Safety and Tolerability of IVIG (octagam®10%) in Patients with Active Dermatomyositis. Results of a Randomized, Double-Blind, Placebo-Controlled Phase III Trial.

Aggarwal, R.[1]; Charles-Schoeman, C.[2]; Schessl, J.[3]; Bata-Csorgo, Z.[4]; Dimachkie, M. M.[5]; Griger, Z.[6]; Moiseev, S.[7]; Oddis, C.V.[1]; Schiopu, E.[8]; Vencovský, J.[9]; Beckmann, I.[10]; Clodi, E.[10]; Levine T.[11] and the ProDERM Investigators[12]

[1]University of Pittsburgh School of Medicine, Pittsburgh, USA, [2]University of California, Los Angeles, USA, [3]Friedrich-Baur-Institute, Department of Neurology, Ludwig-Maximilians University of Munich, Germany, [4]Department of Dermatology and Allergology, University of Szeged, Hungary, [5]University of Kansas Medical Center, Kansas City, USA, [6]Division of Clinical Immunology, University of Debrecen, Hungary, [7]Sechenov First Moscow State Medical University, Moscow, Russia, [8]Division of Rheumatology, Michigan Medicine University Hospitals, Ann Arbor, USA, [9]Institute of Rheumatology, Charles University, Prague, Czech Republic, [10]Octapharma Pharmazeutika Produktionsges.m.b.H., Vienna, Austria, [11]Phoenix Neurological Associates, Ltd., Phoenix, USA, [12]Institutions all over USA, CA and Europe

Introduction

- Intravenous Immunoglobulin (IVIG) has proven efficacy in many immune mediated clinical conditions with FDA approved indications of Idiopathic Thrombocytopenic Purpura (ITP), Multifocal Motor Neuropathy (MMN) and Chronic Inflammatory Demyelinating Polyneuropathy (CIDP).
- Off-label use of IVIG in other neurological and dermatological indications is widespread including Dermatomyositis (DM) and Polymyositis. Very few trials have been published on efficacy and safety of IVIG in DM.

Study Rationale

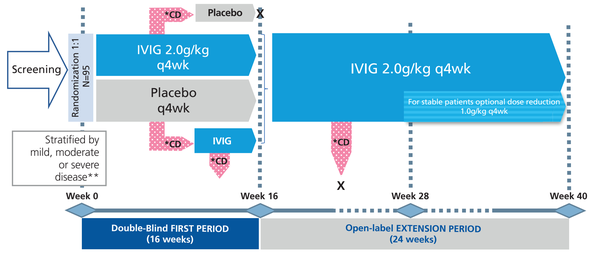
- The **Pro**gress in **DERM**atomyositis (ProDERM) study was planned to investigate efficacy, safety and tolerability of a 10% IVIG (octagam®10%) in DM patients and to confirm in a pivotal trial the efficacy results of previous small randomized controlled trial and case series.
- Efficacy results were presented earlier. This presentation will focus on the safety results of the study.

Methods

Prospective, double-blind, placebo-controlled, multicenter Phase 3 study.

- 1:1 randomization during 16-week First Period (4 infusion cycles)
  - 2.0 g/kg octagam®10% or placebo every 4 weeks.
- Cross-over in First Period for patients with confirmed deterioration on 2 consecutive visits.
- After Week 16 all patients on placebo and patients on IVIg without clinical worsening continued in subsequent 6-month, open-label Extension Period with 2.0 g/kg octagam®10% every 4 weeks.
- Infusions were divided in equal doses given over 2-5 consecutive days (≈ 1 infusion cycle) every 4 weeks.
- Pre-medication was only allowed for patients who experienced adverse events at 2 consecutive infusions.
- Dosing was done according to actual body weight.

Study Design



X: **drop-out**

***CD: Confirmed Deterioration** defined as change from baseline on 2 consecutive visits in Physician's Global Disease Activity VAS worsening ≥2 cm and MMT-8 worsening ≥20%, OR global extra-muscular activity worsening ≥2 cm on the MDAAT VAS, OR any 3 of 5 CSM (core set measures, excl. enzymes) worsening by ≥30%).

