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Omalizumab (Xolair): Treatment of Adults and Adolescents (12 Years of Age and above) with Chronic Idiopathic Urticaria [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2015 Aug.

EXECUTIVE SUMMARY

Introduction

Chronic idiopathic urticaria (CIU) is characterized by the presence of itchy hives, angioedema, or both, lasting for a period of six weeks or longer with no identifiable external cause.¹⁻⁴ The average duration of CIU is between one and five years, with a longer duration in more severe cases.³ Although CIU can manifest at any age, the peak incidence rate is among individuals between 20 and 40 years of age.^{1,3} The prevalence of CIU has been reported to be 0.5% to 1.0% in the overall population, with a twofold higher incidence in women than in men.^{1,3,4} The pathogenesis of CIU is not completely understood, but may be associated with histamine release from cutaneous mast cells and blood basophils.¹

International guidelines on the management of urticaria recommend non-sedating second-generation H₁ antihistamines such as cetirizine or loratadine as first-line treatment for adults and children with CIU.^{5,6} For patients who do not achieve an adequate response, doses up to fourfold higher than approved doses are recommended. If symptoms persist, consideration of add-on therapy using omalizumab (OMA), cyclosporin A, or the leukotriene receptor antagonist (LTRA) montelukast is recommended. A short course of corticosteroids may be used to manage exacerbations.^{5,6} The clinical expert consulted for this review indicated that H₂ antagonists (e.g., ranitidine) are also commonly prescribed for patients with inadequate response to H₁ antihistamines. The only Health Canada-approved drugs for the treatment of CIU are H₁ antihistamines and OMA.

OMA is a humanized, recombinant, monoclonal anti-immunoglobulin E (IgE) antibody that binds to IgE, thereby reducing IgE-induced mast cell and basophil degranulation and the release of histamine.¹ OMA is supplied as a lyophilized, sterile powder in a single-use vial designed to deliver a 150 mg dose for subcutaneous administration upon reconstitution. For CIU, OMA is administered subcutaneously every four weeks at a dose of 150 mg or 300 mg. The manufacturer has requested listing for the treatment of adults and adolescents (12 years of age and above) with persistent (disease duration greater than or equal to six months), moderate to severe (Urticaria Activity Score over seven days [UAS7] ≥ 16 or Dermatology Life Quality Index [DLQI] ≥ 10) CIU who remain symptomatic (presence of hives or associated itching) despite H₁ antihistamine treatment. OMA is also approved in Canada for the treatment of moderate to severe persistent asthma.

Indication Under Review

Treatment of adults and adolescents (12 years of age and above) with chronic idiopathic urticaria who remain symptomatic despite H₁ antihistamine treatment

Listing Criteria Requested by Sponsor

Treatment of adults and adolescents (12 years of age and above) with persistent (disease duration ≥ 6 months) moderate to severe (UAS7 score ≥ 16 or DLQI ≥ 10) chronic idiopathic urticaria who remain symptomatic (presence of hives and/or associated itching) despite H₁ antihistamine treatment. Response to treatment should be assessed 12 weeks following OMA initiation. For patients initiated on 150 mg every 4 weeks and who do not adequately respond by Week 12, consideration to increase the dose to 300 mg every 4 weeks should be given. Response to treatment should be reassessed 12 weeks thereafter.

The objective of this systematic review was to assess the beneficial and harmful effects of OMA for the treatment of CIU in adults and adolescents who remain symptomatic despite H₁ antihistamine treatment.

Results and Interpretation

Included Studies

The evidence for this review was derived from three phase 3, double-blind, multi-centre trials that compared three different doses of OMA (75 mg, 150 mg, and 300 mg, administered every four weeks) with placebo in a total of 978 adult and adolescent patients with H₁ antihistamine-refractory CIU. Because 75 mg is not an approved dose in Canada, data from the 75 mg dose groups were excluded from this report. ASTERIA I (N = 319) and GLACIAL (N = 336) had a treatment period of 24 weeks, and ASTERIA II (N = 323) of 12 weeks. All three trials had a 16-week treatment-free follow-up period.

