

Summary

- ✓ **Rituximab (RTX), a monoclonal antibody, selectively targets CD20⁺ B-cells that are implicated in the pathogenesis of rheumatoid arthritis (RA).**
- ✓ **The use of RTX with methotrexate (MTX) results in statistically significant clinical improvements among RA patients who have an inadequate response to standard therapies, when compared to the use of MTX alone.**
- ✓ **The optimal dose, duration of treatment or re-treatment, long-term efficacy and safety, and placement of RTX in RA treatment algorithms need to be further investigated.**
- ✓ **Health Canada has approved the combination of RTX with MTX for use in adult patients with moderate to severe active RA, who have had an inadequate response or intolerance to ≥ 1 tumour necrosis factor (TNF) inhibitor therapies.**

The Technology

RTX (Rituxan[®], Hoffmann-La Roche Ltd., Mississauga ON) is a monoclonal antibody that selectively targets CD20⁺ B-cells; one of many cell types implicated in the immunopathogenesis of RA. In clinical trials, RTX has been shown to intercept the RA inflammatory cascade without significantly affecting normal immune system function.¹ RTX-induced B-cell depletion lasts up to six months, with levels returning to normal in nine to 12 months.²

Regulatory Status

In June 2006, Health Canada approved the combination of RTX with MTX, to reduce signs and symptoms in adult patients, with moderate to severe active RA, who have had an inadequate response or intolerance to ≥ 1 TNF inhibitor (anti-TNF) therapies.^{3,4} RTX is also approved for the treatment of CD20⁺ B-cell, non-Hodgkin's lymphoma (NHL).

Patient Group

RA is a chronic, progressive, systemic autoimmune disorder characterized by symmetric inflammation of the joint lining, leading to damaged cartilage, bone erosions, and inflammation of internal organs. RA is prevalent in 1% of the adult population, and affects approximately 300,000 (one in 100) Canadians.⁵ It occurs two to three times more frequently in women than in men, and it develops between the ages of 30 and 50 years. Diagnosis is primarily clinical, although laboratory testing and imaging studies can be confirmatory, and useful for tracking progression. Left untreated, 20% to 30% of people with RA become permanently work-disabled within three years of diagnosis.⁵

Current Practice

Symptomatic management with non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (GCs), such as prednisone, may be used initially to relieve joint pain and swelling, and to improve function.⁶⁻⁸ Disease-modifying anti-rheumatic drug (DMARD) therapy should begin within three months of diagnosis, to preserve joint form and function, and to slow disease progression.⁶ DMARDs include MTX, sulfasalazine, cyclophosphamide (CTX), and biological agents such as the anti-TNFs (etanercept, infliximab, adalimumab) and anakinra, an interleukin-1 antagonist. DMARDs are typically used in combination, or with a biological agent, as RA progresses. Patients with severe RA that is refractory to two DMARDs (including MTX), may be candidates for anti-TNF therapy.⁸ Approximately 60% of RA patients respond sufficiently when they use MTX in combination with biologics. The refractory patients are difficult to treat, so there is a need for agents such as RTX that target other inflammatory factors.⁵

The Evidence

Data from three industry-sponsored randomized controlled trials (phases IIa, IIb, III) and an open-label extension study suggest that the combination of RTX

