IFX-1 blocking the anaphylatoxin C5a – an anti-inflammatory effect in patients with *hidradenitis suppurativa*

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Hidradenitis suppurativa, neutrophil activation, and complement C5a

Hidradenitis suppurativa (HS) is a chronic debilitating skin disorder affecting skin areas rich in apocrine glands. Neutrophil activation is supposed to one of the causes in HS development. Anaphylatoxins especially C5a are classic activation products of the complement cascade that can potentially orchestrate the infiltration of neutrophils and strongly activate neutrophils in the affected skin areas.

In this study, we observed the evidence of complement activation in HS patients and confirmed the essential role of C5a on neutrophil activation. We conducted an open-label phase II clinical trial with an anti-human C5a monoclonal antibody IFX-1 in 12 patients with moderate to severe HS. Our data suggest that anti-C5a treatment could be a highly effective therapeutic approach for HS patients.

Significant systemic activation of complement in HS

A total of 41 patients with HS and 14 healthy volunteers were enrolled to explore the kinetics of circulating concentrations of anaphylatoxin C3a and C5a, as well as membrane attack complex C5b-9 in HS.

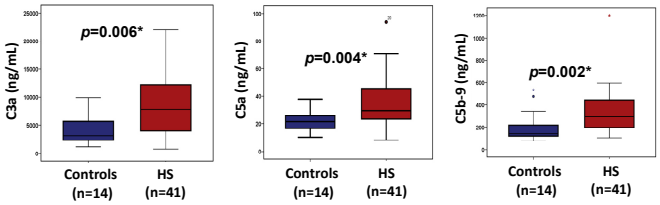


Figure 1. Concentrations of C3a, C5a, and C5b-9 in the plasma of 14 healthy controls (blue) and of 41 patients with HS (red), respectively. Dots denote outliers and asterisks denote extremes. *p* values symbolize significant differences between patients and controls.

C5a as the primary driver for neutrophil activation was blocked by IFX-1 in the pre-clinic *in vitro* assay.

Significant CD11b up-regulation on human neutrophil granulocytes by HS patient plasma sample was observed. The activation of CD11b was caused primarily by the elevation of the C5a level. The CD11b potency assay by flow cytometry confirmed the inhibitory activity of IFX-1 on neutrophil activation (Figure 2) and suggested C5a as a therapeutic target in the treatment of *hidradenitis suppurativa*.

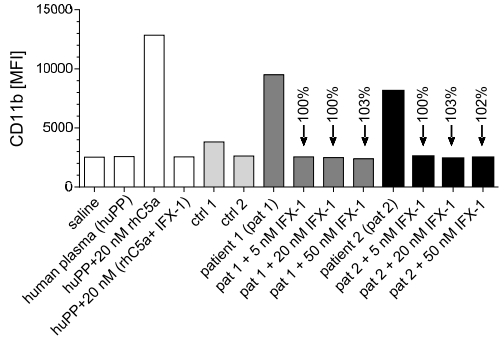


Figure 2. CD11b levels on human granulocytes. Whole blood was incubated with plasma samples (source for eC5a) in the absence or presence of IFX-1. The blocking activity of IFX-1 was indicated as the percentage of each CD11b expression inhibited sample. Two control samples (ctrl) and two patient samples (pat) were tested for the *in vitro* activation and inhibition.

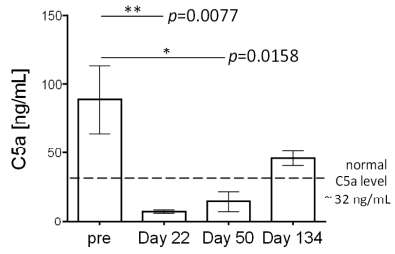
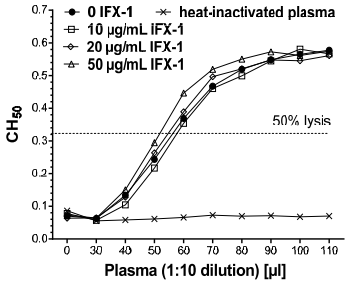


Figure 4. Concentrations of C5a (mean±SEM) in the plasma of 12 patients with HS. During the IFX-1 treatment, the C5a level in patient plasma samples decreased significantly.

IFX-1 does not affect the C5 split and the subsequent formation of membrane attack complex C5b-9.



The total hemolytic complement activity (CH50) test was performed with the presence of various concentrations of IFX-1, and CH50 values were not affected by the presence of IFX-1 in the plasma samples.

Figure 3. IFX-1 has no influence on the membrane attack complex (MAC) C5b-9 formation in human plasma..

Open-label phase II clinical trial on HS patients showed an effective anti-C5a therapy by IFX-1.

IFX-1 was tested in an open-label clinical study in 12 patients with moderate to severe HS (EudraCT 2016-002988-33). All patients received nine intravenous doses of 800 mg IFX-1 on days 1, 4, 8, 15, 22, 29, 36, 43 and 50. The C5a level in patient plasma was determined *via* ELISA before the trial began, at days 22 and 50 during the IFX-1 treatment, and at day 134 in the follow-up period, respectively (Figure 4). *Hidradenitis Suppurativa* Clinical Response (HiSCR) was applied to evaluate the therapeutic outcomes of IFX-1 (Figure 5).

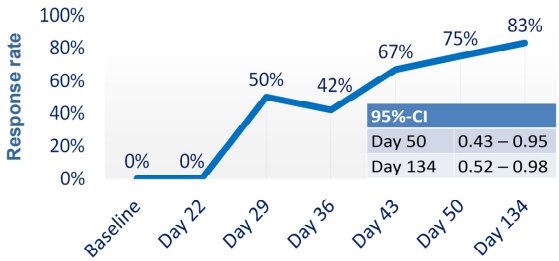


Figure 5. Treatment response utilizing the HiSCR endpoint for the HS patients. With the time of IFX-1 treatment, more and more patients achieved HiSCR (at least 50% reduction in inflammatory lesion count and no increase in abscesses or draining fistulas when compared with baseline).

Conclusions

- Complement activation occurs in HS patients.
- Elevated C5a production in HS patient blood activates neutrophils, which may, in turn, contribute to the HS symptoms.
- The human C5a-specific monoclonal antibody IFX-1 effectively neutralized the overproduced C5a in HS patients.
- Up to 83% response rate was achieved at the endpoint of the IFX-1 treatment in this clinical study. Thus, anti-C5a treatment approach may represent an effective therapeutic strategy for HS patients and other neutrophil-driven diseases.

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