The primary objective of ASTERIA I and ASTERIA II was to evaluate whether OMA was superior to placebo for improving the Weekly Itch Severity Score (WISS) after 12 weeks in patients with refractory CIU receiving concomitant standard-dose H₁ antihistamine therapy. The primary objective of GLACIAL was to evaluate the safety of OMA compared with placebo in patients with refractory CIU receiving up to four times the approved dose of H₁ antihistamines and either H₂ blockers or LTRAs, or both, as concomitant therapies. Other efficacy outcomes included UAS7 and Weekly Number of Hives Score (WNHS). Quality of life was assessed with the DLQI, the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) and the EuroQol 5-Dimensions Questionnaire (EQ-5D). End points were measured at 12 weeks, 24 weeks, and the end of the follow-up period. The main efficacy end points have previously been validated for use in CIU and were considered clinically relevant by the consulting clinical expert.

The included studies were generally of adequate design and assessed clinically relevant outcomes, but relatively high rates of major protocol violations and protocol issues were reported, including enrolment of patients not meeting inclusion and exclusion criteria. The impact of these limitations on the results of the trials is unclear. Baseline characteristics were generally reflective of patients with CIU in Canada according to the consulting clinical expert. However, the inclusion and exclusion criteria of GLACIAL were most aligned with common medical practice in Canada in terms of therapies tried (i.e., high-dose H₁ antihistamines, H₂ antagonists, and LTRAs) before progressing to OMA. A very low proportion of the included patients were adolescent or elderly, thereby limiting conclusions for these subpopulations.

Efficacy

In all three included trials, improvements in CIU symptoms as measured by UAS7 and its subcomponents WISS and WNHS were significantly greater in the OMA treatment groups compared with placebo. When compared with placebo at week 12, OMA 300 mg was associated with an improvement in UAS7 of -10.02 (95% confidence interval [CI], -13.17 to -6.86, $P < 0.0001$) points, in WISS of -4.52 (95% CI, -5.97 to -3.08, $P < 0.0001$) points and in WNHS of -5.90 (95% CI, -7.72 to -4.07, $P < 0.0001$) in the GLACIAL trial. These effects are likely to be clinically significant based on published minimal clinically important differences (MCIDs) for these outcomes. Responses were maintained at 24 weeks. In ASTERIA I and ASTERIA II, the efficacy results observed with OMA 300 mg were similar to or slightly larger than those observed in GLACIAL. The 150 mg dose in these trials failed to provide a clinically significant response on UAS7, WISS, or WNHS compared with placebo based on published MCID values for these outcomes, even though the observed differences were statistically significant at week 12. Moreover, the 150 mg dose was studied in ASTERIA I and ASTERIA II only, therefore the generalizability of the results to real-world practice in which patients are likely to have failed on high doses of H₁ antihistamines and one or more unapproved therapies is uncertain.

Other efficacy outcomes were quality of life measures such as DLQI, CU-Q2oL, and EQ-5D. In GLACIAL, OMA 300 mg appeared to be effective for improving quality of life as measured with DLQI (−4.67 [95% CI, −6.28 to −3.06] points, $P < 0.0001$) and CU-Q2oL (−13.4 [95% CI, −18.2 to −8.6] points, $P < 0.0001$) compared with placebo at week 12, and results were similar at week 24. Change from baseline in DLQI exceeded the MCID at both time points, whereas an MCID for CU-Q2oL was not identified in the literature. Results for EQ-5D did not show any statistically significant improvement with OMA at week 12 or 24; as this is a generic quality of life instrument that does not appear to have been validated for CIU, it is uncertain whether EQ-5D would be sufficiently sensitive to changes in CIU symptoms. Results for quality of life outcomes in the OMA 300 mg groups were similar in ASTERIA I and ASTERIA II. The results for DLQI and CU-Q2oL in the 150 mg dose groups were statistically significant versus placebo only in ASTERIA II.

Outcomes assessed after the 16-week treatment-free follow-up period showed that the majority of efficacy outcomes did not maintain statistically significant improvements compared with placebo.

Patient group input received by CADTH Common Drug Review (CDR) on this submission reflected anxiety, depression, shame regarding the appearance of affected skin, insomnia, and absenteeism from work as key concerns associated with CIU. Although not all of these outcomes were measured in the included trials, the observed benefits of OMA on CIU symptoms and quality of life can be expected to address these concerns of relevance to patients.

