Let's consider Biologic Immunogenicity

OP0301

RISK FACTORS FOR ANTI-INFLIXIMAB ANTIBODY FORMATION: RESULTS FROM THE RANDOMISED CONTROLLED NOR-DRUM A TRIAL

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Background: Immunogenicity is related to loss of efficacy and safety to TNF α inhibitors and is frequently observed early in the treatment course. The highest rate of anti-drug antibody (ADAb) formation has been reported for infliximab (IFX). ¹ Knowledge about risk factors for immunogenicity might contribute to better handling of this problem in clinical practice.

Objectives: To identify risk factors for ADAb formation during the early phase of IFX treatment.

Methods: 411 patients with immune-mediated inflammatory diseases (84 rheumatoid arthritis (RA), 119 spondyloarthritis (SpA), 45 psoriatic arthritis, 83 ulcerative colitis, 58 Crohn's disease and 22 psoriasis) initiating IFX treatment were included in the 38-week NOR-DRUM A trial and randomised 1:1 to therapeutic drug monitoring or standard IFX therapy.² The primary endpoint was clinical remission at week 30. Serum (s) IFX levels and ADAb were measured at each infusion by in-house assays; time-resolved fluorometric assay for sIFX and inhibition assay for ADAb.² In this sub-study, possible risk factors for ADAb formation including demographic variables, diagnosis, comedication, disease activity, IFX dose, sIFX and drug holidays, were assessed using logistic regression. Variables with a p-value <0.25 in univariate analyses were further examined in multivariate analyses adjusting for potential confounders (diagnosis, disease activity, age and gender).

Results: 410 of 411 patients had at least one measurement of sIFX and were included in the present analyses. 76% of patients were biologic-naïve and 45% (18% of RA patients) used IFX as monotherapy. Patients received a mean IFX dose of 3.2-5.9 mg/kg (RA 3.2 mg/kg). ADAb were detected in 78 (19%) patients. The Table 1 shows variables with a significant association to ADAb development. Analyses revealed an increased risk of ADAb development in patients with RA (Odds ratio (OR) 2.1, 95% confidence interval (CI) 1.1-3.9), while SpA had a lower risk (OR 0.5, CI 0.2-0.9) compared to the other diagnoses. These findings were consistent in both univariate- and multivariate analyses (Table 1). Figure 1 shows the cumulative hazard for ADAb development according to diagnosis. Other risk factors for ADAb (Table 1) were smoking (OR 1.8, CI 1.0-3.3) and drug holidays of more than 12 weeks (OR 4.7, CI 1.2-18.3). Additionally, the risk of ADAb increased with higher disease activity (OR 1.5, CI 1.0-2.3) and lower sIFX levels (0.7, 0.6-0.8). Patients co-treated with methotrexate (OR 0.4, CI 0.2-0.9) or thiopurines (OR 0.3, CI 0.1-0.8), or having one or more IFX dose increments (OR 0.4, CI 0.3-0.8), had a reduced risk of immunogenicity.

Table 1. Risk factors for ADAb. Results from logistic regression analyses

	Univariate analyses		Multivariate analyses (Adjusted for diagnosis, disease activity, age and gender)	
	OR	CI	OR	CI
RA	2.2**	[1.3,3.8]	2.1*	[1.1,3.9]
SpA	0.4**	[0.2,0.8]	0.5*	[0.2,0.9]
Methotrexate	1.1	[0.7,1.9]	0.4*	[0.2,0.9]
Thiopurine	0.3*	[0.1,0.9]	0.3*	[0.1,0.8]
Current or former smoking	2.2**	[1.3,3.8]	1.8*	[1.0,3.3]
Mean sIFX	0.7***	[0.6,0.8]	0.7***	[0.6,0.8]
>12 weeks between infusions	4.5*	[1.3,16.0]	4.7*	[1.2,18.3]
IFX dose increment	0.5*	[0.3,0.9]	0.4**	[0.3,0.8]
Mean DAS28 (RA and PsA)	1.5*	[1.0,2.1]	1.5*	[1.0,2.3]
Mean ESR	1.1***	[1.0,1.1]	1.1***	[1.0,1.1]
Mean CRP	1.1**	[1.0,1.1]	1.1**	[1.0,1.1]

* p<0.05, ** p<0.01, *** p<0.001 Only variables with a p-value <0.05 are shown. Non-significant variables include other demographic variables and IFX dose.

Conclusion: This study identified smoking, drug holidays, high disease activity, IFX monotherapy and low sIFX levels as risk factors for ADAb development. Of particular interest, we found that RA patients had significantly increased risk of ADAb compared to the other immune-mediated inflammatory diseases. Whether this novel finding reflects different underlying disease mechanisms or the fact that RA patients receive a lower IFX dose, is not known and needs to be further explored.

REFERENCES:

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Disclosure of Interests: Marthe Kirksæther Brun: None declared, Guro Lovik Goll Speakers bureau: Pfizer, AbbVie, Boehringer Ingelheim, Roche, Orion pharma, Sandoz and Novartis, Kristin Kaasen Jørgensen Speakers bureau: Celltrion, AOP Orphan Pharmaceuticals and Norgine, Joe Sexton: None declared, Johanna Elin Gehin Speakers bureau: Roche, Øystein Sandanger: None declared, Inge Olsen: None declared, Rolf Antonsen: None declared, David J Warren: None declared, Cato Mørk Speakers bureau: Novartis Norge AS, LEO Pharma AS, ACO Hud Norge AS, Cellgene AS, Abbvie, Galderma Nordic and UCB, Tore K. Kvien Speakers bureau: TAmgen, Celltrion, Egis, Evapharma, Ewopharma, Hikma, Oktal, Sandoz and Sanofi, Consultant of: AbbVie, Amgen, Biogen, Celltrion, Eli Lilly, Gilead, Mylan, Novartis, Pfizer, Sandoz and Sanofi, Grant/research support from: Research funding to Diakonhjemmet Hospital from AbbVie, Amgen, BMS, MSD, Pfizer and UCB, Jørgen Jahnsen: None declared, Nils Bolstad Speakers bureau: Roche Pharmaceuticals and Novartis, Consultant of: Janssen, Espen A Haavardsholm Speakers bureau: Pfizer, AbbVie, Celgene, Novartis, Janssen, Gilead, Eli-Lilly and UCB, Silje Watterdal Syversen Speakers bureau: Thermo Fisher.

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Context matters: Placebo and nocebo effects for pain management

OP0302-HPR

IDENTIFYING THE CONTEXTUAL FACTORS IN THE PATIENT-PRACTITIONER ENCOUNTER THAT HAVE THERAPEUTIC EFFECT: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Placebo or contextual effect is an integral part of the treatment effect (1). The factors related to this effect are "contextual factors" (CFs) (2). CFs may be categorised into five groups as factors related to practitioner, patient, practitioner-patient interaction, treatment and therapeutic environment (3). Several CFs have demonstrated their therapeutic effect, whereas others not (4). The majority of musculoskeletal pain relief result from CFs (5). Identifying the key CFs may encourage health practitioners to optimize the contextual aspects of care.