Characteristics and Outcome of COVID-19 in Patients with Relapsing Multiple Sclerosis Receiving Ofatumumab

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Introduction

- Ofatumumab is a fully human anti-CD20 monoclonal antibody approved for the treatment of RMS in adults in the US[1] and other countries*
- Ofatumumab, administered as monthly 20 mg (in 0.4 ml) subcutaneous injection, demonstrated superior efficacy versus teriflunomide and a favorable safety profile in RMS patients in the Phase 3 ASCLEPIOS I and II trials[1,2]
- When delivered subcutaneously, preclinical models suggest preferential distribution to the lymph nodes, where B-cell depletion is thought to be needed in MS, which may help preserve immunosurveillance[3-5]
- In the ASCLEPIOS I and II pivotal trials, serum IgM / IgG levels remained well within the reference ranges over the duration of the study and there was no decrease in mean IgG levels, compared with baseline.[2] Emerging 3 year data where both IgG and IgM levels from the ALITHIOS open label extension has shown to be consistent with these pivotal trial findings, with mean IgG level unchanged and mean IgM levels remaining above the LLN throughout the 3 years period[6]
- Risks of COVID-19 infection in pwMS receiving disease-modifying therapies are of increased interest and is under investigation. There are questions regarding the use of B-cell depleting agents in MS and the risk of COVID-19 infection[7]
- The ongoing ALITHIOS study is evaluating long-term (up to 5 years) safety, tolerability and effectiveness of ofatumumab in ~2000 adult patients with RMS[7]

*Australia, Canada, Singapore, Switzerland, UAE, Albania, Argentina, India, and Japan. COVID-19, coronavirus disease 2019; Ig, immunoglobulin; LLN, lower limit of normal; MS, multiple sclerosis; pwMS, people with MS; RMS, relapsing MS

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Objective

To report the clinical characteristics of COVID-19 infection in people with MS receiving ofatumumab 20 mg subcutaneously every 4 weeks

Methods

- Confirmed or suspected cases of COVID-19 infection in patients receiving ofatumumab in the open-label extension study ALITHIOS were reviewed (data cutoff: **December 21, 2020**)
- COVID-19 cases were classified as confirmed if SARS-CoV2 positive test results were available, or patient was reported to be diagnosed with COVID-19
- Suspected cases of COVID-19 were classified as suspected if without a positive SARS-CoV2 test or definitive diagnosis
- **The following COVID-19 case characteristics were assessed:**
  - Patient demographics
  - COVID-19 seriousness category*
  - Ofatumumab treatment duration and action taken with ofatumumab (treatment interruption)
  - Interventions and COVID-19 outcomes

*Serious criteria is based on the regulatory reporting definition established by ICH, for the purposes of regulatory reporting obligations, and consists of fatal, life-threatening, hospitalization and medically significant

COVID-19, coronavirus disease 2019; MS, multiple sclerosis; SARS-CoV2, Severe acute respiratory syndrome coronavirus 2

Patient characteristics: Overall population

Patient demographics and drug exposure are shown in the table below:

- 45% (466/1026) of patients in the long-term group have drug exposure of 3-4 years
- Over 90% (614/677) of patients in the newly switched group have ofatumumab exposure of 1-2 years

Characteristics	Ofatumumab – long term group N=1026	Ofatumumab – newly switched N=677*	Overall N=1703*
Age, mean, years	38	40	39
Age group, % of patients 18 – 30 31 – 40 41 – 55 >55	 24 37 39 0.3	 17 35 43 5	 21 36 41 2
Sex, n (%) Male Female	 296 (29) 730 (71)	 220 (33) 456 (68)	 516 (30) 1186 (70)
Exposure, months Mean Range Patient-years	 30.9 3.7 – 50.5 2637.7	 15.3 1.0 – 20.2 863.0	 24.7 1.0 – 50.5 3500.7

*one patient was excluded from analysis due to invalid randomization. OMB, ofatumumab; SE, standard error

Results: COVID-19 cases overview

As of 21 December 2020, 35 out of 1703 patients had a confirmed COVID-19 infection and/or COVID-19 pneumonia in the ongoing open-label, extension ALITHIOS clinical trial for ofatumumab (Table)

- **All the non-serious cases were reported as completely recovered**
  - For 21 cases no change in ofatumumab treatment was required and for 5 cases treatment was temporarily interrupted due to confirmed COVID-19 infection
- **Of the 6 serious cases, 5 had complete recovery and in one patient the COVID-19 outcome was fatal (details as below)**
  - A 48 year-old patient, with no associated risk factors*, reported symptoms of COVID-19 (pneumonia, fever, weakness, cough and dyspnoea) after approximately 3 years and 7 months of ofatumumab treatment. The patient was hospitalized and received steroids, antivirals, antibiotics and COVID-19 convalescent plasma. The COVID-19 outcome was reported as not related to ofatumumab treatment by the treating physician

