

Drug-induced retroperitoneal fibrosis: short aetiopathogenetic note, from the past times of ergot-derivatives large use to currently applied bio-pharmacology

C. ALBERTI

SUMMARY: Drug-induced retroperitoneal fibrosis: short aetiopathogenetic note, from the past times of ergot-derivatives large use to currently applied bio-pharmacology.

C. ALBERTI

Among the secondary forms of retroperitoneal fibrosis (RPF), that drug-induced shows very intriguing aspects given both the broad range of involved pharmaceuticals and the considerable interest arisen from the related pathogenetic mechanisms. The particular incidence, in the last four decades past century, of the RPF due to long-term use of ergot alkaloid derivatives (ergotamine, methysergide, pergolide, bro-

mocriptine, cabergoline) and specific L-dopa derived agents, such as methyldopa, as well as to different analgesics, came progressively down given that their long-term use for either the prevention of migraine attacks or the therapy of chronic pathologies (Parkinson's disease, prolactinoma, pain management, etc) has been, year after year, supplanted or even made unavailable in many countries. More recently, instead, the occurrence of the RPF has been sometimes identified with the use of antitumoral chemotherapeutics, such as carboplatin and methotrexate, and, just lately, as an unusual side-effect of certain biological agents, about which it is timely to go into specific pathogenetic problems in more depth.

KEY WORDS: Retroperitoneal fibrosis - Urology - Ergot derivatives - Biological agents - Neuropharmacology - Electroceuticals.

Introduction

Retroperitoneal fibrosis (RPF) is a rare chronic wooden fibroinflammatory process surrounding the infrarenal part of abdominal aorta and iliac vessels with frequent encasement of ureters – hence the arising obstructive uro-nephropathy – and, in addition, the inferior vena cava (1, 2). It includes both the *idiopathic*, likely autoimmune, form (Ormond's disease), still accounting more than half (55-60%) of cases – at times linked with either the IgG4-related sclerosing disease or the pro-fibrotic β -catenin/Wnt signalling hyperactivation as well as in systemic sclerosis expressions (3, 4) – and many *secondary* forms as the outcome of different known conditions, among which retroperitoneal accidental traumas, infections, malignancies (RPF as either desmoplastic local response to primary and metastatic retroperitoneal

tumors or paraneoplastic form due to extra-retroperitoneal neoplasias), occupationally used materials as asbestos (silicate mineral also responsible for a pleural/peritoneal mesothelioma onset), medical procedures (interventional radiology, surgery, external beam radiation therapy, etc) and, just looking down here, long-term intake of certain drugs (5-7).

Charged drugs

The outlined list of charged drugs includes:

- ergot alkaloid-derived agents, including both 6,8-methylergoline- and lysergic acid derivatives, mainly used as anti-migraine drugs (ergotamine, methysergide) and partly as dopaminergic agonists (pergolide, bromocriptine, cabergoline), besides the psychedelic LSD (lysergic acid diethylamide);
- specific L-dopa-derivatives, such as methyldopa;
- β -adrenergic blockers, either nonselective (propranolol, sotalol, oxyprenolol) or β 1-selective agents (metoprolol, atenolol);
- analgesics; particularly phenacetin, paracetamol and aspirin;
- hydralazine;

LD of Surgical Semeiotics

Corresponding author: Contardo Alberti,
e-mail address: eneide94@gmail.com

© Copyright 2015, CIC Edizioni Internazionali, Roma

- antitumoral chemotherapeutics, among which carboplatin and methotrexate;
- bio-pharmaceutical agents, such as the tumor necrosis factor- α (TNF- α) receptor blocker Etanercept and, questionably, the anti-TNF- α monoclonal antibody (Infliximab).

Ergot-derived anti-migraine drugs

A significant occurrence of RPF – sometimes together with pleuropulmonary fibrosis and fibrotic thickening of heart valves – has been found, during the '60-'70s last century, in patients long-term treated, for migraine relief, with either ergotamine tartrate or dihydroergotamine or, particularly, with *methysergide*.

Methysergide maleate (1-methyl-D-lysergic acid butanolamide-maleate, $C_{21}H_{27}N_3O_2 \cdot C_4H_4O_4$) is a specific serotonin 5-HT_{2A} (collaterally also 5-HT_{2C}) receptor antagonist meanwhile with 5HT_{1A} receptor agonist effects. So, methysergide, as an antiserotonergic drug acting against serotonin-induced brain vasodilatation – responsible, according to Wolff's theory, for migraine attacks – has been used, on large scale, for prevention of both cluster and migraine headaches besides to treat the neuroendocrine syndromes, such as particularly that induced by carcinoid tumor.

