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Pharmacy & Pharmacology International Journal

Commentary

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A decade after the TGN1412 disaster: what have we learnt about safety-predicting methods for new biological agents?

Commentary

Volume 4 Issue 7 - 2016

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Received: August 24, 2016 | **Published:** December 30, 2016

Sir–13th March, 2006 was a sad day that will forever be remembered by pharmaceutical companies, regulatory authorities, the public and particularly six young men whose contribution to the advancement of medical research almost became an end to their very own lives. These six apparently healthy male volunteers suffered a cytokine release syndrome` with multi-organ failure after being intravenously infused with a monoclonal antibody known as TGN1412.[1] This occurred during the first-in-man phase 1 trials sponsored by TeGenero and conducted by Parexel; a private clinical research unit, located at Northwick Park Hospital in London. The investigational monoclonal antibody was intended to be the miracle breakthrough for the treatment of B cell chronic lymphocytic leukaemia and rheumatoid arthritis. The trial design was a phase 1, single-centre, double-blind, randomized, placebo controlled, single ascending-dose escalation trial.[2]

The capability of CD28 antibodies activating T-cells coupled with signal from T-cell receptors initiated studies to evaluate the potential of T-cell activation of these CD28 antibodies. Hence, large numbers of mouse hybridomas were isolated to investigate functional activity through CD28 antibodies. A category of the CD28 antibodies was identified as superagonist as it was capable of activating T-cells irrespective of signal received from the T-cell receptor. The superagonists are similar to conventional CD28 antibodies. However, they differed in the epitope-binding site which required an intact CD28 C"D loop for binding. Based on these investigations, TeGenero began the screening of several monoclonal CD28 superagonists antibodies obtained from mouse hybridomas.Following the screening, TGN1412 emerged as the ideal drug candidate. However, TGN1412 is a genetically engineered humanised form of the anti-CD28 antibody from the investigational mouse. This is because the use of mouse antibody in humans would result in dysfunction of the antibody as well as immunogenic toxic responses.[3]

Preclinical tests were conducted in non-human primates using rhesus and cynomolgus monkeys because of the similarity in the CD28 receptors in these species and that of humans. Up to a high dose of 50mg/kg administered over four consecutive weeks was well tolerated by the investigational monkeys with no observable adverse reaction such as down regulation of the systemic immune system or hypersensitivity reactions. On the contrary, a low dose of 0.1mg/kg, which is 500times lower than the maximum tolerated dose in cynomolgus monkeys, when administered to healthy human volunteers, resulted in a cytokine syndrome with multi-organ failure. A first-in-human trial, which had successful preclinical testing, obtained regulatory approval ended abruptly after the first dose.[3]

This unprecedented outcome of the TGN1412 trial, raised many questions regarding safety processes implemented during clinical trials. Invariably, it sent a wakeup call to both the pharmaceutical industries and the regulatory authorities to have a second look at the safety of first-in-man phase 1 clinical trial. In the preceding paragraphs, we discuss relevant safety-predicting methods for new biological agents intended for first-in-human (FIH) clinical trial based on the recommendations issued by the Expert Scientific Group (ESG) on the follow up of the TGN1412 trial and other peer reviewed articles on the matter.

To begin with, the preclinical testing must be substantially predictive of the clinical results. One conclusion drawn by the 2006 ESG report on TGN1412 indicated that the preclinical studies conducted for TGN1412 met regulatory requirements but fell short of predicting a safe dose for human use.[1] Horvath and Milton add that the preclinical studies of TGN1412 would have been capable of predicting the human results if the safety studies had been designed to evaluate the consequences of the anticipated events.[4] Although, there was absence of cytokine release syndrome (CRS) in monkeys and rats during the preclinical studies, attention should have been paid to the phylogenetic variation in the species sensitive to cytokine-releasing stimuli. For example, Nguyen et al.[5] points out that, differences in the expression of immune regulatory molecules e.g. siglecs(Sialic acid-binding immunoglobulin-type lectins) may cause differences in T-cell activation and cytokine release. In addition, most of the adverse events associated with cytokine release such as headache, nausea and myalgia are subjective. It is therefore unlikely to identify such adverse effects in animal studies.[4] Owing to this, in the absence of CRS in non-human primates, careful monitoring of T-cell counts is useful in predicting possible occurrence T-cell activation or depletion in humans.[4] Also, test for allergy should be included in preclinical studies of biological agents. This was not done in the case of the TGN1412 studies. According to Weis, CD28 is also expressed by the cells responsible for allergy.[6] The immediate adverse reactions are suggestive of the release of preformed cytokines in granules of the allergy-mediating immune cells. Hence preclinical allergy test could have predicted massive cytokine release.

