Injection-Related Reactions with Subcutaneous Administration of Ofatumumab in Relapsing Multiple Sclerosis: Data from Clinical Studies and Post Marketing Experience

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Disclosures

John Kramer has received consulting fees from Novartis, Celgene, Genzyme, and EMD Serono. He also received speaker fees from Genentech.

Ratnakar Pingili, Ronald Zielman, Ayan Das Gupta, Pranava Katkuri, Wendy Su, Dee Stoneman, and **Elisabeth Lucassen** are employees of Novartis.

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Background

- Ofatumumab, a fully human anti-CD20 monoclonal antibody with a 20 mg subcutaneous monthly dosing regimen, is approved for treating relapsing multiple sclerosis (RMS) in adults[1]
- In the Phase 3 ASCLEPIOS[a] I/II trials, ofatumumab treatment up to 30 months had a favorable safety profile and was generally well tolerated in RMS patients[2]
  - Imbalance in IRRs (systemic and local-site) between ofatumumab and placebo (in the teriflunomide arm) was observed with the very first dose of ofatumumab
    - These IRRs were predominantly reported with the first ofatumumab injection and incidence decreased with subsequent injections
  - Most IRRs were of mild-to-moderate in severity and nonserious in nature
  - No life-threatening/hypersensitivity reactions leading to treatment discontinuation were observed
- IRRs were the most common AEs by preferred term observed in both clinical trials and post-marketing surveillance[3]
- Updated data on IRRs, including data from newly-switched patients, are available from the open-label extension study, ALITHIOS, and in the post-marketing setting

AEs, adverse events; CD, cluster of differentiation; IRR, injection-related reaction; RMS, relapsing multiple sclerosis.; [a]ASCLEPIOS tested home use and is approved for home use.

1. KESIMPTA® (ofatumumab) Prescribing Information. https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf (accessed February 17, 2022).
2. Hauser SL, et al. *N Engl J Med* 2020;383:546−57.
3. Periodic safety update report. Novartis Pharma AG.

Objective

To report the potential risk of IRRs (systemic and local-site) observed in RMS patients treated with ofatumumab, including newly-switched patients[a], based on updated data[b] from the ALITHIOS trial and in the post-marketing setting

IRR, injection-related reaction; RMS, relapsing multiple sclerosis; [a]patients who were randomized to teriflunomide in ASCLEPIOS I/II and switched to ofatumumab on entering ALITHIOS; [b]data cutoff: 25-Sep-2021.

Study Assessments

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IRRs from clinical trials

1969 RMS patients (Overall ofatumumab) = 1292 RMS patients (Continuous ofatumumab)[a] + 677 RMS patients (Newly-switched ofatumumab)[b]

- Proportions of patients with systemic[c] and local site[d] IRRs were analyzed by treatment group against injection sequence numbers (1 to 10) and cumulatively for all injections
- Severity of reactions was reported using the CTCAE grading, and categorized as mild (Grade 1), moderate (Grade 2), severe (Grade 3), and life-threatening (Grade 4)
- Symptoms were summarized by the number and percentage of patients for all injections
- Incidence of IRRs by premedication category was assessed

IRRs from post-marketing surveillance

Estimated ofatumumab exposure of 4713 patient-years was used for determining post-marketing cases

- A search was conducted in the Novartis safety database for possible injection-related systemic reaction events[e]
- These results were further evaluated to identify those that met the regulatory criteria for serious and likely to be true injection-related systemic reactions, not be confounded by other reported events occurring in conjunction that would have been contributory

CTCAE, Common Terminology Criteria for Adverse Events; IRR, injection-related reaction; PT, preferred term; RMS, relapsing multiple sclerosis.
[a]includes all patients randomized to ofatumumab in ASCLEPIOS I/II, APLIOS and APOLITOS continued in ALITHIOS; or completed/discontinued ofatumumab during one of the four trials and continued in the safety follow-up of their respective trials, but did not enter ALITHIOS; [b]includes patients who were randomized to teriflunomide in ASCLEPIOS I/II and switched to ofatumumab on entering ALITHIOS; [c]Systemic IRRs that occurred ≤24 hours after the injection were assumed to be injection-related and accordingly included in the analysis as PT 'injection-related reaction'; [d]Local site IRRs could be reported without any time limit from the time the injection was administered and were included in the analysis as PT injection-site reactions; [e]expected adverse reaction; the medical review will focus on all fatal, all life-threatening, and only medically confirmed potential serious injection reactions.

