

## Monitoring biological drugs

### REFERENCES:

1. Plasencia C., Pascual-Salcedo D., Nuño L., Bonilla G., Villalba A., Peiteado D., Díez J., Nagore D., Ruiz Del Agua A., Moral R., Martín-Mola E. and Balsa A. 2012. Influence of immunogenicity on the efficacy of long-term treatment of spondyloarthritis with infliximab. *Ann. Rheum Dis.* [Epub ahead of print]
2. Llinares F., J. Rosas-Gómez de Salazar J. M., Senabre-Gallego G., Santos-Soler C., Santos-Ramírez E., Salas-Heredia and J. Molina-García. 2012. Analytical and clinical evaluation of a new immunoassay for therapeutic drug monitoring of infliximab and adalimumab. *Clin.Chem.Lab.Med.* [Epub ahead of print].
3. Jamnitski A., Kriekkaert C.L., Nurmohamed M.T., Hart M.H., Dijkmans B.A., Aarden L., Voskuyl A.E., Wolbink G.J. 2012. Patients non-responding to etanercept obtain lower etanercept concentrations compared with responding patients. *Ann Rheum Dis* 71: 88-91.
4. Pascual-Salcedo D., Plasencia C., Ramiro S., Nuño L., Bonilla G., Nagore D., Ruiz Del Agua A., Martínez A., Aarden L., Martín-Mola E. and Balsa A. 2011. Influence of immunogenicity on the efficacy of long-term treatment with infliximab in rheumatoid arthritis. *Rheumatology*. 50: 1445-52.
5. Steenholdt C., Bendtzen K., Brynskov J., Thomsen O.O. and Ainsworth M.A. 2011. Cut-off levels and diagnostic accuracy of infliximab trough levels and anti-infliximab antibodies in Crohn's disease. *Scand. J. Gastroenterol.* 46: 310-318.
6. Bartelds G.M., Kriekkaert C.L.M., van Schouwenburg P.A., Lems W.L., Twisk J.W.R., Dijkmans B.A., Aarden L., Wolbink G.J. 2011. Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up. *JAMA*. 305: 1460-1468.
7. Afif W., Loftus E.V. Jr., Faubion W.A., Kane S.V., Bruining D.H., Hanson K.A. and Sandborn W.J. 2010. Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. *Am. J. Gastroenterol.* 105: 1133-1139.
8. Jamnitski A., Bartelds G.M., Nurmohamed M.T., van Schouwenburg P.A., van Schaardenburg D., Stapel S.O., Dijkmans B.A., Aarden L. and Wolbink G.J. 2011. The presence or absence of antibodies to infliximab or adalimumab determines the outcome of switching to etanercept. *Ann. Rheum. Dis.* 70: 284-288.
9. Bartelds, G.M., Wijbrandts, C.A., Nurmohamed, M.T., Stapel S.O., Lems W.F., Aarden L., Dijkmans B.A., Tak P.P. and Wolbink G.J. 2009. Anti-infliximab and anti-adalimumab antibodies in relation to response to adalimumab in infliximab switchers and anti-TNF naïve patients: a cohort study. *Ann. Rheum. Dis.* 60: 2541-2542.
10. Wolbink G. J., Aarden L. and Dijkmans B.A.C. 2009. Dealing with immunogenicity of biologicals: assessment and clinical relevance. *Curr. Opin. Rheumatol.* 21: 211-215.
11. Radstake T. R., Svenson M., Eijsbouts A. M., van den Hoogen F. H., Enevold C., van Riel P. L. and Bendtzen K. 2008. Formation of antibodies against infliximab and adalimumab strongly correlates with functional drug levels and clinical responses in rheumatoid arthritis. *Ann. Rheum. Dis.* 68: 1739-1745.
12. Shankar G., Devanarayan V., Amaravadi L., Barrett Y.C., Bowsher R., Finco-Kent D., Fiscella M., Gorovits B., Kirschner S., Moxness M., Parish T., Quarmby V., Smith H., Smith W., Zuckerman L.A., Koren E. 2008. Recommendations for the validation of immunoassays used for detection of host antibodies against biotechnology products. *J. Pharm. Biomed. Anal.* 48: 1267-1281.



## Effective therapy with biological drugs

Lack of treatment efficacy is often associated with an immune response against the drug. Information on drug **immunogenicity and bioavailability** provides valuable information on the patient's response to treatment.



