Common Drug Review

Pharmacoeconomic Review Report

August 2014

Drug	tocilizumab (Actemra, Intravenous)
Indication	For the treatment of signs and symptoms of active polyarticular juvenile idiopathic arthritis in patients two years of age and older who have responded inadequately to previous therapy with disease-modifying antirheumatic drugs and systemic corticosteroids.
Listing request	For patients who are intolerant to, or have had an inadequate response to, one or more disease-modifying antirheumatic drugs.
Manufacturer	Hoffmann-La Roche Limited

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ABBREVIATIONS

ACR	American College of Rheumatology
CMA	cost-minimization analysis
CDR	Common Drug Review
DMARD	disease-modifying antirheumatic drug
IL-6	interleukin-6
IV	intravenous
pJIA	polyarticular juvenile idiopathic arthritis
RA	rheumatoid arthritis

SUMMARY

Tocilizumab is available for intravenous (IV) infusion in 80 mg ($179.20), 200 mg ($448.00), and 400 mg ($896.00) single-use vials. The recommended dosing of tocilizumab for polyarticular juvenile idiopathic arthritis (pJIA) is 10 mg/kg every 4 weeks for patients who weigh less than 30 kg, and 8 mg/kg every 4 weeks for those weighing 30 kg or more. The manufacturer submitted a cost-minimization analysis (CMA) comparing tocilizumab to etanercept pre-filled syringes, adalimumab, abatacept, and two different regimens of infliximab (3 and 6 mg/kg) in pJIA patients (although infliximab is not indicated for use in pJIA in Canada). The perspective of the CMA was that of a public drug plan; it considered annual costs per patient for the first and subsequent years of treatment and the average annual cost of treatment for the first three years. Only drug and administration costs were considered. Based on the manufacturer's analysis, the average annual cost of the first three years for treating an average-weight child with pJIA with tocilizumab was less than each of the selected comparators. According to Common Drug Review (CDR) calculations of costs that assume weight-based dosing, tocilizumab is the least expensive treatment for pJIA patients who weigh between 34 kg and 75 kg, but it is more expensive than abatacept, adalimumab, and etanercept in pJIA patients who weigh more than 75 kg. Tocilizumab may be more expensive than abatacept, etanercept multi-use vials and 3 mg/kg infliximab in some pJIA patients who weigh less than 34 kg.

REVIEW OF THE PHARMACOECONOMIC SUBMISSION

1. INTRODUCTION

Tocilizumab is an anti-human interleukin-6 receptor antibody of the IgG1 subclass indicated for the treatment of signs and symptoms of active polyarticular juvenile idiopathic arthritis (pJIA) in patients two years of age and older who have responded inadequately to previous therapy with disease-modifying antirheumatic drugs (DMARDs) and systemic corticosteroids. Tocilizumab is available for intravenous (IV) infusion in 80 mg, 200 mg, and 400 mg single-use vials at currently market prices of $179.20, $448.00 and $896.00, respectively. The recommended dosing of tocilizumab for pJIA is 10 mg/kg every four weeks for patients weighing less than 30 kg, and 8 mg/kg every four weeks for those weighing 30 kg or more. The manufacturer is seeking reimbursement for the treatment of active pJIA in patients two years of age and older who are intolerant to, or have had an inadequate response to, one or more DMARDs. Actemra previously received a positive recommendation (list with criteria/conditions) from the Canadian Drug Expert Committee (CDEC) for systemic juvenile idiopathic arthritis (JIA) and rheumatoid arthritis (RA) in 2012 and 2010, respectively.

1.1 Cost-Comparison Table

The comparator treatments presented in Table 1 have been deemed the appropriate comparators by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified.

