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Plain Language Summary of Publication

Inhaled molgramostim therapy for the treatment of autoimmune pulmonary alveolar proteinosis (aPAP): a plain language summary of the IMPALA trial

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Where can I find the original article on which this summary is based?

The original article discussed in this summary, titled 'Inhaled Molgramostim Therapy in Autoimmune Pulmonary Alveolar Proteinosis', was published in *The New England Journal of Medicine* in 2020. This article is available for free at: https://www.nejm.org/doi/full/10.1056/NEJMoa1913590#ap3

Keywords

• autoimmune pulmonary alveolar proteinosis • aPAP • GM-CSF • molgramostim • plain language summary • surfactant • whole-lung lavage

Summary

What is this summary about?
This is a plain language summary of a late-stage clinical trial called IMPALA, originally reported in *The New England Journal of Medicine*. The IMPALA trial studied a drug called molgramostim nebulizer solution (molgramostim) to see how well it worked and how safe it was in patients with autoimmune pulmonary alveolar proteinosis (aPAP). Normally, tiny air sacs (alveoli) in the lungs are covered by a thin layer of an oily substance called surfactant that helps to keep them open. In aPAP, surfactant builds up and clogs alveoli making it difficult to breathe. Inhaled molgramostim helps to reduce the amount of surfactant clogging the alveoli.

What were the results of the trial?
After 24 weeks of treatment, patients who received molgramostim every day had better oxygen transfer into blood than patients who received an inactive substance (placebo). Patients' sense of well-being and quality of life was improved more with daily molgramostim than placebo. The amount of surfactant in the lungs measured using scans and the number of whole-lung lavages (lung washes) patients required were lower with daily molgramostim than placebo. The number of medical problems (adverse events) was similar in patients who received molgramostim and placebo except for chest pain, which was more common with molgramostim.

What do the results of the trial mean?
The IMPALA trial demonstrated that molgramostim is a promising treatment option for people with aPAP.

How to say (double click sound icon to play sound)...

- **Molgramostim:** Mol-gram-oh-stim
- **Pulmonary alveolar proteinosis:** Pull-mon-air-i al-ve-oh-lar pro-teen-oh-sis
- **Lavage:** Luh-vahj
- **Surfactant:** Sur-fak-tuhnt

What is the purpose of this plain language summary?

The purpose of this plain language summary is to help you to understand the findings from recent research.

The results of this study may differ from those of other studies. Health professionals should make treatment decisions based on all available evidence not on the results of a single study.

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Who is this article for?

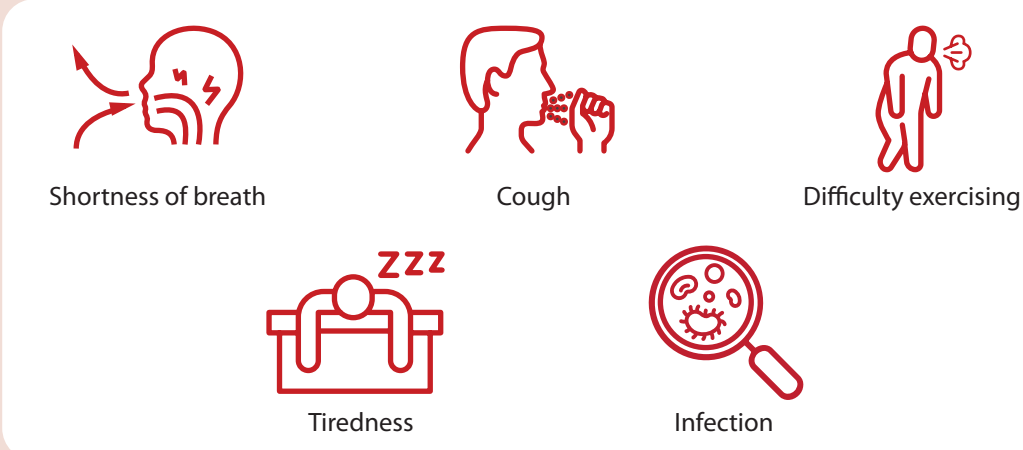
This plain language summary may be helpful for patients with aPAP and their caregivers, patient advocates, and non-specialist healthcare professionals.

What are the normal roles of alveoli, surfactant, macrophages, and GM-CSF in the lungs?

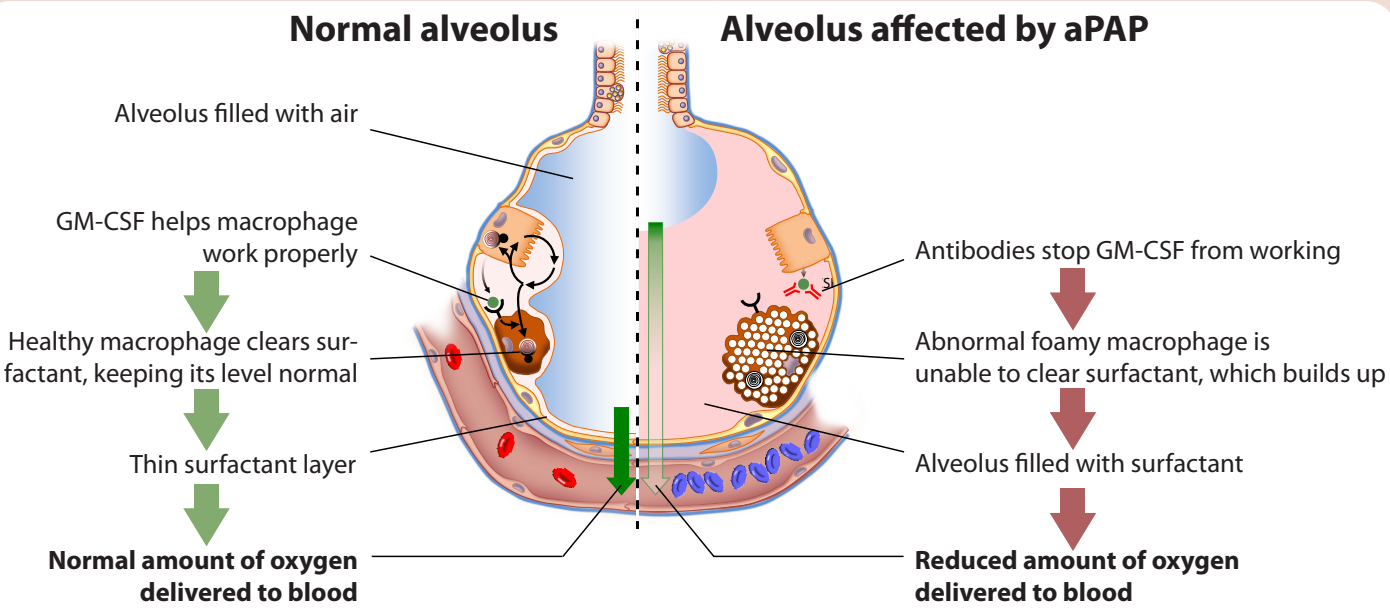
- The lungs contain millions of tiny air sacs (alveoli). They are normally coated with a layer of an oily substance called surfactant that is thick enough to keep alveoli open (by reducing surface tension) but thin enough to allow oxygen in inhaled air to easily pass through it to enter the blood.
- Alveolar macrophages are cells inside alveoli that must continuously remove excess surfactant to maintain this thin layer.
- To work properly, alveolar macrophages require granulocyte/macrophage-colony stimulating factor (GM-CSF). This is a small protein that stimulates numerous alveolar macrophage functions including surfactant removal.

