Comparative Safety Assessment of Ofatumumab Using Data From ASCLEPIOS I and II Versus a Historical Propensity-adjusted Placebo Arm

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Introduction

- Ofatumumab, 20 mg s.c. monthly, is a fully human anti-CD20 monoclonal antibody approved for the treatment of RMS in adults in the US[1] and other countries*
- Ofatumumab demonstrated superior efficacy and a favorable safety profile when compared with the first-line active comparator teriflunomide 14 mg oral once-daily, in the ASCLEPIOS I and II trials in patients with RMS[2,3]
- Establishing the safety profile of a drug can be challenging in the absence of appropriate background/placebo data
- Since teriflunomide, as an active comparator, is associated with certain risks, solely considering numerical imbalances in the incidence of AEs is insufficient to conclude on the possible causal relationship between the AE and ofatumumab
- In such instances where there is a lack of placebo-controlled data, indirect comparisons with a similar population receiving placebo (i.e., with a historical control population with similar inclusion/exclusion criteria and baseline characteristics) can help to define the safety profile of a drug

Objective

- To compare the incidence of selected AEs observed in the ASCLEPIOS I and II trials versus a historical placebo arm using propensity score (PS) adjustments

*Australia, Canada, Singapore, Switzerland, UAE, Albania, Argentina, India, and Japan. AEs, adverse events; CD, cluster of differentiation; FDA, Food and Drug Administration; RMS, relapsing forms of multiple sclerosis; s.c., subcutaneous. 1. KESIMPTA® (ofatumumab) Prescribing Information. https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf (accessed Aug 24, 2020). 2. Hauser SL, et al. Presented at the ECTRIMS. 2019; S17.OP336; 3. Hauser SL, et al. N Engl J Med. 2020;383:546–57.

Data and methods

Data

- This retrospective analysis compared ofatumumab safety data from the ASCLEPIOS I and II trials (conducted between 2015 and 2019) to a PS-adjusted historical placebo arm from the FREEDOMS and FREEDOMS II trials (fingolimod Phase 3 clinical program) in RMS (conducted between 2006 and 2009)
- Patient-level data were available for ofatumumab (n=946), teriflunomide (n=936) and historical placebo (n=773)

Methods

- **Feasibility assessment:** Due to the similarity in patient population, study design, key demographics and MS baseline characteristics, type of AE reporting and observation period, indirect comparison across these clinical programs appears feasible and justified
- **Selected AE terms:** AE terms of interest were selected for which a comparison to a historical placebo group of RMS was judged meaningful because of their occurrence in both (ofatumumab and teriflunomide) treatment arms in the phase 3 study and the plausible but unknown relationship to study drugs or MS
  - The selected AE terms included headache, lower respiratory tract infections, upper respiratory tract infections, urinary tract infections, herpes viral infections, back pain, anxiety, depression, insomnia
- **Propensity methods:** The PS methods are well established to re-balance baseline characteristics in non-randomized settings:
  - For each AE, baseline variables were selected from a list of potential confounders likely to clinically affect the occurrence of the AE
    - The confounders included age, race, duration of MS since first symptom, gender, geographical region, baseline EDSS score, previous MS therapy (naive or non-naive) and medical history (adapted for each AE of specific interest)
  - Conditional OR and 95% CIs for ofatumumab vs historical placebo were estimated after applying the PS-adjusted method (IPTW with stabilized weights[1])

AEs, adverse events; CIs, confidence intervals; EDSS, Expanded Disability Status Scale; IPTW, Inverse probability of treatment weighting; MS, multiple sclerosis; OR, odds ratio; PS, propensity score; RMS, relapsing forms of multiple sclerosis.