Confirmed cases	N=35
Non-serious (n=29)	
Age, mean (range), years	35.6 (range 28 – 50)
Sex	
Female	17
Male	12
COVID-19 outcome	
Recovered	29
Recovering	0
Ongoing	0
Serious (n=6)	
Age, mean (range), years	46 (range 38 to 57)
Sex	
Female	3
Male	3
COVID-19 outcome	
Recovered	5
Fatal	1

COVID-19, coronavirus disease 2019
*relevant comorbidities, such as chronic lung condition, diabetes, hypertension or malignancy

Results: COVID-19 serious cases

- Characteristics of the six serious cases of COVID-19 in patients receiving ofatumumab is listed below:

Patient ID	Age (years)	Sex	Duration of OMB treatment	OMB treatment during COVID-19 infection	COVID-19 symptoms	Relevant medical conditions	COVID-19 treatment	COVID-19 symptoms duration (days)	Outcome*
5409018	39	F	~3 y 1 m	Interrupted	Bilateral pneumonia	H/O respiratory infection	Hydroxycholoroquine Antivirals, Antibiotics	~ 50 d	Complete recovery
5608014	46	M	~2 y 11 m	Interrupted	Fever, sore throat, malaise, pneumonia	Arterial hypertension	Dexamethasone, Antivirals, Antibiotics	18 d	Complete recovery
5800043	57	M	~1 y 4 m	Continued	Fever, weakness, dyspnea, pneumonia	Not reported	Not reported	11 d	Complete recovery
5806001	38	M	~3 y 6 m	Continued	Fever, cough, weakness, bilateral interstitial pneumonia	Pneumocystis jirovecii pneumonia	Steroids, antibiotics	10 d	Complete recovery
5801015	53	F	~3 y 4 m	Interrupted	Fever, chest pain, nausea, pneumonia, dyspnea	Upper respiratory tract infection	Remdesivir	15 d	Complete recovery
5800004	48	F	~3 y 9 m	Drug withdrawn	Pneumonia, fever, cough, weakness, dyspnea	H/O hepatopathy, allergy, upper respiratory tract infection	Remdesivir, COVID-19 convalescent plasma, steroids, antibiotics	~ 30 d	Fatal

- Ofatumumab treatment was continued in two and temporarily interrupted in three patients with serious COVID-19
- Except one case, where information was not reported, all cases had pre-existing comorbidities identified as risk factors for severe COVID-19 outcome in general population (i.e., respiratory disease and hypertension)
- Ofatumumab treatment was reported as not related with the COVID-19 course or outcome in all six cases

COVID-19, coronavirus disease 2019; d, days; H/O, history of; m, months; OMB, ofatumumab; F, female; M, male; y, years
*Last available information Outcomes available at the time of the most recent follow up.

Conclusions

- Of the total 1703 patients in the ongoing ALITHIOS study, 35 confirmed cases of COVID-19 infection and/or COVID-19 pneumonia have been reported. Complete recovery in 34 cases; one case had fatal outcome. None of the cases were suspected because of ofatumumab treatment
- Based on the review of reported cases, the clinical presentations and outcomes of COVID-19 cases in pwMS on ofatumumab therapy was similar to other reports on MS population[1-5] and in the general population[6]
- More surveillance data are needed to determine the risks associated with COVID-19 infection in pwMS treated with ofatumumab
- Deciding to continue ofatumumab treatment should be made based on the individual patient benefit-risk assessment
- New patients can initiate therapy with ofatumumab in accordance with local guidelines

Disclosures

AHC has received honoraria from: Biogen, Celgene, EMD Serono/Merck, Genentech/Roche, and Novartis. AHC has received grant funding (clinical trials) from EMD Serono/Merck and Genentech/Roche. **SD** has received honoraria from Novartis and research grant funding from Novartis, MAPI Pharma, NIH/NINDS and NMSS. **MH** has nothing to disclose. **MD** reports grants and consulting or speaking fees from: Biogen Idec, Celgene/Receptos, Janssen/Actelion, Merck/EMD Serono, Novartis, Roche, and Sanofi Genzyme. **NT** has nothing to disclose. **XM** has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Actelion, Alexion, Bayer, Biogen, Celgene, EMD Serono, Genzyme, Immunic, Medday, Merck, Mylan, Nervgen, Novartis, Roche, Sanofi-Genzyme, Teva Pharmaceutical, TG Therapeutics, Excemed, MSIF and NMSS. **KW** has received honoraria for consulting from: Pfizer, AbbVie, Union Chimique Belge, Eli Lilly & Company, Galapagos, GlaxoSmithKline, Roche, Gilead, BMS, Regeneron, Sanofi, AstraZeneca, Novartis, and for research from: BMS, Pfizer. **RP**, **LM, RS**, **MZ**, **WS**, and **KR** are employees of Novartis.

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COVID-19, coronavirus disease 2019; pwMS, people with MS; SARS-CoV2, Severe acute respiratory syndrome coronavirus 2

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