TABLE 1: COST-COMPARISON TABLE FOR BIOLOGICS FOR POLYARTICULAR JUVENILE IDIOPATHIC ARTHRITIS

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Annual Drug Cost[a] ($)		
					Pt. weight: [redacted] kg[b]	Pt. weight: 39.6 [redacted] kg[c]	Pt. weight: 50.2 [redacted] kg[d]
Tocilizumab (Actemra) *Ages 2 to 17*	80 mg 200 mg 400 mg	Vial	179.2000 448.0000 896.0000	Pts < 30 kg: 10 mg/kg every 4 weeks Pts ≥ 30 kg: 8 mg/kg every 4 weeks	6,989	9,318	12,813
Abatacept (Orencia) *Age 6 to 17*	250 mg / 15 mL	Vial	480.4100	Pts < 75 kg: 10 mg/kg Pts 75 to 100 kg: 750 mg Pts ≥ 100 kg: 1,000 mg Doses weeks 0, 2, and 4, and every 4 weeks thereafter	Y1: 6,726 Y2: 6,245	Y1: 13,451 Y2: 12,491	Y1: 20,177 Y2: 18,736
Adalimumab (Humira) *Age 4 to 17*	40 mg / 0.8 mL	Pen or Syringe	729.4200	24 mg/m^2 BSA (maximum = 40 mg) every other week	18,965[e]	18,965[f]	18,965[g]
Etanercept (Enbrel) *Ages 4 to 17*	25 mg	Vial	194.25	0.8 mg/kg weekly maximum 50 mg	6,775	12,786	16,226
	50 mg / mL	Pen or Syringe	388.61		20,207	20,207	20,207

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Annual Drug Cost[a] ($)		
					Pt. weight: [redacted] kg[b]	Pt. weight: 39.6[redacted] kg[c]	Pt. weight: 50.2[redacted] kg[d]
Not Indicated by Health Canada for pJIA							
Infliximab (Remicade) *Safety/ efficacy not established for children under 6 (UC) or under 9 (CD)*	100 mg / 10 mL	Vial	968.2000	3 mg/kg weeks 0, 2, and 6, then every 8 weeks[h]	Y1: 7,746 Y2: 6,293	Y1: 15,491 Y2: 12,587	Y1: 15,491 Y2: 12,587
				6 mg/kg weeks 0, 2, and 6, then every 8 weeks[h]	Y1: 15,491 Y2: 12,587	Y1: 23,237 Y2: 18,880	Y1: 30,982 Y2: 25,173

BSA = body surface area; CD = Crohn disease; Pt(s) = patient(s); Y = year; UC = ulcerative colitis.
Source: Ontario Drug Benefit Formulary Exceptional Access Program (accessed September 2013), not including markup.
[a] Assumes wastage of partially used vials/syringes except for etanercept multi-dose vial.
[b] CHERISH trial mean weight < 30 kg subgroup = [redacted].
[c] Overall mean weight = 39.6[redacted] kg.
[d] Mean weight ≥ 30 kg subgroup = 50.2[redacted] kg.
[e] < 30 kg subgroup mean body surface area = [redacted].
[f] Overall mean body surface area 1.2[redacted] $m.^2$
[g] ≥ 30 kg subgroup mean body surface area = 1.5[redacted] $m.^2$
[h] Infliximab dosing as per Ruperto et al., 2007.[1]

2. SUMMARY OF PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-minimization analysis (CMA) comparing tocilizumab to etanercept, adalimumab, abatacept, and two different regimens of infliximab in pJIA patients. Etanercept, adalimumab, and abatacept are indicated for pJIA by Health Canada. Infliximab is not indicated for pJIA in Canada, although it is reimbursed for pJIA under exceptional access programs in British Columbia and Ontario. The perspective of the CMA was that of a public drug plan; it considered annual costs per patient for the first and subsequent years of treatment and the average cost of treatment for the first three years. Only drug and administration costs were considered.

The manufacturer chose to submit a CMA because there are no head-to-head trials between active biologic comparators in pJIA patients, and because an indirect comparison was not deemed possible due to heterogeneity among the pJIA populations and study designs for the available placebo-controlled trials. The manufacturer cited the results of an indirect comparison of biologic agents in adult patients with RA[2] to support the assumption that tocilizumab has comparable efficacy in terms of ACR20 and ACR50 response to abatacept, etanercept, adalimumab, and infliximab. However, the indirect comparison based on RA trials cannot be used to determine whether there are differences among treatments in patients with pJIA (see Discussion in the Clinical Report).

