Monthly injections of fitusiran found to reduce bleeds in patients with hemophilia A and B

March 29 2023

Credit: CC0 Public Domain

Monthly prophylactic injections of fitusiran are effective in reducing bleeds in patients with hemophilia A or B, according to randomized

controlled trials publishing simultaneously in *The Lancet* and *The Lancet Haematology* journals.

Hemophilia is a lifelong, inherited bleeding disorder, which mostly affects men and results in patients with hemophilia A or B missing partially or completely different clotting factors—natural proteins that help form blood clots to stop bleeding (VIII and IX, respectively). People with hemophilia A and B bleed spontaneously into joints or muscles and may take much longer to stop bleeding after injury. Prophylactic treatment is aimed at reducing spontaneous bleeding by regularly administering drugs that enhance haemostasis.

Small interfering RNA (siRNA) therapies are a new type of treatment that work by interfering with the production of specific proteins. Fitusiran is the first siRNA developed for hemophilia and targets antithrombin (a protein that reduces blood clotting) to increase clotting ability. Its novel way of stopping bleeds means that it is the first prophylactic treatment that works for both hemophilia A and B patients with or without inhibitors. However, it is not yet approved for use outside of clinical trials.

Patients with hemophilia who are given the replacement clotting factor they are missing, can develop an immune reaction against this treatment. This immune reaction triggers the development of inhibitors which render the replacement therapy ineffective and creates the need for alternative treatments that can avoid this immune reaction.

The authors note that the comparator groups in both studies received on-demand rather than prophylactic treatment. At the time the trial began, there was no effective prophylactic treatment for patients with inhibitors. For patients without inhibitors as well, comparison with on-demand treatment was the norm for an investigational agent. However, this does mean that it is difficult to compare the efficacy data in this trial

with other prophylactic treatments for hemophilia A or B that are currently now in use.

Lead author of *The Lancet* study, Professor Guy Young, Children's Hospital Los Angeles and Professor at the University of Southern California Keck School of Medicine, U.S., says, "Our study looks at the efficacy of the first siRNA therapy used to treat hemophilia with inhibitors. The data is encouraging and suggests it may be the first prophylactic treatment—meaning it can be given to prevent bleeds rather than to treat them after they have already occurred—that works for both hemophilia A and B patients with inhibitors. Hemophilia B patients' treatment options are currently limited to on-demand treatments, which treat bleeds after they have occurred."

Study published in *The Lancet* investigating fitusiran use with inhibitors

This phase 3 randomized controlled trial was conducted at 26 hospitals in 12 countries. It included 56 male patients aged 12 years old or over with severe hemophilia A or B with inhibitors. Two-thirds of the patients (38) were given a monthly 80mg dose of fitusiran, which was administered through under the skin injections. Meanwhile, one-third of patients (19) were given on-demand bypassing treatment. The primary endpoint was annualized bleeding rate, which measures the number of bleeds per year a patient that require treatment. Safety and tolerability were also assessed.

The median observed annualized bleeding rate for patients in the fitusiran group was 0, compared to 16.8 in the in the comparator group given an on-demand bypassing agent.

Among patients given fitusiran prophylaxis with inhibitors, 25 out of 38 (66%) participants had no bleeds after nine months, compared to 1 out

of 19 (5%) in the comparator group given an on-demand bypassing agent.

Among participants with inhibitors given fitusiran, 13 (32%) participants had increased alanine aminotransferase (an enzyme released into the blood when the liver is damaged). Suspected or confirmed blood clotting was reported in two (5%) participants. No deaths were reported.

Commenting on the safety outcomes, Professor Young continues, "The safety outcomes in our trial are consistent with previous data on fitusiran and need further monitoring. Two participants receiving fitusiran experienced blood clotting, which is a risk for treatments that seek to rebalance hemostasis (the mechanism that stops bleeding). The most common adverse effect was increased alanine aminotransferase, which is seen with many medications and indicates liver inflammation. Importantly, most of these elevations were temporary and did not result in discontinuation of fitusiran. In this context, it suggests that fitusiran did not result in any long-term liver damage, but this adverse effect needs continued assessment in this and other trials of fitusiran. Regulators will need to assess the benefits and risks of the drug when deciding whether to approve its use and for which patients it is suitable."

