Tocilizumab with or without steroids in patients with rheumatoid arthritis

This summary of the clinical trial called SEMIRA (Steroid EliMination In Rheumatoid Arthritis) was prepared in October 2018 to provide patients with the main trial results and other information.

SEMIRA: Summary of Trial Results

What were the main results of the SEMIRA trial?

This trial compared two groups of RA patients. All the patients in both groups were taking prednisone and tocilizumab:

- One group **continued** to take prednisone (5 milligrams each day for the whole study)
- The other group had their prednisone dose slowly reduced (from 5 milligrams each day to 0 milligrams; in other words, the prednisone dose was slowly **tapered**).

Each patient was monitored regularly during the study to record how they felt and if their RA symptoms changed during the study. The disease activity was measured by a 'disease activity score' (or DAS). The average DAS was almost the same for both groups at the start of the trial. The average score showed an improvement in RA symptoms for people in both groups (in other words RA symptoms were well controlled with tocilizumab and prednisone).

At the end of the trial (after 24 weeks), the average DAS still showed remission for both groups. However, the tapered prednisone group had a slightly worse DAS compared with the continued prednisone group. The difference between the two groups was small but real, which means the difference might have had an effect on patients' overall health.

The trial also examined how many patients experienced '**treatment success**'. The treatment was successful if the patient did not have a time when their RA symptoms suddenly become worse before improving again (known as an RA flare), disease activity was low at the end of the trial, and if the patient never experienced a dangerous side effect called adrenal insufficiency.

Around three-quarters (77%) of the **continued** prednisone patients experienced **treatment success**. The majority of patients in the tapered group (65%) also achieved treatment success.

Both groups had very few serious adverse events (side effects that can lead to hospitalisation). No patient experienced adrenal insufficiency.

Overall, this trial showed that continuing prednisone was better than tapering prednisone for keeping the disease activity score low. However, this trial also showed that many individual patients did successfully taper and then stop prednisone. Tapering steroids may help to avoid long-term side effects of steroids, and this may be important for some patients.

The SEMIRA trial will help doctors and patients make informed decisions together when considering whether to lower the dose of steroids for patients who are already doing well on tocilizumab.

Thank you for your valuable contribution

Thank you for taking part in this global clinical trial. Your generous contribution is helping medical researchers to answer important health questions.

Roche, the sponsor of this trial, believes it is important for you to know this trial's main results. We hope this summary helps you to understand the results and how they may be used to improve the care of patients with rheumatoid arthritis (RA). If you have any questions about these results, please speak with your trial doctor.

SEMIRA: Detailed Information

What was this trial about?

Rheumatoid arthritis, or RA, is a chronic disease whereby the body's immune system attacks the joints and other tissues, causing inflammation. Symptoms of RA include swelling, pain, stiffness and tiredness.

RA is treated with medicines that reduce the immune system's ability to attack. Methotrexate and tocilizumab change the way the immune system works and are frequently used to treat RA, along with steroids. Prednisone is a type of steroid medicine.

Although steroid medicines (like prednisone) are similar to our bodies' natural steroid hormones, their use at higher doses and over longer periods causes a range of side effects. These include weight gain, thinning of the skin and increased chance of infection. Doctors try to prescribe the lowest dose possible of steroids, and reduce the dose further as symptoms improve. However, for patients receiving long-term steroids, there is a risk of further serious complications if the steroid dose is lowered too much or too quickly.