Systemic IRRs

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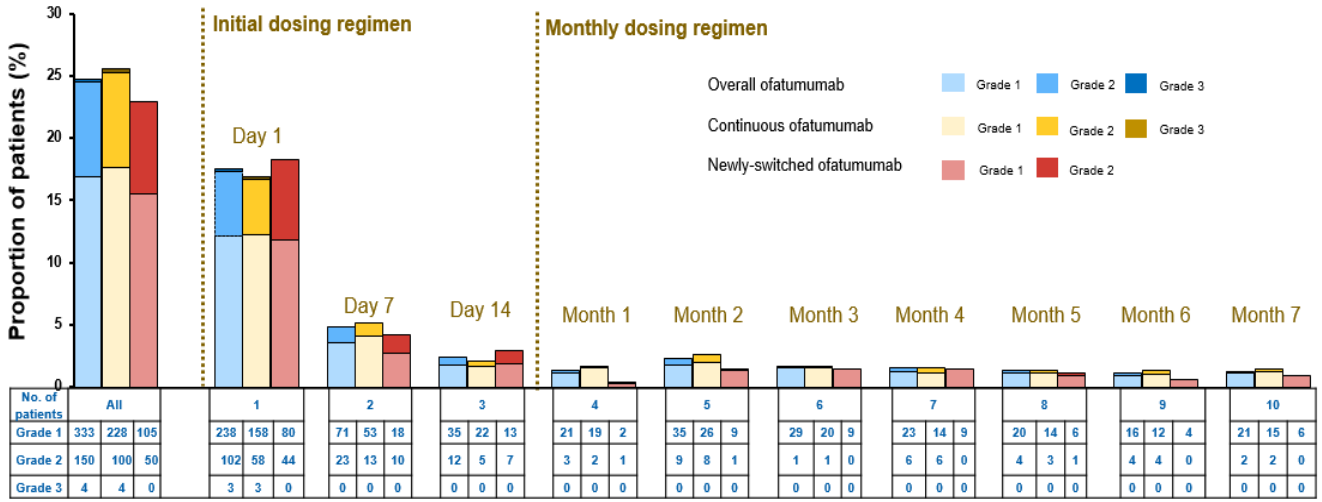
Incidence of systemic IRRs



Incidence of symptoms (≥5% in overall group) related to systemic IRRs

Symptoms	Overall ofatumumab (N=1969); n (%)	Continuous ofatumumab (N=1292); n (%)	Newly-switched ofatumumab (N=677); n (%)
Any symptoms	487 (24.7)	332 (25.7)	155 (22.9)
Fever	199 (10.1)	115 (8.9)	84 (12.4)
Headache	160 (8.1)	114 (8.8)	46 (6.8)
Chills	128 (6.5)	75 (5.8)	53 (7.8)
Other, systemic	122 (6.2)	100 (7.7)	22 (3.2)
Fatigue	99 (5.0)	65 (5.0)	34 (5.0)

- The incidence of systemic IRRs was highest with the first injection in all treatment groups (17.0% in the continuous ofatumumab group, and 18.2% in the newly-switched ofatumumab group); the incidence decreased substantially for subsequent injections
- Most systemic IRRs (99.2%) were mild to moderate (Grade 1/2) in severity and nonserious (99.4%). No life-threatening IRRs were reported
- Four patients (0.6%) with systemic IRRs discontinued the treatment in the newly-switched group; these were mild to moderate in severity and was resolved without concomitant medication/non-drug therapy
- The most common symptoms related to systemic IRRs were fever, headache, chills, and fatigue
- No cases of cytokine release syndrome were reported

IRR, injection-related reaction.