Methysergide, in some ways, may be thought as pro-drug of its active derivative methyl-ergometrine that acts as relatively "dirty drug" even endowed, indeed, with additional dopaminergic properties (8).

The lengthy use of methysergide has led, with an estimated incidence of 1/5,000 treated patients, to RPF onset, sometimes together with mediastinal, pleural, pericardial and subendocardial fibrosis that implies a left-sided cardiac valve dysfunction (8, 9).

The pathogenetic mechanism of lysergic acid derivative-induced RPF could be identified partly with such drug-related profibrotic-reactive haptenic role or, alternatively, with a feed-back rebound release of serotonin resulting in TGF- β /Smads cascade-mediated enhancement of myofibroblast proliferation with following overproduction of extracellular matrix (ECM) components – such as collagen, fibronectin, tenascin, glycosaminoglycans – that, besides the retroperitoneal space, may involve pleura, lung, mediastinum, cardiac valves and pericardium (1, 5-7, 10).

To validate previous clinical findings (11-15), early experimental endorsements have been achieved, about at the end of 60s last century – on my own initiative, with the collaboration of two Medicine undergraduates then (Potenzoni, Cortellini) and a veterinary medicine histologist (doctor Fredi) – by a research work in animal models (rats and rabbits), whose six related reports on pyeloureterographic and histological findings were then published in nonindexed medicine journals (16, 17). Among the researchers which took into consideration

such articles, just only Wagenknecht disagreed on our reports (5). Nevertheless, a further study on this subject, again in an animal model, with like our results, has been elsewhere carried out (18).

Just considering that the long-term use of methysergide was responsible for a significant incidence of RPF, besides other fibrotic disorders, its administration in migraine, after the 70s-80s past century, has been supplanted or even made unavailable in many countries (8). Subsequently nonergot-derived anti-migraine drugs were used, among which particularly *sumatriptan*, as a serotonin 5-HT₁-line receptor agonist together with 5-HT_{2A}/5-HT_{2C} receptor antagonism, it inducing a negative feedback regulation of brain serotonin synthesis, and *tolipramate*, as a blocker of brain cell voltage-dependent sodium channels together with enhancing the GABA (γ -amino-butyric acid) activity at related receptors while antagonizing the glutamate pathway (19-21).

Ergot-derived dopamine receptor agonists

Also other ergot-derived drugs – such as pergolide, cabergoline, bromocriptine – though used as dopamine D₁/D₂ receptor agonists particularly in the management of the Parkinson's disease, besides the hyperprolactinemia and restless leg syndrome, can induce RPF and pleural, pericardial, cardiac valve fibrotic reactions.

Their possible fibrogenic mechanisms are quite same as that of methysergide, by inducing the serotonin rebound release-mediated activation of myofibroblasts to overproduce ECM fibrogenic components, as well as the reactive fibrotic process might be thought, in addition, as an immune response to such drugs acting as haptens (22-24).

The *pergolide* long term use-related frequent heart valve fibrotic damage seems, indeed, to be due to drug action at 5-HT_{2B} serotonin receptors of subendocardial myofibroblasts, with following fibrous valve thickening (25-27).

Cabergoline and *bromocriptine*, as also inhibitors on pituitary both prolactinogenous and growth hormone secreting cells, are first-line drugs in the treatment of prolactinoma and acromegaly. *Cabergoline*, besides dopamine D₂/D₃/D₄ receptor agonist, shows significant affinity, just as ergot-derived drug, particularly for 5-HT_{2B} serotonin receptors, that's why there is the eventuality of fibrotic disorders development. However a detailed study (28) shows that cabergoline, though administered for long-term treatment of hyperprolactinemia/acromegaly, wouldn't seem to be linked with an enhanced risk of fibrotic events. *Bromocriptine* is used not only in the management of Parkinson's disease, neuroleptic malignant syndrome and pituitary prolactinoma, but also at times in the treatment of type 2 diabetes, with possible RPF onset after its long-term administration (22-24).