What is autoimmune pulmonary alveolar proteinosis?

- Autoimmune pulmonary alveolar proteinosis, also called aPAP, is a rare disease affecting the lungs. In 1 million people, only about 7 to 27 people will have aPAP.
- aPAP is caused by the immune system, which mistakenly makes proteins called autoantibodies that stop GM-CSF from working properly.
- Without GM-CSF, macrophages are not able to remove surfactant from alveoli as well as they normally do. As a result, surfactant builds up over time to high levels in the alveoli. This accumulation of surfactant in the alveoli has the following effects:
  - it prevents inhaled air from entering alveoli
  - it increases the barrier through which oxygen must pass to enter the blood
  - it increases lung stiffness.
- Together, these effects reduce the amount of oxygen passing from the lungs into the blood.
- aPAP affects the lungs to cause breathlessness and increases the risk of serious infections.
- Common symptoms of aPAP include:



- Sometimes aPAP can lead to death, most commonly from lung failure or an uncontrolled infection.



McCarthy C, Carey BC and Trapnell BC. 2022. Autoimmune Pulmonary Alveolar Proteinosis. *Am J Respir Crit Care Med.* 205:1016–35.
The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society.

How is aPAP treated?

- No drugs are approved in the USA or Europe to treat aPAP specifically; a form of GM-CSF was recently approved in Japan.
- The effects of the disease are currently managed using a procedure called 'whole-lung lavage', which aims to physically remove excess surfactant by 'washing' it out of the lungs.
  - A medical team performs whole-lung lavage in a hospital operating room using general anesthesia to make the patient lose consciousness or go to sleep. The team connects one lung to a breathing machine and fills the other lung with warmed salt water, which they mix with the oily surfactant by pounding the chest before allowing the mixture to drain out. They repeat this procedure many times for each lung.
- The procedure helps by removing some (but not all) of the excess surfactant.
  - It does not correct the underlying cause of the disease or stop the build-up of surfactant.
  - Its benefit is short lived and most patients require repeated treatments, on average every 15 months.
  - The procedure is not widely available at most medical centers and is more difficult to perform in children.
  - While generally considered safe, whole-lung lavage carries some risks, including sore throat, damage and narrowing of the windpipe, lung collapse, leakage of salt water into the space around the lungs, and infection. Except for sore throat, all these problems are uncommon.
- A series of studies has shown that aPAP can be treated with forms of GM-CSF made in the laboratory by bacteria (recombinant GM-CSF [rGM-CSF]), for example, molgramostim.
  - Although rGM-CSF is not approved for the treatment of aPAP in the USA or Europe, studies show that it improves lung function and lessens symptoms. rGM-CSF treatment may also be able to correct the underlying cause of the disease to stop surfactant building up.

What is molgramostim?

- Molgramostim is a form of rGM-CSF made in the laboratory that can help alveolar macrophages remove excess surfactant from alveoli in patients with aPAP.
  - Molgramostim can be self-administered by the patient at home using a hand-held device called a nebulizer, which turns the liquid medicine into a fine mist that can be inhaled.

Why was the IMPALA trial done?

- Some previous studies have shown that rGM-CSF, especially when inhaled, is a promising treatment for aPAP. However, inhaled rGM-CSF had only been tested in a small number of patients.
- Researchers wanted to test whether inhaled rGM-CSF works in a larger number of patients and find out more about its safety, so they carried out a clinical trial called IMPALA to test a drug called molgramostim in patients with aPAP.

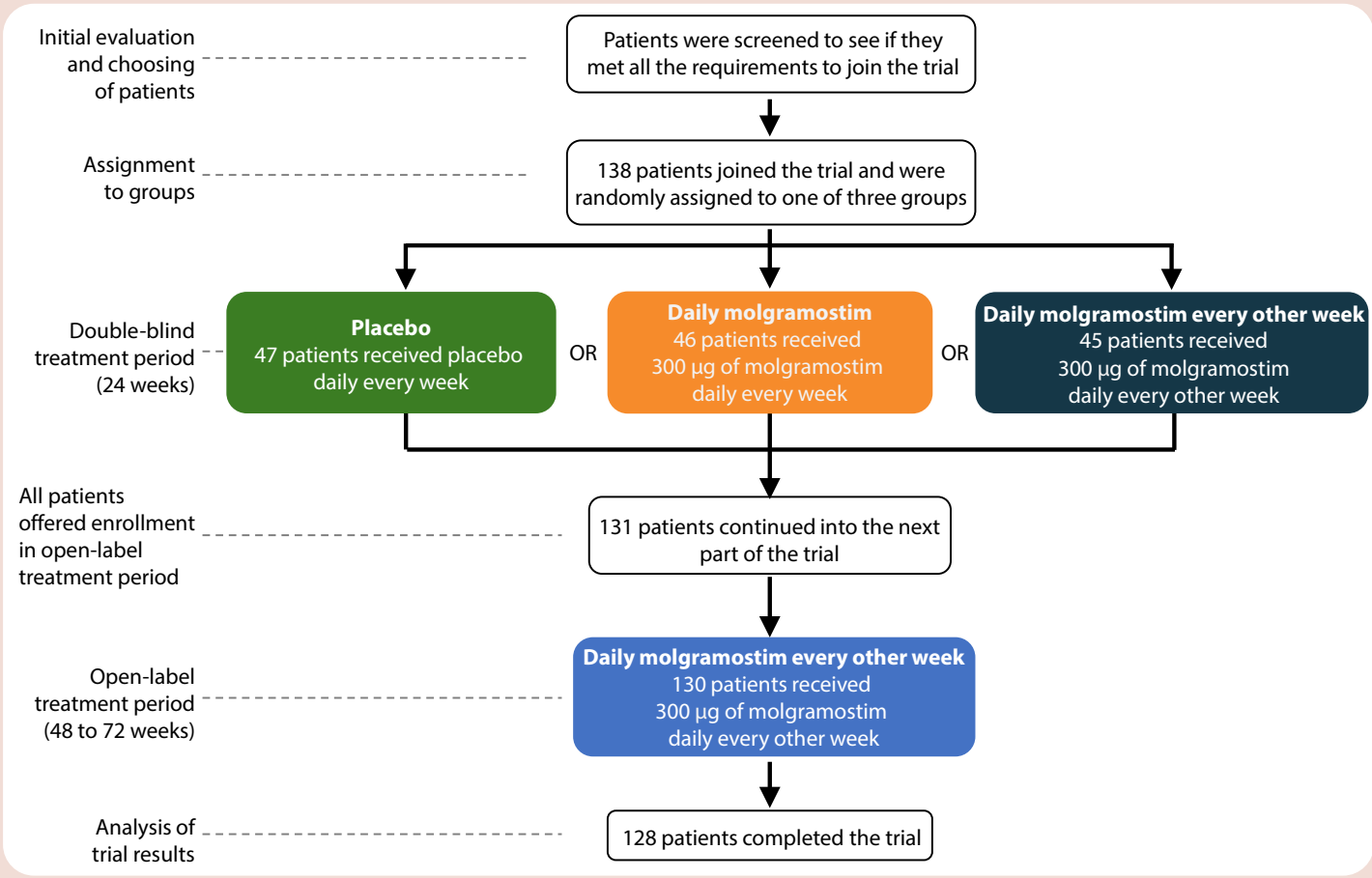
What was done in the IMPALA trial?