Based on the manufacturer's calculations, treatment with tocilizumab is less costly compared with each of the comparators (Table 2). Based on the average annual cost for the first three years of treatment, use of tocilizumab would result in annual savings of $2,376 compared with the least expensive comparator (abatacept), and savings of $9,809 compared with the most expensive comparator (infliximab 6 mg/kg). The annual and incremental costs for all comparators are presented in Table 2.

TABLE 2: MANUFACTURER-CALCULATED ANNUAL TREATMENT AND INCREMENTAL COSTS OF BASE-CASE ANALYSIS

Drug	Annual Cost per Patient[a] ($)	(Incremental Annual Cost (Savings) per Patient on Actemra[a] ($)
Tocilizumab	13,327	Ref
Abatacept	15,703	(2,376)
Adalimumab	20,811	(7,484)
Etanercept pre-filled syringe	22,152	(8,825)
Infliximab 3 mg/kg[b]	15,816	(2,489)
Infliximab 6 mg/kg[b]	23,135	(9,809)

Ref = reference drug.
[a] Average annual cost over the first three years of treatment. Costs assume wastage of partially used vials/syringes, and include administration costs and an 8% markup on medication costs.[3]
[b] Not indicated for polyarticular JIA.

Sensitivity analyses were conducted by the manufacturer under various assumptions, but with the exception of the use of the maximum body weight (BSA) observed in the CHERISH trial and assuming the use of multi-dose etanercept vials, tocilizumab remained the least expensive in all sensitivity analyses.

3. INTERPRETATIONS AND KEY LIMITATIONS

3.1 Comparator Costing

The cost for the initial year for a pJIA patient receiving abatacept was overestimated in the manufacturer's CMA. With loading doses at weeks 0, 2, and 4, and maintenance doses every four weeks thereafter, abatacept would be administered 14 times in the first year rather than 15 times. Maintaining the remaining assumptions, this would yield a first-year cost for abatacept of $16,086 rather than $17,235, and a three-year average annual cost of $15,320 rather than $15,703 (see Table 3).

For etanercept in the base case, the manufacturer assumed that the single-use 50 mg pre-filled syringes would be used, as the mean patient weight of 39.6 kg would require more than one 25 mg multi-use vial per dose, and thus the 50 mg pre-filled syringes would be more convenient (due to one rather than two injections being required). However, as the cost difference between using the 50 mg pre-filled syringes and the 25 mg multi-use vial is substantial for patients weighing 39.6 kg ($8,014 more for pre-filled syringes per year), both methods should have been included (see Table 3).

TABLE 3: CDR-CALCULATED ANNUAL TREATMENT AND INCREMENTAL COSTS FOR ABATACEPT AND ETANERCEPT

Drug	Annual Cost per Patient[a] ($)		(Incremental Cost Savings) per Patient on Actemra ($)	
	First Year	Three-Year Average	First Year	Three-Year Average
Tocilizumab	13,327	13,327	Ref	Ref
Abatacept	16,086	15,320	(2,759)	(1,993)
Etanercept pre-filled syringe	22,152	22,152	(8,825)	(8,825)
Etanercept multi-use vial	14,138	14,138	(811)	(811)

CDR = Common Drug Review; Ref = reference drug.
[a] Costs assume wastage of partially used vials/syringes except for etanercept multi-use vial, and include administration costs and an 8% markup on medication costs.

3.2 Lack of Cost Discounting Beyond One Year

Common Drug Review (CDR) economic guidelines specify discounting costs beyond one year at 5% for the base case. The manufacturer used undiscounted costs. If a 5% discount rate is applied to costs, tocilizumab remains less expensive as in the manufacturer's base-case analysis, although the margin of difference between tocilizumab and the other treatments is smaller (Table 4).

TABLE 4: CDR-CALCULATED ANNUAL TREATMENT AND INCREMENTAL COSTS WITH 5% DISCOUNTING

Drug	Annual Cost per Patient[a] ($)		Incremental Cost (Savings) per Patient on Actemra ($)	
	First Year	Three-Year Average	First Year	Three-Year Average
Tocilizumab	13,327	12,308	Ref	Ref
Abatacept	16,086	13,796	(2,759)	(1,487)
Adalimumab	20,811	19,221	(7,484)	(6,912)
Etanercept Pre-filled syringe	22,152	20,460	(8,825)	(8,152)
Etanercept Multi-use vial	14,138	13,058	(811)	(750)
Infliximab 3 mg/kg[b]	18,075	13,564	(4,748)	(1,256)
Infliximab 6 mg/kg[b]	$26,440	$19,842	($13,114)	($7,533)

CDR = Common Drug Review; Ref = reference drug.
[a] Costs assume wastage of partially used vials/syringes except for etanercept multi-use vial, and include administration costs and an 8% markup on medication costs.
[b] Not indicated for polyarticular JIA.

