Critically Appraised Topic

Title: CD64 upregulation on neutrophils as a marker for prediction of adverse reactions and efficacy in biological treatment.

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Clinical question (PICO):
Can CD64 upregulation on neutrophils be used for prediction and evaluation of adverse events or efficacy in patients on biologicals compared to healthy controls?

Clinical scenario
A patient will start using Infliximab infusions because of her Crohn's disease. She is frightened because her physician told her she is a little bit more vulnerable for infections. The patient asks the doctor whether he can predict infections, other side effects and therapy success of Infliximab looking at her blood in order to start treatment earlier in course.

Search strategy
Medline Search:
CD64[All Fields] OR (high-affinity[All Fields] AND IgG[All Fields] AND "receptor"[All Fields]) OR FcgammaRI[All Fields] OR "fc gamma ri"[All Fields]: *1968 articles*

"Antibodies, Monoclonal/therapeutic use"[Mesh] OR "Recombinant Fusion Proteins/therapeutic use"[Mesh] OR "Receptors, Cytokine/therapeutic use"[Mesh] OR Biologicals OR Biological Drugs OR Biological Therapy: *794932 articles*

"Sensitivity and Specificity"[Mesh] OR "Outcome Assessment (Health Care)"[Mesh] OR "Adverse Drug Reaction Reporting Systems"[Mesh] OR "Drug Toxicity"[Mesh]: *832365 articles*

Combined search: 21 articles (when limited to Clinical Trial, Meta-Analysis, Practice Guideline, Randomized Controlled Trial: 7 articles).

Search outcome
21 articles of which 2 were relevant (Matsui et al. 2006. was included although after agreement of MT and DP due to the large patients group, although it does not pass limits for the study type).

1st Author	Year	Patients	Design	Assay	Result	Comment
Matsui et al. [1]	2006	n = 247 with RA using corticosteroids, DMARDS and biologic agents, with various levels of disease activity or types of infection, n=36 controls including subjects with infection	Prospective	Flow cytometry	1) CD64 on neutrophils expression is higher in Rheumatoid Artritis, with infection than without infection ($p<0.001$), sensitivity for diagnosis of infection 92,7% and specificity of 96,5% (cutoff value 2000 molecules/cell). 2) CD64 expression was	1) Not usefull for Rheumatoid Arthritis pts with pneumonitis or vasculitis

					not effected by using these drugs	
Niitsu et al. [2]	2004	N=15 patients with follicular lymphoma, on R-CHOP therapy (Rituximab + cyclophosphamide, doxorubicin, vincristine, predni-sone)	Safety and efficacy of G-CSF addition (0, 2 or 5μg/kg each group 5 pts) to R-CHOP	Flow cytometry Radioactive ADCC by neutrophils	1) Neutrophil count was increased following G-CSF treatment 2) ADCC correlated with CD64 expression and was higher in G-CSF treated pts. 3) complete remission in 9/10 patient following G-CSF and in 3/5 without G-CSF in the treatment protocol	1) Small study 2) $CD64^{+}$ positive cells appear to be effector cells in killing Rituximab labeled cells by ADCC 3) Although this study was designed as Phase I study there is no follow-up

Comments

CD64 expression in patients treated with biological therapy is not extensively evaluated, despite its role in the immune response. It is known to be used as a marker of phagocyte activation, antibody-dependent cell-mediated cytotoxicity and is also involved in pharmacokinetics of monoclonal antibodies and some fusion proteins [3].

Conclusion

There are no studies directly addressing the validity of CD64 determination in the prediction of adverse reactions or efficacy in patients treated with biologicals and, consequently, it is not possible to judge its value in predicting or evaluating adverse reactions or efficacy in patients treated with these agents. Due to lack of controlled trials in humans, additional investigation is needed to provide more information on levels of expression of CD64 and its suspected interference with antibody distribution.

References

1. Matsui T, Ohsumi K, Ozawa N, Shimada K, Sumitomo S, Shimane K, Kawakami M, Nakayama H, Sugii S, Ozawa Y, Tohma S. CD64 on neutrophils is a sensitive and specific marker for detection of infection in patients with rheumatoid arthritis. The Journal of rheumatology 2006; 33: 2416-2424.
2. Niitsu N, Hayama M, Okamoto M, Khori M, Higashihara M, Tamaru J, Hirano M. Phase I study of Rituximab-CHOP regimen in combination with granulocyte colony-stimulating factor in patients with follicular lymphoma. Clin Cancer Res 2004; 10: 4077-4082.
3. Gurbaxani B. Mathematical modeling as accounting: predicting the fate of serum proteins and therapeutic monoclonal antibodies. Clinical immunology 2007; 122: 121-124.