Lisuride, as an iso-ergoline (diethyl-methyl-hexahydro-indolo-quinoline-urea) class-related drug, can antagonize the 5-HT_{2B} serotonin receptors while acting as agonist on 5-HT_{1A} and 5-HT_{2A/5-HT_{2C}} serotonin receptors, that's why it is used for prevention of migraine attacks. Moreover such drug, as displaying high affinity particularly for D₂/D₃/D₄ dopamine receptors together with prolactin-reducing properties, is useful to treat the Parkinson's disease and to lower the pituitary prolactin secretion. Though it is a lysergic acid-derivative, its use-linked development of RPF and other fibrotic forms (pleural, lung, heart valve) involves a very small number of cases, supporting the concept that the 5HT_{2B} receptor activation role of other ergot-derivatives (particularly, pergolide and cabergoline) might be the crucial cause of the fibrogenic mechanisms (29, 30). What has been recently highlighted even from EMA-Chmp (European medicines agency-Committee for medical products for human use) with properly authoritative precautional instructions (31).

Specific L-dopa derivatives

From L-dopa (L-3,4-dihydroxyphenylalanine) – as a precursor of catecholamine neurotransmitters such as dopamine, norepinephrine, epinephrine – that is used to enhance dopamine brain levels in the management of Parkinson's disease and to treat the dopamine-responsive dystonia, it is achieved, by methylation, the *methyl-dopa* (L- α -methyl-3,4-dihydroxyphenylalanine), endowed, as α_2 -adrenergic selective agonist, with sympatholytic-antihypertensive properties. Its various side-effects include sometimes, over an administration period of 4-5 years, the development of the RPF through likely autoimmunization-related retroperitoneal deposition of collagen (32).

β -adrenergic blockers, analgesics, hydralazine, antitumoral chemotherapeutics

In comparison with many reports on the RPF occurrence following the long term use of either nonselective (propranolol, oxprenolol, sotalol, labetalol) or β_1 -selective *adrenergic blockers* (atenolol, metoprolol) (33-36), subsequent findings of a thorough study (37) led to suggest that such drugs do not cause RPF.

As regards the *analgesics*, the literature displays interesting articles on some RPF cases occurred during lengthy treatment with such drugs – particularly phenacetin, aspirin, paracetamol – where the retroperitoneal fibrous pathology was at times associated with analgesic-due nephropathy, particularly just with renal papillary necrosis (38-42).

Hydralazine (1-hydrazinylphthalazine), though inducing arterial smooth muscle relaxation, isn't used as a primary antihypertensive agent given that it, by eliciting heart sympathetic baroreceptor reflex stimulation,

may lead to increase heart rate/cardiac output with following risk, in patients with coronaropathy, of angina pectoris or even myocardial infarction. Hence, to prevent such serious side effects, its prescription is often associated with β -blockers and also diuretics given plasma renin increase due water retention too. It has been reported that long-term use of such drug, in association with hydrochlorothiazide, may induce RPF (43).

As far as the *antitumoral drugs*, some chemotherapeutics, such as carboplatin and methotrexate, would be assessed as possible inductive factors of RPF (44-46), so that the withdrawal of such drugs could sometimes result in a spontaneous regression of fibrotic retroperitoneal damage (45). The extreme infrequency of reports concerning this chemo-induced RPF occurrence makes problematic to identify its pathogenetic mechanisms.

Bio-pharmaceutical agents

With reference to possible induction of RPF from the use of biological agents, there are so far few but significant reports concerning etanercept, a biotechnologically made TNF- α receptor blocker, and, more questionably, regarding the anti-TNF- α monoclonal antibody infliximab, both drugs used to mainly treat the autoimmune diseases, such as rheumatoid arthritis, psoriasis, Crohn's disease, sarcoidosis.

Etanercept is a dimeric protein-based drug biotechnologically obtained by fusion of TNF- α receptor 2-related DNA gene sequence with IgG1 immunoglobulin-related DNA gene sequence, resulting in a final expression of DNA linked-derived chimeric protein that acts as a TNF- α decoy receptor, so opposing such factor effects and therefore inhibiting the evolution of autoimmune diseases. Quite recently it has been described the etanercept-induced development of RPF, that forced to give up, in such occasion, this therapeutic measure (47).