IMPALA was a **phase 2/phase 3**, **placebo-controlled**, **randomized**, **double-blind** trial.

Phase 2/phase 3 trial: A type of trial that researchers carry out to find out whether a drug (for example, molgramostim) works in a large number of patients with a disease (phase 2) and whether the patients have any health issues during the trial treatment (phase 3).
Placebo: An inactive substance that looks like the medicine being tested.
Placebo-controlled trial: A type of trial in which patients receive either an active drug (for example, molgramostim) or an inactive placebo. The vial containing the placebo will look like the one containing the active drug but will not have any active medicine in it. Researchers use a placebo to help to make sure that any of the effects they see in the patients who receive the active drug are actually caused by the drug.
Randomized trial: A type of trial in which patients are put into groups by chance to get either the active drug or inactive placebo. This helps to make sure that patients are placed in each group without any bias. Researchers do this so that comparing the results of each treatment is as accurate as possible.
Double-blind period: A part of a clinical trial in which patients, study doctors, other staff, and researchers do not know whether the treatment given is the active drug (for example, molgramostim) or an inactive substance (placebo). This is done because knowing which treatment the patients get can affect the results of the trial. After the results have been analyzed, the researchers find out which treatments the patients got so that they can create a report of the trial results.

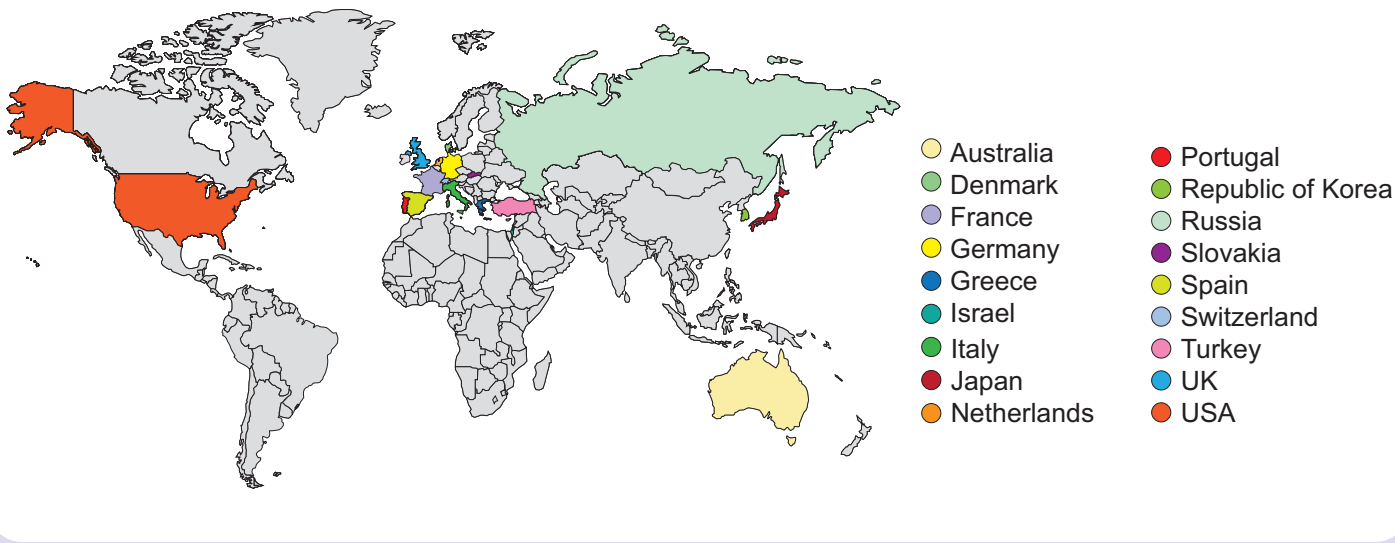
The figure on the next page shows the design of the IMPALA trial. The dose of molgramostim was measured in units of weight called micrograms (μg).

The IMPALA trial was conducted according to international and local guidelines ensuring the research was conducted in an ethical manner.



Who took part in the IMPALA trial?

The IMPALA trial included 138 patients with aPAP in 18 countries:



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Patients could join the trial if they met all the following conditions:

The IMPALA trial included patients who:

- were at least 18 years of age
- had a diagnosis of aPAP
- had an alveolar–arterial oxygen difference of 25 mmHg or more (a lower number indicates less severe disease)
- did not have a whole-lung lavage procedure within 1 month before joining the trial
- did not have previous treatment with rGM-CSF within 3 months before joining the trial
- did not have certain treatments before joining the trial

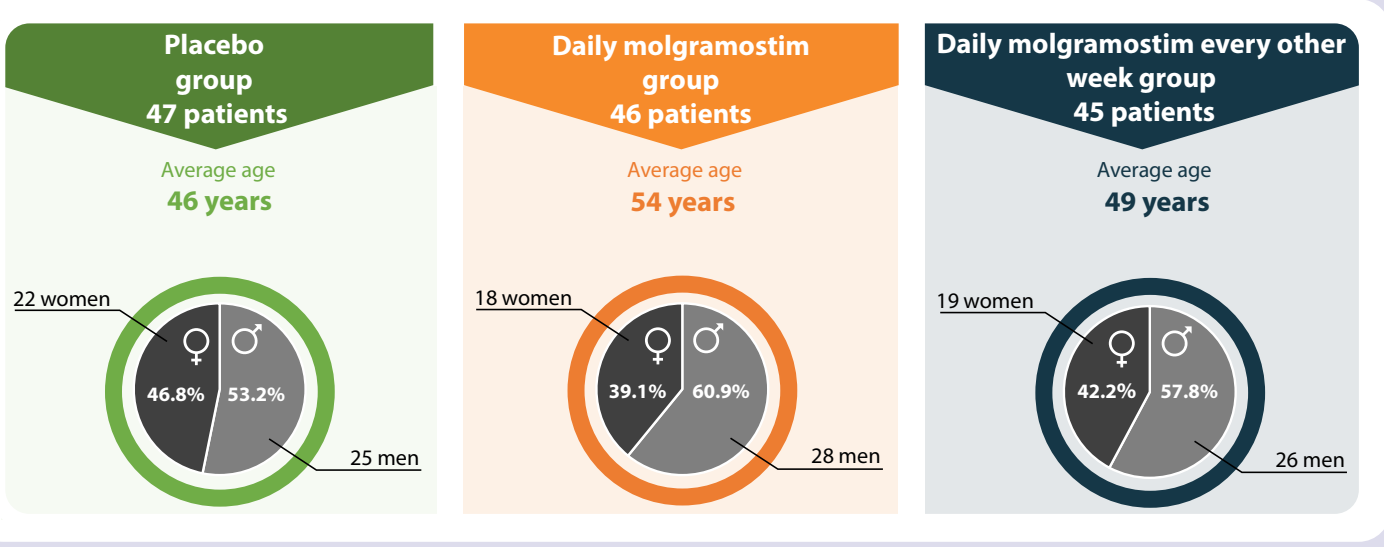
AND

- had a partial pressure of arterial oxygen of 75 mmHg or less while at rest (this is a measure of the amount of oxygen dissolved in the blood in the artery)

