Reviewer's report

Title: Development of Hypoglycemia in Patients Treated with Tumor Necrosis Factor Alpha Inhibitors: An Observational Case Study.

Version: 1  Date: 7 August 2011

Reviewer: Dimitrios Papazoglou

Has the case been reported coherently?: Yes

Is the case report authentic?: Yes

Is the case report ethical?: Yes

Is there any missing information that you think must be added before publication?: Yes

Is this case worth reporting?: Yes

Is the case report persuasive?: Yes

Does the case report have explanatory value?: No

Does the case report have diagnostic value?: No

Will the case report make a difference to clinical practice?: Yes

Is the anonymity of the patient protected?: Yes

Comments to authors:

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1. Were the hypoglycemic episodes symptomatic or only biochemical?
   If they were symptomatic how do authors explain that glucose concentrations were not too low. If not do they think that biochemical hypoglycemia is possibly even more often since most of patients on anti-TNF therapy do not measure blood glucose regularly at home.

2. Did the hypoglycemic episodes occur in the postprandial or fasting state?

2. The following paragraphs in Discussion should better to be omitted.
   Discussion has to be focused on the relation between TNF-, anti-TNF- agents and glucose metabolism
“Recent studies examining relationship of monokines and the production of factors associated with the pituitary-adrenal axis suggested that recombinant IL-1 induces both adrenocorticotropic hormone (ACTH) and corticosterone when injected into mice [15] and that recombinant TNF alpha in induces increased levels of ACTH and cortisol [16]. Tumor necrosis factor alpha (TNF alpha) has been recognized as a major player in the lipopolysaccharide (LPS)-induced phenomena. Lipopolysaccharide (LPS), the biologically active moiety of gram-negative endotoxin, has long been associated with both toxic and beneficial bioactivities [14].

“There is evidence that passive administration of rabbit anti-TNF immune serum or hamster monoclonal anti-TNF immunoglobulin G (IgG) significantly protects mice from lethal challenge with LPS. Other studies have shown that administration of TNF-alpha induces production of other cytokines, such as interleukin-1 (IL-1) and colony-stimulating factor (CSF). Even though, many studies over the past twenty years have hypothesized a role of the TNF-alpha in the toxicity induced by LPS, the exact role for TNF-alpha in every LPS-induced manifestation, still has not been fully established.”

“In patients with Rheumatoid Arthritis, anti-TNF-alpha therapy was found to improve suppressive abilities of regulatory T cells [18]. Since patients with type I and some with type II Diabetes have impaired T cell function, potential for incorporating TNF-alpha inhibitors as therapy might be addressed.”

Minor comment

“So, this patient developed three hypoglycemic episodes after initiation treatment with
Adalimumab on /12/08”

(month is missing)