Site Specific Immunomodulation – A Novel Therapeutic Approach for the Management of Moderate-to-Severe Crohn's Disease

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Introduction & Objective

Qu Biologics is developing a new platform of immunotherapies called Site Specific Immunomodulators (SSIs), designed to 'reboot' the immune response in the targeted organ, reversing the immune dysfunction and chronic inflammation underlying cancer and immune mediated diseases, including Crohn's disease (CD). SSIs are novel complex biologics, each derived from components of a single species of inactivated pathogenic bacteria. The aim of this study was to summarize the clinical and safety data in the compassionate use program, as a preliminary assessment of the safety and potential therapeutic benefit of QBECO SSI in subjects with active moderate-to-severe CD.

Methods

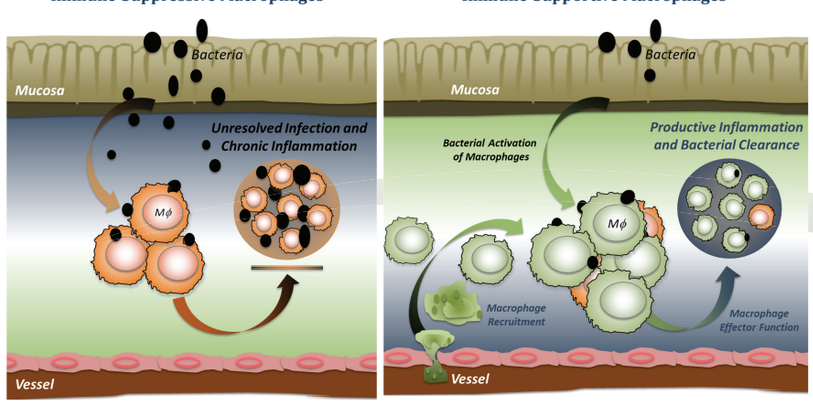
Ten CD subjects between 24 and 44 years of age with active CD refractory to current treatments received QBECO SSI according to a compassionate use protocol. Subjects receiving conventional CD treatments and/or complementary therapies were included, with the exception of subjects receiving anti-TNF alpha monoclonal antibody therapies. Subjects were taught to self-administer between 0.05 and 0.2 mL (median dose = 0.1 mL) of study treatment subcutaneously every second day, for a treatment duration of a minimum of 3 months, and a maximum of 11 months. Dose, dose frequency and side-effects were captured daily in a subject diary, and subjects were followed closely by a physician who regularly assessed their adverse events and clinical symptoms of CD. Ethics approval and informed written consent were obtained.

Mechanism of Action

Macrophage defect or deficiency, leading to a reduced ability to clear bacterial infection and necrotic debris, may be the underlying trigger for CD. SSIs are designed to induce organ specific macrophage recruitment and activation, resulting in clearance of bacterial infection and necrotic debris, removing this underlying trigger for chronic inflammation and immune system dysfunction.

Pre-SSI:
Predominance of Immune-Suppressive Macrophages

SSI Treatment:
Recruitment of Immune-Supportive Macrophages



Results

Table 1. Characteristics of Patients with Crohn's disease (*Montreal classification of Crohn's disease)

Patient	Sex	Disease prior to SSI (yrs)	Age at start of SSI*	Location of CD*	Behavior*	Previous resection	Prior CD therapy	Past use TNF-α blocker	Symptoms at initiation of SSI	Medications at initiation of SSI
1	M	4	A2	L3	B1	0	Prednisone, Imuran	0	Pain, diarrhea, weight loss	Imuran, Prednisone
2	F	2	A2	L1	B3	0	Prednisone, antibiotics	0	Pain, diarrhea, RLQ abcess, weight loss	Prednisone
3	F	15	A2	L2	B2	1	Prednisone, Remicade	1	Pain, diarrhea, anemia	Prednisone
4	F	3	A2	L3	B3p	1	Prednisone, Imuran, Remicade	1	Pain, diarrhea, fistulae	Imuran
5	F	3	A2	L3	B3p (RV fistula)	0	5ASA	0	Pain, diarrhea	5ASA
6	F	13	A2	L2	B1	0	Prednisone, Purinethol, 5ASA, Entocort	0	Pain, diarrhea	none
7	F	15	A2	L2	B1	0	Prednisone, Remicade, 5ASA	1	Pain, diarrhea	5ASA
8	M	3	A2	L2	B1	0	Prednisone, 5ASA	0	Pain, diarrhea, weight loss	none
9	M	16	A2	L3 + L4	B3p	1	Prednisone, Remicade, 5ASA	1	Pain, diarrhea, fistulae	Prednisone
10	F	0.5	A3	L3	B3p	0	Prednisone, Enbrel, Imuran, 5ASA	1	Pain, diarrhea	Prednisone, 5ASA

Efficacy profile

Ten of ten subjects reported improvement of symptoms while on QBECO SSI treatment. Seven subjects reported full resolution of clinical symptoms with a course of QBECO SSI treatment of three months or more. Four subjects have had sustained clinical remission after discontinuing all medications including SSI treatment. The longest case of clinical remission reported is still ongoing, after more than 3.5 years. Four subjects have had a follow-up colonoscopy or CT scan with confirmation of remission of CD.

Safety profile

With a maximum follow-up period of over 42 months, no treatment-related serious adverse events have been observed or reported to date. The only reported treatment-related adverse events were 2-3 episodes of transient fever lasting 12-24 hours in three patients which resolved without treatment within 12–24 hours and a larger than anticipated transient local skin immune response to initial treatment dose in one patient, which was corrected with appropriate dose reduction.

Table 2. Patient response to QBECO SSI treatment

Patient	QBECO SSI therapy duration	Response while on SSI treatment	Status after SSI treatment	Current medications	Confirmation of ongoing remission
1	11 months	Remission	Ongoing remission 3.8 years	None	Colonoscopy
2	3 months	Remission	Ongoing remission 2.8 years	None	CT scan
3	6 months	Remission	Ongoing remission 2.7 years	Off all GI medications	Colonoscopy
4	8 months	Remission, resolution of fistulae	Ongoing remission 2.2 years	None	Colonoscopy
5	3.5 months	Remission	Remission 1.2 years, disease recurrence	Standard care	n/a
6	5 months	Remission	Remission 3 months, disease recurrence	Standard care	n/a
7	7.5 months	Remission	Recurrence post SSI Less severe symptoms	Standard care	n/a
8	6.5 months	Improvement	Symptom return post SSI Less severe symptoms	Standard care	n/a
9	5 months	Improvement, reduction in prednisone	Symptom return post SSI	Standard care	n/a
10	2.5 months	Improvement	Symptom return post SSI	Standard care	n/a

Table 3. Summary: Response to SSI therapy for patients with active moderate-to-severe Crohn's disease

Total patients (n)	10
Clinical improvement (n)	10
Clinical remission during treatment (n)	7
Sustained remission off all medications** (n)	4
Duration of sustained remission**	2 - 3.8 years

**ongoing as of May 2014

Conclusion

Based on the initial promising clinical and safety observations in a compassionate use cohort of 10 subjects with active moderate-to-severe Crohn's disease treated with Site Specific Immunomodulators, QBECO SSI treatment is now being evaluated in a Phase 1/2 randomized, placebo-controlled, double-blind clinical trial in patients with active moderate-to-severe Crohn's disease.