CRS

ZUMA-1, cohort 6

Voor details zie KTE-C19 ZUMA 1 studieprotocol amendement 8
En dus NIET de IB vanwege profylaxe met dexamethason

CRS Grading and Management Cohort 6
In the protocol not in the IB!

This is the same as in cohort 4

CRS Grade	Supportive Care	Tocilizumab	Steroids	Follow up
Grade 1: • **Symptoms are not life threatening and require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgia, malaise)**	• Supportive care per institutional standard of care	N/A	N/A	Not improving after 24 h: Tocilizumab per Grade 2 guidance Not improving after 3 days: **Dexamethasone 10 mg x1**
Grade 2: • **Symptoms require and respond to moderate intervention** • **Oxygen requirement <40% FiO2 or hypotension responsive to fluids or low dose of one vasopressor[a] or Grade 2 organ toxicity[b]**	• Continuous cardiac telemetry and pulse oximetry as indicated • IV fluids bolus for hypotension with 0.5 to 1.0 L isotonic fluids • Vasopressor support for hypotension not responsive to IV fluids • Supplemental oxygen as indicated	• Tocilizumab: 8mg/kg over 1 hour (not to exceed 800 mg) • Repeat tocilizumab every 4 to 6 hours as needed if not response to IV fluids or increasing supplemental oxygen; maximum of 3 doses in a 24-hour period • Maximum total of 4 doses if no clinical improvement in the signs and symptoms of CRS	**Dexamethasone 10mg x 1**	Improving: Discontinue tocilizumab Taper corticosteroids Not Improving: Manage as Grade 3 (below)
Grade 3: • **Symptoms require and respond to aggressive intervention** • **Oxygen requirement ≥ 40% FiO2 or hypotension requiring high-dose or multiple vasopressors[a] or Grade 3 organ toxicity or Grade 4 transaminitis[b]**	Management in monitored care or intensive care unit	Per Grade 2	Methylprednisolone 1 mg/kg IV BID or equivalent dexamethasone	Improving: Discontinue tocilizumab Taper corticosteroids Not Improving: Manage as Grade 4 (below)
Grade 4: • **Life-threatening symptoms** • **Requirements for ventilator support or continuous veno-venous hemodialysis (CVVHD)** • **Grade 4 organ toxicity (excluding transaminitis)[b]**	Per Grade 3 Mechanical ventilation and/or renal replacement therapy may be required	Per Grade 2	High-dose corticosteroids: Methylprednisolone 1000 mg/day IV x 3 day	Improving: Discontinue tocilizumab Taper corticosteroids Not improving: Consider 1 gram BID to TID of methylprednisolone and other immunosuppressive (e.g. siltuximab) and anti-thymocyte globulin (ATG 2mg/kg x 1 and reassess)

NB organ toxicity is scored according to CTCAE V 4.03
NB2: AMC geen low dose vasopressors: als hypotensie ondanks 2 L vullen naast 2 L basisinfuus → IC voor telemetrie en vasopressie

Neurotoxiciteit

ZUMA-1, cohort 6

Voor details zie KTE-C19 ZUMA 1 studieprotocol amendement 8
En dus NIET de IB vanwege profylaxe met dexamethason

Neurologic Events Grading and Management Cohort 6

In the protocol not in the IB!

This is the same as in cohort 4

Neurologic Toxicities	Supportive Care	Tocilizumab	Corticosteroids	Follow up
Grade 1 examples include: • **Somnolence-mild drowsiness or sleepiness** • **Confusion-mild disorientation** • **Encephalopathy-mild limiting of ADLs** • **Dysphasia-not impairing ability to communicate**	Supportive care per institutional standard of care Closely monitor neurologic status Consider prophylactic levetiracetam	N/A	**Dexamethasone 10mg x 1**	**Not improving after 2 days:** **Repeat dexamethasone 10mg x 1** Continue supportive care
Grade 2 examples include: • **Somnolence-moderate, limiting instrumental ADLs** • **Confusion-moderate disorientation** • **Encephalopathy-limiting instrumental ADLs** • **Dysphasia-moderate impairing ability to communicate spontaneously** • **Seizure(s)**	Continuous cardiac telemetry and pulse oximetry as indicated Closely monitor neurologic status with serial neuro exams to include fundoscopy and Glasgow Coma Score. Consider neurology consult Perform brain imaging (eg, MRI), EEG, and lumbar puncture (with opening pressure) if no contraindications Levetiracetam/ antiepileptics if subject has seizures	In case of concurrent CRS: • Tocilizumab: 8mg/kg over 1 hour (not to exceed 800 mg) • Repeat tocilizumab every 4 to 6 hours as needed if not response to IV fluids or increasing supplemental oxygen; maximum of 3 doses in a 24-hour period • Maximum total of 4 doses if no clinical improvement in the signs and symptoms of CRS	**Dexamethasone 10mg QID**	Improving: Discontinue tocilizumab Taper corticosteroids Not improving: Manage as Grade 3 (below)
Grade 3 examples include: • **Somnolence-obtundation or stupor** • **Confusion-severe disorientation** • **Encephalopathy-limiting self-care ADLs** • **Dysphasia-severe receptive or expressive characteristics, impairing ability to read, write, or communicate intelligibly**	Management in monitored care of intensive care unit	Per Grade 2	**Methylprednisolone 1 gram daily**	Improving: Discontinue tocilizumab Taper corticosteroids Not improving: Manage as Grade 4 (below)
Grade 4 examples include: • **Life-threatening consequences** • **Urgent intervention indicated** • **Requirement for mechanical ventilation** • **Consider cerebral edema**	Per Grade 3 Mechanical ventilation, may be required	Per Grade 2	**Methylprednisolone 1 gram BID**	Improving: Taper corticosteroids Not improving: Consider 1 gram of methylprednisolone TID, alternative immunsuppressive (e.g. siltuximab) and anti-thymocyte globulin (ATG 2mg/kg x 1 and reassess)