Another concern about preclinical studies of novel biological agents is the reliance on sound science.[1] Prior to TGN1412 incident, there was similar incidence of cytokine release syndrome with other monoclonal antibodies (mAb) directed at T-cell surface antigen. Two

noticeable examples were the ant-CD3 mAb OKT3 and Visilizumab. Preclinical studies in these drugs concluded that non-human primates appear not to predict cytokine release in humans.[4] In addition, the preclinical studies of TGN1412 reported low levels of cytokine release which was mentioned in the investigator's brochure.[7] This minor, yet potentially significant effect should have raised caution in transition to FIH phase 1 trial. Further down this line, there was also no mention of a 100% homology of CD28 receptor between primates used for the preclinical studies and humans.[3] A review by Hansen and Leslie, revealed differences of up to 4% existing in the amino acid sequence of the C"D loop of CD28 receptors in rhesus and cynomolgus monkeys compared with human.[8] Therefore extensive immunological investigation based on sound science and historical data are necessary to predict certain unforeseen adverse events.

Furthermore, the selection of FIH dose should be based on strong pharmacology data other than exclusive toxicology algorithm.[4] The calculation of the FIH dose for TGN1412 was based on the 'no adverse effect level' (NOAEL) of 50mg/kg in cynomolgus monkeys. In the TGN1412 trial protocol, there was no mention of projected plasma concentration of TGN1412, CD28 receptor occupancy as well as the possible pharmacological effects of the FIH dose in immunocompetent humans.[2] This highlights the relevance of calculating the 'minimal anticipated biological effect level' (MABEL) which takes into account receptor binding and occupancy data obtained from in vitro human and in vivo animal studies.[1] Two methods employed by Horvath and Milton for TGN1412 based on MABEL resulted in lower FIH doses of 0.03mg/kg and 0.005mg/kg compared with 0.1mg/kg employed in the TGN1412 trial.[4] In addition to MABEL approach, the ESG final report further recommends the significance of the pharmacodynamic effects in determining FIH doses.[1] Hence, calculations by ESG for receptor occupancy based on the dissociation constant of TGN1412 and an assumption of the volume of distribution further lowered that obtained from MABEL by three-five folds and recommended a dose of 0.001mg/kg to achieve a low level of occupancy for TGN1412.[1] Therefore, all relevant methods in predicting wider margins of safety for FIH doses should be thoroughly explored prior to dose selection.

Additional concern with the administration of a novel biological agent is the dosing interval between subjects.[9] A ten-minute dosing interval between subjects was applied to 0.1mg/kg TGN1412. However, for a 'high risk' biological agent, much longer time should have been allowed between the dosing of the participants to enable investigators to observe any possible adverse events that may arise.[7]

Conclusion

The unexpected event must also be expected in preparations for FIH trial of novel biological agents.[9] In the case of TGN1412, preparations for possible CRS were inadequate because investigators did not expect CRS to occur and thus delayed in the diagnosis and treatment of affected volunteers. Moreover, it would have been much appropriate if a hospital premise was selected for the trial site other than a privately leased unit by Parexal which was inadequately resourced for the diagnosis and treatment of affected volunteers.[7] As we mark 10years of this unfortunate TGN1412 incident, the lessons learnt by both the pharmaceutical industry and regulatory authorities must be rigorously applied, and history must never be made to repeat again.

Acknowledgements

None.

Conflict of interest

Author declares that there is no conflict of interest.

References

1. Expert Scientific Group (ESG) On Phase One Clinical Trials. *Final Report*. 2006:1–107.
2. Parexel. Clinical trial protocol: A phase-1, single-centre, double-blind, randomised, placebo-controlled, single escalating dose study, to assess the safety, pharmacokinetics, pharmacodynamics and immunogenicity of TGN1412 administered intravenously to healthy volunteers. 2000:1–58.
3. Attarwala H. TGN1412: From Discovery to Disaster. *J Young Pharm*. 2010;2(3):332–336.
4. Horvath CJ, Milton MN. The TeGenero Incident and the Duff Report Conclusions: A Series of Unfortunate Events or an Avoidable Event? *Toxicol Pathol*. 2009;37(3):372–383.
5. Nguyen DH, Hurtado Ziola N, Gagneux P, et al. Loss of Siglec expression on T lymphocytes during human evolution. *PNAS*. 2006;103(20):7765–7770.
6. Weis JH. Allergy test might have avoided drug-trial disaster. *Nature*. 2006;441(7090):150.
7. Suntharalingam G, Perry MR, Ward S, et al. Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412. *N Engl J Med*. 2006;355(10):1018–1028.
8. Hansen S, Leslie RG. TGN1412: scrutinizing preclinical trials of antibody-based medicine. *Nature*. 2006;441(7091):282.
9. Dayan CM, Waith DC. Preparing for first-in-man studies: the challenges for translational immunology post-TGN1412. *Clin Exp Immunol*. 2008;151(2):231–234.