1. Xu S, et al. Value Health. 2010;13:273-7.

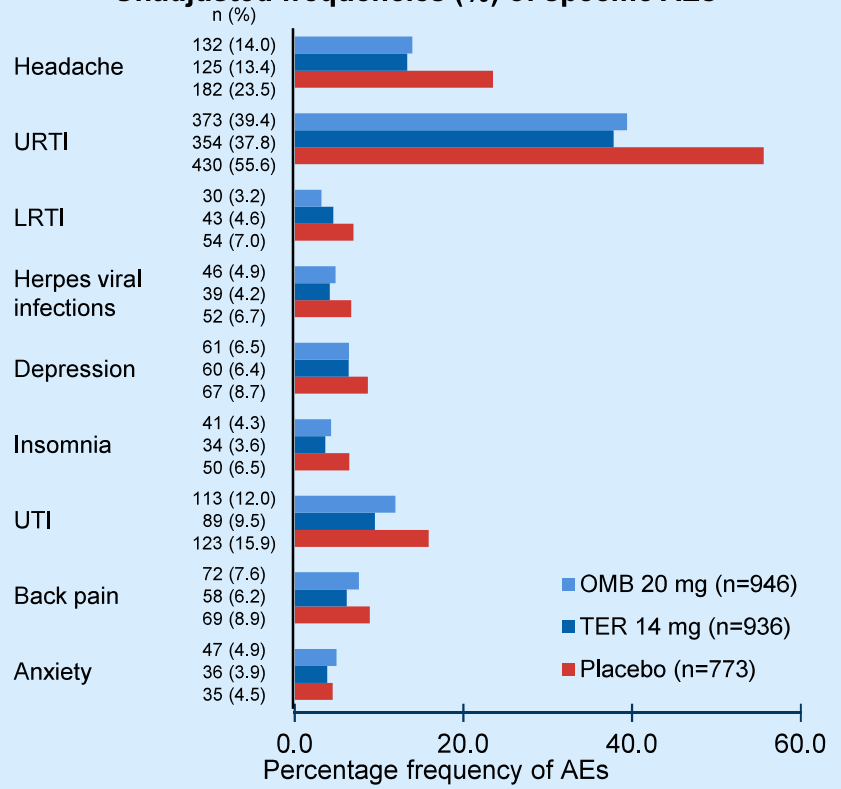
Results

Comparison of key patient baseline characteristics and treatment exposure*

Parameters	ASCLEPIOS		FREEDOMS
	OMB 20 mg (n=946)	TER 14 mg (n=936)	Historical placebo (n=773)
Mean (SD) age, years	38.4 (9.04)	38.0 (9.22)	38.6 (8.63)
Female, %	67.3	67.9	75.8
Mean (SD) EDSS score	2.9 (1.4)	2.9 (1.4)	2.5 (1.3)
Treatment naive, %	40.8	38.8	44.6
Region, %			
Eastern Europe	29.6	29.7	24.6
North America and Australia	22.5	22.8	48.5
Western Europe	22.3	21.9	21.3
Others	25.6	20	5.6
Mean exposure, in years	1.57	1.49	1.63

- Closer similarities were observed in baseline characteristics and treatment exposure after PS trimming and adjustment