Table 1: 24-week efficacy and safety data from phases IIa, IIb, and III RCTs

	Phase IIa ^{**†9}	Phase IIb ^{**‡} (DANCER) ¹⁰	Phase III ^{**‡} (REFLEX) ¹¹
Study Design	161 RF+ pts randomized to receive MTX (≥10 mg/wk), or RTX 1,000 mg, or RTX+MTX (same doses), or RTX (1,000 mg)+CTX (750 mg)	465 pts (79% RF+) randomized among 9 groups: RTX 500 mg, or RTX 1,000 mg, or PLR each receiving PLGC or MP, or MP+oral P; ITT=367 RF+ pts	520 pts (81% RF+) randomized to receive RTX 1,000 mg, or PLR with MP+oral GC between infusions
Efficacy and Safety Measurements at 24 weeks			
ACR20	MTX: 38%; RTX 1,000 mg: 65% (p=0.025); RTX+MTX: 73% (p=0.003); RTX+CTX: 76% (p=0.001)	PLR: 28%; RTX 500 mg: 55% (p<0.0001); RTX 1,000 mg: 54% (p<0.0001)	PLR: 18%; RTX 1,000 mg: 51% (p<0.0001)
ACR50	MTX: 13%; RTX 1,000 mg: 33% (p=0.059); RTX+MTX: 43% (p=0.005); RTX+CTX: 41% (p=0.005)	PLR: 13%; RTX 500 mg: 33% (p<0.001); RTX 1,000 mg: 34% (p<0.001)	PLR: 5%; RTX 1,000 mg: 27% (p<0.0001)
ACR70	MTX: 5%; RTX 1,000 mg: 15% (NR); RTX+MTX: 23% (p=0.048); RTX+CTX: 15% (NR)	PLR: 5%; RTX 500 mg: 13% (p=0.029); RTX 1,000 mg: 20% (p≤0.001)	PLR: 1%; RTX 1,000 mg: 12% (p<0.0001)
RR/NNT (95% CI) (fixed)	ACR 20: RR 2.23 (1.77, 2.81) (p<0.0001)/NNT 3 (3, 4) ACR 50: RR 3.34 (2.24, 4.99) (p<0.0001)/NNT 5 (4, 6) ACR 70: RR 5.37 (2.64, 10.94) (p<0.0001)/NNT 8 (6, 11)		
SAEs n (%)	MTX: 3 (8%); RTX 1,000 mg: 2 (5%); RTX+MTX: 3 (8%); RTX+CTX: 6 (15%)	PLR: 4 (4%); RTX 500 mg: 9 (7%); RTX 1,000 mg: 13 (8%)	PLR: 20 (10%); RTX 1,000 mg: 21 (7%)
RR (95% CI) (fixed)	SAE, RR: 0.93 (0.57, 1.50) (p=0.75)		

pts=patients; RF=rheumatoid factor; MTX=methotrexate; RTX=rituximab (two infusions, days 1 and 15); CTX=cyclophosphamide (two infusions, days 3 and 17); NR=not reported; PLR=placebo for RTX; PLGC=placebo for glucocorticoids; MP=intravenous methylprednisolone premedication; P=prednisolone; GC=glucocorticoids; RR=relative risk; NNT=number needed to treat; CI=confidence interval; SAEs=serious adverse events; *intention-to-treat (ITT) population; †p values are for comparisons with MTX alone; ‡p values relative to PLR.

plus MTX reduces the signs and symptoms of moderate to severe active RA in patients who did not respond to DMARDs and anti-TNFs (Table 1).⁹⁻¹³ The American College of Rheumatology (ACR) clinical response rates improved significantly among recipients of RTX plus MTX versus MTX alone, with no differences in the rates of serious adverse events (SAEs). When the data at 24 weeks are pooled, 54%, 31%, and 15% of RTX plus MTX recipients achieved ACR clinical response rates of 20, 50, and 70 versus 25%, 10%, and 3% in MTX recipients. To achieve these improvements for one person, three, five, and eight people respectively would need to be treated.

The interim results of open-label RTX re-treatment extension studies (i.e., two infusions of RTX 1,000 mg with MTX and GCs, as used in the DANCER and REFLEX trials) show similar 24-week responses without evidence of cumulative toxicity.¹²⁻¹⁴ Efficacy up to 48 weeks was observed in some patients after one course of RTX.^{15,16} Infusion-related adverse events (AEs) declined in frequency and severity with re-treatment, and prolonged B-cell depletion was not associated with an increased rate of infections.^{13,14}

Preliminary findings, based on radiographic assessment at one year, suggest that RTX may have a role in the prevention of structural damage to the joint.¹⁷