OR

- had an oxygen level in the blood that fell by more than 4% when a patient walked for 6 minutes (a smaller fall indicates that a patient has better ability to exercise)

The figure below shows some of the characteristics of the patients at the beginning of the trial.



What questions did the researchers want to answer in the IMPALA trial?

The main question the researchers wanted to answer was:

Did molgramostim improve the transfer of oxygen from the lungs to the blood?

The researchers also wanted to answer some other questions. These included:

Did molgramostim reduce the amount of surfactant in the lungs as seen in a CT scan?

Did molgramostim increase the patients' quality of life and ability to exercise?

Did molgramostim reduce the number of whole-lung lavage procedures a patient needed?

What were the most common medical problems (adverse events)?

- To find answers to these questions, the researchers performed multiple tests and measurements throughout the trial.
  - They compared measurements from patients taken at the beginning of the trial with the measurements taken after they had received molgramostim or placebo for 24 weeks.
  - The researchers then compared the average measurements for the patients who received molgramostim with the average measurements for those who received placebo.

What were the results of the IMPALA trial?

We describe the results for patients who received daily molgramostim, daily molgramostim every other week, or placebo, all for 24 weeks (double-blind period).

We also describe the results from the **open-label period** of the trial (from weeks 24 to 72), when all patients received daily molgramostim every other week.

Open-label period: A part of a clinical trial in which everyone involved, including patients, study doctors, other staff, and researchers, knows whether the treatment given is the active drug (for example, molgramostim) or an inactive substance (placebo).

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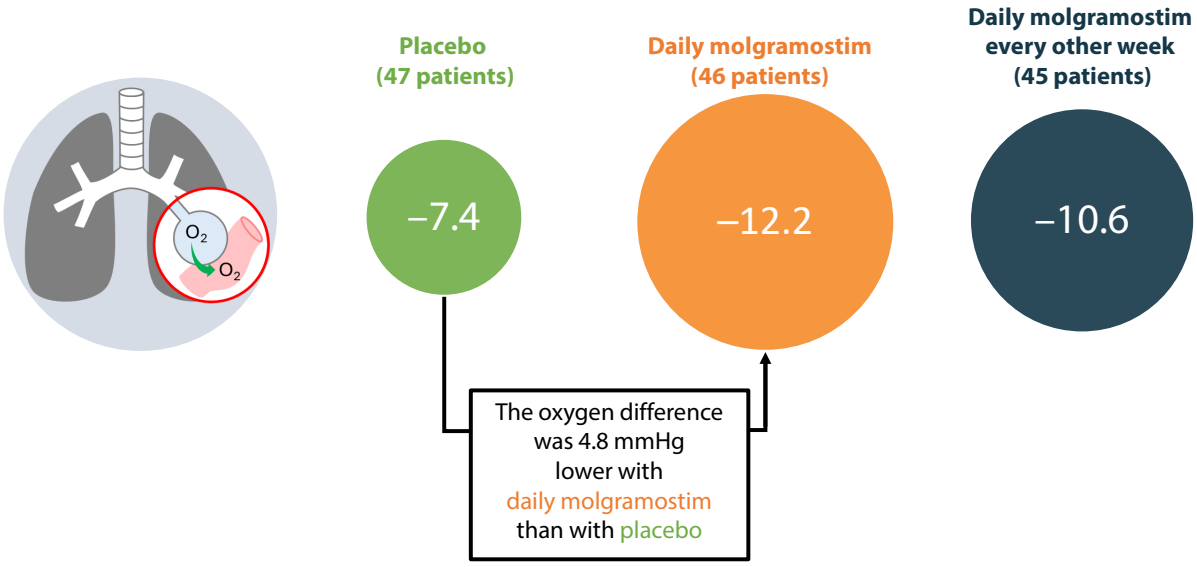
Did molgramostim improve the transfer of oxygen from the lungs to the blood?

- To answer this question, the researchers used a mathematical equation to calculate the difference between the amount of oxygen in the alveoli in the lungs and the amount of oxygen in the arterial blood, which is the blood that carries oxygen from the heart to the rest of the body.
  - This is called the alveolar–arterial oxygen difference. It is measured using a unit of gas pressure called millimeter of mercury (mmHg).
- After 24 weeks of treatment, the alveolar–arterial oxygen difference was similar between patients who received daily molgramostim and those who received placebo.
- This shows that oxygen transfer from the lungs to blood was similar between these groups of patients.

- The researchers found that the alveolar–arterial oxygen difference measurement was not performed properly in four patients.
  - These patients had received supplemental oxygen therapy through their noses while the measurements were being taken. The problem with this is that the amount of oxygen they inhaled was unknown, so it was not possible to calculate the true alveolar–arterial difference for these patients.
- When researchers did the calculation without the incorrect data from these four patients, they found that oxygen transfer in the lungs improved more in patients who received daily molgramostim than in patients who received placebo.

The figure below shows changes in the alveolar–arterial oxygen difference after 24 weeks of treatment in patients who received placebo, daily molgramostim, or daily molgramostim every other week.

