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

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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 is anecdotal evidence that a significant proportion are is being used off-label for the management of a variety of diseases.

Aims

- To provide a snapshot of the extent of off-label rituximab use;
- To describe off-label indications for which rituximab is being prescribed; and
- To understand the cost burden of off-label rituximab prescription.

Methods

An online survey tool prospectively collected data of off-label rituximab prescription for a six months period from April 2012 to October 2012. All Australian hospitals were contacted and provided a survey link via the State and Territory Therapeutic Advisory Groups.

Individual hospitals entered data to the survey. Data recorded included clinical indication, dosing schedule, previous therapy and efficacy assessment. For each of the clinical indications reported a literature search was conducted to assess the available level of evidence for rituximab use.

Table 1: Levels of evidence

Level	Evidence
Level 1*	Systematic review of randomized trials
Level 2*	Randomized trial or observational study with dramatic effect
Level 3*	Non-randomized controlled cohort/follow up study
Level 4*	Case-series or case-control studies or historically controlled studies
Level 5*	Mechanism-base 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

Ethics approval was granted by The University of Sydney Human Research and Ethics Committee.

Results

Table 2: Subject and hospital demographics

Characteristics	Approvals (n=364)
Median age (range)	46 (1-89) 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%)

Table 3: Most commonly reported clinical conditions instigating off-label rituximab prescribing and level of evidence for use, n= 353

Condition	Number of cases	Level of Evidence
Idiopathic thrombocytopenia purpura	23	3
Autoimmune haemolytic anaemia	11	4
Acquired haemophilia	10	4
Systemic lupus erythematosus	27	4
Rheumatoid arthritis	6	1
Vasculitides	42	
Granulomatosis with polyangiitis	22	1
ANCA vasculitis	7	1, 4
Neuromyelitis optica	15	4
Antibody-mediated rejection transplant (lung, cardiac, renal)	18	3
PTLD liver, renal or cardiac	10	3
Lymphoma unspecified	25	*
Polymyositis/Dermatomyositis/ Myositis	14	4
Myasthenia gravis	11	4
GN / Nephrotic syndrome	12	*

ANCA = Anti-Neutrophil Cytoplasmic Autoantibody; PTLD= post-transplant lymphoproliferative disease
GN= glomerulonephritis

Level 1 evidence of efficacy existed only for rheumatoid arthritis and granulomatosis with polyangiitis. Level 4 evidence was available to support the use of rituximab for 40% of the indications due to the lack of sufficiently powered clinical trials or the rarity of the conditions. Many of the listed conditions are extremely rare and a high level of evidence leading to a registered indication is unlikely to arise.

Graph 1: Reported dosing schedules (n = 348)

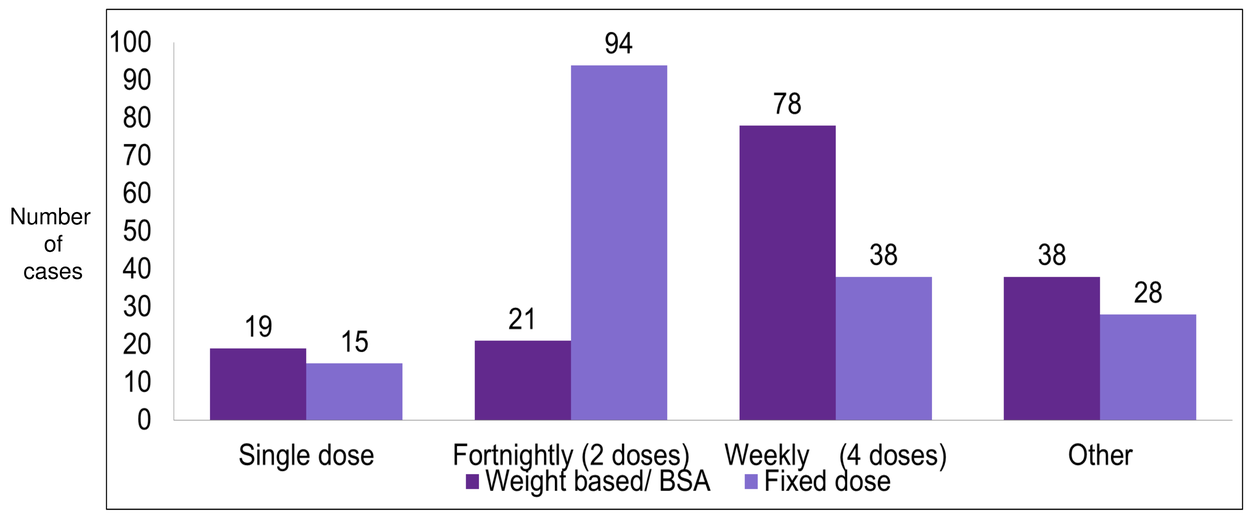

Figure 1 demonstrates the variation in dose regimens for rituximab off-label prescribing. This likely reflects the lack of evidence-based guidance for an effective and safe dose for a particular condition.

Conclusions

The audit highlighted the extensive and heterogeneous nature of medical conditions for which rituximab is considered a therapeutic option for all ages. Given the paucity of evidence for many rituximab-treated conditions, standardised consistent drug approval mechanisms with requirements for monitoring and reporting of outcomes is recommended so that future decision-making may be informed by collated data analysis.

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Further information:
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