**Physician's Global Disease Activity (GDA) value of 0-3 [mild], 4-6 [moderate], 7-10 [major]

#Placebo patients having confirmed deterioration at Week 16 continued in open-label part

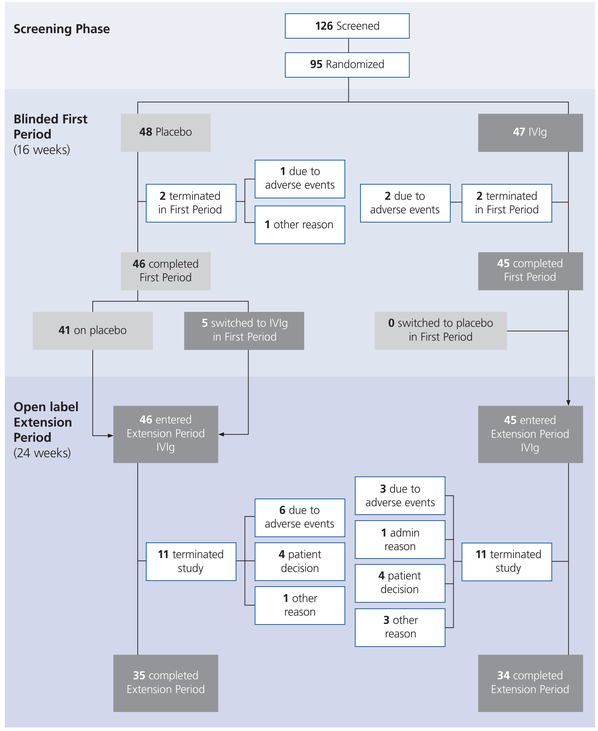
Results

Patients

Median age was 52 years, and the majority of patients were female (74.7%) and white (91.6%).
Median time since diagnosis was 2.6 years, and 70.5% of patients had definite dermatomyositis.
All patients experienced symmetric proximal muscle weakness and typical skin rash.
Patients had significant muscle weakness and active disease with at baseline

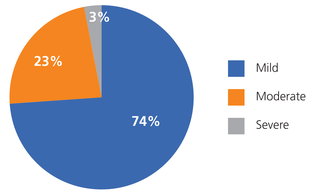
- mean MMT-8 score of 120.9 and
- mean physician GDA of 5.0.

During the study 664 infusion cycles were administered.



In total 96% of patients completed the first period and 73% the extension period.
In the First Period 3 patients discontinued due to adverse events, all 3 experienced the adverse event after IVIG treatment (one patient in the placebo group experienced the AE after having been switched to IVIG).
In the Extension period 9 patients discontinued due to adverse events.

Figure 1: Intensity of related adverse results



- During the study a total of 545 adverse events (AE) were reported.
- 282 in 62 (65%) subjects were assessed as being related to study drug.
- Most related AEs were infusion related/reactions (92%, 260).
- Five patients experienced 9 severe related events: 4 events of headache and 1 event each of nausea, muscle spasms, dyspnoea, deep vein thrombosis, pulmonary embolism.

Adverse events related to study drug

Table 1: IVIG-related AEs reported in more than 2% of patients

	% of Subjects (Total N=95)
Headache	42.1
Fever	19.0
Nausea	15.8
Vomiting	8.4
Chills	7.4
Musculoskeletal pain	7.4
Blood pressure increased	6.3
Coombs test positive	5.3
Dizziness	4.2
Tachycardia	4.2
Infusion site condition	3.2
Haemoglobin decreased	3.2
Dyspnoea	3.2
Asthenia	2.1
Fatigue	2.1
Pain	2.1
Peripheral swelling	2.1
Arthralgia	2.1
Muscle spasms	2.1
Pain in extremity	2.1
Pulmonary embolism	2.1
Anaemia	2.1
Lymphopenia	2.1
Vision blurred	2.1

The adverse event profile was consistent with commonly reported adverse events for IVIG administration. Premedication for IVIG infusion was required by only 21.3% of patients.