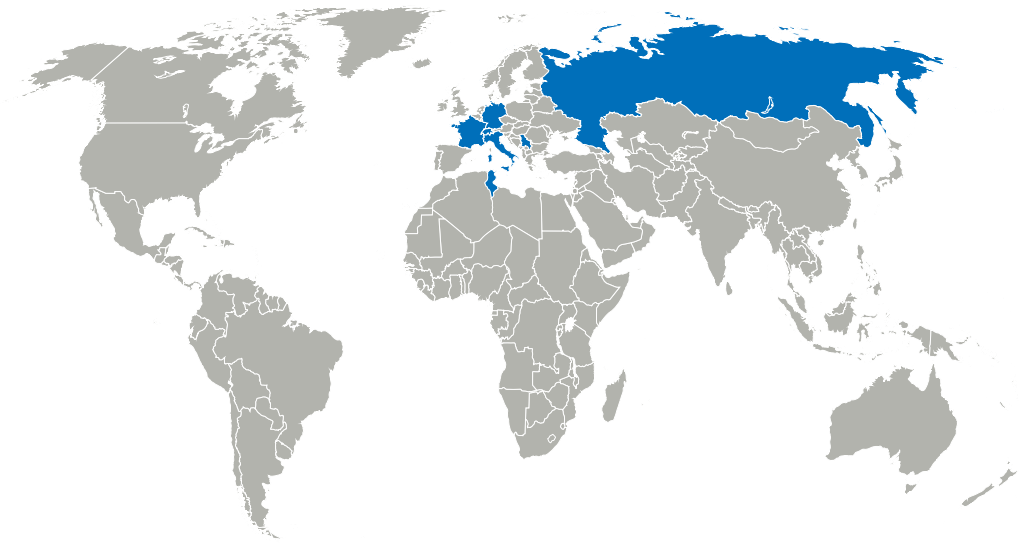
The SEMIRA study was designed with several aims, including:

- To help doctors understand the impact on disease activity of lowering and then stopping steroids in patients with RA also taking tocilizumab
- To find out if the steroid-lowering schedule used in the trial is safe, especially with regard to lowering the risk of developing adrenal insufficiency.

The steroid used in SEMIRA was **prednisone**.

Who took part?

In total, 259 patients with RA were included in the SEMIRA clinical trial. Patients from 41 centres in seven countries have taken part (France, Germany, Italy, Russia, Serbia, Switzerland and Tunisia).



259 patients

41 centres

7 countries

All patients enrolled in the main part of the 24-week trial met the following criteria:

- Patients had received both glucocorticoids and tocilizumab during the 6 months before entry into the trial
  - The daily glucocorticoid doses received in this period were between 5mg and 15mg of prednisone (or equivalent, if another glucocorticoid was used)
- Their RA was well controlled and patients were only receiving prednisone 5mg per day for at least 4 weeks prior to entry
- If patients had any other additional RA medications, like methotrexate, then that medication(s) had to have been at the same dose for at least 4 weeks prior to starting the trial, without changes.

