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SPOTLIGHT COMMENTARY

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Spotlight Commentary: How to prove pharmacology of immunomodulatory drugs in a phase 1 trial?

In drug development, it is of importance to establish safety, tolerability, and efficacy of a new investigational compound. For anti-inflammatory drugs, this often entails first-in-human trials where pharmacokinetics (PK) safety and tolerability are the main aim. However, these drugs also need to be investigated for their pharmacological properties such as target engagement and functional pharmacodynamics (PD), and this often poses a major challenge in the healthy population. This has also been emphasized by the recently revised EMA first-in-human guideline.[1] To highlight the different approaches several groups have taken to tackle this challenge, we are commenting here on phase 1 examples the Journal has published recently.

An interesting illustration is the development of the monoclonal antibody against interleukin (IL)-7 as performed by Ellis et al.[2] The group reported an elegantly designed randomized, double-blind, placebo controlled study of GSK2618960 to investigate pharmacokinetics, safety, and tolerability as well as pharmacodynamics. The latter was performed by a target engagement assay as illustrated by receptor occupancy of the interleukin-7 receptor after single administration of the compound. In the T-lymphocytes of the PBMCs already with the lowest dose, a complete receptor occupancy was observed for 7 consecutive days while the higher dose showed 21-day full occupancy of the IL-7Ra. The functional evaluation of the compound was performed by investigating the phosphorylation status of IL-7R downstream inhibition of STAT5 upon ex vivo IL-7 exposure of PBMCs. The authors showed that the highest dose lead to full STAT5 inhibition. In addition, the PK-PD relationship was established showing a target concentration of 2 μg/ml necessary to obtain full receptor occupancy. With these PK-PD results, it was then possible to take rational steps into *proof-of-concept* studies in different autoimmune diseases.

Another example is the first-in-human RCT of a selective Janus kinase inhibitor type 1 (JAK-1) with single and multiple ascending doses up to 10 days in healthy volunteers.[3] Activity of PF-04965842 on PD was established by investigating different biomarkers and cellular read-outs that were relevant for the mechanism of action. Clear dose-dependent reductions were observed on human interferon-inducible protein (IP)-10 which is downstream of interferon γ and high sensitivity C-reactive protein which is downstream of IL-6. Also, the reported cellular markers showed effects, eg, remarkable reductions on reticolucytes and neutrophils specifically with the highest dose over placebo. While the inclusion of lymphocyte subset analysis by fluorescence-activated cell sorting can be commonly considered very valuable for these type of programs, Peeva et al only reported marginal effects. This indicates that broad exploration of target engagement and functional biomarkers enrich the knowledge at early clinical development tremendously; however, not always each single measurement adds to the full understanding.

Smith and colleagues reported a first-in-human study with a covalently binding drug inhibiting Bruton's tyrosine kinase.[4] Receptor occupancy with the drug PRN1008 showed a dose-response relationship that could be quantified in a PK-PD model offering the possibility to rationally select doses for the subsequent phase 2 trial.

The last example is about an anti-oncostatin M monoclonal antibody, ie, GSK2330811, that was tested with single subcutaneous injections in a first-in-human, double-blind RCT.[5] Besides PK and safety, Reid et al report an extensive list of outcomes including platelet count and blood cells parameters, target engagement biomarkers, and in vivo affinity assessment of the compound in serum and interstitial fluid with the skin blister technique to investigate the target compartment for both PK and PD. The higher doses of the oncostatin M antibody clearly show saturation of the target and also availability in the interstitial fluid indicating availability and engagement in the target tissue. This study is therefore an excellent example how various PD markers yield important information in healthy volunteers.

In summary, these 4 examples show encouraging momentum in drug development for auto-immune diseases. Also, these studies illustrate the necessity and the actual implementation of pharmacodynamics markers into phase 1 programs of immunomodulators. Of note, various levels of pharmacodynamic information are observed from solely target occupancy studies over studies including functional pharmacodynamic markers up to more advanced PK-PD modelling approaches. However, an obvious limitation of the phase 1 study in healthy subjects is the absence of pathology which might question the representativity of the diseased state. On the contrary, only with

an integrated view from PK, target engagement to functional effects in relevant tissues such as the skin will yield sufficient information to design a rational phase 2 study in the patient population.

COMPETING INTERESTS

There are no competing interests to declare.

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