

Nephrogenic systemic fibrosis or nephrogenic fibrosing dermopathy (NSF/NFD)

Nephrogenic systemic fibrosis or nephrogenic fibrosing dermopathy (NSF/NFD) was first described in the medical literature in 2000, with the first reported case going back to 1997⁽¹⁾. The disease is seen in patients that have advanced renal impairment or are on dialysis. Males and females are affected in approximately equal numbers, with onset generally during middle age. NSF/NFD causes fibrosis of the skin and connective tissues throughout the body. Symptoms may include progressive thickening and induration of the skin, with or without pigment alterations; contractures around the joints that may impair mobility; swelling (mostly of the lower extremities); redness; pruritus; and a burning sensation. The clinical course of NSF/NFD can be progressive, may involve internal organs and may be fatal. Currently, there is no known cure for NSF/NFD. Improving renal function seems to slow or arrest NSF/NFD and may even result in a gradual reversal.

The etiology of NSF/NFD is still unknown but is likely to be multifactorial. Specific triggers currently under scientific evaluation include surgery and/or the occurrence of thrombosis or other vascular injury⁽²⁾, the administration of high doses of erythropoietin⁽³⁾, and the use of gadolinium-based contrast agents^(4,5,6,7).

On May 29, 2006, the Danish health authorities (DMA) issued a public health announcement regarding 25 cases of NSF/NFD, associated with the administration of Omniscan®. In this context the Danish authorities requested safety updates with a focus on NSF/NFD for all Gd-containing contrast agents by all companies.

On June 8, 2006 the FDA issued a Public Health Advisory titled “Gadolinium-containing Contrast Agents for Magnetic Resonance Imaging (MRI): Omniscan, OptiMARK, Magnevist, ProHance, and MultiHance”, including the demand to report all adverse events via MedWatch to FDA on the occurrence of NFD in patients with severe renal impairment following CE-MRI with gadolinium-containing contrast agents. On December 22, 2006, the FDA issued updates to its [Public Health Advisory on MRI Contrast Agents Containing Gadolinium and Nephrogenic Fibrosing Dermopathy](#), its [Questions and Answers on Gadolinium-Containing Contrast Agents](#), and its [Information for Healthcare Professionals on Gadolinium-Based Contrast Agents for Magnetic Resonance Imaging Scans](#). These updates indicated that as of December 21, 2006, the FDA had received reports of 90 patients with moderate to end-stage kidney disease who developed NSF/NFD after they had an MRI or MRA with a gadolinium-based contrast agent.

On January 29, 2007, the European Pharmacovigilance Working Party (PhVWP) stated that there was strong indication of a causal association between gadodiamide (Omniscan®) and NSF/NFD in patients with severe renal failure. Furthermore, the PhVWP noted that there were

differences in the complex stability of the different marketed gadolinium-based contrast agents that may impact on their propensity to trigger NSF/NFD. On the basis of current evidence, the PhVWP advised all contrast media manufacturers to add warnings about the occurrence of NSF/NFD with gadolinium-based contrast agents to section 4.4 of the Summary of Product Characteristics (SPC) for all such agents. Bayer Schering Pharma AG has initiated respective regulatory actions.

The excellent safety and tolerability of Magnevist® has been well established in more than 80 Mio applications.

From July 2006 until April 12, 2007, 53 reports of NSF associated with the administration of Magnevist® have been received by Bayer Schering Pharma AG and its US affiliate Bayer Healthcare Pharmaceuticals from worldwide sources. Prior to July 2006, no ADR reports on Magnevist® and the occurrence of NSF/NFD had been received. To date, Magnevist® has been used in over 80 million applications in more than 100 countries.

Of the 53 reports, 19 were assessed as possibly related, 4 were assessed as unlikely related, and 30 were assessed as unclassifiable, meaning that the information provided was insufficient for causality assessment. Onset of NSF-symptoms in all available reports dates back up to several years. The time span between administration of MR contrast medium and occurrence of symptoms ranges between 2 days and several years.

22 of the 53 reports became recently known to us from one single institution.

Analysis of the currently available safety data from world-wide spontaneous reporting of Magnevist® to date has not resulted in a change of the overall positive risk / benefit assessment. To date there are no reports of NSF/NFD for Gadovist, Primovist and Vasovist in our databases.

Preclinical studies and interdisciplinary discussions between researchers and dermatology experts are ongoing to investigate the possible relationship of NFD/NSF and Gd-containing contrast agents and to evaluate in more detail the pathogenesis of this new disease entity and potential differences in risk among the various extracellular MR contrast agents.

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