Local-site IRRs

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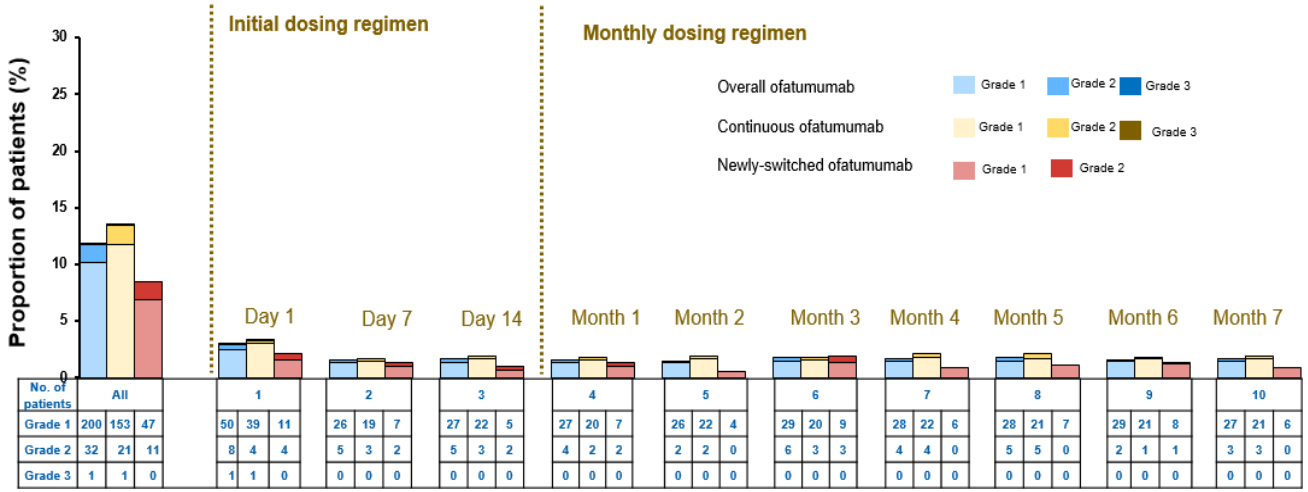
Incidence of local-site IRRs



Incidence of symptoms (≥2% in overall group) related to local-site IRRs

Symptoms	Overall ofatumumab (N=1969); n (%)	Continuous ofatumumab (N=1292); n (%)	Newly-switched ofatumumab (N=677); n (%)
Any symptoms	233 (11.8)	175 (13.5)	58 (8.6)
Erythema/redness	132 (6.7)	99 (7.7)	33 (4.9)
Pain	76 (3.9)	54 (4.2)	22 (3.2)
Other, site	67 (3.4)	56 (4.3)	11 (1.6)
Itching	55 (2.8)	37 (2.9)	18 (2.7)
Induration/ swelling	45 (2.3)	32 (2.5)	13 (1.9)

- The incidence of local-site IRRs was highest with the first injection in all treatment groups (3.4% in the continuous ofatumumab group, and 2.1% in the newly-switched ofatumumab group); the incidence decreased substantially for subsequent injections
- Most local-site IRRs (99.5%) were mild to moderate (Grade 1/2) in severity and nonserious (99.6%). No life-threatening IRRs were reported
- One patient (0.1%) with local-site IRRs discontinued the treatment in the newly-switched group; they were mild in severity and resolved without concomitant medication/nondrug therapy
- The most common symptoms related to local-site IRRs were erythema/redness, pain, itching, and induration/swelling

IRR, injection-related reaction.