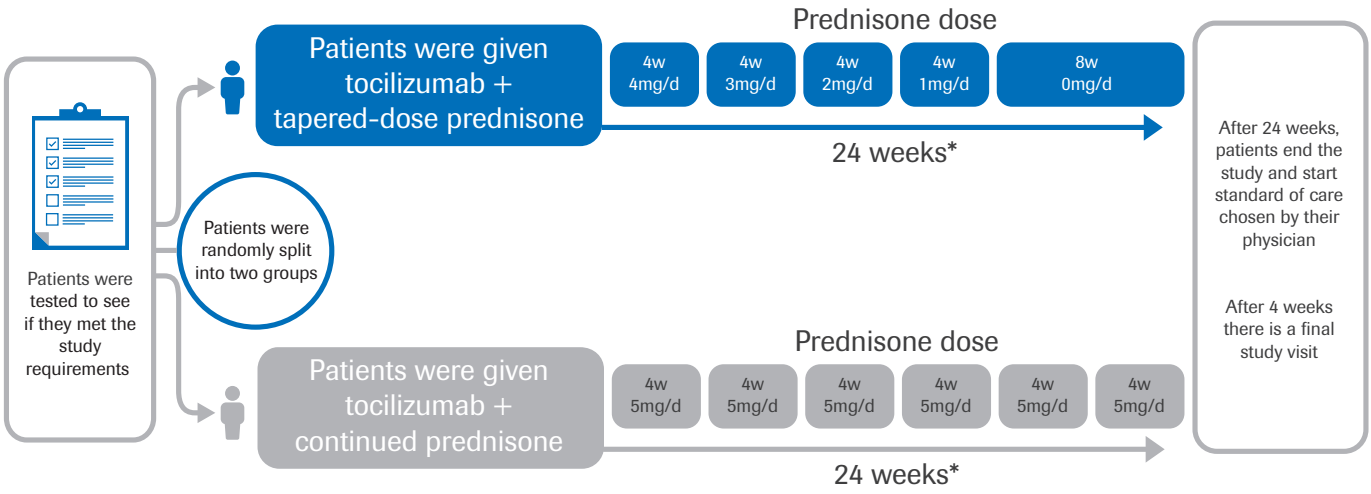
Note

*If patients did not meet the above criteria because they were **not** receiving tocilizumab, they did have the option to enrol in a 24-week 'lead-in' phase for the SEMIRA trial if they had RA with active symptoms and were taking steroids. Patients were given tocilizumab during the 24 weeks to try to bring their RA under control and they had their steroid dose lowered if appropriate. At the end of the 24 weeks, **patients who then met the main trial criteria** (as shown above) were enrolled in the 24-week long main trial. If they did not meet the trial criteria (for example if their RA was still not well controlled), then they left without starting in the main trial.*

What happened during the main trial?

Patients enrolling in the main 24-week trial were randomly assigned by a computer to receive tocilizumab with one of the following:

1. Continue prednisone at 5mg per day for 24 weeks, or
2. Slowly reduce the prednisone dose to 0mg using a uniform prednisone-lowering schedule (also called "prednisone taper" or "steroid taper"). The daily prednisone dose was reduced by 1mg at trial entry and then by 1mg every 4 weeks after that, until 0mg was achieved at week 16. Patients then continued until the end of the trial at week 24 on 0mg of prednisone.



*Patients continued treatment for 24 weeks, or until they withdrew from the study or they experienced undesirable side effects

To improve the scientific quality of the trial, the patients, doctors and sponsor were 'blinded'. This means that none of them knew which of the glucocorticoid treatments the patient was randomly assigned to receive. The special prednisone packaging and the trial databases helped to ensure the blind nature of the trial. After all patients had completed the trial, the blind was lifted, and the medical researchers found out which treatment each patient had received.

Patients were monitored throughout the trial to ensure their safety and to measure the effect of continuing the prednisone at 5mg per day compared with gradually lowering the prednisone dose to 0mg per day. If a patient's RA became much worse during the study it was treated by stopping the patient from continuing in the trial or by treating with additional prednisone for a short period. The medical researchers were particularly interested in the following questions:

- **Was the patients' RA worse at the end of the trial?**
  - This question was answered by using a measure called the DAS28-ESR score to grade RA activity: the more active the RA, the higher the score. The score is calculated based on a formula that takes into account the following four pieces of information collected during visits to the doctor:
    1. The number of painful joints
    2. The number of swollen joints
    3. The amount of inflammation in the body (measured by a blood test)
    4. Patient's own report of the degree of RA symptoms.
  - The DAS28-ESR score at week 24 was compared with the score at trial entry to see if the patients' RA had worsened over time.

- **Were patients able to reach the end of the trial successfully?**
  - Patients were considered to have successfully reached the end of the trial if all three of the following criteria were met at the same time:
    1. The patient experienced no RA flares during the trial (an RA flare is a large worsening of RA disease activity, for example, more joints suddenly becoming swollen than before)
    2. At the end of the trial, the patient's final DAS28-ESR score was **less than** 3.2. This score (3.2) marks the division between 'low disease activity' (less than 3.2) and "active disease" (3.2 and higher)
    3. The patient did not experience adrenal insufficiency requiring treatment.

What were the results of the main trial?

