Management of Patients with Infusion-Related Reactions

Infusion-related reactions (defined as events occurring during or within 24 hours after an infusion) have been reported with tocilizumab. In clinical trials, infusion-related reactions were somewhat more common with tocilizumab than with the placebo (6.9% with tocilizumab 8 mg/kg + methotrexate versus 5.1% with the placebo + methotrexate). The manifestations reported to date are listed below.

- **In most cases, the manifestations were minor and required no change in the treatment:**
  - hypertension (usually during the infusion); and headaches, rash, and urticaria (chiefly after the infusion).

- **More rarely, severe allergic reactions requiring treatment discontinuation occurred.** Thus, hypersensitivity reactions (severe allergic reactions):
  - occurred in 0.3% of patients in the clinical trials and open-label extensions,
  - usually between the second and fifth infusion.
  - Severe anaphylactic reactions
  - occurred in 0.2% of patients in clinical trials,
  - and were more common with 4 mg/kg than with 8 mg/kg.

An immune response to tocilizumab seems uncommon. In the clinical trials, anti-tocilizumab antibodies were found in only 1.6% of patients. Most of the patients with hypersensitivity reactions had detectable anti-tocilizumab antibodies.

Whether anti-tocilizumab antibodies may play a role in potential escape phenomenon (decrease in effectiveness) is unknown.

The extremely low rate of infusion-related reactions does not warrant routine premedication.
Course of action in the event of an infusion-related reaction

The management depends on the severity of the reaction.

Severe reaction (anaphylaxis, rapid development of a rash):

- Stop the infusion immediately.
- The other measures depend on the severity of the symptoms:
  - antihistamines for moderate reactions,
  - intravenous glucocorticoid therapy
  - resuscitation in the most severe forms.

Mild reaction (moderate blood pressure elevation, headaches):

- decrease the infusion rate,
- or stop the infusion for a few minutes then re-start at a slower rate.

Course of action in the event of a delayed reaction

An urticarial skin rash may develop 24 to 72 hours after the infusion. Patients with severe symptoms should be admitted. In moderate forms, the treatment may consist in glucocorticoid therapy (or a transient increase in the previous glucocorticoid dosage), if needed combined with an antihistamine agent.

When can tocilizumab therapy be re-started?

A severe allergic reaction is a definite contraindication to further tocilizumab therapy.

After a moderate reaction, tocilizumab therapy may be re-started, although caution is in order and the infusion should be started at a slower rate.

After a mild skin rash, premedication with an antihistamine agent and a glucocorticoid may be in order.