[SS-001]

Plasminogen eye drops for the treatment of ligneous conjunctivitis and the prevention of recurrences in patients with type 1 plasminogen deficiency: results from the phase II/III clinical trial

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INTRODUCTION/BACKGROUND
Ligneous conjunctivitis (LC) is a rare form of chronic conjunctivitis characterized by the development of fibrin-rich, woody pseudomembraneous lesions, mainly on the palpebral conjunctivae. LC is the most common clinical manifestation of type-1 plasminogen deficiency and, in the most severe cases, can lead to visual impairment/loss and blindness. Although some non-specific treatment modalities, like FFP, have been reported to result in partial lesion improvement/resolution, only topical/systemic plasminogen have been shown to be consistently effective. Surgical intervention without effective replacement therapy results in recurrence of pseudomembranes formation. Availability of a locally administered plasminogen concentrate will represent an important advance in the therapeutic options for LC. We report the results of part 1 of this 2 part, Phase II/III study.
OBJECTIVES
To evaluate the efficacy and safety of human plasma-derived plasminogen eye drops for LC associated with Type I plasminogen deficiency. Primary Efficacy Endpoint: Prevention of pseudomembrane recurrence after regression or surgery. Secondary efficacy endpoint: Regression of surface areas of existing ligneous pseudomembranes.
METHODS
Open-label, multicenter, historically-controlled trial, divided into part 1 (efficacy and safety evaluation) and part 2 (continuation segment- safety evaluation), conducted at three participating sites (1 US, 2 Italy).
RESULTS
A total of 11 patients (15 symptomatic eyes) were enrolled in the first part of the trial.
Primary Efficacy Endpoint: No recurrence was reported in any of 12 eyes included in the evaluation following complete regression and/or surgical excision, yielding a 100% success rate.
Secondary Efficacy Endpoint: 15 eyes were evaluated. 3/15 (20%) eyes reported a complete regression (>90% of the surface of the lesion), 7/15 (46,7%) partial regression (>20% but <90% of the surface of the lesion), and 5/15 (33,3%) were classified as failure (<20% of the surface of the lesion).
Historical evaluations completed by an independent reviewer showed that the treatment is associated with improved clinical outcomes when compared with each eye's clinical history documented pre-study.
Safety Endpoints: Topical administration of eye drops were well tolerated. Treatment-emergent antibody (Ab) development (anti-aprotinin and/or anti-plasminogen) was detected in 5 patients; two had pre-existing antibodies, two subjects developed transitory anti-plasminogen Ab and three new anti-aprotinin Ab. None of the AEs reported by patients with anti-plasminogen or anti-aprotinin Ab development required modification, interruption, or discontinuation of study treatment and there was no effect on treatment efficacy. No other casually-related adverse events were reported.
CONCLUSIONS
Kedrion Human Plasminogen eye drops were well tolerated and effective in preventing pseudomembrane recurrence after both initial total regression and surgical excision, and in reducing existing pseudomembranes.

Keywords: Ligneous Conjunctivitis, Plasminogen, Type 1 Plasminogen deficiency

[SS-003]

Circumcision in Haemophilia with Inhibitors During Emicizumab Prophylaxis

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Introduction: Emicizumab® (Roche, Basel, Switzerland) is a bispecific antibody that binds to factor (F) IX/IXa and FX/FXa and activates FX to FXa in the absence of FVIII. It has been shown to reduce bleeding episodes in haemophilia A with or without inhibitor. Despite the reduction in bleed rate, some breakthrough bleeds and also surgeries are inevitable and these may require additional haemostatic treatment. Clinical haemostasis during surgery in patients receiving Emicizumab is unpredictable and data are very limited. Herein, we report a patient with Haemophilia A with inhibitor who had circumcision while on Emicizumab prophylaxis.
Case: The patient, aged 10 years old, had high-responding inhibitors and treated bleeds with aPCC and rFVIIa. He previously underwent bilateral elbows (repetad) radiosynovectomy for each that were both managed with rFVIIa. Because of the frequency of bleeding, he received alternating aPCC and rFVIIa. Despite this treatment, he continued to experience several bleding events. After Emicizumab in Clinical Trial became avaible, the patient enrolled the trial and emicizumab started in this patient once a week. He had only 1 severe quadriceps muscle haematoma due to major trauma. Circumcision was arranged to coincide with patient's regularly scheduled emicuzumab maintenance dose of 1.5 mg/kg, which was administered the morning of surgery. The patient received 40 mg/kg/day tranexamic asid before 12 hours the surgery and continued for 10 days. Laboratory examination of D-dimer and fibrinogen were not elevated in the postoperative period. There was no evidence of bleeding and no blod transfusions were necessary. Additionally, no other adverse events were recorded.
Conclusion: Data describing surgery in patients receiving Emicizumab are very limited. Circumcision is a cultural and traditional surgical intervention, and many patients want to be circumcised around the world. Our patient who is under prophylaxis with Emicizumab, only received tranexamic acid and did not received BPAs. Patients with haemophilia A with inhibitors who underwent mostly minor surgical procedures while receiving emicizumab prophylaxis, the majority of patients did not receive pre-operative treatment with BPAs. This patient demonstrate that only Emicizumab prophylaxis is well tolerated and efficacious for circumcision, which is actually considered a major surgical intervention without any factor support.

