Biosimilars
Hot Topic:
Determining Immunogenic Potential

Why is the Assessment of Immunogenicity Important for Biosimilars?

- Immunogenic responses, generally manifesting as anti-drug antibodies (ADAs), can develop in patients who are treated with biologic agents, including biosimilars.[1] ADAs may influence efficacy and/or safety[1-3]

Binding ADA[3,4]
All antibodies that bind to the protein

Neutralizing ADA (NAb)[3,4]
Antibodies that affect therapeutic protein-target interactions (eg bind to the active site) and prevent biological activity

Non-neutralizing ADA[3,4]
Antibodies that bind to the protein but do not directly affect biological activity – may still have a clinical effect (eg may influence tolerability or have an indirect effect on efficacy by reducing bioavailability)

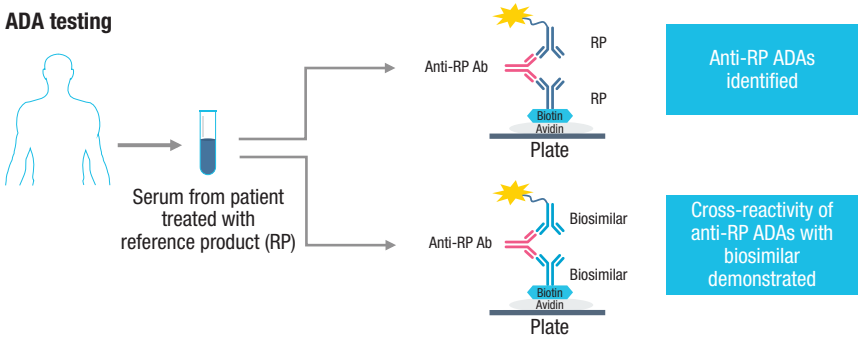
Small Differences Between a Biosimilar and the Reference Biologic Product Could Lead to Differences in the Development of ADAs[2,3,5]

Potential differences in:[1,3,5]

- Expression system
- Post-translational modifications
- Purity/aggregates
- Excipients
- Packaging

A High Degree of Similarity Between a Biosimilar and Reference Product Suggests Possible Cross-Reactivity of ADAs

- Cross-reactivity may occur from reference biologic ADA to biosimilar or from biosimilar ADA to reference biologic[6]
- ADAs may bind to the same epitope on the reference biologic and biosimilar[6]



Assessment of comparative immunogenicity is an essential part of the biosimilar development process[2,5]

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How is Immunogenicity of Biosimilars Assessed in Clinical Trials?

- At least one comparative, parallel-arm clinical study to assess potential differences in immunogenicity between the reference product and biosimilar is recommended[2,3,5]

Key Considerations for Clinical Immunogenicity Testing of Biosimilars in Inflammatory Diseases[2,4,5,7]

Patient population

- Sufficiently sensitive to detect differences should they exist
  - Treatment-naïve patients recommended
  - Patients not receiving immunosuppressants preferred (those on immunosuppressants are less likely to develop immune responses)
  - Capable of predicting response in extrapolated indications

Duration of follow-up

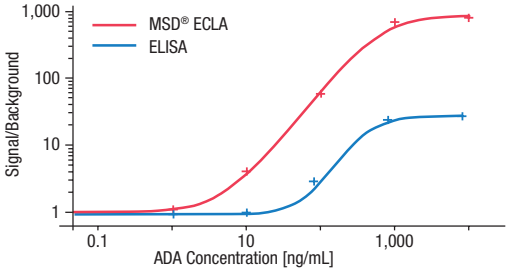
- Consider time course of immune response
  - May take >6 months for neutralizing ADAs to be detected
  - 1 year follow-up generally recommended for chronically administered agents

Assays to detect ADAs

- Validated
- Sufficiently sensitive
- Should assess binding and neutralizing antibodies

Assays to Detect ADAs Have Evolved Over Time to Become More Sensitive and Specific[3,8,9]

Comparison of ECLA & ELISA Immunogenicity Assays[9]



Assay modality	ELISA	MSD ECLA
Sensitivity	**Lower** ~100 ng/mL	**Higher** ~10 ng/ml
Free drug tolerance	**Lower**	**Higher**

ECLA, Electrochemiluminescence assay; ELISA, Enzyme-linked immunosorbent assay; MSD, Meso Scale Discovery®
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- ADAs have generally been detected in a larger proportion of patients when using more sensitive assays[3]

Immunogenicity testing aims to demonstrate that the risk of ADA development with a biosimilar is no greater than with the reference product[2,3,5]

References

1. Ben Horin S, et al. Exp Rev Gastroenterol Hepatol 2015;9(S1):S27-S34; 2. FDA. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. Guidance for Industry, 2015. Available at: https://www.fda.gov/downloads/drugs/guidances/ucm291128.pdf; 3. Pineda C, et al. BioDrugs 2016;30:195-206; 4. FDA. Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products Guidance for Industry. Draft guidance, 2016. Available at: https://www.fda.gov/downloads/Drugs/Guidances/UCM192750.pdf; 5. EMA. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, 2014. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/ WC500180219.pdf; 6. Reinisch W et al. BioDrugs 2017;31;223-237; 7. Felis-Giemza A & Moots R. Rheumatology 2015;54(11):1941–3; 8. Collet-Brose J, et al. J Immun Research. [epublished ahead of print May 3, 2016]. 2016:5069678. doi: 10.1155/2016/5069678; 9. MSD. Immunogenicity assays from Meso Scale Discovery. Available from: https://www.mesoscale.com/~/media/files/brochures/immunogenicity%20assays.pdf. All links accessed March 2018.

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