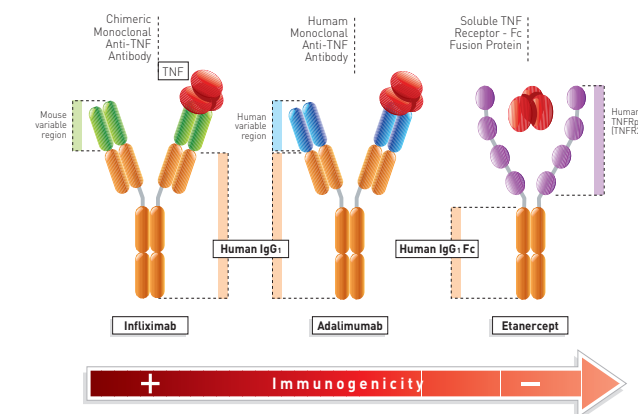
**PROMONITOR** measures both drug bioavailability and immunogenicity with validated assays. This information allows objective decision making on dosing and drug switching and can help clinicians optimize their patients' treatment.

## Biological drugs and inflammatory diseases

Therapies based on modified antibody molecules have revolutionized the treatment of Rheumatoid Arthritis (RA) and antibody-based therapies are increasingly being used to treat other chronic inflammatory diseases.

<b>Rheumatology</b> <ul style="list-style-type: none"> <li>Rheumatoid Arthritis</li> <li>Ankylosing Spondylitis</li> <li>Spondyloarthropathies</li> <li>Psoriatic Arthritis</li> <li>Juvenile Idiopathic Arthritis</li> </ul>	<b>Gastroenterology</b> <ul style="list-style-type: none"> <li>Crohn's Disease</li> <li>Ulcerative Colitis</li> </ul>
<b>Ophthalmology</b> <ul style="list-style-type: none"> <li>Uveitis</li> </ul>	<b>Hematology</b> <ul style="list-style-type: none"> <li>Non Hodgkin's Lymphoma</li> <li>Chronic Lymphocytic Leukemia</li> </ul>
	<b>Dermatology</b> <ul style="list-style-type: none"> <li>Psoriasis</li> <li>Psoriatic Arthritis</li> </ul>

The use of TNF- $\alpha$  blockers, which can prevent disease progression and induce remission in RA patients, has increased substantially in recent years. However, some patients do not respond to these drugs or cease to respond after initially benefiting from treatment. Loss of clinical response has been attributed to immunogenicity and pharmacokinetics. [1,2,3,5,6,9,10] Three of the most commonly used biological drugs are: infliximab, adalimumab and etanercept, which vary in immunogenicity due to their different structures.



## Clinical consequences of immunogenicity

Antibody production against TNF- $\alpha$  antagonists affects treatment efficacy necessitating changes in drug dosage and/or frequency of administration. In some cases switching to an alternative biological therapy may benefit the patient. [1,3,4,6,7]

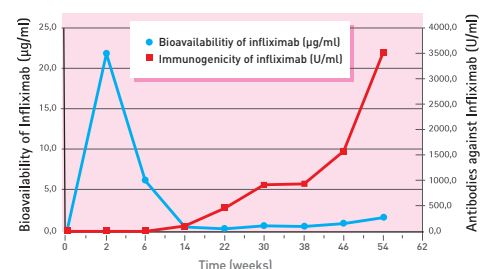


Fig 2. Pharmacokinetic and immunogenicity profile of EULAR non-responder RA patients.