3.3 Relative Costs Sensitive to Body Weight

While tocilizumab is the least expensive treatment when the body weight data from the CHERISH trial are used in the analysis, the relative costs of the comparators vary according to body weight. According to CDR calculation of costs that assume weight-based dosing (see APPENDIX 1: COMPARATOR COSTS BY BODY WEIGHT), tocilizumab is the least expensive treatment for patients who weigh between 34 kg and 75 kg. However, abatacept, adalimumab, and etanercept are all less expensive in patients who weigh more than 75 kg (Figure 1). Also, tocilizumab may be more expensive than abatacept, etanercept multi-use vials, and 3 mg/kg infliximab in some patients who weigh less than 34 kg (see Figure 1). The costs of tocilizumab versus each comparator across the full range of body weights for pJIA patients enrolled in the CHERISH trial (10 kg to 85 kg) are presented in Figure 1.

3.4 Relative Efficacy and Safety Uncertain

The manufacturer assumed that tocilizumab had similar clinical efficacy and safety to other biologics used in the treatment of pJIA; however, with no head-to-head trials or indirect treatment comparisons done within the pJIA population, this assumption is uncertain.

4. ISSUES FOR CONSIDERATION

4.1 Administration Costs

The manufacturer included administration costs, as they assumed that, despite the availability of outpatient clinics that administer these agents at no cost to ministries of health or patients, pediatric patients would most likely receive treatment in a hospital setting and thus administration costs would apply. Administration costs were those presented in a cost-effectiveness analysis by Unger et al., 2011[4] and may differ from the administration costs applicable in different jurisdictions. Should manufacturers, in fact, cover the costs of administration, all comparators, but especially those given by IV infusion (i.e., tocilizumab, abatacept, and infliximab), would have lower annual costs than indicated in the CMA.

4.2 Drug Wastage

All cost calculations by both the manufacturer and CDR have included the wastage of partially used units, with the exception of etanercept multi-use vials. It should be noted that these assumptions may be considered a “worst case scenario” for affected comparators, as it is likely that physicians in practice would prescribe doses to minimize such wastage whenever possible.

