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

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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 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 injection-related reactions (IRRs; systemic and local-site) between ofatumumab and placebo (in the teriflunomide arm) was observed with the very first dose of ofatumumab
  - 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 (PT) 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

Objective

- To summarize the characteristics of IRRs (systemic and local-site) observed in RMS patients treated with ofatumumab, including newly-switched patients, based on updated data (cut-off:25-Sep-2021) from the ALITHIOS trial (up to 4 years) and in the post-marketing setting

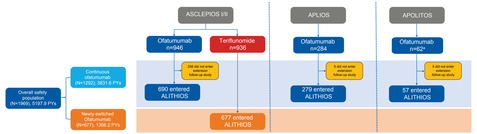
Methods

Patient population and treatment patterns

Clinical trials:

- The overall safety population included 1969 patients, of whom 1292 were in the continuous ofatumumab group and 677 in the newly-switched ofatumumab group (**Figure 1**)
  - **Continuous ofatumumab:** Patients who were treated with ofatumumab in the core studies (ASCLEPIOS I/II, APLIOS, or APOLITOS), regardless of whether they entered ALITHIOS
  - **Newly-switched ofatumumab:** Patients who were randomized to teriflunomide in ASCLEPIOS I/II and switched to ofatumumab on entering ALITHIOS

Figure 1. Patient disposition



*Patients were either randomized to or switched to OMB during the core study.

- Patients received or self-administered the first four injections at the clinic/under supervision; after the fourth injection, most patients self-administered ofatumumab at home
- Premedication with acetaminophen and/or antihistamines (or equivalent) was recommended and administered at the discretion of the investigator, 30 to 60 minutes prior to the injection of the study drug. For the first injection only, the addition of premedication with steroids (methylprednisolone 100 mg iv or equivalent) was recommended

Post-marketing surveillance:

- Estimated ofatumumab exposure of 4,713 patient-years was used for determining post-marketing cases (cut-off:25-Sep-2021)

Study assessments and analysis

Clinical Trials:

- Safety analyses were conducted using the safety dataset (all patients who received at least one dose of ofatumumab)
- The investigators reported IRRs as systemic IRRs or local-site IRRs
  - **Systemic IRRs:** IRRs that occurred within 24 hours after the injection (i.e., time to onset of reaction ≤24 hours) were assumed to be injection-related and the PT used is "injection-related reaction"
  - **Local-site IRRs:** IRRs that could be reported without any time limit from the time the injection was administered, and the PT used is 'injection-site reactions'
- Proportion of patients with systemic and local-site IRRs were analyzed by treatment group against injection sequence numbers (0 to 10) and cumulatively for all injections
- **Severity:** IRRs were reported using the Common Terminology Criteria for Adverse Events (CTCAE) grading, and categorized as: mild (Grade 1), moderate (Grade 2), severe (Grade 3), and life threatening (Grade 4)
- **Symptoms:** Symptoms were summarized by the number and percentage of patients by each injection and cumulatively for all injections
- Incidence of IRRs by premedication category was also assessed

Post-marketing surveillance:

- A search was conducted in the Novartis safety database for possible systemic IRRs (expected adverse reaction; the medical review will focus on all fatal, all life-threatening, and only medically confirmed potential serious IRRs)
- Results were further evaluated to identify those that met the regulatory criteria for serious, were likely to be true systemic IRRs, and not confounded by other reported events occurring in conjunction that would have been contributory

Results

Clinical trials data

Systemic IRRs

- 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 (**Figure 2**)

Figure 2. Incidence of systemic IRRs (safety set)

IRR, injection-related reaction

- Most systemic IRRs (99.2%) were mild to moderate (Grade 1/2) in severity and nonserious (99.4%) in nature
- Grade 3 IRRs were observed in four patients. Of these, 3 patients (0.2%) reported IRR after the first injection and one patient after the 13th injection
  - In one patient, the event was also reported as a serious AE. The symptoms (fever, nausea, tachycardia and vomiting) reported 4 hours after first injection were resolved with symptomatic medication and the patient completed the study with no recurrences
  - In the second patient, the event was not assessed as a serious AE (as per investigator), but the patient discontinued the study treatment due to IRR. The symptoms (abdominal pain, asthenia, pruritus, and urticaria) reported 10 hours after first injection were resolved with antihistamine treatment
  - In the third patient, the event was not assessed as a serious AE (as per investigator). The symptoms (abdominal pain, arthralgia, asthenia, chills, dizziness, fatigue, fever, headache, myalgia, nausea, rash) reported 4 hours after injection were resolved with symptomatic treatment
  - In the fourth patient, the event was reported as a serious AE, and the drug was interrupted due to IRR. The symptoms (myalgia, fever, hypertension and chills) reported 10 hours after injection were resolved with symptomatic treatment
- 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 resolved without concomitant medication/non-drug therapy