Systemic IRRs by Premedication Category

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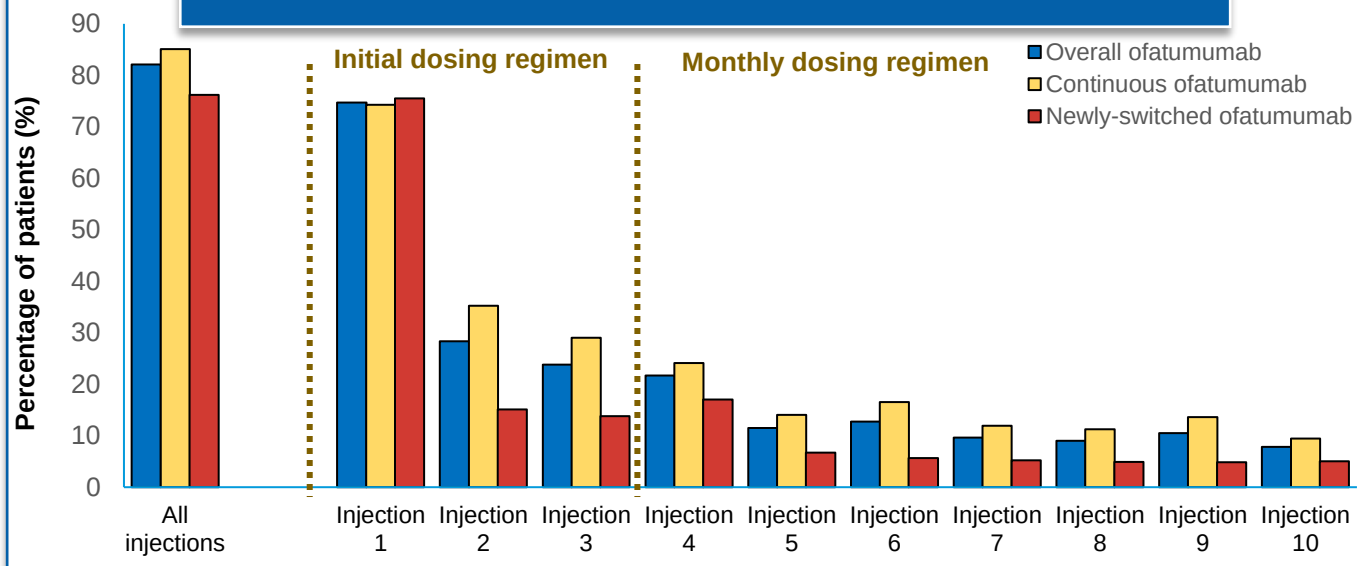
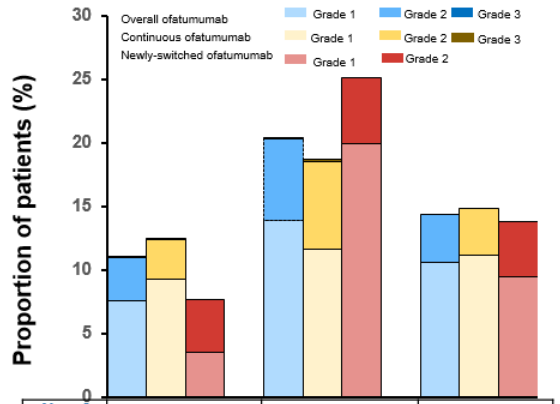
Percentage of patients taking premedication



Severity of systemic IRRs at all injections by premedication category



No. of patients	Steroids			Non-steroids			None		
Grade 1	106	91	15	104	62	42	197	135	62
Grade 2	48	30	18	48	37	11	71	43	28
Grade 3	1	1	0	1	1	0	2	2	0

- Proportion of patients taking premedication was highest with first injection (74.7%) and decreased with subsequent injections (second injection, 28.3%; third injection, 23.8%)
- Most systemic IRRs were mild to moderate irrespective of the premedication category, and only limited benefit from steroid premedication was observed

IRR, injection-related reaction.
Injection-related premedication was recommended but not required per protocol and could be administered at the discretion of the Investigator

IRRs From Post-marketing Surveillance

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- With an estimated exposure of 4713 patient-years, there were no medically confirmed fatal or life-threatening IRRs identified with ofatumumab treatment

8 of 103
medically confirmed cases were reported as serious

7 patients were hospitalized[a]

1 patient in which the events were determined to be medically significant but did not require hospitalization[b]

Most frequently reported events in the 8 cases[c]