Adverse events leading to study discontinuation

Table 2: Related AEs leading to study discontinuation

Treatment at time of event	Patient	MedDRA Preferred Term	Intensity	Outcome	Serious	Causality
First Period IVIG	Pt 1	Muscle spasms	Severe	Recovered/ resolved	Yes	Probable
		Sinus tachycardia	Moderate	Recovered/ resolved	No	Probable
		Chills	Mild	Recovered/ resolved	No	Probable
		Body temperature increased	Mild	Recovered/ resolved	No	Probable
		Dyspnoea	Severe	Recovered/ resolved	Yes	Probable
		Back pain	Moderate	Recovered/ resolved	No	Probable
Extension Period (all IVIG)	Pt 2	Myalgia	Mild	Recovered/ resolved	No	Possible
		Paraesthesia	Mild	Recovered/ resolved	No	Possible
		Dizziness	Mild	Recovered/ resolved	No	Possible
		Condition aggravated	*Mild*	*Recovered/ resolved*	*No*	*Not related*
	Pt 3	Headache	Moderate	Recovered/ resolved	No	Probable
		Nausea	Moderate	Recovered/ resolved	No	Probable
	Pt 4	Deep vein thrombosis	Severe	Recovered/ resolved	Yes	Probable
		Pulmonary embolism	Severe	Recovered/ resolved	Yes	Probable
	Pt 5	Hypersensitivity	Mild	Recovered/ resolved	No	Probable
	Pt 6	Vomiting	Mild	Recovered/ resolved	No	Probable
	Pt 7	Vertigo	Moderate	Recovered/ resolved	No	Possible
		Vision blurred	Mild	Recovered/ resolved	No	Possible
		Cerebrovascular accident	Moderate	Recovered/ resolved with sequelae	Yes	Possible
	Pt 8	Pulmonary embolism	Moderate	Recovered/ resolved with sequelae	Yes	Possible

- AEs leading to discontinuation assessed as not related:

Extension Period:

- Sepsis
- Basilar artery stenosis
- Escherichia bacteraemia
- Condition aggravated (2 patients)

Serious AEs

Table 3: Serious adverse events assessed as related

Treatment at time of event	Patient	MedDRA Preferred Term	Intensity	Outcome	Serious Criteria	Causality
First Period IVIG	Pt 1	Muscle Spasm	Severe	Recovered/ resolved	Life threatening	Probable
		Dyspnoea	Severe	Recovered/ resolved	Life threatening	Probable
Extension Period (all IVIG)	Pt 4	Deep vein thrombosis	Severe	Recovered/ resolved	Hospitalization and Life threatening	Probable
		Pulmonary embolism	Severe	Recovered/ resolved	Hospitalization and Life threatening	Probable
	Pt 7	Cerebrovascular accident	Moderate	Recovered/ resolved with sequelae	Hospitalization and Medically important	Possible
	Pt 8	Pulmonary embolism	Moderate	Recovered/ resolved with sequelae	Hospitalization and Medically important	Possible
	Pt 9	Loss of consciousness	Moderate	Recovered/ resolved	Hospitalization	Probable
	Pt 10	Cerebral Infarction	Mild	Recovered/ resolved with sequelae	Hospitalization and Medically important	Possible
	Pt 11	Hypoaestesia	Mild	Recovered/ resolved	Medically important	Possible

- Serious AEs assessed as not related:

First Period:

- Sepsis and Pulmonary embolism
- Ventricular extrasystoles
- Tropical spastic paresis
- Sinus tachycardia and hypertension

Extension Period:

- Squamous cell carcinoma
- Condition aggravated and atypical pneumonia
- Condition aggravated
- Pneumonia, cardiac failure congestive, sepsis, acute respiratory failure and acute kidney injury

The incidence of serious AEs was similar in the two treatment groups during the First Period: 3 subjects (5.8%) experienced 5 serious AEs after IVIg and 2 subjects (4.2%) experienced 4 serious AEs after placebo.

- Dermatomyositis patients are reportedly at an increased risk for TEEs, and the study therefore placed special emphasis on TEE monitoring.
- After evaluation of 4 TEE events (1 unrelated in the First Period, 3 related in the Extension Period), the protocol was modified to reduce the maximum infusion rate from 0.12 to 0.04 ml/kg/min. This reduction led to a decrease in the incidence (95% CI) of TEEs from 1.54 (0.42, 3.94) per 100 patient months prior to the amendment to 0.54 (0.07, 1.95) post-amendment.

Summary

- The safety profile of IVIG administration even at high dosages of 2 g/kg was consistent with commonly reported adverse events for IVIG administration.
- Most related events were mild to moderate (97%). Severe related AEs were seen in 5 patients and led to discontinuation in 2/5.
- Related AEs led to discontinuation in 8% of patients in the extension period.
- DM patients are at increased risk for thromboembolic events and patients were specifically observed for occurence of TEEs.

Conclusions

- IVIG (octagam®10%) is an efficacious, safe and well tolerated treatment for dermatomyositis.
- Observed AEs are generally consistent with the previously reported IVIG safety profile; in DM patients risk of TEEs can be reduced by lowering IVIG infusion rate.
- The results of the ProDERM study have led to approval of octagam 10% for treatment of dermatomyositis in the USA and Europe.

Disclosures
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