Average change in alveolar–arterial oxygen difference (in mmHg) after 24 weeks of treatment



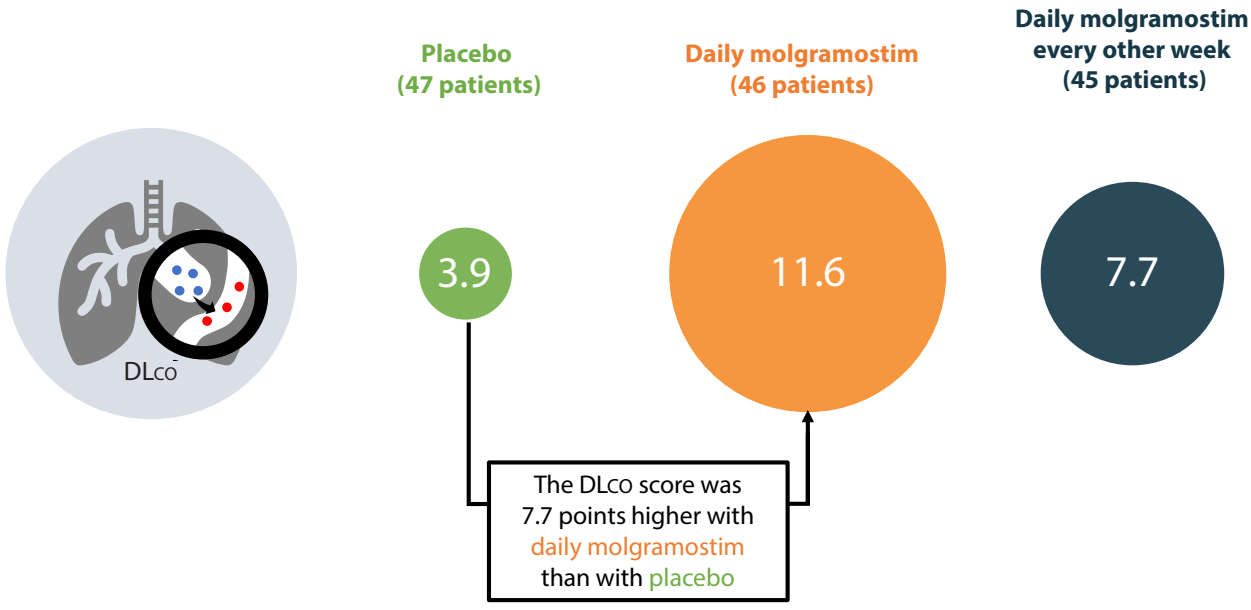
Explanation: The negative numbers show that the average difference between the amount of oxygen in the alveoli and the amount of oxygen in the blood was smaller after 24 weeks of treatment than at the start of the trial (a larger decrease is better). This indicates that oxygen transfer from the lungs to the blood improved during the trial. The change during the trial was greater with daily molgramostim than with placebo, and it was similar with placebo and daily molgramostim every other week.
Conclusion: The greatest improvement in oxygen transfer in the lungs was seen with daily molgramostim.

- During the open-label period of the trial (from weeks 24 to 72, when all patients received daily molgramostim every other week), the researchers saw improvements in the alveolar–arterial oxygen difference.

- The researchers also used another test, called diffusing capacity of the lungs for carbon monoxide (DLco). This test is used to assess how well the lungs transfer inhaled gas into the bloodstream.
  - It measures the transfer of carbon monoxide from inhaled air into the blood. This is a gas that binds strongly to hemoglobin, which is a protein in red blood cells that carries oxygen to tissues of the body.
  - The result of a DLco test is often given as a percentage of what researchers predict the normal value should be (percent predicted).
- After 24 weeks of treatment, patients who received daily molgramostim had more improvement in their DLco scores than patients who received placebo.
- This measurement was similar between patients who received daily molgramostim every other week and patients who received placebo.

The figure below shows the changes in DLco scores after 24 weeks of treatment in patients who received placebo, daily molgramostim, or daily molgramostim every other week.

Average change in DLco after 24 weeks of treatment



Explanation: Gas transfer from the lungs into the blood, measured by DLco scores, increased after 24 weeks of treatment compared with the start of the trial (a higher score is better). This indicates an improvement in gas transfer from the lungs to the blood during the trial. Average DLco scores were greater with daily molgramostim than with placebo, and were similar between placebo and daily molgramostim every other week.
Conclusion: The greatest improvement in gas transfer in the lungs was seen with daily molgramostim.

- During the open-label period of the trial (from weeks 24 to 72, when all patients received daily molgramostim every other week), researchers saw further improvements in DLco.

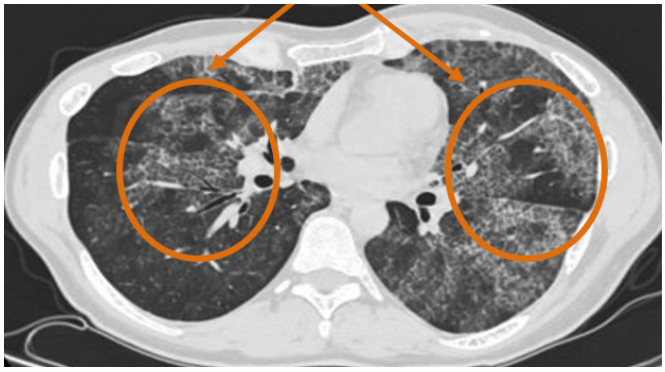
Did molgramostim reduce the amount of surfactant in the lungs as seen in a CT scan?

- To answer this, the researchers used computed tomography (CT) scans, which are computerized x-ray scans that can be used to make detailed pictures of the inside of the lungs.
- The researchers assessed the ground-glass opacification, which is a measurement of the 'cloudy' appearance of the lungs seen on the CT scan that can indicate an excess of lung surfactant. They assigned a score, which is higher when the alveoli are filled with surfactant (lower is better).
- After 24 weeks of treatment, the amount of surfactant in the lungs tended to be less in patients who received daily molgramostim than in patients who received placebo.
- There was no difference between patients who received daily molgramostim every other week and those who received placebo.

The figure below shows some example CT scan images of the lungs of a patient at trial start and after 24 weeks of treatment with molgramostim.

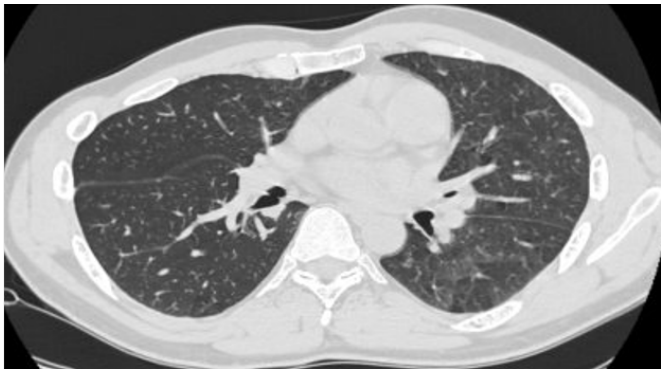
CT scan images of the lungs of a patient at trial start and after 24 weeks of treatment

Ground-glass opacifications are irregularly-shaped, hazy, cloud-like areas seen on a lung CT scan, indicating some abnormal tissue, typically found in the lungs of people with aPAP



CT scan of the chest of a patient with aPAP at the start of molgramostim treatment