Adverse Effects

In the clinical trials, AEs were experienced more frequently by patients taking RTX than by those receiving placebo.⁴ The most frequent AEs were acute infusion reactions, reported by 15% (RTX) versus 5% (placebo) of patients after the first infusion. The rates dropped to 2% after the second infusion in both groups.⁴ There was no significant difference in life-threatening SAEs between recipients who received RTX plus MTX (7%) versus MTX (8%) (95% CI: -0.045, 0.029). Serious mucocutaneous reactions and hepatitis B reactivation subsequent to the use of RTX in NHL have been the topic of Health Canada safety advisories.^{18,19}

Administration and Cost

Rituxan is supplied as a preservative-free liquid concentrate (10 mg/mL) for intravenous (IV) infusion in

100 mg (10 mL) and 500 mg (50 mL) single-use vials. The cost of the 500 mg vial is C\$2,563.²⁰ The dosage for RA is two 1,000 mg RTX infusions separated by two weeks (C\$10,252 per treatment).⁴ Additional costs include MTX (10 mg/week to 25 mg/week), and GCs as pre-medication or taken on intervening days.²¹ The DANCER study showed that 500 mg and 1,000 mg RTX infusions produced similar ACR 20 and ACR 50 responses.¹⁰ The product monograph advises that the safety and efficacy of re-treatment have not been established in controlled trials, although patients have received two to five courses (two infusions per course) in uncontrolled settings at 16 to 24 week intervals.⁴ Peripheral costs include the personnel and supply costs associated with IV drug administration.

Concurrent Development

Biologics in clinical development for RA include abatacept, alefacept, and efalizumab, which inhibit T-cell activation, and MRA, an IL-6 receptor antibody.²² RTX is in phase III trials for antineutrophil cytoplasmic antibody-associated vasculitis, lupus nephritis, RA (DMARD non-responders), primary progressive multiple sclerosis, and systemic lupus erythematosus.²³ Phase II trials are underway for relapsing remitting multiple sclerosis, and Food and Drug Administration action for indolent frontline NHL is pending.²³ There is also anecdotal evidence about the efficacy of RTX in autoimmune diseases, including Wegener's granulomatosis, dermatomyositis, thrombotic thrombocytopenia purpura, and graft versus host disease.²⁴

Rate of Technology Diffusion

It is estimated that approximately 4,000 patients may be eligible for RTX treatment in Canada (Michael Brogan, Brogan Inc., Ottawa: personal communication, 2006 Aug 8). Patients who have tried at least one biologic therapy for RA and subsequently discontinued therapy were included in this eligible patient pool. The reasons for discontinuation of therapy were unavailable from the data source. These may include reasons other than a non-response to therapy (Michael Brogan: personal communication, 2006 Aug 8). In light of its potential efficacy in the treatment of autoimmune diseases, RTX may be used in non-approved indications, leading to an expansion of patient groups and increased associated costs.

Implementation Issues

The implementation of RTX therapy for RA would likely follow the model of outpatient infusion clinics that deliver anti-TNF therapy. It is expected that RTX would be reserved for patients who fail after taking ≥ 1 anti-TNFs, and would be used as a replacement therapy. RTX could be used by patients who are non-responsive to DMARDs, in combination with DMARDs other than MTX, or with other biologics, despite a lack of supportive data. Given the shift to early aggressive DMARD therapy in RA, there may be an incentive for patients who are naïve to anti-TNF therapy to try RTX, despite a lack of data to show a slowing of disease progression in early RA, and a lack of head-to-head studies with other biologics.

The combination of RTX plus MTX reduces the signs and symptoms of RA in patients with an inadequate response to DMARDs and anti-TNF therapy, compared with MTX alone. More investigation is needed to determine the optimal dose, duration of treatment or re-treatment, long-term efficacy and safety, and placement of RTX in RA treatment algorithms.²⁵

