, Fervenza FC, Sanchez-Guerrero J *et al*. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the lupus nephritis assessment with rituximab study. *Arthritis Rheum* 2012; **64**: 1215–26.
12 Merrill J, Buyon J, Furie R, Latinis K, Gordon C, Hsieh HJ *et al*. Assessment of flares in lupus patients enrolled in a phase II/III study of rituximab (EXPLORER). *Lupus* 2011; **20**: 709–16.
13 Terrier B, Amoura Z, Ravaud P, Hachulla E, Jouenne R, Combe B *et al*. Safety and efficacy of rituximab in systemic lupus erythematosus: results from 136 patients from the French AutoImmunity and Rituximab registry. *Arthritis Rheum* 2010; **62**: 2458–66.
14 Vela P, Sivera F, Batlle-Gualda E, Mayor M, García-Manzanares A, Pascual E. Severe ischemia following treatment with rituximab in a patient with mixed connective tissue disease: an unusual complication. *Lupus* 2010; **19**: 1005–6.
15 Leiper K, Martin K, Ellis A, Subramanian S, Watson AJ, Christmas SE *et al*. Randomised placebo-controlled trial of rituximab (anti-CD20) in active ulcerative colitis. *Gut* 2011; **60**: 1520–6.
16 Ardelean DS, Gonska T, Wires S, Cutz E, Griffiths A, Harvey E *et al*. Severe ulcerative colitis after rituximab therapy. *Pediatrics* 2010; **126**: e243–6.
17 Van Allen EM, Miyake T, Gunn N, Behler CM, Kohlwes J. Off-label use of rituximab in a multipayer insurance system. *J Oncol Pract* 2011; **7**: 76–9.
18 Galarza-Maldonado C, Kourilovitch MR, Molineros JE, Cardiel MH, Zurita L, Soroka NF *et al*. The administration of low doses of rituximab followed by hydroxychloroquine, prednisone and low doses of mycophenolate mofetil is an effective therapy in Latin American

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patients with active systemic lupus erythematosus. *Autoimmun Rev* 2010; **10**: 108–11.
19 Ramos-Casals M, Diaz-Lagares C, Soto-Cardenas MJ, Brito-Zeron P, Cuadrado MJ, Sanna G *et al*. Rituximab therapy in lupus nephritis: current clinical evidence. *Clin Rev Allergy Immunol* 2011; **40**: 159–69.
20 Diaz-Lagares C, Croca S, Sangle S, Vital EM, Catapano F, Martinez-Berriotxoa A *et al*. Efficacy of rituximab in 164 patients with biopsy-proven lupus nephritis: pooled data from European cohorts. *Autoimmun Rev* 2012; **11**: 357–64.
21 Tokunaga M, Saito K, Kawabata D, Imura Y, Fujii T, Nakayamada S *et al*. Efficacy of rituximab (anti-CD20) for refractory systemic lupus erythematosus involving the central nervous system. *Ann Rheum Dis* 2007; **66**: 470–5.
22 Narvaez J, Rios-Rodriguez V, de la Fuente D, Estrada P, Lopez-Vives L, Gomez-Vaquero C *et al*. Rituximab therapy in refractory neuropsychiatric lupus: current clinical evidence. *Semin Arthritis Rheum* 2011; **41**: 364–72.
23 Barcellini W, Zaja F, Zaninoni A, Imperiali FG, Battista ML, Di Bona E *et al*. Low-dose rituximab in adult patients with idiopathic autoimmune hemolytic anemia: clinical efficacy and biologic studies. *Blood* 2012; **119**: 3691–7.
24 Horvath B, Huizinga J, Pas HH, Mulder AB, Jonkman MF. Low-dose rituximab is effective in pemphigus. *Br J Dermatol* 2012; **166**: 405–12.
25 Blum S, Gillis D, Brown H, Boyle R, Henderson R, Heyworth-Smith D *et al*. Use and monitoring of low dose rituximab in myasthenia gravis. *J Neurol Neurosurg Psychiatry* 2011; **82**: 659–63.
26 Genberg H, Hansson A, Wernerson A, Wennberg L, Tyden G. Pharmacodynamics of rituximab in kidney transplantation. *Transplantation* 2007; **84** (Suppl 12): S33–6.
27 Vital EM, Rawstron AC, Dass S, Henshaw K, Madden J, Emery P *et al*. Reduced-dose rituximab in rheumatoid arthritis: efficacy depends on degree of B cell depletion. *Arthritis Rheum* 2011; **63**: 603–8.
28 Carmona L, Descalzo MA, Ruiz-Montesinos D, Manero-Ruiz FJ, Perez-Pampin E, Gomez-Reino JJ. Safety and retention rate of off-label uses of TNF antagonists in rheumatic conditions: data from the Spanish registry BIOBADASER 2.0. *Rheumatology (Oxford)* 2011; **50**: 85–92.
29 FDA. Rituximab. FDA alert: information for healthcare professionals. Rockville, MD. 2006. [cited 2013 Jun 24]. Available from URL: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126519.htm
30 EMEA. European public assessment report: Mabthera (revision). 2007. [cited 2013 Jun 24]. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000165/WC500025821.pdf
31 South San Francisco, CA: Genentech; 2006. Rituximab (Rituxan) [package insert].
32 WHO. WHO pharmaceuticals newsletter. 2007. [cited 2012 Dec 13]. Available from URL: http://www.who.int/medicines/publications/newsletter/PN_3_2007.pdf
33 Carson KR, Evens AM, Richey EA, Habermann TM, Focosi D, Seymour JF *et al*. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. *Blood* 2009; **113**: 4834–40.

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