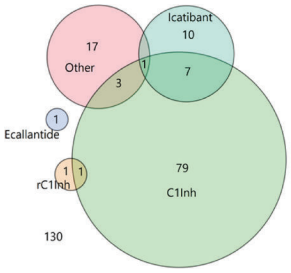

STP Agents	Number of Subjects Receiving STP
Icatibant	18
C1-Inh	91
Ecallantide	01
rC1-Inh (recombinant)	02
Other	21

Fig. 1 Diagram of counts of subjects reporting the specific STP agents (choices were "C1Inh", "Icatibant", "Ecallantide", "rC1Inh", "other"). Of the 120 subjects who received STP, a total of 91 subjects reported receiving C1Inh [human] as STP (which includes 79 subjects exclusively on C1Inh [human], 1 subject on rC1Inh + C1Inh, 7 on Icatibant + C1Inh, 3 on Other + C1Inh, and 1 on Other + Icatibant + C1Inh.). 10 received Icatibant only as STP, 1 received Ecallantide only, and 1 received rC1Inh only. 17 subjects reported receiving other STP agent (choices were "C1Inh. 130 subjects did not receive STP

O15

A *SERPING1* variant that causes C1-inhibitor deficiency without hereditary angioedema

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More than 400 mutations (around 25% de novo) in *SERPING1* have been described to cause functional C1-inhibitor (C1-INH) deficiency and hereditary angioedema (HAE). Angioedema symptoms and C1-INH deficiency co-segregate within the families with autosomal dominant inheritance. Two promoter and two structural *SERPING1* variants escape this rule. These four mutations represent a recessive character: they cause the clinical phenotype of HAE only when present in homozygosity.
Here we describe variant g.22006G > A (p.Arg494Gln) in *SERPING1*, detected in 12 subjects from four families with C1-INH deficiency and no HAE. The variant is located in a region of the molecule that is critical for regulating SERPIN conformational state.
Index cases in each family were identified due to urticaria symptoms that prompted measurements of C1-INH and C4. In none of the four families there was evidence for inherited angioedema without wheals while inherited C1-INH and C4 deficiency were clearly present. Inhibitory function of C1-INH against C1s, kallikrein and FXIIa was below 50% of normal. Repeated measurements of complement parameters in C1-INH deficiency carriers, showed a degree of variability, which is never detected in typical C1-INH-HAE. When these subjects underwent danazol treatment, complement parameters rapidly normalized. All C1-INH deficient subjects in the four families, carried the mutation g.22006G > A (p.Arg494Gln) in *SERPING1*. When the mutant protein was expressed in a murine hepatoma cell line, analysis of the supernatant failed to detect the protein, which was instead abundant in the insoluble fraction of cell lysate. We hypothesize that intracellular accumulation is due to polymer formation.
Our findings indicate that p.Arg494Gln-C1-INH allows protein synthesis, but impaired cytoplasmic secretion. The same condition seems to apply to the other *SERPING1* structural variants that cause recessive forms of HAE. No homozygous p.Arg494Gln has ever been described and we cannot conclude that also this mutant leads to recessive HAE. However, variability of C1-INH plasma levels in this as in other variants that are clinically silent in heterozygous presentation, suggests a lower degree of impairment in the synthesis of functional C1-INH. Whether this is due to the mutant contributing to C1-INH function in plasma or to the mutant that has reduced trans-inhibition effect on the wild type allele remains to be elucidated.
The study was approved by Milano Area 1 Ethics Board, approval number 11846/2017. Informed consent to publish has been obtained from the patients.

O16

Activation of complement MASP-3 in healthy donors and in patients with C1-inhibitor deficiency

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Activation of the lectin pathway of complement is initiated by mannose-binding lectin (MBL)-associated serine proteases 1 and 2 (MASP-1 and MASP-2). MASP-1 and MASP-2 circulate in the blood as zymogens in complex with pattern recognition molecules (PRMs), such as MBL, other collectins, and ficolins. The third serine protease of the lectin pathway (MASP-3), which is also complexed with PRMs, was shown to be the major physiological activator of pro-factor D (pro-FD) in the blood, linking the alternative and the lectin complement pathways. We have demonstrated earlier that only activated MASP-3 is capable of converting pro-FD to factor D (FD), and indeed the major form of MASP-3 in the blood is the active form. The activation mechanism of MASP-3, however, remains unclear. *In vitro* MASP-1 can activate MASP-3, and C1-inhibitor is the major physiological regulator of MASP-1. We hypothesized that if MASP-1 is the physiological activator of MASP-3 then individuals with low C1-inhibitor levels would exhibit altered MASP-3 activation.
The activation state of endogenous MASP-3 was detected by Western blot, whereas in other experiments fluorescently labeled recombinant MASP-3 variants were used. We found that a significant portion of full-length, labeled MASP-3 became "activated" (cleaved) in hirudin-plasma in the matter of hours even when the inactive S664A variant was used. The activation was less efficient, but still occurred, when the N-terminally truncated catalytic fragment was used. On the other hand, we found that the ratio of active MASP-3 in type I HAE patients was virtually identical with that in healthy individuals, namely 82 ± 3%, versus 81 ± 4%. This indicates that a protease other than MASP-1 is responsible for the activation of MASP-3. To confirm this assumption we monitored the cleavage of labeled MASP-3 in the presence or absence of a MASP-1-specific inhibitor. Again, no difference was observed.
In conclusion, our results imply that a protease is present in the blood that converts MASP-3 to the active form. The activation is not autoactivation because the inactive variant got cleaved as well. Activation is more pronounced with the full length protein implying that binding of MASP-3 to PRMs might be necessary for efficient activation. Activation of MASP-3 is probably carried out by a protease not inhibited by C1-inhibitor.

O17

Simultaneous determination of human plasma serine proteases complexed with C1-inhibitor in vivo

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