Symptoms associated with systemic IRRs

- The most common (≥5%) systemic IRR symptoms observed during all injections across all groups include fever, headache, chills, other systemic reactions and fatigue (**Table 1**)
- No cases of cytokine release syndrome were reported

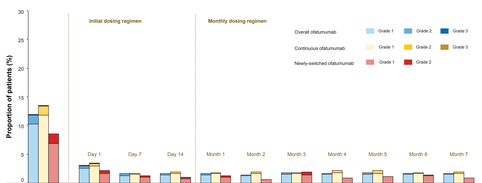
Table 1. Incidence of symptoms (at least 5% in overall group) related to systemic IRRs

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)

Local-site IRRs

- 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 (**Figure 3**)

Figure 3. Incidence of local-site IRRs (safety set)



IRR, injection-related reaction

- Most local-site IRRs (99.5%) were mild to moderate (Grade 1/2) in severity and nonserious (99.6%)
- Grade 3 injection site reaction was observed in one patient and symptoms (pain and warmth) were resolved in 2 days with symptomatic medication; the same patient also reported Grade 3 injection systemic reactions
- No life-threatening IRRs were reported during the study
- 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

Symptoms associated with local-site IRRs

- The most common local-site IRR symptoms (≥2%) observed during all injections across all groups include erythema/redness, other site reactions, pain, itching, and induration/swelling (**Table 2**)

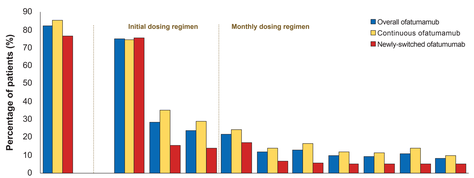
Table 2. Incidence of symptoms (at least 2% in the overall group) related to local-site IRRs

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)

Use of premedication

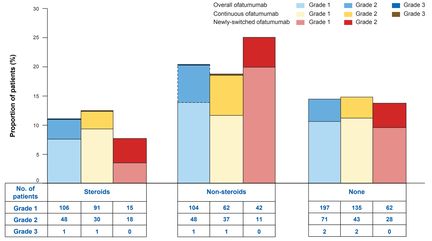
- Proportion of patients taking premedication was highest with first injection (74.7%) and decreased with subsequent injections (second injection, 28.3%; third injection, 23.8%) (**Figure 4**)

Figure 4. Percentage of patients taking premedication



- When no premedication was used at all injections, the proportion of patients with systemic IRRs in overall, continuous and newly-switched group were 14.6%,15.0%, 13.8% respectively (**Figure 5**)
- When any premedication was used at all injections, the proportion of patients with systemic IRRs in overall, continuous and newly-switched group were 11.0%, 12.5%, 7.8% for steroids and 20.5%,18.7%, 25.1% for non-steroids respectively. Premedication is considered not required, considering limited benefit of premedication with steroids and the potential risks associated with the use of steroids
- Most systemic IRRs were mild to moderate irrespective of the premedication category (**Figure 5**)

Figure 5. Severity of systemic IRRs at all injections by premedication category



Post-marketing surveillance data

- With an estimated exposure of 4,713 patient-years, there were no medically confirmed fatal or life-threatening IRRs identified
- 8 of 103 medically confirmed cases were reported as serious:
  - 7 patients were hospitalized, of which, 3 patients continued on therapy and action taken was unknown in 4 cases
  - 1 patient in which the events were determined to be medically significant but did not require hospitalization, who continued on therapy
- The most frequently reported events in these 8 cases included pyrexia (n=7), chills (n=3), vomiting (n=2), asthenia (n=2), and fatigue (n=2); 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]

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