5. CONCLUSIONS

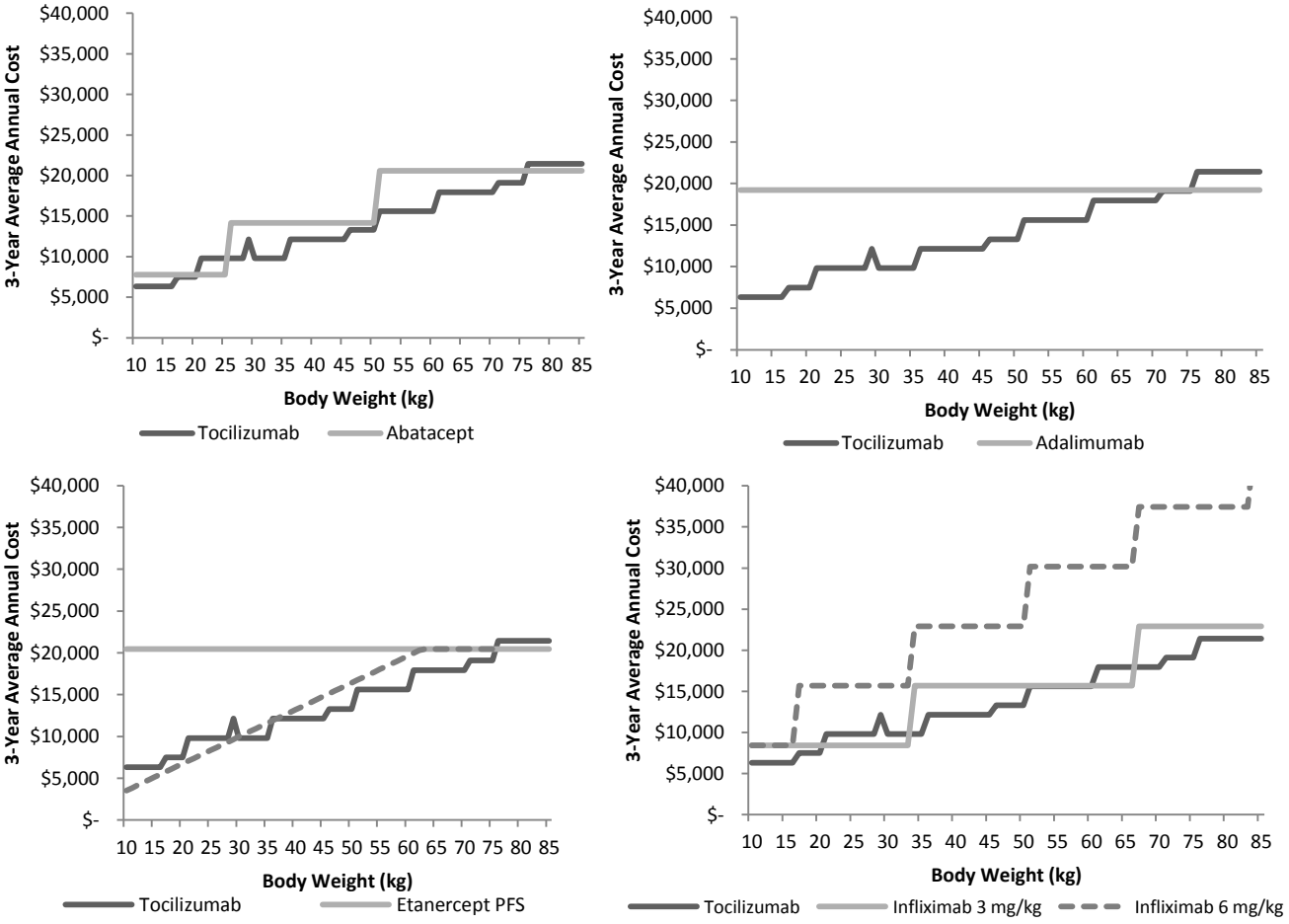
At the current marketed prices of $179.20 (80 mg vial), $448 (200 mg), and $896 (400 mg), tocilizumab is the least expensive treatment for pJIA patients who weigh between 34 kg and 75 kg; however, tocilizumab is more expensive than abatacept, adalimumab, and etanercept in pJIA patients who weigh more than 75 kg (CDR analyses). Tocilizumab may be more expensive than abatacept, etanercept multi-use vials, and 3 mg/kg infliximab in some pJIA patients who weigh less than 34 kg.

APPENDIX 1: COMPARATOR COSTS BY BODY WEIGHT

Figure 1 shows the average annual cost for the first three years of treatment for each comparator, using weight-based dosing for the range of body weights observed in the CHERISH trial.

Based on these data, tocilizumab is the least expensive treatment option for polyarticular juvenile idiopathic arthritis (pJIA) patients who weigh between 34 kg and 75 kg. However, in pJIA patients who weigh 76 kg or more, tocilizumab is more expensive than abatacept, adalimumab, and etanercept, but remains less expensive than infliximab. At certain points below 34 kg, abatacept (from 21 kg to 25 kg), etanercept multi-use vial (below 29 kg), and infliximab 3 mg/kg (21 kg to 33 kg) cost less than tocilizumab.

FIGURE 1: THREE-YEAR AVERAGE ANNUAL COST OF TOCILIZUMAB VERSUS EACH COMPARATOR BY BODY WEIGHT



[a] Costs assume wastage of partially used vials/syringes, with the exception of etanercept multi-use vial; they also include administration costs and an 8% markup on medications. A 5% discount is applied after the first year. Patients' weights in CHERISH trial ranged from 9.6 kg to 85.1 kg. Adalimumab dosing is based on body surface area; however, as its cost is flat across all body surface areas due to wastage, it is also possible to consider it flat across all body weights.

REFERENCES

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