Altogether, 259 patients entered the main trial and were randomly assigned to receive tocilizumab plus one of the two prednisone treatment groups. Of these 259 patients:

- 128 were assigned to continue prednisone at 5mg per day
- 131 were assigned to have their prednisone tapered (until 0mg per day).

How did the participants' RA disease activity change over 24 weeks for each of the prednisone treatment groups?

As previously described, the DAS28-ESR score was the measure used to monitor RA disease activity. The higher the score, the worse the disease. Doctors also use the following ranges to describe the numbers in words:

- Less than 2.6: Disease remission (no activity)
- Between 2.6 to 3.2: Low disease activity
- Between 3.2 to 5.1: Moderate disease activity
- More than 5.1: Severe disease activity.

The table below shows the change in RA disease activity over 24 weeks for the two treatment groups; these are not individual patient scores, but reflect the mean or average for the whole group.

	Continued prednisone patient group	**Prednisone taper patient group**
Average DAS28-ESR score at trial entry	1.9	1.9
Average DAS28-ESR score at week 24	1.8	2.4
Average Change in DAS28-ESR score over 24 weeks	-0.1 (slight improvement)	+0.5 (slight worsening)

Note

Altogether, 246 patients with active RA entered the initial 24-week 'lead-in phase' and started to receive tocilizumab. RA symptoms improved for most of these patients after starting tocilizumab, and 191 patients achieved a low disease state and met other main trial criteria and were entered into the main trial.

The difference between the average change in DAS28-ESR score over 24 weeks for the two groups is +0.5 minus -0.1 = 0.6. This difference of 0.6 is considered by experts to be small but at the border of clinically meaningful (i.e. the patients in the continued prednisone group felt an improvement in their symptoms compared with the group with prednisone tapered; however, the difference was small). At the end of the study, the average disease activity for each treatment group corresponded with remission.

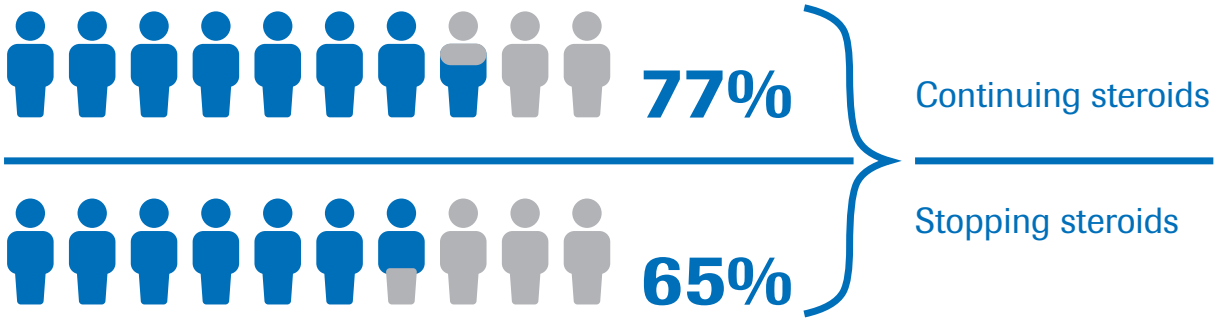
This difference was statistically significant. 'Statistically significant' is a technical term and is not the same as saying clinically significant or meaningful to health. To statisticians, "statistically significant" means the difference was likely to be real and not due to chance alone.

How many patients achieved 'treatment success' in the two arms?

At the end of the trial, most of the patients in each treatment group achieved "treatment success". This means that they were still in low disease activity at the end of the trial, had not experienced any flares at any time during the trial, and did not experience adrenal insufficiency requiring treatment.

However, more patients in the continued prednisone group had treatment success versus the prednisone taper group, and this difference was 'statistically significant'.