References

1. *Biogen Idec and Genentech submit a supplemental biologics license application for FDA review of Rituxan® for the treatment of rheumatoid arthritis* [news release]. Cambridge (MA): Biogen Idec; 2005 Aug 31. Available: http://www.biogen.com/site/019_1.html.
2. Shaw T, et al. *Ann Rheum Dis* 2003;62 Suppl 2:55-9.
3. *Notice of compliance* [database online]. Ottawa: Therapeutic Products Directorate, Health Canada; 2006. Available: <http://www.nocdatabase.ca>.
4. *RITUXAN®: rituximab 10 mg/ml intravenous infusion, professed standard antineoplastic* [product monograph]. Mississauga (ON): Hoffmann-La Roche; 2006. Available: <http://www.rochecanada.com/pdf/rituxanHPE.pdf>.
5. Rindfleisch JA, et al. *Am Fam Physician* 2005;72(6):1037-47.
6. Badley E, et al. *Arthritis and related conditions in Ontario: ICES research atlas*. 2nd ed. Toronto: Institute for Clinical Evaluative Sciences; 2004. Available: <http://www.acreu.ca/research/pub/atlas04.html>.
7. Guidelines for the management of rheumatoid arthritis: 2002 update. *Arthritis Rheum* 2002;46(2):328-46.

8. Bykerk VP, et al. *Canadian consensus statement of early optimal therapy in early rheumatoid arthritis*. Newmarket (ON): Canadian Rheumatology Association; 2004 Aug. Available: <http://www.rheum.ca/Resources/Pdf/ERA.pdf>.
9. Edwards JCW, et al. *N Engl J Med* 2004;350(25):2572-81.
10. Emery P, et al. *Arthritis Rheum* 2006;54(5):1390-400.
11. Cohen SB, et al. Presentation at ACR/ARHP Annual Scientific Meeting; 2005 Nov 12; San Diego. Abstract no 1830.
12. Emery P, et al. Presentation at EULAR; 2006 Jun 21-24; Amsterdam. Abstract no OP0017. Available: http://www.abstracts2view.com/eular/view.php?nu=EULAR06L_2006OP0017.
13. Keystone E, et al. Presentation at EULAR; 2006 Jun 21-24; Amsterdam. Abstract no FRI0125. Available: http://www.abstracts2view.com/eular/view.php?nu=EULAR06L_2006FRI0125.
14. Moreland LW, et al. Presentation at EULAR; 2006 Jun 21-24; Amsterdam. Abstract no FRI0151. Available: http://www.abstracts2view.com/eular/view.php?nu=EULAR06L_2006FRI0151.
15. Emery P, et al. Presentation at EULAR; 2006 Jun 21-24; Amsterdam. Abstract no THU0240. Available: http://www.abstracts2view.com/eular/view.php?nu=EULAR06L_2006THU0240.
16. Cohen S, et al. Presentation at EULAR; 2006 Jun 21-24; Amsterdam. Abstract no THU0220. Available: http://www.abstracts2view.com/eular/view.php?nu=EULAR06L_2006THU0220.
17. Keystone E, et al. Presentation at EULAR; 2006 Jun 21-24; Amsterdam. Abstract no OP0016. Available: http://www.abstracts2view.com/eular/view.php?nu=EULAR06L_2006OP0016.
18. Hoffmann-La Roche. In: *Advisories, warnings & recalls*. Ottawa: Health Products and Food Branch, Health Canada; 2001. Available: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2001/rituxan_hpc-cps_e.html.
19. Hoffmann-La Roche. In: *Advisories, warnings & recalls*. Ottawa: Health Products and Food Branch, Health Canada; 2004. Available: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2004/rituxan_2_hpc-cps_e.html.
20. *PPS pharma publication: buyers guide*. Ontario ed. Moncton: Total Pricing System; 2006 Jan.
21. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. In: *Rituxan® (Rituximab). Company: Genentech. Application No: 103705. Approval date: 28/02/2006* [FDA approval package]. Rockville (MD): The Center; 2006. Available: http://www.fda.gov/cder/foi/label/2006/103705s5211_lbl.pdf.
22. Voll RE, et al. *Ann N Y Acad Sci* 2005;1051:799-810.
23. *Development pipeline*. San Francisco: Genentech; 2006. Available: <http://www.gene.com/gene/pipeline/status/index.jsp>.
24. Eisenberg R. *Ann Rheum Dis* 2005;64 Suppl 4:55-7.
25. Summers KM, et al. *Ann Pharmacother* 2005;39(12):2091-5.

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