There were fewer of these hazy, cloud-like areas after molgramostim treatment

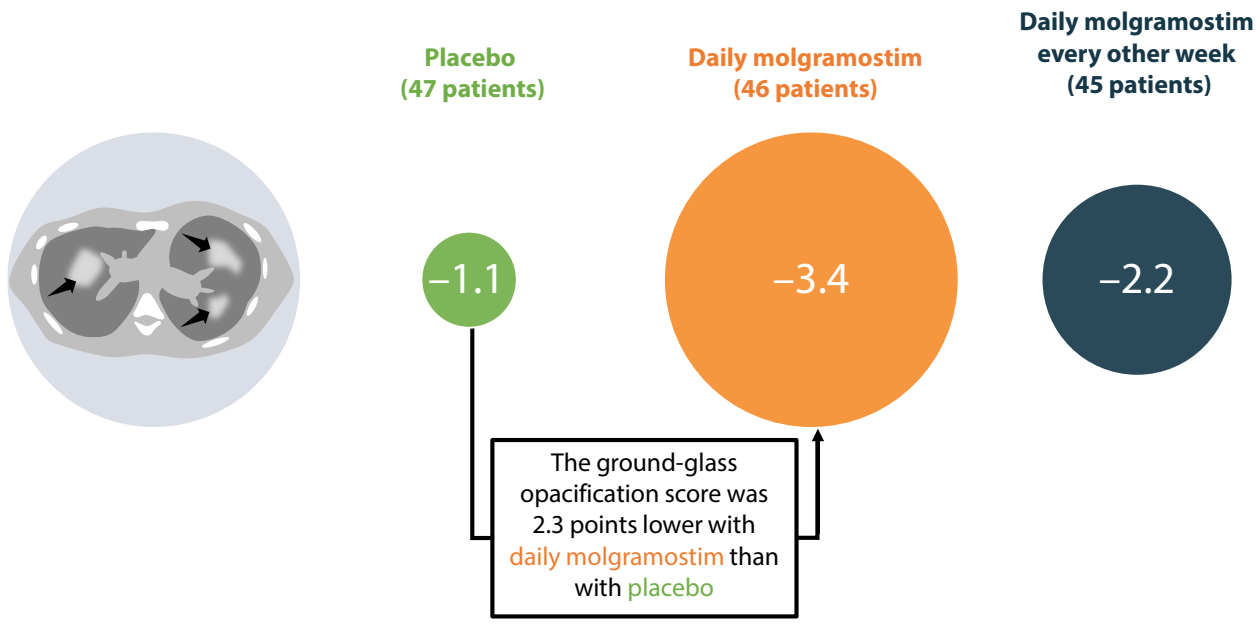


CT scan of the chest of the same patient with aPAP after 24 weeks of molgramostim treatment

Explanation: In the lungs of patients with aPAP, hazy, cloud-like areas are often seen on CT scan images where alveoli are filled with surfactant. After treatment with daily molgramostim, the appearance of these hazy areas was reduced. This indicates that there is less surfactant filling the alveoli.
Conclusion: Patients who responded to molgramostim treatment had less surfactant in their lungs (seen on CT scan images as ground glass opacification) than they had before treatment.

The figure below shows changes in the ground-glass opacification scores after 24 weeks of treatment for patients who received placebo, daily molgramostim, or daily molgramostim every other week.

Average change in ground-glass opacification score after 24 weeks of treatment



Explanation: Ground-glass opacifications are hazy areas often seen on a lung CT scan where alveoli are filled with surfactant. The negative numbers show that average ground-glass opacification scores were lower after 24 weeks of treatment than at the start of the trial (a larger decrease is better). This indicates a reduction in the amount of surfactant in the lungs. The change during the trial was greater with daily molgramostim than with placebo, and it was similar with placebo and daily molgramostim every other week.
Conclusion: The greatest reduction in the amount of surfactant in the lungs was seen with daily molgramostim.

Did molgramostim increase the patients' quality of life and ability to exercise?

- To answer this question, the researchers asked the patients to complete:
  - A survey called St George's Respiratory Questionnaire (SGRQ). This was used to measure patients' feelings about the impact of aPAP on their overall health, daily life, and well-being. It gives an idea of the overall quality of life of the patients.
  - A test called the 6-minute walk test. This measures how far a patient can walk in 6 minutes. This test can show how well patients' lungs are working and how much impact aPAP has on their ability to exercise without feeling too breathless.

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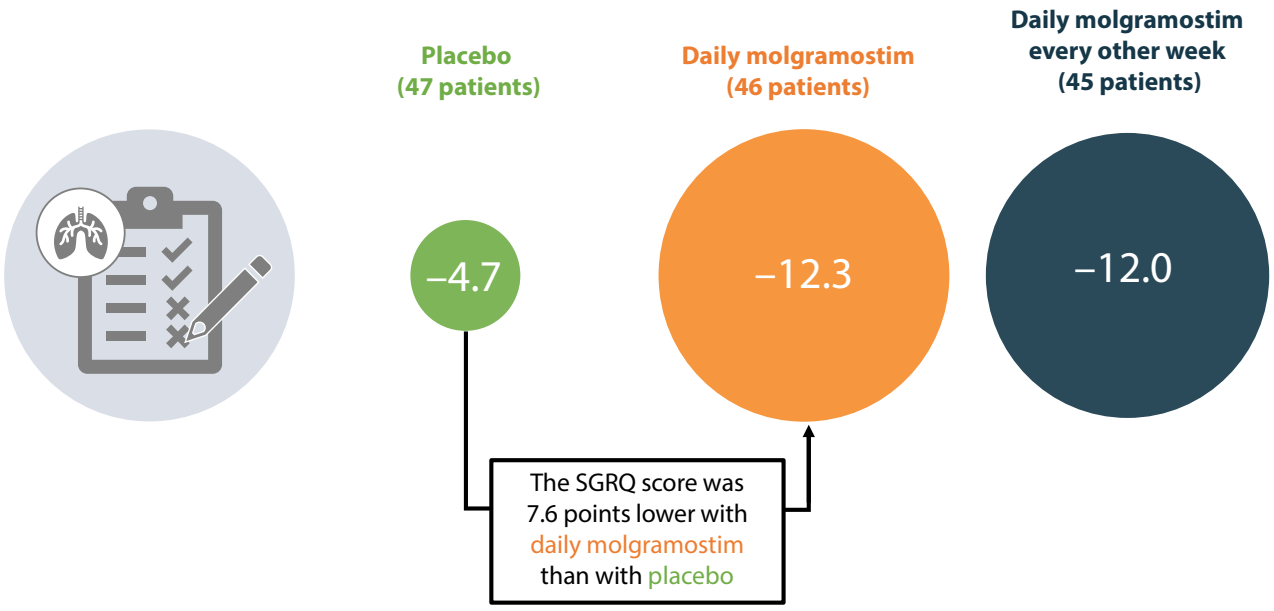
SGRQ

- After 24 weeks of treatment, patients who received daily molgramostim, or daily molgramostim every other week showed more improvement from the start of the trial in their own assessment of their health and quality of life than patients who received placebo.

The figure below shows the changes in SGRQ scores after 24 weeks in patients who received placebo, daily molgramostim, or daily molgramostim every other week.

Average change in SGRQ score after 24 weeks of treatment



Explanation: SGRQ scores are a measure of patients' own assessment of their health and quality of life. The negative numbers show that average SGRQ scores were lower after 24 weeks of treatment than at the start of the trial (a larger decrease is better). This indicates that patients' quality of life improved during the trial. Quality of life improved more with daily molgramostim or daily molgramostim every other week than with placebo.
Conclusion: The greatest improvement in quality of life was seen with daily molgramostim.