Study published in *The Lancet Haematology* investigating fitusiran use without inhibitors

Also part of the ATLAS trial, this phase 3 randomized controlled trial was conducted at 45 hospitals in 17 countries. It included 120 male patients aged 12 years old or over with severe hemophilia A or B. Two-thirds of the patients (79) were given a monthly 80mg dose of fitusiran, which was injected under the skin. Meanwhile, one-third of patients (40) were given on-demand clotting factor concentrate replacement therapy. The primary endpoint was ABR. Safety and tolerability were also

assessed.

The observed annualized bleeding rate for patients in the fitusiran group was 0, compared to 21.8 in the comparator group given an on-demand bypassing agent.

Among patients without inhibitors given monthly injections of fitusiran, 40 out of 80 (51%) of participants experienced no bleeds requiring treatment, compared to 2 out of 40 (5%) in the comparator group which was given an on-demand bypassing agent.

Among the patients given fitusiran, 28 (23%) were found to have increased alanine aminotransferase. There were no instances of blood clotting or death.

Lead author on *The Lancet Haematology* study, Professor Alok Srivastava, Christian Medical College, Vellore, India, says, "Our study looks at the use of fitusiran in patients with hemophilia A or B without inhibitors and complements the findings from the study looking at fitusiran with inhibitors—also finding that it is very effective in preventing bleeds. Fitusiran is administered by under the skin injections, which can be easily taken at home. With this drug being administered just once a month or even less frequently, there is marked reduction of treatment burden. This means patients with hemophilia could manage their condition with fewer trips to hospital, which can cause worry and be and disruptive to daily life. This would lead to an improved quality of life as documented in the study."

The authors note some additional limitations that apply across both studies. Patients were followed up for nine months, so further studies are needed to confirm longer-term efficacy. In addition, the patients in the trials were those with severe hemophilia, so outcomes may be different in patients with milder cases of the condition.

Writing in a linked Comment published in *The Lancet*, Professor Flora Peyvandi, Università degli Studi di Milano, says, "Fitusiran might be the first prophylactic option for people with hemophilia B and perhaps an alternative approach to emicizumab, the first approved subcutaneous, non-replacement therapy in people with hemophilia A. Because of the high efficacy in the annualized bleeding rate reduction, easy route of administration, and low frequency of infusion for both emicizumab and fitusiran, choosing which drug to use in people with hemophilia A will be challenging. Potential benefits and harms and the differential responses of new rebalancing products should be examined in comparative studies between similar available treatments.

"Moreover, standard outcome measure[s], such as annualized bleeding rate, are subjective and might limit the full assessment of the efficacy of new treatments; therefore, comparative studies should also include outcome measures from both physician and patient perspective. The available clinical data on non-replacement and rebalancing drugs are changing the hemophilia therapeutic scenario, but several key challenges remain, despite the benefits of rebalancing hemostasis, the potential risk of thrombosis, particularly with concomitant use."

More information: Efficacy and safety of fitusiran prophylaxis in people with haemophilia A or haemophilia B with inhibitors (ATLAS-INH): a multicentre, open-label, randomised phase 3 trial, *The Lancet* (2023). DOI: 10.1016/S0140-6736(23)00284-2 , www.thelancet.com/journals/lan … (23)00284-2/fulltext

Alok Srivastava et al, Fitusiran prophylaxis in people with severe haemophilia A or haemophilia B without inhibitors (ATLAS-A/B): a multicentre, open-label, randomised, phase 3 trial, The Lancet Haematology (2023). DOI: 10.1016/S2352-3026(23)00037-6 , www.thelancet.com/journals/lan … (23)00037-6/fulltext

Provided by Lancet