Something from the Center

US HAEA Angioedema Center at UC San Diego·woensdag 27 december 2017

Dr C:

Greetings,

Today I thought that it would be something of interest to discuss the following question passed on by Tony Castaldo, President of the HAEA:

“My doctor wants me to go on the Ruconest which is a recombinant C1 inhibitor. I recently read a social media post where someone stated that Ruconest caused blood clots. I did see, however, that this person used a port to take her medicine. Another patient posted that Ruconest causes allergic reactions because the C1 inhibitor medicine is derived from the milk of rabbits. Can you provide some expert advice?”

This is a very timely question for multiple reasons. As many of you are aware there have been recent manufacturing problems at Shire with Cinryze and resulting shortages. CSL has also announced that they will not be able to meet the demand for plasma derived C1 inhibitor (pdC1INH), with their available stocks. Patients are rightfully anxious about running out of medication. Recombinant C1 inhibitor (rC1INH) is identical to the plasma derived C1 inhibitor protein. It is expressed and purified from the milk of transgenic rabbits. Intravenous rC1INH, has been shown to be safe and effective for the treatment of acute attacks of angioedema in a pivotal phase III study. A Phase II study led by Marc Riedl demonstrating efficacy for prophylaxis of attacks has also been published this last year. Fortunately for patients there is no shortage of supply of rC1INH and the manufacturer, Pharming, is dedicated to facilitating availability to patients. As is the case for pdC1INH there have been no significant safety concerns. The questioner raises the issue of rabbit allergy. A warning about rabbit allergy is included in the package insert in the US, which stems from a single case of anaphylaxis during the trials in an individual with rabbit allergy - which had not been disclosed to the investigators. With the manufacturing process there are very low levels of host related impurities (HRIs) in the final product and such that the risk is very low of a reaction even in rabbit allergic patients. A large study in a rabbit allergic cohort has not been done however. In the event that rC1INH is the best option for a patient with a history of rabbit allergy everything has a risk benefit ratio. I would consider skin testing with rabbit and the rC1INH to check prior to use. If the testing for rC1INH is negative and the rabbit positive to err on the side of caution I would then give a test dose of rC1INH under observation in the office to see if it is safe to use. Marc, you have had a lot of experience with rC1INH, could you elaborate further on the rabbit issue?

Dr R: In order to address the question about allergic reactions to the recombinant human C1INH (rhC1INH/Ruconest), let’s quickly review the process by which it’s manufactured. rhC1INH is produced in rabbits that have been designed to generate the human C1INH protein in their milk. The rabbit milk goes through extensive complex processing to purify the human C1INH protein and remove all other materials. At the end of the process, the medication contains less than 0.002% rabbit-related proteins. So it is an incredibly pure human C1INH medication. To my knowledge, there has been only one confirmed case of an allergic reaction to rhC1INH due to rabbit allergy. This occurred during the early clinical studies with the drug when a young woman treated in the study did not mention to study physicians that she had previously had allergic reactions to rabbits. On receiving the medication, she developed symptoms of a serious allergic reaction, but was treated and recovered without complication. Since that time additional studies have carefully monitored for this potential allergy issue, but no additional allergic reactions related to rabbit allergy have been observed. For a while, the European regulatory agency required that all patients have rabbit allergy testing performed prior to using rhC1INH, but this requirement was removed in early 2016 due to the fact no additional issues with such allergic reactions had been seen. The FDA has never required such testing though of course warns of the possible risk in the medication label. Since FDA- approval, an additional study investigating this issue

showed that 4 of 5 individuals with positive allergy tests to rabbit in fact tolerated rhC1INH treatment without any allergy issues. (The fifth individual was the aforementioned woman who had an allergic reaction in the study; she also had the strongest rabbit allergy test of the group.) All told, it appears that rabbit allergy issues related to rhC1INH are exceedingly rare. If someone has a history of allergic reactions to rabbit exposure, then it would be important for them to speak with their physician about rabbit allergy test (blood or skin test) prior to using rhC1INH. But for the vast majority of people, this is not going to be a significant risk or concern, since rabbit allergy is quite uncommon.

Dr C: Thank you Marc. Let's turn our attention to the other concern raised by our questioner—clotting. As to the thrombosis (clotting) issue there is no more concern than has been raised for the pdC1INH. The rC1INH is identical to the pdC1INH with the exception of a small difference in the carbohydrate decoration on the plasma human derived protein. It does have a shorter half-life then the pdC1INH however the higher dose (50 IU/kg) appears to compensate. There is really no published data linking rC1INH to thrombosis and no cases during the trials with the drug. There is much more data on pdC1INH, all of which is reassuring and can be extrapolated for the rC1INH. In a study by Henriette Farkas of 144 patients over 29 years the incidence of thromboembolism was actually less then for individuals not treated by pdC1INH. Paula Busse has also published results from an international registry on 135 subjects with 3196 infusions of pdC1INH and found no evidence to suggest that pdC1INH was an independent causative risk factor for thromboembolism. Concern about potential thrombogenesis stems from a report of off label use in 13 neonates without HAE who developed thrombus at up to 500 IU/kg in an attempt to prevent capillary leak during cardiac bypass for sever congenital heart defects. There have been 5 reports of thrombosis on Cinryze in the open label study but all patients had underlying risk factors. Studies in animals have actually reported that C1INH may be antithrombogenic rather than prothrombogenic. All this being said there are still concerns for patients with indwelling port which is a risk factor for thrombosis. Bruce, you have had a lot of experience dissecting the pathophysiology of the contact system cascade and overlapping clotting pathways. Can you share your insight about C1INH and risk of clotting as well as any concern about rC1INH?

Dr Z: I can only echo what you've already said. C1INH inhibits two clotting factors, activated factor XII and activated factor XI. In C1INH deficient patients, the clotting times are shorter, possibly indicating an enhanced tendency to clot (although the relationship between these lab measurements and the clinical risk of clotting is far from simple or clear). Replacing C1INH activity with either pdC1INH or rC1INH should improve the inhibition of these clotting factors and thus reduce the risk of thrombosis. My own sense is that it is the other risk factors, especially indwelling ports, that increase the risk of clotting, and that both plasma-derived and recombinant C1INH concentrates do not contribute to this risk.

Dr C: Thank you Marc and Bruce. As usual, I would like to close with the hope that this week's topic has provided something of interest for our followers with HAE. Dr Z and I will be out of the country next month to see the Mountain Gorillas in Rwanda and Uganda. We will be back with fresh topics/news when we return. We look forward to hearing from you and our next SFTC.