- During the open-label period of the trial (from weeks 24 to 72, when all patients received daily molgramostim every other week), the researchers saw further improvements in the SGRQ scores.

6-minute walk test

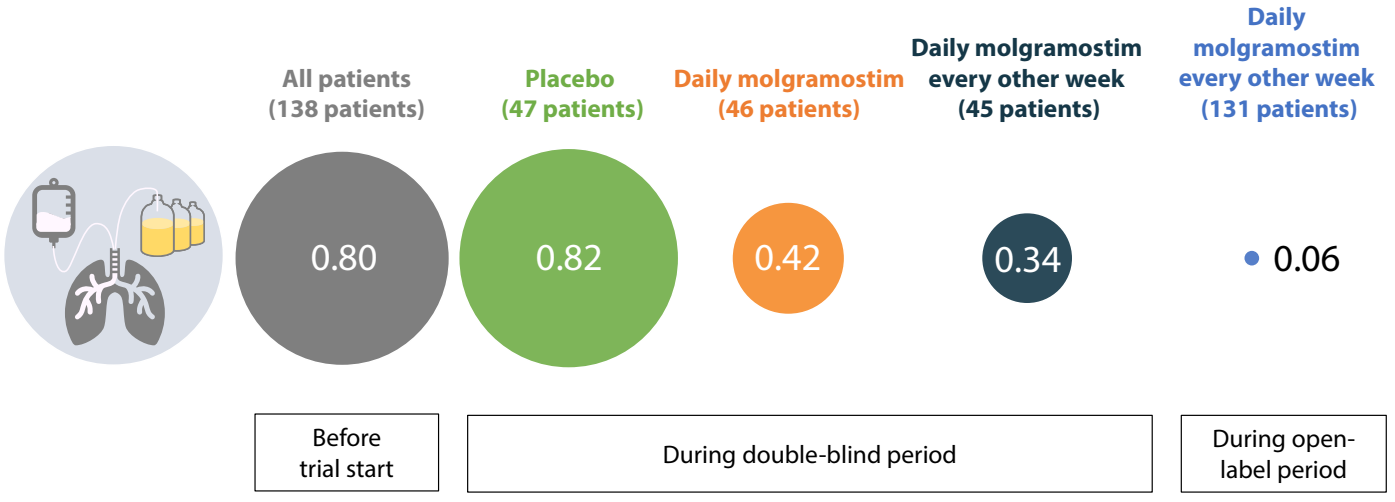
- After 24 weeks of treatment, there was no difference in the distance patients could walk in 6 minutes between those who received molgramostim and those who received placebo.

Did molgramostim reduce the number of whole-lung lavage procedures a patient needed?

- To answer this question, the researchers kept a record of the number of whole-lung lavage procedures the patients needed before the trial and while receiving molgramostim or placebo during the trial.
  - They calculated this as the number of procedures per patient-year. A patient-year is calculated as the average number of procedures each patient had divided by the number of years during which the number of procedures were counted.

The figure below shows the number of whole-lung lavage procedures per patient-year before the start of the trial and while the patients received placebo or molgramostim in the double-blind and open-label periods of the trial.

Number of whole-lung lavage procedures per patient-year



Explanation: Before the start of the trial, patients needed more frequent whole-lung lavage procedures than when receiving molgramostim during the trial. During the double-blind period of the trial, the patients who received molgramostim needed less frequent whole-lung lavage procedures than patients who received placebo. The frequency of whole-lung lavage was further reduced during the open-label period of the trial, when all patients received daily molgramostim every other week.

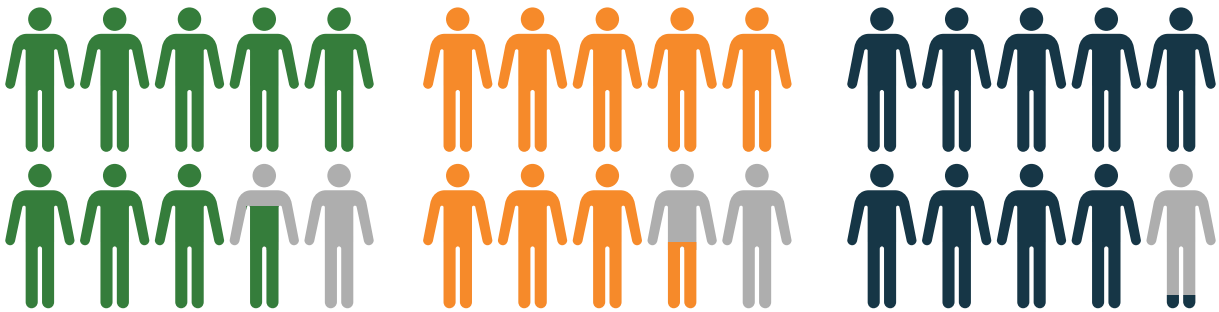
Conclusion: Patients needed whole-lung lavage procedures less frequently during daily molgramostim treatment.

What were the most common medical problems (adverse events)?

- To answer this question, the researchers kept a record of all the medical problems that any patient experienced during the trial.
  - Researchers call these medical problems adverse events.

The figure below shows the proportions of patients who had medical problems in the 24-week double-blind part of the trial.

Proportions of patients who had medical problems during the 24 weeks of treatment



87.2%
patients receiving placebo

84.8%
patients receiving daily molgramostim

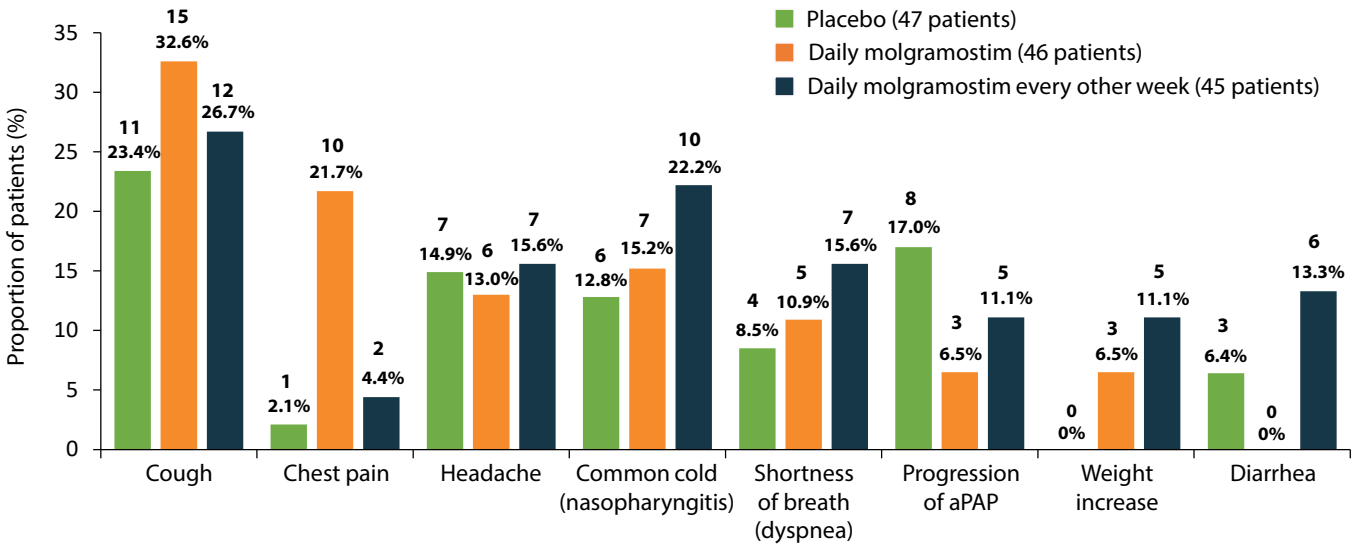
91.1%
patients receiving daily molgramostim every other week