Pyrexia, n=7


Chills, n=3


Vomiting, n=2


Asthenia, n=2


Fatigue, n=2

IRR, injection-related reaction.
[a]of the 7 hospitalized cases, 3 patients continued on therapy and action taken was unknown in 4 cases; [b]patient continued on therapy; [c]a patient may experience more than one event

Conclusions

- Systemic and local-site IRRs reported upon first injection with ofatumumab in the core clinical trials and ALITHIOS trial, including newly-switched patients and post-marketing surveillance were mostly mild to moderate in severity and nonserious in nature
- IRRs were predominantly reported with first injection, and the incidence decreased with subsequent injections
- No life-threatening/hypersensitivity reactions leading to treatment discontinuation were observed
- Only limited benefit of premedication with corticosteroids, antihistamines, or acetaminophen was observed in RMS clinical trials; if IRRs occur, symptomatic treatment is recommended[1]
- These results are consistent with findings from the Phase 3 ASCLEPIOS I/II trials[2]

IRR, injection-related reaction; RMS, relapsing multiple sclerosis

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2. Hauser SL, et al. *N Engl J Med.* 2020;383:546−57.

Systemic IRR Symptoms by Premedication Category

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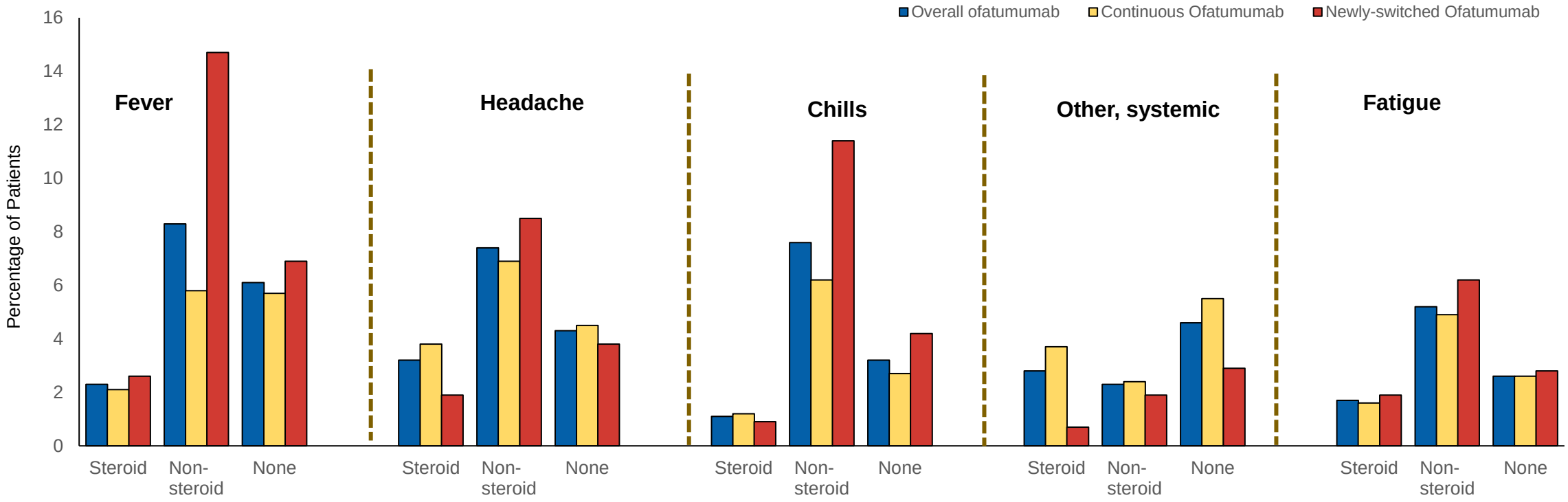
Incidence of systemic IRR symptoms by premedication



- Management of systemic IRR symptoms (such as fever, myalgia, and chills etc) can be easily mitigated with symptomatic treatment, should they occur.[1]

1. KESIMPTA® (ofatumumab) Prescribing Information. https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf (accessed February 17, 2022).