Harms

Patients in ASTERIA II had a lower incidence of adverse events (AEs) (from 40.5% to 47.7%) compared with patients in ASTERIA I (from 51.3% to 69.0%) or GLACIAL (63.9% and 65.1%), possibly due to the study's shorter duration. Compared with patients in the placebo groups, patients who received OMA were more likely to experience AEs across all trials. Patients randomized to the OMA 300 mg groups had a numerically higher (from 1% to 6% more) frequency of AEs than patients in the placebo groups. The most common AEs were nasopharyngitis (7.7%) and headache (6.6%). The only AE that appeared to be associated with OMA was headache. According to the clinical expert consulted on the review and patient input received by CDR, this AE is unlikely to significantly affect the tolerability of the treatment or result in treatment discontinuation.

Withdrawals due to adverse events (WDAEs) (1.1%) and serious adverse events (SAEs) (2.1%) did not occur more frequently in patients who received OMA than in patients who received placebo. The most frequent cause of WDAEs was urticaria (54.5% of all WDAEs). No deaths occurred during the trials. Based on published literature related to the use of OMA in asthma, safety warnings from regulatory agencies, and expert opinion, three notable harms were identified a priori for this review: arterial thrombotic events, anaphylaxis, and malignancies. The US FDA⁷ noted that arterial thrombotic events were shown to be slightly elevated in patients who used OMA (incidence of 0.135% over five years) compared with placebo (incidence of 0.081% over five years). As with other biologic drugs, anaphylaxis may occur with OMA; approximately 0.2% of patients who use OMA experience this AE.⁸ Long-term prospective data have not confirmed the suggestion from earlier studies of OMA in asthma that the drug may increase the risk of malignancy.⁹ Arterial thrombotic events, anaphylaxis, and malignancies were rare in the included trials and none appeared to be related to the study drug.

Conclusions

The results of three double-blind, multi-centre, randomized, placebo-controlled trials suggest that 12 weeks of OMA 150 mg or 300 mg administered every four weeks statistically significantly improves UAS7 and its subcomponents (WISS and WNHS) compared with placebo in patients with CIU refractory to H₁ antihistamines. However, only OMA 300 mg every four weeks was associated with a statistically and clinically significant improvement in UAS7 of 10 points

compared with placebo at 12 weeks, an improvement that was maintained at 24 weeks. Patients who received OMA 300 mg also demonstrated statistically and clinically significant improvements in quality of life measures such as DLQI and CU-Q2oL at 12 and 24 weeks compared with placebo. Upon discontinuation of OMA, treatment response was not sustained over time, such that differences between OMA and placebo were no longer statistically significant at 16 weeks after discontinuation. Due to the chronic nature of the condition, it is likely that many patients with CIU will require long-term therapy with OMA; however, there were no data regarding its efficacy upon re-treatment nor was there evidence to inform the optimal interval between courses of treatment. Patients receiving OMA 300 mg appeared more likely to experience adverse effects overall, and headaches in particular, than patients in the placebo groups, but the risks of other harm outcomes did not appear to differ across treatment groups.

Table 1 Summary of Results

Outcome	ASTERIA I			ASTERIA II			GLACIAL	
	OMA (150 mg)	OMA (300 mg)	PBO	OMA (150 mg)	OMA (300 mg)	PBO	OMA (300 mg)	PBO
Change From Baseline in UAS7 at Week 12								
Baseline (SD)	30.26 (7.26)	31.32 (5.79)	31.10 (6.67)	31.35 (6.99)	29.47 (6.90)	31.04 (6.58)	31.17 (6.57)	30.24 (6.66)
Mean value at week 12 (SD)	15.83 (13.78)	10.57 (12.28)	23.09 (12.55)	13.47 (12.64)	7.74 (11.14)	20.69 (12.64)	12.16 (13.77)	21.74 (11.55)
Change from baseline, mean (SD)	-14.44 (12.95)	-20.75 (12.17)	-8.01 (11.47)	-17.89 (13.23)	-21.74 (12.78)	-10.36 (11.61)	-19.01 (13.15)	-8.50 (11.71)
Difference vs. PBO, LSM (95% CI) ^a	-6.54 (-10.33 to -2.75)	-12.80 (-16.44 to -9.16)	–	-7.69 (-11.49 to -3.88)	-12.40 (-16.13 to -8.66)	–	-10.02 (-13.17 to -6.86)	–
<i>P</i> value vs. PBO ^b	0.0008	< 0.0001	–	0.0001	< 0.0001	–	< 0.0001	–
Change From Baseline in WISS at Week 12								
Baseline (SD)	14.09 (3.77)	14.20 (3.31)	14.37 (3.48)	14.23 (4.14)	13.66 (3.53)	14.02 (3.45)	14.05 (3.61)	13.82 (3.63)
Mean value at week 12 (SD)	7.44 (6.59)	4.80 (5.55)	10.73 (5.99)	6.09 (5.94)	3.89 (5.30)	8.88 (5.83)	5.50 (6.32)	9.81 (5.41)
Change from baseline, mean (SD)	-6.66 (6.28)	-9.40 (5.73)	-3.63 (5.22)	-8.14 (6.44)	-9.77 (5.95)	-5.14 (5.58)	-8.55 (6.01)	-4.01 (5.87)
Difference vs. PBO, LSM (95% CI) ^c	-2.95 (-4.72 to -1.18)	-5.80 (-7.49 to -4.10)	–	-3.04 (-4.85 to -1.24)	-4.81 (-6.49 to -3.13)	–	-4.52 (-5.97 to -3.08)	–
<i>P</i> value vs. PBO	0.0012	< 0.0001	–	0.0011	< 0.0001	–	< 0.0001	–
Change From Baseline in WNHS at Week 12								
Baseline (SD)	16.17 (4.61)	17.12 (3.82)	16.73 (4.42)	17.13 (4.14)	15.82 (4.62)	17.03 (4.20)	17.12 (4.20)	16.42 (4.59)