About the *anti-TNF- α monoclonal antibody* (infliximab, adalimumab, golimumab) there are not, up to now, particular reports regarding its direct implication in a *de novo* RPF onset. It would seem, indeed – as it results from a recent “personalized health information and FDA research report, May 2015” – that, among 85,107 people reported to have side effects when taking infliximab (Remicade) only two people (0.0016%) show RPF. The development, instead, of other autoimmune diseases – such as sarcoidosis, psoriasis, inflammatory bowel disease – has been significantly found, as paradoxical phenomenon, just during therapies with TNF- α antagonists (48, 49).

Conclusion

Taking into consideration the above detailed review of the literature on different drug use-linked RPF on-

set, it wouldn't seem that emerge, over the last ten years, quite significant innovative knowledges in comparison to what has been formerly pointed out apart from recent data concerning the RPF occurrence related to novel biotherapies.

Just with reference to the past, a proper treatment of any theme – both in humanities and positive sciences – should include the pre-comprehension of its significant historical aspects without overlooking them because of either carelessness or supercilious attitude.

The most RPF secondary to use of either ergot- or L-dopa-derivatives or even analgesics, are dated at the 60s-80s of last century, given that furtherly their long-term use has been supplanted or kept under careful measures to prevent the RPF onset (8, 9, 11-15, 22-32). In this regard, to avoid, during the management of Parkinson's disease, the reported ergot derivative-related fibrotic damages, many experimental studies are today in progress, among which the piece of research, in animal models – with the resort to optical/chemogenetic switches – to rea-

ch proper cell therapy measures fit for increasing the release of dopamine from midbrain neurons (50).

As regards the use of novel biological agents, both the TNF- α receptor blocker Etanercept and the anti-TNF- α antibody Infliximab may lead to extremely rare occurrence of RPF, what, however, implying next thorough studies to properly identify underlying pathogenetic mechanisms (47-49).

To come up against the risk of RPF onset dependent on such anti-TNF α agents, other drugs, targeting particular molecules or pathways – among which the B-cell surface protein CD20, interleukin-6 cytokine or Janus kinase/Stat – may be used to treat patients seriously suffering from autoimmune disorders (51-55). Moreover, regarding such diseases, the resort to anti-inflammatory nerve vagus-mediated electroceutical approaches could be a foreseeable alternative to drug use (56), as well as the administration of centrally(brain)-acting muscarinic acetylcholine receptor agonist cytokine-lowering xanomeline (57).

References

- van Bommel EF. Retroperitoneal fibrosis. *Neth J Med.* 2002;60:231-232.
- Estrade V, Traxer O, Sibony M, Haab F. Fibrose rétro-péritonéale. *Ann Urol.* 2004;38:3-13.