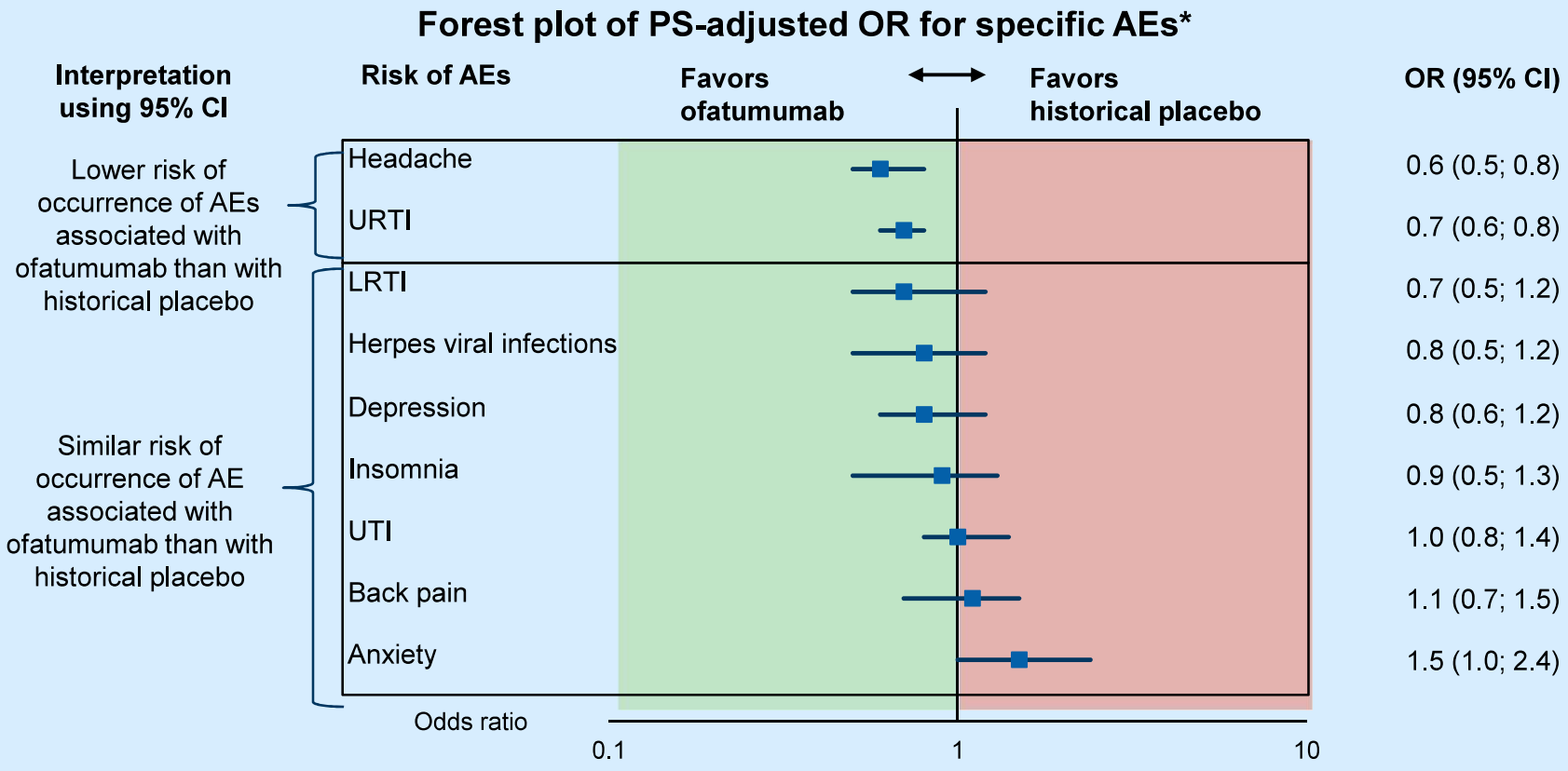
Unadjusted frequencies (%) of specific AEs*



*Ofatumumab vs teriflunomide ASCLEPIOS I and II trials vs placebo arm of fingolimod FREEDOMS/FREEDOMS II trials.

AEs, adverse events; EDSS, Expanded Disability Status Scale; LRTI, lower respiratory tract infections; PS, propensity score; n, frequency OMB, ofatumumab; TER, teriflunomide; URTI, upper respiratory tract infections; UTI, urinary tract infections.

Results: PS-adjusted OR



*Weighted logistic regression model.
AEs, adverse events; CI, confidence interval; LRTI, lower respiratory tract infections; OR, odds ratio; PS, propensity score; URTI, upper respiratory tract infections; UTI, urinary tract infections.

Conclusions

- The risk of occurrence of AEs of specific interest observed with ofatumumab treatment during the ASCLEPIOS I and II trials was similar or lower to that previously observed in a historical placebo cohort of patients with RMS
- These indirect comparisons using PS methods provide supporting evidence that headache, upper and lower respiratory tract infections, herpes viral infections, depression, insomnia, urinary tract infections, back pain and anxiety, do not occur with higher risk than would be expected in a typical RMS population

Disclosures

Ayan Das Gupta,[1] Ratnakar Pingili,[2] Dieter Haering[3] and Valentine Jehl[3] are employees of Novartis.

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AEs, adverse events; PS, propensity score; RMS, relapsing forms of multiple sclerosis.