Explanation: During the 24 weeks of treatment, doctors made a record of any medical problems (adverse events) each patient experienced. The colored portions of the people fiures represent the proportion of patients within each treatment group who experienced a medical problem.
Conclusion: The percentages of patients who had medical problems during the trial were similar between the three groups.

- The most common medical problems during the trial included cough, chest pain, headache, common cold (nasopharyngitis), and shortness of breath.
  - Not all patients will experience these medical problems if they take this medication, but some patients may.
- In the double-blind part of the trial, the percentage of patients with medical problems was similar between the groups, except for chest pain, which was more common in those who received daily molgramostim (21.7%) than in patients who received daily molgramostim every other week (4.4%) or placebo (2.1%).
  - The chest pain events were not considered to be serious by the doctors and no changes to the treatment doses were made.
    - A medical problem is considered to be serious when it is life-threatening, causes lasting problems, or requires hospital care.

The figure below shows the medical problems that happened in at least 10% of the patients in any group. There were other medical problems, but they happened in fewer patients.

Medical problems that happened in at least 10% of the patients in any group



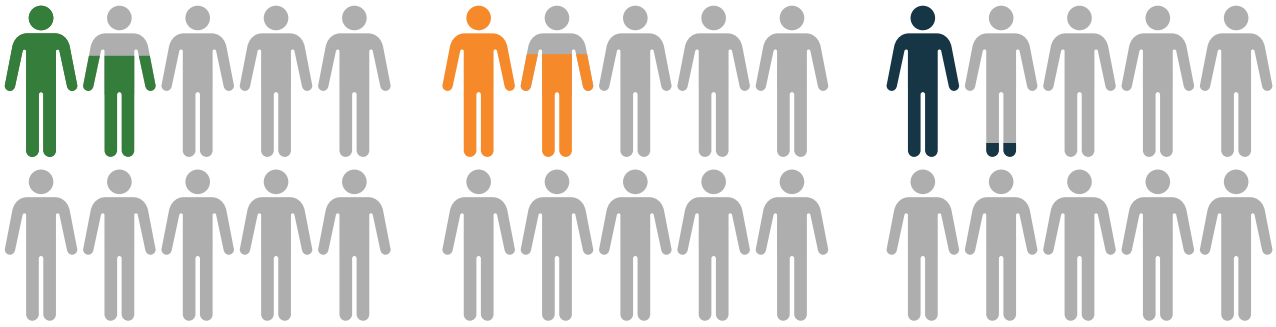
Explanation: During the 24 weeks of treatment, cough was the most common medical problem. Medical problems were not more common in patients who received molgramostim than in those who received placebo, apart from chest pain, which was more common in patients who received daily molgramostim.

Conclusions: Except for chest pain, medical problems were similar between treatment groups, and are therefore not expected to be a side effect of molgramostim. Chest pain was more common among molgramostim treated-patients than among placebo-treated patients, and may therefore be a possible side effect of molgramostim.

- In the open-label part of the trial (from weeks 24 to 72, when all patients received daily molgramostim every other week), 66.9% of the patients had at least one medical problem – this was 87 out of 130 patients.
- The most common medical problems during the open-label period were common cold (24 patients [18.5%]), cough (11 patients [8.5%]), and progression of aPAP (7 patients [5.4%]).
- The most common serious medical problem was progression of aPAP, which was less common in patients who received daily molgramostim (3 patients [6.5%]) or daily molgramostim every other week (3 patients [6.7%]) than in those who received placebo (6 patients [12.8%]).

The figure below shows the proportions of patients who had serious medical problems in the double-blind part of the trial.

Proportions of patients who had serious medical problems during the 24 weeks of treatment



17.0%
patients receiving placebo

17.4%
patients receiving daily molgramostim

11.1%
patients receiving daily molgramostim every other week

Explanation: During the 24 weeks of treatment, doctors made a record of any serious medical problems (serious adverse events) each patient experienced. The colored portions of the people figures represent the proportion of patients within each treatment group who experienced a serious medical problem.
Conclusion: The percentages of patients who had serious medical problems during the trial were similar between the three groups.

- In the open-label part of the trial, 12.3% of the patients had serious medical problems – this was 16 out of 130 patients.

What do the results of the trial mean?

- In the IMPALA trial, the researchers found that treatment with inhaled daily molgramostim compared with placebo:
  - Improved transfer of oxygen from inhaled air into the blood
  - Tended to reduce the amount of surfactant in the lungs as seen in a CT scan
  - Tended to reduce the number of whole-lung lavage procedures needed by patients
  - Increased the patients' perception of health and quality of life
  - Made no difference to patients' ability to exercise
- For most tests, in comparison with placebo, improvements were greater for daily molgramostim than for daily molgramostim every other week.
- Apart from pain in the chest that affected some patients who received daily molgramostim, the health issues were similar between patients receiving molgramostim and placebo during the double-blind part of the trial.
- These results show that molgramostim is a promising treatment option for people living with aPAP.

Additional information

The original article "Inhaled Molgramostim Therapy in Autoimmune Pulmonary Alveolar Proteinosis" was published in *The New England Journal of Medicine* in 2020 (Trapnell BC et al. *N Engl J Med.* 2020;383:1635–44). You can read the full article for free at: https://www.nejm.org/doi/full/10.1056/NEJMoa1913590

This trial started in February 2016 and finished in September 2019.

Additional information on the IMPALA trial is available at ClinicalTrials.gov (www.clinicaltrials.gov). Type NCT02702180 into the search bar.

Another larger clinical trial called IMPALA-2 is in progress to further test daily molgramostim treatment for people living with aPAP (www.clinicaltrials.gov, type NCT04544293 into the search bar).

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Declaration of financial/other relationships

BC Trapnell reports having received fees from Savara Pharmaceuticals for Advisory Board membership and consulting services for his role as principal investigator of the IMPALA trial, Cincinnati Children's Hospital Medical Center received clinical trial support from Savara Pharmaceuticals. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. Peer reviewers on this manuscript have received an honorarium from HPRAC for their review work but have no other relevant financial relationships to disclose.

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