- Takahashi H, Yamanoto M, Suzuki C, Naishiro Y, Shinomura Y, Imai K. The birth-day of new syndrome: the IgG4-related diseases constitute a clinical entity. *Autoimmun Rev.* 2010;9:539-551.
- MacDonald BT, Tamai K, He X. Wnt/ β -catenin signaling: components, mechanisms and diseases. *Dev Cell.* 2009;17:9-26.
- Wagenknecht LV. *Retroperitoneale fibrosen.* Georg Thieme Verlag. Stuttgart, 1978.
- Alberti C. Current aetiopathogenetic and diagnostic aspects on periureteritis and retroperitoneal fibrosis. *Riv Radiol.* 1979;19:369-378.
- Alberti C. Retroperitoneal fibrosis: updating note. *Urol prat.* 2002;2:40-54.
- Koeler P, Tfelt-Hansen P. History of methysergide in migraine. *Cephalalgia.* 2008;28:1126-1135.
- Silberstein SD. Methysergide. *Cephalalgia.* 1998;18:421-435.
- Alberti C. Retroperitoneal fibrosis: aetiopathogenesis and taxonomic assessment. *Eur Rev Med Pharmacol Sci.* 2007;11:375-382.
- Graham JR, Suby H, LeCompte P, Sadowsky N. Fibrotic disorders associated with methysergide therapy for headache. *N Engl J Med.* 1966;274:359-368.
- Utz DC, Rooks EO, Spittel JA, Bartholomew LG. Retroperitoneal fibrosis in patients taking the methysergide. *JAMA.* 1965;191:983-998.
- Weiss AJ, Hinman F. Reversible retroperitoneal fibrosis with ureteral obstruction associated with ingestion of sansert. *J Urol.* 1962;95:771-778.
- Carr RJ, Biswas BK. Methysergide and retroperitoneal fibrosis. *Br Med J.* 1966;1:1116-1120.
- Seymour R. Retroperitoneal fibrosis associated with methysergide therapy. *J Can Ass Radiol.* 1968;19:61-63.
- Alberti C, Freddi M, Macaluso G, Potenzoni D, Culzoni V. Histological findings about drug-induced periureteritis in an animal model. *Rass Urol Nefrol.* 1968;6:235-240.
- Alberti C, Piacentini L, Cortellini P. About drug-induced pyeloureteral pathology: statistical data on our experimental studies. *Rass Urol Nefrol.* 1968;6:133-140.
- Tomasino R, Marosa L. Experimental research on methysergide-induced retroperitoneal fibrosis. *Arch De Vecchi Anat Pat.* 1977;62:173-180.
- Schurks M, Diener H, Goadsby P. Update on prophylaxis of migraine. *Curr Treat Options Neurol.* 2008;10:20-29.
- Ueda T, Torihara Y, Tsuneyoshi N, Ikeda Y. Effect of sumatriptan on cerebral blood flow during migraine headache: measurements by sequential SPECT used 99Tc-ECD background subtraction method. *No To Shinkel.* 2001;53:625-630.
- Ferrari A, Tiraferri I, Neri L, Sternieri E. Clinical pharmacology of the topiramate in migraine prevention. *Expert Opin Drug Metabol Toxicol.* 2011;7:1169-1181.
- Shaunak S, Wilkins A, Pilling JB, Dick J. Pericardial, retroperitoneal and pleural fibrosis induced by pergolide. *J Neurol Neurosurg Psychiatry.* 1999;66:79-81.
- Bowler J, Ormerod I, Legg N. Retroperitoneal fibrosis and bromocriptine. *Lancet.* 1986;ii:466.
- Ward C, Thompson J, Humby M. Pleuropulmonary and retroperitoneal fibrosis associated with bromocriptine treatment. *J Neurol Neurosurg Psychiatry.* 1987;50:1706-1707.
- Zanettini R, Antonini A, Gatto G, Gentile R, Tesei S, Pezzoli G. Valvular heart disease and the use of dopamine agonists for Parkinson's disease. *N Engl J Med.* 2007;356:39-46.