Patients with Treatment Success

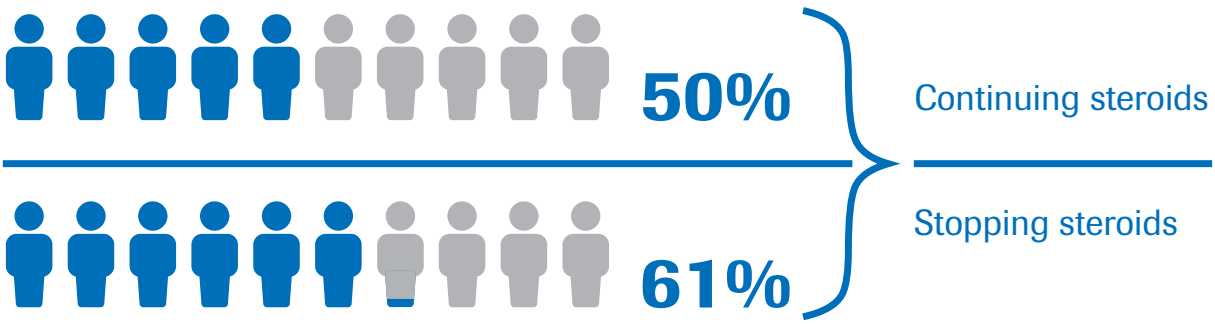


How many patients had adverse events?

An adverse event is any unwelcome medical event during the trial. Adverse events can be drug side effects or they can be events that are not connected to the drug at all. The trial doctors monitored patients for any kind of adverse event.

More patients in the prednisone taper group had an adverse event compared with patients in the continued prednisone group. It is not clear why patients in the prednisone taper group had more adverse events. However, most of these events were mild or moderate. Most adverse events were not severe.

Patients with any adverse event



How many patients had serious adverse events?

Serious adverse events include events that lead to hospitalisation. An example of a serious adverse event is a lung infection requiring hospitalisation and intravenous antibiotics.

There were very few serious adverse events in either group. Five percent of patients had such an event in the prednisone taper group. Three percent of patients had such an event in the continued prednisone group. There were no deaths in this trial. There were no cases of the dangerous side effect called adrenal insufficiency.

How many patients had to stop the trial due to an adverse event?

Four percent of patients had to stop treatment with tocilizumab because of adverse events. The rate of stopping was the same for both the continued prednisone and tapered prednisone groups.

None of the patients in the prednisone taper group and one patient in the continued prednisone group had to stop the trial because they could not control an RA flare.

What do these results mean for doctors and patients?

SEMIRA will help doctors and patients to make better decisions together about whether to continue prednisone at 5mg per day (or other steroid medication) or to taper the steroid dose. These decisions mainly apply to patients receiving tocilizumab who have well-controlled RA. Prior to SEMIRA, the effects of steroid tapering on RA disease activity and disease flares were not known.

The decision to continue or taper the steroid dose will also consider other factors that were not measured in SEMIRA. These factors may include:

- The doctor's assessment of harmful side effects caused by long-term steroid use in his or her patient. Some patients are not able to take steroids without having side effects. Some patients are at greater risk of these side effects compared to other patients.
- The patient's feelings about steroids and how many side effects he or she has while taking them. Some patients may not experience side effects while others may experience steroid-related weight gain or skin thinning, or other side effects.

Doctors aim to maintain RA disease as being well controlled. SEMIRA shows that continuing steroids is better than tapering steroids for keeping RA symptoms under control. However, the chance that an individual patient may be able to reduce their steroid dose without any problems is still quite high. So, for the right patients, doctors may feel that the potential benefits of reducing steroids are greater than the possibility of their RA disease worsening. In case a doctor and patient decide that tapering is best for them, the taper schedule used in SEMIRA is likely safe for avoiding the side effect of adrenal insufficiency.

Future trials

This trial was funded by F. Hoffmann-La Roche. Some clinical trials with tocilizumab have been completed and other trials are ongoing.

Any more questions?

Follow this link to ClinicalTrials.gov for more information on this trial. The trial number is NCT02573012. If you have any further questions, please contact a representative at your local Roche office.