Outcome	ASTERIA I			ASTERIA II			GLACIAL	
	OMA (150 mg)	OMA (300 mg)	PBO	OMA (150 mg)	OMA (300 mg)	PBO	OMA (300 mg)	PBO
Mean value at week 12 (SD)	8.39 (7.59)	5.77 (7.17)	12.36 (7.22)	7.38 (7.32)	3.85 (6.35)	11.80 (7.45)	6.66 (7.89)	11.93 (6.89)
Change from baseline, mean (SD)	-7.78 (7.08)	-11.35 (7.25)	-4.37 (6.60)	-9.75 (7.28)	-11.97 (7.58)	-5.22 (6.56)	-10.46 (7.74)	-4.49 (6.33)
Difference vs. PBO, LSM (95% CI) ^d	-3.44 (-5.57 to -1.32)	-6.93 (-9.10 to -4.76)	–	-4.51 (-6.65 to -2.36)	-7.09 (-9.26 to -4.93)	–	-5.90 (-7.72 to -4.07)	–
P value vs. PBO	0.0017	< 0.0001	–	< 0.0001	< 0.0001	–	< 0.0001	–
Withdrawals								
Total, n/N (%)	16/80 (20.0)	12/81 (14.8)	15/80 (18.8)	9/83 (10.8)	12/79 (15.2)	5/79 (6.3)	28/252 (11.1)	18/84 (21.4)
Harms								
SAEs, n/N (%)	3/87 (3.4%)	0	4/80 (5.0%)	0	2/79 (2.5%)	2/79 (2.5%)	7/252 (2.8%)	3/83 (3.6%)
WDAEs, n/N (%)	2/87 (2.3%)	1/81 (1.2%)	2/80 (2.5%)	1/88 (1.1%)	0	1/79 (1.3%)	3/252 (1.2%)	1/83 (1.2%)
Notable Harms								
Arterial thrombotic events	1/87 (1.1%)	0	0	0	0	0	0	1/83 (1.2%)
Anaphylaxis	0	1/81 (1.2%)	0	0	0	0	0	0
Malignancies	0	0	1/80 (1.3)	0	1/79 (1.3%)	0	0	0

AE = adverse event; ANCOVA = analysis of covariance; CI = confidence interval; LSM = least squares mean; OMA = omalizumab; PBO = placebo; SAE = serious adverse event; SD = standard deviation; UAS7 = Urticaria Activity Score over seven days; vs. = versus; WDAE = withdrawal due to adverse event; WISS = Weekly Itch Severity Score; WNHS = Weekly Number of Hives Score.

- The LSM was estimated using an ANCOVA model. The strata or covariates are baseline UAS7 (less than median versus greater than or equal to median) and baseline weight (< 80 kg versus ≥ 80 kg).
- P value is derived from ANCOVA t-test.
- The LSMs were estimated using an ANCOVA model. The strata are baseline WISS (< 13, ≥ 13) and baseline weight (< 80 kg versus ≥ 80 kg).
- The LSM was estimated using an ANCOVA model. The strata are baseline WNHS (less than median versus greater than or equal to median) and baseline weight (< 80 kg versus ≥ 80 kg).

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