Keywords: emicizumab, surgery, circumcision

[SS-004]

Clinical problems and surgical interventions in inherited factor VII deficiency

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Aim: Factor VII deficiency is one of the hereditary coagulation disorders that has autosomal reccessive inheritance and is observed relatively frequently (1/500 000). It is clinically heterogeneous, and may be asymptomatic or lead to life-threatening hemorrhage. Thus, there is no correlation between FVII activity and clinical findings. Plasma-derived and recombinant FVII concentrates are currently used for treatment. In countries where access to these products is lacking, fresh frozen plasma and prothrombin complex concentrates are also used, though they contain low amounts of factor FVII. In this study, we present the clinical properties, treatments, and surgical interventions used in patients followed up in our clinic with a diagnosis of factor FVII deficiency.
Material-Methods: Patients who were diagnosed as having FVII deficiency in Istanbul University Oncology Institute, Division of Pediatric Hematology and Oncology between July 1997 and July 2018, were included in the study. The patients' demographic characteristics, symptoms at presentation, PT, aPTT, and FVII values, types of hemmorhage, and treatments and surgical interventions used, were recorded. The hemorrhages observed in the patients were classified by severity as asymptomatic, minor, and major.
Results: A total of 18 patients (7 girls and 11 boys) with a mean age of 9.64±9.63 years were included in the study. The mean follow-up time was found as 78.06±54.38 months. When the hemorrhages were classified clinically, no hemorrhage was observed in eight patients (44.4%). The factor FVII level was found as <10% in three of these eight asymptomatic patients and above 20% in the others. Minor hemorrhage was observed in nine patients (50%) and major hemorrhage was observed in one patient. When the patients were classified as asymptomatic and symptomatic, there was no significant difference between the two groups in terms of FVII level (p=0.57). A total of 21 surgical interventions were performed in 14 (78%) of 18 patients who were being followed up.
Conclusion: FVII deficiency has a very wide spectrum both clinically and in terms of approach to surgical interventions. Therefore, patients with factor FVII deficiency should be followed up and treated by specialized coagulation disorder centers with close collaboration of multiple disciplines.

Keywords: Clinic, factor VII, surgery

[SS-005]

IS DENTAL IMPLANT TREATMENT SAFE IN HEMOPHILIA PATIENTS?

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Implant treatments applied to restore the lost of aesthetics and function of missing teeth are among the most frequently used current treatments in oral surgery. Hemophilia patients may also experience tooth loss due to tooth decay, periodontitis, cysts, trauma, and then implant treatments can be applied under appropriate conditions. However, the number of cases applied worldwide is very rare. In this presentation, implant treatments applied to hemophilia patients, consultation, premedication, precautions to be taken and complications that may be encountered during the use of the implant will be evaluated in the light of current articles.

[SS-006]

Five years of experience for treatment regimens of PUP patients in Hemophilia-A: experience from Ege Hemophilia Center

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Inhibitor development is the most frequent and serious treatment complication in Hemophilia. Formerly, Recombinant Factor VIII (Rec-FVIII) products were most preferred for (previously untreated patients) PUP patients in Turkey. After SIPPET publication, plasma derived Factor VIII (pd-FVIII)s are now mostly preferred for PUP patients. In this study, we collected data from PUP patients in our center for last 5 years. Totally 20 PUP patients were followed. All patient were <FVIII: 1% and all FVIII mutations were found. Two patients were not included for <10 exposure days (ED) and 1 patient discarded for mix using (pd and Rec-FVIII) in the first 50 ED as well. After 5 years of follow up; inhibitor rate was 1/12 (8%) LR in pd-FVIII group, however, inhibitor rate was 1/5 (20%) HR in Rec-FVIII group. For resolution of LR inhibitor, same pd-FVIII product was continued for prophylaxis after 1 year. However, HR inhibitor was persisted 2 years. ITI using with Pd-FVIII was used for 6 months. However inhibitor was eradicated 6 months after ending of ITI. In conclusion, pd-FVIIIs are found much safer than rec-FVIIIs in respect of inhibitor development. Another important issue was shifting rec-FVIII from pd-FVIII after 50 EDs is seemed to be safe in these patients. So for initiating of prophylaxis, pd-FVIII products are much safer. However after 50 EDs, Rec-FVIIIs can be shifted with safely
or pd_FVIII products may be continued with same products.

Keywords: Inhibitor, PUP, Hemophilia

Prophylactic regimens in PUP patients

	Shift from Pd-FVIII to Rec-FVIII	Pd-FVIII continuation	Rec-FVIII continuation	Lower than 10 EDs
Patients (n)	7 pd -> 7 Rec	5	5	2
Inhibitor rate	0/7	1/5	1/5	-
Inhibitor type (peak titers)	NA	LR inhibitor (3.5 BU/ml)	HR inhibitor (12 BU/ml)	-
Outcome	NA	İnhibitor resolution after 1 year of pd-FVIII prophy with same product	Inhibitor tolerance after one year of 6 months of ITI	-
Current status	Prophy with Rec-FVIII	Prophy with pd-FVIII	Prophy with Rec-FVIII	-