26. van Camp GV, Flanez A, Cosyns B, Goldstein J, Perdaens C, Schoors D. Heart valvular disease in patients with Parkinson's disease treated with high-dose pergolide. *Neurology*. 2003;61:859-861.
27. Bleumink GS, van der Molen-Eijgenraam M, Strijbos JH, Sanwikarja S, van Puijenbroek EP, Stricker BHCh. Pergolide-induced pleuropulmonary fibrosis. *Clin Neuropharmacol*. 2002;25:290-293.
28. Labefer M, Stades AM, Valk GD, Cramer MJ, Teding van Berkhout F, Zelissen PMJ. Absence of major fibrotic adverse events in hyperprolactinemic patients treated with cabergoline. *Eur J Endocrinol*. 2010;162:667-675.
29. Andersson F, Garbe E. Cardiac and noncardiac fibrotic reactions caused by ergot- and nonergot-derived dopamine agonists. *Mov Disord*. 2009;24:129-133.
30. Hofman C, Penner U, Dorow R, Pertz HH, Jahnichen S, Horowski R, Latté KP, Palla D, Schurab B. Lisuride, a dopamine receptor agonist with 5-HT_{2B} receptor antagonist properties: absence of cardiac valvulopathy adverse drug reaction reports supports the concept of a crucial role of 5-HT_{2B} receptor agonism in cardiac valvular fibrosis. *Clin Neuropharmacol*. 2006;29:80-86.
31. European Medicines Agency. Restrictions on use of medicines containing ergot derivatives. Report EMA/750626/2013, 27 June.
32. Ahmad S. Methyldopa and retroperitoneal fibrosis. *Am Heart J*. 1983;105:1037-1038.
33. McClusky D, Donaldson RA, McGeown MG. Oxyprenolol and retroperitoneal fibrosis. *Br Med J*. 1980;281:1459-1460.
34. Johnson JN, McFarland J. Retroperitoneal fibrosis associated with stenolol. *Br Med J*. 1980;280:864-866.
35. Pierce JR, Trostle DC, Warner JJ. Propranolol and retroperitoneal fibrosis. *Ann Intern Med*. 1981;95:244-246.
36. Mitchinson MJ. Retroperitoneal fibrosis associated with metoprolol. *Br Med J*. 1982;30:e347.
37. Pryor JP, Castle WM, Dukes DC, Smith JC, Watson ME, Williams JL. Do β -adrenoceptor blocking drugs cause retroperitoneal fibrosis? *Br Med J*. 1983;287:639-641.
38. Alvarez-Mugica M, Jalon Mouzon A, Bulnes Vazquez V, Anes Gonzalez G, Gonzales Alvarez RC, Martin Benito J. Retroperitoneal fibrosis in relation to use of analgesic tramadol and paracetamol. *Arch Esp Urol*. 2006;59:923-930.
39. Lewis CT, Molland E, Marshall V, Tresidder GC, Blandy JP. Analgesic abuse, ureteric obstruction and retroperitoneal fibrosis. *Br Med J*. 1975;2:76-78.
40. Ristagno RL. Drugs associated with retroperitoneal fibrosis. *West J Med*. 1981;135:159-160.
41. Finan BF, Finkbeiner AE. Renal papillary necrosis and retroperitoneal fibrosis secondary to analgesic abuse. *J Urol*. 1981;126:533-534.
42. MacGregor GA, Jones NF, Barraclough MA, Wing AJ, Cranston WI. Ureteric stricture with analgesic nephropathy. *Br Med J*. 1973;2:271-272.
43. Waters VV. Hydralazine, hydrochlorothiazide and ampicillin associated with retroperitoneal fibrosis report. *J Urol*. 1989;141:936-937.
44. Adab FA, Mould JJ. Carboplatin and retroperitoneal fibrosis. *Clin Oncol*. 1992;5:327-329.
45. Yamakawa H, Yoshida M, Katagi H, Hirooka S, Okuda K, Ishikawa T, Takagi M, Kuwano K. Pulmonary and retroperitoneal lesions induced by methotrexate-associated lymphoproliferative disorder in patient with rheumatoid arthritis. *Mod Rheumat*. 2014 Apr 1 (Epub ahead of print).
46. Fassina A, Boscolo Berto R, El Mazloum R, Gottardo F, Artibani W. Retroperitoneal fibrosis after chemotherapy. *Eur Urol*. 2007;51:270-271.
47. Couderc M. Retroperitoneal fibrosis during Etanercept therapy for rheumatoid arthritis. *J Rheum*. 2013;40:1931-1933.
48. Massara A, Cavazzini L, La Corte R, Trotta F. Sarcoidosis appearing during anti-TNF α therapy: a new "class effect" paradoxical phenomenon. Two case reports and literature review. *Semin Arthritis Reum*. 2010;39:313-319.
49. Collamer AN, Guerrero KT, Henning JS, Battafarano DF. Psoriatic skin lesions induced by TNF α antagonist therapy: a literature review and potential mechanisms of action. *Arthritis Rheum*. 2008;59:996-1001.
50. Chen Y, Xiong M, Zhang SC. Illuminating Parkinson's therapy with optogenetics. *Nat Biotechnol*. 2015;33:149-150.
51. Ferraccioli G, Gremese E. Should we consider tumor necrosis factor as the only target of spondyloarthritides? *J Rheumat*. 2012;89:94-92.
52. Alberti C. Revisiting retroperitoneal fibrosis: are there any significant news about the aetiopathogenesis and diagnostic approaches? *Eur Rev Med Pharmacol Sci*. 2012;16:1078-1094.
53. Scheel PJ, Feeley N. Retroperitoneal fibrosis. *Rheum Dis Clin*. 2013;39:365-381.
54. Cristian S, Cristian M, Cristian P, Costantin G, Savu C, Huri E, Sinescu I. Management of idiopathic retroperitoneal fibrosis from the urologist's perspective. *Ther Adv Urol*. 2015;7:85-89.
55. Glazer S. Retroperitoneal fibrosis. *CJEM*. 2015 Mar 3:1 (Epub ahead of print).
56. Andersson U, Tracey KJ. A new approach to rheumatoid arthritis: treating inflammation with computerized nerve stimulation. *Cerebrum*. 2012 Mar;3. (Epub ahead of print).
57. Rosas-Ballina M, Valdés-Ferrer SI, Dancho ME, et al. Xanomeline suppresses excessive proinflammatory cytokine responses through neural signal-mediated pathways and improves survival in lethal inflammation. *Brain Behav Immun*. 2015;44:19-27.