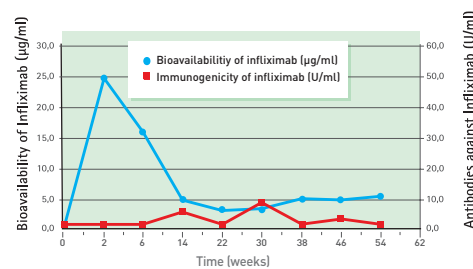
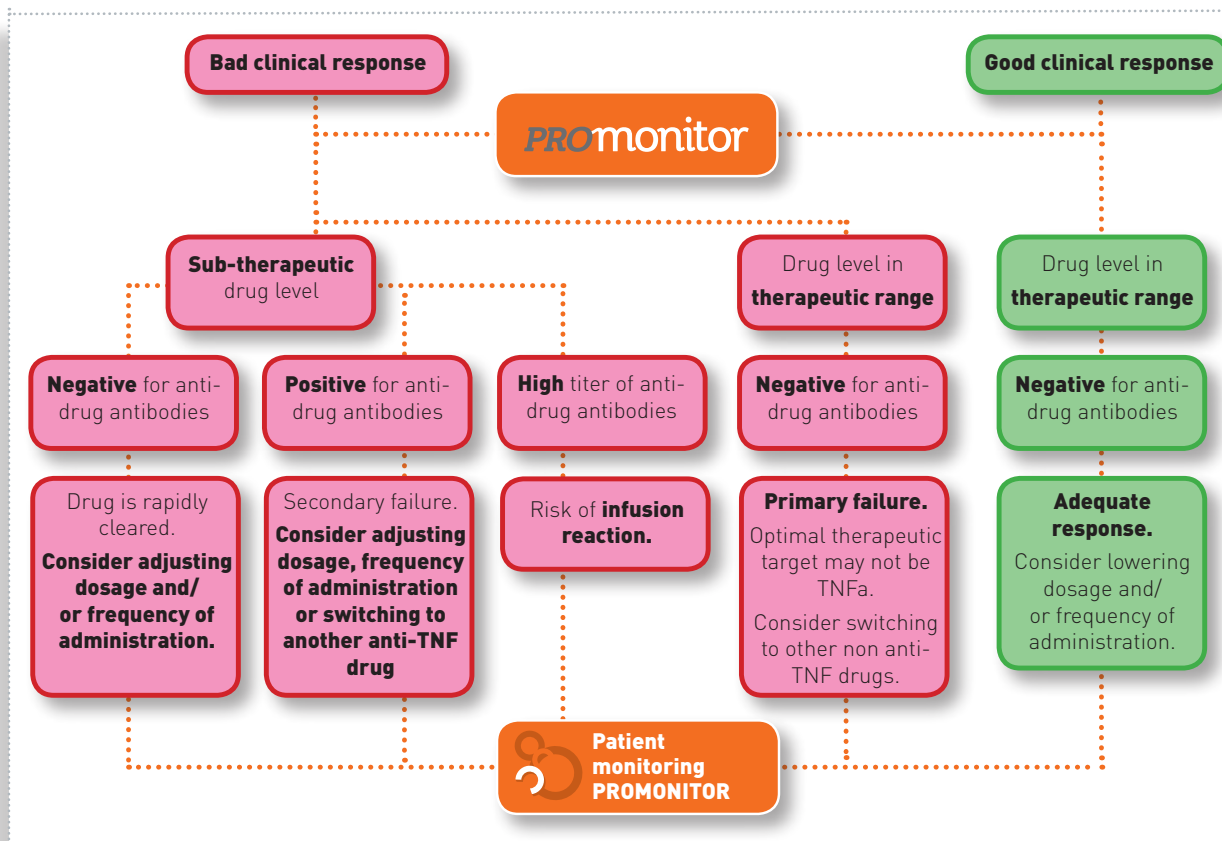


Fig 3. Pharmacokinetic and immunogenicity profile of EULAR good-responder RA patients.

## What is PROMONITOR?

**PROMONITOR** is a diagnostic test that measures serum levels of biological drugs and detects anti-drug antibodies. Test results allow the patient's response to treatment to be monitored.

### Optimized therapy for every patient



## Benefits

- **Individualized treatment for every patient.** Promonitor enables a personalized approach to therapy with biological drugs.
- **Early prediction of reduced drug efficacy.** Promonitor provides early warning that the treatment regime may require modification.
- **Objective clinical decision making.** Adjustment of dosing or drug switching is based on objective criteria.
- **Effective management of biological drugs.** Promonitor helps reduce the use of ineffective treatment strategies, allowing more efficient use of resources and improved clinical outcomes.
- **Clinical excellence.** The use of Promonitor allows improved patient management.

## PROMONITOR ELISA kit



- Allows a flexible number of samples to be analysed simultaneously.
- High specificity and sensitivity (>90%).
- Easy to perform ELISA test for routine use in clinical laboratories.

**DIAGNOSTIC SERVICE → PROMONITOR** is also available as a diagnostic service in Proteomika's facilities where testing is performed by qualified personnel in an accredited laboratory. An easy to use sample collection and shipping service is provided and the ordering physician receives a report detailing results and reference values.

- Promonitor IFX<sup>CE</sup>** Levels of free infliximab and anti-infliximab antibodies.
- Promonitor ADA<sup>CE</sup>** Levels of free adalimumab and anti-adalimumab antibodies.
- Promonitor ETN<sup>CE</sup>** Levels of free etanercept and anti-etanercept antibodies.
- Promonitor RTX<sup>CE</sup>** Levels of free rituximab and anti-rituximab antibodies.